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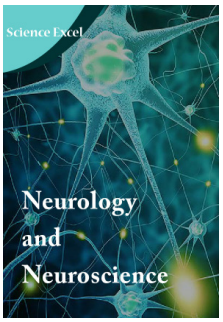

Peripheral Arterial Disease and Age-Related Changes in Arterial Stiffness: Findings from a Large Cohort of Patients

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Keywords

Arterial stiffness, Ankle-Brachial Index (ABI), Augmentation Index (AI), Ejection Elasticity Index (EEI), Dicrotic Elasticity Index (DEI), Dicrotic Dilation Index (DDI), Peripheral arterial disease (PAD), Diabetes mellitus, Cardiac autonomic neuropathy (CAN), smoking, critical limb ischemia (CLI), cardiovascular disease, vascular system

Abstract

Peripheral Arterial Disease (PAD) affects over 200 million people globally, with prevalence rising from 164 million in 2000 to 236 million in 2015. This study utilizes Medeia Inc.'s VitalScan-Vascular+ system, which integrates ABI, PWV, and PVR technologies, to improve PAD screening and management. By analyzing arterial stiffness across various indices (ABI, AI, EEI, DEI, DDI, C1, and C2) in a large cohort (n=227,173), the study found that most indices, except AI and C2, decline linearly with age, reflecting reduced arterial elasticity and increased stiffness. Despite these changes, ABI values remained within normal ranges for all participants. Male indices consistently exhibited higher values than those of females. These findings underscore the importance of using multiple indices for a comprehensive assessment of arterial health. Integrating ABI with arterial stiffness metrics offers a robust framework for evaluating cardiovascular risk and PAD, highlighting the need for diverse diagnostic tools to enhance patient management. Medeia Inc. aims to leverage this framework to develop cardiovascular databases for PAD diagnosis that go beyond age-related effects and support personalized treatment protocols. Future research should focus on refining these metrics and exploring their interactions to improve diagnostic accuracy and clinical practice in cardiovascular care.

Introduction

The global burden of Peripheral Arterial Disease (PAD) is significant, affecting over 200 million people worldwide, with a notable increase in prevalence from 164 million in 2000 to approximately 236 million in 2015 [1-5]. PAD is notably higher in high-income countries compared to low- and middle-income countries, although the majority (72.9%) of individuals with PAD reside in low- and middle-income regions [4]. From 2000 to 2015, the global prevalence of PAD increased by approximately 45%, with significant rises observed in both high-income and low- and middle-income nations [4].

In North America and Europe, around 20% of adults over 55 are affected by PAD, totalling approximately 27 million individuals, with about half being asymptomatic [6-17]. PAD is more prevalent in those with risk factors such as smoking, hypertension, and diabetes [6-8,18]. In the 1990s, PAD affected about 8.5 million individuals in the United States (U.S.), but recent data show nearly 12 million affected [19,20]. Changes in risk factors, such as increased diabetes and decreased smoking, suggest updated prevalence estimates are needed [21-23.

PAD, a type of peripheral vascular disease (PVD) caused mainly by atherosclerosis, leads to reduced blood flow to the legs due to plaque buildup in the arteries]24-26]. It is classified by clinical presentation using Rutherford or Fontaine staging, with symptoms ranging from intermittent claudication (calf pain during walking relieved by rest) to severe cases with ulceration or gangrene [27,28]. Other symptoms can include foot pain at rest, non-healing ulcers, hair loss, erectile dysfunction, numbness, tingling, cyanosis, gangrene, and functional impairment [26,27,29]. Many patients with a low Ankle-Brachial Index (ABI) may remain asymptomatic or have atypical symptoms, making diagnosis challenging [30].

In its milder forms, PAD may present with atypical symptoms such as tingling, numbness, or decreased mobility, complicating diagnosis and delaying treatment [31-33]. About one-third of individuals with PAD experience atypical exertional leg symptoms, while approximately 20% show typical symptoms like intermittent claudication, rest pain, ulceration, or gangrene [17]. Incidence rates vary globally: in the Netherlands, intermittent claudication occurs at about 1.0 per 1,000 annually, with higher rates in women, whereas the Framingham Study reported a higher

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incidence with a two-fold predominance in men [16,34]. Severe PAD can progress to critical ischemia, characterized by rest pain, ulceration, and gangrene, potentially leading to limb amputation if left untreated. Only 0.25 to 0.45 per 1,000 people annually progress to critical ischemia, which is notably more common in patients with diabetes [18,35,36]. About 5% to 10% of those with asymptomatic PAD will develop symptoms within five years [37]. Despite this, nearly two-thirds of PAD patients are either asymptomatic or have only mild symptoms, making early diagnosis challenging [31-33].

Despite its gradual onset, PAD is associated with ongoing atherogenesis in other vascular regions and a high mortality rate, primarily due to stroke and myocardial infarction (MI) [32,38-49]. Approximately 25% to 30% of patients with symptomatic PAD die within five years [32,38-49]. PAD significantly increases cardiovascular morbidity and mortality, regardless of symptom status or gender [50,51]. This risk is particularly high for patients undergoing peripheral revascularization, who often face severe vascular impairment and elevated preoperative risk due to comorbidities such as advanced age, renal dysfunction, diabetes, or smoking [24,38,52].

According to the World Health Organization's Global Atlas on Cardiovascular Disease Prevention and Control (2011), cardiovascular diseases (CVDs) are the leading cause of death and disability worldwide, with around 17.9 million global fatalities in 2019 [53]. Vascular aging contributes to CVD by causing degeneration of the heart and blood vessels, which can impair the arterial system. In the United Kingdom (UK), about 20% of individuals aged 55 to 75 have PAD, characterized by the narrowed arteries due to factors like wall thickening or fatty deposits [54,55]. CVD remains the top global cause of death, with rising rates linked to aging populations [56]. South Asian migrants in the UK have 50% to 100% higher mortality rates from coronary heart disease (CHD) and stroke compared to the White British population [57]. Conversely, individuals of Black African and African Caribbean descent experience lower rates of CHD but higher stroke mortality compared to South Asians [57].

Early detection is crucial for preventing cardiovascular death, especially for asymptomatic patients. The increased cardiovascular risk among migrant populations extends beyond the UK, with South Asian migrants in Norway facing higher risks of MI and stroke, and elevated stroke rates among those from sub-Saharan Africa and Southeast Asia [58-60]. Similar patterns have been observed in the Netherlands [61,62]. Traditional cardiovascular and metabolic risk factors, such as hypertension, dyslipidemia, central adiposity, or insulin resistance, do not fully account for these ethnic disparities in cardiovascular risk [63,64].

CVD impact the heart, blood vessels, and vascular system throughout the body and brain [65]. Non-modifiable risk factors include age, gender, and family history of CVD, while modifiable factors such as smoking and physical inactivity also play significant roles [66,67]. In the absence of traditional risk factors, assessing arterial health can help identify potential cardiovascular issues. PAD, an independent predictor of cardiovascular mortality, is a more critical factor for survival than a clinical history of coronary artery disease (CAD) [52].

Key risk factors for PAD include CAD, diabetes, high cholesterol, high blood pressure, obesity, physical inactivity, and smoking, with aging also being significant [68-77]. As Western populations age, the burden of PAD and its complications is expected to rise unless effective and accessible prophylactic therapies are implemented [78]. However, PAD is often underdiagnosed, leading to delayed recognition and management, particularly in its subclinical stages, necessitating vigilant attention from healthcare providers [79].

Many cases of PAD go unnoticed or undiagnosed, even when documented in medical records, often resulting in less intensive management compared to other cardiovascular disorders like CAD [6,80]. The U.S. Preventive Services Task Force (USPSTF) concluded in 2013 that there was insufficient evidence to evaluate the benefits and harms of screening for PAD and cardiovascular risk assessment with ABI in asymptomatic adults, which may further exacerbate the number of undiagnosed cases [81].

Digital subtraction angiography (DSA) is the gold standard for diagnosing PAD, particularly for detecting 50% or more stenosis, with sensitivity and specificity over 90% [82-84]. However, DSA is invasive and carries risks such as nephrotoxicity, hypersensitivity reactions to the contrast medium, and complications from arterial catheter access [85-87]. Consequently, less invasive methods like magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are often used for anatomical localization and assessing stenosis, particularly in patients who may need revascularization [88,89].

Despite advancements in diagnostic techniques, PAD remains a significant burden. Managing PAD cost as much as or more than treating congestive heart failure and cerebrovascular disease [90,91]. Data from the Agency for Healthcare Research and Quality indicate that the average annual expenditure for an individual with PAD is $11,553, compared to $4,219 for those without PAD [92]. For patients with severe PAD requiring major amputation, annual costs can reach up to $55,700 per patient post-procedure [93].

PAD significantly affects health-related quality of life and work-related factors such as absenteeism [94]. Patients with claudication, which impairs walking and reduces physical activity, have lower quality-of-life scores compared to those with CAD and congestive heart failure [95,96]. Although the rate of PAD-related amputations has decreased, major lower-extremity amputations still pose a high mortality risk, with approximately 50% of patients dying within one year [97,98]. The rising prevalence and associated morbidity of PAD underscore the urgent need for improved awareness and care strategies [99]. In response to these challenges, Medeia Inc. is working to enhance PAD screening and management through standardized diagnostic methods, aiming to reduce undiagnosed cases and enable earlier diagnosis.

Developed by Medeia Inc., the VitalScan-Vascular+ system integrates advanced technologies for comprehensive vascular health assessment (Figure 1). This system combines ABI, pulse wave velocity (PWV), and pulse volume recording (PVR) to streamline the recording and analysis of vascular responses, providing automated, standardized, and clinically intuitive results. The VitalScan-Vascular+ system, which is FDA-cleared (K191266), captures, stores, and analyzes data on PWV, blood pressure, volume, heart rate variability (HRV), and electrocardiography (ECG).

The VitalScan-Vascular+ platform features specialized databases for ABI and PWV tailored to various cardiovascular disorders, aiding in the establishment of clinical profiles for diagnosis and treatment. This study employs the ABI,

Figure 1. *This is an image of the VitalScan-Vascular+ System developed by Medeia Inc. The VitalScan-Vascular+ System is portable, easy-to-use, and non-invasive.*

PWV, and PVR technologies to explore peripheral arterial functionality across different age and sex subgroups within a large neurological patient cohort. Key metrics include ABI (n=135,846), Augmentation Index (AI) (n=227,173), and three VitalScan-Vascular-derived arterial stiffness indices (EEI, DEI, DDI) (n=227,173).

Arterial compliance, which reflects the ability of arteries to adjust volume in response to pressure changes, naturally declines with age, starting from childhood, and is further reduced in conditions such as hypertension, end-stage renal disease, and diabetes [100-106]. Increased arterial stiffness, a key indicator of CVD, is linked to ventricular hypertrophy, atherosclerosis, and functional changes in PAD due to altered arterial wall viscoelasticity [107-110]. This stiffness can be non-invasively measured using pulse PWV and ABI [110-113]. Arterial stiffness is a significant outcome for cardiovascular events and mortality, especially when traditional cardiovascular risk factors are less predictive [114-116].

The study evaluates ABI, the gold standard for PAD detection, across all ages and sexes. ABI, a simple and non-invasive PAD screening tool, shows at least 90% sensitivity and 98% specificity for detecting PAD defined as more than 50% stenosis of a peripheral artery [117,118]. It remains a widely used test in clinical settings [79,119]. PWV and arterial wave reflections, such as the AI, are emerging as critical markers of vascular health and cardiovascular risk [120,121]. This study also explores the potential of peripheral AI as a predictor of cardiovascular risk and PAD.

Additionally, the study investigates how age influences arterial elasticity and contractility, measured by EEI, DEI, and DDI, focusing on the leg arterial segments (n=127,193) to identify PAD beyond age-related changes. Objectives include establishing population-based reference values for these three arterial stiffness indices and assessing their utility in PAD beyond normal aging. The analysis aims to enhance understanding of how age, gender and these indices impact peripheral arterial health and PAD. It also addresses current data limitations by providing insights into PAD prevalence in individuals aged 80 and older, a growing demographic [122]. Medeia Inc. aims to standardize these indices as diagnostic markers in the VitalScan-Vascular+ databases for neurological, neuropsychological, and autonomic disorders, expand the discriminant databases to include PAD, and support personalized medicine approaches.

Materials and methods

Patient data acquisition occurred between 2014 and 2023 across multiple neurology offices. Patients who qualified for the VitalScan-Vascular+ assessment were concurrently evaluated for their ABI/PWV/ECG/HRV data. The subject selection criteria for a VitalScan-Vascular+ assessment are detailed below.

Inclusion/Exclusion Criteria, Demographics and Gender [123]

For subjects aged 4 to 18 years, parents completed a neurological history questionnaire for them, and psychometric evaluations were conducted. Adults (≥ 18 years) also completed a neurological questionnaire, and those deemed unhealthy were excluded based on questionnaire responses and/or physician comments. Physicians have access to the following questionnaires: DSM-5 Level 1 (Cross-Cutting Symptom Measures), PHQ-9 (Depression), and general neurological questionnaires. Inclusion required at least one questionnaire score below moderate and physician-verified health in that the patient was deemed healthy. Any patient records or previously known medical records with questionnaire score of 'moderate' or 'severe' were excluded from the VitalScan-Vascular+ database, regardless of other information.

Demographic Characteristics [123]

It is crucial that the demographic mixture of males and females, various ethnic groups, and socioeconomic statuses be reasonably representative of the expected North American clientele. This diversity was derived from a large pool of subjects obtained from eight geographically dispersed sites, reflecting the North American demographics and addressing a wide range of ethnic and socioeconomic statuses found in the de-identified patient data before review.

Client-Based VitalScan-Vascular+ Database [123]

Each client in the VitalScan-Vascular+ database completed a DSM-based questionnaire. Regression analysis was utilized to remove any psychopathology-related variance from the ECG, PWV, ABI, AI, BP, and HRV data. This process ensures that the variance in the PWV of 'healthy' subjects, which is explained by the variance in the questionnaire, is removed to create a 'psychopathology-free' Vascular+ normative database or discriminant databases for various brain disorders.

Utilizing a client-based normative or discriminant database has its own set of advantages. Clients may harbor expectations distinct from those of 'healthy' subjects concerning Vascular+ recordings.

Patients were prepared for a VitalScan-Vascular+ assessment, where ABI/PWV/ECG/HRV data were collected concurrently.

To Prepare the Patient for a VitalScan-Vascular+ Assessment [123]

To perform a reliable VitalScan-Vascular+ assessment, it is essential to observe the following patient preparations: patients should abstain from consuming caffeine at least 2 hours before the assessment, avoid taking any new medications or supplements unless directed by a healthcare provider, and refrain from smoking and using alcohol, marijuana, or other recreational drugs at least 6 hours prior to the assessment. Vigorous exercise should also be avoided for at least 12 hours before testing. Patients with pacemakers should not undergo testing during the visit and are required to complete a brief neuropsychological questionnaire about their symptoms before testing.

During the testing, ensure the patient is comfortably seated in a chair for 5-10 minutes before resting heart rate and systolic and diastolic blood pressure are measured. Fluctuations in blood pressure do not affect ABI measurements, as ABI is a ratio that effectively cancels out confounding physiological factors [50].

Brief Guide to Operate the VitalScan-Vascular+ System for Patient Assessment [123]

The VitalScan-Vascular+ System comprises a workstation with three BP Cuffs, three photoplethysmography (PPG)/ SpO2 finger and toe sensors, and three-lead ECG sensors.

To operate the VitalScan-Vascular+ System, follow these steps: Turn on your laptop, open the VitalScan-Vascular+ software, and ensure that the VitalScan-Vascular amplifier device's USB is properly connected. To confirm the connection, click on the settings button and press "Check Device Connection." Position the patient comfortably.

For patient preparation, apply the three-lead ECG sensors—place the red lead under the right clavicle, the black lead under the left clavicle, and the yellow lead below the last left rib. Attach the pulse Ox SpO2 finger and toe sensors, along with three BP Cuffs – one on the right arm, and one each on the left and right ankles. In the software, select "New Measurement" and then "Vascular Response Test." Choose options for Resting.

Proceed to the patient information section, select "New" or "Existing Patient," and enter the patient's details, including name, date of birth, gender, weight, height, medications, symptoms, or previous diagnoses. Progress to the patient questionnaire, guiding the patient through detailed answers—an essential step. In the pre-test screen, check signal quality.

After a successful test, view the results on the overview page and disconnect the patient. The software results, starting with the neurofunctional test option, provide a general summary with scales ranging from red (abnormal) to green (healthy), helping diagnose and assess the patient's cardiovascular health. Light green is borderline, while yellow and orange indicate areas of concern.

The VitalScan-Vascular+ collects information using arm and ankle cuffs, along with a finger PPG sensor, resting in a supine position for 5-10 minutes before test recording, to provide a broad range of measurements. This data is then used to compute various indices and classifications, including:

- Ankle/Brachial Index (ABI)
- Augmentation Index (AI)
- Ejection Elasticity Index (EEI)
- Dicrotic Elasticity Index (DEI)
- Dicrotic Dilation Index (DDI)
- Large (C1)/Small (C2) Artery Compliance

Results are presented as mean ± standard deviation (SD).

Results and discussion

ABI versus Age

The ABI is a key diagnostic tool in assessing cardiovascular risk and diagnosing PAD due to its simplicity and non-invasive nature. The ABI, which measures the ratio of systolic blood pressure at the ankle to that at the brachial artery, can identify individuals at high risk even in the absence of symptoms [124]. This is particularly valuable since PAD can be asymptomatic, with many patients not displaying typical leg symptoms [124,125]. The 2016 American Heart Association and American College of Cardiology (AHA/ACC) guidelines endorse ABI as the preferred initial test of choice for diagnosing PAD, due to its high sensitivity (95%) and specificity (near 100%) for detecting significant vascular stenosis [126,127].

Epidemiological data shows PAD prevalence ranges from 3-10% in the general population, increasing with age—from 3% in age 40 to 15-20% in those over 70 [7,128]. Global estimates between 2000 and 2010 indicated 202 million PAD cases, with significant increases in both low- and middle-income countries (28.7%) and high-income countries (13.1%) [4]. For every symptomatic patient, approximately four individuals have asymptomatic PAD [9]. ABI values less than 0.90 suggest PAD, and the European Stroke Organization considers values between 0.9 and 1.4 as normal (6, 31, 129). Higher ABI values (1.3 to 1.4) often indicate medial artery calcification rather than true PAD [50,130,131].

The current study found that ABI values across a large cohort (n=135,846) were within the normal range, with no significant differences across age groups or genders (Figure 2a). Values ranged from 1.159 ± 0.224 to 1.184 ± 0.221 for males and 1.108 ± 0.246 to 1.155 ± 0.234 for females (Table 1). No readings exceeded 1.30, which would indicate non-compressible arteries [26]. This aligns with previous studies, which report ABI above 1.40 as indicative of non-compressible arteries, a condition more prevalent in older adults and those with CVD risk factors [29,132-135].

Although all ABI readings in this study fell within the normal range, stress test is recommended for symptomatic patients as resting ABI may not always detect PAD [125]. Stress tests can enhance PAD detection by about 30%, with a 15-20% decrease in ABI following exercise suggesting PAD [125,136,137]. The

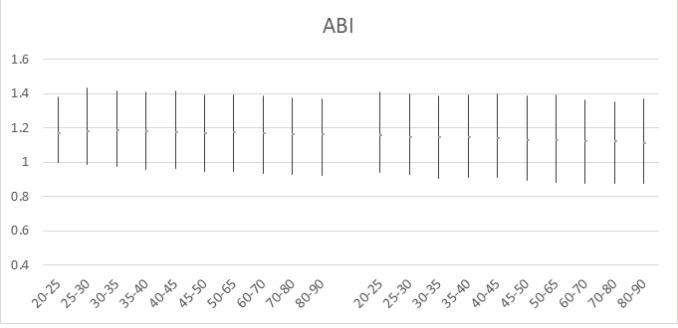

Figure 2a. *ABI versus age curve, with error bars, shows a decrease with age in both men (left) and women (right) aged 20-90 years.*

Table 1. *Mean ABI and Standard Deviation (SD) for Male and Female Patients Aged 20-90 Years. Total Number of Patients: 135,846.*

Age	Sex	# of patients	Mean	SD
20-25	male	743	1.168	0.194
25-30	male	1514	1.181	0.225
30-35	male	2382	1.184	0.221
35-40	male	3247	1.177	0.226
40-45	male	4394	1.172	0.227
45-50	male	5366	1.168	0.224
50-65	male	6595	1.170	0.223
60-70	male	15191	1.166	0.227
70-80	male	13436	1.163	0.223
80-90	male	3717	1.159	0.224
20-25	female	1673	1.155	0.234
25-30	female	2889	1.144	0.238
30-35	female	4056	1.142	0.242
35-40	female	5160	1.143	0.243
40-45	female	6878	1.140	0.245
45-50	female	8097	1.126	0.247
50-65	female	10144	1.125	0.257
60-70	female	21438	1.118	0.244
70-80	female	19088	1.119	0.237
80-90	female	5650	1.108	0.246

European Society of Cardiology supports this recommendation, emphasizing the utility of post-exercise ABI measurements for improved PAD diagnosis [138].

Interestingly, findings from this study show a gradual but insignificant downward trend in ABI with age for both sexes (Figure 2b). This is consistent with observations from Smith et al. and Hiatt et al., suggesting ABI decreases with age, likely due to higher PAD prevalence among older adults [139,140]. Females showed a greater magnitude of decline compared to males. The relative decline from ages 20 to 90 was 4.07% [(1.108-1.155)/1.155] in females and 0.77% [(1.159-1.168)/1.168] in males. Furthermore, males exhibited higher ABI values than females across all age groups. Moreover, while women generally have slightly lower ABI values compared to men [11,50,84,140-142], the difference is minimal and does not affect the use of a standard ABI threshold of ≤0.9 for PAD diagnosis across genders [126,143].

Race also impacts ABI values, with Black individuals having slightly lower ABI values compared to non-Hispanic Whites, correlating with a higher prevalence of PAD [114,139,140,144-147]. Lifetime risk estimates suggest that 30% of Black individuals and 20% of non-Hispanic Whites will develop PAD [148]. European ancestry individuals have a lower relative risk compared to Hispanic or Black individuals [50]. This trend is consistent with data showing Black individuals exhibit a higher prevalence of PAD, while Asian individuals have the lowest rates [21].

The study's results underscore the reliability of the ABI measurement. Hirsch et al. reported that ABI measurements generally exhibit good reproducibility, with variance ranging

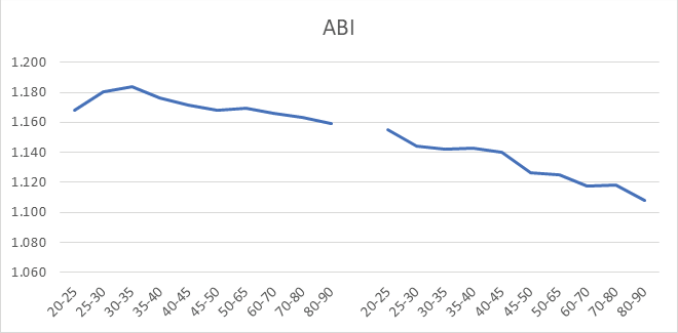

Figure 2b. *ABI versus age curve shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a downward trend.*

from 0.10 to 0.25 [26,50]. The Atherosclerosis Risk in Communities (ARIC) study found that a single ABI measurement can vary by ±0.25 from the average, with three measurements reducing variability to ±0.12 (0.25/√3) (ARIC study) [50]. This variability is influenced by factors such as age, height, race, and observer experience, highlighting the importance of multiple measurements for accuracy [50]. Despite these variations, the ABI measurements using the VitalScan-Vascular+ system were consistent, validating the system's reliability for assessing cardiovascular risk.

In conclusion, while ABI remains a robust tool for PAD diagnosis, incorporating stress testing and considering demographic factors can enhance its diagnostic accuracy and help manage cardiovascular risk more effectively.

AI versus Age

AI measures wave reflection in the arteries, reflecting the ratio of the amplitude of the reflected wave to the systolic wave [149,150]. It is used to assess arterial function and cardiovascular health [151-154]. High blood pressure and wave reflection are significant in evaluating systolic blood pressure and hypertension. AI helps in understanding these factors. AI typically increases with age, indicating higher wave reflection amplitude and velocity [152,155]. The current study shows a general rise in AI with age for both males and females, consistent with previous studies (Figure 3a) [156,157]. AI values increased from -0.277 ± 0.127 in the 20-25 age group to 0.063 ± 0.207 in the 80-90 age group for males, and from -0.215 ± 0.137 to 0.133 ± 0.212 for females (Table 2). With higher AI values, the female curve is above the male curve (Figure 3b). The observed upward trend aligns with previous findings suggesting a positive correlation between AI and age [152,158].

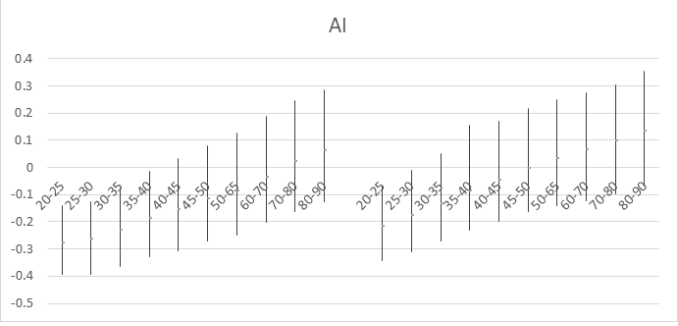

Figure 3a. *AI versus age curve, with error bars, shows an increase with age in both men (left) and women (right) aged 20-90 years.*

Table 2. *Mean AI and Standard Deviation (SD) for Male and Female Patients Aged 20-90 Years. Total Number of Patients: 227,173.*

Age	Sex	# of patients	Mean	SD
20-25	male	743	-0.277	0.127
25-30	male	1514	-0.261	0.133
30-35	male	2382	-0.231	0.144
35-40	male	3247	-0.188	0.158
40-45	male	4394	-0.153	0.171
45-50	male	5366	-0.115	0.176
50-65	male	6595	-0.085	0.189
60-70	male	15191	-0.034	0.198
70-80	male	13436	0.023	0.206
80-90	male	3717	0.063	0.207
20-25	female	1673	-0.215	0.137
25-30	female	2889	-0.176	0.152
30-35	female	4056	-0.133	0.162
35-40	female	5160	-0.085	0.199
40-45	female	6878	-0.045	0.187
45-50	female	8097	-0.002	0.193
50-65	female	10144	0.034	0.196
60-70	female	21438	0.065	0.198
70-80	female	19088	0.097	0.201
80-90	female	5650	0.133	0.212

However, the relationship between AI and age is not entirely consistent across all studies [149,159,160]. While some research confirms a positive correlation, suggesting that AI increases with age, other studies do not support this relationship [158,161,162]. Some research shows that AI correlates with age primarily in younger individuals and loses this correlation in older age [159,160]. Murakami et al. suggest that AI in children is more strongly influenced by body height rather than changes in arterial stiffness [160]. Despite AI being an important parameter for assessing cardiovascular risk, elevated levels in children are less indicative of CVD risk compared to adults and may relate more to normal physiological processes such as cardiac growth. Conversely, Caceres reports a negative correlation between peripheral AI and age, based on the data from a homogenous population, which contrasts with the generally observed positive correlation [149,157,163,164].

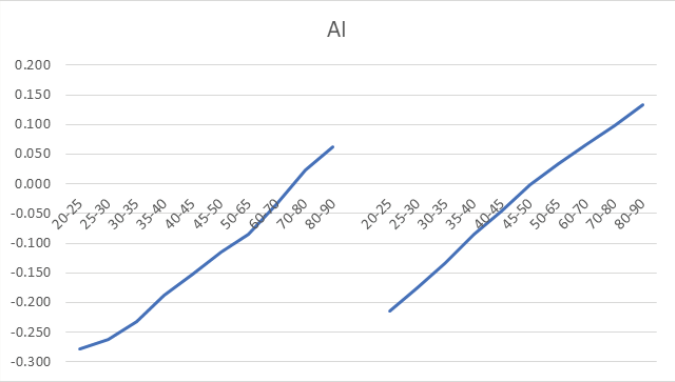

Figure 3b. *AI versus age curve shows an upward trend in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel upward trend.*

AI values are generally higher in women compared to men. Hughes et al. found that, in a group of healthy normotensive individuals, central AI was higher in women than in men [150]. The current study shows that AI is generally higher in females across all age groups, although the absolute values were lower than those reported by Hughes et al [150]. The discrepancies between studies may arise due to differences in sample characteristics, measurement sites, and other factors.

AI inversely correlates with height and is generally higher in women, although height alone does not fully explain the gender differences observed [156,157,162,165]. In children under 15, AI shows a negative correlation with body height, indicating a decrease in AI as children grow taller [160]. This is attributed to the earlier return of reflected pressure waves in shorter bodies [156,166-170].

Previous studies, like those by Hughes and Murakami, report varying AI values and trends [150,160]. The typical pattern in adults is that AI increases with age and crosses the zero line in individuals in their late 20s [159,171,172]. However, this study found that AI values did not cross the zero line until age 70+ in males and 50+ in females, differing from other research.

Previous research shows that AI increases with age, but the relationship may plateau or vary in older populations [164]. Fantin's study found that AI continues to rise with age until about 55 years before leveling off, even though augmentation pressure continues to rise [164]. In the current study, AI continues to rise with age, reaching positive values after age 70 in males and 50 in females. The relative change in male AI from age 20 to 90 is approximately 122.5% [(0.063 + 0.277) / -0.277] increase. Females showed a greater increase of 162% [(0.133 + 0.215) / -0.215]. Fantin et al. also noted that AI is about 7% higher in women over 55 years compared to men, partly due to lower pulse pressure in women, although augmentation pressure is also higher in women [164]. Fantin suggests that AI might not accurately reflect arterial compliance in the elderly because it plateaus with age, while augmentation pressure continues to rise [164]. Therefore, augmentation pressure could be a better measure of arterial stiffness in older populations.

AI's reliability is debated due to its sensitivity to factors like PWV and waveform types [150,156,157,169,170,173-175]. Type C waveforms, which can produce negative AI values, are more common in younger individuals and men [150]. Hughes et al. highlighted that negative AI values resulting from type C waveforms should not be interpreted as reflecting wave reflection magnitude [150]. When type C waveforms were excluded, there was no significant link between AI and age. AI may provide limited insights into wave reflection and may be influenced by various factors including age, height, sex, and waveform type.

AI should be complemented with other indicators such as PWV and augmentation pressure for a comprehensive assessment of cardiovascular health. These measures offer additional insights into arterial function and stiffness. While AI provides valuable information on arterial function and cardiovascular risk, its accuracy can be affected by various factors. Therefore, using AI in conjunction with other diagnostic tools ensures a thorough evaluation of cardiovascular health.

EEI, DEI, DDI versus Age

Vascular aging is characterized by structural changes in arterial walls, consisting of three layers: the intima, media, and adventitia [176]. As people age, these walls undergo significant transformations primarily due to alterations in collagen and elastin fibers. Specifically, elastin is increasingly replaced by collagen, resulting in reduced arterial elasticity and increased stiffness [177]. This process contributes to higher blood pressure and various cardiovascular conditions, including heart attacks and CAD [178].

Vascular aging affects different arteries in distinct ways. In central arteries, aging leads to an increase in collagen fibers and a decrease in elastic fibers and smooth muscle cells [179-182]. This shift results in heightened stiffness. Peripheral arteries, being naturally more muscular and stiffer, exhibit less pronounced changes with aging [183,184]. Notably, the stiffness of the femoral artery in men does not change significantly with age, whereas in women, it markedly increases after age 60 [185]. Conversely, the carotid artery, which is more distensible, shows less pronounced stiffness changes with age [157,174].

Arterial stiffness, which refers to the reduced ability of arteries to expand and contract with pressure changes, is assessed using parameters like compliance and distensibility [186]. Compliance measures the change in arterial volume in response to blood pressure changes, with lower compliance indicating stiffer arteries. Distensibility, adjusted for the initial volume of the artery, is more directly related to wall stiffness. The aorta undergoes structural changes such as elastin fracture, increased collagen, and calcium deposits, while peripheral arteries show less or no increase in stiffness with age [157,168,186]. The gold standard for assessing arterial stiffness, PWV measures the time it takes for pulse pressure waves to travel between two points along the arterial tree [187]. Higher PWV values are indicative of greater arterial stiffness and are predictive of cardiovascular events and mortality.

In this large study involving both male and female populations (n=227,173), the Ejection Elasticity Index (EEI), Dicrotic Elasticity Index (DEI), and Dicrotic Dilation Index (DDI) were analyzed across various age groups. These indices reflect different aspect of arterial compliance:

- EEI (capacitative): Indicates large artery elasticity and left ventricular thickness.
- DEI: Reflects peripheral artery and arteriole elasticity.
- DDI (oscillatory): Reflects contractility and stiffness in small arteries.

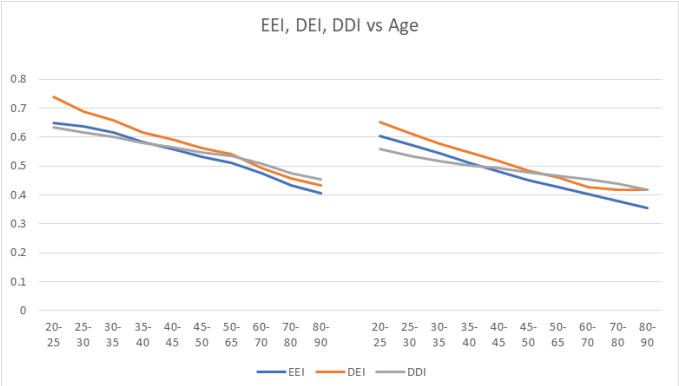

Figure 4. *EEI, DEI, and DDI versus age curves show a downward trend with age for both males (left) and females (right), indicating a linear decline.*

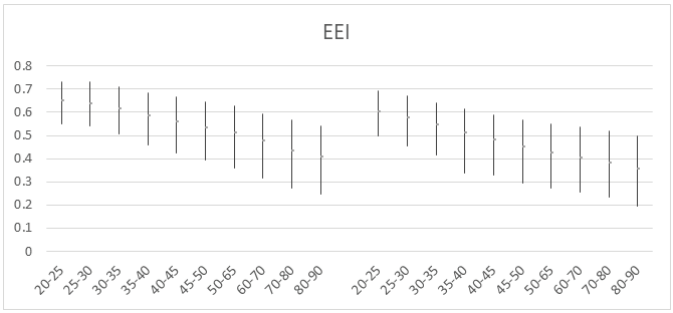

Figure 5a. *EEI versus age curve, with error bars, shows a decline with age in both men (left) and women (right) aged 20-90 years.*

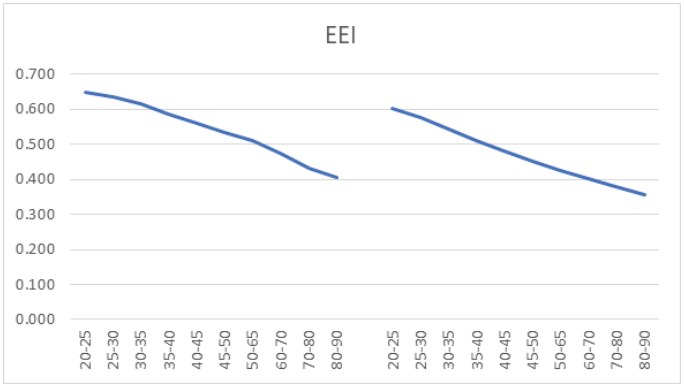

Figure 5b. *EEI versus age curve shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel downward trend.*

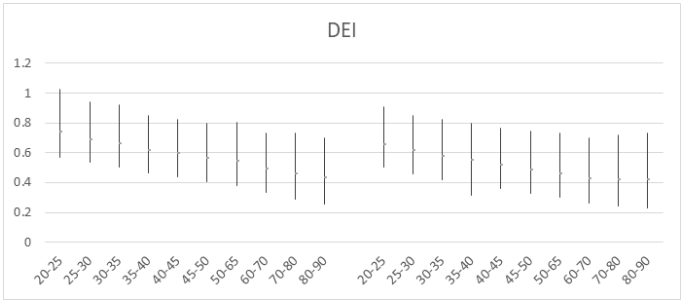

Figure 6a. *DEI versus age curve, with error bars, shows a decline with age in both men (left) and women (right) aged 20-90 years.*

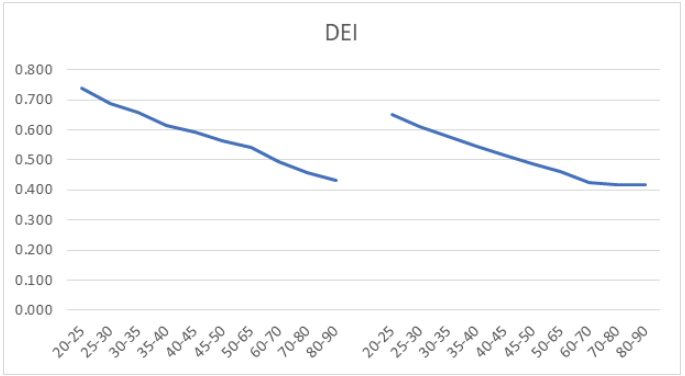

Figure 6b. *DEI versus age curve shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a similar downward trend.*

Figure 3. *Mean EEI and Standard Deviation (SD) for Male and Female Patients Aged 20-90 Years. Total Number of Patients: 227,173.*

Age	Sex	# of patients	Mean	SD
20-25	male	743	-0.277	0.127
25-30	male	1514	-0.261	0.133
30-35	male	2382	-0.231	0.144
35-40	male	3247	-0.188	0.158
40-45	male	4394	-0.153	0.171
45-50	male	5366	-0.115	0.176
50-65	male	6595	-0.085	0.189
60-70	male	15191	-0.034	0.198
70-80	male	13436	0.023	0.206
80-90	male	3717	0.063	0.207
20-25	female	1673	-0.215	0.137
25-30	female	2889	-0.176	0.152
30-35	female	4056	-0.133	0.162
35-40	female	5160	-0.085	0.199
40-45	female	6878	-0.045	0.187
45-50	female	8097	-0.002	0.193
50-65	female	10144	0.034	0.196
60-70	female	21438	0.065	0.198
70-80	female	19088	0.097	0.201
80-90	female	5650	0.133	0.212

Figure 4. *Mean DEI and Standard Deviation (SD) for Male and Female Patients Aged 20-90 Years. Total Number of Patients: 227,173.*

Age	Sex	# of patients	Mean	SD
20-25	male	1934	0.738	0.236
25-30	male	3142	0.690	0.209
30-35	male	5032	0.658	0.216
35-40	male	6323	0.616	0.199
40-45	male	8204	0.593	0.196
45-50	male	10366	0.563	0.198
50-65	male	12884	0.541	0.217
60-70	male	30431	0.494	0.203
70-80	male	25071	0.457	0.229
80-90	male	7153	0.433	0.226
20-25	female	3109	0.651	0.209
25-30	female	5205	0.613	0.199
30-35	female	7524	0.577	0.206
35-40	female	9458	0.547	0.240
40-45	female	12391	0.517	0.207
45-50	female	15178	0.486	0.217
50-65	female	19055	0.460	0.221
60-70	female	43404	0.426	0.226
70-80	female	36538	0.419	0.244
80-90	female	11107	0.419	0.258

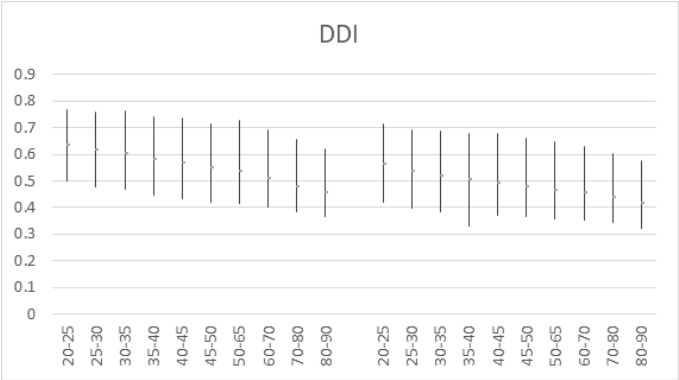

Figure 7a. *DDI versus age curve, with error bars, shows a decline with age in both men (left) and women (right) aged 20-90 years.*

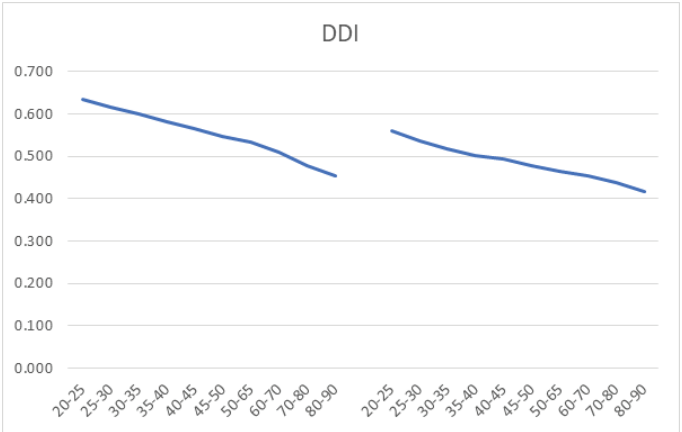

Figure 7b. *DDI versus age curve shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel downward trend.*

All three indices (EEI, DEI, DDI) decreased with age in both sexes (Figure 4), reflecting decreased arterial compliance and increased stiffness. The male indices were consistently higher than female indices across all ages (Figures 5-7), indicating greater arterial elasticity in males. For instance (Table 3-5):

- Male EEI: 0.648±0.090 (ages 20-25) vs. 0.405±0.148 (ages 80-90)
- Female EEI: 0.603±0.098 (ages 20-25) vs. 0.355±0.152 (ages 80-90)
- Male DEI: 0.738±0.236 (ages 20-25) vs. 0.433±0.226 (ages 80-90)
- Female DEI: 0.651±0.209 (ages 20-25) vs. 0.419±0.258 (ages 80-90)
- Male DDI: 0.634±0.134 (ages 20-25) vs. 0.455±0.135 (ages 80-90)
- Female DDI: 0.561±0.147 (ages 20-25) vs. 0.418±0.132 (ages 80-90)

The magnitude of decline observed in each index is as follows (Table 6):

Figure 5. *Mean DEI and Standard Deviation (SD) for Male and Female Patients Aged 20-90 Years. Total Number of Patients: 227,173.*

Age	Sex	# of patients	Mean	SD
20-25	male	1934	0.634	0.134
25-30	male	3142	0.615	0.140
30-35	male	5032	0.601	0.150
35-40	male	6323	0.582	0.148
40-45	male	8204	0.565	0.152
45-50	male	10366	0.547	0.149
50-65	male	12884	0.535	0.162
60-70	male	30431	0.509	0.150
70-80	male	25071	0.477	0.144
80-90	male	7153	0.455	0.135
20-25	female	3109	0.561	0.147
25-30	female	5205	0.536	0.148
30-35	female	7524	0.519	0.152
35-40	female	9458	0.503	0.174
40-45	female	12391	0.493	0.156
45-50	female	15178	0.479	0.152
50-65	female	19055	0.466	0.149
60-70	female	43404	0.455	0.143
70-80	female	36538	0.438	0.135
80-90	female	11107	0.418	0.132

Figure 7. *Mean Leg-EEI and Standard Deviation (SD) for Male and Female Patients Aged 20-90 Years. Total Number of Patients: 127,193.*

Age	Sex	# of patients	Mean	SD
20-25	male	664	0.683	0.138
25-30	male	1302	0.678	0.134
30-35	male	2182	0.665	0.142
35-40	male	2961	0.654	0.147
40-45	male	4074	0.643	0.153
45-50	male	5049	0.638	0.155
50-65	male	6249	0.618	0.160
60-70	male	14299	0.583	0.160
70-80	male	12695	0.539	0.162
80-90	male	3549	0.505	0.171
20-25	female	1499	0.627	0.130
25-30	female	2605	0.611	0.140
30-35	female	3683	0.597	0.132
35-40	female	4703	0.575	0.140
40-45	female	6442	0.561	0.147
45-50	female	7579	0.541	0.145
50-65	female	9505	0.523	0.148
60-70	female	20467	0.500	0.155
70-80	female	18126	0.477	0.171
80-90	female	5310	0.451	0.160

Figure 6. *Leg and Non-Leg EEI, DEI, and DDI versus age: Comparison of the relative decline between Leg and Non-Leg indices.*

Index/Site	Male Leg	Female Leg	Male Non-Leg	Female Non-Leg
Ejection Elasticity (EEI)	26.1%	28.1%	37.5%	41.1%
Dicrotic Elasticity (DEI)	29.3%	28.8%	41.3%	35.6%
Dicrotic Dilation (DDI)	20.2%	21.5%	28.2%	25.5%

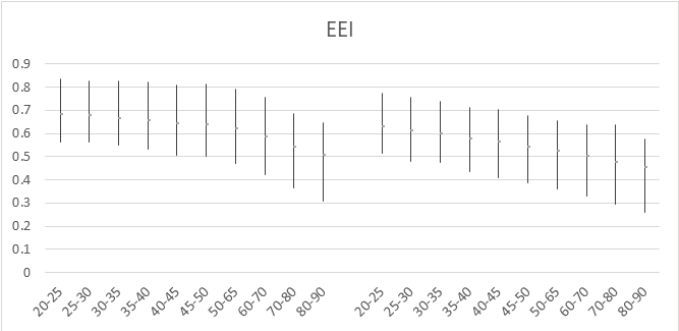

Figure 8a. *Leg-EEI versus age curve, with error bars, displays a decline with age in both men (left) and women (right) aged 20-90 years.*

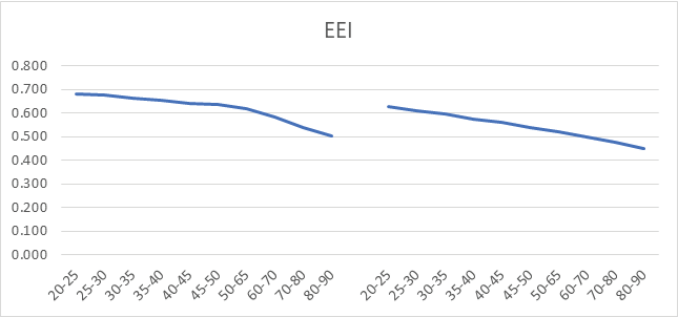

Figure 8b. *Leg-EEI versus age curve shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a similar downward trend.*

Figure 8. *Mean Leg-DEI and Standard Deviation (SD) for Male and Female Patients Aged 20-90 Years. Total Number of Patients: 127,193.*

Age	Sex	# of patients	Mean	SD
20-25	male	664	0.658	0.306
25-30	male	1302	0.669	0.287
30-35	male	2182	0.656	0.282
35-40	male	2961	0.643	0.281
40-45	male	4074	0.631	0.274
45-50	male	5049	0.608	0.265
50-65	male	6249	0.594	0.275
60-70	male	14299	0.543	0.288
70-80	male	12695	0.488	0.277
80-90	male	3549	0.465	0.297
20-25	female	1499	0.605	0.399
25-30	female	2605	0.585	0.348
30-35	female	3683	0.565	0.321
35-40	female	4703	0.548	0.303
40-45	female	6442	0.539	0.353
45-50	female	7579	0.508	0.310
50-65	female	9505	0.483	0.306
60-70	female	20467	0.464	0.306
70-80	female	18126	0.445	0.411
80-90	female	5310	0.431	0.316

Figure 9. *Mean Leg-DDI and Standard Deviation (SD) for Male and Female Patients Aged 20–90 Years. Total Number of Patients: 127,193.*

Age	Sex	# of patients	Mean	SD
20-25	male	664	0.751	0.142
25-30	male	1302	0.753	0.153
30-35	male	2182	0.733	0.156
35-40	male	2961	0.727	0.165
40-45	male	4074	0.715	0.161
45-50	male	5049	0.709	0.160
50-65	male	6249	0.693	0.163
60-70	male	14299	0.663	0.163
70-80	male	12695	0.622	0.165
80-90	male	3549	0.599	0.161
20-25	female	1499	0.711	0.173
25-30	female	2605	0.695	0.168
30-35	female	3683	0.676	0.164
35-40	female	4703	0.658	0.170
40-45	female	6442	0.655	0.170
45-50	female	7579	0.640	0.170
50-65	female	9505	0.623	0.167
60-70	female	20467	0.602	0.167
70-80	female	18126	0.575	0.167
80-90	female	5310	0.558	0.160

Figure 10. *Arterial Stiffness Indices (EEI, DEI, DDI): Reference Ranges and Interpretation in the VitalScan-Vascular+ System.*

Index Interpretation	Ejection Elasticity (EEI)	Dicrotic Elasticity (DEI)	Dicrotic Dilation (DDI)
Normal (0.3-0.7)	Normal	Normal	Normal
Low (<0.3)	• Left ventricular ejection insufficiency • Atherosclerosis • hypercholesterolemia	• decreased vessel elasticity • arteriosclerosis in peripheral portion of arteries	• hypertension • arteriosclerosis • small artery constriction
High (>0.7)	• increased ventricular ejection power (anxiety as potential cause)	• arteriole dilation (decreasing vascular resistance)	• arterial dilation (anxiety as potential cause)

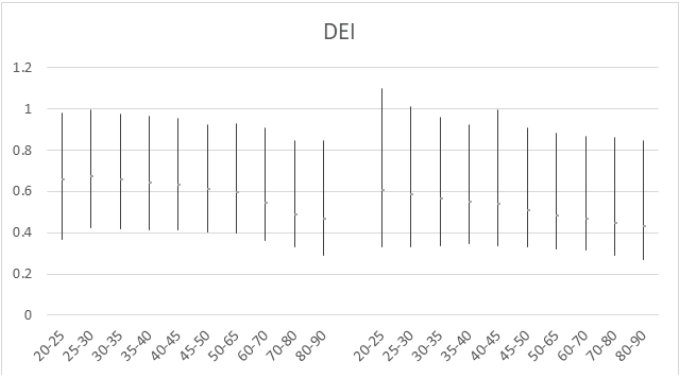

Figure 9a. *Leg-DEI versus age curve, with error bars, demonstrates a decline in both men (left) and women (right) aged 20-90 years.*

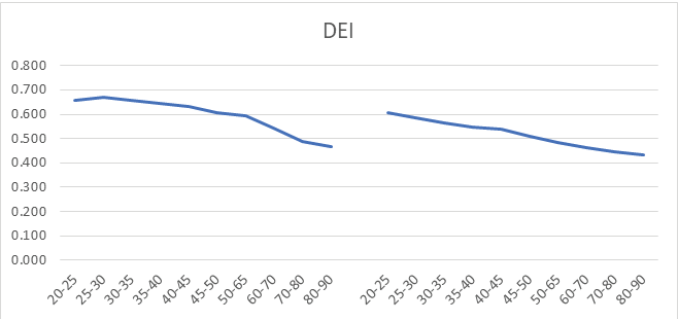

Figure 9b. *Leg-DEI versus age curve shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a similar downward trend.*

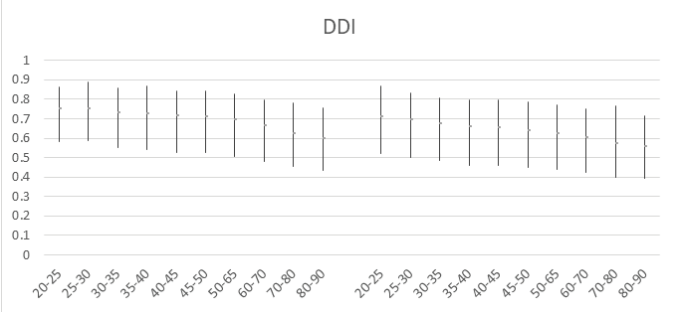

Figure 10a. *Leg-DDI versus age curve, with error bars, demonstrates a decline in both men (left) and women (right) aged 20-90 years.*

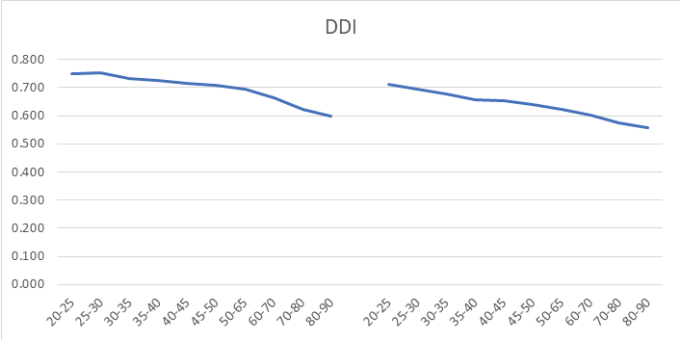

Figure 10b. *Leg-DDI versus age curve shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a similar downward trend.*

- Male EEI: 37.5% [(0.405/0.648)/0.648]
- Male DEI: 41.3% [(0.433-0.738)/0.738]
- Male DDI: 28.2% [(0.455-0.634)/0.634]
- Female EEI: 41.1% [(0.355-0.603)/0.603]
- Female DEI: 35.6% [(0.419-0.651)/0.651]
- Female DDI: 25.5% [(0.418-0.561)/0.561]

The relative decline in EEI was more pronounced in females, while males showed more significant changes in DEI and DDI. While some studies indicate a linear increase in stiffness with age, others note accelerated stiffening between ages 50 and 60 [162,168]. Results of this study aligned with the former observation, showing a linear increase in arterial stiffness as the indices declined with age. Additionally, the female DEI curve appeared to plateau after age 60. Overall, age impacts the three indices, but sex differences are also evident.

Findings from the Leg measurement site (n=127,193) revealed downward trends (Figures 8-10). All three indices (Leg-EEI, Leg-DEI, Leg-DDI) showed a decrease with age, with males consistently having higher values compared to females (Tables 7-9). For males, the relative decline ranged from 20.2% [(0.599-0.751)/0.751] to 29.3% [(0.465-0.658)/0.658], and for females, from 21.5% [(0.558-0.711)/0.711] to 28.8% [(0.431-0.605)/0.605] (Table 6). The relative decline in Leg indices was less pronounced compared to the non-Leg indices, suggesting slower progression of stiffness in the legs.

The VitalScan-Vascular+ database provides population-based reference ranges of 0.3 to 0.7 for EEI, DEI, and DDI (Table 10). Values outside these ranges may indicate disease, such as a low EEI (<0.3) correlating with left ventricular insufficiency or a high EEI (>0.7) indicating increased left ventricular ejection. Abnormal values may warrant further testing using a combination of indicators (ABI, AI, EEI, DEI, DDI, C1, C2) to confirm PAD.

Large (C1) and Small (C2) Artery Compliance versus Age

Previous studies have identified correlations between the ABI and the C2 index, with lower C2 values being associated with conditions such as hypertension, diabetes, and elevated cardiovascular risk scores [188-191].

The C1 and C2 indices, derived from a modified Windkessel model, reflect compliance in large (C1) and small (C2) arteries (188, 192). Previous studies showed C1 and C2 correlate with ABI values and vascular conditions (188-191). C1 is influenced by aging, while C2 is sensitive to conditions like hypertension and atherosclerosis [188,190,193,194].

The current study observed a decline in C1 and a gradual increase in C2 with age. The decline in C1 was more pronounced than the increase in C2, indicating a greater reduction in large artery compliance compared to small artery compliance. Males had higher C1 values than females, but both sexes exhibited similar age-related changes in C1 and C2 (Figure 11). Differences in C1 and C2 values compared to previous studies may be due to variations in population characteristics, test protocols, and technology [195,196]. Early changes in arterial compliance, particularly in small vessels (C2), may offer valuable insights for detecting early arterial dysfunction and PAD progression.

The study's results highlight the significant impact of aging on arterial stiffness and the differential effects on central versus peripheral arteries. While all indices show a decline with age, the extent and pattern of this decline vary by index and sex. The findings underscore the importance of considering both large and small artery compliance in assessing cardiovascular health and the need for further research to refine diagnostic and monitoring tools for arterial stiffness and PAD.

Discussion

Changes in Arterial Indices with Age and Gender

This study presents comprehensive insights into age-related changes in arterial stiffness, as reflected by C1, C2, EEI, DEI, DDI, AI, and ABI. The findings confirm that arterial stiffness increases with age, as evidenced by the significant decline in these indices, except for AI and C2, across a broad age range from 20 to 90 years. This decline was consistent across both male and female participants, though with notable sex differences in magnitude.

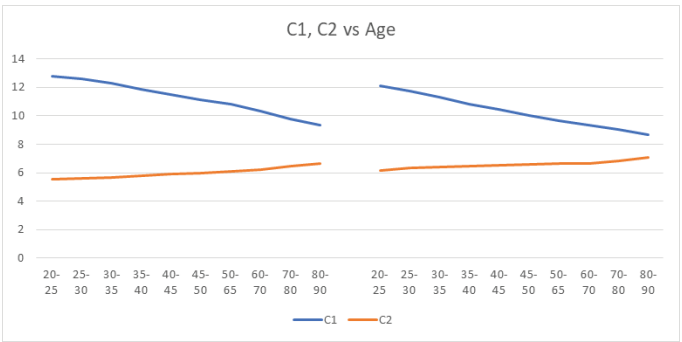

Figure 11. *Arterial Compliance, measured by C1 (large artery) and C2 (small artery), versus age: Male C1/C2 curves mirror the female C1/C2 curves, showing a downward trend. Both male and female C1 curves decreased with age, while the C2 curves increase with age.*

Age-Related Changes in Arterial Stiffness:

Both ABI and AI are influenced by age and gender. ABI tends to decrease with advancing age due to the progression of arterial disease, while AI generally increases with age, reflecting greater wave reflection and arterial stiffness.

The study's results align with previous studies showing that arterial stiffness increases with age due to structural changes in the arterial walls, such as the replacement of elastin with collagen and the accumulation of calcium deposits [177,178]. The linear decline in EEI, DEI, and DDI observed in this study reflects the progressive loss of arterial elasticity and contractility. This is consistent with the findings of Avolio et al. and McEniery et al., who reported similar trends in arterial stiffness with aging [162,168].

Interestingly, while both central and peripheral arteries show increased stiffness with age, the data suggest that central arteries are more affected compared to peripheral arteries. This supports previous research indicating that central arteries, such as the aorta, undergo more pronounced structural changes than peripheral arteries [157,162,186]. The slower progression of stiffness in peripheral arteries observed in the current study aligns with previous studies and suggests that peripheral vascular aging may be less aggressive than central vascular aging [168,174,175,180,183,184,186].

Sex Differences in Arterial Stiffness:

Gender differences are also observed, with females often showing higher AI values than males, while the opposite is true for ABI, consistent with previous studies [11,84,141]. Moreover, the observed higher values of arterial stiffness indices in males compared to females, particularly in the EEI and DEI, are in line with existing literature highlighting sex differences in vascular aging [174,183,185]. The more pronounced decline in EEI for females and the greater relative changes in DEI and DDI for males could be attributed to hormonal differences, differences in body fat distribution, or varying impacts of aging on vascular health between sexes. These findings underscore the need for sex-specific reference ranges for arterial stiffness indices and suggest that different mechanisms may be influencing vascular aging in men and women. Understanding these variations (age, sex) is crucial for accurate interpretation and assessment of cardiovascular risk.

Peripheral Arterial Stiffness and PAD:

The slower decline in leg indices (Leg-EEI, Leg-DEI, Leg-DDI) compared to central indices and the lower relative decline in peripheral stiffness support the notion that PAD affects peripheral arteries less aggressively compared to central arteries. This finding is consistent with studies suggesting that peripheral arterial stiffness increases less markedly with age than central arterial stiffness [157,162,168,174,175,180,183,184].

Potential Implications for PAD Diagnosis:

The data on indices C1 and C2 provide additional insights into large and small vessel compliance. While C1 showed a pronounced decline with age, indicating reduced large artery compliance, C2 increased gradually, reflecting changes in small artery compliance. The different trajectories of C1 and C2 suggest that small artery compliance might serve as an early marker for arterial dysfunction, potentially identifying individuals at risk for PAD before more severe changes in large arteries become apparent.

While ABI and AI are valuable, they each have limitations. AI's accuracy can be affected by factors like waveform types and height, and its role as a standalone indicator of wave reflection is debated. ABI can be less reliable in individuals with non-compressible arteries, such as those with diabetes or advanced age.

Together, these metrics (ABI, AI, EEI, DEI, DDI, C1, C2) can help in identifying individuals at risk for a range of cardiovascular conditions, including PAD, and overall arterial dysfunction.

Diabetes and PAD

The relationship between PAD and cardiovascular risk is particularly intricate in patients with type 2 diabetes mellitus (T2DM). PAD is frequently underdiagnosed in this population despite its significant impact on functional capacity and cardiovascular risk [197]. Although diabetes is a well-established risk factor for PAD, its effect can be exacerbated by other cardiovascular risk factors [80,198].

Diabetic metabolic disorders substantially contribute to the progression of PAD. A 1% increase in HbA1c is linked to a 28% higher risk of developing PAD [199]. Diabetes raises the risk of PAD by 3 to 4 times and doubles the risk of claudication. Lower HbA1c levels are associated with a reduced rate of amputation, and individuals with diabetes and PAD experience significantly worse walking performance compared to those without diabetes [199-201].

Recent data show a troubling rise in non-traumatic lower extremity amputation rates among people with diabetes, with a 50% increase from 2009 to 2015 [202]. Diabetes, alongside smoking, is a major risk factor for PAD, with smoking having the highest odds ratio for PAD, followed by diabetes [4,18]. Diabetes is particularly linked to severe PAD, with studies indicating a high hazard ratio for critical limb ischemia (CLI) in diabetic patients with elevated HbA1c [202]. Diabetes accounts for about 70% of lower extremity amputations in the U.S. [202]. Diabetes is associated with a higher risk of peripheral atherosclerosis and severe PAD, with a systematic review finding that diabetes increases the odds of PAD by almost two times [4]. Elevated HbA1c levels correlate with an increased risk of cardiovascular events, including PAD [125].

In diabetic patients, traditional ABI measurements can be misleading due to vessel stiffening or calcification, leading to falsely elevated ABI values [203,204]. Elevated ABI values are often seen in individuals with glucose metabolism abnormalities and higher body mass index, which are associated with medial artery calcification (MAC) [131]. MAC contributes to increased arterial stiffness and elevated ABI values due to factors such as inflammation and oxidative stress [50].

Recent findings from Gasparini et al. indicate that 5.49% of participants had a low ABI, suggesting potential PAD, while a significant 45.05% had elevated carotid-femoral pulse wave velocity (cfPWV), which is associated with older age and longer diabetes duration [197]. These findings highlight the importance of measuring both ABI and PWV for a comprehensive cardiovascular risk assessment and early PAD diagnosis in T2DM patients.

For more accurate diagnosis, measuring toe pressure and calculating the Toe-Brachial Index (TBI) is recommended, particularly when ABI readings are ≥1.3 or when discrepancies are noted in Doppler pulse curves [83,125]. The TBI provides a more reliable assessment of cardiovascular risk in diabetic patients compared to ABI [205,206].

Overall, the prevalence of PAD is increasing with the aging

population and rising diabetes rates, leading to an anticipated 40% increase in the workload for vascular medicine by 2020 (207).

CAN and PAD

Cardiac autonomic neuropathy (CAN) also plays a crucial role in cardiovascular outcomes, especially when arterial stiffness is present [208]. In diabetes, CAN initially disrupts vagal control and increases sympathetic activity, which may later diminish [209]. Experimental studies suggest that increased sympathetic activity exacerbates arterial stiffness, while vagal activity may offer protective effects [210,211]. In individuals with type 1 diabetes, CAN is linked to higher pulse pressure, a marker of arterial stiffness, and alterations in left ventricular function [212]. Higher sympathetic activity in diabetic and hypertensive patients correlates with arterial stiffness, and elevated sympathetic nerve activity acutely increases pulse wave velocity (PWV) [213-215]. CAN is associated with increased arterial stiffness in type 1 diabetes and correlated with peripheral neuropathy and retinopathy in T2DM [216,217]. Endothelial dysfunction linked to arterial stiffness is also seen in hypertensive and diabetic patients [218,219]. Overall, CAN and related autonomic imbalances contribute to adverse cardiovascular changes and prognosis in diabetes.

Smoking and PAD

PAD shares many risk factors with coronary atherosclerosis, with smoking and diabetes being the most significant [69]. Smokers face a 2-3 times higher risk of developing PAD compared to non-smokers, with the risk escalating based on the amount and duration of smoking [145,146,220-222]. For instance, the ARIC study found that those with ≥25 pack-years of smoking had approximately a fourfold higher risk of PAD, with the elevated risk for PAD lasting up to 30 years, compared to other atherosclerotic diseases where the risk normalizes within 20 years [223]. Recent research and Mendelian randomization studies highlight that smoking more strongly contributes to PAD than to CAD or stroke [224,225]. Even adolescents who smoke have increased carotid intima-media thickness, underscoring the need for continued smoking prevention and cessation efforts across all age groups [225].

Additionally, smoking just before measuring the ABI can artificially lower ABI readings by 0.09 units. Therefore, it is advisable to wait at least 12 hours after smoking before measuring ABI (50). PAD prevalence increases with age, becoming more common after age 50, particularly after 70. Racial factors also influence PAD incidence, with higher rates observed among Caucasians and Blacks [31,147,226].

Smoking also contributes to more severe PAD, higher amputation rates, and increased mortality [227,228]. Smoking cessation can slow PAD progression, though its effects on walking performance in intermittent claudication are less clear [229,230]. Effective cessation strategies include nicotine replacement therapy, formal programs, and medications like bupropion, complemented by regular medical supervision and group therapy [231-233].

CLI and PAD

PAD of the lower limbs is caused by blood circulation disorders in the arteries, typically due to atherosclerosis in about 95% of cases [125]. PAD can be asymptomatic early on and affect both large and small vessels . Inflammatory, genetic, and traumatic causes are less common with age, whereas embolic events become more frequent [26]. PAD, along with MI and stroke, represents severe manifestations of atherosclerosis, with the most critical form leading to tissue necrosis and potential limb amputation [234].

The prognosis of lower extremities in patients with PAD is influenced by the extent of atherosclerosis, the severity of limb ischemia, and the effectiveness of revascularization [26]. For chronic atherosclerosis leading to CLI, limb viability is poor without revascularization, while acute occlusive events rely on prompt revascularization to prevent irreversible damage [26].

Approximately 25% of claudication patients experience spontaneous symptom improvement, one-third to one-half see no change, and about 25% worsen [125]. The progression of claudication is influenced by cardiac and cerebral events, with only 2% of claudication patients undergoing amputation within 10 years [137]. A 2016 review by Sigvant et al. found that 7% of asymptomatic PAD patients developed intermittent claudication within five years, and 21% of these progressed to CLI, with symptomatic PAD patients having a five-year cardiovascular mortality rate of 13% compared to 5% in the general population [235].

CLI patients face even higher mortality risks, up to 80% with pain at rest and 95% with trophic lesions [236]. Generally, 60-80% of PAD patients have significant coronary artery stenosis, and two-thirds show ischemia on stress tests [237]. Historically, Wolfe reported a 20% one-year mortality rate for CLI, whereas recent COPART registry data showed a one-year mortality rate of 5.7% for stable intermittent claudication and 21.1% for CLI, with ulcerated patients at 28.7% [238,239]. The BASIL study reported one- and three-year amputation-free survival rates of 70% and 55%, respectively, with a one-year mortality rate of about 20% [240].

CLI, an advanced stage of PAD, is associated with elevated arterial stiffness [241]. While the ABI is a known marker of mortality and morbidity, its relationship with arterial stiffness has been under-researched [242]. Increased arterial stiffness correlates with shorter walking distances in claudication patients [243]. Studies have investigated arterial stiffness in claudication but are limited for CLI, with findings showing mixed results on PWV and pulse wave reflection (AI) [110,244-250].

Guidelines from the Society for Vascular Surgery (2015) and the AHA/American College of Cardiology Foundation [2016] recommend against routine PAD screening in asymptomatic individuals without risk factors [126,251,252]. However, screening is advised for asymptomatic individuals at elevated risk, such as those over age 70, smokers, diabetics, and those with abnormal pulse exams or other cardiovascular disease. The 2013 AHA/ACC guidelines suggest ABI could aid decision-making when treatment options are uncertain, though the American Academy of Family Physicians considers the evidence insufficient to justify routine ABI-based PAD screening [253,254].

PAD Therapy

PAD therapy focuses on reducing cardiovascular risk factors and improving peripheral blood flow [125]. Treatment strategies vary by disease stage and may include antihypertensive drugs, exercise, and hormonal therapies to enhance compliance [104,255,256]. PAD screening offers two main benefits: early detection and treatment, which can slow atherosclerosis progression, and identifying individuals at risk for systemic atherosclerosis, potentially improving CVD risk management [86]. Abnormal ABI results can refine risk predictions and

guide more aggressive treatment. Studies consistently show that PAD reduces physical quality of life, but its impact on mental quality of life is less clear [257-260].

Conclusion

In summary, combining ABI with arterial stiffness indices (AI, EEI, DEI, DDI, C1, C2) provides a robust and comprehensive framework for evaluating arterial health and cardiovascular risk. The study reinforces the value of integrating these metrics to enhance cardiovascular risk assessment and patient management, offering complementary insights into an individual's cardiovascular status. Future research should focus on refining these metrics, exploring their interactions, and improving diagnostic accuracy to better inform clinical practice and patient outcomes in cardiovascular care.

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