

# Heart-rate variability: a biomarker to study the influence of nutrition on physiological and psychological health?

Hayley A. Young and David Benton

As the influence of diet on health may take place over a period of decades, there is a need for biomarkers that help to identify those aspects of nutrition that have either a positive or a negative influence. The evidence is considered that heart-rate variability (HRV) (the time differences between one beat and the next) can be used to indicate the potential health benefits of food items. Reduced HRV is associated with the development of numerous conditions for example, diabetes, cardiovascular disease, inflammation, obesity and psychiatric disorders. Although more systematic research is required, various aspects of diet have been shown to benefit HRV acutely and in the longer term. Examples include a Mediterranean diet, omega-3 fatty acids, B-vitamins, probiotics, polyphenols and weight loss. Aspects of diet that are viewed as undesirable, for example high intakes of saturated or trans-fat and high glycaemic carbohydrates,

have been found to reduce HRV. It is argued that the consistent relationship between HRV, health and morbidity supports the view that HRV has the potential to become a widely used biomarker when considering the influence of diet on mental and physical health. *Behavioural Pharmacology* 29:140–151 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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Department of Psychology, University of Wales Swansea, Swansea, Wales, UK

Correspondence to David Benton, DSc, Department of Psychology, University of Wales Swansea, Swansea SA2 8PP, Wales, UK  
E-mail: d.benton@swansea.ac.uk

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## Introduction

Biomarkers are important as proxy measures when studying health or disease states that develop over long periods. As a disease can develop over decades, this is an area where there is a need for biomarkers that identify aspects of life style that are potentially beneficial or problematic. The case will be made for using heart-rate variability (HRV) as an indicator of the physiological response to food by those interested in the association between diet and various health outcomes, and by manufacturers developing functional foods with potential health benefits. HRV is of interest as a wide range of diseases are associated with decreased variability, including diabetes, cardiovascular disease and psychiatric disorders. In addition, there is an increasing literature that reports that HRV responds to various aspects of the diet, raising the possibility that HRV offers a convenient measure of potential benefit.

Traditionally, heart rate (HR) has been considered a product of emotional response or stress, but it is becoming apparent that the interval between beats is a marker of the capacity to regulate internal and external demands. The intervals are not constant, but differ from beat to beat: essentially a higher HRV indicates better

general health (Jarczok *et al.*, 2015). In essence, the multitude of ways in which different physiological mechanisms modulate each other ensures that studying one aspect of the body in isolation limits our understanding.

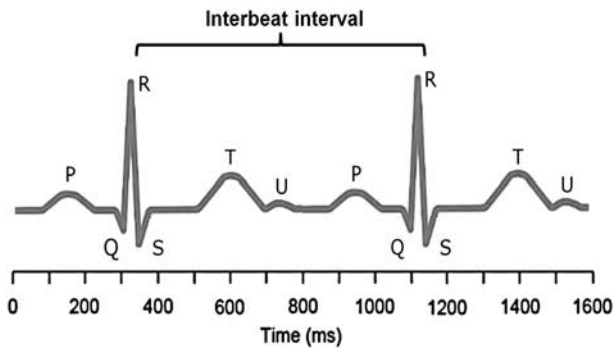
In 1948, the WHO defined health as ‘a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity’. As complete well-being is practically impossible, more recent definitions have emphasized resilience, the capacity to cope and the ability to maintain a sense of well-being. To assess the level of existing health and to evaluate dietary interventions, such definitions need to be operationalized. With this in mind, HRV may serve as a biomarker relating to the above definition, and thus serve as an indicator of the response to diet. In this review, the control of HR and the measurement of HRV are first outlined and then associations between HRV, health and aspects of diet are considered.

## Control of heart rate

Figure 1 shows an ECG trace from which the R-to-R intervals are measured, although it is the variability in the differences between these intervals that is of interest. In the brain stem, the medulla oblongata controls HR through the vagus, the tenth cranial nerve: vagal tone reduces HR by inhibiting the sinoatrial node, the heart’s pacemaker. Although there is a tendency to view HR as an involuntary mechanism, the medulla oblongata

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Fig. 1



A heart-rate trace. A typical electrocardiogram trace is illustrated. R is the peak of the QRS complex (electrocardiogram trace) and heart-rate variability is measured by considering consecutive R–R intervals. The R–R interval is not constant, but varies within a normal range of 0.6–1.2 s. It is the degree of this R–R variability that is of interest as greater variability is associated with better health.

receives information from the rest of the brain: including the central autonomic network (CAN) (Benarroch, 1993), with the prefrontal cortex playing a leading role (Thayer and Lane, 2009). Indeed, the cortical regulation of the CAN has been well described; there are both direct and indirect pathways (involving the cingulate and insula cortices, amygdala, hypothalamus and medulla oblongata) linking the frontal cortex to autonomic motor circuits responsible for both the excitatory and inhibitory effects on the heart (see Thayer and Lane, 2009 for a review). Therefore, the moment-to-moment control of HR reflects complex interactions between physiology, emotion and cognition (Benarroch, 1993; Thayer and Lane, 2009), encompassing the integration of a wide variety of information. Thus, it has been suggested that HRV reflects the overall capacity of the body to deal with on-going demands (Young and Benton, 2015). ‘HRV may serve as a proxy for the ‘vertical integration’ of the brain mechanisms that guide flexible control over behaviour with peripheral physiology, and as such provides an important window into understanding stress and health’ (Thayer *et al.*, 2012). In this way, HRV may act as a biomarker when considering the influence of diet on health-related mechanisms.

### Indices of heart-rate variability

Three approaches are used to monitor HRV: time-domain and frequency-domain measures are linear in nature, whereas complexity measures offer a nonlinear approach. The simplest approach is to summarize differences in the interbeat interval as a mean and SD, so-called time-domain measures (Fig. 2). Second, a spectral analysis allows frequency domain indices to be calculated and describes the interbeat intervals as a complex sum of waveforms. The variance in HR is distinguished in terms of the underlying rhythms that occur at different

frequencies. There is growing evidence that frequency-domain indices measure the functioning of the autonomic nervous system. The high-frequency (HF) measure (power in the range 0.15–0.4 Hz) is more easily understood as it is said to reflect the parasympathetic nervous systems (PNSs) (Katona *et al.*, 1970; Appel *et al.*, 1989; Billman and Hoskins 1989; Camm *et al.*, 1996; Thayer *et al.*, 2010). In contrast, low-frequency (LF) (power in the range: 0.04–0.15 Hz) is less readily interpreted as it is influenced by both the PNS and also baroreceptor activity (Houle and Billman, 1999; Billman, 2013). A frequently considered index is the LF/HF ratio, which is said to reflect the balance between PNS and the sympathetic nervous system activity (Malik, 1998), although this contention has been challenged recently (Billman, 2013).

More recently, nonlinear indices have been developed: as one example, approximate entropy provides an indication of the irregularity or randomness in a data set. The time series 1, 2, 3, 1, 2, 3 has the same variability as the time series 1, 1, 2, 2, 3, 3 and 3, 1, 2, 2, 3, 1, but different underlying patterns. Nonlinear analysis enables the quantification of this extra information. Essentially, the nonlinear approach measures the complexity of the signal; how frequently do similar patterns reoccur? Although frequency measures in particular have been studied widely, it has become apparent that nonlinear indices of complexity reflect different underlying mechanisms (Young and Benton, 2015). For example, a recent study reported that nonlinear measures of HRV were better able to predict the performance of cognitive tests than linear measures (Young and Benton, 2015). In addition, a meta-analysis of the impact of depression and antidepressant treatment on HRV found that the effects were most apparent with nonlinear measures of HRV (Kemp *et al.*, 2010). There is an impression that those capable of generating more complex signals have a greater ability to respond to environmental demands in a more subtle manner (de la Torre-Luque *et al.*, 2016).

### Heart-rate variability, inflammation and disease

Inflammation is part of the immune response, with too much and too little inflammation indicating, or leading to, a wide range of diseases. Hotamisligil (2006) noted that metabolic regulation and the immune system are highly integrated: he suggested that this interaction reflects a central homeostatic mechanism that, if dysfunctional, results in chronic metabolic disorders, particularly obesity, type 2 diabetes and cardiovascular disease. An inadequate response creates immunodeficiency that can result in infection or cancer (Mellemkjaer *et al.*, 2002). As the inflammatory response is in part regulated by the autonomic nervous system, HRV is of interest.

The vagus plays a role in the inflammatory reflex that controls innate immune responses when tissue is injured

Fig. 2

Linear domain - Time indices	
Index	Interpretation
Mean RR interval (ms)	The average of NN intervals. A longer NN interval indicates a lower heart rate.
SDNN (ms)	Standard deviation of the NN intervals. Indicates total variability with a high value is thought to associate with better health.
RMSSD (ms)	The square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) is thought to indicate parasympathetic nervous system activity.
Linear domain - Frequency indices	
Index	Interpretation
Total power (ms <sup>2</sup> )	Variance of all inter-beat intervals ( $\leq 0.4$ Hz). Indicates total variability with a high value is thought to associate with better health.
ULF (ms <sup>2</sup> )	Power in the ultra-low frequency range ( $\leq 0.003$ Hz). Might reflect circadian, neuroendocrine, activity, other unknown rhythms.
VLF (ms <sup>2</sup> )	Power in the very low frequency range (0.003–0.04 Hz). Might reflect vasomotor changes, thermoregulatory and possibly parasympathetic influences on heart rate.
LF (ms <sup>2</sup> )	Power in the low frequency range (0.04–0.15 Hz). Thought to reflect a combination of parasympathetic and baroreceptor activity.
HF (ms <sup>2</sup> )	Power in the HF range (0.15–0.4 Hz). Reflects parasympathetic activity.
LF/HF	Ratio LF (ms <sup>2</sup> )/HF (ms <sup>2</sup> ). Frequently used index of autonomic balance although this has been debated.
Non-linear analysis	
Index	Interpretation
ApEn	Approximate Entropy measures irregularity or randomness in a set of data, such that smaller values reflect a greater regularity. Sample entropy (SampEn) is a similar measure that is more suitable for short recordings.
DFA	Detrended Fluctuation Analysis quantifies the fractal like correlation properties of a time series and reveals short-range (DFA1) and long-range (DFA2) correlations within a series.

Various measures of heart-rate variability. The variability in consecutive differences in the R–R interval can be expressed using a number of different approaches that are one of three types: time or frequency based or nonlinear. HF, high-frequency; LF, low-frequency.

or there is a pathogen invasion (Pavlov and Tracey, 2012). The inflammatory reflex has an afferent component that is activated by cytokines that relay information to the hypothalamus. This input can then initiate an anti-

inflammatory response that prevents the release of inflammatory products into the blood stream (Tracey, 2002). It is becoming increasingly clear that the nervous system, through the vagal nerve, both monitors

peripheral inflammation and dampens the immune response (Boeckxstaens, 2013). The sympathetic arm of the autonomic nervous system also plays a role: it releases noradrenaline, which appears to act at sites other than the synapse, as many immune cells, including lymphocytes and macrophages, have adrenergic receptors (Kavelaars *et al.*, 1999).

HRV is associated with the levels in the blood of C-reactive protein (CRP), a protein that is produced by the liver as a response to inflammation, with the levels increasing following the secretion of interleukin (IL)-6 from macrophages and T cells. The role of the protein is to bind to lysophosphatidyl choline on the surface of dead cells and to enhance the ability of antibodies and phagocytic cells to remove pathogens. Higher levels of CRP are associated with a greater risk of hypertension, diabetes and cardiovascular disease (Dehghan *et al.*, 2007). Jarczok *et al.* (2014) reported that the HF component of HRV predicted the level of CRP when it was measured 4 years later; this is important as both inflammation and HRV have been implicated in conditions such as diabetes and cardiovascular disease (Kudat *et al.*, 2006; Thayer *et al.*, 2010).

Madsen *et al.* (2007) related low-grade inflammation to autonomic dysfunction in those with suspected coronary heart disease. The mean SD of normal to normal R–R (SDNN) was higher in those with lower levels of CRP, with the association being greater in those with a previous history of myocardial infarction. However, CRP remained associated with HRV independent of disease, a finding interpreted as a relationship occurring between low-grade inflammation and autonomic dysfunction. Experimental evidence is beginning to emerge and support these associations. For example, a recent study found that vagus nerve-stimulation in epilepsy patients inhibited peripheral blood production of tumour necrosis factor, IL-1 $\beta$  and IL-6 (Koopman *et al.*, 2016).

Whether by influencing inflammation or by other mechanisms, HRV has been associated with a range of diseases, in some cases predicting subsequent problems and in others being an index of disease progression (RenuMadhavi and Ananth, 2012). As a generalization, a healthy biological system tends to be both variable and complex, characteristics that decline with disease. Irrespective of disease, HRV declines with age, reaching, in some older than 65 years of age, levels that are a risk factor for mortality (Umetani *et al.*, 1998).

The American Heart Association states that diabetes increases the risk of heart disease or a stroke and thus early diagnosis of complications is the key to decreasing mortality. A systematic review of those with diabetes concluded that HRV can help to predict cardiac morbidity and mortality, and that it can be used at an early stage to indicate the future risk of complications (Fakhrzadeh *et al.*, 2012). As one example, Yoshioka and

Terasaki (1994) reported that the HF component, which indicates parasympathetic nervous activity, was lower in diabetics rather than controls, and there were inverse correlations between the LF and HF. It was concluded that these measures of HRV are useful when evaluating diabetic autonomic and peripheral neuropathies. The Atherosclerosis Risk in Communities study (Schroeder *et al.*, 2005) also found that diabetics differed in HF power and that HF in nondiabetics was greater in those with lower levels of fasting insulin. Thus, there was a relationship between insulin resistance, as indicated by higher levels of fasting insulin, and lower HRV. In addition, after a 9-year follow-up, there was a general decline in HRV. Such findings suggest that an impairment of the functioning of the autonomic nervous system, reflected in HRV, occurs during the early stages of diabetes and becomes progressively worse over time.

A more general question is the association between HRV and blood glucose levels. The Framingham Heart Study (Singh *et al.*, 2000) related HRV to fasting levels of blood glucose: LF and HF power was reduced in those with diabetes or impaired levels of fasting glucose. In addition, a recent study found that resting HRV (average R–R interval, HF power, sample entropy) predicted the increase in blood glucose following a high glycaemic load drink (Young and Watkins, 2016). Overall, HRV appears to be associated inversely with plasma glucose levels. It is plausible that the links between insulin resistance, blood glucose and HRV are attributable to deficits in the inflammatory reflex (Pavlov and Tracey, 2012). Vinik (2012) noted that activation of inflammatory cytokines in newly diagnosed type 2 diabetes correlated with changes in sympatho–vagal balance. As, in type 2 diabetes, changes in the autonomic nervous system predict sudden death, such measures offer the chance of an early intervention.

As mentioned above, a reduction in HRV predicts macrovascular disease, for example carotid artery atherosclerosis (Gottsäter *et al.*, 2006). Indeed, a recent study found that insulin resistance mediated the association between HF-HRV and carotid intima–media thickness (Kemp *et al.*, 2016). In fact, it has been known for many years that following myocardial infarction, HRV is related to the risk of consequent morbidity and mortality (La Rovere *et al.*, 1998). In addition, the rate at which congestive heart failure and arrhythmias occur has been related to a reduced HRV (Sandercock and Brodie, 2006) and lower HRV complexity is associated with a worse outcome in cardiac patients (Souza *et al.*, 2015). Although fewer studies have considered those without a history of coronary heart disease, a meta-analysis examined those without any problem at baseline (Hillenbrand *et al.*, 2013). A lower HRV, measured as SDNN, was associated with a subsequent 40% increase in the risk of suffering a first cardiovascular event.

### Heart-rate variability, obesity and weight loss

Decreased HRV is associated with a significantly increased risk of death from cardiovascular disease (Bigger *et al.*, 1993; Makikallio *et al.*, 1999). Therefore, Kim *et al.* (2005) considered whether the high rate of cardiovascular disease in obese individuals might be associated with changes in HRV. They found that the RMSSD (a frequently used index of parasympathetic activity) was correlated negatively with fat mass and the hip-to-waist ratio. Similar effects were noted for LF power, although as noted above, this index is not easily interpretable. Nonetheless, it seems that obesity can alter HRV.

For example, Mouridsen *et al.* (2013) examined the impact of weight loss on HR and HRV in overweight postmenopausal women. An average weight loss of 3.9 kg was associated with a decrease in HR and increased HRV, as indicated by SDNN and the interbeat interval. Previously, Karason *et al.* (1999) had considered obese patients, who, after surgery, had lost 28% of their body weight, on average 32 kg. SDNN and HF power were attenuated in those with obesity compared with lean patients; HRV improved with weight loss. Adachi *et al.* (2011) examined the influence of obesity on autonomic activity during sleep. Volunteers were allocated randomly to a standard diet or one that over 8 weeks increased weight by 4 kg. After weight gain, HF power decreased both when awake and when asleep, changes that resolved with weight loss. A related finding was that caloric restriction may reverse the autonomic changes that occur as we age. A decline in HRV with age is well described: for example, Zulfiqar *et al.* (2010) compared HRV in patients of ages ranging from 10 to 99 years. Several measures of HRV all decreased rapidly from the second to fifth decades, although the decline then slowed. They concluded that a healthy long life depends on the preservation of autonomic functioning, more specifically, the influence of the PNS on HRV. Stein *et al.* (2012) found that in patients who had practiced caloric restriction, for on average 7 years, HR was lower and several measures of HRV values were significantly higher. In fact, HRV was comparable to the norms for those 20 years younger. The overall impression is that weight gain adversely influences HRV, although this effect may be reversible with weight loss and/or dietary restriction.

### Heart-rate variability and eating behaviour

HR variables have also been related to dieting and eating behaviour. A recent review concluded that most, although not all, studies investigating HRV in those with anorexia nervosa find parasympathetic dominance (Mazurak *et al.*, 2011). Similarly, those with bulimia nervosa are characterized by higher vagal activity, particularly HF-HRV (Peschel *et al.*, 2016). In a healthy sample, Meule *et al.* (2012b) found that restrained eating, which is the intentional restriction of food intake to

prevent weight gain or to promote weight loss, was associated with low cardiac vagal control (Table 1). The restraint score and the extent to which weight fluctuated predicted HF-HRV negatively. In a further study, Meule *et al.* (2012a) qualified this finding by considering successful versus unsuccessful dieters: success was associated positively with HF-HRV. They concluded that vagal-cardiac control reflected the strength of self-regulation such that successful restrained eaters were characterized by higher cardiac vagal control. These findings are in line with two studies that found reduced HR variability and complexity (R-R interval, HF power, sample entropy) in those with a propensity towards disinhibited eating, which is a tendency to overeat in the presence of palatable foods or other disinhibiting stimuli, such as emotional stress (Young and Watkins, 2016; Young *et al.*, 2017a). Importantly, these effects remained after controlling for the healthiness of the diet. Thus, it appears that tonic HRV might index individual differences in the capacity to self-regulate in the face of temptation. Indeed, Geisler *et al.* (2016) reported that restrained eaters who suppressed their feelings about a distressing film had higher vagally mediated HRV (RMSSD) during subsequent exposure to a palatable food (jelly beans). In an earlier study, Segerstrom and Nes (2007) found an increase in RMSSD when participants were told to resist warm cookies and instead eat carrots. A caveat is that caloric restriction and intermittent fasting, behaviours commonly observed in restrained eaters, have been shown to increase HF oscillatory components in HR (Mager, 2006). Thus, the higher HF-HRV observed in this population may be because of lifestyle factors rather than differences in self-regulatory capacity. Future research should explore this possibility. That said, these associations between eating behaviour and HRV offer the possibility of examining the association between the ability of different types of food to influence HRV and their ability to reduce or prevent pathological eating behaviours.

### Heart-rate variability and psychiatric disorders

A dysfunctional autonomic nervous system, with an associated reduction in HRV, has been found in a wide range of psychiatric disorders, a contention supported by a number of recent meta-analyses. Kemp *et al.* (2010) examined the association between depression and HRV in those without cardiovascular disease. When depressed patients and healthy controls were compared, the former had a lower HRV; it was particularly lower in those with more severe symptoms. Similar meta-analytic reviews have shown HRV reductions in a range of psychiatric disorders: bipolar disorder (Faurholt-Jepsen *et al.*, 2017), anxiety disorders (Chalmers *et al.*, 2014), post-traumatic stress disorder (Nagpal *et al.*, 2013) and schizophrenia (Clamor *et al.*, 2016). Notably, such effects are most consistently examined using HF-HRV or other vagally mediated HRV indices (e.g. RMSSD), although on

**Table 1 The relation between heart-rate variability and eating behaviour**

References	Sample	Design	Outcome
Segerstrom and Nes (2007)	168 students aged 19 years	Asked to resist eating palatable food and consume less palatable. Then, they performed an anagram task that needed persistence	Increase in RMSSD when eating cookies was resisted, and carrots consumed. HRV seen as an index of self-regulatory strength
Meule <i>et al.</i> (2012a)	47 females aged 24 years BMI 22	Compared those who were and were not restrained eaters	A high HF associated with less weight fluctuation. Weight fluctuation predicted LH/HF
Meule <i>et al.</i> (2012b)	50 females aged 18–40 years BMI between 17.5 and 25	Compared those who were or were not currently dieting	Successful dieting positively associated with HF and negatively with LH/HF
Geisler <i>et al.</i> (2016)	111 students aged 23 years	Participants took on a task that did or did not require self-control. Then, they were exposed to palatable food. Effortable self-control measures as HRV	Restrained eaters, who suppressed feelings, had higher RMSSD when exposed to a palatable food, but not when self-control had not been exercised. Suggested dieting required self-control as indicated by HRV
Young and Watkins (2016)	66 females between 18 and 29 years BMI 17–31	Studied the relation between HRV and glucose tolerance	Disinhibited eaters had reduced HRV (HF and sample entropy). Those with low HRV had poorer glucose tolerance – the levels remained higher for longer
Young <i>et al.</i> (2017a)	156 healthy adults from 18 to 34 years, 122 healthy adults From 18 to 30 years	Cross sectional study asked whether diet mediated the association between HRV and mood	Diet shown to mediate the relation between HRV (HF and sample entropy) and mood

HF, high-frequency; HRV, heart-rate variability; LF, low-frequency.

occasion, larger effect sizes have been noted with non-linear indices (Kemp *et al.*, 2010). Importantly, HRV predicted the onset of psychological illness 10 years later (Jandackova *et al.*, 2016). Given the links between HRV, emotion regulation and executive functioning (Williams *et al.*, 2015; Zahn *et al.*, 2016; Holzman and Bridgett, 2017), it has been proposed that HRV is a transdiagnostic biomarker of mental illness (Beauchaine and Thayer, 2015).

This brief overview illustrates that HRV is a risk for, or a marker of, a wide range of disorders. As such, any intervention that impacted positively on HRV has the potential to benefit health. Evidence suggests that lifestyle may be one such factor. Young *et al.* (2017a) reported that smoking cigarettes and drinking alcohol negatively influenced HRV, measured using linear (HF power) and nonlinear (sample entropy) measures. In addition, these aspects of the HR time series were increased in those who took regular exercise and consumed a healthy diet. Notably, diet quality at least partially explained the association between mood, disinhibition and HRV (Young *et al.*, 2017a); thus, dietary modification may improve HRV in those at risk of psychological disorders.

### The nature of the diet and heart-rate variability

In an early study, Lu *et al.* (1999) examined the postprandial changes in HRV following a 500 kcal test meal (turkey sandwich: 32.4% fat, 17.5% protein and 50.1% carbohydrate). HF power decreased during the first and second 30 min following consumption, suggesting a reduction in vagal tone. Similarly, after a mixed meal of 501.8 kcal that comprised 31% protein, 18% lipids and 51% carbohydrates, a decrease in HF power was observed from 40 to 120 min after the meal, an effect that

correlated negatively with ghrelin concentrations (Chang *et al.*, 2010). In relation to specific macronutrients, Kanaley *et al.* (2007) studied the influence of an acute glucose load on HRV in obese women with and without diabetes. Total power decreased in response to the glucose challenge compared with what was observed in the fasted state. In addition, a high-carbohydrate meal was reported to augment HRV reactivity (in response to mental stress) compared with a high-protein meal: HR decreased more quickly poststress after the carbohydrate meal (Uijtdehaage *et al.*, 1994). Over a 2-day period, Lima-Silva *et al.* (2010) examined the impact of a low-carbohydrate diet in those who had been exercising. Compared with a high-carbohydrate diet, the low-carbohydrate diet increased LF and decreased HF power. There were, however, no differences in HR or R–R interval. As this study considered those who had been exercising, there is a need to look at those simply going about their everyday life.

Nagai *et al.* (2005) reported that a high-fat meal increased the VLF component of HRV. Although the physiological processes underlying VLF-HRV are unclear, Nagai *et al.* (2005) interpreted this as an indication of thermoregulatory sympathetic nervous system activity. Other components of HRV may also be influenced by the nature of dietary fat, at least in the longer term: Soares-Miranda *et al.* (2012) reported that in two cohorts, either 19 or 72 years of age, a greater consumption of trans-fats was associated with a less favourable HRV; SDNN, RMSSD and total power were lower. Importantly, trans-fat consumption predicted lower HRV 5 years later.

When considering the influence of diet, by far the majority of work has involved supplementation with

omega-3 fatty acids. For example, in a secure forensic inpatient facility, Hansen *et al.* (2014) randomly allocated patients to a diet containing salmon three times a week compared with meat in the control group. The changes in HRV associated with fish consumption correlated negatively with sleep latency and positively with a measure of daily functioning. Table 2 lists a representative sample of studies that show that research has been driven by an interest in disease states, particularly heart disease, and has typically involved the examination of older adults. There is a general impression that omega-3 supplementation resulted in greater parasympathetic activity, although greater confidence in this conclusion comes from a meta-analysis. Xin *et al.* (2013) integrated fifteen studies. The time-domain measures, SDNN and RMSSD, did not differ after supplementation. However, although there was no effect on the frequency measure LF, fish oil significantly increased HF. The authors concluded that the 'enhancement of vagal tone may be an important mechanism underlying the antiarrhythmic and other clinical effects of fish oil'. Similarly, the review of Christensen and Schmidt (2007) concluded that: 'In most (Billman *et al.*, 1994; Christensen *et al.*, 1999; Christensen and Schmidt 2007; Billman and Harris, 2011; Christensen, 2011), although not all, studies, dietary n-3 PUFA levels and n-3 PUFA supplementation are related to improved HR variability'. The findings suggested that an increased parasympathetic regulation of cardiac functioning occurred.

More generally, the Mediterranean diet, which has fish as a component, is also associated with HRV. Dai *et al.* (2010), using a food-frequency questionnaire, established the extent to which middle-aged male twins ate a Mediterranean diet. After adjusting for genetic contributions, those who conformed to the Mediterranean diet had higher HRV across a range of indices: SDNN, RMSSD, ULF, VLF, HF and LF. Although it was unclear which aspect of the diet was beneficial, it is tempting to suggest that one factor is eating fish and in this way increasing the intake of omega-3 fatty acids. Billman (2013) reviewed the evidence that the intake of omega-3 fatty acids influenced cardiac rhythms. He concluded that supplementation with n3-PUFAs affects ion channels and calcium-regulatory proteins, although these depended on the route of administration. Immediately, there is a direct effect of the fatty acids on ion channels, although over the longer term, after the incorporation of the fatty acids into the cell membrane, cardiac electrical activity changes. HR is reduced and HRV increases, reflecting alterations in the intrinsic pacemaker rather than regulation by the activity of the autonomic nervous system.

Other contributions to a Mediterranean diet have also been found to influence HRV. In a randomized trial, the influence of a multivitamin-mineral preparation on HRV was assessed (Pomportes *et al.*, 2015). Faster reactions in a

test of the ability to inhibit responses were associated with a stable HF, indicative of PNS activity. In those taking micronutrients, HF remained stable, whereas in the placebo condition, HF decreased over time. Jaatinen *et al.* (2014) studied the influence of yoghurt enriched with  $\alpha$ -lactalbumin, bioactive peptides and B vitamins in individuals with high-trait anxiety. In the active group, vagally mediated HRV (RMSSD) was higher. They concluded that this yoghurt combination may aid coping with stress. As nut consumption is associated with a lower risk of cardiovascular disease, Sauder *et al.* (2014) studied its influence on HRV. The pistachio diet was associated with a higher HF and greater total variation in beat-to-beat intervals. Similar effects have been observed in relation to the consumption of polyphenol-rich red wine. Intake of wine, but not of spirits or beer, is positively and independently (after controlling for other health behaviours) associated with HRV (SDNN, total power, VLF power, LF power and HF power) in women with CHD (Janszky *et al.*, 2005).

There is also some evidence that particular nutrients influence HRV. Sucharita *et al.* (2014) considered HRV in a healthy elderly Indian sample with either a high or a low vitamin B<sub>12</sub> status. The LF was lower in those with a poorer vitamin B<sub>12</sub> status, although no effects on HF power or HR were observed. Supplementation for 3 months increased LF to levels comparable to those with an initially good vitamin B<sub>12</sub> status. Sodium intake is also linked to HRV. In a randomized-controlled trial, Allen *et al.* (2014) asked participants, with normal blood pressure, to consume for 5 days a diet with low (10 mmol/day), normal (150 mmol) or high (400 mmol) levels of sodium. The response to low sodium was consistent with sympathetic activation and reduced vagal activity; LFnu (normalized) increased and SDNN, RMSSD and HFnu (normalized) decreased compared with both normal and high sodium conditions.

In summary, although there has been limited systematic study, there is a series of reports that relate various indices of HRV to the intake of a range of food items. As such, there is good reason to support the further consideration of HRV as a biomarker with the potential to indicate the potential influence of food on health.

## Discussion

There is growing evidence that a range of diseases are accompanied by a decrease in HRV, including, amongst others, diabetes (Yoshioka and Terasaki, 1994), cardiovascular disease (Gottsäter *et al.*, 2006) and psychiatric disorders (Kemp *et al.*, 2014). Although indices of HRV do not distinguish between types of disorder, there is a consistent pattern of a reduced variability in HR being associated with disease: a higher HRV is associated with psychological flexibility and allostatic resilience. Indeed, longitudinal studies support the view that reduced HRV predicts psychological and physiological morbidity years

**Table 2 The influence of fish oil supplementation and eating fish on heart-rate variability**

References	Sample	Design	Intervention	Outcome
Christensen <i>et al.</i> (1996)	49 patients with CAD aged 63 years	Parallel	4.3 g EPA/DHA a day or placebo for 12 weeks	SDNN and mean RR increased from baseline in the active, but not the control condition. No significant difference between active and control
Christensen <i>et al.</i> (1998)	17 patients with RF aged 52 years	Parallel	4.7 g EPA/DHA a day or placebo for 12 weeks	High cell fatty acids associated with higher SDNN Those with CRF had lower HRV
Christensen <i>et al.</i> (1999)	40 healthy individuals aged 38 years	Parallel	1.68, 5.9 g EPA/DHA a day or placebo for 12 weeks	Baseline positive correlation between SDNN, RMSSD and levels of DHA in cell. Dose-dependent increase in HRV Effects found in men, but not women
Dyerberg <i>et al.</i> (2004)	49 healthy individuals aged 38 years	Parallel	3.2 g EPA/DHA a day or placebo for 8 weeks	SDNN, RMSSD, NN50, NN6% were not significantly influenced
Holguin <i>et al.</i> (2005)	52 elderly individuals aged 77 years	Parallel	1.55 EPA/DHA a day or placebo for 16 weeks	Supplementation increased LF, HF and RMSSD
O'Keefe <i>et al.</i> (2006)	36 patients with CAD aged 68 years	Cross-over	0.8 EPA/DHA a day or placebo for 16 weeks	Supplement increased HF and reduced HR at rest SDNN and LF not effected
Hamaad <i>et al.</i> (2006)	38 patients with CAD aged 60 years	Parallel	0.8 EPA/DHA a day or placebo for 16 weeks	No significant influence on SDNN, RMSSD, LF, HF and LF/HF
Radaelli <i>et al.</i> (2006)	25 patients with CAD aged 60 years	Parallel	1.68 EPA/DHA a day or placebo for 16 weeks	Supplementation increased LF, HF, SDNN, RMSSD
Ninio <i>et al.</i> (2008)	46 overweight patients aged 50 years	Parallel	0.8 EPA/DHA a day or placebo for 12 weeks	Supplement increased HF but did not affect LF or LF/HF. Resting HR decreased after supplement
Nodari <i>et al.</i> (2009)	41 patients with Idiopathic dilated cardiomyopathy aged 63 years	Parallel	1.44 g EPA/DHA a day or placebo for 24 weeks	The LF/HF ratio increased after supplement when under mental stress. VLF decreased in the placebo group, but not in the active group
Carney <i>et al.</i> (2010)	72 depressed patients with CAD aged 57 years	Parallel	1.68 g EPA/DHA a day or placebo for 10 weeks	No effect on LF or HF
Sjoberg <i>et al.</i> (2010)	67 overweight patients aged 52 years	Parallel	0.64, 1.28, and 1.92 g EPA/DHA a day or placebo for 12 weeks	There was a dose-dependent reduction in the LF/HF, although neither LH or HF was significantly influenced
Valera <i>et al.</i> (2014)	180 French Polynesian adults	Cross-sectional	The DHA in red cells was related to HRV	Increasing DHA concentrations were associated with lower HR and greater HF, RMSSD
Fish intake				
Mozaffarian <i>et al.</i> (2008)	4263 ECGs 1152 24 h holter	Cross-sectional	Eating tuna and other fish assessed using FFQ	Eating fish associated with greater RMSSD and HF and lower LF. A lower Poincaré ratio and higher short-term fractal scaling exponent suggested less erratic sinoatrial node firing
Hansen <i>et al.</i> (2014)	95 male forensic inpatients	Parallel	Ate either fish or meat meals three times a week for 6 months	Fish group showed a significant increase in HF. The increased variability associated with fish consumption correlated negatively with sleep latency and positively with a measure of daily functioning
Grung <i>et al.</i> (2015)	49 male forensic inpatients	Parallel	Ate either fish or meat meals three times a week for 6 months	Principal component analysis of HRV parameters produced a parasympathetic factor that increased when fish was eaten

CAD, coronary artery disease; CRF, chronic renal failure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; HF, high-frequency; HR, heart rate; HRV, heart-rate variability; LF, low-frequency; SDDN, SD of normal to normal R-R.



later (Carnethon *et al.*, 2003; Jandackova *et al.*, 2016). Thus, HRV may serve as a biomarker for future health.

Various aspects of diet have been found to be associated with HRV. In general, the types of diet and particular foods that have been found to be associated with a healthy life-style are associated with higher HRV. For example, a Mediterranean diet (Mozaffarian *et al.*, 2008; Soares-Miranda *et al.*, 2012), fish consumption (Mozaffarian *et al.*, 2008), multivitamins (Pomportes *et al.*, 2015) and losing weight (Zulfiqar *et al.*, 2010) all increased HRV. However, aspects of diet that are commonly viewed as undesirable, for example a high fat or trans-fat diet, reduced HRV (Soares-Miranda *et al.*, 2012).

Although it is clear that diet influences HRV, the mechanisms and pathways underlying such effects are multifactorial. In relation to physical health, it is clear that vagal tone is central to the regulation of a number of allostatic systems, including the cardiovascular system, glucose regulation, the hypothalamic–pituitary–adrenal axis function, and inflammatory processes (Thayer and Sternberg, 2006; Young and Benton, 2015; Viljoen and Claassen, 2017). Thus, reduced vagal tone may directly contribute towards increased allostatic load (Koopman *et al.*, 2016). However, chronic diseases such as diabetes contribute towards autonomic neuropathy (Vinik *et al.*, 2003), which is associated with reduced HRV (Fakhrzadeh *et al.*, 2012). Such bidirectional effects make causality difficult to determine.

Similarly, it has been argued that vagal afferent signals might mediate the influence that diet has on psychological health (Kemp *et al.*, 2017). Indeed, emerging evidence suggests that cardiac interoceptive sensations contribute towards one's mental health (Craig, 2003; Critchley *et al.*, 2004; Seth, 2013; Young *et al.*, 2017b); however, it is difficult to isolate diet-related effects on afferent vagal signals. In addition, influential models such as the neurovisceral integration model (Thayer and Lane, 2009) consider HRV to be the product of the CAN, which guides goal-directed behaviour; the prefrontal cortex plays a central inhibitory role (Thayer and Lane, 2000; Smith *et al.*, 2017). Thus, HRV may capture primarily efferent vagal activity. With this in mind, it is plausible that the effects of diet on HRV operate indirectly through changes in mental health. That is, diet influences brain functioning, cognition and mood, which is then reflected in changes in HRV. Indeed, a study supports the view that diet influences psychological health not only acutely (Young and Benton, 2014, 2015) but also chronically (Jacka *et al.*, 2010). However, whether these effects mediate or are mediated by HRV remains to be determined.

Furthermore, the link between HRV and pathological eating behaviours (Young and Watkins, 2016) points towards the possibility of mutual causation. That is, reduced HRV, by virtue of its connections with the

prefrontal cortex (Dietrich *et al.*, 2006; Chang *et al.*, 2013; Jennings *et al.*, 2016), may indicate a predisposition to make poor dietary choices. In turn, a poor-quality diet could exacerbate the reduction in HRV. In support of this proposition, Young *et al.* (2017a) found that disinhibited eating and poor diet quality were associated independently with deficits in HRV. Notably, HRV is related positively to interoceptive sensitivity (Ainley *et al.*, 2012), raising the possibility that diet-related reductions in vagal tone may diminish the ability to detect interoceptive signals, including information about one's current homeostatic state (Attuquayefio *et al.*, 2017, Smith *et al.*, 2017), and contribute towards mental illnesses (Paulus and Stein, 2010). Irrespective of the mechanisms involved, the association between HRV and so many types of disease state suggests that it is a measure of factors with a wide-spread significance. Thus, HRV may serve as a useful biomarker for identifying potentially beneficial or detrimental aspects of diet.

A distinction should be drawn between phasic and tonic HRV as this will impinge upon interpretation of research findings. In relation to emotion, demanding situations may give rise to an increase or a decrease in phasic HRV. The former might arise when an individual successfully self-regulates to deal with the demands of the situation (Park *et al.*, 2014; Geisler *et al.*, 2016) and the latter may arise when the situation is perceived as threatening and an individual shows an autonomic stress response (Segerstrom and Nes, 2007).

The vast majority of research linking health and HRV has focused on tonic resting-state HRV (Chalmers *et al.*, 2014; Kemp *et al.*, 2014, 2016). Although tonic HRV predicts phasic changes in vagal tone, lower tonic HRV was associated with phasic HRV suppression and higher tonic HRV was associated with phasic HRV enhancement (Park *et al.*, 2014). This is an important methodological consideration when considering the effects of diet.

Phasic changes represent real-time adaptations to the external or the internal environment; as such, a temporary decline in HRV need not necessarily be pathological. An example can be considered in relation to the literature on fluid consumption. Hypohydration necessitates a counter-regulatory increase in HR to maintain blood pressure: for every 1% decrease in body mass during exercise, there is an increase in HR of 3.29 bpm (Adams *et al.*, 2014). Even in the absence of hypohydration, water ingestion is followed by an increase in cardiac vagal control (Helen *et al.*, 2002). Under such circumstances, an inability to flexibly alter the variability of HR may be viewed as detrimental. Thus, whether tonic HRV influences one's ability to effectively counter regulate during the postprandial period is an important question. Young and Watkins (2016) provided the first evidence that this might be the case: individual differences in tonic vagal tone moderated the postprandial response to drinks that

differed in glycaemic load. Whether a higher resting-state HRV confers greater metabolic resilience during the post-prandial period is an important question for future research.

Although we have argued that decreased HRV may serve as a biomarker of future health, there are caveats that need to be considered. For example, it has been observed that black individuals have higher HRV, and yet are at greater risk of future cardiovascular disease (Hill *et al.*, 2017). In addition, although most psychiatric disorders are characterized by reduced HRV, those with anorexia nervosa (Mazurak *et al.*, 2011) or bulimia nervosa (Peschel *et al.*, 2016) tend to have parasympathetic dominance (higher HF-HRV). Although both these conundrums may be explained by dietary differences in these populations – for instance, there are clear racial differences in nutritional behaviour – the literature to date has typically not explored this possibility. This will be an important avenue for future research.

There are three types of approach by which HRV can be measured: the linear time-based and frequency-based approaches and also nonlinear methods. To date, limited research has considered nonlinear methods when studying diet, although there are reasons to believe that they contribute additional information to that supplied by the linear methods (Young and Benton, 2015). In addition, there is some evidence that nonlinear HRV indices capture the influence of endogenous hormonal fluctuations and thermoregulation (Bai *et al.*, 2009; Young and Benton, 2015), which may be pertinent when considering the influence of diet. Thus, future studies should incorporate both linear and nonlinear approaches into their designs.

In summary, the consistent relationship between HRV, health and morbidity supports the view that HRV can be considered an index of psychological and physiological resilience. An increasing number of studies report that particular foods, nutrients and dietary styles influence HRV, supporting its future use when examining the impact of what we eat. The insidious influence of diet will be cumulative and take place over a period of many decades (Benton, 2010). As such HRV may prove to be a means for identifying beneficial or detrimental aspects of diet.

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### Conflicts of interest

There are no conflicts of interest.

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