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## FACTORS ASSOCIATED WITH TASTE PERCEPTION AND DIETARY CONSUMPTION PATTERNS IN INDIVIDUALS WITH OR AT-RISK FOR CARDIOVASCULAR DISEASE

Jennifer L. Smith

University of Kentucky, [jennifer.smith7@uky.edu](mailto:jennifer.smith7@uky.edu)

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Jennifer L. Smith, Student

Dr. Gia Mudd-Martin, Major Professor

Dr. Susan Frazier, Director of Graduate Studies

FACTORS ASSOCIATED WITH TASTE PERCEPTION AND DIETARY  
CONSUMPTION PATTERNS IN INDIVIDUALS WITH OR AT-RISK FOR  
CARDIOVASCULAR DISEASE

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DISSERTATION

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A dissertation submitted in partial fulfillment of the  
requirements for the degree of Doctor of Philosophy in the  
College of Nursing at the University of Kentucky

By

Jennifer L. Smith

Lexington, KY

Director: Dr. Gia Mudd-Martin, Associate Professor of Nursing

Lexington, KY

2018

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## ABSTRACT OF DISSERTATION

### FACTORS ASSOCIATED WITH TASTE PERCEPTION AND DIETARY CONSUMPTION PATTERNS IN INDIVIDUALS WITH OR AT-RISK FOR CARDIOVASCULAR DISEASE

Excessive intake of sodium, sugar, fats, and other unhealthy dietary patterns significantly contribute to cardiovascular disease (CVD) risk and, among those with diagnosed CVD, to deleterious outcomes. Taste perception is one of the most important factors influencing dietary intake and there are many factors that can alter it such as medication and genetic variations. Yet there has been relatively little research on influences of taste perception on self-management of CVD and CVD risk.

The purpose of this dissertation is to examine the association of various factors and taste perception in order to add to our understanding of what may or may not influence dietary consumption behaviors among persons at-risk for or with diagnosed CVD. The specific aims of this dissertation were to 1) examine the association between dietary sodium consumption and antihypertensive medication regimen in patients with heart failure (HF); 2) examine the associations between variants of the *TAS2R38* haplotype and dietary intake patterns of salt, sugar, fat, alcohol and vegetables in community dwelling adults in Appalachia Kentucky with 2 or more CVD risk factors; and 3) examine associations between the *TAS2R38* haplotype and salt taste sensitivity and sodium consumption in patients with HF and their family caregivers.

Specific aim one was addressed by evaluating whether prescribed diuretic, beta blocker, angiotensin II receptor blockers (ARBs), and angiotensin converting enzyme (ACE) inhibitors predicted sodium consumption as evidenced by sodium density in a sample of patients with HF when controlling for age, gender, ethnicity, smoking status, New York Heart Association (NYHA) class and body mass index (BMI). The results of this study indicate that, among patients with HF, prescribed ACE inhibitor is predictive of higher sodium consumption but not prescribed diuretics, beta blockers and angiotensin receptor blockers. To address specific aim two, a secondary analysis of data of a sample

of adults living in rural Appalachia with 2 or more CVD risk factors was conducted. We examined if having one or two PAV haplotypes was predictive of patterns of salt, sugar, fat, alcohol and vegetable consumption, controlling for age, gender, smoking status, BMI, and prescribed ACE and ARB. There were no associations between *TAS2R38* haplotype and any of these dietary intake patterns. Specific aim three was addressed in a study to examine the associations between the *TAS2R38* haplotype and salt taste sensitivity and sodium consumption as indicated by 24-hour urinary sodium excretion in patients with HF and their family caregivers, controlling for age, gender, ethnicity, smoking status, and fungiform papillae number. Our outcomes indicated that haplotype did not predict salt taste sensitivity but did predict 24-hour urinary sodium excretion, with significantly less levels of urinary sodium excretion among participants who were homozygous for the PAV haplotype compared to those who were heterozygous for the PAV haplotype or homozygous for the AVI haplotype. The results of these studies, separately and in concert, provide greater understanding of influences of taste perception on self-management among people who are at-risk for or who have diagnosed CVD.

**KEYWORDS:** Taste perception, dietary patterns, salt taste perception, cardiovascular disease, genetics

Jennifer Smith

Student Signature

November 20, 2018

Date

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By

Jennifer L. Smith

Gia Mudd-Martin

Director of Dissertation

Susan Frazier

Director of Graduate Studies

November 20, 2018

Date

This work is dedicated to my supportive spouse Todd and my children, Soren and Midori.  
Thank you for the years of love and support and doing without me when I needed to  
study these past few years.

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## CHAPTER ONE:

### Introduction

In the United States, the average daily sodium consumption in the general population is much higher than the daily recommended amount. Nearly 90% of adults have a dietary intake that exceeds the recommended guideline of less than 2,300 mg a day,<sup>1-3</sup> with the majority consuming more than 3500 mg a day.<sup>1,4,5</sup> This is of particular importance when one considers that high dietary sodium consumption has been linked to hypertension, while reducing sodium intake can lower blood pressure.<sup>6,7</sup> Excess sodium intake has also been associated with higher risk of stroke and cardiovascular disease.<sup>7,8</sup>

Addressing dietary sodium intake is of particular concern for individuals already living with cardiovascular disease (CVD) such as heart failure (HF). Annually, over 870,000 people in the U.S. are newly diagnosed with heart failure (HF) and more than 5.8 million Americans are currently living with HF.<sup>9,10</sup> Heart failure carries a significant burden of morbidity and mortality with 50% likelihood of death within 5 years of initial diagnosis. It also results in an estimated \$30.7 billion annually in health care expenditures,<sup>10</sup> a substantial portion of which is due to HF re-hospitalizations.<sup>11</sup> Fluid overload due to excessive sodium intake is a major cause of HF exacerbation resulting in re-hospitalization.<sup>12</sup>

The linkages between overconsumption of sodium and risk for CVD as well as exacerbation of existing conditions such as HF underscore the importance of interventions directed toward decreasing dietary sodium consumption. Yet sodium reduction has proven to be difficult. To more effectively intervene to reduce dietary sodium intake requires understanding of mechanisms associated with sodium

consumption. There are many important determinations of salt consumption such as culture,<sup>13</sup> cost, and convenience.<sup>14</sup> Among the most important influences, however, is taste.<sup>14,15</sup>

### **Taste perception and dietary consumption**

Taste perception occurs when chemical particles from our food are received by the taste receptor cells on our tongue, setting off chemical and neural processes that result in identification and appraisal of the stimulus.<sup>15</sup> Taste receptor cells are located in taste buds, called papillae on the tongue. There are three types of papillae: circumvillae papillae on the posterior aspect of the tongue, foliate papillae on the lateral sides of the tongue, and fungiform papillae on the anterior portion of the tongue.<sup>16</sup> There are four types of taste cells: I, II, III, and basal.<sup>16,17</sup> Types I-III are open to the oral cavity and interact directly with tastants, or taste-provoking chemicals, through binding with taste receptor proteins. Most of these are G protein-coupled receptors (GPCR).<sup>18,19</sup> GPCR cells are highly sensitive, with one cell activating dozens of different g proteins.<sup>20</sup> Of the five taste modalities, bitter, sweet, and umami all use GPCRs to detect a particular taste.<sup>21</sup> Salt taste, on the other hand, is not as well understood. While the amiloride sensitive epithelial sodium channel (ENaC) is involved in salt taste, other mechanisms that have a role in salt taste perception have yet to be identified<sup>22</sup> and more research into these mechanisms is required. As salt taste has been mistaken for bitter,<sup>22</sup> bitter taste is a possible mechanism to explore. Moreover, we know that some forms of bitter taste perception are highly heritable and passed down genetically in families, indicating the importance of genetics in determining taste.<sup>23</sup>

Bitter taste is detected with a mixture of at least 30 high-affinity GPCRs that respond to a wide variety of bitter compounds and are called T2Rs, most of which are located in fungiform papillae.<sup>16,20</sup> The development of so many receptors (more than any other of the taste modalities) is largely protective as bitter taste serves as a warning that a substance may be toxic to the body. Bitter taste is a deterrent to consumption.<sup>18,20</sup> Of particular interest are the taste receptors coded by the *TAS2R38* gene, which are well-known to denote sensitivity to phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP), two substances that can taste exceptionally bitter depending on genotype.<sup>18,24</sup> The *TAS2R38* receptors are known to interact selectively with compounds that contain the N-C=S thiourea group, which results in the bitter taste of both PROP and PTC.<sup>17,25,26</sup> It is also known that substances that are chemically related to PROP and PTC but do not contain this chemical group do not activate the *TAS2R38* receptors.<sup>25</sup> Neither PROP nor PTC appear naturally in foods, however glucosinolates are chemically similar to PROP and PTC and naturally occur in some bitter tasting vegetables such as broccoli, cabbage, and brussels sprouts. These vegetables activate this receptor.<sup>23-25,27</sup>

### ***TAS2R38* gene and salt taste**

Ability to taste these chemicals has been linked to the haplotype inherited on the *TAS2R38* gene. There are two common haplotypes associated with bitter taste status: PAV and AVI. These haplotypes occur from base pair substitutions at three different single nucleotide polymorphisms (SNPs) locations, which alter the protein synthesized: proline versus alanine at position 49 (*rs713598*), alanine versus valine at position 262 (*rs1726866*), and valine versus isoleucine at position 296 (*rs1024639*).<sup>18,23,26,28,29</sup> These SNPs occur in strong linkage disequilibrium with each other.<sup>23,26</sup>

PROP supertasters are known to be highly sensitive to select bitter chemicals; it has also been proposed that sensitivity to PROP bitterness may also correlate with heightened taste sensitivity in the other taste modalities (salty, sweet, and sour). The relationship between salt and bitter taste was proposed by Bartoshuk et al. in their article published in 1998,<sup>30</sup> which debunked the notion that salt taste intensity was a good control measure to compare with bitterness intensity. In this study, the authors found that PROP super tasters tended to rate salt taste as more intense than those who were medium tasters and nontasters when samples were giving in as scaling order with PROP presented last.<sup>30</sup> Bajec et al performed an experiment that examined the interaction of thermal taste status and PROP taste status in the four basic taste modalities. Despite finding no interaction effects between thermal taste and PROP taster status with taste intensity ratings across taste modalities; researchers found that supertasters report higher intensity in salt taste as well as in the other taste modalities.<sup>31</sup>

Likewise, Hayes et al found that taste intensity ratings were positively correlated to PROP bitterness taste intensity; individuals that reported greater PROP bitterness also reported greater saltiness than those who reported PROP bitterness as less bitter.<sup>32</sup> These results indicate that PROP supertasters may experience greater saltiness due to greater sensitivity to changes in sodium concentration.<sup>32</sup> Fischer et al. conducted a study that examines associations between PROP taste intensity, other taste intensities and *TAS2R38* genotype.<sup>29</sup> These results confirmed that correlations existed between PROP bitterness intensity and the intensity of the other taste modalities (salt, sweet, sour, and quinine bitterness).<sup>29</sup> This was particularly evident for PAV homozygotes, who showed a stronger relationship between PROP and intensity of the 4 basic tastes.<sup>29</sup>

Finally, there is some anatomical evidence that links the two taste modalities. In a recent study that examined taste receptor cells expressed in human derived cell lines, researchers noted that common genes expressed in these cells were *TAS2R38*, which codes for the bitter taste receptor in questions, as well as *SCNN1B* and *SCNN1D*.<sup>19</sup> The latter two genes, *SCNN1B* and *SCNN1D*, are known to code for the ENaC that are responsible, in part, for salt taste.<sup>19</sup> While this study does not confirm any links between these two taste modalities, it is interesting to note that the receptors for them are expressed in the same cells. As these cells are located in fungiform papillae,<sup>19</sup> it is possible that this becomes relevant when one considers that PROP supertasters often have greater numbers of fungiform papillae. It extends logically that the expression of these receptors in the same cells may explain in part the relationship between the two taste modalities and intensity ratings.

### **Other factors that affect salt taste**

While the relationship between *TAS2R38* genotype and salt taste intensity has been explored through research, the relationship between genotype and salt taste sensitivity has not. Moreover, the relationship of fungiform papillae number, genotype, salt taste sensitivity, and dietary sodium consumption has not been investigated. Understanding the links between these variables is crucial, particularly in those patients who must limit their sodium intake: those with hypertension, heart failure, or other cardiovascular disease. Further research is necessary to explore these factors in order to inform the development of dietary interventions to decrease dietary sodium consumption.

Genotype is not the only known factor that affects taste perception. Other factors such as age, gender, smoking status, prescribed medication, and number of fungiform



papillae are all known to be correlated with changes in taste.<sup>18,33,34</sup> Two of the most well researched factors are fungiform papillae number and age.

*Fungiform Papillae.* As discussed earlier, the sensory equipment that allows us to taste, namely taste receptors, lie on the tongue and in the oral cavity. While there are different types of taste buds, the receptors for bitter taste are found predominantly in fungiform papillae. Number of fungiform papillae, also known as taste bud density, is known to alter ability to taste across taste modalities. In 1990, Miller et al. conducted an experiment in university student where participants were divided into high density and low density taste bud numbers in which the high density group was found to have significantly higher intensity ratings for sucrose, salt, and PROP bitterness.<sup>33,35</sup> It was later theorized that those who possessed the PAV haplotype anatomically had more fungiform papillae on the surface of the tongue as well as increased nerve density. This would increase the intensity of the signal because a greater area is stimulated.<sup>31</sup> Evidence has been contradictory on this point.

There is some evidence that those with the PAV haplotype may have more fungiform papillae than those with the AVI haplotype however, this occurs independently of *TAS2R38* genotype.<sup>18,36</sup> In a more recent study, there were no difference in fungiform papillae between the different haplotypes.<sup>37</sup> That said, Hayes et al. found that PROP bitterness taste increased in individuals who were homozygous for the AVI haplotype who also had greater numbers of fungiform papillae and this effect extended to PAV homozygotes.<sup>18</sup>

*Age.* It is well known that taste sensitivity is altered by age though natural changes in the body. Taste thresholds for food are known to rise as a person ages.<sup>38</sup> These

thresholds are the amount of a tastant required to sense the taste and identify the flavor; if the amount needed is low, our taste threshold is considered low. If we require a lot of the substance, our threshold is high.<sup>38</sup> With high thresholds, the normal amount of a tastant, like salt for example, will not produce the sensation of saltiness that we are used to tasting and this may render foods tasteless.<sup>38</sup> The root in these differences is thought to be related to changes in the speed of neural signaling and in functional Magnetic Resonance Imaging (fMRI) studies, lower brain activation is seen in older individuals to bitter taste.<sup>39</sup>

In particular, it has been noted that younger individuals are often more sensitive to the bitter taste of PTC and PROP than older individuals.<sup>40</sup> This difference seems to be more prevalent with PAV/AVI heterozygotes; children with this haplotype have been shown to be more sensitive to PROP bitterness than either adolescents or adults with the same haplotype.<sup>40</sup> This effect was not seen in either homozygous haplotype.

*Gender.* Gender may also influence taste sensitivity and intensity. In some studies, women have shown greater mean PROP intensity ratings than men.<sup>29</sup> Hormonal changes in women have been shown to be correlated with heightened liking and consumption for salt.<sup>32,41</sup> In a recent magnetoencephalography (MEG) study, female participants showed more high frequency channels than males, which is assumed to mean that they had better taste response than men.<sup>42</sup> In some study populations, there have been more females with enhanced bitter taste and a corresponding increase in nontasters among men.<sup>43</sup> Finally, PROP taster status has been shown to that *TAS2R38* haplotype was associated with healthy eating habits but only in female participants.<sup>44</sup>

*Medication.* Another key factor, though less well understood, is medication prescribed to the individual. Medications such as antihypertensive (such as angiotensin converting enzyme [ACE] inhibitors, beta blockers, and angiotensin II receptor blockers [ARBs]) and chemotherapy drugs are well known to alter taste sensation and sensitivity.<sup>34</sup> Of particular concern are ACE inhibitors because they are widely prescribed to patients with hypertension and heart failure, both of which need to limit their sodium intake. ACE inhibitors are known to alter taste sensitivity both alone and in conjunction with other medications such as ARBS or beta blockers.<sup>34,45</sup> What is not known about these medications is how the resulting alteration in taste sensitivity effects eating behavior. In particular, the links between medication and dietary sodium consumption are not well defined or understood. Appropriate understanding of this association is crucial in order to appropriately prepare patients on these medications for the additional barrier to reducing dietary sodium intake.

### **Purpose of Dissertation and Summary of Subsequent Chapters**

The purpose of this dissertation was to examine factors that are associated with salt taste perception to elucidate possible connection to sodium consumption behavior among persons with cardiovascular disease and heart failure. The chapters of this dissertation focus on the factors separately and together.

In Chapter 2, medication was considered for its association with sodium density in the diet of patients with heart failure. The focus of Chapter 3 was *TAS2R38* genotype and its association with sodium consumption as well as the consumption of other nutrients among people at-risk for cardiovascular disease. Chapter 4 is a report on *TAS2R38* genotype associations with sodium consumption among patients with HF and

their family caregivers, controlling for fungiform papillae number, age, and medication prescribed.

Little is known regarding the association of anti-hypertensive medication regimen and sodium consumption in patients with heart failure. In Chapter 2 we present a study conducted to examine the association between sodium consumption and medications commonly prescribed to patients with HF. Specifically, we examined associations with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers and diuretics, antihypertensive medications that are known to reduce sodium taste sensitivity. Linear regression was conducted in order to examine predictors of sodium consumption using sodium density as a proxy, controlling for age, gender, ethnicity, BMI, and NYHA class.

Current literature contains little information regarding the association of *TAS2R38* haplotype with adherence to daily recommendations for sodium, sugar, or saturated fats, as well as consumption of vegetables and alcohol. Chapter 3 is a study in which we examined associations between haplotype variants of the *TAS2R38* gene and sodium consumption as well as the consumption of other nutrients including saturated fat, sugar, alcohol, and vegetable consumption. This was a secondary analysis of data from a study conducted with community dwelling individuals with two or more cardiovascular disease risk factors. We hypothesized that people with one or two PAV haplotypes of the *TAS2R38* gene, associated with greater bitter taste sensitivity, would have greater sodium, sugar, and saturated fat consumption than those with the AVI haplotype because they add greater salt or sugar in order to offset the bitter taste of food. Because alcohol and vegetables have greater bitter taste properties, we also hypothesized that those with the

PAV haplotype would have decreased consumption of these compared to those who were homozygous for the AVI haplotype.

There is little known regarding the associations of salt taste sensitivity, fungiform papillae density, and sodium consumption among patients with heart failure and their family caregivers. Chapter 4 is a study in which we examined the association of *TAS2R38* genotype, salt taste sensitivity, and dietary sodium consumption in patients with heart failure and their family caregiver. We hypothesized that those with the PAV haplotype would be more sensitive to salt taste and would have lower 24-hour urinary sodium excretion. Linear regression was conducted to examine predictors of salt taste sensitivity and 24-hour urinary sodium excretion controlling for age, gender, ethnicity, smoking status, and fungiform papillae density.

Chapter 5 is a synthesis of the results of our studies and a discussion of their impact on the state of the science of taste perception factors and their relationship with dietary consumption of key nutrients that affect heart health such as sodium. This dissertation provides evidence of the importance of understanding factors that alter taste perception and their associations with eating behavior both in healthy individuals and in those with cardiovascular disease.

## CHAPTER TWO:

### **Dietary sodium intake is predicted by anti-hypertensive medication regimen in patients with heart failure**

#### **Introduction**

In patients with heart failure, self-care is pivotal to appropriate management of the condition including adhering to a low sodium diet.<sup>46</sup> Unfortunately, many patients with heart failure do not follow the recommended low sodium diet with rates of adherence reported to be as low as 22%.<sup>12,46-53</sup> Patients have identified taste of food as one reason for not adhering to this recommendation.<sup>54,55</sup> Most patients report that reducing salt makes food unpalatable and limits the enjoyment of eating, negatively affecting quality of life.<sup>54,55</sup>

Salt taste sensitivity, defined as the ability of an individual to identify the taste of sodium, is comprised of two dimensions: recognition and detection.<sup>34</sup> Recognition is the minimum amount of salt required to identify sodium in a food; detection is the minimum amount of salt required to detect a change in amount of sodium in a food.<sup>34</sup> Salt taste sensitivity is a complex phenomenon that is affected by factors that include neural, chemical, and structural inputs which can be altered by external factors such as medications, dietary salt intake, or health conditions such as heart failure.<sup>34,56,57</sup> Some antihypertensive medications and cardiac drugs, including angiotensin converting enzyme (ACE) inhibitors commonly prescribed in heart failure, cause a decrease in salt taste sensitivity,<sup>34,45,58</sup> which may result in increased salt consumption.<sup>45,59-61</sup> However, the relationship between angiotensin converting enzyme (ACE) inhibitors and salt

consumption has not been well-studied. Therefore, the purpose of this study was to examine if prescription of an ACE inhibitor predicted sodium consumption. We hypothesized that sodium consumption (as calculated based on amount of sodium consumed per kilocalorie or sodium density), would be higher in patients with heart failure prescribed ACE inhibitors than in patients who were not prescribed ACE inhibitors.

## **Methods**

*Design.* This was a secondary analysis of data from patients with heart failure enrolled in an observational longitudinal study examining the relationships between body fat mass, body fat distribution, cytokine activity, and nutritional intake.

*Sample.* Data from 255 patients were included in this analysis. Patients were recruited from three large academic healthcare facilities; two located in the southeastern region of the U.S. and one in the midwestern region. Inclusion criteria were: (a) confirmed diagnosis of chronic heart failure and (b) ability to read and speak English. Exclusion criteria were: (a) valvular heart disease as a cause of the heart failure; (b) myocardial infarction within the last 3 months; (c) referral for heart transplant; (d) uncontrolled diabetes mellitus (H<sub>g</sub>A<sub>1c</sub> > 8%); (e) presence of illness associated with systemic inflammation, weight loss, or decreased appetite; or (f) cognitive impairment that prevented giving informed consent.

### ***Measurement of Variables.***

*Demographic and Clinical Data.* Participant demographic data including age, gender, race/ethnicity, and smoking status were collected through self-report via a

sociodemographic questionnaire. New York Heart Association (NYHA) class and prescribed medications (i.e., ACE inhibitors) were ascertained by trained research nurses using a structured patient interview. Body mass index (BMI) was ascertained using the standard  $\text{kg}/\text{m}^2$  formula as BMI has been linked to excessive sodium consumption in prior research.<sup>62</sup>

*Dietary Sodium Consumption.* Dietary sodium consumption was defined as the averaged four-day sodium intake divided by averaged four-day kcal intake. This was chosen as the metric for salt consumption because it controls differences in sodium consumed due to differences in amount of food consumed and is a better indicator of patients' preferred saltiness of food. Nutritional data were collected by weighed food diaries that patients completed for a four-day period, including three weekdays and one weekend day. The use of four-day food diaries is a valid method from which nutrients in the diet, including sodium, can be measured.<sup>60,63</sup> Prior to recording food diaries, patients met with a research assistant in their homes who, using food models and pictures of appropriate portion sizes, instructed the patients how to accurately weigh and record dietary information. Each participant was given an electronic digital scale for accurate recording of portion sizes. At the end of the four-day food diary collection, patients met with a dietitian who collected missing information, verified serving sizes, and verified food preparation methods. Food diaries were analyzed using the Nutrition Data System for Research software (NDS-R 2007; NRCC, Minneapolis, MN).

***Procedure.***

Approval for this study was obtained from the Institutional Review Boards at each study site. Patients were recruited from affiliated outpatient clinics after referral from a



nurse or physician. After providing written informed consent, patients were visited in their homes and instructed how to complete four-day food diaries. The morning after completing diaries patients visited the Clinical Research Center to provide demographic and clinical data and review food diaries with a dietitian.

### ***Data Analysis.***

Patients were categorized into two groups: those who were prescribed ACE inhibitors and those who were not. Differences in demographic and clinical characteristics and in dietary sodium consumption between the two groups were compared using independent t tests or chi square as appropriate. A multivariable linear regression was conducted to determine whether prescribed ACE inhibitors independently predicted dietary sodium density. In the model we controlled for age, gender, ethnicity (non-Hispanic whites vs other races), BMI, NYHA class (I-IV), smoking status (smokers vs non-smokers), prescribed beta blocker, prescribed angiotensin II receptor blocker (ARB) and prescribed diuretics. All independent variables were entered into one model for analysis. An alpha of 0.05 was set *a priori*.

### **Results**

*Sample characteristics.* The majority of patients were white males with slightly more than half in NYHA class I/II. Mean BMI was  $29.7 \pm 6.8$ . Diuretics (74.5%), beta blockers (88.6%), and ACE inhibitors (69.8%) were commonly prescribed, but fewer than a quarter of patients were prescribed an ARB. Sample characteristics and comparisons between patients who were and were not prescribed an ACE inhibitor are

presented in Table 2.1. The only significant between-group differences were that more males were prescribed an ACE inhibitor and a beta blocker than females.

Patients prescribed an ACE inhibitor consumed approximately 13% more sodium per kcal than patients who were not prescribed an ACE inhibitor ( $1.8 \pm 0.6$  mg sodium/kcal vs.  $1.6 \text{ mg} \pm 0.4$  sodium/kcal;  $p = .001$ ). In our regression model, prescription of an ACE inhibitor predicted higher dietary sodium consumption ( $b = .230$ ,  $t(234) = 2.566$ ,  $p = .011$ , controlling for age, smoking status, ethnicity, NYHA class, and other prescribed medications [Table 2.2]).  $R^2$  for the model without ACE inhibitors was 0.038 and when ACE inhibitor was added to the model  $R^2$  changed to 0.057, accounting for 5.7% of the variance in the data. No other medications predicted dietary sodium consumption.

## Discussion

In support of our hypothesis, prescription of an ACE inhibitor predicted higher consumption of sodium per kcal. In accord with current practice guidelines,<sup>64,65</sup> patients with heart failure are commonly prescribed medications including ACE inhibitors in conjunction with a low sodium diet.<sup>64</sup> However, as indicated by the results of our study, prescribing ACE inhibitors may present a barrier to low sodium diet adherence.

Supporting our findings are studies that have shown ACE inhibitors are associated with taste disturbances.<sup>34,45,66</sup> Taste disturbances most commonly associated with ACE inhibitors range from taste loss, to alteration of salty, sweet, or metallic tastes that include a lingering taste in the mouth or taste confusions such as sweet for salty or sweet for bitter.<sup>58,67,68</sup> These disturbances may result in lowered salt taste sensitivity and increased salt consumption.<sup>60</sup>

Other medications are also suspected to produce taste disturbances, such as ARBs, diuretics, and beta blockers.<sup>34,45</sup> However, similar to other studies,<sup>34</sup> only ACE inhibitors predicted sodium consumption of diets in our patients with heart failure. The effect of ACE inhibitors may be exacerbated by heart failure induced over-activation of the renin-angiotensin-aldosterone system (RAAS), with angiotensin II and aldosterone implicated in inducing salt appetite in response to changes in sodium concentration.<sup>34,56</sup> ACE inhibitors work by preventing the conversion of angiotensin I to angiotensin II. ACE inhibitors are also known to chelate serum zinc which results in depletion of zinc levels.<sup>69</sup> It is possible that the depletion of zinc that occurs with the chelating action of ACE inhibitors causes a disturbance in the functioning of gustin, a protein necessary for the healthy growth and differentiation of taste buds,<sup>70</sup> which in turn produces a disturbance in salt taste. This could be the mechanism by which ACE inhibitors induce taste disturbances: by serum zinc concentration dependent mechanisms.<sup>69,71</sup>

In contrast, ARBs work by selectively blocking angiotensin II from binding to receptors but have not been linked to serum zinc depletion.<sup>45,67</sup> This may explain why prescribed ARBs did not predict dietary sodium density. Although some diuretics have also been linked to salt taste sensitivity alteration, this has only been demonstrated for diuretic medications that are less commonly prescribed today. For example, the potassium-sparing diuretic amiloride, rarely used today among patients with heart failure, was hypothesized to block ion channels in the taste receptor membrane altering the flow of sodium ions.<sup>67</sup> The majority of patients in our study were prescribed loop diuretics which have not been associated with salt taste sensitivity, as supported by our findings.

de Souza et al. reported that patients with heart failure may have a greater preference for salt in their food<sup>56</sup>. These authors further suggested that because most patients with heart failure have taken multiple medications over a long period of time, the medication could affect the palatability of food, although the authors do not define the length of time or the particular medication.<sup>56</sup> Consequently, patients with heart failure taking a medication that reduces the ability to taste the salt in their food<sup>34</sup> may need to use more salt to meet their already heightened preference. This behavior, in turn, can increase the risk of heart failure exacerbation. Our results suggest that ACE inhibitors may be one of those medication.

BMI was the only other variable in the model that was found to be a significant predictor of sodium density in the diet. This is not a surprising finding as sodium has been linked to BMI previously. In particular, excessive sodium consumption is thought to be linked with high calorie foods and the consumption of sugar sweetened beverages which can lead to being overweight or obese.<sup>62,72</sup> Specifically, sodium consumption in patients with heart failure has been linked to fluid retention which in turn leads to increasing weight.<sup>73</sup> Our results confirm previously reported associations between BMI and sodium consumption.<sup>62,72,73</sup>

Our finding that gender was not a significant predictor of sodium density may appear to be contrary to findings from previous studies in which men were shown to have higher rates of non-adherence to low sodium diet.<sup>50</sup> However, because the amount of sodium consumed is tied to the amount of food consumed, using sodium density instead of total sodium intake controlled for differences in amount of food consumed between

men and women. Consequently, this method allowed us to directly compare level of sodium in food between men and women.

The findings from our study can inform educational efforts. Understanding that ACE inhibitor use is associated with an increase in sodium consumption per kcal possibly due to alteration in salt taste sensitivity will allow providers to preemptively plan for this side effect. For example, some researchers have shown that prescribing zinc with ACE inhibitors may decrease the influence on salt taste sensitivity.<sup>69</sup> The reason for this may be due to an effect of ACE inhibitors that is thought to alter zinc at the receptor level which changes the conversion of angiotensin I to angiotensin II because zinc is necessary for the catalytic action of angiotensin converting enzyme.<sup>56,67,74</sup> In addition, taste disturbance is linked to zinc deficiency which may explain why this drug produces the effect.<sup>34,66,69,75</sup> Depletion of zinc interferes with production of gustin, a protein which is necessary for the growth and development of healthy taste buds; without gustin there are fewer taste buds.<sup>76</sup> Likewise, when educating patients with heart failure, consideration of possible taste disturbance may allow health care providers to be more specific when discussing the barrier of taste change when patients attempt to alter their diets. Providers may be able to offer advice on how to acclimate to decreased sodium in the diet while also dealing with a possible decrease in sensitivity to the taste. More research is required to further refine information regarding the association of ACE inhibitor use and sodium consumption as well as to develop educational interventions aimed at helping those on ACE inhibitors decrease their sodium consumption.

## Conclusions

The finding that prescribed ACE inhibitors predicted sodium consumption of patients with heart failure has implications for interventions to improve heart failure self-care. Aware of the potential alteration of sodium consumption associated with ACE inhibitors, nurses and other health professionals can closely monitor dietary sodium intake of patients prescribed ACE inhibitors and provide appropriate education and interventions. These measures can better support heart failure patients' adherence to low sodium diet recommendations thereby decreasing the risk of heart failure exacerbation and rehospitalization.

Table 2.1. Sample Characteristics by Angiotensin Converting Enzyme inhibitor (ACEi) grouping.

Characteristic	Total Sample (N=255)	Not prescribed ACEi (n=77)	Prescribed ACEi (n=178)	P-value
Age (years)	61.1 ± 11.8	61.2 ± 12.2	61.0 ± 11.7	.39
Gender (male)	174 (68.2%)	42 (54.5%)	132 (74.2%)	.003
Ethnicity (White)	185 (72.5%)	54 (70.1%)	131 (73.6%)	.64
Smoker (current or recent)	66 (25.9%)	23 (29.9 %)	43 (24.2%)	.35
NYHA class (III/IV)	112 (43.9%)	32 (41.6%)	80 (44.9%)	.78
BMI (kg/m <sup>2</sup> )	29.7 ± 6.8	29.4 ± 7.0	29.8 ± 6.7	.51
Prescribed diuretic (yes)	190 (74.5%)	59 (76.6%)	131 (73.6%)	.87
Prescribed beta blocker (yes)	226 (88.6%)	64 (83.1%)	162 (91.0%)	.08
Prescribed angiotensin receptor blocker (yes)	48 (18.8%)	41 (53.2%)	7 (3.9%)	.001

Data are mean ± SD or n (%), Angiotensin Converting Enzyme Inhibitor (ACEi)

Table 2.2. Predictors of Dietary Sodium Density

	<b><i>b (CI)</i></b>	<b>SE</b>	<b><math>\beta</math></b>	<b>P value</b>
<b>Age (years)</b>	.000 (-.006, .006)	.003	-.007	.925
<b>Gender (male reference group)</b>	.047 (-.097, .190)	.073	.042	.523
<b>Ethnicity (non-Hispanic White reference group)</b>	-.113 (-.274, .047)	.082	-.096	.166
<b>Smoking (past or never smoke reference group)</b>	.101 (-.062, .264)	.083	.085	.225
<b>NYHA Class (Class I/II reference group, III/IV non-reference group )</b>	.021 (-.115, .158)	.069	.020	.758
<b>BMI (kg/m<sup>2</sup>)</b>	.018 (.007, .028)	.005	.224	.002
<b>Prescribed diuretic (not prescribed reference group)</b>	.077 (-.082, .237)	.081	.064	.339
<b>Prescribed beta blocker (not prescribed reference group)</b>	-.092 (-.296, .112)	.104	-.056	.376
<b>Prescribed angiotensin II receptor blockers (not prescribed reference group)</b>	.005 (-.201, .212)	.105	.004	.959
<b>Prescribed angiotensin converting enzyme inhibitors (not prescribed reference group)</b>	.230 (.053, .406)	.089	.204	.011

*Note.* The dependent variable was sodium density.  $R^2$  for the full model = .070,  $p = .044$ .

New York Heart Association (NYHA), Body Mass Index (BMI)



## CHAPTER THREE:

### **Dietary Consumption of Sodium, Sugar, Saturated Fat, Alcohol, and Vegetables is Not Predicted by *TAS2R38* Haplotype**

#### **Introduction**

Cardiovascular disease (CVD) is the number one cause of death in the United States and costs our healthcare system \$320 billion dollars per year.<sup>2,77</sup> The most effective way to decrease rates of CVD is through prevention that targets risk factors such as obesity, physical inactivity and smoking.<sup>78</sup> Unhealthy diet is among the risk factors critical to target in risk reduction strategies. The association of diet with CVD risk is well-known. Excessive intake of sodium has been linked with hypertension, cardiovascular disease and stroke<sup>7,8</sup> while reduction of sodium has associations with lowering of blood pressure.<sup>6</sup> Excessive intake of sugar is not necessary for our health and provides no nutrients to our bodies.<sup>79</sup> Reducing saturated fat intake has been shown to reduce low density lipoprotein cholesterol<sup>80</sup>, which has been linked to an increase of CVD risk through adherence to the artery walls.<sup>81</sup> Increased consumption of alcohol can lead to hypertension, heart failure, and increased calorie intake.<sup>82</sup> Research has shown that vegetables in the diet are associated with a reduction of risk for many chronic diseases and certain types of cancer.<sup>49</sup>

Although essential to maintenance of good health and prevention of CVD, the diets of most people in the United States are poor. For example, the average sodium consumption for American adults is double the American Heart Association (AHA) recommendation of no more than 2,400 milligrams (mg) per day.<sup>78,83</sup> According to

USDA guidelines, less than 10% of daily calories should come from sugars or saturated fats. Despite this, the average adult consumes 13% of their calories from sugars and 11% from saturated fats per day.<sup>49</sup> Similar patterns are seen with alcohol and vegetable intake. According to data from the 2016 Behavioral Risk Factor Surveillance System (BRFSS), 16.5% of U.S. adults overindulge in alcohol, consuming on average more than 4 drinks per day despite recommendations that men have no more than 2 drinks per day and women no more than 1 drink per day.<sup>84</sup> According to data from the 2016 BRFSS, most adults in the U.S. don't consume adequate amounts of fruits and vegetables.<sup>49,84</sup>

Much research has been conducted to better understand dietary choices including studies examining the influence of socioeconomic status,<sup>85</sup> access to healthy food choices,<sup>86</sup> food preparation time and knowledge,<sup>87</sup> and culture.<sup>88</sup> Less studied has been the role of the taste of foods that in turn can affect food choices and eating patterns. Among the few studies conducted, important patterns emerge regarding the importance of taste. In experiments where participants were asked to rate the importance of food taste when considering items for purchase, 77% rated taste as very important.<sup>89</sup> Healthier food choices have been frequently identified as being less desirable due to poor taste. For example, although following a low sodium diet is critical to lowering risk for heart failure exacerbation, adherence to low sodium diet is difficult for many patients with this condition due to the perception of low sodium foods as not tasting good.<sup>54,55,90</sup>

Taste is a unique sense that varies greatly among individuals and cultures. It is an important factor in decisions regarding food choices and eating behavior.<sup>15</sup> Taste preferences are based on learned patterns, social behavior, and genetic variations in taste receptors.<sup>15</sup> The emerging science of genetics in taste perception and sensation holds

promise for elucidating the underpinnings of the wide variation of taste preferences between individuals. Differences in genotype can produce variation in proteins that determine the structure and function of taste receptors in the tongue.<sup>25,43,91</sup> Taste receptors, in turn, have a central role in the detection and processing of flavors in foods and are ultimately responsible for variations in the 5 taste modalities: salty, sweet, bitter, sour, and umami, or savory. Genetic variations can result in differences in taste receptors that in turn may lead to differences in how flavors are perceived.

One of the most well studied genetic variations that influence taste is the *TAS2R38* gene which codes for a bitter taste receptor and is known to enhance the taste of glucosinates in food and the associated 6-n-propylthiouracil (PROP) chemical that is sensed as bitter.<sup>18,91,92</sup> The two well characterized haplotypes of the *TAS2R38* gene are the PAV and the AVI haplotype. The ability to taste these two chemicals varies greatly depending on which haplotype of the *TAS2R38* gene is inherited. The PAV haplotype results in the two chemicals tasting especially bitter while the AVI haplotype results in the chemicals having no taste. Approximately 70% of people have at least one copy of the PAV haplotype and are able to taste bitter properties of foods and chemicals (referred to as the taster phenotype) whereas 30% are homozygous for the AVI haplotype and are unable to taste these properties (referred to as the non-taster phenotype).<sup>18,91</sup> While these haplotypes are known to affect bitter taste perception and have been associated with patterns of cruciferous vegetable consumption, very little is known regarding their association with other perceived tastes including sodium, sugar, fat, and alcohol despite known associations with taste intensity of other taste modalities of sour, salty, and

sweet.<sup>93</sup> Similarly, the association between haplotype and vegetable consumption in general has not been well investigated.

Therefore, we conducted a study to better understand the potential role of the PAV and AVI haplotypes in dietary patterns. The purpose of this study was to examine associations of the *TAS2R38* haplotype with daily sodium, sugar, saturated fat, and alcohol intake in adults with two or more CVD risk factors. We hypothesized that compared to people who are AVI homozygous, those who are heterozygous or homozygous for the PAV haplotype would a) be less likely to meet standard dietary recommendations for sodium, sugar, and saturated fat consumption and b) would have lower vegetable and alcohol intake.

## **Methods**

*Design, Sample and Setting.* This was a secondary analysis of baseline data from 344 participants in the *Gene Environment Interactions Regulating CVD Inflammation and Success of Behavioral Therapies*. The original study was conducted to examine the effects of genotype on responses to a self-management intervention to reduce CVD risk among rural community-dwelling populations at-risk for CVD. Participants were included who had 2 or more CVD risk factors including unhealthy diet, being physically inactive, being overweight or obese; being a current smoker; age 45 years or older for males and 55 years or older for females; having a family history of heart attack or stroke; having diagnosed hypertension, diabetes, or abnormal lipids; or experiencing depression or anxiety. Patients were excluded if they 1) were taking medication that interfered with lipid metabolism, 2) were cognitively impaired, 3) were non-English speaking, 4) suffered from chronic drug abuse, 5) had end-stage renal, liver, or pulmonary disease, 6)

had current, active cancer, 7) had a GI disease that required a special diet, 8) had any condition that prohibited physical activity, or 9) had known coronary artery disease or genetic or congenital heart disease. Data analyses were limited to those who self-identified as Caucasian (>92% of participants) to control for population stratification. Carriers of the dominant PAV haplotype on the *TAS2R38* gene were compared to non-PAV carriers, i.e., AVI homozygotes; participants with rare non-PAV or AVI haplotypes were excluded from analyses for a total of 211 participants.

### ***Measures***

*Demographics:* Age, gender, smoking status, and medications were assessed using self-report. These factors were included as they have been previously reported to have associations with taste perception.<sup>44,94,95</sup>

*Body mass index (BMI):* Weight was measured on a professional digital scale and height on a stadiometer with participants in light clothing and shoes removed. BMI was calculated as weight in kilograms divided by height in meters squared.

*Dietary intake patterns.* Data on dietary intake of sodium, sugar, saturated fats, alcohol and vegetable consumption were obtained using the Viocare Food Frequency Questionnaire (FFQ). Evidence has shown web-based FFQs to be a reliable method for estimating dietary quality.<sup>96</sup> This web-based, self-report, food frequency questionnaire was completed by participants on computer. Participants indicated how often foods were consumed over the past 90 days as well as portion sizes. Questions covering how food was purchased and prepared were also included to more accurately calculate nutrient intake. Participants opted to complete the questionnaire independently during the baseline

data collection period or to have questions read aloud by a research nurse who then completed the instrument based on participant responses. The FFQ were analyzed using NDSR (Nutrition Data System for Research) software which provided output on the number of portions of vegetables consumed daily as well as milligrams of sodium, grams of sugar and saturated fats, and number of alcoholic drinks consumed daily.

*DNA.* DNA was obtained from expectorated saliva collected using Oragene-DNA Collection Kits (DNA Genotek Inc., Ottawa, Ontario, Canada). Saliva has been shown to be as accurate as whole blood for DNA isolation and genotyping, to have lower participant burden,<sup>97-100</sup> and to provide high quantity and quality DNA.<sup>101,102</sup> DNA was quantified by UV absorbance with a Nanodrop. Genotyping was performed using Taqman® according to manufacturer's instructions. Primers and probes (FAM and VIC labelled) were supplied by Life Technologies. DNA samples were genotyped in a genetics lab with capacity to isolate, genotype, and appropriately store genetic material. The DNA samples were pipetted onto a 96 well plate. Genotypes were determined using an MJR Chromo-4 RT-PCR system (MJ Research). Two SNPs, *rs713598* and *rs1726866*, from the *TAS2R38* gene were genotyped using samples from all participants who consented to DNA analyses. These SNPs are associated with the PAV/AVI haplotype and code for the first and second positions respectively. The third SNP, *rs10246939* was not genotyped because it is in perfect linkage disequilibrium with the *rs1726866* SNP. Both SNPs genotyped have been associated with enhanced bitter taste perception.

### ***Procedure***

Approval from the Institutional Review Board was obtained prior to initiating the study. All participants gave informed consent before baseline data were collected

including demographic data through self-report questionnaires, clinical measurements, FFQ, and the Oragene kit for saliva DNA sample. Patients were randomized to intervention and control group then post-intervention data were collected. For this secondary data analysis, only baseline data from participants who had provided a DNA sample were included.

*Data Analysis* Dietary intake of each of the dietary components of interest was categorized as either adherent or non-adherent to the United States Department of Agriculture (USDA) Dietary Guidelines<sup>49</sup> for intake for sodium ( $\leq 2.3$  g), sugar (< than 10% of total calories [kcal]), and saturated fats (<than 10% of total kcal). Alcohol and vegetables were taken from the FFQ as number of servings per day consumed. Patients were grouped by *TAS2R38* genotype as either a) PAV homozygous or heterozygous or b) AVI homozygous. To ascertain differences between groups, independent t -tests and chi square analyses were conducted as appropriate for the level of measurement. Logistic regressions were conducted to examine whether genotype predicted adherence to dietary recommendations for sodium, sugar, and saturated fat. We controlled for factors that affect taste including age, gender, smoking status (current or recent smokers compared to past or never smokers), BMI, and prescribed angiotensin converting enzyme inhibitor (ACEi) (yes/no) and angiotensin II receptor blocker (ARB) medications (yes/no). Linear regressions were used to examine whether genotype predicted consumption of alcohol and vegetable intake, controlling for factors previously delineated that affect taste and dietary intake (age, gender, smoking status, BMI, and prescribed ACEi and ARB medications). Data were analyzed using SPSS, v. 24. An alpha level of 0.05 was used for all analyses.

*Power considerations.* An *a priori* power analysis indicated that with alpha equal to .05 and a sample size of 125 (representing an anticipated 38 participants with at least one PAV dominant haplotype and 87 heterozygous or homozygous AVI individuals), the power for group comparison of genotypes would be at least 85%, assuming the ratio of the standard deviation of the group means to the standard deviation of the observations within the populations is as small as 0.36; this effect size was more modest than that reported previously in a similar study.<sup>103</sup>

## **Results**

*Sample Characteristics.* Of the 211 participants (mean age 52.0±13.4 years; 73.5% female), the majority were overweight or obese (mean BMI 32.9 kg/m<sup>2</sup> ± 7.7 and non-smokers (84.4 %); 22.3% were taking ACEi and 3.3% ARB; 82.5% were homozygous or heterozygous for the PAV haplotype. The percentage of participants who met daily recommended intake of sodium, consuming <2.3 g/day was 18%; 1.6% of participants consumed <10% of their calories of sugar and 25.1% of participants consumed <10% of their calories as saturated fats. Mean alcohol consumption was 2.9 ± 9.6 drinks per day. Mean vegetable consumption was 1.4 ± 1.3 servings of vegetables per day. As shown in Table 3.1, there were no significant group differences in characteristics between participants who were homozygous or heterozygous for the PAV haplotype and those who were homozygous for the AVI haplotype.

*Predictors of Dietary Intake Patterns.* Neither the PAV nor the AVI haplotype was predicted dietary intake of sodium, sugar, saturated fats, alcohol or vegetable consumption (Tables 3.2, 3.3, 3.4, 3.5, and 3.6). In the logistic regression models, BMI



was the only significant predictor of adherence to dietary sodium recommendations ( $p=0.014$ ) and saturated fat recommendations ( $p=0.015$ ).

## Discussion

We examined adherence to standard dietary sodium, sugar, and saturated fat recommendations as well as dietary intake patterns of vegetables and alcohol in adults as a function of the PAV and AVI haplotype of the *TAS2R38* gene. Our hypotheses that people who were heterozygous or homozygous for the PAV haplotype would be less likely to adhere to recommended sodium, sugar, and saturated fat consumption and would have lower vegetable and alcohol consumption than those who were homozygous for the AVI haplotype were not supported. We found no significant difference between haplotypes on adherence to dietary recommendations for consumption of sodium, sugar, or saturated fats. Likewise, neither alcohol nor vegetable consumption was significantly different between those with the PAV homozygous or heterozygous haplotype and those who were AVI homozygotes. Results of other studies have demonstrated links between the taster phenotype due to the PAV haplotype and intensity of sodium taste.<sup>93,104</sup> People with the taster phenotype that corresponds to PAV homozygous individuals (PROP supertasters) tended to taste greater intensity of sodium over those with the phenotype that corresponds to the AVI homozygous haplotype (PROP nontasters).<sup>93,104,105</sup> Hayes et al. also showed that PROP supertasters were also more likely to detect differences in sodium at lower concentrations than PROP nontasters and showed greater dislike for sodium at higher concentrations.<sup>104</sup> In a prior study, salt sensitivity was positively correlated with sensitivity to bitter chemicals associated with the PAV haplotype of the *TAS2R38* gene<sup>106</sup> and this would suggest that the haplotype may also have a relationship to salt taste perception. While these studies examined food taste testing in the laboratory, they did not examine sodium consumption in day to day life. In our study, we found no

relationship between *TAS2R38* haplotypes and preference for foods higher in sodium among community dwelling adults. This may indicate that experiencing greater salt intensity does not translate to food selection and increased sodium consumption, despite its relationship with greater dislike of highly concentrated salt.

Similar to studies of sodium consumption, prior studies have also demonstrated an association between *TAS2R38* haplotype and sugar consumption. Specifically, it has been demonstrated that the homozygous PAV haplotype was associated with significantly higher consumption of sugar in both children<sup>107</sup> and adults.<sup>107</sup> Furthermore, PROP supertasters, have been shown to have higher fat and calorie intake when compared to non-tasters, indicating that the same difference could be seen between PAV homozygotes and AVI homozygotes.<sup>108</sup> Additionally, *TAS2R38* haplotype was associated with vegetable intake in college students,<sup>27</sup> higher intakes of folate and vitamin B<sub>6</sub> (found in green leafy vegetables) in women,<sup>44</sup> and higher vegetable consumption in a sample of adults in Brazil.<sup>27,107-109</sup> The PAV homozygous haplotype has also been associated with avoidance of such bitter tasting foods as cabbage, broccoli, coffee, tea, chocolate, and alcoholic beverages.<sup>27,110</sup>

While the relationship between *TAS2R38* has been confirmed in many studies, results of other studies have not confirmed these conclusions. In their study of dietary patterns in Irish children, O'Brien et al found that while bitter taste perception may have influenced some individual food consumption, it did not affect overall dietary patterns.<sup>111</sup> Furthermore, Risso et al found in their study of smoking behaviors and *TAS2R38* haplotype that genotype was only related to smoking behaviors in European Americans

and not in African Americans.<sup>112</sup> These contradictory findings emphasize the need for further research into the relationship between haplotype and eating behavior.

There may be many reasons that, in contrast to previous studies, we did not find a relationship between *TAS2R38* haplotype and sodium, sugar, fat, vegetable or alcohol consumption. Given that our sample was drawn from a rural population of low socioeconomic means, socioeconomic variables not accounted for in our analyses could be more important moderators of diet than taste preferences conferred by the *TAS2R38* haplotype. For example, rural populations such as participants in our study frequently have limited access to healthy foods compared to urban populations.<sup>113</sup> These populations are often served by smaller grocery store chains that are less likely to stock fresh fruits and vegetables and hence may be food deserts.<sup>114</sup> Access is also closely related to the lower socioeconomic conditions common in rural areas.<sup>113</sup> As has been noted in previous studies, those who live in food deserts spend more money on low quality food items and less money on fresh vegetables and fruits.<sup>114</sup> It is possible that our participants were burdened by poor access to healthy foods and this factored more strongly into their food choices.

Our findings may also suggest that there is a different mechanism for taste modalities with PROP taster phenotype that is not associated with *TAS2R38* haplotype. This is likely as density of fungiform papillae, the number of taste buds on the tongue, was previously thought to correspond with *TAS2R38* haplotype but has since been found to operate through a separate mechanism.<sup>18</sup> Indeed, greater taste intensity could be related to the greater fungiform papillae density that has been found to accompany PROP supertaster phenotype, which appears independently of *TAS2R38* haplotype.

A limitation to our study was that, as this was a secondary analysis, we did not have data available on PROP taster phenotype and fungiform papillae number, which would have important control variables. Another limitation was that, because our sample was comprised of Caucasians of European descent, our findings are not generalizable to other racial and ethnic groups. Likewise, the sample was primarily female and thus may not generalize to males. Finally, it is important to note that FFQs are not a reliable measure of sodium intake. However, as this project is comparing across groups, the use of relative amounts of sodium are sufficient as each individual was measured in the same way.

## **Conclusions**

In this study, *TAS2R38* haplotype was not found to independently predict adherence to recommended dietary intake of sodium, saturated fats, or sugar nor did it predict intake of vegetables or alcohol. These findings may indicate that other physiological as well as socioeconomic factors play a stronger role in these dietary behaviors. Future research to elucidate the contributions of *TAS2R38* haplotype to eating behaviors should consider a wider array of social and behavioral variables, such as taster phenotype, and fungiform papillae density. Also, because PROP phenotype has been shown to be a strong predictor of food choices and is easy to determine using an inexpensive non-invasive test, it may be more beneficial to examine PROP phenotype in future studies rather than genotype alone.

Table 3.1: Demographic Characteristics by *TAS2R38* Haplotype

Mean $\pm$ SD or % (n)	Total Sample N=211	PAV/PAV or PAV/AVI (n=174)	AVI/AVI (n=37)	P value
<b>Age</b>	52.0 $\pm$ 13.4	51.9 $\pm$ 13.1	51.5 $\pm$ 14.9	.287
<b>Gender (female)</b>	73.5% (155)	71.8% (125)	81.1% (30)	.308
<b>BMI</b>	32.9 kg/m <sup>2</sup> $\pm$ 7.7	32.9 $\pm$ 8.0	32.5 $\pm$ 6.4	.154
<b>Smoking status (non-smoker)</b>	84.4% (178)	82.2% (143)	94.6% (35)	.079
<b>Prescribed ACEi (yes)</b>	22.3% (47)	22.4% (39)	21.6% (8)	.830
<b>Prescribed ARB (yes)</b>	3.3% (7)	2.9% (5)	5.4% (2)	.619
<b>Sodium (mg)</b>	3785.1 $\pm$ 1939.7	3837.0 $\pm$ 2003.4	3540.8 $\pm$ 1608.4	.593
<b>Saturated fats (g)</b>	30.5 $\pm$ 19.8	31.1 $\pm$ 20.6	27.6 $\pm$ 15.7	.262
<b>Sugars (g)</b>	138.6 $\pm$ 117.2	141.5 $\pm$ 124.9	125.0 $\pm$ 69.8	.215
<b>Alcohol (servings per day)</b>	2.9 $\pm$ 9.6	2.7 $\pm$ 8.3	3.7 $\pm$ 14.2	.237
<b>Vegetables (servings per day)</b>	1.4 $\pm$ 1.3	1.2 $\pm$ 1.1	1.9 $\pm$ 1.6	.021

Abbreviations: ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers

Table 3.2: Predictors of Adherence to Dietary Sodium Consumption ( $\leq 2.3\text{g}$ )

<b>Variable</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>P</b>
<b>Age</b>	1.01	0.97 - 1.04	.537
<b>Gender</b>	0.52	0.18 - 1.49	.227
<b>Smoking status (non-smoker)</b>	2.71	0.58 – 12.76	.206
<b>BMI</b>	1.08	1.02 – 1.14	.014
<b>Prescribed ACEi (yes)</b>	0.53	0.21 – 1.35	.185
<b>Prescribed ARB (yes)</b>	0.84	0.90 – 7.91	.882
<b>PAV Haplotype</b>	1.12	0.43 – 2.91	.817

Abbreviations: ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; body mass index = BMI

Table 3.3. Predictors of Sugar Consumption Adherence (<10% of total calories)

<b>Variable</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>P value</b>
<b>Age</b>	0.95	0.85 – 1.06	.376
<b>Gender</b>	1.06	0.07 – 17.19	.965
<b>Smoking Status (non-smoker)</b>	0.03	0.01 – 0.80	.036
<b>BMI</b>	0.93	0.75 – 1.14	.461
<b>Prescribed ACEi (yes)</b>	59017904.46	0.00 – 0.00	.997
<b>Prescribed ARB (yes)</b>	43429086.94	0.00 – 0.00	.999
<b>PAV Haplotype</b>	6.69	0.29 – 151.79	.233

Abbreviations: ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; body mass index = BMI



Table 3.4: Predictors of Saturated Fat Consumption Adherence (<10% of total calories)

<b>Variable</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>P value</b>
<b>Age</b>	0.97	0.94 – 0.99	.039
<b>Gender</b>	0.61	0.26 0 1.46	.265
<b>Smoking status (non-smoker)</b>	1.05	0.35 – 3.14	.936
<b>BMI</b>	1.07	1.01 – 1.13	.015
<b>ACEi Prescribed (yes)</b>	1.13	0.48 – 2.67	.784
<b>ARB Prescribed (yes)</b>	1.99	0.22 – 17.89	.538
<b>PAV Haplotype</b>	0.66	0.26 – 1.69	.383

Abbreviations: ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; body mass index = BMI

Table 3.5: Predictors of Alcohol Consumption (servings per day)

<b>Variable</b>	<b>b (CI)</b>	<b>SE</b>	<b><math>\beta</math></b>	<b><i>P</i> value</b>
<b>Age</b>	0.08 (-0.03 – 0.18)	0.05	0.12	.135
<b>Gender</b>	-2.42 (-5.37 – 0.53)	1.49	-0.12	.107
<b>Smoking Status</b>	3.37 (-0.33 – 7.07)	1.87	0.13	.074
<b>BMI</b>	-0.14 (-0.30 – 0.03)	0.09	-0.12	.109
<b>ACEi Prescribed</b>	-0.54 (-3.60 – 2.52)	1.55	-0.03	.727
<b>ARB Prescribed</b>	-3.46 (-10.06 – 3.14)	3.34	-0.08	.302
<b>PAV Haplotype</b>	-1.91 (-5.09 – 1.28)	1.61	-0.09	.239

Model F = 1.981; R2 = 0.073; P = 0.060

Abbreviations: ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; body mass index = BMI

Table3.6: Predictors of Vegetable Consumption (servings per day)

<b>Variable</b>	<b>b (CI)</b>	<b>SE</b>	<b><math>\beta</math></b>	<b>P value</b>
<b>Age</b>	0.01 (-0.01 – 0.03)	0.007	0.13	.090
<b>Gender</b>	0.06 (-0.32 – 0.44)	0.19	0.02	.754
<b>Smoking status</b>	-0.61 (-1.09 – -0.13)	0.24	-0.19	.012
<b>BMI</b>	0.00 (-0.02 -0.02)	0.01	0.001	.992
<b>Prescribed ACEi</b>	0.05 (-0.35 – 0.44)	0.20	0.02	.812
<b>Prescribed ARB</b>	-0.14 (-0.99 – 0.71)	0.43	-0.33	.745
<b>PAV Haplotype</b>	-0.09 (-0.49 – 0.32)	0.21	-0.03	.674

Model F = 1.764; R2 = 0.029; P = 0.097

Abbreviations: ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers

## CHAPTER FOUR:

### **TAS2R38 Haplotype predicts 24-hour Urinary Sodium Excretion in Patients with Heart Failure and their Family Caregivers**

#### **Introduction**

Heart failure (HF) carries a significant burden of morbidity and mortality with 50% likelihood of death within 5 years of initial diagnosis. It is also an economic burden, resulting in an estimated \$30.7 billion annually in health care expenditures,<sup>10</sup> a substantial portion of which is due to HF re-hospitalizations.<sup>11</sup> Rehospitalizations are often related to exacerbations that are preventable with appropriate self-care.<sup>46</sup> Critical self-care activities for HF include taking medication as prescribed, monitoring of symptoms, evaluating symptom severity, and adhering to a low sodium diet (LSD).<sup>46</sup> Adherence to LSD is of particular concern because excessive sodium intake leads to fluid overload which is a major reason for rehospitalization.<sup>12,46</sup>

Despite the importance, adherence rates are alarmingly low, with estimates of nonadherence to LSD ranging from 22% to 51% in patients with HF.<sup>48-53</sup> Adherence is associated with numerous barriers including lack of information from providers about diet, insufficient social support for dietary changes, and limited low sodium food choices.<sup>54,55</sup> Among the most commonly reported barriers, however, are altered taste of and decreased pleasure derived from eating low sodium foods.<sup>54,55</sup> Much research has been conducted to improve patient education regarding LSD<sup>48-50,52-54,90</sup> and more recently to improve social support.<sup>49,115-121</sup> Few studies have been conducted to elucidate genetic and biological determinants of preference for higher sodium foods that may impede

adherence. Identifying these determinants has the potential to guide the development of personally tailored interventions to improve adherence to LSD among patients with HF.

### ***Salt taste sensitivity and associated phenotypes and genotypes***

Tastes experienced by humans are triggered by five distinct modalities: sweet, salty, sour, bitter, and umami.<sup>15</sup> Taste is mediated by receptors located in taste buds on papillae on the surface of the tongue. The receptors bind with molecules to trigger sensory signals that are transmitted to the brain and interpreted as particular tastes; G protein-coupled receptors bind with molecules associated with sweet, bitter, and umami taste.<sup>17,122,123</sup> Salt taste is primarily detected through the epithelial sodium channel (ENaC)<sup>124</sup> but also involves other receptors.<sup>22,124,125</sup>

Because taste receptors are located in taste buds situated within papillae, taste perception is also mediated by number and type of papillae. Fungiform papillae that are located on the tongue's anterior surface have a prominent role in taste perception. In particular, fungiform papillae are associated with salt, bitter, and sweet taste. Greater density of fungiform papillae is in part responsible for greater taste perception associated with these modalities.<sup>94,126,127</sup> Fungiform papillae density is an important variable to consider when examining taste. Two bio-behavioral factors related to taste perception are the focus of the proposed study, salt taste sensitivity and bitter taste perception.

*Salt taste sensitivity.* How acutely a person can taste salt, or the level of sodium concentration at which a person perceives and identifies 'salty' taste is defined as salt taste sensitivity.<sup>75,125</sup> A person with high salt taste sensitivity is able to detect salty taste at lower sodium concentration levels than someone with low salt taste sensitivity. There is a wide range of salt taste sensitivity variability among individuals.<sup>32,128</sup> One explanation for

this is variations in number of fungiform papillae, with greater fungiform papillae density associated with higher salt taste sensitivity.<sup>126</sup>

*Genetic variants and salt taste.* Genetic variants may also influence salt taste sensitivity but those directly associated with salt taste have yet to be identified.<sup>75,125,129</sup> However, a haplotype for bitter taste perception has been identified and may also influence salt taste. This haplotype is associated with ability to taste glucosinates in food and the associated 6-n-propylthiouracil (PROP) chemical. Approximately 70% of people are able to taste bitter properties of foods and chemicals (referred to as tasters) whereas 30% are unable to (referred to as non-tasters).<sup>18,91</sup> Tasters have higher salt taste sensitivity but paradoxically consume more sodium than non-tasters.<sup>32</sup> It has been hypothesized that higher sodium consumption among tasters may be due to greater salt taste enjoyment or that sodium may be used to mask the bitter taste of foods.<sup>130,131</sup>

Bitter taste perception is highly heritable<sup>18,91</sup> and is influenced by the taste 2 receptor member 38 (*TAS2R38*) gene that encodes the G protein-couple receptor associated with bitter taste.<sup>92</sup> Three common single nucleotide polymorphisms (SNPs) of the *TAS2R38* gene (*rs714598*, *rs1726866* and *rs10246939*) code for variations in amino acids at three positions: Ala49Pro (alanine [Ala] or Proline [Pro] at amino acid position 49), Val262Ala (valine [Val] or alanine [Ala] at amino acid position 262) and Ile296Val (isoleucine [Ile] or valine [Val] at amino acid position 296), respectively. These single nucleotide polymorphisms (SNPs) are in strong linkage disequilibrium, giving rise to one of two common haplotypes: the proline-alanine-valine (PAV) haplotype, which is associated with being a taster sensitive to bitter taste, and the alanine-valine-isoleucine (AVI) haplotype, which is associated with being a non-taster who is not sensitive to particular

bitter taste.<sup>18,132</sup> In a U.S. sample of 980 White and African-American individuals, the most common haplotypes were PAV at 43.1% and AVI at 41.2%.<sup>95</sup> A worldwide study of 5,589 individuals from 105 populations similarly demonstrated that the PAV and AVI haplotypes were most frequent with similar frequencies across populations.<sup>23</sup> Reflecting reported percentages of population tasters and non-tasters, genetic studies have similarly demonstrated that ~69% of the population is heterozygous or homozygous for the PAV and ~30% are homozygous for the AVI haplotype.<sup>92</sup> The frequency of variation from these haplotypes is rare.<sup>28</sup>

The importance of the PAV and AVI haplotypes for salt taste is as-yet not well determined. While there is strong evidence of the association of haplotype variations with ability to taste bitter,<sup>18,132</sup> and of associations between the ability to taste bitter and salt taste sensitivity, evidence of associations between PAV and AVI haplotypes and salt taste sensitivity is limited.<sup>29</sup> Because taste sensitivity influences food selection and dietary patterns, elucidating associations among taste-related genotypes and salt taste sensitivity as well as dietary sodium intake in patients with HF may provide greater understanding of barriers to LSD adherence. To our knowledge, no study of the associations of PAV and AVI haplotypes with adherence to LSD in this population has been conducted. Therefore, we examined whether *TAS2R38* haplotypes predicted salt taste sensitivity and dietary sodium intake among patients with HF controlling for age, gender, ethnicity, smoking status, and fungiform papillae density. We hypothesized that a) participants with the PAV haplotype would be more sensitive to salt taste than those who were heterozygous or homozygous for the AVI haplotypes and b) participants with the PAV

haplotype would consume less salt and would have lower 24-hour urinary sodium excretion compared to the other two groups.

## **Methods**

*Design, Setting and Sample.* This was a descriptive comparative study of salt taste sensitivity and *TASR38* genotype measured at baseline in the ongoing parent grant, *Effects of Family Sodium Watcher Program on Outcomes in Heart Failure Patient-Family Caregiver Dyads' (FAMSWaP)*. The *FAMSWaP* study is a randomized, controlled trial testing the effects of an intervention for the patient with HF and family caregiver dyads to improve LSD adherence.

Participants for the *FAMSWaP* study were recruited from clinical settings in a Southeastern state. Eligible participants had a diagnosis of chronic HF with either preserved or reduced ejection fraction and were able to speak and write English. Patients were excluded if they had: (1) major clinical cognitive impairment, (2) a co-existing terminal illness, (3) referral for heart transplantation, or (4) a dietary prescription that prevents following a 2 to 3 gram sodium diet. Major cognitive impairment was determined through medical record screening for diagnosis of Alzheimer's disease or dementia. Eligible caregivers were included if they were: (1) a primary caregiver identified by the patient, (2) the spouse, committed partner, or family member living with the HF patient, (3) able to speak and understand English, and (4) without cognitive



impairment of dementia and Alzheimer's disease. We invited 46 patients with HF and their family caregivers participating in the *FAMSWaP* study to take part in this study.

## *Measures*

*Demographic and clinical variables.* Data collected at baseline for the *FAMSWaP* study included age, gender, smoking status, and heart failure diagnosis. These were obtained via patient interview (age, gender, smoking status, caregiver characteristics) and chart review (heart failure diagnosis).

*Blood DNA collection, isolation, and laboratory analysis.* We selected three SNPs from the *TAS2R38* gene that code for a G-coupled protein receptor: *rs713598*, *rs1726866*, and *rs10246939*. DNA was isolated from whole blood sample using the Qiagen Blood Mini Kit (Qiagen, Hilden, Germany). Whole blood is the gold standard for DNA isolation and genotyping, and the Blood Mini Kit is sufficient to provide high quantity and quality DNA.<sup>133-136</sup> This test required 251  $\mu$ L of blood which was collected via finger stick to reduce participant burden. DNA was quantified by UV absorbance with a Nanodrop.<sup>137</sup> Genotyping was performed using TaqMan® according to manufacturer's instructions. Primers and probes (FAM and VIC labelled) are supplied by Life Technologies. DNA samples were plated out on a 96 well plate. Genotypes were determined using a CFX Real Time PCR system (BioRad). The resulting data were analyzed for genotype and allele frequency. Haplotypes were assigned based on genotyping analysis.

*Salt taste sensitivity.* Salt taste sensitivity is defined as the smallest concentration of sodium at which the individual first perceives and can identify the 'salty' taste.<sup>75,125</sup> This was tested using the "up-down" procedure, a commonly used and reliable method.<sup>138</sup> Salt taste sensitivity is measured using 8 levels of salt (NaCl) concentration from 0.2% to 1.6% in samples of distilled water. To test sensitivity, room temperature samples containing different salt concentration levels are served in 10 mL portions in a disposable

cup marked with colored sticker dots not interpretable by patients and caregivers. In the up trial, samples were given from lowest to highest salt concentration. Patients swished samples in the mouth for 2 to 3 seconds, expectorated, and then judged the saltiness of solution. The mouth was rinsed with 10 mL of distilled water between samples. When patients detected salt taste in two consecutive samples, the lower concentration of the two samples was recorded as the level of salt taste sensitivity. In the down trial, patients were given samples in reverse order from highest to lowest concentration and when no salt taste was detected in two consecutive samples, the level of salt taste sensitivity was then recorded as the concentration of the immediately preceding sample. The level of salt taste sensitivity was calculated by averaging the two sensitivity levels in the up and the down trial.

*Fungiform papillae density.* Fungiform papillae density refers to the number of fungiform papillae present on the tongue.<sup>91</sup> The protocol for this test is based on the Denver Papillae Protocol.<sup>139</sup> Briefly, subjects rinsed the mouth with deionized water, the tongue was dried with paper towel, and three ml of blue food dye at 1:36 concentration was applied to the apex of the tongue using a sterile cotton swab. The subject was asked to swallow to remove excess dye. With tongue protruding, a 2.5 cm piece of filter paper with a 10 mm diameter center hole was applied to the left anterior side of the tongue next to midline. Three close up images of the tongue were taken using a high quality digital camera. Images were uploaded to a computer and analyzed using ImageJ software. Personnel that counted the fungiform papillae were research nurses who were trained on how to use the software and how to identify fungiform papillae. The fungiform papillae

were counted under 50% magnification. This method has been demonstrated to be reliable and valid in numerous studies.<sup>103,127,140,141</sup>

*Adherence to LSD.* 24-hour urinary sodium excretion provides an objective marker of dietary sodium intake. Patients with HF in the study would have received a recommendation for LSD adherence as part of the general education all HF patients receive. Family member caregivers may or may not receive this information, but according to general U.S. dietary recommendations, all people should be following a LSD as well.<sup>49</sup> As urine is the major route for sodium excretion with up to 98% of dietary sodium excreted by the body through urine, urine sodium serves as a measure of dietary sodium consumption.<sup>63</sup> Dietary sodium intake is estimated through total amount sodium excreted through the urine in 24 hours since most of the sodium taken in is excreted in this manner. The 24 hour urinary sodium excretion has been used as a validated measure of adherence to low-sodium diet.<sup>48-50,52,53,63</sup> Patients and caregivers received testing materials including a urine collection container and instructions at enrollment and were asked to collect urine during the 24 hours prior to baseline data collection. To reduce measurement errors, patients and caregivers received detailed verbal instructions with a written instruction form and were asked to write down the time of urination and amount of urine and to keep the collection container in a cool area. Specimen containers were collected during the baseline data collection home visit. A normal urinary sodium level is 40 to 120 mEq/L/d. To compare urine sodium excretion to the recommended sodium intake (2000-3000 mg), urine sodium excretion in mmol were converted into mg (mg = mmol x 22.99).

## ***Procedure***

Approval from the Institutional Review Board was obtained before beginning the study. All participants gave informed consent before baseline data were collected including demographic data through self-report questionnaires, salt taste sensitivity, fungiform papillae number, blood DNA sample, and 24-hour urine sodium excretion. Patients were randomized to intervention and control group. Data was collected by trained research assistants in the patient's home. Fungiform papillae density was tested first, then salt taste acuity was tested. Patients and caregivers were tested one at a time, in separate rooms. For this analysis, only baseline data from participants who had provided DNA sample, salt taste sensitivity, and fungiform papillae number were included.

## ***Statistical Analyses***

We conducted descriptive analyses including frequency, means, and standard deviations as appropriate to levels of measurement for the variable, comparing participants grouped by haplotype. Using independent samples t-test, participants were grouped based on their status as patient or a caregiver to ascertain if there were differences between the groups in salt taste sensitivity, fungiform papillae number, and 24-hour urinary sodium. Participants were grouped by haplotype as (PAV homozygous, PAV/AVI, or AVI homozygous). To examine if PAV homozygous or PAV heterozygous haplotype predicted salt taste sensitivity we conducted a linear regression with AVI homozygous haplotype as the reference group. In the model, we controlled for age, gender, non-Hispanic Caucasians referenced to participants from all other races, current smoker referenced to nonsmokers, and fungiform papillae density. To determine whether PAV homozygous or PAV heterozygous haplotype predicted baseline 24-hr urinary

sodium excretion, we ran a linear regression with AVI homozygous haplotype as the reference group controlling for age, gender, ethnicity, smoking status, and number of fungiform papillae. All data analysis were conducted using SPSS v 24; with an a priori P value of  $\leq 0.05$ .

## Results

Three of the 46 participants were not included due to possessing a rare haplotype and one was excluded for not having urine data resulting in a total of 42 participants included in the analyses. The mean age of study participants was  $64.6 \pm 13.4$  years, 46.5% were male, and 97.7% were Caucasian. The majority (90.7%) were either non-smokers or former smokers (Table 4.1). The mean of the salt taste sensitivity was  $0.40 \pm 0.12$ ; mean number of fungiform papillae was  $63.1 \pm 18.3$  and the mean 24-hour urinary sodium was  $4233.9 \pm 2046.8$ . There were no significant differences between patients and caregivers for salt taste sensitivity ( $.42 \pm .13$  vs  $.37 \pm 0.9$ ;  $p = .16$ ), fungiform papillae number ( $62.5 \pm 19.5$  vs  $63.7 \pm 17.5$ ;  $p = .83$ ), and 24-hour urinary sodium ( $4350.1 \pm 2161.1$  vs  $3703.9 \pm 1868.9$ ;  $p = .31$ ). There were 10 PAV homozygotes, 19 PAV/AVI, and 13 AVI homozygotes. More women than men were homozygous for the PAV haplotype. There were no significant differences between those who were homozygous PAV and those who were homozygous or heterozygous for the AVI haplotype.

*Salt taste sensitivity.* Neither PAV homozygous nor PAV/ AVI haplotype predicted higher salt taste sensitivity in patients with HF or their family caregivers when compared to the reference group, AVI homozygotes. No control variables predicted salt taste sensitivity (Table 4.2).

*24-hour urinary sodium excretion.* Participants who were PAV homozygous had significantly lower levels of sodium in the 24-hour urinary excretion samples than those who were AVI homozygous or PAV/AVI heterozygous. In the linear regression model, PAV homozygosity predicted lower sodium excretion controlling for age, gender, ethnicity, smoking history, and fungiform papillae density ( $b = -1780.59$ ,  $t(41) = -2.18$ ,  $p = 0.036$ ) (Table 4.3).

## **Discussion**

Our hypothesis was partially upheld; although haplotype did not predict salt taste sensitivity, being homozygous for the PAV haplotype predicted lower 24-hour urinary sodium excretion, compared to AVI homozygotes. Lower 24-hour urinary sodium excretion in patients with HF who are PAV homozygous may be due to lower consumption of sodium. Earlier studies in which people who had greater intensity of PROP bitterness during taste tests also had more intense salt taste (particularly in PAV homozygotes) than those who didn't detect PROP bitterness.<sup>29,142</sup> They were also more sensitive to changes in sodium concentration in food items.<sup>32</sup> Lower 24-hour urinary sodium excretion in PAV homozygotes in our study may be related to this increased sensitivity. Although this was not supported by our salt sensitivity testing, it has been shown in other studies including Hayes and colleagues who found that people who were supertasters tended to notice changes in the concentration of sodium sooner and with less sodium than those who were not supertasters.<sup>32</sup> Moreover, people with the supertasting phenotype were also more sensitive to changes in concentration of salt in food items, which suggests a higher sensitivity to salt.<sup>32</sup> Logically it would extend that

those possessing the PAV haplotype who find the taste of salt more intense may also be more sensitive to it in concentration, however our results did support this.

In this small pilot study, we did not find a difference in salt taste sensitivity between PAV homozygotes and AVI homozygotes or between the AVI heterozygotes and AVI homozygotes. This may be due to the method of testing we used, a staircase up-down trial that offered one solution at a time. It is possible that the test used to measure salt taste sensitivity, which increased in 0.2% increments wasn't sensitive enough to detect the differences in salt taste sensitivity between haplotypes. In prior studies, thresholds for salt taste sensitivity have been measured using a forced choice test where the participant is offered two samples; one with salt solution and one with water, and are asked to identify which one has the taste in it.<sup>143</sup> This test also used 12 different concentrations of salt solution instead of 8, as our test did.<sup>143</sup> It might be more informative to use a test with increases in concentration of salt in smaller increments than 0.2% as well as a forced choice option.

Another finding was that there was a significant gender difference in haplotype. In our small sample, more females than males were homozygous or heterozygous for the PAV haplotype. This finding has been noted before in a study that took place in a genetically isolated population in Italy. In that sample there were more women who were supertasters (PAV homozygotes) and more males who were nontasters (AVI homozygotes).<sup>144</sup> However, it is interesting given that in an earlier study with 42 women and 45 men, Hayes and colleagues found , that women liked higher concentrations of salt in chicken broth compared to men when tasting seven different sodium concentrations of broth.<sup>32</sup> Although the sample for our study was small and may not be representative of



the population, our findings do support those of the two previous studies and suggest the need to further explore genetic variations that may underlie sex-based taste differences.

Findings from this study should be interpreted with caution given the small sample size of 42 people. Despite this, we did detect significant differences in 24-hour urinary sodium excretion in PAV homozygotes compared to participants who were AVI homozygotes. As previously discussed, our study was further limited in the test used for salt taste sensitivity. Taste samples with increases in concentration much smaller than 0.2% coupled with forced choice may have been a more effective means of testing salt taste sensitivity. Reflective of the Midwestern population served by clinics from which we recruited for the parent study, the majority of our participants were of European descent, limiting the generalizability of our findings to this population. While our research was exploratory in nature, in light of our findings, replicating this study with a larger sample drawn from a more diverse population is warranted.

## **Conclusions**

In our sample of patients with HF and their family caregivers, being homozygous for the PAV haplotype was the only significant predictor of 24-hour urinary sodium excretion. This indicated that, compared to those who are homozygous AVI, persons with the PAV/PAV genotype whereas there was not a significant difference from those who were PAV/AVI. The findings in this small sample provide an exciting indication that should be further explored in future research. Better understanding of genetic influences on taste preferences and dietary choices are critical. This information can provide a basis for the development of more effective personalized interventions for patients with HF.

Table 4.1: Demographic Characteristics by *TAS2R38* Haplotype

Characteristic	Mean (SD) or % (n)				<i>P</i> value
	Total Sample N=42	PAV/PAV n=10	PAV/AVI n=19	AVI/AVI n = 13	
Age (years)	64.6 ± 13.4	60.1 ± 15.6	66.3 ± 10.5	67.5 ± 14.8	.396
Gender (male)	46.5 % (20)	50.0% (5)	26.3% (5)	71.4% (10)	.019
Ethnicity (Caucasian)	97.7 % (41)	90.0% (9)	100.0% (19)	100% (13)	.194
Smoking status (nonsmoker)	90.7 % (39)	90.0% (9)	100%% (19)	92.3% (12)	.406
Salt taste Sensitivity	0.40 ± 0.12	0.38 ± 0.10	0.38 ± 0.10	0.42 ± 0.15	.606
Fungiform papillae density per 10mm	63.1 ± 18.3	64.0 ± 19.0	67.8 ± 16.8	54.9 ± 19.1	.151
24 hour urine sodium (mg)	4234.0 ± 2046.8	3313.7 ± 1178.7	3723.9 ± 1399.8	5018.6 ± 2890.3	.088

Table 4.2: Associations of *TAS2R38* Haplotype and Salt Taste Sensitivity.

Variable	<i>b</i>	Standard error	$\beta$	<i>P</i> value
Age	-0.002	0.002	-0.275	.152
Gender	-0.052	0.042	-0.221	.228
Ethnicity	-0.139	0.140	-0.179	.326
Smoking history	0.054	0.070	0.135	.446
Fungiform papillae density	0.000	0.001	0.059	.725
Haplotype [AVI homozygotes (ref)]				
PAV/AVI	-0.019	0.048	-0.079	.698
PAV homozygotes	-0.037	0.052	-0.135	.476

Model F = 0.937; R<sup>2</sup> = 0.158; P = 0.491

Table 4.3: Predictors of 24-Hour Urinary Sodium Excretion

Variable	<i>b</i>	Standard error	$\beta$	<i>P</i> value
Age	-32.893	25.567	-0.214	.207
Gender	-1069.95	652.728	-0.267	.110
Ethnicity	-1883.915	2150.844	-0.144	.387
Smoking History	2335.645	1184.842	0.301	.057
Fungiform Papillae Density	29.325	16.907	0.268	.092
Haplotype [AVI homozygotes (ref)]				
PAV/AVI	-1103.123	754.524	-0.275	.153
PAV homozygotes	-1780.593	815.531	-0.380	.036

Model F= 2.33;  $R^2 = 0.32$ ; P= 0.047

## CHAPTER FIVE:

### Conclusions

#### Background and Purpose

The overall purpose of these studies was to examine key factors that influence dietary intake patterns with a particular focus on sodium consumption. Understanding taste perception and dietary consumption of sodium as well as other dietary components among persons with CVD disease risk and those with HF is critical to developing effective nutrition interventions. Those with CVD risk and with HF are particularly vulnerable to experience negative health outcomes related to overconsumption of sodium and can most benefit from reducing sodium consumption to 2,300 mg of sodium per day or less.<sup>78</sup> Three data-based manuscripts are included in this dissertation that focus on taste perception and dietary consumption of sodium and other nutrients: 1) a secondary analysis of data to examine the associations of prescribed anti-hypertensive medication and sodium consumption in patients with HF, 2) a secondary analysis of data to elucidate associations of *TAS2R38* haplotype and dietary consumption of key nutrients that effect cardiovascular health such as sodium, saturated fats, sugars, alcohol, and vegetables, and 3) a cross sectional study to examine the association of *TAS2R38* haplotype with salt taste sensitivity and 24-hour urinary sodium excretion.

The common element across each of these studies is a focus on dietary sodium intake patterns. Although current dietary guidelines recommend consuming 2,300 mg of sodium a day, nearly 90% of Americans consume 3,500 mg or more a day.<sup>1-5</sup> Excess sodium consumption has been linked with poor health outcomes including hypertension,

high risk of stroke, and worsening heart failure.<sup>2,7,12</sup> It is crucial to explore the issue of excess sodium consumption to uncover new and innovative solutions to help people to reduce their sodium consumption, particularly those who already have or are at high risk of developing CVD. As taste strongly influences dietary choices, it is imperative to examine associations of taste perception and underlying factors with dietary sodium consumption.

The purpose of this chapter is to summarize and synthesize the findings of this dissertation and to discuss the implications for advancing the state of the science on taste perception and the consumption of dietary sodium and other nutrients.

### **Summary of findings**

Chapter Two was a secondary analysis of data examining the relationship between prescribed anti-hypertensive medication regimen and dietary sodium consumption as evidenced by sodium density among patients with HF. Patients prescribed ACE inhibitors consumed approximately 13% more sodium per kilocalorie than those who were not prescribed ACE inhibitors. No other hypertensive medication, including ARBs, beta blockers, and diuretics, predicted sodium density. Only being prescribed an ACE inhibitor was significantly associated with higher sodium consumption. Nurses could use this information to tailor education for patients on ACE inhibitors to help them reduce their sodium intake with the knowledge that their medication regimen may make it more difficult to adjust their diets.

Chapter Three was a secondary analysis of data examining the association between *TAS2R38* haplotype and dietary consumption of sodium, sugar, saturated fats,

alcohol and vegetables in community dwelling adults with two or more CVD risk factors. Findings of this study demonstrated that *TAS2R38* haplotype was not associated with dietary consumption of sodium, sugar, saturated fat, alcohol, and vegetables in this population. While other variables in the model did predict dietary consumption of some of these nutrients, genotype was not a significant predictor.

Chapter Four was a prospective, cross sectional study of the relationships among *TAS2R38* haplotype and salt taste sensitivity and sodium consumption as indicated by 24-hour urinary sodium excretion. *TAS2R38* genotype was not a significant predictor of salt taste sensitivity, however, genotype was a significant predictor of 24-hour urinary sodium excretion. Participants with the PAV homozygous haplotype had significantly lower sodium excretion than those homozygous for the AVI haplotype. If supported by future research, this information could be used by nurses and other health professionals to develop tailored dietary interventions to lower sodium consumption based on genotype and other factors that influence taste perception.

### **Impact of dissertation on the state of the science**

There is little information regarding how factors related to salt taste perception are associated with sodium consumption in patients with high CVD risk or who are currently living with CVD. Although it is well known that taste is one of the most important factors in food choice, there is little in the way of interventions that incorporate the importance of the sense to improve dietary adherence to healthy dietary recommendations including low sodium diet. This dissertation adds to the scientific literature in several important ways. Our first study provides evidence that patients with HF who were prescribed ACE inhibitors consume more sodium per kilocalorie than those who are not prescribed ACE

inhibitors. In our second study, we did not find evidence that the *TAS2R38* haplotype predicted patterns of sodium, sugar, saturated fat, alcohol, and vegetable consumption in community-dwelling adults with two or more CVD risk factors. Results from our third study did not show *TAS2R38* haplotype to be predictive of salt taste sensitivity but did show that the haplotype predicted 24 hour urinary sodium excretion in patients with HF and their family caregivers.

First, in Chapter Two, we explored the role of medication in adherence to low sodium diet in patients with HF through the examination of prescribed medications and dietary consumption of sodium. ACE inhibitors are frequently prescribed to patients with HF as part of the medical management of the condition as stipulated by the guidelines put forth by the American Heart Association and the American College of Cardiology.<sup>145</sup> In the same set of guidelines, it is also recommended that the reduction of dietary sodium<sup>145</sup> which offers a unique contradiction to patients, particularly if the medication they take indirectly influences them to eat more sodium in their diets. Understanding of the challenges presented by taking an ACE inhibitor allows practitioners to plan for these challenges and give precise educational instructions to better assist patients with HF in meeting both treatment goals. This information furthers the knowledge that ACE inhibitors disturb taste function by adding the information that those on these medications consume more sodium, possibly because of taste disturbance. Education can be altered pre-emptively to incorporate prescription of ACE inhibitors in order to prepare patients for the possibility of taste disturbance and give them understanding of how this may affect their attempts to lower sodium in their diets.



In Chapter Three we explored the contributions of *TAS2R38* genotype, which has been known to alter dietary behavior through enhancement of the bitter modality of taste, to dietary consumption of several nutrients that are known to be influential in cardiac health and risk for CVD. The results of this study support reported outcomes from several recent community-based studies in which no significant differences in dietary consumption patterns have been found based on the PAV or AVI haplotype,<sup>111</sup> it is contrary to other studies that have shown haplotypic differences in both alcohol<sup>146</sup> and vegetable intake.<sup>27</sup> While adding to the scientific debate regarding the influence of the bitter-tasting genotype on consumption patterns for a sample of community dwelling adults, the study also elucidated the need to control for certain variables and thus to refine the design of our prospective study, presented in Chapter Four. In particular, phenotype testing should be added along with the genotype testing approach as well as adding a representation of fungiform papillae density to control for sensory equipment and function. Furthermore, this study elucidated the role of *TAS2R38* genotype in healthy eating patterns in people with cardiovascular risk factors, which had not been investigated before now, thus furthering the state of the science.

In Chapter Four, we report on a study conducted to examine the associations of *TAS2R38* genotype with salt taste sensitivity and 24-hour urinary sodium excretion in a sample of patients with HF and their family caregivers. In a prior study, Hayes and colleagues found that *TAS2R38* phenotype was related to sodium taste ability and liking of sodium in chicken broth and commonly consumed food items, though this study did not test for phenotype.<sup>32</sup> Our study filled the gap in the literature by directly examining the association of *TAS2R38* haplotype with both 24-hour urinary sodium excretion as a

proxy for sodium consumption and with salt taste sensitivity. The findings of this study that the PAV homozygotes had significantly higher 24-hour urinary sodium excretion than AVI homozygotes suggests that in patients with HF and their family members there may be differences in sodium consumption based on the TAS2R38 haplotype. Although contrary to the findings from our previous study with a community dwelling adult at-risk for CVD, it may be that for people for whom LSD adherence is critical, genetic influences on taste perception may have a stronger role in consumption patterns. This pilot study provides direction to inform future research to enhance our understanding of genetic influences on dietary patterns.

### **Recommendations for Nursing Practice and Research**

Taking an ACE inhibitor is associated with greater dietary consumption of sodium and it is thought to produce this effect through reduction of salt taste perception. Because ACE inhibitors are frequently prescribed to HF patients who are also recommended to follow a low sodium diet, it is imperative to consider medication regimen when planning out educational interventions to assist these patients in adherence to low sodium diet. Future research into this area should involve testing basic sensory perception such as salt taste sensitivity in individuals taking an ACE inhibitor who also have HF in order to elucidate how much salt taste perception is altered by the medication. As it is suspected that ACE inhibitors cause taste disturbance through depletion of zinc, we also recommend examining the addition of a zinc supplement to the medication regimen for patients with HF who are also taking an ACE inhibitor to examine its efficacy in relieving taste disturbance. Any future studies should also control for other medications taken such as ARBs, diuretics, and beta blockers.

It is perhaps surprising that in Chapter Three we found that this genotype did not associate with consumption of sodium, sugar, saturated fat, alcohol, and vegetables in community dwelling adults with two or more risk factors for CVD. However, the literature is rife with contradictory reports of associations with this genotype and dietary consumption patterns. Future community studies should be conducted that include testing for the bitter taste phenotype of supertasting as well as the *TAS2R38* haplotype, which may give a more informative result. Such studies should be tightly controlled for factors such as fungiform papillae number, salt taste sensitivity, and socioeconomic variables in order to better account for possible confounders.

Conversely, as detailed in Chapter Four, *TAS2R38* genotype did relate to 24 hour urinary sodium excretion in a sample of patients with HF and their family caregivers. Although our sample for this study was small, our findings can guide the efforts of future research in the area of *TAS2R38* haplotype and dietary food choices. Future research should utilize a larger, more heterogenous sample to further examine the association of PAV homozygosity and 24-hour urinary sodium excretion. Better understanding genetic and other influences on dietary choices can support more effective dietary interventions supportive of adherence to low sodium diet. Educational interventions can be tailored to address variations in taste perceptions that may otherwise present a barrier to adherence to low sodium diet.

## Summary

Future research is needed to better elucidate the associations between *TAS2R38* haplotype and dietary consumption patterns as well as between haplotype and taste preferences. Such studies conducted with heterogeneous samples and controlling for variables that impact taste including fungiform papillae density and taste perception using high sensitivity tests will be able to provide important insights into diet choices. As additional genes that have a role in taste perception are discovered, subsequent research could also expand the number of genetic variants examined to provide broader understanding of genetic influences on taste and diet patterns and choices. This research can inform development of tailored dietary interventions that may more effectively reduce CVD risk among those at risk and improve health outcomes for those with CVD.

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**VITA**  
**Jennifer Smith**

**Educational Background**

Year	Degree	Institution
2014	Bachelor of Science in Nursing	St. Catharine College, St. Catharine, KY
2013	Associate degree in Nursing	St. Catharine College, St. Catharine, KY
2000	Bachelor of Arts in Theatre	Maryville College, Maryville, TN

**Professional Positions Held**

Dates	Institution and Location	Clinical Position
2016 – present	Hospice of the Bluegrass, Lexington, Ky	Staff Nurse, Home Team
2015 – 2016	Frankfort Regional Medical Center Frankfort, Ky	Medical/Surgical Nurse
2015 – 2017	University of Kentucky Lexington, Ky	Teaching Assistant
2014 – 2018	University of Kentucky Lexington, KY	Research Assistant
2014 –2015	Baptist Health Lexington Lexington, KY	Home Health Nurse
2013 –2014	Sts. Mary and Elizabeth Hospital Louisville, KY	Intermediate/Telemetry Nurse

**Scholastic and Professional Honors**

2018	Recipient of the UK Center for Clinical and Translational Science Scholars Seed Grant
2017	Recipient of Sigma Theta Tau International, Delta Psi Chapter Dissertation Award
2016	Presentation highlighted in American Heart Association (AHA) Scientific Sessions Media.
2016	UK Center for Clinical and Translational Science, College of Nursing Scholarship Showcase, Lexington, Kentucky. Presentation selected as Best PhD Poster
2015	Recognized as Sigma Theta Tau Rising Star
2015, 2016	Recipient of Dorothy Luther Fellowship, University of Kentucky, Lexington, KY

2014	New Beginnings Scholarship, University of Kentucky, Lexington, KY
2012	Darrel W. Richardson Psychiatric Nursing Excellence Aware, St. Catharine College, St. Catharine Kentucky
2012-2013	Dean's List, St. Catharine College, St. Catharine KY
2010-2011	President's List, St. Catharine College, St. Catharine, KY

### **Professional Publications (\*indicates data-based publication)**

#### **Journal Articles**

\*Smith, J. L., Lennie, T.A., Chung, M. L., Mudd-Martin, G. (under review) Dietary sodium intake is predicted by anti-hypertensive medication regimen in heart failure patients. *Journal of Cardiovascular Nursing*.

#### **Published Abstracts**

\*Smith, J. L., Estus, S., Lennie, T. A., Moser, D. K., Chung, M. L., **Mudd-Martin, G. T.** (November 2016). TASR genotype is associated with adherence to dietary sodium recommendations in adults with cardiovascular disease risk factors. [AHA 19630 abstract]. *Circulation*, 134(Suppl 1), A19630.