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Discussion Kernel

Can the vagus nerve serve as biomarker for *vata dosha* activity?

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ABSTRACT

This 'discussion paper' raises 'provocative questions' to identify physiological systems underlying *vata dosha* and candidate biomarkers for *vata* activity. We explained the strong correlations between survival and homeostatic functions of the parasympathetic vagus nerve, and functions governed by the five major sub-types of *vata dosha* (*Praana, Udana, Vyaana, Samaana,* and *Apana*). Four reasons were provided to hypothesize that vagal activity is a reliable candidate biomarker of important *vata dosha* functions. First, normal *vata dosha* and the vagus maintain neural, respiratory, and digestive homeostasis, and dysfunctions in both entities cause very similar diseases. Second, *vata dosha* regulates higher neural functions such as mental health and behaviour, and the 'polyvagal theory' proposes similar functions for the vagus. Third, the similar roles of *vata dosha* and vagus in maintaining gut homeostasis, suggest that vagal activity in the 'gut-brain' link is a candidate biomarker of *pakwashaya* (lower gut), a primary regulatory site for *vata dosha*. Fourth, the vagus is the only vital nerve whose activity can be reliably measured and manipulated. Indeed, vagal nerve stimulation is a USA-FDA approved therapy for certain ailments attributed to impaired *vata dosha.* No other nerve or *dosha,* has such multi-functional and life-sustaining properties. These arguments position vagal activity as a suitable candidate biomarker for certain functions of *vata dosha*.

1. Introduction

OMICS studies have made important contributions by proving that specific genotypes and phenotypes are significantly correlated with each of the 3 major *dosha-prakritis*. Thus, individuals of major prakritis (*vata, pitta, and kapha*) show statistically significant, differential expression of genes, single nucleotide polymorphisms and specific plasma metabolites [1–3]. Notably, individuals of *vata dosha prakriti* versus *kapha dosha prakriti,* showed significantly different values of body mass index [4]. *Doshas* are considered as forces/entities which cannot be equated with a specific biological system, organ, cell type, or signalling pathway. However, deciphering the physiological systems underlying *doshas* would significantly contribute to biomarker development [5]. This 'discussion paper' formulates scientific hypotheses to identify biomarkers for *vata dosha.* These hypotheses are developed as answers to 'provocative questions' on the link between *vata dosha* and the nervous system, and are based on three premises. First, ayurvedic clinical practice involves assessment and treatment of *vata dosha* abnormalities. Since *vata dosha* is evaluated, manipulated, and rectified, it should be possible to identify the major neurological component underlying *vata dosha.* Second, this neurological component should explain major functions of *vata dosha* and provide insights on its regulation. Third, this neurological component should provide candidate biomarkers that estimate functional status of some aspects of normal and abnormal *vata dosha* in modern medical terms.

1.1. Vata dosha and the nervous system

Of the three *doshas*, *vata* is undoubtedly the most fundamental and crucial *dosha* for survival [[6] (Sootrasthana/Chapter 12/Verse 7–8)]. *Vata* is derived from the root words *gati* (movement) and *gandhana* (senses) [[7] (Sootrasthana/Chapter 21/Verse 5)]. Just as nerve impulses instantly convey information from one body part to another, *vata dosha* is *daruna* (with severe impacts), *bahu-śighra* and *anavasthita* (constantly moving) [[6] (Sootrasthana/Chapter 12/

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Verse 3) [7], (Nidanasthana/Chapter 1/Verse 8)]. These classical descriptions have prompted reports to link major functions of normal *vata dosha* with the nervous system [8]. Indeed, two articles carefully assigned *vata* sub-types to specific neural functions, and their control centers within the nervous system [9,10]. Conversely, impaired *vata dosha* results in mental diseases such as *vishada* and *anavasthita chithata* [[11] (Sootrasthana/Chapter 20/Verse9)]. Brain injury/*shiras marma,* and *marmabhighata,* also cause different fatal conditions ranging from *vata vyadhi* to sudden death [[6](Chikitsasthana/Chapter 28/Verse 6) [7], (Shareerasthana/Chapter 6/Verse 27)].

Vata is the primary force underlying normal sensory and motor functions for survival and maintenance of normal health (homeostasis). Notably, impaired *vata dosha* is directly correlated with serious neurological disorders [[6] (Chikitsasthana/Chapter 28/Verse 6) [7], (Shareerasthana/Chapter 6/Verse 27) ([11] Sootrasthana/Chapter 20/Verse 9)]. Therefore, ayurvedic texts provide a firm basis for a physiological and functional link between *vata dosha* and the nervous system.

2. Methods

Provocative questions (PQs) were raised to identify neurological systems that best represent *vata dosha.* This idea comes from the 'PQ' initiative of the National Cancer Institute (NCI), USA. *"Provocative Questions address non-obvious, understudied, and paradoxical questions in cancer research"* (https://provocativequestions.nci.nih.gov/). Our hypothesis aims to identify a suitable candidate biomarker for vata dosha activity. It is comprised of eight provocative questions (PQ) with suitable answers.

Together, these eight PQs were examined for relevant information from Ayurvedic texts, Neurophysiology, and Clinical studies. We could obtain sufficient evidence to hypothesize that the vagal activity is a candidate biomarker for certain functions of *vata dosha*.

PQ-1: The autonomic nervous system and *vata dosha* are essential for survival and homeostasis. Is there a functional correlation between them?

Linking the autonomic nervous system with *Vata Dosha*: Ayurveda links a healthy *vata dosha* with functions governing basic survival and homeostasis. Thus, the terms *'aashukari'* and *'pranamscha uparunadhi'* describe negative consequences of impaired *vata dosha*, and imply that normal *vata dosha* is essential for survival [[6] (Sootrasthana/Chapter 12/Verse 9) [7], (Nidanasthana/Chapter 1/Verse 8)]. Similarly, homeostatic functions of *vata dosha* explained as *'tantra yantra dhara'*, maintain normalcy [[6] (Sootrasthana/Chapter 12/Verse 7–8)]. Survival and homeostasis are controlled by the ANS which works involuntarily ('automatically'), without our conscious effort. The ANS regulates vital functions of the cardiovascular, gastrointestinal, excretory and reproductive systems. With few exceptions, these vital functions are turned 'on' and 'off' by the sympathetic and parasympathetic components of the ANS, respectively [12].

Linking the autonomic nervous system with *vata* sub-types: *Praana vata***:** *Praana vata* is responsible for protective reflexes required for survival. Six of these reflexes are in Table 1 [[13] (Sootrasthana/Chapter 12/Verse 4)]. Accordingly, *praana vata* is correlated with involuntary survival functions of the ANS (pupil response, sneezing, swallowing, and vomiting). Since *praana vata* stabilizes cardiac functions and circulation, Table 1 correlates *praana vata* with respiration and regulation of heart rate and blood pressure [[11] (Sootrasthana/Chapter 20/Verse 2)]. Impaired *praana vata* causes diseases of upper respiratory tract, cardiovascular system, and death [[7](Nidanasthana/Chapter 1/Verse 13)].

Udaana vata: In the chest, *udaana vata* controls energy, speech, and intellect [[13] (Sootrasthana/Chapter 12/Verse 5)]. Since speech and strength require normal respiratory and cardiac function, Table 1 correlates *udaana vata* with homeostatic functions regulating respiration and heart rate. Impaired *udaana vata* causes altered sensory perception, speech disorders, and cognitive disorders such as memory deficits [[7] (Nidanasthana/Chapter 1/Verse 14–15)].

Vyaana vata: *Vyaana vata* controls voluntary physical movement, and is required for peripheral blood circulation [[7] (Nidanasthana/Chapter 1/Verse 13) [13], (Sootrasthana/Chapter 12/Verse 7)]. Since circulation depends on partially voluntary functions such as respiration, which influences heart rate and blood pressure; Table 1 correlates *vyaana vata* with these partially voluntary functions of the ANS.

Samaana vata: *Samaana and apana vata* together constitute gastrointestinal functions [[13] (Sootrasthana/Chapter 12/Verse 8), 13 (Sootrasthana/Chapter12/Verse 9)]. Susrutha mentions *samaana vata* as the basis for *viveka* (digestion, absorption and segregation of waste) [[7] (Sootrasthana/Chapter 15/Verse 3)]. Accordingly, Table 1 shows *samaana vata* corresponding to regulation of digestion by the ANS. Impaired *samaana vata* causes reduced digestive capacity and gastrointestinal motility [[7] (Nidanasthana/Chapter 1/Verse 16)].

Apana vata: *Apana vata* is mentioned as the cause for *dharana* (controller of natural urges/excretory reflex) [[7] (Sootrasthana/Chapter 15/Verse3)]. Thus, Table 1 correlates *apana vata* with autonomic pelvic reflexes required for excretion and sexual activity. Diseases of the lower gastrointestinal and genitourinary tracts result from impaired *apana vata* [[7] (Nidanasthana/Chapter 1/Verse 16].

In summary, Table 1 shows that the vagus controls functions attributed to the four sub-types of *vata dosha (praana, udaana, samaana,* and *apana*). Interestingly, the vagus nerve also has four 'nuclei' (control points) that regulate the cardiovascular, respiratory, and digestive systems [12,14]. The vagus is the longest cranial nerve in the parasympathetic component of the ANS, and is critical to survival because it links the brain stem with the gut, heart, and lungs. Notably, these same organs are also the most active sites of *vata dosha,* which is crucial for survival (*ayusha pratyayabhuta*) [[6] (Sootrasthana/Chapter 12/Verse 7–8)].

PQ-2: If vagal nerve activity accounts for key survival and homeostatic functions of *vata dosha*, can it serve as a biomarker for *vata* activity?

Defining a suitable biomarker for *vata dosha*: The World Health Organization (WHO), the United Nations, and the International Labor Organization, define a biomarker as *"any substance, structure, or process, that can be measured in the body or its products, and influence or predict the incidence of outcome or disease"* [15]. While *vata dosha* is essential for survival, monitoring survival is unacceptable for human clinical research. Therefore, a useful biomarker of *vata dosha* should estimate normal or abnormal homeostatic functions attributed to *vata dosha*. Table 1 clearly shows that normal activities of *vata dosha* and the vagus nerve maintain homeostasis of the neural, respiratory, and digestive systems. Table 2 shows that abnormal functioning of both *vata dosha* and the vagus nerve, cause similar disorders in these same systems [[6] (Ckikitsasthana/Chapter 28/Verse 6) [11], (Sootrasthana/Chapter 20/Verse 9) [13], (Chikitsasthana/Chapter 9/Verse 121–123) [13], (Nidanasthana/Chapter 7/Verse 10–14)], [14,16,17]. Notably, the vagus nerve also has the pervasive, dynamic, and multi-functional properties of *vata dosha*. Such properties require 'high connectivity', and the *"vagus nerve can form a 'connectome' for many functions, which means that interventions via the vagus have the potential to help*

Table 1
Functional Correlation between *Vata* sub-types and the Vagus.

Autonomic Nervous System (ANS) Functions	Functions Controlled by Vagus	*Vata Sub-Types*	Functions Controlled By *Vata* Sub-Types
Pupil response	Swallowing	*Praana*	*Shteevana* (salivation)
Sneezing	Vomiting		*Kshavathu* (sneezing)
Swallowing			*Udgaara* (hiccups)
Vomiting			*Prachwaasa* (expiration)
			Uchwaasa (inspiration)
			Anna praveshana (swallowing)
Respiration	Respiration	*Praana*	*Hrudaya dharanam* (cardiac stability)
Heart rate	Heart rate		*Dhamani dharanam* (circulatory stability)
Blood Pressure	Blood Pressure	*Udaana*	*Vaak pravrutti* (speech)
			Urja (tolerance/stamina)
			Bala (energy), *Dhee* (intellect)
Respiration	Respiration	*Vyaana*	*Rasa samvahana* (peripheral circulation)
Heart rate	Heart rate		Cardiac function
Blood Pressure	Blood Pressure		
Digestion	Gastric secretions and motility	*Samaana*	*Viveka* (digestion, absorption and segregation of waste)
	Blood Sugar		*Anna grahana, paachana, vivechana and munchana* (Gastrointestinal functions)
	Intestinal inflammation		
Urination	kidney function	*Apana*	*Shakrut nishkramana* (intestinal motility)
Defecation	Fertility		Dharana (excretory reflex)
Sexual drive	Sexual activity		*Shukra nishkramana and Artava nishkramana* (sexual activity)

Autonomic Nervous System (ANS) functions are involuntary or partially voluntary (bold). Most survival and homeostasis functions governed by the five sub-types of *Vata*, are also controlled by the vagus nerve of the ANS.

with the recovery of multiple functions" [18]. Key reasons for the vagus nerve as *'connectome'*, include its enormous length and innervation to all major organs. Thus, afferent, sensory vagal fibres convey signals from different organs to the brain; which responds via efferent, vagal motor branches to individual organs. This network of vagal nerve fibres ensures homeostasis of all organs [12,14]. The *'connectome'* concept further expands, since the vagus also interacts with the neuroendocrine system [19]. Overall, the information in Tables 1 and 2 and the *'connectome'* concept, suggest that vagal activity can serve as a candidate biomarker for *vata dosha* activity.

PQ-3: Besides regulating survival and homeostasis, *vata dosha* controls higher neural functions. Does the vagus regulate higher neural functions?

The vagus was only considered as a major parasympathetic nerve. The polyvagal theory proposes additional 'neuroception' functions for the vagus. *Vata dosha* is the most crucial factor in mental well-being (*niyanta, praneta cha manasa*) [[6] (Sootrasthana/Chapter 12/Verse 7–8)]. Just as yoga and *pranayama* are thought to improve *vata dosha* status, some practitioners of yoga experienced increased vagal activity, improved autonomic functions, mood, and cognition [19]. These clinical results suggest that the brain senses changing mind–body interactions, and accordingly modulates vagal parasympathetic activity and 'higher' neural functions. Indeed, the 'polyvagal theory' proposes hierarchical levels of vagal activity beginning with regulation of gut homeostasis and ending with "neuroception" functions such as cognition, emotional expression, resilience, and social engagement [20]. Thus far, clinical research upholds the polyvagal theory [21,22].

Both *vata dosha* and the vagus regulate and integrate vital neurological functions that ensure survival, homeostasis, mental health, and social behaviour. No other *dosha* or nerve has such multi-functional and life-sustaining properties (Table 1). Indeed, *vata dosha* and the vagus can be considered quintessential '*connectomes*'.

PQ-4: *Vata dosha* is primarily regulated at the gut. Can vagal activity in the 'gut-brain' link be a biomarker for processes that regulate *vata dosha*?

Vagus and *vata dosha* are major regulators of gut homeostasis. The gut-brain interaction involves communication between the enteric nervous system (ENS), and the ANS. Although the ENS ('second brain') independently controls some gastro-intestinal functions [16,23], extensive ENS-ANS interactions occur via a physiological and anatomical 'gut-brain' link, which operates via

Table 2
Disorders caused by Dysfunctional *Vata Dosha* and Vagus.

Vagus Dysfunction	*Vata* Dysfunction
Difficult Swallowing	*Niswasa uchwasa samrodha,* (Breathlessness)
Impaired Cough	*Swasa, kasa* (Asthma, Cough)
Mood Disorders	*Vishada* (Depression)
	Samjna moha, moha, pralapa (Reduced cognition)
	Indreeya bhramsha (Altered perception)
Fainting, Seizures	*Kampa, Gatra sphurana, Aakshepa* (Body Tremors)
Bradycardia	*Hridroga* (Cardiovascular Diseases)
	Alpa bhashana (Speech disorders)
Gastroparesis (Delayed Gastric Emptying)	*Agni sada* (Reduced digestive capacity)
	Vit mootra vata graham, adhmana (Reduced Gastrointestinal Motility)
Nausea, Spasms	*Chardi, Praseka* (Nausea)
Obesity	*Ati-sthoulya*

Respiratory, Mental, Cardiac, and Digestive disorders result from dysfunctional *Vata Dosha* and Vagus.

specific branches of the vagus [16,23]. Thus, gastric and hepatic vagal afferent branches send signals about appetite, stress, food intake, and food composition, via the 'gut-brain' link to the brain. The brain responds via vagal efferent branches which directly or indirectly signal different target organs by triggering release of certain enteric hormones. Therefore, vagal signalling via the 'gut-brain' link enables maintenance of gut homeostasis, regulation of gut inflammation, and certain functions of the immune system [16,19,23,24]. Recently, these same functions were attributed to the 'gut microbiome'. This is not a contradiction, since vagal activity in the 'gut-brain' link is strongly influenced by the gut microbiome [25,26].

Pakwashaya (large intestine), is the site of daily *vata dosha* production during the last stage of digestion (*'katu-avasthapaka'*). Therefore, *vata* functions originate within the gut/*koshta* (gastro-intestinal tract), which is termed *koshtasthavata.* It is inferred that *koshtasthavata* formed at the level of *pakwashaya* influences *apana vata*, which functions at the level of *pakwashaya. Apana vata* then interacts with *samaana vata*, since both these sub-types of *vata* function at varied levels of *koshta. Ahara rasa* at *koshta* is converted to *rasa dhathu* which is carried to *hrudaya*, and transported to different body parts by *vyana vata* [[11] (Nidanasthana/Chapter 20/Verse 2)]. Therefore, *vata dosha* functioning at the level of *koshta* has direct access to *ahara rasa* and *rasa dhatu* (end product of digestion). For these reasons, gut homeostasis and overall nutrient status are dependent on integrity of *koshta* and *pakwashaya* [[13] (Sootrasthana/Chapter 12/Verse 1)]. Accordingly, prolonged abnormality of *koshtasthavata* can hamper functions of all sub-types of *vata.* Thus, the five sub-types of *vata dosha* require nourishment and support of *koshtasthavata*-as mentioned *'panchatmake vayukoshte pradurbhavati'* [[11] (Shareerasthana/Chapter 6/Verse 47)]. These principles suggest that integrity of *praana vata* depends on normal functioning of the *koshtasthavata* with importance to *apana vata,* since *pakwashaya* is the crucial regulatory site of *vata dosha*.

The previous paragraph explained the ayurvedic principles underlying *vata dosha* functions and interactions between *vata* sub-types. These same principles provide evidence for a possible'gut-brain' link involving *praana* and *apana vata.* Based on these principles, disturbances in *apana vata* should negatively affect multiple systems. Indeed, during *apana vaigunya*, an inappropriate upward movement in *pakwashaya* can decrease gastro-intestinal motility (*udavarta*). Notably, *Udavarta* can cause disorders due to poor gastro-intestinal motility (*aruchigulma, grahani, pravahika*), as well as cardiac (*hrudroga, raktapitta*), respiratory (*pratisyaya, swasa, kasa*), psychological (*manovikara*), and brain (*shiro-abhitapa*) disorders. *Udavarta* is treated by methods which restore homeostasis of *apana vata* (*virechana* and *basti*) [[27] (Chikitsasthana/Chapter 26/Verse 5–10)].

In summary, afferent-efferent vagal fibres in the 'gut-brain' link maintain gut homeostasis by regulating electrical signalling, enteric hormone release, and gut–microbiome interactions. Integrity of *koshta* and *pakwashaya* ensure normalcy of *apana vata* and *samaana vata,* which in turn, maintain gut homeostasis and support all sub-types of *vata* [[7] (Sootrasthana/Chapter15/Verse3) [7], (Nidanasthana/Chapter 1/Verse 16)[11], (Sootrasthana/Chapter20/Verse2)[13], (Sootrasthana/Chapter12/Verse1)[13], (Sootrasthana/Chapter 12/Verse 8–9)]. Therefore, it is not surprising that dysfunctions of the vagus nerve and *vata dosha* are associated with gastric, cardiac, respiratory, and brain disorders (Table 2) [12]. Many of these disorders arise due to *udavarta,* wherein symptoms of *vata kopa* develop at *pakwashaya,* and progress to entire *koshta.* Hence, vagal activity in the 'gut-brain' link is a strong candidate biomarker for interactions and processes that link integrity of *koshta* (especially *pakwashaya*-the *apana vata* site), with functional vitality of *praana vata* and *vata dosha* itself.

PQ-5: Most hypotheses have limitations. What are the limitations to the hypothesis that proposes vagal activity as biomarker for *vata dosha*?

1. *Vagal activity and the sympathetic nervous system: Vata dosha* governs both parasympathetic and sympathetic functions of the ANS, whereas the vagus is a major parasympathetic nerve which opposes activity of sympathetic nerves and thereby returns 'activated organs' to their 'resting state'. Although the magnitude and timing of vagal activity depends on sympathetic activity, the vagus nerve itself, is not a suitable biomarker of sympathetic nerve activity. *Since parasympathetic activity of the vagus may represent important functions of vata dosha, can vagal activity be a 'specific' biomarker of certain functions of vata dosha* ? There are examples of 'specific', clinically useful biomarkers. For example, the electrocardiogram (ECG) measures only one vital property-the sequential, rhythmic pumping of heart chambers. The ECG does not measure ventricular pumping efficiency or diagnose heart valve disorders. An ECHO cardiogram is required to evaluate the latter parameters. Another example is the electroencephalogram (EEG), which records the brain's electrical activity, and can diagnose epilepsy, head injuries, headaches, brain tumours, and sleep disorders. However, the EEG cannot determine location of any abnormal brain function that it detects. Surprisingly, the EEG also cannot detect abnormalities in cranial nerves (such as vagus), at the brain stem. A separate 'nerve conduction velocity' test is required for diagnosing any abnormal nerve condition.

Despite being highly 'specific' biomarkers', the ECG and EEG are essential clinical tests that measure basic heart and brain functions, respectively. Similarly, vagal activity could be a useful 'specific' biomarker' for one of *vata dosha's* vital functions. This function is the maintenance of survival and homeostasis.

2. *Vagal activity and skin health: Vyana vata* carries *rasa dhathu* from *hrudaya* to the skin and peripheral organs for nourishment. Impaired *vata dosha* at the level of peripheral tissues can hamper *rasa dhathu* and produce symptoms of *twak rookshata* (dry skin), *nakha bheda* (cracked nails), and *twak sputana* (cracked skin). Indeed, *vata prakruti* individuals have greater tendency of *twak rookshata* because of *vata dosha's* dominance. Interestingly, atopic dermatitis which is associated with low vagal activity, is aggravated by cold, and improved by moisture [28]. Notably, *vata dosha* is similarly affected by cold and moisture. Daily *abhyanga* (oil massage) with special mention to ears, head, and foot, can alleviate *vata dosha*, and thereby rehydrate dry skin [[13] (Sootrasthana/Chapter 2/Verse 8)]. One report showed that acupuncture near the ears and head stimulated vagal activity [29]. Therefore, some beneficial effects of *abhyanga* on *vata dosha* and skin health, may involve modulating activity of specific vagal branches. These two reports suggest a possible correlation between impaired *vata dosha*, low vagal activity, and dry skin disorders. However, firm conclusions require new research.

In summary, these two limitations demonstrate that vagal activity may not be an appropriate biomarker for certain functions of *vata dosha*. However, certain 'specific' biomarkers' like the ECG and EEG, have proven clinical utility. Therefore, vagal activity may serve as a clinically useful 'specific' biomarker' for certain vital functions of *vata dosha*.

PQ-6: *Vata dosha* status is evaluated by time-tested methods. Are there reliable methods for measuring vagal activity?

Vagal activity is measured and modulated for therapeutic purposes. Gastric and cardiac vagal activity are measured by established, validated methods.

The efferent vagal fibres in the 'gut-brain' link, can modulate the levels of certain enteric hormones. Indeed, release of pancreatic polypeptide (plasma PP), is used as a specific marker of gastric vagal

efferent activity in clinical trials on diabetes and obesity [30,31]. Most studies measure cardiac vagal activity (CVA), rather than gastric vagal activity. This is because CVA is measured by the simple, standardized, ECG. The ECG is used because the cardiac vagus rhythmically regulates heart rate during breathing. Thus, high cardiac vagal activity inhibits heart rate during expiration, and this 'cardio-inhibitory' effect of the vagus decreases during inspiration [12]. These changes in CVA during breathing cause 'respiratory sinus arrhythmia' (RSA) or heart rate variability (HRV). HRV is easily quantified by measuring maximum and minimum heart rates during spontaneous or paced breathing. Thus, HRV is equivalent to the variation in the time interval between heartbeats, and is measured as ventricular rate or time interval between two successive QRS complexes on the ECG [12,32]. Interestingly, *nadi pariksha* analyses pulse rate variability (PRV), but the relationship between PRV and HRV is unclear [33]. To summarize, plasma PP is a biomarker of gastric vagal activity, and amplitude of HRV is a sensitive marker of the influence of cardiac vagal activity on heart rate.

HRV as a biomarker and therapeutic target for multiple diseases. Typically, increased HRV correlates with increased CVA, increased vagal tone, and cardiac wellness, whereas; decreased HRV significantly correlates with poor vagal tone and greater risk for cardiovascular disease [12,32]. Interestingly, drugs which increased HRV also reduced sudden death in large clinical trials [34]. HRV was also used to evaluate efficacy of therapies for certain inflammatory, metabolic, and neurological disorders [35]. These studies found that increased HRV was significantly correlated with improved 'neuroception' functions of the vagus nerve (section 3.3) [20–22]. Accordingly, analytics of HRV data from wearable sensors is being proposed as a sensitive biomarker for wellness and personalized medicine [22]. These clinical studies prove that HRV and therefore cardiac vagal activity, is a reliable biomarker and potential therapeutic target for several diseases [14,34,35].

PQ-7: Are there distinct therapeutic effects of stimulation versus inhibition of vagal activity?

Vagal nerve stimulation and inhibition, are USA-FDA approved therapies for distinct diseases. Many of these diseases are attributed to abnormalities in *vata dosha*.

Vagal Nerve Stimulation (VNS) is approved for several diseases mainly because HRV (which represents cardiac vagal activity), is a potential therapeutic target for many diseases [14,34,35]. However, manipulation of the cardiac vagus nerve can endanger survival. Therefore, vagal branches to the neck and ear (cervical and auricular vagus), are preferred sites for VNS because these branches are predictably stimulated by controlled electrical pulses transmitted via the overlying skin. Interestingly, VNS is used for certain diseases attributed to impaired *vata dosha*. For example, pain management through ayurveda is mainly achieved by therapies which pacify *vata dosha*, and VNS is approved for alleviation of pain in migraines and rheumatoid arthritis [14,17,35]. Abnormal *vata dosha* is considered the primary cause for mal-absorption and inflammation in the gut (*grahani*) [[7] (Nidanasthana/Chapter1/Verse 17) [13], (Nidanasthana/Chapter 7/Verse 10–14)], and VNS therapy is approved for inflammatory bowel diseases [35]. In fact, VNS may soon be approved for additional diseases attributed to aggravated *vata dosha* (stroke, auto-immune diseases, heart and lung failure, pain management, and fibromyalgia) [35].

Although VNS is a promising new therapy for several diseases, there are challenges. First, VNS significantly decreased frequency and severity of epilepsy, migraines, and depression, without curing the underlying disease. Second, a significant percentage of patients eligible for VNS therapy, do not respond to it [35].

Vagal nerve inhibition is an approved therapy for obesity, and abnormal *vata dosha* plays a role in obesity ('*ati-sthoulya*'). Based on results of animal studies and a long-term clinical trial, the USA-FDA has approved vagal blocking therapy (vBLoc®), as a new treatment for obesity [31]. Although impairment of *kapha dosha* and *medo dhathu* are causally linked with obesity/'*ati sthoulya*', a cardinal condition underlying this disease is *'prabhootavata'* (increased *vata dosha* activity in *koshta*). Pathological increases in appetite and digestion in *'ati-sthoulya'* are due to *'prabhootavata'* rather than impaired *kapha dosha* [[27] (Sootrasthana/Chapter 21/Verse 4–5)]. Thus, in addition to methods which pacify *kapha dosha* and *medo dhathu,* patients with *'ati sthoulya'* are given restricted diet and *teekshana basti* to pacify *vata dosha* [[27] (Sootrasthana/Chapter 21/Verse 21)]. In summary, obesity is in part due to abnormal activities of *vata dosha* and the vagus.

PQ-8: Based on all the above evidence, are *vata dosha* and vagal activity correlated or causally connected?

Due to lack of relevant clinical data, there is no conclusive answer. However, existing evidences are summarized below: We presented four lines of evidence for a correlative relationship between *vata dosha* activity and the vagus nerve. First, the multifunctional, life sustaining functions of *vata dosha* correlate with the '*connectome*' concept of vagus nerve function [[6] (Sootrasthana/Chapter 12/Verse 7–8)]. Second, *vata dosha* is essential for mental well-being (*niyanta, praneta cha manasa*) [[6] (Sootrasthana/Chapter 12/Verse 7–8)], and the polyvagal theory proposes similar neuroception functions for the vagus nerve [20–22]. Third, vagal activity in the 'gut-brain' link is a suitable candidate biomarker of the regulatory site of *vata dosha* (*pakwashya*). The fourth piece of correlative evidence involves the aging process. *Vata dosha* is thought to get weaken with age, and clinical studies measuring HRV, report an age-related decline in vagal tone [36].

Causal relationship between *vata dosha* and vagal activity: Three pieces of evidence support a causal link between *vata dosha* and the vagus nerve. First, Tables 1 and 2 suggest that functional similarities between *vata dosha* and the vagus nerve represent a causal link between these 2 entities. A pragmatic test of this causal link is to determine whether modulation of vagal activity is therapeutic for diseases caused by aggravated *vata dosha*. Accordingly, the second causal link is the striking similarity in diseases attributed to impaired *vata dosha* and diseases wherein vagal nerve stimulation or inhibition provides therapeutic benefits (Table 2 and section PQ-7). The third causal link is the fact that both *vata dosha* and the vagus nerve can be stimulated by cold, bitter taste, induced vomiting, and relaxation techniques. However, a causal link between *vata dosha* and the vagus nerve, may be conditional. For example, causality maybe restricted to patients at certain stages of specific diseases. Causality can also be conditional, if vagal nerve abnormality is one of several factors responsible for specific *vata dosha* related disorders.

3. Conclusion

The role of the parasympathetic vagus nerve in maintaining survival and homeostasis has been known for decades. However, the crucial role of the vagus in integrated control of mental and physiological networks regulating gut homeostasis, metabolic status, inflammation, immunity, physical wellness, mental health, and social behaviour; has recently emerged. Since the earliest report of vagal nerve stimulation in 1988, thousands of patients have undergone VNS therapy, and >100,000 patient-years of experience are accrued worldwide [17,18,34,35]. Similarly, ayurveda has successfully diagnosed and treated *vata dosha* related disorders for centuries. Whether the relationship between vagal activity and *vata dosha* status is correlative, causal, or conditional; the topic merits research for several reasons. First, the methods for measuring vagal

activity and *vata dosha* are well established, and are tested and validated by successful clinical trials in both systems of medicine. Therefore, new clinical trials that can evaluate possible links between activities of *vata dosha* and the vagus are feasible. Second, analysis of *prakriti* and *dosha* status of patients undergoing VNS therapy, may provide valuable insights on clinical characteristics of responders versus non-responders to VNS. Third, HRV (a biomarker of cardiac vagal activity), is an accepted therapeutic target for several diseases [14,32–35], and is accurately measured by certain wearable sensors [22]. Therefore, clinical studies examining the relationship between HRV and different *vata dosha* parameters, maybe directly applicable to personalized medicine. Indeed, one study found that ayurvedic therapy for depression increased HRV (cadiac vagal activity [37]. In summary, there is sufficient evidence to hypothesize that vagal nerve activity is a suitable, specific, candidate biomarker for certain vital functions of *vata dosha*. Research that tests this hypothesis may contribute towards whole-person centred clinical trials and add impetus to clinical research in personalized and integrative medicine [38].

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Conflict of interest

None.

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