ISSN: 2755-0141

Japan Journal of Clinical & Medical Research

SCIENTIFIC Research and Community

Research Article

Open Access

The Role of Endothelin-1 (ET-1) as a Biomarker for Early Detection of Endothelial Dysfunction in the Context of National Health Security (NHS) and Sustainable Development Goals (SDGs): A Paradigm Shift

Aldian A Pratama

Program Pendidikan Dokter Spesialis Patologi Klinik, Fakultas Kedokteran, Universitas Brawjaya, Indonesia

ABSTRACT

Endothelin-1 (ET-1) is a potent vasoconstrictor and functions as a non-invasive biomarker for endothelial dysfunction from a biomolecular standpoint. Endothelial dysfunction is a precursor to hypertension and various cardiovascular diseases. According to the Sustainable Development Goals (SDGs), the financial burden associated with cardiovascular diseases has been increasing annually. This necessitates a paradigm shift within the national health resilience framework, moving from a focus on illness to one that emphasizes health promotion and prevention, with the aim of mitigating the financial impact of cardiovascular diseases.

The purpose of this research is to investigate the essential role of endothelin-1 (ET-1) in advancing the Sustainable Development Goals (SDGs) and enhancing national health resilience. The investigation seeks to emphasize the unique and clinical significance of endothelin-1 (ET-1) across various sectors, particularly concerning cardiovascular risk, as well as the potential economic advantages of alleviating the disease burden.

Findings: The results reveal that endothelin-1 (ET-1) plays a significant role in contributing to the SDGs by facilitating the early detection of endothelial dysfunction, thereby helping to reduce the incidence of cardiovascular diseases.

Originality and value lie in its use of a novel statistical analysis to explore the relationship between endothelin-1 (ET-1) and other pertinent parameters. This research highlights the integrative function of Endothelin-1 (ET-1) in harmonizing the objectives of the SDGs with those of National Health Resilience, providing actionable insights for decision-makers across various sectors. The findings establish a basis for policymakers and practitioners to utilize endothelin-1 (ET-1) in promoting comprehensive and sustainable development.

***Corresponding author**

Aldian A Pratama, Pusat Kesehatan TNI-AD, Kementerian Pertahanan Republik Indonesia.

Received: May 22, 2025; **Accepted:** May 27, 2025; **Published:** July 01, 2025

Keywords: ET-1, Early Detection, Endothelial Dysfunction, National Health Security (NHS)

List of Abbreviations	
ET-1:	Endothelin-1 (ET-1)
NHS:	National Health Security
SDGs:	Sustainable Development Goals
NCDs:	Non-communicable diseases
LMICs:	low- and middle-income nations
WHO:	World Health Organization
CVD:	Cardiovascular disease
UN:	United Nations
ET-A:	Endothelin-A
ET-B:	Endothelin-B
JNC-7:	Joint National Committee-7
GSR:	Global Status Report
USD:	United Stated Dollars
BMI:	Body Mass Index
HDL-C:	High density lipoprotein cholesterol
LDL-C:	Low density lipoprotein cholesterol
SD:	Standard deviation
TG:	Triglycerides
NHR:	National Health Resilience
EBM:	Evidence-based medicine

Introduction

Non-communicable diseases (NCDs) were responsible for a minimum of 43 million fatalities in 2021, constituting 75% of deaths not attributable to pandemics on a global scale. Furthermore, 18 million individuals died from an NCD before reaching the age of 70, with 82% of these premature fatalities occurring in low- and middle-income countries. The analysis further reveals that 73% of NCD-related deaths occur in these low- and middle-income nations

(LMICs) [10]. The leading cause of NCD deaths is cardiovascular disease, accounting for a total of at least 19 million deaths in 2021. This is followed by cancer (10 million), chronic respiratory diseases (4 million), and diabetes (over 2 million, including deaths from kidney disease linked to diabetes). Collectively, these four categories account for 80% of all premature deaths attributable to NCDs. Tobacco use, lack of physical activity, harmful alcohol consumption, poor dietary habits, and air pollution have all been identified as factors that elevate the risk of dying from an NCD. Key elements in addressing NCDs include their detection, screening, treatment, and palliative care [1].

The impact of NCDs is pervasive, affecting individuals across all age groups, regions, and countries. While these diseases are often linked to older populations, it is important to note that approximately 18 million NCD deaths occur before the age of 70. Indeed, NCDs result in more deaths in this age group than all other causes combined, with an estimated 82% of these premature deaths occurring in low- and middle-income countries. The risk factors associated with NCDs are pervasive and include, but are not limited to, unhealthy diets, physical inactivity, exposure to tobacco smoke, and harmful alcohol use or air pollution [1].

The manifestation of unhealthy eating habits and insufficient physical activity can be evidenced in individuals through elevated blood pressure, increased blood glucose levels, high blood lipid levels, and obesity. These conditions are collectively termed metabolic risk factors and have been identified as a major contributing factor to the development of cardiovascular disease (CVD), which is the leading NCD in terms of premature mortality [1].

Figure 1: SDGs can be Linked together Economically, Societally and Ecologically

Source: WHO (2015) [10].

The Sustainable Development Goals (SDGs) are a global initiative that calls upon all nations to foster prosperity while safeguarding the environment. The overarching ambition is to eradicate poverty through the implementation of strategies that stimulate economic growth and address various social needs, including education, healthcare, social protection, and employment opportunities. Concurrently, there is a necessity to confront climate change and ensure environmental sustainability [2].

A particular emphasis is placed on Goal 3, which aims to ensure the promotion of health and well-being for individuals of all ages. Specifically, Goal 3.4 aims to reduce premature mortality from non-communicable diseases (NCDs) by one-third by 2030 through a combination of prevention and treatment efforts, as well as to enhance mental health and well-being [2].

A particular emphasis is placed on reducing high blood pressure, which is recognized as the primary cause of cardiovascular disease. The target set for 2025 is to achieve a 25% reduction in high blood pressure, a key indicator of progress towards achieving Goal 3.4 [2].

Figure 2: NCD Global Action Plan For 2025

Source: WHO (2025) [1].

In the context of addressing the challenges associated with the Sustainable Development Goals (SDGs), the concept of National Health Resilience (NHR) refers to a nation's capacity to proactively prepare for, respond to, and recover from public health threats, while ensuring the continuity of essential health services and adapting to evolving situations [1].

Hypertension, also known as high blood pressure, poses a significant health risk to millions of individuals, leading to a wide range of preventable health complications, including heart attacks, strokes, heart failure, and premature mortality [1].

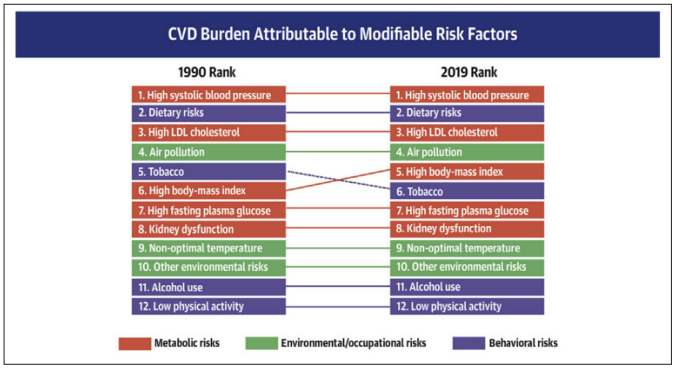

Figure 3: CVD Burden Attributable to Modifiable Risk Factors

Source: Roth (2020) [3].

The prevention and management of hypertension have been shown to have significant health benefits, including the potential to save lives, reduce healthcare costs, and enhance overall health, well-being, and resilience. The initial step toward achieving these benefits is to recognise that hypertension, often referred to as the "silent killer" due to its tendency to go unnoticed until it causes significant damage, is also a "silent pandemic." While it is not a contagious threat in the conventional sense, hypertension requires increased focus and urgency in addressing it [4].

The advent of a cuff-based device that facilitates straightforward and non-invasive blood pressure measurement is less than 150 years ago. By the mid-20th century, the medical community had advanced its understanding of the risks associated with hypertension, leading to increased concern about the various health

problems that can arise from even mild cases of elevated blood pressure. Since that time, there has been a significant increase in public awareness of the dangers of hypertension [5].

Nevertheless, with the rising global prevalence of hypertension, it has become evident that implementing early detection strategies before hypertension develops is crucial for mitigating potential future impacts [5].

Peripheral vascular resistance has been identified as a contributing factor to hypertension. The regulation of vascular tone is a complex process involving various mediators, including Endothelin-1 (ET-1). Endothelin-1 (ET-1) is a peptide composed of 21 amino acids that is produced by vascular endothelial and smooth muscle cells [6].

Endothelin-1 is recognised as one of the strongest vasoconstrictors. It functions through two types of receptors: endothelin-A (ET-A) and endothelin-B (ET-B). ET-A is predominantly located on vascular smooth muscle cells and is primarily responsible for mediating vasoconstriction and promoting cell proliferation. Conversely, ET-B has the capacity to induce vasodilation, inhibit cell growth, and function as a receptor for clearance [6].

Furthermore, it was demonstrated that endothelin-1 (ET-1) antagonists cause a greater degree of vasodilatation in the forearm vessels of hypertensive patients compared with normotensive subjects, thereby suggesting an increase of endothelin-1 activity in endothelial dysfunction in hypertensive patients [6].

Furthermore, it has been demonstrated that endothelin-1 (ET-1) antagonists induce a more significant vasodilation in the forearm blood vessels of hypertensive patients compared to those with normal blood pressure. This finding indicates that there is heightened endothelin-1 activity associated with endothelial dysfunction in individuals with hypertension [7].

Endothelial dysfunction is a pivotal factor in the pathophysiology of cardiovascular disease, influencing both its development and clinical manifestation. It is characterised by reduced vascular reactivity and lower nitric oxide (NO) availability, which are also associated with the presence of established atherosclerosis [8].

Endothelial dysfunction has been identified in various disease conditions, encompassing all significant cardiovascular risk factors and coronary artery disease. Furthermore, it has been demonstrated to serve as a predictor of adverse cardiovascular events, both in healthy individuals and those with pre-existing cardiovascular conditions. The reduction in nitric oxide (NO) availability, attributable to elevated levels of endothelin-1 (ET-1), has been identified as a key factor in the development of endothelial dysfunction [8].

Endothelin-1 (ET-1) exerts a powerful vasoconstrictive effect, influencing vascular tone and thus serving as a molecular marker for endothelial dysfunction in adults with prehypertension. Consequently, endothelial dysfunction can be regarded as a "risk factor for risk factors" that requires early identification. From an epidemiological perspective, this initiative for early detection forms part of a population-based strategy [9].

The seventh Joint National Committee (JNC-7) report on the prevention, detection, evaluation, and treatment of high blood pressure defines prehypertension as having a systolic blood pressure ranging from 120 to 139 mmHg and/or a diastolic pressure between 80 and 89 mmHg. The identification of prehypertension is paramount for the classification of patients who are at an elevated risk of developing arterial hypertension and a heightened probability of cardiovascular disease. Cardiovascular disease is a major non-communicable disease (NCD) that is a key target of the preventive strategies established in the Sustainable Development Goals (SDGs) [9].

The proactive identification of endothelial dysfunction is anticipated to enhance overall health resilience. This research and development initiative requires the support of policymakers to mitigate the curative effects of cardiovascular disease and bolster national health resilience. Sustainable efforts are recognised as fundamental components in the realisation of the Sustainable Development Goals (SDGs) and the reinforcement of national health resilience, thus highlighting the strategic importance of these initiatives [9].

The role of Endothelin-1 (ET-1) can contribute to the success of these two World Health Organization [10]. initiatives, as enhancing preventive measures and promoting a healthy paradigm are anticipated goals for the future. This approach is a more strategic one in comparison to the traditional sick paradigm, which is based on evidence-based medicine and has led to a gradual increase in health financing impacts each year [9].

Non-Communicable Diseases (NCDs) are the most significant public health challenges facing the world in the twenty-first century. They are responsible for health issues, economic losses, premature deaths, reduced quality of life, and hindered social development in both high-income and low-income countries. The Global Status Report (GSR) on non-communicable diseases, published by the World Health Organization [10]. indicates that out of 38 million annual deaths attributed to NCDs, over 40% are considered premature and preventable [10].

According to projections from the World Health Organization [10]. by 2025, Non-Communicable Diseases (NCDs) are expected to account for more than 70% of all global deaths, with 85% of these fatalities occurring in developing nations. Evidence indicates that without the implementation of effective prevention strategies, approximately 41 million individuals in low-resource countries could die from NCDs by 2025, primarily due to cardiovascular diseases (CVDs) (48%), cancers (21%), chronic respiratory diseases (12%), and diabetes (3%) [11].

The prevalence of non-communicable diseases (NCDs) is responsible for a significant portion of preventable illness and mortality, including cardiovascular disease, coronary heart disease, hypertension, diabetes, and obesity. The mortality rates associated with these major NCDs vary across three global regions: high-resource countries, low-resource countries, and Africa [12].

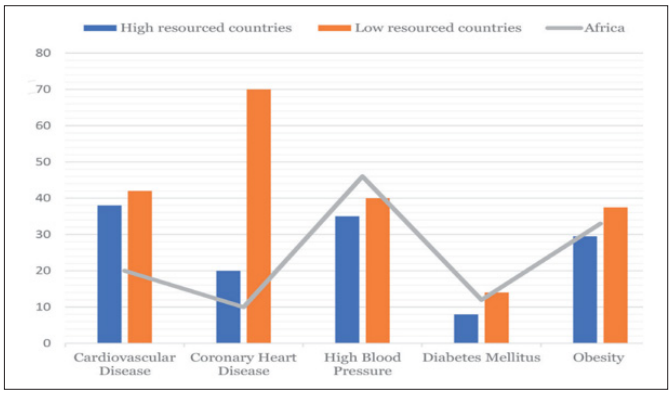

Figure 4: Percentage of mortality associated with NCDs in Africa, high-resourced and low-resourced countries.

Source: [10].

In high-income countries, the mortality rate associated with non-communicable diseases (NCDs) such as cardiovascular disease, coronary heart disease, hypertension, diabetes, and obesity is declining. Conversely, in low-resource countries and within the African context, there is an observed increase in this rate. For instance, the mortality rate from cardiovascular disease is 38% in high-resource countries, compared to 42% in low-resource countries, with Africa accounting for 20% of this figure. In these regions, cardiovascular diseases account for a disproportionately high proportion of deaths [10].

In Africa, high blood pressure accounts for 46% of mortality, which exceeds the overall death rate in low-resource countries (40%). Conversely, in high-income countries, high blood pressure accounts for a lower proportion of deaths, at 35%. The mortality rates from diabetes are 8% in high-resource countries, 12% in low-resource countries, and 14% in Africa. Furthermore, obesity is responsible for 29.5% of deaths in high-income countries and 37.5% in low-resource countries [10].

In Indonesia, cardiovascular diseases (CVDs) accounted for 38% of total deaths in 2019, with stroke and ischemic heart disease being the two primary causes, responsible for 19% and 14% of all fatalities, respectively. The rising prevalence of non-communicable diseases (NCDs) has also resulted in higher healthcare expenditures, totaling USD 4,078 million, which represents 22% of the overall healthcare spending in 2019. Of these expenditures, 24% were attributable to cardiovascular diseases (CVDs) [13, 14].

Furthermore, approximately one-third of Indonesia's elderly population suffers from multimorbidity, with more than 43% of National Health Insurance (NHI) beneficiaries who visit hospitals being diagnosed with chronic multimorbidity. The most prevalent combinations of these conditions are hypertension in conjunction with either diabetes mellitus, cerebral ischemia/chronic stroke, or ischemic heart disease [9].

The overarching objective of the Global Action Plan is to enhance the resilience of national health systems through the implementation of comprehensive and enabling measures. This includes the integration of highly cost-effective interventions for non-communicable diseases (NCDs) into the essential primary healthcare package, in addition to the establishment of referral systems across all levels of care to promote the agenda of universal health coverage [10].

Early detection and coverage are to be enhanced and expanded, respectively, by focusing on highly cost-effective, high-impact interventions, including those that target behavioral risk factors. Furthermore, the implementation of additional cost-effective strategies and policy measures outlined in the recommendation, with the aim of strengthening and aligning health systems in addressing non-communicable diseases and their risk factors through people-centered healthcare and universal health coverage [10].

A national multisectoral policy and plan for NCD prevention and control should be formulated and executed through engagement with multiple stakeholders. The implementation of additional policy measures is also recommended in order to enhance national capacity. Furthermore, the encouragement and enhancement of the national capacity for conducting high-quality research and development aimed at preventing and controlling non-communicable diseases is to be encouraged [10].

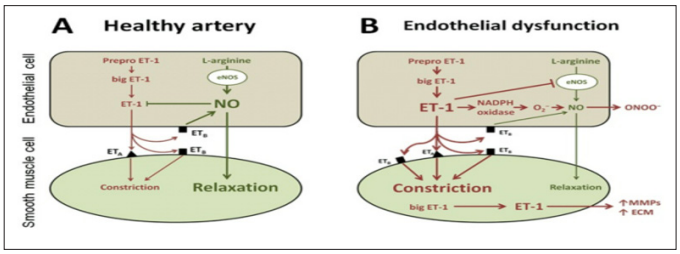

Figure 5: Simplified schematic diagram of ET-1 signaling in the vasculature to cause vasoconstriction

Source: Banecki (2023) [15].

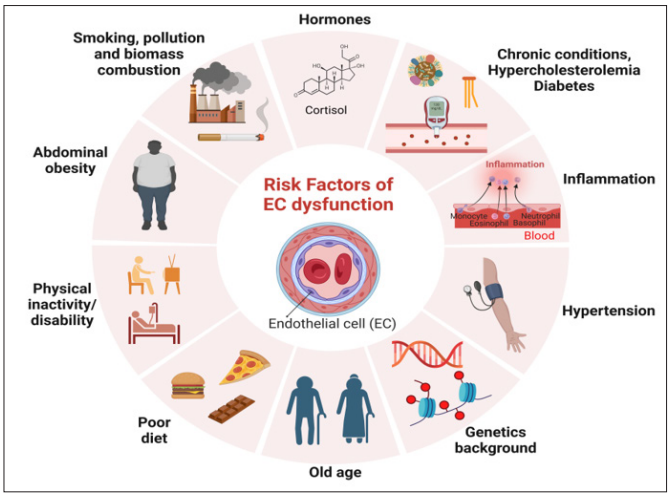

Figure 6: Multiple risk factors contribute to endothelial dysfunction in a complex interplay

Source: Hojjat (2024)

Understanding the causes of endothelial cell dysfunction (ECD) is of paramount importance, ECD stems from a cluster of interrelated risk factors (Figure 6), such as hypertension, diabetes mellitus, smoking, obesity, dyslipidemia, aging, inflammation, oxidative stress, abnormal shear stress, and genetic susceptibility. These factors are intricately linked, often forming a cycling pattern where the progression of one aggravates others, perpetuating the dysfunction.

Smoking, a widespread behavior with extensive health consequence, is a major factor contributing to endothelial dysfunction. Endothelial cells, which play a key role in maintaining vascular health, are adversely affected by the harmful substances found in cigarette smoke. Smoking disrupts the delicate balance of endothelial function by reducing the production of nitric oxide (NO), an essential molecule that promotes blood vessel dilation. The decrease in NO availability impairs vasodilation and increases the risk of vasoconstriction.

The oxidative stress caused by smoking generates reactive oxygen species (ROS) that damage endothelial cells, provoke inflammation, and initiate dysfunction. Additionally, toxic components of cigarette smoke accelerate endothelial cell aging, reducing their ability to repair and regenerate, which further advances endothelial impairment. Smoking also stimulates the increased expression of adhesion molecules on endothelial surfaces, creating a pro-inflammatory environment that disrupts cellular communication and facilitates the infiltration of harmful agents. This inflammatory state, combined with a shift toward a pro-thrombotic condition, disturbs the balance between clot-promoting and clot-preventing factors, raising the risk of thrombosis. Moreover, smoking has been linked to the induction of endothelial-to-mesenchymal transition (EndMT), a process where endothelial cells transform into mesenchymal cells, contributing to fibrosis and vascular remodelling, thereby woresing cascular health.

Climate change, through its impact on environmental temperatures and pollution, is increasingly recognized as a contributor to endothelial cell dysfunction, which underlies many cardiovascular diseases. Studies have shown that short-term exposure to colder temperatures reduces endothelial-dependent vasodilatation, a key indicator of vascular health, thereby increasing cardiovascular risk. Personal-level temperature exposure, reflecting actual conditions experienced indoors and outdoors, has been found to be a more accurate predictor of endothelial function than ambient outdoor temperatures alone.

Cold exposure activates the sympathetic nervous system and causes vasoconstriction, impairing endothelial function and raising blood pressure, which may explain the higher incidence of cardiovascular events during colder seasons. Additionally, air pollutants associated with climate change, such as particulate matter and gaseous toxins, further damage endothelial cells by inducing oxidative stress and inflammation, exacerbating vascular dysfunction. These combined environmental stressors linked to climate change contribute to the onset and progression of endothelial dysfunction–related diseases, emphasizing the need for preventive strategies like improving indoor climate control and reducing exposure to extreme temperatures and pollution to protect cardiovascular health.

Climate change, through its impact on environmental temperatures and pollution, is increasingly recognized as a contributor to endothelial cell dysfunction, which underlies many cardiovascular diseases. Studies have shown that short-term exposure to colder temperatures reduces endothelial-dependent vasodilatation, a key indicator of vascular health, thereby increasing cardiovascular risk.

Personal-level temperature exposure, reflecting actual conditions experienced indoors and outdoors, has been found to be a more accurate predictor of endothelial function than ambient outdoor temperatures alone. Cold exposure activates the sympathetic nervous system and causes vasoconstriction, impairing endothelial function and raising blood pressure, which may explain the higher incidence of cardiovascular events during colder seasons. Additionally, air pollutants associated with climate change, such as particulate matter and gaseous toxins, further damage endothelial cells by inducing oxidative stress and inflammation, exacerbating vascular dysfunction. These combined environmental stressors linked to climate change contribute to the onset and progression of endothelial dysfunction–related diseases, emphasizing the need for preventive strategies like improving indoor climate control and reducing exposure to extreme temperatures and pollution to protect cardiovascular health [16].

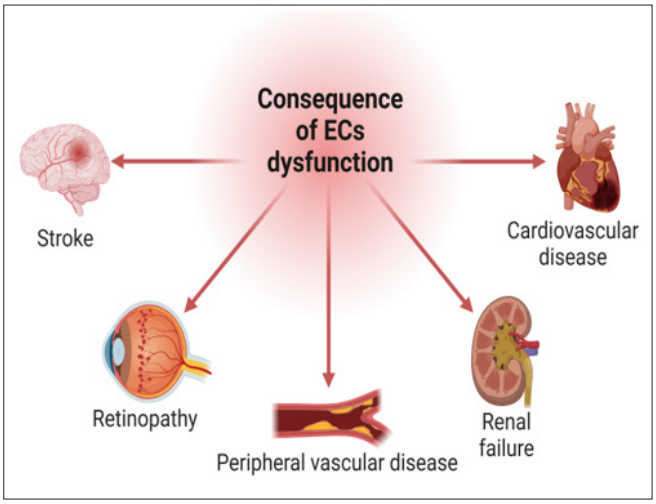

Figure 7: The cascade of endothelial cells (ECs) dysfunction on organ health

Source: Hojjat (2024)

Methods

The experimental research design of this study employed a cross-sectional approach to examine the relationship between Endothelin-1 (ET-1) and the triglyceride to high-density lipoprotein ratio in relation to obesity levels at RSUD dr. Saiful Anwar Malang. The sample consisted of individuals who met the inclusion criteria of being overweight and/or obese, with a total of 85 samples collected. The demographic characteristics of the study participants were then categorized into different groups.

The general characteristics included age, waist circumference, and body mass index (BMI), while the clinical characteristics encompassed total cholesterol, HDL-C, LDL-C, triglycerides, the TG/HDL ratio, and endothelin-1 (ET-1) levels. The subsequent table displays the results of the demographic characteristics, presented as frequency, percentage, mean, and standard deviation (SD).

The collection of research subject identities involves the completion of an identity sheet that includes patient status, such as BMI measurements. The subjects' weight is recorded using a digital scale, while their height is measured with a stadiometer. The results of these measurements are analyzed using both difference tests and correlation tests. In the event that the data is found to be normal and homogeneous, parametric tests will be conducted; otherwise, non-parametric tests will be utilized. The testing is conducted at a confidence level of 95% with an alpha value of 0.05. The analysis was performed using SPSS version 24 software.

Result and Discussion

Result

Table 1: Correlation test of Endothelin-1 (ET-1) and TG/HDL Ratio

Body Mass Index (BMI)	n (%)	p-*value*	Correlation coefficient (r)
Endothelin-1	85 (100%)	<0.001	0.553
TG/HDL-C ratio	85 (100%)	<0.001	0.410

HDL ratio in relation to body mass index (BMI) and HDL, conducted utilizing the Spearman correlation test, indicated statistically significant values. Specifically, a significant correlation was observed between Endothelin-1 (ET-1) and body mass index (BMI), as well as between the TG/HDL ratio and both body mass index (BMI) and HDL ($p<0.05$). The correlation coefficient for Endothelin-1 (ET-1) with body mass index (BMI) was 0.553, while the TG/HDL ratio with body mass index (BMI) was 0.410, and the TG/HDL to HDL ratio was -0.738.

Table 2. Multivariate Test Results on the Research Parameters Examined

Variables	n (%)	p-*value*
Age	85 (100)	0.297
BMI	85 (100)	<0.001
Waist circumference	85 (100)	<0.001
Endothelin-1 (ET-1)	85 (100)	<0.001
Total-Cholesterol	85 (100)	<0.001
LDL-Cholesterol	85 (100)	<0.001
HDL-Cholesterol	85 (100)	0.031
Trygliceride	85 (100)	<0.001
TG/HDL ratio	85 (100)	<0.001

The findings from the multivariate analysis in this study revealed significant variables, including Endothelin-1 (ET-1), BMI, waist circumference, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides (TG), and the TG/HDL ratio, all with a p-value of less than 0.05. These parameters demonstrate a statistically significant relationship among the variables and exhibit an independent association with the study's outcomes.

The correlation between the Sustainable Development Goals (SDGs) and National Health Resilience (NHR), particularly in relation to Goal 3, underscores the notion that the attainment of optimal health and well-being can be realized through a series of systematic steps, as outlined below:

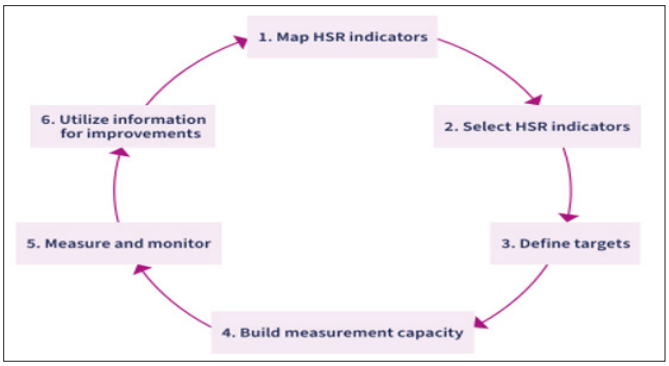

Figure 8: Steps in using the package of NHR indicators to enhance measurement, monitoring and building of health system resilience

Source: WHO (2024) [11].

The initial step in this process is to align the National Health Resilience (NHR) indicators with current indicators and methods for monitoring and evaluation. These include those found in routine health information systems. Following the identification of the existing indicators related to resilience, the selection of any additional indicators from the NHR indicator package can then be undertaken to enhance the monitoring and strengthening of resilience in a comprehensive manner [11].

Given the inherently context-dependent and continuous nature of resilience, it is imperative to acknowledge that there is no universally applicable targets or levels for the indicators. Within this framework, targets refer to specific, intended outcomes that are to be achieved, typically within a designated timeframe. These targets are subject to variation based on the indicator type and other factors, including the administrative level at which data is collected (national, subnational, community, or facility) [11].

Once the indicators have been established, particularly in the domain of access to health products and technologies, they are selected with meticulous consideration of national contexts. This involves the consideration of factors such as disease prevalence, evidence of efficacy and safety, and comparative cost-effectiveness. The overarching objective is to ensure the consistent availability of these products within functioning health systems, thereby maintaining assured quality and affordability for both individuals and health systems [11].

In this context, the management of hypertension, the primary contributor to cardiovascular diseases, is identified as a key target. Endothelial dysfunction is a major risk factor, and the examination of Endothelin-1 (ET-1) levels is crucial for the implementation of early detection strategies at the primary prevention level. This approach is predicated on the objective of diminishing the incidence of cardiovascular diseases, the consequences of which are twofold: a) health complications and b) a substantial economic burden on healthcare systems.

The assessment of Endothelin-1 (ET-1) levels will yield valuable insights into endothelial function prior to the development of hypertension.

Discussion

The incorporation of the role of endothelin-1 (ET-1) as a tool for the early detection of endothelial dysfunction into the framework of national health resilience and the Sustainable Development Goals (SDGs), especially Goal 3.4, aims to decrease premature deaths from non-communicable diseases by one-third by 2030. This initiative prioritizes cardiovascular diseases, which are the leading cause of these deaths, by enhancing prevention and management strategies and refining health promotion initiatives.

It is imperative to provide counsel to relevant stakeholders, particularly policymakers responsible for decision-making, as current data indicates an annual escalation in the financial burden of curative care, suggesting a persistent emphasis on remedial measures. Enhanced early detection and prevention initiatives, when coupled with Indonesia's increasing life expectancy and demographic dividend, are poised to transform this situation into a valuable opportunity for improvement.

This transition necessitates a shift in focus from the prevailing illness-focused paradigm to a health-oriented approach. This transition is expected to enhance the efficiency of healthcare financing, moving away from a focus on curative services towards

a more proactive model that emphasizes health promotion and prevention. Consequently, there is a need for increased investment in areas related to development and research, which will support this shift.

Endothelial dysfunction is a fundamental factor that precedes the development of hypertension at the molecular level. It is therefore crucial to have non-invasive and suitable quantification methods that can be applied across all healthcare levels, from primary to tertiary. This is particularly pertinent in the context of endothelin-1 (ET-1), which has the capacity to inherently enhance the national resilience system and contribute to the Sustainable Development Goals (SDGs) agenda.

Besides, air pollution refers to the presence of gaseous, liquid, and solid contaminants in the atmosphere, originating from both human activities, such as; industry, agriculture, and farming, and natural events like volcanic eruptions, soil dust, and wildfires. Historically, research has focused primarily on gaseous pollutants including nitrogen oxides (NOx), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3), which are common byproducts of industrial processes. More recently, attention has expanded to include other gases such as volatile organic compounds (VOCs), non-methane hydrocarbons, and polycylic aromatic hydrocarbons (PAHs) [13].

According to the 2019 global burden of disease (GBD) study published in the Lancet, ambient particulate matter (PM) was ranked seventh among risk factors for disability-adjusted life years (DALYs), rising from 13th place in 1990. Conversely, household air pollution dropped from fourth to tenth place, highlighting the growing impact of outdoor pollution. The GBD study estimated that air pollution contributes to approximately 6.5 million deaths annually worldwide, an increase from the 4.2 million deaths reported by the [11]. in 2016. New hazard-response models suggest that air pollution may be responsible for up to 8.79 million premature deaths globally each year. Non-communicable diseases, particularly cardiovascular diseases (CVD), are major contributors to these health burdens, underscoring the importance of understanding the relationship between air pollution and cardiovascular health [13].

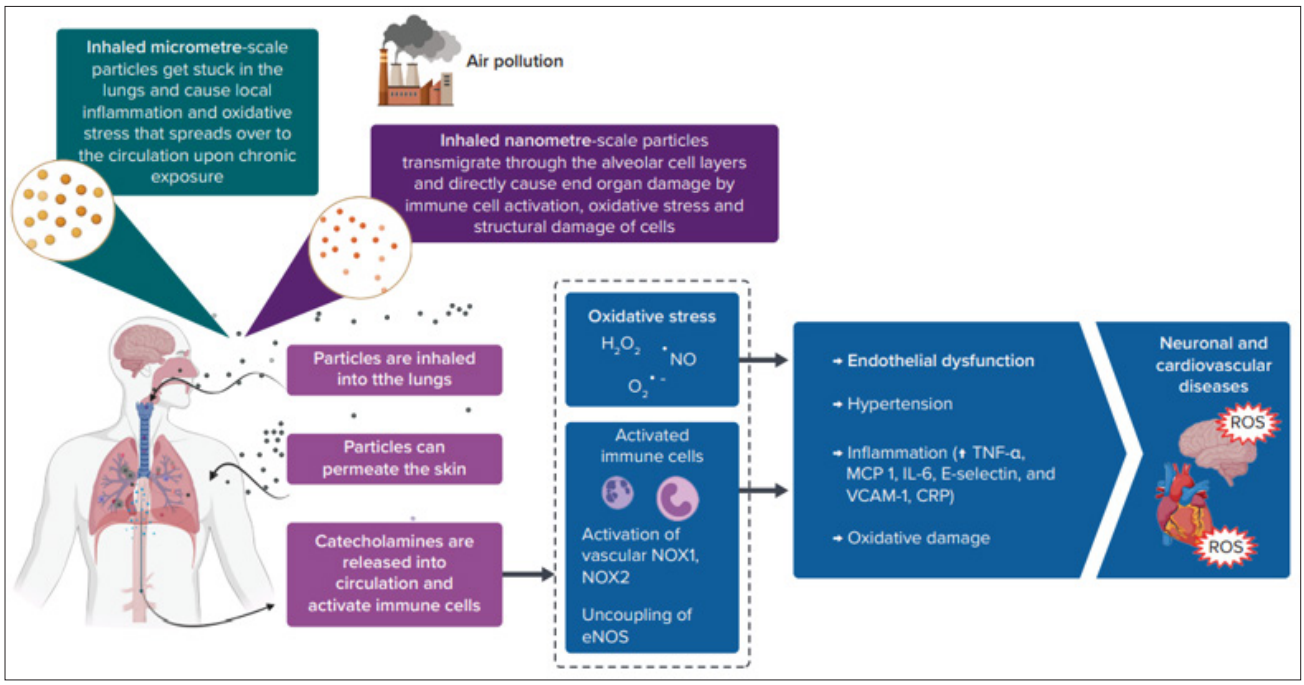

Figure 9: Proposed pathophysiological mechanisms of cardiovascular and neuronal disease induced by air pollution

Source: Maria (2023) [13].

Impact of air pollution on endothelial function, that gaseous pollutants can readily cross the air-blood barrier and enter circulation, where they may directly damage endothelial cells by interacting with their components or indirectly cause harm by triggering immune responses and oxidative stress. Ultrafine particulate matter at the nanometer scale can also penetrate this barrier and enter the bloodstream directly. Larger particles, typically in the micrometer range, usually remain in the respiratory tract but induce local inflammation that can spread systematically. The main mechanisms driving endothelial dysfunction due to air pollution are oxidative stress and inflammation, which contribute to the initiation and progression of vascular damage [13].

The global and national statistics on the prevalence of hypertension, a major contributor to cardiovascular diseases, have not shown a decrease; instead, they continue to rise. A salient issue at the healthcare service level is that hypertension is predominantly identified through blood pressure measurements obtained with a sphygmomanometer. Once hypertension has been diagnosed, it indicates that endothelial dysfunction has already occurred.

This progression to hypertension could have been prevented with broader and more precise interventions at the population level. In this context, the role of endothelin-1 (ET-1) is vital for effectively advancing the previously mentioned Sustainable Development Goals (SDGs) agenda.

Endothelin-1 (ET-1) is a crucial biomarker in the initial identification process, as the biomarkers commonly utilized in everyday healthcare, such as cardiac enzymes troponin I and CK-MB, indicate that heart muscle damage has already taken place. Evidence-based medicine (EBM) underscores the significance of early intervention in prehypertensive states to avert the progression to full-blown hypertension and mitigate cardiovascular risks, as emphasized by (Weil et al, 2012).

The clinical significance of timely intervention in prehypertensive states, with the objective of averting the progression to full hypertension and reducing cardiovascular risk. Endothelial dysfunction, being an indicator of cardiovascular events, underscores that prehypertension should not be considered harmless.

Furthermore, elevated levels of endothelin-1 have been demonstrated to contribute to greater arterial stiffness and vascular remodelling by promoting the proliferation of vascular smooth muscle cells. Consequently, heightened endothelin-1 activity in individuals with prehypertension may lead to increased vascular tone and structural alterations in the blood vessels.

In summary, the research conducted by Weil et al offers valuable insights into the progression of hypertension, highlighting that prehypertension should not be regarded as a harmless condition. Consequently, further studies are needed to investigate whether early pharmacological treatment could be appropriate and advantageous for patients experiencing endothelial dysfunction and prehypertension.

A study undertaken by the author at RS dr. Saiful Anwar Malang, a medical education center in Indonesia, utilized the Spearman's rho correlation test and revealed significant p-values for the relationships between endothelin-1 (ET-1) and body mass index (BMI), as well as between the TG/HDL ratio and both body mass index (BMI) and HDL ($p<0.05$).

The statistical analysis employing multivariate testing methods indicated significant results for the variables endothelin-1 (ET-1), BMI, waist circumference, total cholesterol, HDL, LDL, TG, and TG/HDL ($p<0.05$). In addition, statistically significant relationships were identified among these variables, along with an independent association with endothelial dysfunction.

Conclusion

In summary, endothelin-1 (ET-1) functions as both a biomarker and a vital element of biodefense, significantly contributing to the advancement of Sustainable Development Goals (SDGs) and the enhancement of national health resilience systems. The employment of ET-1-based strategies facilitates the timely detection and prevention of conditions associated with endothelial dysfunction, which are pivotal risk factors for the imposition of substantial financial strain on national health insurance systems [16-20].

In Indonesia, cardiovascular diseases accounted for 38% of total deaths in 2019 [8]. emphasizing the critical need to prioritize endothelial health to reduce healthcare expenses and enhance patient outcomes. It is estimated that approximately one-third of the Indonesian population is susceptible to developing cardiovascular diseases (CVDs), a condition attributable to a number of factors, including but not limited to unhealthy lifestyles, poor dietary choices, and insufficient physical activity. This alarming trend underscores the pressing need for effective strategies to address these issues.

To address this issue, there is a need to implement comprehensive health promotion initiatives. These initiatives should focus on educating the public about the risk factors associated with cardiovascular diseases (CVDs), promoting healthier lifestyle choices, and enhancing access to healthcare services. The incorporation of early detection techniques, such as the utilization of biomarkers like endothelin-1 (ET-1), holds promise in facilitating timely interventions and potentially mitigating the impact of CVDs on the Indonesian healthcare system.

In conclusion, the Indonesian government, healthcare providers, and communities must collaborate to implement a comprehensive strategy to address the increasing prevalence of cardiovascular diseases (CVDs) and promote a healthier future for the Indonesian population.

Ethics statement

Ethical approval for this study was obtained from the Health Research Ethics Commission General Hospital Dr. Saiful Anwar, Malang, Republic of Indonesia with Ethical Approval Number: 400/055/K.3.102.7/2023 The research was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013). All participants were provided with written and verbal explanations of the study's purpose, procedures, potential risks, and benefits prior to enrollment.

Consent statement

Written informed consent was obtained from all participants prior to their inclusion in the study. Participants were informed about the purpose, procedures, risks, and benefits of the research, and their anonymity and confidentiality were assured.

Funding Statement

The author received no financial support for the research, authorship, and/or publication of this article.

Reference

1. Adelowo A B (2021) Analyzing the Magnitude of Global Epidemiological Transition in Sub-Saharan Africa: A Need to Review the Current Healthcare Management Approach. *Texila International Journal of Public Health* https://doi.org/10.21522/TIJPH.2013.09.03.Art018.
2. Banecki KMRM, Dora KA (2023) Endothelin-1 in Health and Disease. Int J Mol Sci 24:112-195.
3. Bappenas (2019) *Roadmap of SDGs Indonesia A Highlight* 27-36.
4. Naderi Meshkin H, Setyaningsih, W A W (2024) Endothelial Cell Dysfunction: Onset, Progression, and Consequences. In *Frontiers in Bioscience – Landmark* 29: 223.
5. Kassa M, Grace J (2020) The Global Burden and Perspectives on Non-Communicable Diseases (NCDs) and the Prevention, Data Availability, and Systems Approach of NCDs in Low-Resource Countries. *Public Health in Developing Countries - Challenges and Opportunities, November*. https://doi.org/10.5772/intechopen.89516.
6. Kostov K (2021) The causal relationship between endothelin-1 and hypertension: Focusing on endothelial dysfunction, arterial stiffness, vascular remodeling, and blood pressure regulation *Life* 11: 986.
7. Maria Teresa Bayo Jimenez, Omar Hahad, Marin Kuntic, Andreas Daiber, Thomas Münzel (2023) Noise, Air and Heavy

Metal Pollution as Risk Factors for Endothelial Dysfunction, *European Cardiology Review* 18: e09.

8. Bayo Jimenez MT, Hahad O, Kuntic M, Daiber A, Münzel T (2023) Noise, Air, and Heavy Metal Pollution as Risk Factors for Endothelial Dysfunction. Eur Cardiol 4: e09.
9. Mozaffarian D, Wilson PWF, Kannel WB (2008) Beyond established and novel risk factors, lifestyle risk factors for cardiovascular disease. *Circulation* 117: 3031-3038.
10. PERKI (2022) Panduan Prevensi Penyakit Kardiovaskular Arterosklerosis. In *Perhimpunan Dokter Spesialis Kardiovaskular Indonesia* 2022.
11. Poredos P, Poredos AV, Gregoric I (2021) Endothelial Dysfunction and Its Clinical Implications. Angiology 72: 604-615.
12. Ramadani RV, Svensson M, Hassler S, Hidayat B, Ng N (2024) The impact of multimorbidity among adults with cardiovascular diseases on healthcare costs in Indonesia: a multilevel analysis. *BMC Public Health* 24: 1-12.
13. Gregory A Roth, George A Mensah, Catherine O Johnson, Giovanni Addolorato, Enrico Ammirati, et al. (2020) Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *Journal of the American College of Cardiology* 76: 2982-3021.
14. Schneider A, Herbst MC, Williams RW, Cascio W, Hinderliter A, et al. (2008) Endothelial dysfunction: associations with exposure to ambient fine particles in diabetic individuals. *Environmental health perspectives* 116: 1666-1674.
15. Segers VFM, Bringmans T, De Keulenaer GW (2023) Endothelial dysfunction at the cellular level in three dimensions: severity, acuteness, and distribution. *American Journal of Physiology - Endocrinology and Metabolism* 325: H398-H413.
16. Sena CM, Gonçalves L, Seiça R (2022) Methods to evaluate vascular function: a crucial approach towards predictive, preventive, and personalized medicine. *EPMA Journal* 13: 209-235.
17. United Nations (2020) Global indicator framework for the Sustainable Development Goals and targets of the 2030 Agenda for Sustainable Development. Work of the Statistical Commission Pertaining to the 2030 *Agenda for Sustainable Development* 1-21.
18. WHO (2024) Tackling NCDs. In World Health Organization. © *World Health Organization* https://www.who.int/publications/i/item/9789240091078.
19. WHO (2024) *Health system resilience indicators*. Health system resilience indicators an integrated package for measuring and monitoring health system resilience in countries © World Health Organization https://www.who.int/publications/i/item/9789240088986.
20. Widlansky ME, Gokce N, Keaney JF, Vita JA (2003) The clinical implications of endothelial dysfunction. *Journal of the American College of Cardiology* 42: 1149-1160.