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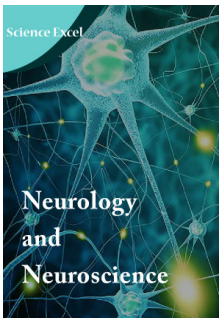

Assessing Autonomic Function in Aging and Disease Using VitalScan

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Abstract

The autonomic nervous system plays a critical role in maintaining homeostasis by regulating vital physiological functions, including cardiovascular, respiratory, and thermoregulatory processes. Autonomic dysfunction, often seen in chronic conditions such as Type 2 Diabetes Mellitus, cancer, and cardiovascular diseases, can lead to severe complications if left undiagnosed and untreated. This review explores the importance of autonomic dysfunction in the context of aging, diabetic autonomic neuropathy and cardiovascular autonomic neuropathy, with a focus on novel diagnostic tools like Heart Rate Variability (HRV) and the VitalScan technology. HRV, evaluated using the VitalScan-ANS system, is emerging as a key marker for evaluating autonomic imbalance, providing valuable insights into cardiovascular health, disease progression, and even early cancer detection.

The VitalScan-SudoCheck system, which evaluates sudomotor function, offers a non-invasive, efficient approach for diagnosing early signs of autonomic neuropathy, particularly in individuals with diabetes. Additionally, the review discusses the integration of arterial stiffness indices and Ankle-Brachial Index (ABI), assessed using the VitalScan-Vascular system, to enhance cardiovascular risk assessment. The combination of these diagnostic technologies holds promise for improving early detection, personalized treatment, and patient outcomes. Future research should aim to refine these diagnostic tools, standardize their clinical application, and expand their use across diverse populations to facilitate more effective management of autonomic dysfunction and related complications. Ultimately, this review underscores the need for comprehensive diagnostic strategies to monitor and address autonomic dysfunction, enhancing clinical care for patients with a wide range of chronic conditions.

Introduction

Autonomic Nervous System

The autonomic nervous system (ANS), a crucial part of the peripheral nervous system, regulates involuntary physiological processes such as heart rate (HR), blood pressure (BP), digestion, fluid balance, and thermoregulation. It operates unconsciously to maintain internal stability (homeostasis) by responding to both internal and external stimuli [1-4]. The ANS comprises neurons that transmit impulses from the central nervous system to various organs, glands, and muscles [5].

The primary role of the ANS is to ensure homeostasis by fine-tuning organ functions in response to changing conditions [1,4,6,7]. It regulates critical functions, including hormone secretion, circulation, digestion, and excretion, enabling the body to function efficiently without conscious effort [8].

The ANS has two branches: the sympathetic and parasympathetic systems. These systems work together to maintain balance by regulating excitation and inhibition across various organs [1,4,6,7]. The sympathetic nervous system (SNS) triggers the "fight-or-flight" response, increasing HR, pupil dilation, BP, glucose release, and muscle strength, while inhibiting functions like digestion [4]. In contrast, the parasympathetic nervous system (PNS) promotes "rest-and-digest" activities, slowing HR, constricting pupils, lowering BP, and supporting digestion and metabolic recovery [4,6,9]. These systems release different chemical messengers—norepinephrine for the SNS and acetylcholine for the PNS—which bind receptors on target organs to initiate specific physiological responses that maintain balance [10-12].

Autonomic regulation plays a key role in maintaining homeostasis, but dysfunction can arise if the system is damaged, leading to temporary or chronic issues [5]. Stress occurs when perceived threats result in a decrease in PNS tone and an increase in SNS activity [4,13-16]. Homeostasis and stress are interdependent: while homeostasis regulates internal function, stress focuses on external demands. Measuring

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PNS tone helps define stress and stress vulnerability, with lower PNS tone indicating greater susceptibility to stress.

The most accessible measure of PNS activity is respiratory sinus arrhythmia, where HR increases during inhalation and decreases during exhalation, controlled by parasympathetic impulses via the vagus nerve [17-19]. This HR pattern reflects the nervous system's status and quality of neural feedback [20]. Stress disrupts both behavioral and autonomic rhythms, and cardiac vagal tone can predict behavioral competence. Individuals with higher vagal tone tend to exhibit greater flexibility and fewer signs of distress [18,19,21-24].

Heart rate variability (HRV), the variation in time between heartbeats, is a reliable measure of ANS function [22,24]. High HRV indicates a healthy, well-balanced autonomic system, while low HRV suggests dysfunction and imbalance between the SNS and PNS. The balance between these two systems determines HRV and reflects the overall functioning of the ANS [11,12]. SNS dominance, indicated by lower HRV, suggests chronic stress and a vulnerability to further stress [22-24]. In contrast, a balanced ANS supports effective stress coping [25-31]. ANS analysis is used as a diagnostic tool in various diseases, providing insights into overall health and autonomic function.

A healthy ANS is characterized by efficient neural control, rhythmic variability within normal limits, and a wide range of behavioral responses. In contrast, reduced HRV indicates diminished flexibility in response to environmental demands. The complementary roles of the SNS and PNS are essential for the body's adaptation to internal and external stimuli. Dysfunction in the ANS can lead to various disorders, underscoring its importance for maintaining health and resilience.

ANS and Aging

Aging causes structural and functional changes in the ANS, which significantly impact overall health and well-being [32,33]. As people age, PNS activity decreases, while SNS activity increases. This imbalance raises the risk of conditions such as hypertension, metabolic disorders, and cognitive decline [33,34]. Declining functional capacity in older adults is a key health indicator, as it correlates with higher risks of adverse health outcomes and greater care needs [35,36]. The ANS plays a crucial role in maintaining physiological balance, and its dysfunction is closely linked to a decline in functional capacity [37-40].

Maintaining the balance between the SNS and PNS is critical for health, particularly in aging individuals, as the risk of age-related diseases increases [41]. In older adults, heightened SNS activity and reduced PNS tone—a condition known as ANS dysfunction—are common [42]. This dysfunction plays a significant role in the development of autoimmune diseases, as the ANS regulates both innate and adaptive immunity. Autonomic imbalance is also a major factor in the progression of various diseases, particularly cardiovascular conditions [43]. Increased SNS activity is linked to hypertension, thickening of the aortic and ventricular walls, endothelial dysfunction, and kidney failure [44-47]. Longitudinal studies, such as the Framingham Heart Study and the Baltimore Longitudinal Study, show that systolic blood pressure rises with age while diastolic pressure decreases, contributing to higher rates of cardiovascular disease and mortality in individuals over 65 [48-52]. Reduced PNS activity is also associated with arrhythmias and age-related cardiac deaths [53,54]. Overall, aging results in ANS dysregulation, impacting various organs and their functions.

ANS imbalance can alter inflammatory responses, contributing to conditions such as rheumatoid arthritis, lupus, and systemic sclerosis [55]. This dysfunction is linked to increased inflammation and a higher risk of cardiovascular disease, the leading cause of morbidity and mortality in autoimmune patients [56]. ANS imbalance is also observed in immune-mediated inflammatory diseases (IMIDs) such as inflammatory bowel disease, obesity, hypertension, chronic pulmonary disease, and coronary heart disease [57]. It contributes to chronic systemic inflammation, or "inflammaging", a low-grade proinflammatory state that worsens with age and can be detected through proinflammatory markers in blood and tissues [58,59]. Autonomic dysfunction affects inflammation regulation in both chronic and acute conditions and may play a key role in the development of age-related diseases, including autoimmune diseases, cardiovascular diseases, and ischemic stroke [60].

Age-related changes in the SNS and PNS are complex, influenced by both genetic and environmental factors [60,61]. However, the precise relationship between ANS dysfunction and compensatory mechanisms remains unclear and warrants further investigation [62]. Aging also affects the PNS, leading to declines in nerve conduction, muscle strength, sensory responses, and overall autonomic function [63]. This deterioration is associated with a proinflammatory state, endothelial dysfunction, and a reduced ability to regenerate nerve fibers, increasing the risk of age-related diseases [42,64]. Chronic inflammation further hinders nerve regeneration in older individuals [65]. Overactivation of the SNS and diminished PNS activity are considered significant risk factors for cardiovascular diseases, including heart failure, obesity, hypertension, and metabolic disorders [66-68].

ANS and Disease

Disturbances in autonomic regulation can lead to various neuropathic conditions, affecting the body's ability to regulate BP, sweating, HR, and digestion [69]. Autonomic neuropathies are a group of disorders that impact the SNS or PNS, potentially causing a range of symptoms depending on which ANS components are affected. These conditions can be hereditary or acquired later in life.

Autonomic disorders, or dysautonomia, arise from damage to the ANS, disrupting vital functions such as HR, BP, digestion, and respiration [70-72]. These conditions can be primary (e.g., orthostatic intolerance syndromes, small fiber neuropathies) or secondary (e.g., Parkinson's disease, diabetes, cancer), cause symptoms that vary from mild to severe and affecting multiple organ systems [69]. Common symptoms include dizziness, fainting, fatigue, insomnia, chest pain, mood swings, and headaches [73,74].

Key conditions include orthostatic hypotension, where BP drops upon standing, leading to dizziness or fainting; Postural Orthostatic Tachycardia Syndrome (POTS), characterized by an increased HR upon standing, causing fatigue and dizziness; and syncope, which results in temporary loss of consciousness [69,75,76]. Baroreflex failure, in which BP regulation is impaired, can cause dangerous fluctuations [69]. Multiple system atrophy, a neurodegenerative disease, affects both movement and autonomic functions [69]. Autonomic neuropathy, including small fiber neuropathy (SFN), can results from conditions like diabetes and autoimmune diseases, leading to symptoms such as burning pain or numbness [77,78]. Treatment for these disorders typically focuses on symptom management through

lifestyle changes, medications, and supportive therapies aimed at improving the quality of life [69,79].

VitalScan Technology

The VitalScan is an all-in-one diagnostic device designed for use in general and family medicine clinics to help physicians assess patients for various chronic conditions. Comprising three technology platforms—VitalScan-ANS (Figure 1), VitalScan-Vascular+ (Figure 2), and VitalScan-SudoCheck (Figure 3)—the device quickly evaluates symptoms like dizziness, faintness, leg pain, or neuropathy, which can be indicative of conditions such as diabetes or vascular disease. VitalScan is particularly valuable in identifying early-stage illnesses related to metabolic disorders, vascular abnormalities, and autonomic neuropathies.

Figure 1. *This is an image of the VitalScan-ANS System developed by Medeia Inc. performing the tilt table test. The VitalScan-ANS System is portable, easy-to-use, and non-invasive.*

Figure 2. *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.*

Figure 3. *This is an image of the VitalScan-SudoCheck System developed by Medeia Inc. performing the sudomotor function test. The VitalScan-SudoCheck System is portable, easy-to-use, and non-invasive.*

This device is beneficial across multiple medical specialties, including primary care, cardiology, pulmonology, endocrinology, neurology, and pain management. It helps identify at-risk patients, such as those with Type 1 (T1DM) or Type 2 Diabetes Mellitus (T2DM), where cardiovascular autonomic neuropathy (CAN) is common but often undiagnosed. FDA 510(k) cleared, the VitalScan device offers expansive clinical applications, providing insights that inform personalized treatment approaches and enhance patient care.

This review integrates the role of the ANS in aging and disease, focusing on findings from large-cohort studies conducted by Medeia Inc., the developer of VitalScan [80-82]. The review aims to deepen understanding of how factors such as age, gender, and prevalent conditions like alcoholism, cancer, and diabetes impact ANS activity. By utilizing VitalScan's autonomic testing protocols, the review assesses cardiovascular and sudomotor functions through indices like HRV, Ankle-Brachial Index (ABI), and Sudomotor Autonomic Neuropathy Index (SANI). These tests provide a holistic view of overall autonomic health. Early detection of peripheral and autonomic neuropathies is critical for implementing interventions that can preserve nerve function and prevent severe complications, particularly in aging and diseased populations.

VitalScan Autonomic Testing

Autonomic testing, which began with neurophysiological experiments at the turn of the 19th century, has evolved into a standardized series of tests used in clinical practice to assess patients with suspected autonomic disorders [83]. For over 50 years, autonomic testing has been widely utilized, supported by extensive research and textbooks on its methods and purposes [84-87]. The tests cover the sympathetic, parasympathetic, and enteric branches of the ANS and assess various organ functions, including sudomotor (sympathetic cholinergic), cardiovagal (parasympathetic), and sympathetic adrenergic systems. While randomized controlled trials have not been conducted to establish efficacy, accumulated clinical experience and research have defined the role of autonomic testing in diagnosing and managing autonomic disorders [83].

Autonomic testing is widely used to assess cardiovascular and sudomotor dysfunction in various conditions [83,88,89]. Key clinical indications include:

1. **Generalized Autonomic Failure:** Testing helps diagnose conditions like multiple system atrophy (MSA), pure autonomic failure (PAF), or autonomic neuropathies (e.g., diabetic, amyloid, Sjogren's syndrome), providing insights into prognosis [90].
2. **Limited Autonomic Failure:** Identifies conditions such as chronic idiopathic anhidrosis, syncope, orthostatic intolerance, or distal small fiber neuropathy, which may present with subtle autonomic dysfunction.
3. **Differentiating Benign vs. Life-Threatening Disorders:** Helps distinguish benign conditions like neurocardiogenic syncope or chronic idiopathic anhidrosis from more severe disorders like generalized autonomic failure.
4. **Orthostatic Intolerance:** Assesses symptoms of orthostatic hypotension, syncope, or postural orthostatic tachycardia syndrome (POTS), helping to differentiate whether these symptoms stem from autonomic failure [91].
5. **Differentiating MSA from Parkinson's Disease:** Autonomic testing aids in distinguishing MSA from Parkinson's disease by evaluating cardiovascular and sudomotor function [92].
6. **Monitoring Autonomic Dysfunction:** Non-invasive testing tracks the progression of autonomic dysfunction over time, providing quantitative data.
7. **Evaluating Treatment Response:** Quantitative methods are used to assess how well a patient responds to treatments aimed at autonomic dysfunction.

All patients with diabetes are recommended to undergo autonomic testing by the American Diabetes Association (ADA)—assessing sudomotor, cardiovagal, and adrenergic functions—at the time of diagnosis for T2DM or five years after diagnosis for T1DM [83,93-98]. This recommendation is based on evidence showing that individuals with diabetes and CAN face significantly higher risks of mortality and silent myocardial ischemia [83,99,100]. CAN is also associated with greater perioperative risks, including BP instability and hypothermia, which can increase perioperative mortality [101-104]. This knowledge informs decisions on elective procedures and helps prepare anesthesiologists for potential hemodynamic changes, reducing morbidity and mortality [93,95,105].

The VitalScan Autonomic Function Testing is a next-generation diagnostic tool designed to quickly identify ANS disorders, as well as imbalances in parasympathetic and sympathetic function. It provides comprehensive, interpretive reports in minutes, assisting in the detection of conditions like hypertension, diabetic neuropathy, vascular abnormalities, orthostatic hypotension, silent heart attacks, and more.

Medeia Inc. has conducted large cohort studies using client data acquired between 2014 and 2023 from multiple neurology offices to validate the use of the VitalScan technology in evaluating ANS functions with age and disease. For participants aged 4 to 18 years, parents completed a neurological history questionnaire, and psychometric evaluations were conducted. Adults (≥18 years) also completed a neurological questionnaire. Participants were included if they had at least one questionnaire score below the moderate level and were verified as healthy by a physician. Exclusion criteria involved any participant with a moderate or severe score on questionnaires, including GAD-7 (Anxiety Severity), DSM-5 Level 1 (Cross-Cutting Symptom Measures), PHQ-9 (Depression), PCL-C (PTSD Severity), or general neurological assessments. Patient records or previous medical histories with moderate or severe scores were excluded from the VitalScan-ANS, VitalScan-Vascular+, and VitalScan-SudoCheck databases.

Each client in the VitalScan-ANS, VitalScan-Vascular+, and VitalScan-SudoCheck databases completed a DSM-based questionnaire. Regression analysis was used to remove psychopathology-related variance from the data (ECG, PWV, BP, HRV, ABI, and SANI) to create a 'psychopathology-free' normative or discriminant database for various neuropathy disorders. This ensures that the variance due to psychological factors, such as anxiety or stress, is excluded, providing a more accurate assessment of ANS function. Using a client-based normative or discriminative database that accounts for these factors ensures more reliable comparisons and improves treatment effectiveness.

Large Cohort Study 1 utilizes the VitalScan-ANS system to evaluate ANS functions using HRV parameters [80]. Large Cohort Study 2 uses the VitalScan-Vascular system to further assess the vascular aspect through indices such as ABI, Augmentation Index (AI), and arterial stiffness indices [81]. Lastly, Large Cohort Study 3 applies the VitalScan-SudoCheck system to evaluate sudomotor functions using SANI [82].

Impact of Aging on ANS

Large Cohort Study 1: HRV Parameters [80]

Autonomic testing, which evaluates the function of the ANS is essential for understanding various physiological responses, particularly in the cardiovascular and respiratory systems [106]. Historically, testing methodologies have evolved, with a standard battery of maneuvers proposed by Ewing and Clarke, including the Valsalva maneuver, active standing, and deep breathing, which are commonly used for clinical evaluations [107]. These tests are valuable for assessing the sympathetic and parasympathetic functions of the ANS, but no single test provides a comprehensive assessment due to variations in laboratory conditions, protocols, and patient-related factors [106,108,109]. Caution is thus required when interpreting results, particularly when using normative values for comparison.

Over the years, several methods have been developed to evaluate ANS function, and the complexity of the ANS necessitates combining multiple tests for a comprehensive assessment [106,108-110]. Common tests for assessing cardiac ANS function include the Valsalva maneuver, deep breathing, handgrip test, cold pressor test, mental arithmetic test, active standing, head-up tilt test, and others [110]. These tests provoke cardiovascular reflexes, requiring continuous monitoring of HR, BP, and other hemodynamic variables is essential for analysis [88]. Typically, SNS function is assessed through BP changes, while PNS function is evaluated by observing HR changes during specific maneuvers [70].

Aging impacts autonomic functions, similar to the changes observed in various disease states [26]. Our study with 328,591 participants found that HRV steadily declined from ages 20 to 90, with decreases observed across all HRV metrics [80]. This decline in HRV, a marker of ANS function, suggests a gradual weakening of both sympathetic and parasympathetic activity, regardless of sex. Both males and females showed a gradual decline in resting HR, with resting HR used as an indicator of vagal nerve function and the balance between sympathetic

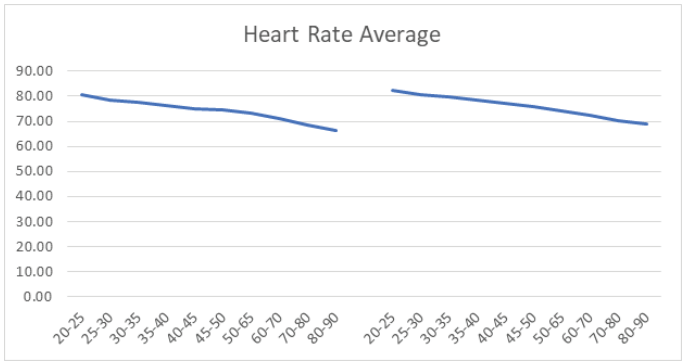

Figure 4. *This is an image of the VitalScan-Vascular+ System developed by Medeia Inc. The VitalScan-Vascular+ System is portable, easy-to-use, and non-invasive.*

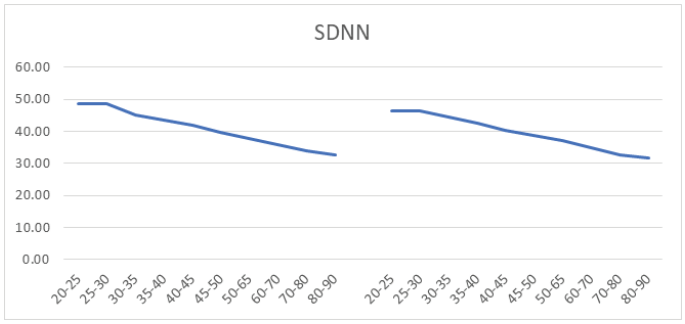

Figure 5. *Mean SDNN (ms) versus age shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel downward trend.*

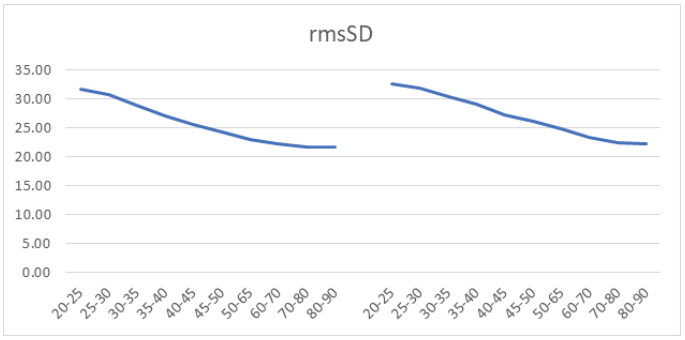

Figure 6. *Mean RMSSD (ms) versus age shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel downward trend.*

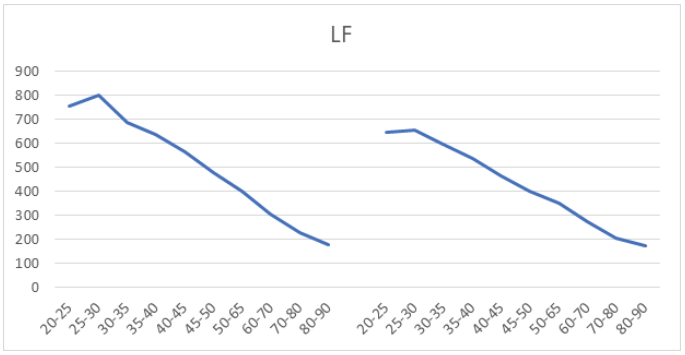

Figure 7. *Mean LF (ms2) versus age shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel downward trend.*

and parasympathetic influences on the heart (Figure 4) [111]. However, the decline was consistent across genders, indicating that the aging process impacts autonomic function similarly in both males and females.

Time-domain indices like SDNN (Standard Deviation of NN intervals) and RMSSD (Root Mean Square of Successive Differences) offer insights into HRV and autonomic functions. SDNN is widely regarded as the "gold standard" for assessing cardiac risk, with values above 100 ms linked to reduced morbidity and mortality [112,113]. Our study found that SDNN values decreased with age for both men and women, and values below 50 ms were associated with a higher mortality risk, indicating poor health (Figure 5) [114,115]. RMSSD, a key metric for assessing PNS function, reflects short-term HR fluctuations and was generally higher in women than men, particularly in the younger age groups, though it also declined with age (Figure 6) [80,116].

Low-frequency (LF) and high-frequency (HF) components of HRV provide further insights into ANS function. LF reflects both sympathetic and parasympathetic modulation, while HF primarily serves as a marker for parasympathetic activity [117]. Our study showed that both LF and HF power significantly declined with age (Figures 7 and 8) [80]. From ages 20 to 90, LF power decreased by 76.4% in males and 73.5% in females, while HF power decreased by 66.4% in males and 68.2% in females. The decline in LF power, suggesting reduced sympathetic activity, was more pronounced in males, while females exhibited a steeper decline in HF power, reflecting parasympathetic decline. This shift underscores the age-related weakening of both branches of the ANS.

The LF/HF ratio, which indicates the balance between sympathetic and parasympathetic activity, was higher in males, suggesting greater sympathetic dominance. This ratio showed the most significant increase between ages 35-50 in males, reflecting higher sympathetic activity relative to parasympathetic activity, especially in this age group. The decline in HRV components and the shift in the LF/HF ratio indicate that as individuals age, there is a higher dominance of sympathetic over parasympathetic activity, which may impact overall health and functional capacity (Figure 9) [118, 119].

Finally, “autonomic tone” serves as a regulatory mechanism for the ANS, similar to a rheostat [120]. Autonomic tone declines with age, particularly in the HR parameter, with both males and females showing a decrease in HR with aging (Figure 10). Although the decrease in HR was similar across genders, females tended to have slightly higher HRs throughout life. These findings underscore the aging-related weakening of the ANS, with significant declines in sympathetic and parasympathetic functions over time, which can have implications for cardiovascular health and overall well-being.

Large Cohort Study 1: Valsalva Maneuvers Test (VM) [80]

The Valsalva ratio, which is used to assess autonomic function, is a measure of cardiovascular reflexes in response to a forced expiration against a closed airway (Valsalva maneuver). In healthy individuals, a Valsalva ratio of 1.2 or higher is considered normal, while ratios between 1.1 and 1.2 are borderline, and ratios below 1.1 are indicative of abnormal autonomic function [69, 70, 121-124].

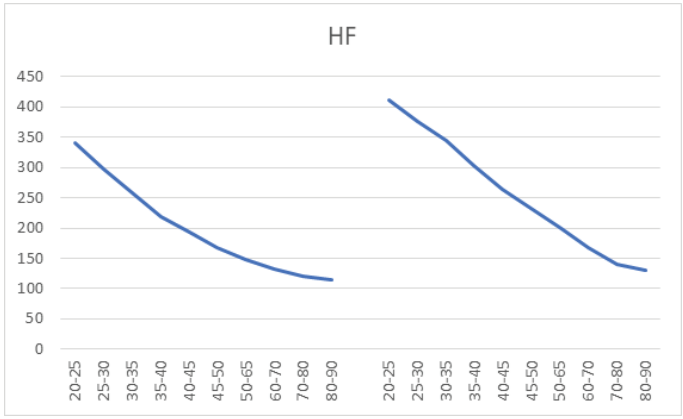

Figure 8. *Mean HF (ms2) versus age shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel downward trend.*

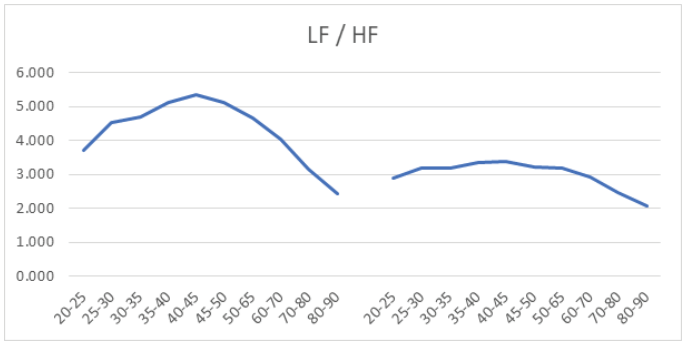

Figure 9. *Mean LF/HF ratio versus age shows a decline starting from age 45+ years in both men (left) and women (right) aged 20-90 years. The male curve consistently lies above the female curve, indicating higher LF/HF ratios in males across all ages.*

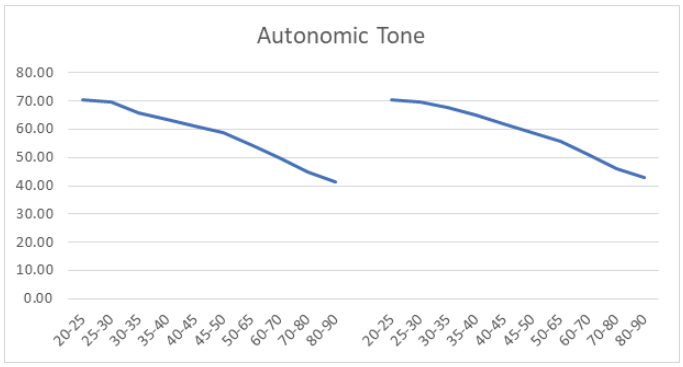

Figure 10. *Reduction in autonomic tone with age, depicted by declining average HR (bpm) in males (left) and females (right), aged 20-90 years, with both curves demonstrating a parallel downward trend.*

In our study, both male and female participants aged 20-90 generally maintained a healthy Valsalva ratio, which started to become borderline in individuals aged 80-90 (Figure 11) [80]. Both sexes exhibited a similar age-related decline in the Valsalva ratio, with no significant difference between men and women. Previous research has demonstrated a linear decrease in the Valsalva ratio with age [124]. For example, Risk et al. observed that the Valsalva ratio for women decreases from around 2.1 to 1.4, and for men, from 2.1 to 1.3 124). Our findings corroborated this trend, showing that men's ratios decreased from 1.44 to

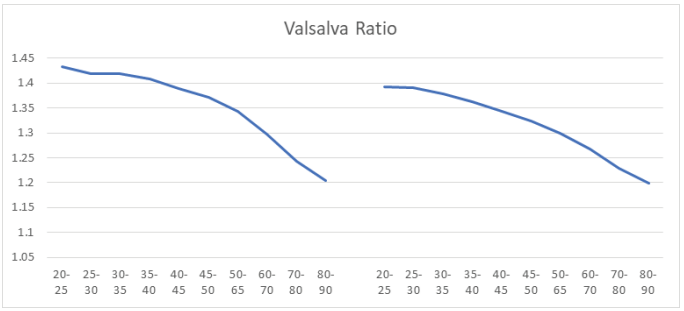

Figure 11. *The graph displays the Valsalva ratio of HR response to VM. Mean Valsalva ratio versus age shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a similar downward trend.*

1.20, and women's from about 1.40 to 1.20 with aging. These results align with Risk's findings, indicating a consistent age-related decline in the Valsalva ratio across both genders [124].

Furthermore, Jha et al. noted slightly higher Valsalva ratios in women aged 18-25 compared to men, but in our study, the decline in Valsalva ratios with age was not dependent on gender [122]. This suggests that while there may be slight differences in younger age groups, the overall pattern of decline in the Valsalva ratio with age is similar for both men and women. This age-related changes is consistent with the broader trend of diminishing ANS function as individuals age, highlighting the gradual decline in cardiovascular reflexes across the lifespan.

Large Cohort Study 1: Deep Breathing Test (DBT) [80]

The expiration-to-inspiration (E/I) ratio is an important measure reflecting parasympathetic activity, specifically cardiac parasympathetic function, during deep breathing. This ratio is influenced by resting HR; a lower resting HR tends to result in a higher E/I ratio [125]. A normal HR response to deep breathing should show a change of 15 beats per minute (bpm) or more. A response between 10-15 bpm is considered borderline, while a response below 10 bpm is considered abnormal [70,121,126].

In our study, the mean E/I ratio observed in participants aged 80-90 was above 1.2, indicating that these individuals demonstrated a normal HR response to deep breathing similar to young adults (Figure 12a) [70,80]. Both males and females exhibited a linear decline in the E/I ratio with age, in line with findings from previous studies on healthy adults aged 16-70 [127]. Interestingly, gender did not significantly affect the HR response during deep breathing, suggesting that the decline in parasympathetic function is comparable across both sexes with aging.

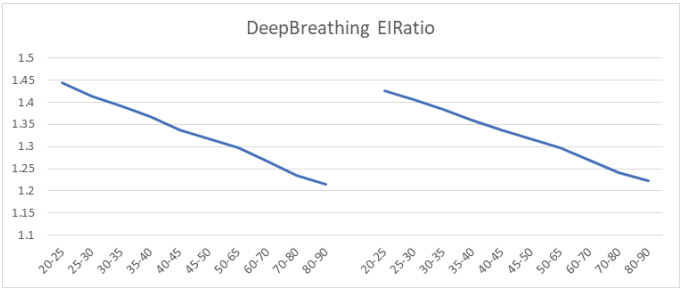

Figure 12a. *Reduction in autonomic tone with age, depicted by declining average HR (bpm) in males (left) and females (right), aged 20-90 years, with both curves demonstrating a parallel downward.*

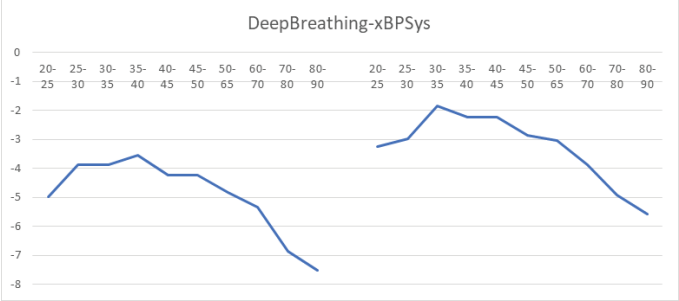

Figure 12b. *The graph illustrates the BP response to the DBT. Mean BP ratio versus age exhibits a decline starting from age 40+ years in males (left) and 35+ in females (right), aged 20-90 years. The female curve consistently remains above the male curve, indicating higher BP ratios in females across all ages.*

Additionally, BP followed a similar age-related decline in both males and females, but females consistently showing higher BP values across all age groups (Figure 12b). BP in females peaked around ages 35-40 and declined thereafter, while in males, it peaked slightly later, between ages 40-45. Parasympathetic dominance, as induced by slow deep breathing, has been shown to lower BP [128]. Studies indicate that slow breathing exercises can significantly reduce both systolic and diastolic BP [128,129]. Additionally, slow breathing is believed to improve baroreflex sensitivity, which might explain the reduction in BP and HR during such exercises [130]. These findings underscore the potential cardiovascular benefits of slow breathing, particularly for controlling BP and promoting overall cardiovascular health. These results highlight the importance of parasympathetic function in regulating cardiovascular stability, and the role that interventions like slow breathing can play in improving autonomic regulation in aging populations.

Large Cohort Study 1: Passive Tilt Table Test (TTT) [80]

The transition from a supine to an upright position induces significant changes in autonomic function, which can be effectively measured through HRV parameters. In the supine position, the body experiences baseline HRV and HR during relaxed breathing, reflecting a balanced autonomic state. Upon standing, parasympathetic activity typically decreases, resulting in a reduction of PNS dominance. This shift is reflected in changes in both time-domain and frequency-domain HRV metrics, such as the LF and HF components, which provide insights into the balance between sympathetic and parasympathetic activity.

One key measure of HRV during this transition is the 30:15 ratio, which captures HR dynamics shortly after standing. It is defined by the longest RR interval around the 30th beat after standing and the shortest RR interval around the 15th beat [121]. In healthy adults, a typical 30:15 ratio is around 1.29, with values above 1.05 considered normal [70,121,123]. Our study shows both males and females exhibited a decline in the 30:15 ratio with age, though the pattern was consistent across genders (Figure 13a) [80]. Males showed slightly higher values than females across all age groups, with values of 1.29 vs. 1.27 in the 20-25 age group and 1.19 vs. 1.18 in the 80-90 age group. This decline in the 30:15 ratio suggests a gradual reduction in parasympathetic response with age.

BP responses to postural changes also exhibited gender differences. In younger adults aged 20-25, females showed a higher mean BP ratio (+1.75) compared to males (-0.60) (Figure 13b). Over time, both sexes experienced a decline in

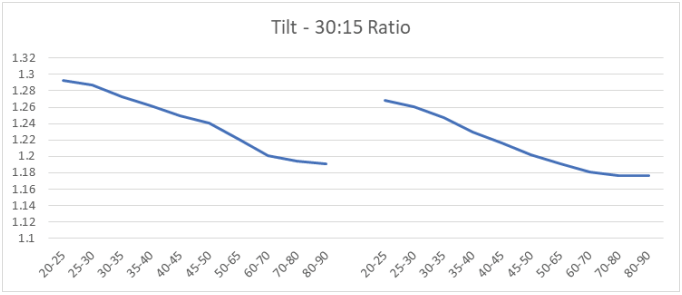

Figure 13a. *The graph illustrates the 30:15 ratio of HR response to the TTT. Mean 30:15 ratio versus age shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel downward trend.*

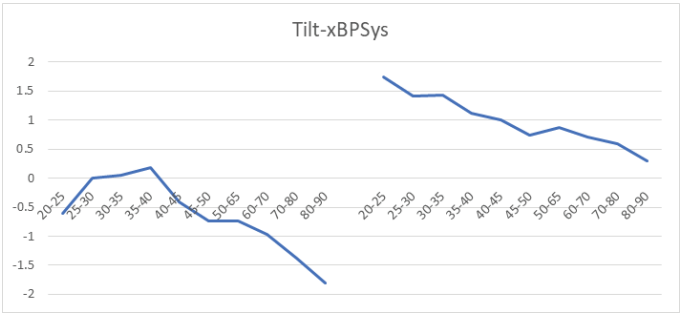

Figure 13b. *The graph illustrates the BP response to the TTT. Mean BP ratio versus age exhibits a decline starting from age 40+ years in males (left) and 25+ in females (right), aged 20-90 years. The female curve consistently stays above the male curve, indicating higher BP ratios in females across all ages.*

BP ratio, but females consistently maintained higher BP ratios. For instance, in the 80-90 age group, females had a BP ratio of +0.75, while males showed a significantly lower BP ratio of -1.90. These findings highlight that the autonomic responses to postural changes, particularly in BP, differ between males and females, with females generally demonstrating higher BP ratios, suggesting a more robust BP response to standing.

Overall, the autonomic function in our cohort remained within normal limits, although age-related declines in HRV parameters, such as the 30:15 ratio and BP response, were observed. These HRV measures and BP responses are important indicators of autonomic function and cardiovascular health, helping to assess and manage cardiovascular risks more effectively. Understanding these dynamics is crucial for optimizing patient care and making informed clinical decisions.

Impact of Aging on Vascular Functions

The ANS plays a critical role in regulating cardiovascular functions such as vascular tone, HR, and BP [131]. The sympathetic branch of the ANS promotes vasoconstriction through the norepinephrine release, which increases vascular resistance and elevates BP [132-134]. Conversely, the parasympathetic system counters this effect by inducing vasodilation and reducing HR. Together, these systems maintain homeostasis, ensuring appropriate blood flow to organs based on physiological needs, such as during exercise or stress [135]. Dysfunction in the ANS is significant risk factor for various vascular diseases, including hypertension, heart failure, and

diabetes mellitus, with excessive sympathetic activity being particularly harmful to blood vessels [131].

The ANS also plays a pivotal role in maintaining vascular homeostasis, and its dysfunction is a key factor in the severity of Peripheral Arterial Disease (PAD). PAD patients often exhibit sympathetic overactivity and parasympathetic underactivity, which exacerbates vascular constriction and impairs blood flow, especially during physical activity or stress [131,136-139]. Sympathetic overactivity impairs the ability of peripheral arteries to dilate in response to exercise, resulting in inadequate oxygen delivery to tissues and aggravating ischemic symptoms [138,140]. This altered autonomic regulation in PAD patients can also hinder wound healing and increase the risk of complications like infections and ulcerations, as local blood flow to tissues in need of repair is disrupted [138]. Therefore, understanding autonomic dysregulation in PAD is crucial for developing targeted interventions that mitigate these detrimental effects.

Arterial vascular assessment is vital for diagnosing and managing PAD and other cardiovascular conditions. PAD, which is caused by the accumulation of plaque in arteries, leads to narrowing, stiffening, and reduced functionality, ultimately causing ischemia and decreased blood flow, particularly in the legs [141,142]. This can lead to severe complications such as tissue death or even limb amputation [142-145]. Despite the severe implications, PAD is asymptomatic in over 75% of cases [146]. PAD significantly increases the risk of heart attacks, strokes, and ischemic events, with PAD patients being six times more likely to die from cardiovascular disease within 10 years compared to healthy individuals [146]. PAD is considered a stronger predictor of cardiovascular mortality than a clinical history of coronary artery disease, making it a critical indicator of survival [147].

Many patients with PAD, especially those with low ABI values, may remain asymptomatic or present with atypical symptoms, complicating the diagnosis [148]. Though the condition progresses slowly, PAD is associated with ongoing atherosclerosis in other vascular regions, contributing to its high mortality rate, largely due to strokes and myocardial infarctions (MI) [149-161]. The prevalence of PAD increases with age, and approximately 25% to 30% of patients with symptomatic PAD die within five years, underscoring its impact on cardiovascular morbidity and mortality [149-163].

The VitalScan-Vascular system plays a crucial role in assessing cardiovascular risk and vascular function, including the identification of PAD. This tool allows for evaluation beyond typical age-related changes in arterial stiffness. Arterial compliance, which reflects the ability of arteries to adapt to pressure changes, declines with age and is further compromised by conditions like hypertension, diabetes, and end-stage renal disease [164-170]. Increased arterial stiffness, a key indicator of cardiovascular disease (CVD), is associated with conditions such as ventricular hypertrophy, atherosclerosis, and PAD [171-174]. Non-invasive tests like pulse wave velocity (PWV) and the ABI are commonly used to measure arterial stiffness [174-177]. These measurements are essential for predicting cardiovascular events and mortality, especially when traditional risk factors may not fully capture cardiovascular risk [178-180].

By advancing understanding of arterial function and autonomic regulation, these assessments can aid in early detection and intervention for PAD, ultimately improving outcomes for patients and helping to mitigate the risk of cardiovascular events.

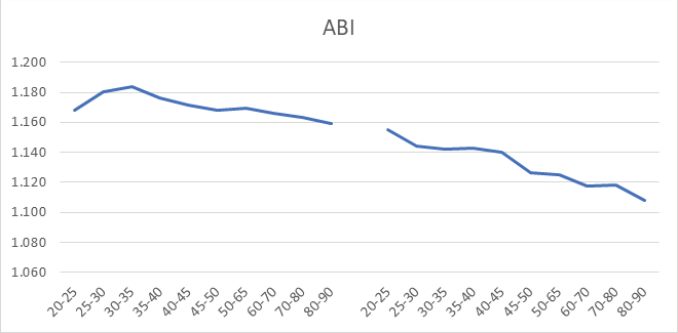

Figure 14. *ABI versus age curve shows a decline in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a downward trend.*

Large Cohort Study 2: ABI Test [81]

The 2016 AHA/ACC guidelines recommend ABI as the preferred initial test for diagnosing PAD due to its high sensitivity (95%) and near-perfect specificity (nearly 100%) in detecting vascular stenosis [181,182]. PAD affects 3-10% of the general population, with its prevalence increasing with age [162,163]. In our study (n=135,846), we found that ABI values remained within the normal range, with no significant differences across age groups or between genders (Figure 14) [81]. However, it was noted that ABI values tend to decrease slightly with age, especially in women.

Although resting ABI is a useful tool for detecting PAD, it may not always identify the condition in symptomatic patients. Stress testing, recommended for individuals with symptoms, can improve PAD detection by approximately 30%, as it provides additional information beyond the resting ABI measurement [183-186]. This approach is particularly beneficial in cases where PAD is suspected but the resting ABI does not show significant abnormalities.

Large Cohort Study 2: AI Test [81]

The Augmentation Index (AI) is a crucial parameter used to assess arterial function and cardiovascular health by measuring the ratio of reflected wave amplitude to the systolic wave [187-193]. It provides insight into arterial stiffness by reflecting the contribution of the early reflected pulse wave to late systolic blood pressure in the ascending aorta [194]. As arteries lose elasticity with age, the reflected wave returns earlier, increasing aortic systolic pressure and contributing to higher AI values [195]. Alongside PWV, AI is used to assess arterial stiffness, though the two metrics provide different insights and are not interchangeable [196,197].

PWV measures the speed at which a pulse wave travels between two arterial sites, serving as an indicator of arterial stiffness. When arteries become less elastic, PWV increases [198]. PWV can be measured at various arterial segments, such as carotid-brachial, brachial-ankle, and carotid-femoral arteries. AI is influenced by both PWV and the distance between the aortic root and major impedance mismatch sites, making its age-related changes distinct from those of PWV [196]. According to Li et al. AI is a more relevant measure of age-related arterial stiffness for individuals over 18, while cfPWV reflects the progression of arterial stiffness across the lifespan [187].

In our study, AI showed a gradual increase with age for both sexes, consistent with previous studies (Figure 15) [189,191,199-201]. However, the relationship between AI

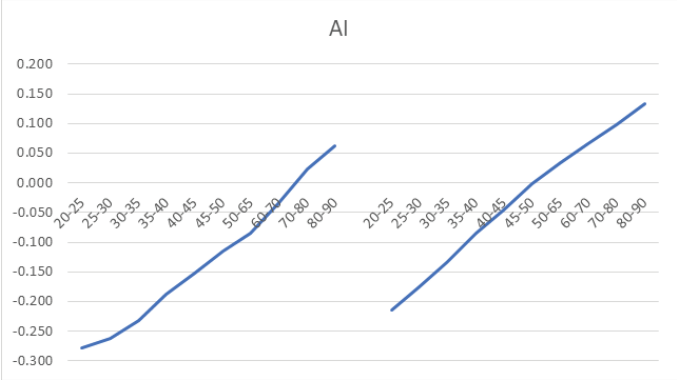

Figure 15. *AI versus age curve shows an upward trend in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel upward trend.*

and age is not universally consistent. Some studies suggest a correlation in younger individuals that weakens in older populations [188,202-206]. Additionally, AI is typically higher in young children and decreases until adolescence, likely due to the shorter length of the aorta [207,208]. After puberty, AI increases with age, showing a nearly five-fold increase from adolescents (20 years) to the elderly (96 years) [196]. AI demonstrates two key turning points: one during adolescence, where it shifts from decreasing to increasing, and another in middle age when the rate of increase slows [202,209].

Our findings also confirm that AI values are generally higher in women, although discrepancies across studies may arise from differences in sample characteristics, measurement sites, and other factors [81,189,191,204]. AI correlates inversely with height, especially in children, where it decreases as body height increases [200,201,203,206,210]. While AI is a reliable tool for assessing cardiovascular risk, its utility in older populations may be limited as AI tends to plateau after a certain age, while augmentation pressure continues to rise. This suggests that augmentation pressure may be a better measure of arterial stiffness in the elderly [211].

Furthermore, AI's sensitivity to factors such as PWV and waveform types (e.g., type C waveforms) can influence its accuracy [189,200,201,212-216]. Negative AI values, which are more common in younger individuals due to type C waveforms, may not accurately reflect the magnitude of wave reflection [189]. Therefore, AI should be used alongside other diagnostic tools, including PWV and augmentation pressure, to provide a comprehensive assessment of cardiovascular health.

Large Cohort Study 2: Elasticity Indices [81]

Vascular aging is characterized by structural and functional changes in the arterial walls, particularly in the intima, media, and adventitia layers, which are influenced primarily by the replacement of elastin with collagen. This shift contributes to increased arterial stiffness, higher BP, and an increased risk of various cardiovascular conditions [217,218]. The aging process affects different arteries in distinct ways: central arteries become stiffer due to a higher collagen-to-elastin ratio, while peripheral arteries show less pronounced changes [219-224].

As blood vessels age, their structure, function, and compliance change, all of which can be detected to assess vascular aging [187]. Key changes in arterial health include:

1. **Structure:** Increased arterial wall thickness and lumen diameter.
2. **Function**: Desensitization of endothelium-dependent vasodilation, typically triggered by acetylcholine or reactive hyperemia.
3. **Compliance**: Increased stiffness, commonly measured by PWV or AI.

These parameters reflect different aspects of arterial health and are not always interchangeable, even within the same category [187]. For instance, PWV and AI may not align consistently across all age groups. While AI shows a more pronounced increase in individuals under 50, cfPWV tends to increase more significantly in individuals over 50 [201,206].

Arterial stiffness, measured through compliance and distensibility, increases with age [225]. PWV, considered the gold standard for assessing arterial stiffness, has been linked to cardiovascular events and mortality [226]. In our study of 227,173 participants, we found that arterial compliance indices – such as the Ejection Elasticity Index (EEI), Dicrotic Elasticity Index (DEI), and Dicrotic Dilation Index (DDI) – all decreased with age in both sexes (Figure 16) [81]. Males consistently showed higher values than females across all age groups. For instance, EEI in males decreased from 0.648 in the 20-25 age group to 0.405 in the 80-90 age group, while in females, it decreased from 0.603 to 0.355.

The decline in these indices was more pronounced in females for EEI, while males showed more significant changes in DEI and DDI. Some studies have shown a linear increase in stiffness with age, with accelerated stiffening typically observed around age 50-60 [206,227]. In our study, the DEI curve for females plateaued after age 60 [81]. When analyzing the leg measurements (n=127,193), we observed a similar downward trend in indices, with males consistently showing higher values [81]. However, the relative decline in leg indices was less pronounced compared to non-leg indices, suggesting slower progression of stiffness in the legs.

The VitalScan-Vascular+ database provides reference ranges for EEI, DEI, and DDI between 0.3 and 0.7, with values outside this range indicating potential cardiovascular issues. Abnormal values, such as low EEI (indicating left ventricular insufficiency) or high EEI (suggesting increased left ventricular ejection), may require further testing to confirm conditions like PAD.

In summary, our study highlights the role of arterial stiffness in vascular aging, the impact of sex differences, and the importance of various arterial stiffness indices for assessing

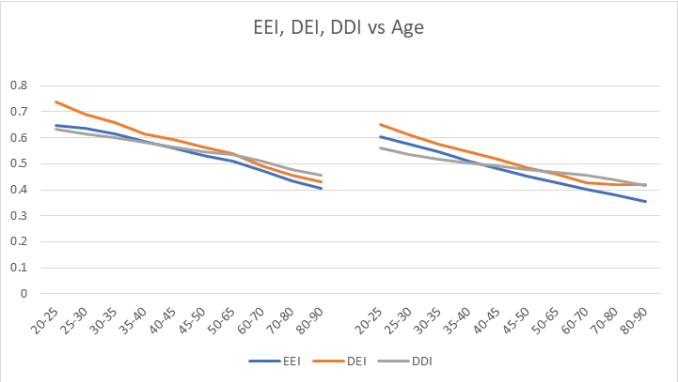

Figure 16. *EEI, DEI, and DDI versus age curves show a downward trend with age for both males (left) and females (right), indicating a linear decline.*

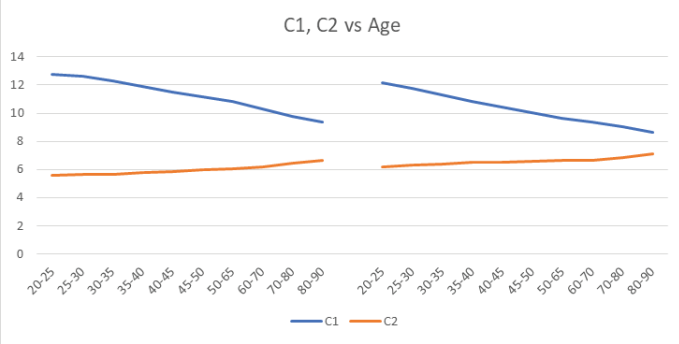

Figure 17. *Arterial Compliance, measured by C1 (large artery) and C2 (small artery), versus age: Male C1/C2 curves mirror the female C1/C2 curves, showing a downward trend. Both male and female C1 curves decreased with age, while the C2 curves increase with age.*

PAD and overall cardiovascular health [81]. Understanding these indices and their changes with age is critical for early detection of cardiovascular risks and the management of vascular diseases such as PAD.

Large Cohort Study 2: C1 and C2 [81]

The C1 and C2 indices, derived from a modified Windkessel model, provide valuable insights into the compliance of large and small arteries, respectively [228,229]. C1 reflects the compliance of large arteries, while C2 is primarily influenced by smaller arteries. Aging predominantly affects C1, leading to a decrease in the compliance of large arteries, while conditions such as hypertension and atherosclerosis tend to impact C2, causing an increase in the stiffness of small arteries [228-232].

In our study, we observed that C1 decreased with age, reflecting the stiffer nature of large arteries over time (Figure 17) [81]. In contrast, C2 showed a gradual increase, indicating growing stiffness in smaller arteries. The decline in large artery compliance (C1) was more pronounced than the increase in small artery compliance (C2), suggesting that aging has a greater impact on the elasticity of large arteries. Although males generally had higher C1 values compared to females, the age-related changes in both C1 and C2 were similar across genders.

These findings emphasize the significant role of aging in arterial stiffness, with a more pronounced effect on central arteries (C1) compared to peripheral arteries (C2). While all arterial stiffness indices (such as ABI, AI, EEI, DEI, DDI, C1, and C2) show a decline with age, the extent and pattern of this decline can vary by index and sex. For example, the large artery compliance (C1) showed a greater decrease than the smaller artery compliance (C2), but both types of arteries contribute to overall vascular health.

Our study also highlights the importance of considering both large and small artery compliance when assessing cardiovascular health, as both indices provide critical information about arterial function [81]. Given the variability in how these parameters change with age and health conditions, it's essential to measure multiple indices to gain a comprehensive understanding of vascular health. These indices, including ABI, AI, EEI, DEI, DDI, C1, and C2, are potentially useful for identifying individuals at risk of cardiovascular conditions like PAD and overall arterial dysfunction.

Furthermore, factors such as gender, lifestyle, and underlying health conditions can influence these parameters, and not all of them follow a linear relationship with age – some, such as C2, may only show significant changes in older individuals [187]. Therefore, incorporating multiple parameters into diagnostic and monitoring tools for arterial stiffness and PAD will enhance the accuracy of cardiovascular risk assessments and improve patient care strategies. Further research is needed to refine these tools and develop more effective approaches for early detection and management of vascular diseases.

Impact of Aging on Sudomotor Functions

The sympathetic branch of the ANS plays a crucial role in regulating sweating, which is essential for thermoregulation and maintaining fluid balance. Sweating is regulated by cholinergic fibers that innervate sweat glands, responding to environmental stimuli, temperature fluctuations, or emotional stress. This regulation is integral to the body's ability to maintain homeostasis, particularly in response to heat [233].

Sweating, or the sudomotor autonomic function, is critical in conjunction with cardiovascular control to maintain the body's core temperature at approximately 37°C. It operates through two main mechanisms: the dilation and constriction of cutaneous blood vessels, and the production of sweat [88]. These functions are primarily controlled by the hypothalamus, which processes input from thermoreceptors and adjusts body temperature using somatic motor fibers (to induce shivering) and sympathetic fibers (to control blood vessels and sweat glands) [88]. Sympathetic sudomotor pathways originate in the hypothalamus, travel through the pons and reticular medulla, and synapse in the intermediolateral column of the spinal cord, where cholinergic neurons influence sweat glands through unmyelinated C-fibers capable of producing up to 3.5 liters of sweat per day [88].

Sudomotor dysfunction refers to abnormal sweating patterns, which can present as either hyperhidrosis (excessive sweating) or hypohidrosis (reduced or absent sweating) [234-236]. Such dysfunction is often observed in patients with autonomic neuropathy due to conditions like diabetes mellitus, Parkinson's disease, and chronic alcohol use [237,238]. These conditions damage the sympathetic fibers that regulate sweat glands, leading to dysfunctional sweating responses. For instance, in diabetic autonomic neuropathy (DAN), reduced sweat production, especially in the lower extremities, can increase the risk of foot ulcers and delayed wound healing [233,239,240]. Conversely, in conditions like Parkinson's disease, excessive sympathetic stimulation can cause hyperhidrosis [237]. These sudomotor abnormalities not only impact daily life but also exacerbate other comorbid conditions, including vascular problems and skin infections.

Sudomotor dysfunction, whether it results in excessive or reduced sweating, can significantly impair a person's quality of life [88]. It can lead to heat intolerance, discomfort, and social embarrassment, especially in the case of hyperhidrosis [88]. Identifying these dysfunctions early is crucial, as they may signal SFNs before clinical symptoms become apparent [78,241]. Early detection of SFN is vital for preventing the progression of neuropathy and managing associated conditions.

Several tests are available for assessing sudomotor function, but they present challenges. Routine use is hindered by the need for specialized equipment and trained personnel, and many newer methods lack standardization, leading to variable results. Furthermore, sudomotor function can be influenced by external factors like humidity, temperature, hydration, medications, and skin treatments, all of which can introduce errors into results [108,242-245]. The gold standard for invasive assessment is a

punch biopsy, which is highly sensitive but impractical due to its invasive nature and associated risks [235,246]. Non-invasive methods like the Quantitative Sudomotor Axon Reflex Test (QSART) and Sympathetic Skin Response (SSR) are more patient-friendly but also have limitations [242]. Despite these challenges, sudomotor assessments remain one of the most sensitive methods for detecting SFNs.

Improvements in testing methodologies, along with standardization, are needed to enhance the clinical utility of sudomotor function tests and ensure more reliable diagnoses. These efforts will be crucial in detecting early neurophysiological changes and improving the management of autonomic neuropathies and other related conditions.

Large Cohort Study 3: SANI [82]

Quantitative assessment of sudomotor function is essential for evaluating autonomic dysfunction, confirming diagnoses, monitoring disease progression, and assessing the effectiveness of treatments. VitalScan-SudoCheck provides a comprehensive approach by measuring the ability of sweat glands to release chloride ions in response to electrical stimulation on the palms and feet. This method helps detect impairments in sweat gland innervation, which can be an early indicator of nerve damage, particularly in individuals with autonomic neuropathies.

A key feature of SudoCheck is its integration of multiple testing methods, including QSART, and SSR test. By combining these techniques, SudoCheck offers rapid and reliable results, which are reflected in the SANI. The SANI provides a risk index for sudomotor autonomic neuropathy, and it is particularly useful for monitoring aging populations and individuals with diabetes. This technology allows Medeia Inc. to develop reference ranges that track changes in sudomotor function as individuals age, offering valuable insights for clinicians.

Our study, which involved 143,900 participants, found that the SANI increased with age for both males and females (Figure 18) [82]. Although there were no statistically significant gender differences in the overall results, females had higher mean SANI values across most age groups. Notably, in the 20-25 age group, males had slightly higher SANI values than females, but this trend reversed as individuals age. The increase in SANI from youth to old age was comparable for both genders, with females exhibiting a slightly greater relative increase (55.34%) compared to males (53.21%). This suggests that females may be at a slightly higher risk of developing sudomotor autonomic neuropathy as they age.

These findings align with previous studies [26,247]. For example, Lee's study indicated that men typically demonstrate better sudomotor function than women, suggesting a lower risk of developing sudomotor autonomic neuropathy in males [247]. Similarly, Parashar et al. found that sudomotor function decreases with age, particularly in the elderly (60-80 years), a trend that was reflected in our study as the mean SANI values increased with age, indicating a greater risk of sudomotor autonomic neuropathy in older adults [26].

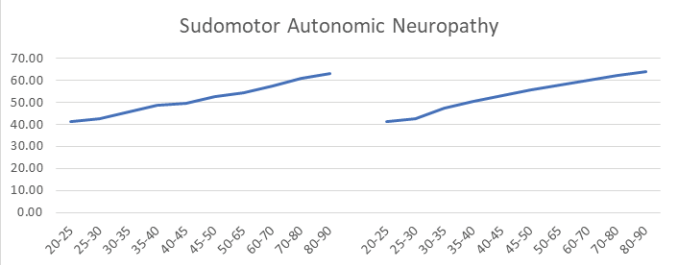

Figure 18. *Average Sudomotor Autonomic Neuropathy Index (SANI) versus age curves increase with age in both men (left) and women (right) aged 20-90 years, with both curves demonstrating a parallel upward trend.*

The effectiveness of VitalScan-SudoCheck in early detection of SFNs makes it a valuable tool for clinical settings. Its ability to provide rapid, non-invasive assessments of sudomotor function offers a promising approach for diagnosing and tracking autonomic neuropathies, especially in aging and diabetic populations. As research continues to refine and standardize sudomotor testing, the integration of SudoCheck could significantly improve patient care by enabling earlier diagnosis and more accurate monitoring of neuropathy progression.

Impact of Disease on ANS

The ANS plays a pivotal role in regulating numerous vital functions, including HR, BP, digestion, and temperature control. As a result, autonomic neuropathies – damage to the autonomic nerves – can lead to a wide variety of symptoms across various bodily systems (Table 1) [248]. These symptoms are often diverse and may affect several organs or systems simultaneously, making diagnosis and management challenging.

In the cardiovascular system, autonomic neuropathies can cause issues such as palpitations, tremors, and blurry vision, and difficulty regulating BP [69]. Individuals may experience lightheadedness, dizziness, or shortness of breath, and even fainting episodes, which result from impaired blood flow regulation [73,74]. Some patients also report chest pain, ringing in the ears (tinnitus), or discomfort in the lower extremities [69,73,74]. The cardiovascular symptoms are typically related to the autonomic dysfunction that disrupts the normal regulation of HR, BP, and vascular tone.

The nervous system can also be significantly affected, with patients often experiencing burning sensations in the feet,

Table 1. *A list of symptoms across various bodily systems due to autonomic neuropathies [248].*

Body System	Symptoms
Cardiovascular system	Palpitations, tremors, blurry vision, lightheadedness, dizziness, shortness of breath, chest pain, fainting
Gastrointestinal system	Diarrhea or constipation, early satiety, difficulty swallowing, incontinence, reduced saliva production, gastroparesis, vomiting
Genitourinary system	Erectile dysfunction, sexual dysfunction, urinary urgency, retention, incontinence, nocturia, incomplete bladder emptying
Integumentary system	Pale skin, inability to sweat (sometimes on one side of the face), itching, hypersensitivity, dry skin, cold feet, brittle nails, hair loss on lower legs
Nervous system	Burning feet, difficulty regulating body temperature
Ocular system	Blurred vision, light sensitivity, tunnel vision, difficulty focusing, reduced tearing, changes in papillary size
Respiratory system	Impaired bronchoconstriction, poor response to low blood oxygen levels

difficulty maintaining body temperature, and issues with sweating [246,249,250]. These symptoms occur due to damage to small nerve fibers, which are responsible for sensations and regulating temperature. As the nervous system becomes involved, patients may find it difficult to manage homeostasis, leading to discomfort, heat intolerance, and sometimes, an inability to regulate sweating.

In summary, autonomic neuropathies can manifest in a wide range of symptoms, which may vary depending on which parts of the ANS are affected. Symptoms can evolve over time as more areas of the ANS become involved, and they often present in complex, overlapping ways. Given the breadth and variability of symptoms, healthcare providers must closely monitor patients with autonomic neuropathies for any changes in symptoms or the emergence of new signs of dysfunction. Early detection and intervention are crucial for managing these conditions and improving patient outcomes.

ANS and Alcoholism [80]

Autonomic neuropathy can result from a wide range of conditions, diseases, medications, and surgical procedures (Table 2), with chronic alcohol consumption being one of the most common causes [248]. Alcohol toxicity leads to damage of both peripheral and autonomic nerve fibers, impairing their function over time. This damage disrupts axonal transport and weakens nerve structures, leading to autonomic dysfunction. As alcohol progressively damages autonomic nerves, individuals may experience a range of cardiovascular, neurological, and systemic issues.

Table 2. *A list of common causes of autonomic neuropathies and their effects [248].*

Common Cause	Effects
Alcoholism	Chronic alcohol use can damage nerves, impair axonal transport, and affect nerve structure, leading to autonomic dysfunction.
Amyloidosis	In this condition, abnormal protein deposits damage organs and tissues, commonly causing autonomic dysfunction.
Autoimmune Diseases	Conditions such as acute intermittent porphyria, Holmes-Adie syndrome, and multiple sclerosis can involve the immune system attacking body tissues, including nerves, leading to autonomic dysfunction
Diabetes	The most common cause of autonomic neuropathy, diabetes can damage both sensory and motor nerves, contributing to neuropathy.
Medications	Certain drugs used to treat other conditions may have side effects that affect the autonomic nervous system.
Multiple System Atrophy	A neurological disorder that causes nerve cell degeneration, leading to problems with autonomic functions, movement, and balance.
Nerve Damage	Physical trauma or surgery can result in autonomic dysfunction due to nerve injury.

Chronic alcohol consumption affects several physiological, behavioral, psychological, and perceptual processes. Ethanol, a potent central nervous system depressant, is particularly harmful to autonomic nerve fibers. This damage can lead to autonomic imbalance, arrhythmias, and cardiovascular problems [251]. Research from the Global Burden of Disease study (2020) highlighted that 59.1% of individuals aged 15-39 consume harmful amounts of alcohol, with males representing 76.9% of this group [252]. Alcohol consumption has become a leading cause of death, especially for males aged 15-49 [252]. Moreover, alcohol intoxication impairs heart function and reduces HRV, which has been linked to poor health outcomes, including higher cardiovascular risk [253].

In particular, alcohol dependence is associated with neurotoxic effects that can lead to CAN. CAN is characterized by diminished PNS activity and increased SNS dominance, both of which contribute to cardiovascular risk. Early-stage CAN often remains undetected during routine exams, making the analysis of HRV an essential tool for early diagnosis and prognosis [251,254].

Our study of 34 individuals exposed to alcohol toxicity demonstrated significant autonomic changes (Table 3) [80]. We found a high LF/HF ratio in alcoholics, indicative of reduced parasympathetic tone, which suggests the presence of autonomic imbalance. The LF/HF ratio, which indicates the balance between the sympathetic and parasympathetic systems,

Condition	Sample (n)	HRV Metric	Mean	Standard Deviation (SD)	Sensitivity	Specificity
Alcohol Toxicity	34	LF/HF	6.7	4.1	70.9	88.8
Cancer	165	HR	41.2	9.8	72.4	70.5
T2DM	1,267	HR	42.1	10.3	76.6	74.7

was tripled in alcohol-dependent individuals (AD group) compared to sedentary controls [255]. This suggests a dominant SNS, particularly during physical stress, and aligns with Hans Selye's general adaptation syndrome, where stress triggers sympathetic activation and reduces PNS function [256]. The VitalScan-derived LF/HF ratio proved to be a reliable marker for detecting alcohol toxicity, with high specificity (88.8%) and sensitivity (70.9%) (Table 3).

These findings are consistent with those of Muthuswamy et al., who reported similar autonomic dysfunction in alcohol-dependent individuals, with reduced parasympathetic and heightened sympathetic activity [251,257,258]. The elevated LF/HF ratio is indicative of alcohol-induced cardiac autonomic dysfunction, a pattern commonly observed in alcoholics, particularly those with alcoholic cardiomyopathy [253,254,259-261].

Overall, these results emphasize the importance of HRV analysis as a non-invasive and effective tool for assessing autonomic dysfunction and cardiac risk in individuals with alcohol dependence. Early identification of autonomic imbalance could facilitate timely clinical interventions, such as detoxification and rehabilitation, and potentially reduce the risk of alcohol-related cardiovascular issues and sudden cardiac events. Moreover, HRV analysis could also be useful in diagnosing and predicting outcomes in patients with other chronic conditions, such as cancer and T2DM.

ANS and Cancer [80]

ANS dysregulation is commonly observed in several conditions, including depression, schizophrenia, multiple sclerosis, and cancer, characterized by reduced parasympathetic activity and increased sympathetic dominance [262-265]. Time domain measures of HRV, established tool in cardiology and diabetes research, is increasingly being applied in cancer studies as a measure of autonomic function [266]. Despite advancements in cancer treatments, cancer remains a leading cause of death, and HRV has emerged as a valuable prognostic tool, helping predict and monitor cancer-related outcomes [267-270].

Studies have highlighted a significant correlation between autonomic dysfunction and cancer. Common symptoms in advanced cancer patients, such as irregular sweating, orthostatic hypotension, and bladder or bowel dysfunction, may be linked to autonomic dysfunction [271]. The dysfunction can result from reduced physical activity, medications, or paraneoplastic processes [272-277]. However, the precise role of autonomic dysfunction in cancer prognosis remains unclear, with linkage between autonomic dysfunction and shorter survival [278-282].

Evidence from studies on cancer patients indicates significantly reduced parasympathetic activity. For example, cancer patients exhibit reduced E/I ratios and resting HR, suggesting impaired cardiovascular parasympathetic control [271,283-285]. Our study, involving 165 patients, found that the autonomic tone of these patients (n=165) closely resembled that of individuals aged 80-90, with a mean HR of 41.2±9.8 beats per minute (bpm), similar to the HR of male patients in that age group (41.41±16.42 bpm) [80]. This suggests that the autonomic dysfunction in cancer patients may mirror the physiological changes typically seen in older age.

Ben-David's research on 798 cancer patients revealed progressively reduced HRV metrics as cancer advanced [286]. Key HRV parameters such as SDNN and RMSSD were lower in advanced stages of cancer, independent of comorbidities like cardiovascular disease or diabetes. These findings suggest that HRV could serve as a non-invasive marker for cancer detection and staging [286]. Moreover, lower HRV is associated with poorer prognosis, and increased sympathetic drive in advanced cancer stages may contribute to tumor growth and metastasis [268,280, 287-293].

Chemotherapy can also affect the ANS, typically leading to reduced HRV. The extent of this reduction varies depending on the specific chemotherapy drugs used [268,294,295]. Short-term HRV recordings may not fully capture chemotherapy's effect, with drugs like vincristine and doxorubicin associated with reduced HRV, reflecting an imbalance in the ANS [268,295-299]. Despite mixed findings regarding chemotherapy's impact on HRV, the overall trend suggests sympathetic dominance, which could contribute to higher metabolic stress and poorer health outcomes [300,301]. The decline in ANS function with age, coupled with the impact of comorbidities, is well-documented [87]. Additionally, medications can influence both ANS and cardiovascular responses, potentially complicating study outcomes. Further research is needed to fully understand HRV's role in cancer prognosis, particularly in advanced stages, and its potential as a tool for evaluating the impact of cancer treatments.

ANS and Diabetes

Cardiovascular Functions

Diabetes, particularly T2DM, is the most common cause of autonomic neuropathy, a condition where nerve damage leads to dysfunction in the ANS. Chronic high blood glucose levels, common in diabetes, can lead to nerve damage, particularly affecting both sensory and motor nerves. Over time, this impairs the function of various bodily systems controlled by the ANS, including cardiovascular and digestive systems. T2DM is notably linked to both vascular dysfunction and autonomic imbalance, which can progress together, further increasing complications [131].

T2DM is marked by abnormal metabolism, and impaired autonomic function plays a significant role in its development [302]. Overactive SNS activity in diabetes is associated with reduced sensitivity to β-adrenergic receptors, leading to increased vascular resistance, elevated HR, and higher sodium retention [303-305]. Such changes contribute to the progression of the disease and increase the risk of cardiovascular issues, including atherosclerosis. Early research suggests that autonomic dysfunction could even contribute to the development of T2DM, with excess SNS activity linked to higher risk of cardiovascular events [306].

CAN is one of the most significant complications of autonomic dysfunction in diabetes. CAN affects up to 73% of individuals with T2DM, and up to 90% in those with long-standing T1DM [97,307,308]. CAN often starts as a subclinical condition, with early signs including reduced HRV, a marker of autonomic imbalance (309-311). In clinical practice, the diagnosis of CAN is typically made using the five standard cardiovascular autonomic reflex tests (CARTs), which assess HR responses to various stressors like deep breathing, standing, and the Valsalva maneuver [121,312]. These tests help diagnose CAN in its clinical stages, though they may miss subclinical CAN [312], making early HRV monitoring essential for early detection [311,312].

Studies have confirmed that reduced HRV is a common finding in T2DM patients, often detectable even in pre-diabetes

[313]. HRV decreases as a result of the adverse effects of prolonged hyperglycemia on autonomic function. Factors such as dyslipidemia and hypertension exacerbate this decline [116,314-319]. In a study by Benichou et al., HRV parameters like SDNN, RMSSD, and both LF and HF components were significantly reduced in individuals with T2DM [319].

Parasympathetic dysfunction is more prominent than sympathetic dysfunction in T2DM [320]. This is especially important because parasympathetic dysfunction, which involves reduced parasympathetic tone (vagal activity), often precedes sympathetic dysfunction and serves as an early indicator of autonomic imbalance. Goit et al. found that parasympathetic dysfunction was more severe in T2DM patients and correlated with the disease's progression [320]. The combination of hyperglycemia and advancing age further impairs parasympathetic function, leading to higher HRs and reduced HRV, characteristics commonly seen in elderly individuals [321-323].

HRV is a valuable early marker for assessing the progression of T2DM-related complications. For instance, we found that the HRs of T2DM patients (n=1,267) were comparable to those of individuals aged 80-90, further demonstrating that autonomic dysfunction in diabetes leads to premature aging of cardiovascular function [80]. While there is no universally agreed-upon threshold for diagnosing CAN through HRV, researchers have proposed criteria for abnormal HRV values [315,319,324-328]. Monitoring these parameters using tools like VitalScan-ANS can help detect autonomic dysfunction early and guide interventions to prevent severe cardiovascular complications.

The VitalScan-ANS test, for example, has been found to be a reliable tool for detecting autonomic dysfunction in individuals with T2DM, offering high sensitivity (76.6%) and specificity (74.7%) [80]. It helps monitor changes in HRV, which reflects the balance between sympathetic and parasympathetic activity. Early intervention, especially through HRV monitoring, can mitigate the progression of CAN and improve long-term health outcomes for individuals with diabetes.

In conclusion, HRV is a crucial diagnostic tool in the assessment of autonomic dysfunction, particularly in diabetes. As a non-invasive and early indicator, HRV can help clinicians detect CAN before clinical symptoms appear. With regular monitoring, particularly through technologies like the VitalScan-ANS system, healthcare providers can intervene early to prevent cardiovascular complications, improve patient quality of life, and reduce the long-term risks associated with autonomic neuropathy. Further research is needed to refine HRV-based diagnostic thresholds and better understand its role in managing diabetes-related complications [313,329]. Understanding the intricate link between HRV, blood glucose control, and autonomic dysfunction is essential for developing more targeted treatment strategies and improving patient outcomes in diabetes [313,330,331].

Sudomotor Functions

The VitalScan-SudoCheck system is a cutting-edge tool for diagnosing DAN, particularly sudomotor dysfunction (SMD), which is a common manifestation of the disease [94]. Diabetes can cause damage to small, non-myelinated nerve fibers, especially those that regulate sweat glands, leading to early dysfunction. This dysfunction often occurs before overt clinical symptoms appear, making early detection critical in preventing severe complications, like foot ulcers, infections, and even amputations [102,249,332]. The VitalScan-SudoCheck device is non-invasive and measures sweat response at multiple sites on the body after bioimpedance stimulation, assessing the integrity of the postganglionic sudomotor system. This enables early identification of autonomic dysfunction, which is crucial for timely intervention and management.

SMD in diabetes is primarily characterized by reduced or absent sweating, particularly in the feet [240,333,334]. This dysfunction leads to dry, cracked skin, which increases the risk of foot ulcers—one of the leading causes of amputations in diabetic patients [102,249,332]. Sympathetic SMD also impairs temperature regulation, causing heat intolerance and fluctuations in body temperature [335]. SMD is a key feature of diabetic peripheral neuropathy (DPN), which affects a significant portion of both T1DM and T2DM individuals [78,241]. Approximately 50% of diabetic patients experience DPN, which increases the likelihood of foot ulcers and other complications, including infections [235,336,337].

In diabetes, small nerve fibers, particularly C fibers that innervate sweat glands, are especially vulnerable to damage [246,250,338-341]. The metabolic effects of chronic hyperglycemia, such as oxidative stress and inflammation, contribute to this damage [342-347]. Research has shown that nerve fiber density in sweat glands correlates with glycemic control, including HbA1c levels, meaning poor blood sugar management accelerates nerve damage [348]. Furthermore, SMD can be observed even before the clinical onset of diabetes, in individuals with impaired glucose tolerance or metabolic syndrome [349,350]. Early signs of diabetic neuropathy, such as SFN, can appear prior to more extensive nerve damage [351,352].

The VitalScan-SudoCheck provides valuable insights into the health of the sudomotor system by calculating a SANI. This index helps in diagnosing sudomotor autonomic neuropathy, a condition often caused by diabetes. The system's high sensitivity and specificity – 74.3% and 72.8%, respectively – make it an effective tool for early diagnosis. In a study of 2,560 T2DM patients, it was found that the mean SANI score for T2DM patients (69.7±12.3) was similar to those aged 80-90 years, indicating that T2DM patients may experience autonomic neuropathy at a younger age [82]. Moreover, T2DM patients exhibited higher SANI scores than non-diabetic individuals across various age groups, reinforcing the link between diabetes and an increased risk of autonomic dysfunction.

The American Diabetes Association recommends annual screening for peripheral and autonomic neuropathy in diabetic patients to detect early signs of DAN [83]. The VitalScan-SudoCheck system aligns with this recommendation by providing an effective, non-invasive method to assess sudomotor function. It offers faster, more comprehensive results compared to traditional diagnostic methods, which can help physicians intervene early, preventing complications like foot ulcers, infections, and heat intolerance, and ultimately improving patient quality of life. Sudomotor dysfunction is often an early indicator of neuropathy, and its early detection is crucial to prevent severe complications [78,99,235,242,353-361].

The VitalScan-SudoCheck system is grounded in over a decade of peered reviewed research. The goal of establishing a reference range for the SANI is to facilitate early detection of autonomic neuropathy in large populations, especially those with diabetes. By targeting high-risk groups, such as the aging population and individuals with diabetes, the system enables

timely interventions that could prevent the progression of diabetic neuropathy and related complications. While invasive tests like skin biopsies remain the gold standard, the VitalScan-SudoCheck offers a faster, less resource-intensive alternative with broad potential for population screening [362-365].

Conclusion

The ANS is critical in maintaining homeostasis and regulating various physiological processes, including cardiovascular, respiratory, digestive, and thermoregulatory functions. Dysregulation of the ANS is implicated in a wide range of diseases, including diabetes, cancer, and other conditions, often leading to significant complications. As discussed, autonomic dysfunction—whether in the form of autonomic neuropathy or sympathetic-parasympathetic imbalances—is commonly associated with these diseases, significantly affecting patient outcomes and overall health.

The role of HRV in assessing autonomic function has emerged as a valuable diagnostic tool, particularly in diabetes and cancer. Studies consistently highlight the importance of HRV as an early indicator of autonomic imbalances, with changes in parasympathetic and sympathetic activity reflecting the severity and progression of disease. DAN, for example, is particularly prevalent in individuals with poorly controlled T2DM, and HRV reductions, along with tests assessing sudomotor function, have become essential for diagnosing and managing complications like CAN and SMD.

Emerging diagnostic tools, such as the VitalScan-ANS, VitalScan-Vascular+, and VitalScan-SudoCheck systems, have proven to be critical in detecting early-stage autonomic dysfunction. These systems provide valuable insights for timely intervention, reducing the risk of complications like foot ulcers, infections, and even amputations in diabetic patients. Its ability to monitor and assess autonomic imbalance makes it an essential tool for improving patient management, particularly in populations at higher risk, such as aging individuals or those with long-standing diabetes.

Overall, this review emphasizes the critical need for continuous research to better understand the full scope of ANS dysregulation in various diseases, particularly in chronic conditions like diabetes and cancer. As our understanding of the relationship between autonomic dysfunction, aging population, disease progression, and patient outcomes grows, incorporating advanced diagnostic technologies like HRV analysis and VitalScan will enhance the accuracy and effectiveness of early detection, leading to improved disease management and patient care. These advancements hold great potential to mitigate the impact of autonomic dysfunction, prevent serious complications, and ultimately improve the quality of life for individuals affected by these conditions. Future research should aim to refine these diagnostic tools, standardize their clinical application, and expand their use across diverse populations to facilitate more effective management of autonomic dysfunction and related complications.

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