OLFACTORY IDENTIFICATION, DETECTION THRESHOLDS, AND SENSITIVITY IN KIDNEY DISEASE PATIENTS

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OLFACTORY DETECTION THRESHOLDS AND SENSITIVITY IN END-STAGE RENAL DISEASE AND CHRONIC KIDNEY DISEASE PATIENTS

By

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ABSTRACT

While there is evidence for a decline in olfactory identification scores for patients with Kidney Disease, there are contradictory results for detection thresholds. Some results indicate higher thresholds while others found similar thresholds or elevated thresholds for one odorant, but not others. The current study evaluated the olfactory abilities with participants diagnosed with Kidney Disease for numerous odorants. No significant differences were found in olfactory identification, detection thresholds, or sensitivity compared to healthy controls. Despite the non-significant results, there did appear a trend of poorer olfactory abilities in Kidney Disease participants. The differences in olfactory performance also varied from odorant to odorant which indicates that a standardized set of odorants should be used when assessing threshold detection scores in the Kidney Disease population.

DEDICATION

I would like to dedicate this thesis to those who have tolerated and supported me throughout my selfish pursuit of continued education. Specifically, my family for all the lessons taught, including the ones I learned the hard way, and all the times they sacrificed their own well-being for the benefit of sustaining and improving that of my own. Also, Hi Grandma.

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LIST OF ABBREVIATIONS

AD, Alzheimer's Disease

AML, Ascending Method of Limits

CESD-R, Center for Epidemiologic Studies Depression – Revised Scale

CKD, Chronic Kidney Disease

DCI, Dialysis Clinic, Inc.

DSM-IV, Diagnostic Statistical Manual, 4th ed.

DT, Detection Threshold

ESRD, End-Stage Renal Disease

HC, Healthy Controls

KD, Kidney Disease

MCS, Method of Constant Stimuli

OI, Olfactory Identification

OSA, Obstructive Sleep Apnea

PD, Parkinson's Disease

PSQI, Pittsburg Sleep Quality Index

REM, Rapid Eye Movement

SDT, Signal Detection Theory

SERRI, Southeastern Renal Research Institute

SPSS, Statistical Package for the Social Sciences

SS, Single Staircase Method

UPSIT, University of Pennsylvania Smell Identification Test

WUTC, Wheeler University of Tennessee at Chattanooga Threshold Test

CHAPTER I

INTRODUCTION

Our olfactory abilities are a sense that most of us take for granted. At one point, our sense of smell was actually classified as a "*lower*" or "*minor*" sense (Blake & Sekuler, 2005). Such little attention is paid to the olfactory abilities that some individuals are not even aware that they lost their ability to smell (Landis, Hummel, Hugentobler, Giger, & Lacroix, 2003). Unfortunately, most people do not realize the importance of a normal sense of smell or that deficits in olfactory abilities can lead to issues in nutrition, quality of life, and psychological well-being (Doty, 2006).

Furthermore, most people are not educated in the various applications of olfactory functioning assessment. Assessments of olfactory abilities can allow for early detections of diseases and disorders as well as assist in differential diagnoses (Haehner, Hummel, & Reichmann, 2011; Rahayel, Frasnelli, & Joubert, 2012; Solomon, Petrie, Hart, & Brackin Jr, 1998). Fortunately there has been an increase in the availability of olfactory tests for clinicians (Doty, 2006). These tests can be used to assess a wide variety of olfactory performance.

There are several different assessments that can be used to measure olfactory abilities. Some of the more popular assessments are: Olfactory Identification (OI), Detection Thresholds (DT), Sensitivity, Odorant Discrimination, and Memory Tasks. For the purpose of this study, only OI, DT, and Sensitivity are discussed.

One disease that is associated with of olfactory decline is Kidney Disease (KD), specifically, Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD). CKD is characterized by having kidney damage for three months or more. The disease can be broken into five stages (1-5), with a decrease in filtration rates from one stage to the next. Stage 5 of CKD and ESRD are both described as kidney failure, but differ in that ESRD requires chronic kidney dialysis (Bronnert, 2007). The incidence and prevalence of CKD has increased by 30% (Hallan & Vikse, 2008) and as of 2005, there were an estimated 1.9 million people suffering from ESRD (Grassmann, Gioberge, Moeller, & Brown, 2006). Like most illnesses, treatment can be very expensive which may deter people from seeking treatment and lead to prolonged symptoms (Hallan & Vikse, 2008).

Frasnelli, Temmel, Quint, Oberbauer, and Hummel (2002) found that 56% of the patients in chronic renal failure had olfactory deficits. This becomes a serious issue given the impact olfactory abilities can have on quality of life and appreciation for food (Griep et al., 1997). Specifically, it was found that renal patients with the greatest olfactory dysfunction also are the most likely to become malnourished (Raff et al., 2008).

While there is an association of olfactory deficits with KD, there is conflicting data. Some research indicates that those suffering from renal problems actually have normal olfactory functioning (Vreman, Venter, Leegwater, Oliver, & Weiner, 1980) while others depict some type of olfactory deficit (Griep et al., 1997). These results may actually be a result of the methods used to assess olfaction or a result of other symptoms associated with the disease.

There are variables other than diseases that can affect our sense of smell. Age and Gender are two of the more commonly known. There is a long history of anecdotal evidence suggesting that females are better smellers. More recently a significant amount of research has been

conducted to justify those claims (Good & Kopala, 2006). Moreover, certain physical and mental disorders can affect olfactory performance. In the CKD and ESRD population, for example, there is an increased risk of sleep disorders (Kimmel, Miller, & Mendelson, 1989; Pierratos & Hanly, 2011). Depression is the most common psychiatric disorder in this population (Kimmel & Peterson, 2004; Kimmel, Weihs, & Peterson, 1993). These disorders will be discussed in the current study in the context of declines in olfactory performance with kidney disease.

Olfactory Measures

Since the mid to late 1980s, the number of easily administered measures for assessing olfaction has increased (Doty, 2006). These measures became generally available during the 2000s (Doty, 2009). In addition, they allow for reliable measures of olfactory tasks and have many applications (Doty, 2006). It should be noted that most olfactory measures correlate positively with one another, but DTs correlate negatively with OI tasks (Doty, 2009). This negative correlation occurs because as one's threshold increases, there is a decrease in the ability to detect odorants. This increased threshold accounts for the decrease in scores on OI tasks.

Odorant Identification

The assessment of OI has proven to be very reliable and has helped shape the current knowledge of human olfaction (Doty, 2006). A common way for measuring a person's ability to identify an odorant is through the use of a microencapsulated odorant, or "scratch 'n' sniff" card (Blake & Sekuler, 2005). The University of Pennsylvania Smell Identification Test (Doty, Shaman, & Dann, 1984), a 40-item multiple forced choice smell test, is arguably the most popular and widely used assessment of OI (Doty, 2009). This test is administered by having a

participant scratch the surface of a "scratch and sniff" card, smell the odorant, and then decide which smell on a list of choices best represents the odorant. Even if the participant does not detect an odorant, or the choices provided do not match what the participant believes the odorant to be, a choice from the list must still be selected (Doty, 1995), which is referred to as a forced-choice test. This test has been shown to be sensitive enough to distinguish variances in gender, smokers vs. nonsmokers, and ethnic groups (Doty et al., 1984).

Smell identification tests have been proven to be reliable. These tests can actually have only three questions and still have relatively high reliability and sensitivity (Duff, McCaffrey, & Solomon, 2002). Reliability coefficients have been shown to be > .7 for multiple measures (Doty, Newhouse, & Azzalina, 1985). However, there is a positive relationship of reliability with the length of the test (Doty, 2006; Doty, Frye, & Agrawal, 1989). This relationship may occur as a result of the decreased probability of correctly guessing multiple odorants.

Given the sensitivity and reliability of the OI test, it has been used for diagnosing purposes. Solomon et al. (1998) were able to distinguish participants by either major depression or Alzheimer's Disease (AD). The researchers discovered that the AD group performed significantly worse than the depressed group. Using similar methods, an olfactory measure was again used as a diagnostic tool to distinguish AD from vascular dementia (Duff et al., 2002).

Detection Threshold

The minimum amount of a stimulus (odorant, sound, light, etc.) needed in order to be detected is referred to as the DT (Møller, 2003). There are currently several methods for threshold task administration, but all present olfactory tasks follow the Ascending Method of Limits (AML) or Single Staircase (SS) methods (Doty, 2009). The AML procedure presents an

odorant at various levels, first with the lowest dilution presented followed by the next higher dilution and so forth. Two successive odorant detections determine the threshold. Other threshold tasks follow the same procedure, but then present the odorant dilutions in a descending fashion (thresholds determined from two successive non-detections) and average the two obtained thresholds (Doty, 2006).

The SS procedure follows a similar basis as AML; except the dilutions are increased with a no detection response and dilutions are decreased with a detection response. After five reversals, the stimuli where the reversals occurred are averaged to obtain the threshold (Doty, 2009). The more popular version of threshold tasks uses the staircase method and adds blanks (a stimulus that contains no odorant, also referred to as noise). Instead of presenting the blanks at a separate time, the blanks are presented with the odorant (again with various dilutions) and the participant is asked to pick (forced choice response similar to OI) which one contains the odorant (Doty, 2009; Landis et al., 2011). The reversals are dependent on whether or not the response was correct (dilutions increase with incorrect response and vice versa). The advantage of adding blanks is the control provided from those who may guess. For example, Suzuki et al. (2001) used a similar method to determine olfactory thresholds by increasing the dilution after an incorrect response, and then repeating the same stimuli after a correct response. After 5 correct responses, the dilution in the presented stimuli becomes the threshold.

Unfortunately, there are limitations to the current methods of DTs, especially in reliability and validity (Doty, 2009). Doty (2006, 2009) recommends using a SS procedure for measuring DTs because of the increased reliability and stability. This increase is obtained by using reversals and presenting certain stimuli multiple times; more trials increase reliability and stability. However, this method still does not allow for every stimulus to be presented multiple

times. The stimuli presented are dependent on the participant's responses. The location of reversals may be within a specific range which would never allow the participant to be presented the extended range of concentrations. To alleviate these problems, a new threshold test was developed to better align with other perceptual threshold tasks measuring vision and audition.

The new measure created for obtaining olfactory DTs is called The Wheeler University of Tennessee at Chattanooga (WUTC) Threshold Test (Tewalt, 2013). The WUTC consists of not one, but five odorants and blanks. Vanillin, L-α-Pinene, Ethanol, Isoamyl Acetate (Banana), and P-cresol. P-cresol, a uremic toxin found in ESRD patients (Lin et al., 2011; Meijers et al., 2010) with an odorant characterized as pig manure (Le, Aarnink, Ogink, Becker, & Verstegen, 2005), was chosen to see if a build-up of this toxin in the blood system would affect the ability to detect the odorant. McKinney (2013) showed that there is no presence of P-cresol in the healthy population. Vanillin was chosen as it has a similar chemical structure to P-cresol. Banana has a chemical structure that is different from Vanillin, yet it has a similar sweet smell. L- α-Pinene and Ethanol do not have a sweet smell like Vanillin and Banana. None of the above odorants overstimulate the fifth trigeminal nerve (the cranial nerve that supplies somatic nerves to the nose). Stimulation of this nerve could cause a warm, sharp, or cool sensation (Hawkes & Doty, 2009).

The WUTC uses a slightly different method for obtaining the threshold through the use of the Method of Constant Stimuli (MCS) and Signal Detection Theory (SDT). While this methodology does differ slightly from existing methods used currently in detecting thresholds, SDT is broadly accepted by psychologists and is applied whenever two possible stimuli need to be discriminated from one another, or a stimulus needs to be detected, (Stanislaw & Todorov, 1999). The methods discussed above are concerned with whether or not a participant detects an

odorant when the odorant is actually present although it is possible for a participant to say a stimulus was detected when in fact nothing was actually there. SDT was adapted to overcome this shortfall and accomplishes this through the use of "*hits*" and "*false alarms*" (Levine, 2000). The hit rate (*H*) is calculated by taking the proportion of "*yes*" responses to signal stimuli and the false alarm rate (*F*) is calculated by the proportion of "*yes*" responses to the blanks.

As stated earlier, the SS method incorporates blanks where a participant has to distinguish between the stimuli and the blank. The difference in the methodology comes from the requirement of MCS to have the test present the stimuli multiple times in a random order (Blake & Sekuler, 2005). Note the SS procedure is not completely random, but instead relies upon the participant's response (a correct or incorrect response dictates what will be presented next) and some individuals' responses can generate shorter tests. When using AML or SS, it was actually possible for the participant to figure out what intensity to expect next. The MCS was specifically developed in order to alleviate these problems (Levine, 2000)

The WUTC uses nine different dilutions for each odorant and nine blank stimuli. Each stimulus (both odorants and blanks) is presented one at a time to the participant in a random order twice, in which he or she is asked to respond with a "*yes*" or "*no*" as to whether or not an odorant was detected (Tewalt, 2013). A "*yes*" or "*no*" response is given for each presentation. By creating the dichotomous response from the participant for both the odorants and blanks, further methods can be used to assess other performance factors covered through SDT (Møller, 2003).

In order to determine the thresholds for the various odorants, the yes/no responses to the odorant containing stimuli were analyzed using Logistic Regression. Through the Logistic Regression analysis, estimated probabilities are obtained for each concentration of an odorant. By graphing the relationship of the logarithmic concentration and probabilities with a sigmoid

curve, the concentration associated with a probability value of .5 becomes the estimated threshold (Tewalt, 2013). This method is identical to the general means of assessing auditory thresholds (Møller, 2003). See Figure 1.1 below for a graphical representation of obtaining the estimated threshold.

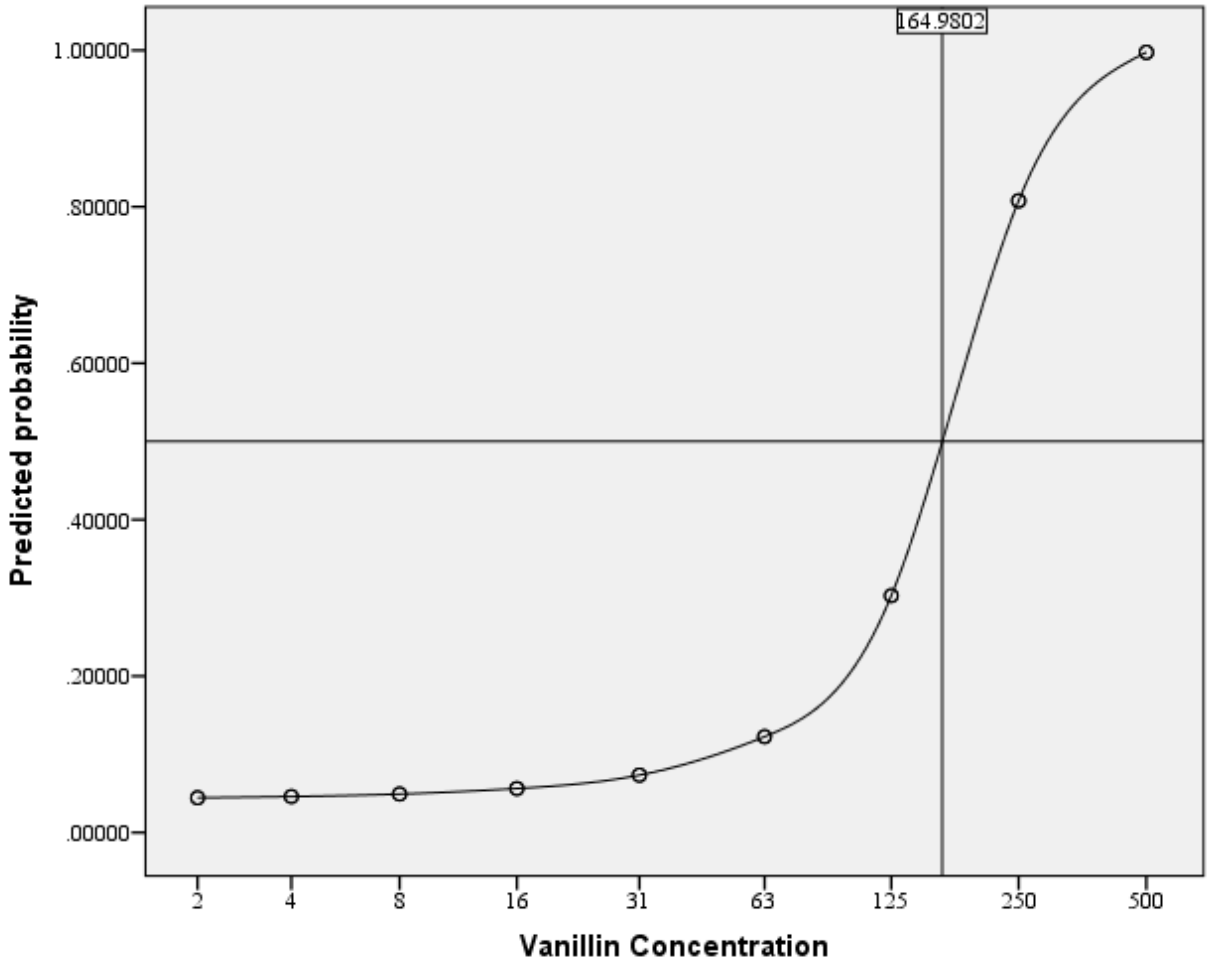

Figure 1.1 Individual's Predicted Probability vs. Vanillin Concentration

The horizontal scale is graphed using a logarithmic scale to avoid skewness. Each point on the graph represents the probability of that concentration being detected with an ogival curve added. The horizontal line depicts where the probability of .5 would intersect the probability curve. The vertical line was placed in the intersection to find the concentration for the threshold. The text box attached to the horizontal line depicts the threshold.

The logistic regression analysis also gives a *B* coefficient. This coefficient helps determine the size and direction in the probability of detecting the observed concentrations (Tabachnick & Fidell, 2013). In other words, the B coefficient indicates if the change in probabilities is a very sudden and sharp or more shallow and gradual. Moreover, the sign of the coefficient allows for any detection in response confusion and guessing. The *B* coefficients help identify any response confusion and determine if a change in concentrations for one odorant seems to have more of an impact than others odorants.

In addition to using a more reliable method for obtaining thresholds, the WUTC incorporates the use of blanks (but not in the fashion that blanks are used with the SS method). Instead, the blanks are individually presented randomly with all of the other odorant containing stimuli. This allows is for the participant to respond with a "*yes*" or "*no*" to the blanks themselves and can be used for manipulation checks. As stated earlier, the previous methods discussed force the participant to distinguish between an odorant containing stimuli and a blank. This does not tell us if the participant detected something in the blank (it is possible the participant *thought* they detected an odorant in both stimuli and guessed). The reason this new addition of a response to a blank is important because it also allows for further calculations to be made for Sensitivity through SDT.

Sensitivity

Additional measures of olfactory performance can be assessed by using SDT in the WUTC. Specifically, the incorporation of a dichotomous response to each individual blank in addition to the odorants enables the WUTC to calculate sensitivity. Sensitivity is an individuals' ability to discern a signal from noise (or an odorant from blanks) and can be calculated from hit

and false alarm rates (Stanislaw & Todorov, 1999). Although there is literature on olfactory sensitivity, it is actually being used interchangeably with DT. Specifically, most of this research refers to sensitivity as the inverse of DT. It may be counterintuitive to think of higher DT as poorer performance, so some researchers refer to thresholds as sensitivity.

One method of calculating sensitivity is *d'* (Miller, 1996). Sensitivity using *d'* is calculated by obtaining the *z* scores for the hit and false alarm rates, and then subtracting the false alarm *z* score from the hit rate *z* score (Macmillan, 1993). This statistic can be affected by response bias which is the tendency for a participant to respond with "*yes*" or "*no*" which is why some researchers prefer a non-parametric measure of Sensitivity (Stanislaw & Todorov, 1999).

Response bias can be computed through the nonparametric statistic Grier's *B''* (Grier, 1971). Ranges for *B''* can range from -1 to +1, with negative numbers indicating a bias towards responding with "*yes*" and a bias to responding with "*no*" indicated by positive numbers. The further away from 0 *B''* is, the greater the response bias. It seems counterintuitive to think of yes with a negative affect, so the present study will multiply a -1 to B'' in order to flip the signs, resulting in positive numbers indicating a response bias of yes. The modified formula from (Stanislaw & Todorov, 1999) is as follows:

$$B'' = \big(sign(F - H)\big)\frac{\big(H(1-H) - F(1-F)\big)}{H(1-H) + F(1-F)} \qquad \textit{Eq. 1.1}$$

Note: *H* = Hit Rate and *F* = False Alarm Rate

"*sign(F – H)*" equals +1 when *F* > *H*, 0 when *F* = *H*, and -1when *F* < *H*.

By calculating response bias, it will allow for a determination of DT being skewed as a result response bias.

Given that *d'* can be affected by response bias; *A'*, a non-parametric statistic of sensitivity (Macmillan, 1993) is used. The formula for calculating *A'* is as follows (Stanislaw & Todorov, 1999):

$$A' = .5 + \left[sign(H - F) \frac{(H - F)^2 + |H - F|}{4 \max(H, F) - 4HF} \right] \qquad \textit{Eq. 1.2}$$

Note: *H* = Hit Rate and *F* = False Alarm Rate

"*max(H,F)*" indicates using which ever value is larger.

The ranges of *A'* typically range from .5 – 1, with a value of .5 depicting no ability to distinguish stimuli from blanks. It should also be noted that absolute lowest possible value of A' is 0, but any value lower than .5 is generally a result of error in sampling or response confusion (Stanislaw & Todorov, 1999).

Sensitivity can be calculated for the entire test as well as for each individual odorant. This will give the test the ability to analyze if there are varying performances between the odorants for individual participants. This analysis is important because olfactory performance can vary between odorants (Good & Kopala, 2006). For example, Landis et al. (2011) found that when compared to healthy individuals, KD participants had elevated thresholds for one odorant, but normal thresholds in a different odorant. These multiple calculations for the entire WUTC and each individual odorant will help discern which specific odorants may be influenced by specific variables and which should be used when assessing the KD population.

Variables Affecting Olfaction

Individuals vary in olfactory abilities and sensitivity. Some people are able to detect the faintest odorant from across the room while others struggle to find its source. There are several

variables affecting olfactory abilities, arguably the most notable being gender. As anecdotal evidence and research suggest, women outperform males on almost every olfactory task, (Good & Kopala, 2006).

Additionally, these gender effects can be made greater with age (Good & Kopala, 2006). The proportion of olfactory problems in the general population increases from 1-2% in those younger than 65 years of age to >50% in those older than 65 (Doty, 2006). While olfactory abilities do generally decrease with age, the decrease in performance is different for males and females. There is a decrease in OI abilities as age of participant increases. As expected, female performance is consistently greater than male performance, yet male performance begins to drop further below female performance at 50-59. Female decline is not as steady as male decline (Performance for both genders is similar at age 80-89, but females' performance decreases less gradually) (Doty et al., 1984). Similar effects from age were found in other studies for DTs (Kobal et al., 2000). These differences in age may result from decreasing neurological activity with increasing age (Suzuki et al., 2001).

While gender and age are common factors that affect olfactory abilities, other more complex issues can also hinder olfactory abilities. Fortunately, if these deficits are discovered early enough, they can be used to diagnosis underlying disease. For example, one of the earliest symptoms of both AD and Parkinson's Disease (PD) is an impaired olfactory sense (Haehner et al., 2011; Rahayel et al., 2012). Olfactory tests have been used to be able to distinguish neurodegenerative diseases from other disorders that generate difficult differential diagnoses (Solomon et al., 1998). Even though there has been an increase in the number of easily administered clinical smell tests for many noted medical conditions (i.e. AD, PD, Depression, Sleep Disorders) (Doty, 2006), there has not been one developed for KD.

Kidney Disease

One of the first studies to research olfaction in the KD population found that patients showed poorer performance on odorant discrimination tasks and rated odorants as more unpleasant when compared to healthy controls (Schiffman, Nash, & Dackis, 1978). Additionally, Corwin (1989) found that renal patients on dialysis had poor OI abilities compared to healthy controls. Raff et al. (2008) also found that participants diagnosed with ESRD had significantly lower OI scores than controls and that these olfactory deficits can lead to serious health issues like malnutrition (up to 75% of ESRD patients are malnourished) due to an inverse relationship between nutrition scores and OI scores. This olfactory deficit is thought to be the cause of the malnourishment (Landis et al., 2011).

Treatment for KD patients can actually improve olfactory function. Landis et al. (2011) found after just one session of hemodialysis, OI performance was significantly improved. However, this result is temporary and the KD patients suffer from long term consequences of olfactory performance. If a patient receives a kidney transplant, his or her olfactory function returns to levels similar to the healthy population (Griep et al., 1997). Unfortunately, like any transplant, this treatment is complex and costly. However, the mechanisms responsible for these recoveries in olfactory performance are still unknown (Landis et al., 2011).

While there is evidence for a decline in OI scores for patients in renal failure, there are contradictory results for DTs. These results vary greatly, both in the initial testing for comparisons and when measuring for treatment effects. The initial comparisons show the disease population to have either normal thresholds (Frasnelli et al., 2002; Vreman et al., 1980), have elevated thresholds (Griep et al., 1997), varied thresholds or an elevated threshold for one odorant but a normal one for another (Landis et al., 2011). Similarly, when looking for

improvements in olfaction after treatment, results show either no change in threshold (Griep et al., 1997), an improvement for thresholds (Korytowska & Szmeja, 1993), or an improvement in one odorant threshold but not a second odorant (Landis et al., 2011).

Studies have shown that KD is associated with increased risks for depression (O'Donnell & Chung, 1997) and sleep disorders (Lüdemann, Zwernemann, & Lerchl, 2001; Unruh et al., 2006). Each of these disorders also has associations with impaired olfactory performance, adding more confusion to olfactory impairment in KD patients.

In addition to olfactory dysfunction, another symptom of renal failure is a significant reduction in normal nocturnal melatonin levels compared to healthy controls (Parker, 2003). This change may be the cause of the observation of day-night reversal in sleep patterns of dialysis patients (Parker, Bliwise, Bailey, & Rye, 2003). Over 50% of ESRD patients have sleep apnea (Kimmel et al., 1989; Unruh et al., 2006) compared to the 2-4% in the general population (Pierratos & Hanly, 2011).

Olfactory function has been shown to decrease with disturbances in Rapid Eye Movement (REM) sleep (Fantini, Postuma, Montplaisir, & Ferini-Strambi, 2006; Miyamoto et al., 2009; Postuma, Gagnon, Vendette, Desjardins, & Montplaisir, 2011). Parker et al. (2003) found that REM and total sleep time was reduced by up to 50% in ESRD patients. Moreover, it has been shown that even one night's sleep loss can impair olfactory performance (Killgore & McBride, 2006). While all of these studies have only shown a decline in OI, Stiasny-Kolster et al. (2005) found that those with REM sleep disorders to have significantly reduced olfactory abilities for OI, DT, and discrimination tasks.

As stated earlier, depression is also very prevalent in the KD population. Depression has actually been under diagnosed in the ESRD population, with only ~14% being diagnosed by a

physician although reliable scales of depression depict 43% as having major depressive symptoms (Lopes et al., 2004). Olfactory deficits have been found in depression, yet there are some discrepancies in the literature (Pantelis & Brewer, 2006). As opposed to KD, there is conflicting data regarding the OI abilities, not the DTs. Serby, Larson, and Kalkstein (1990) found OI deficits in depressed patients while Amsterdam, Settle, Doty, Abelman, and Winokur (1987) and Solomon et al. (1998) found no dysfunction in OI abilities. However, there is a clear consensus of a negative relationship between depression and DTs (Negoias et al., 2010; Pause, Miranda, Göder, Aldenhoff, & Ferstl, 2001; Pollatos et al., 2007).

The Present Study

The present study is a small part of a much larger and still ongoing project supported by Dialysis Clinics, Inc. (DCI) (Tumlin, 2012). The study as a whole will investigate neurotransmitter levels, the safety of a drug supplementation, sleeping patterns and habits, quality of life, depression, blood and plasma analyses, and olfactory performance over a two month time period for each participant. However, only the olfactory portion will be presented in this work. The present study will address and clarify the discrepancy in the literature by obtaining several measures of olfactory ability. Additionally, a new measure for assessing olfactory DTs was used in order to improve on the current methodology and to validate its use. Lastly, the relationship of additional variables that may be better predictors of olfactory performance and KD was assessed.

The main objective of the present study is to address and clarify the discrepancy in the literature. While there are discrepancies in the DT literature for the KD population, there does appear to be a trend of poor OI performance. The first hypothesis is:

H1: The Kidney Disease participants will have significantly lower OI scores compared to the control subjects.

The methodology in the new olfaction threshold test (the WUTC) will allow for a more reliable measure of olfactory DTs. Olfactory performance can vary based on different odorants, and the discrepancies in the threshold literature may be a result of using an unreliable or irrelevant odorants for the population. Basing the DT measure on scents relevant to the CKD and ESRD population should also allow for a greater accountability of variances in detection performance between different populations (i.e. ESRD/CKD and control subjects). This increased test accuracy leads to the second hypothesis:

H2: The Kidney Disease participants will have significantly higher threshold scores compared to the control subjects.

Through the use of SDT and the dichotomous response to every stimulus (including blanks), it will be possible to obtain actual measures of sensitivity for subjects. Since KD is associated with olfactory deficits, they should have a decreased ability to distinguish odorants from blanks. Thus, the third hypothesis is:

H3: The Kidney Disease participants will have significantly lower sensitivity scores compared to the control subjects.

In addition to the increased reliability from the methods used in the WUTC, the test was specifically designed to test olfactory abilities in the CKD and ESRD population. This specificity should allow for the test to be used as a diagnostic tool. The fourth hypothesis is:

H4: The measures of the WUTC will be able to distinguish those with Kidney Disease from the controls subjects with high specificity and sensitivity.

Also, given the high prevalence of disorders that also affect olfaction in the ESRD and CKD population, analyses will be utilized to assess for any possible moderating relationship that may account for the varying results. This analysis was conducted by adding covariates into regression models to see if any significant predictors of olfactory performance emerged. The specific covariates assessed are sleep quality and depression. These variables are important given the high prevalence of these disorders in the KD population.

CHAPTER II

METHODS

Participants

The recruitment of KD participants was supported by DCI and conducted through the Southeastern Renal Research Institute (SERRI). Control Subjects were recruited through a community sample to be age and gender matched to the KD participants. The inclusion and exclusion criteria differed for the KD participants and control subjects who also went through slightly different procedures.

Kidney Disease Participants

Inclusion criteria for the KD population were that participants be between 18 and 85 years old. Participants also had to be diagnosed with either CKD or ESRD and if undergoing dialysis, duration had to be greater than 3 or more months. Participants could also not be on any sleep medications. Participants were recruited from the Chattanooga, TN area. There were a total of 15 participants recruited, with a total of 8 participants (1 female) completing all requirements for participating. Mean age was 56.2 (SD = 11.9) and 75% were African American (n = 6). For a full list of inclusion and exclusion criteria, see Appendix A. Demographic information for these participants were obtained through medical records. Any individual involved in the collection of this data received certifications in the protection of human rights as research participants.

Control Participants

Control participants were recruited based on characteristics of the KD participants. After completion of protocols from KD participants, control subjects were recruited from the same geographical area to be age and gender matched. Of the 8 KD participants, only 5 (1 female) controls were obtained. Mean age was 54.4 (*SD* = 11.8, not significantly different from KD participants) and 20% (*n* = 1) were African American. Controls were also matched based on ethnicity. The discrepancies in the numbers were a result of a KD participant being excluded from the current study as a result of incomplete olfactory data. Demographic information for the control subjects was obtained through a demographic questionnaire. The questionnaire asked participants to indicate age, gender, ethnicity, occupation, etc. It also asked participants to indicate any history of specific illnesses and medication use in order to further match the KD participants (See Appendix B for the complete demographics).

Materials

Materials include: the University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al., 1984), the WUTC (Tewalt, 2013), the Center for Epidemiologic Studies Depression – Revised Scale (CESD-R) (Eaton, Smith, Ybarra, Muntaner, & Tien, 2004), and the Pittsburg Sleep Quality Index (PSQI) (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). These materials can be found in Appendices C, D, E, and F, respectively.

University of Pennsylvania Smell Identification Test

The UPSIT is a 40 item test consisting of four booklets. Each booklet contains 10 different odorants located on separate pages with 4 possible choices to choose from for each

odorant. The participants were instructed to use the pencil provided to scratch and release an odorant and try to identify the odorant by selecting one of the provided choices as per the instruction manual (Doty, 1995). A forced choice test, for the test to be valid each item must be answered. If the participant does not detect an odorant or the choices do not represent what the participant believes the odorant to be, they must still pick one of the choices. Each test booklet and its odorants were presented to each participant in the same order. The participant score was based on the percentage of correct responses (See Appendix C for UPSIT Key).

Wheeler University of Tennessee at Chattanooga Threshold Test

The WUTC consists of 54 tubes with nine different dilutions for five odorants and blanks. Each tube contains 10*ml* of the odorant dilution or blank. The presentation of the tubes is double blind, requiring two people to administer the test. One person was responsible for recording responses and handing the tubes based on a randomized sequence sheet to the presenting researcher. See Appendix D for a picture of the test and an example sequence sheet. The odorants are Vanillin, L-α-Pinene, Ethanol, Isoamyl Acetate (Banana), and P-cresol. The dilutions are made so the middle dilution coincides with detection threshold norms and are a clear liquid. The blanks contain 10*ml* of purified distilled water. The tubes are presented to each individual in a completely random order and each tube is presented for a total of two times. Responses of, "*yes*," for being able to detect the odorant and, "*no*," for not being able to detect the odorant were recorded for each tube presentation. An analysis using Logistic Regression was used to obtain the projected threshold for each participant. If any *B* coefficient is negative, then threshold cannot be computed as a result of response confusion.

Measures of sensitivity were also obtained from the WUTC. Values for the non-parametric measure *A''* were obtained by taking the proportion of detections in all stimuli that contained odorants and the proportion on "*yes*" responses to blanks. These values were then calculated using equation 1.2 to obtain an overall sensitivity measure. Since values less than .5 indicate some type of response confusion or sampling error, any participant whose *A''* <.05 was omitted from analyses. Moreover, measures of A'' were also calculated for each individual odorant.

Center for Epidemiologic Studies Depression – Revised Scale

In order to obtain depression scores, the CESD-R was used. It is designed to measure depression based on the 4th edition of the Diagnostic Statistical Manual (DSM-IV) and has been shown to have high reliability (Eaton et al., 2004). This measure consists of 20 items using a 4 point Likert scale (0-3) asking participants to rate his or her feelings during the past week. The final depression scores is a summation of the 20 items resulting in a range of scores from 0 to 60. A higher score indicates greater depression. Scores 16 and over are indicative of being clinically depressed and is used as a diagnostic cut off. See Appendix E for the complete CESD-R.

Pittsburg Sleep Quality Index

The PSQI is a 19 item self-report measure for assessing sleep quality and disturbances in the past month. Four of the items ask for open ended responses such, "How many hours of actual sleep do you get at night?" The rest of the items are rated on a 4 point Likert Scale (0-3). The open ended items were recoded into a 0-3 scale. These recodes were made according to the scoring instructions. The PSQI is broken up into 7 components, each with instructions for

scoring based on the responses from the 19 items. Scores can range from 0 to 21 with higher scores indicating poor sleep. Scores 5 and higher are typically indicative of poor sleep. See Appendix F for the full PSQI. Specific scoring instructions can be found through Buysse et al. (1989).

Procedure

All data collected was managed and analyzed using the IBM Statistical Package for the Social Sciences (SPSS). No personal identifying information was entered into these files, and all data files were kept on an encrypted hard drive to further protect personal information. The following procedures were approved by the Institutional Review Board (See Appendix G for the Kidney Disease IRB Approval Letter and Appendix H for the Control IRB Approval Letter)

Kidney Disease Procedure

Upon giving consent for the larger study, KD participants were scheduled to come into a research facility for a morning and afternoon appointment. If the participant was on dialysis, the scheduled appointments fell on a non-dialysis days. During each of the times, protocols for the blood analysis investigation which was part of the larger study would be implemented. After completing this necessary aspect of the study which also included the PSQI, participants were brought into a room and were given a battery of psychometric tests for this study which included the CESD-R, UPSIT, and WUTC. Participants first completed the CESD-R. Detailed instructions were given to each participant verbally, as well as having written instructions at the top of every page. After completing the questionnaire packet, participants were given the first booklet from the UPSIT. Verbal instructions were given based on the instructions attached with

the UPSIT. Subsequent booklets were given after completing the previous one. Lastly, the WUTC was administered. Since the WUTC is a double blind administration, the participant was seated facing away from the researchers. One researcher was responsible for presenting the tube to the participant, while the other pulled tubes based on the randomized sequence sheet. Participants were instructed that some of the tubes contained an odorant while others did not and the ones that do contain odorants have varying amounts. Participants were then instructed they had 3-5 seconds to smell the tube and to then respond with whether or not they detected an odorant. After completing the WUTC, participants were free to leave.

Since the KD participants were also participating in the larger study, they were not debriefed as to the nature of the study or given results of their performance. This was done to prevent any future response bias in the follow up examinations when the procedure is replicated.

Control Subject Procedure

The protocol for the controls was matched as much as possible to the KD procedure. After recruitment, participants were brought to a local university. Upon arriving, consent was first obtained from participants (See Appendix I). Next, the controls took the same battery of psychometric tests as the KD participants did with the addition of the demographic questionnaire. The same verbal and written instructions were given for completing the questionnaires and olfactory measures. When administering the WUTC, controls were set up in a similar fashion as the KD participants.

The procedure differed for the controls in that they were debriefed about the purpose of the study. There was no need to prevent any future response bias as controls participated in only one session.

Statistical Analyses

An independent samples *t* test was used to analyze the hypotheses regarding poorer olfactory performance in the KD participants compared to the controls. The *t* test was also used to compare age between the two groups. In order to obtain thresholds for each participant, a logistic regression analysis was used. This analysis allowed for predicted probabilities to be saved for each concentration. A graph was then created with the concentrations on the *x*-axis and probabilities on the *y*-axis for each participant. An ogival curve was then plotted through points on the graph and a horizontal line was added at .5 on the *y*-axis. A vertical line was then placed at the intersection of the ogival curve and horizontal line. Where the horizontal line fell on the *x*-axis was determined to be the estimated threshold. See Figure 1.1 for the graphical representation. Logistic regression was also used to assess the significance of variables in predicting KD.

CHAPTER IV

RESULTS

Group Comparisons

Although there was not a control for every KD participant, there was no significant difference in ages between the two groups ($t(11) = -.328$, $p = .749$). Table 3.1 below shows the group means for age as well as provides a comparison of genders and ethnicities. Table 3.2 shows group means and standard deviations for each of the olfactory measures excluding DTs. Table 3.3 illustrates the differences between KD and controls in mean thresholds for each odorant.

Table 3.1 Comparative Means of Age and Percentage of Demographics between KD and Control Subjects
Standard Deviations are in parentheses

Group	*Age*	*Males*	*Females*	*Caucasian*	*African American*
Kidney Disease	56.2 (11.9)	87.5%	12.5%	25.0%	75.0%
No Kidney Disease	54.4 (11.8)	80.0%	20.0%	80.0%	20.0%

Olfactory Identifications

The first hypothesis was that KD participants would have lower OI scores compared to the controls. The hypothesis was not supported (t (11) = 1.395, p = .191). However, average OI scores for KD participants were lower compared to the controls. See Table 3.2.

Detection Thresholds

The second hypothesis was not supported either. Results for all odorants indicate that none of the thresholds are significantly higher than the controls. The corresponding results for Vanillin, Pinene, Ethanol, Banana, and P-Cresol are t (7) = -.243., p = .815, t (6) = -.919, p = .394, t (7) = -.891, p = .403, t (8) = -.589, p = .572, and t (3) = -.769, p = .498, respectively. Although the results showed no significant differences between KD and control DTs, the KD thresholds were higher for all odorants.

Sensitivity

Sensitivity was hypothesized to be lower for KD participants, indicating that they would have a harder time distinguishing odorants from blanks compared to the controls. Similar to the analysis for the first hypothesis, the t test again did not reach significance (t (9) = 1.239, p = .247) despite the fact that sensitivity scores were lower than the controls (with the exception of vanilla). Further group comparisons were made for each odorant sensitivity, but nothing significant was found, although sensitivity of P-Cresol approached significantly lower scores for KD participants (t (9) = 2.225, p =.053).

Table 3.2 Comparative Means of OI and Sensitivity between KD and Control Subjects
Standard Deviations are in parentheses

Group	*OI*	*Overall A''*	*Vanillin A''*	*Pinene A''*	*Ethanol A''*	*Banana A''*	*P-Cresol A''*
Kidney Disease	.70 (.18)	.67 (.08)	.77 (.06)	.57 (.21)	.53 (.15)	.75 (.10)	.61 (.21)
No Kidney Disease	.82 (.12)	.74 (.11)	.73 (.18)	.70 (.10)	.66 (.15)	.81 (.07)	.84 (.06)

Table 3.3 Comparative Means of DT for Each Odorant between KD and Control Subjects
Concentration Ranges in parts per million are below odorant name. Standard Deviations are in parentheses

Group	*Vanillin 1.95-500.00*	*Pinene 7.81-2000.00*	*Ethanol 3.91-1000.00*	*Banana .48-125.00*	*P-Cresol .03-8.00*
Kidney Disease	51.56 (43.72)	1273.27 (2102.58)	1245.60 (2084.01)	10.29 (21.03)	3.16 (5.21)
No Kidney Disease	41.24 (82.49)	282.52 (482.23)	279.07 (558.15)	2.86 (2.50)	0.17 (0.18)

Prediction of Kidney Disease

None of the measures were significant predictors, nor were any combinations of olfactory measures and/or disorders.

CHAPTER V

DISCUSSION AND CONCLUSION

Implications of Results

None of the hypotheses were supported by the data analyses. With the exception of sensitivity to Vanillin, the KD participants performed worse than the controls on all olfactory measures. Although the prior evidence supported an olfactory deficit in identification abilities (Corwin, 1989; Raff et al., 2008), the current statistical analyses did not reach significance. The results from this study do not necessarily mean that these previous studies are not supported, but instead suggest deficiencies in the current procedure.

The main factor affecting the results is the amount of variance in each olfactory measure. The only way for the variance in the data to be reduced is by including more participants. Additionally, there are still too few participants for a representative sample of the population as whole. Tables 3.1 and 3.2 indicate that this is especially true for DTs; the standard deviations actually exceed the means and far surpass the differences between the groups. Once enough participants have been added to generate a high enough statistical power, it may be possible to see the trends of poorer performance become significant differences.

Even though there was no significant difference in DTs between the two groups, there too appears a trend of poorer performance on this task. Every single odorant used indicated higher thresholds for the KD participants. Further analyses showed an interesting factor affecting performance for both KD and controls. The factors distorting the results are both a floor and

ceiling effect. This effect is seen separately for the different groups. Control performance appears to be influenced by a floor effect, while the KD participants are affected by a ceiling effect. It was discovered that on average, there was not a stimulus with a low enough concentration to be undetectable for the controls. These floor effects were present for the controls on Vanillin and Ethanol. Figures 4.1 and 4.2 are graphs that show the relationship of the average predicted probabilities for each group based on the concentration.

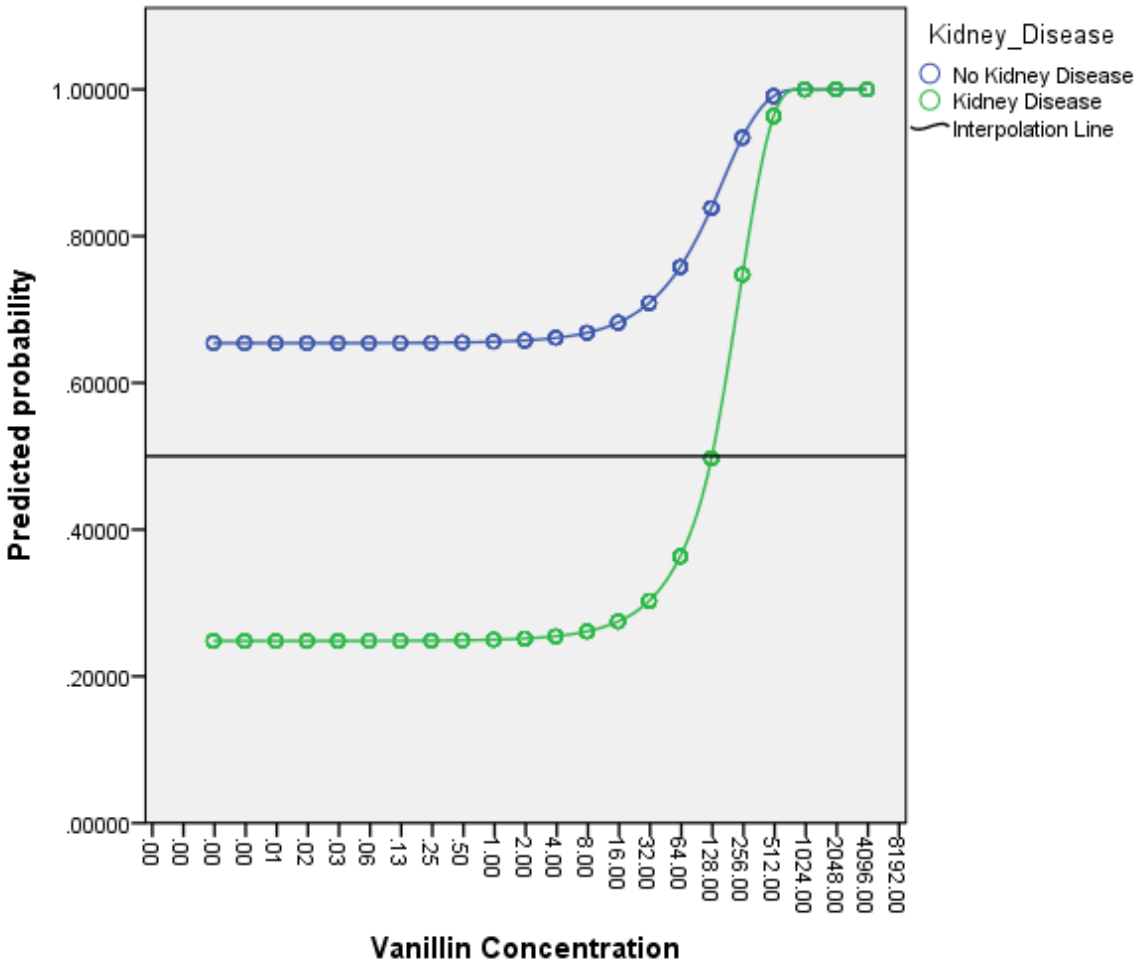

Figure 4.1 Predicted Probability Curve of Vanillin by Group with Evidence of a Floor Effect in Control Groups

The horizontal scale is graphed using a logarithmic scale to avoid skewness. Each point on the graph represents the probability of that concentration being detected with an ogival curve added for each group. The horizontal line depicts where the probability of .5 would intersect the probability curve. The corresponding concentration at the intersection of the horizontal line and probability curve is the estimated threshold. The floor effect is present for the controls given the predicted probability never drops below .5.

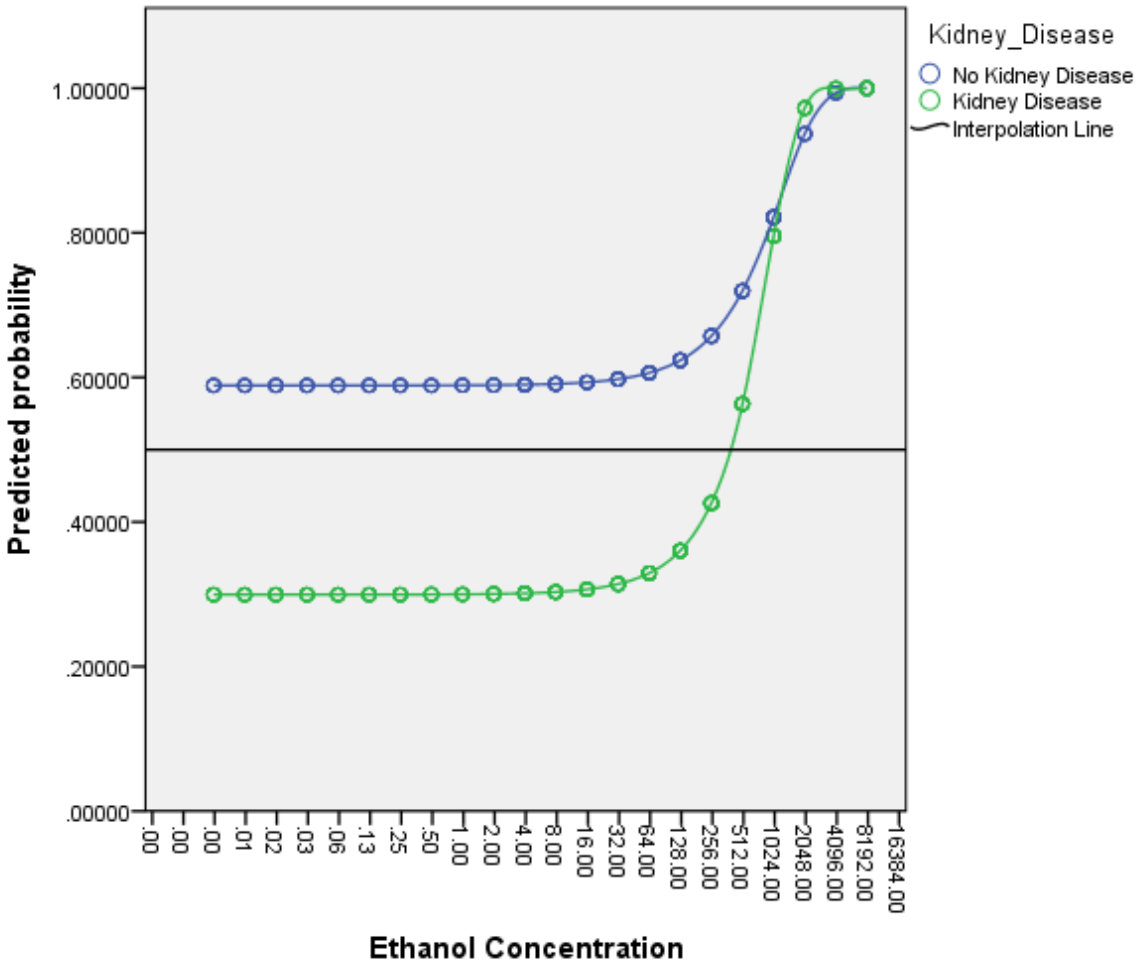

Figure 4.2 Predicted Probability Curve of Vanillin by Group with Evidence of a Floor Effect in Control Groups

The horizontal scale is graphed using a logarithmic scale to avoid skewness. Each point on the graph represents the probability of that concentration being detected with an ogival curve added for each group. The horizontal line depicts where the probability of .5 would intersect the probability curve. The corresponding concentration at the intersection of the horizontal line and probability curve is the estimated threshold. The floor effect is present for the controls given the predicted probability never drops below .5.

On the other end of the spectrum, there was no concentration strong enough for KD participants to detect on average. For example, Table 3.2 in the previous section shows the average threshold for Ethanol higher than the range that was tested. This occurred as a result of three separate KD participants having their threshold calculated by extrapolating the graph

beyond the thresholds measured. That is, the predicted probabilities never cross the .5 probability line for the range of concentrations tested, indicating the presence of a ceiling effect. For those three participants, this effect occurred on every odorant except Banana.

Despite not having a concentration low enough to measure thresholds for the controls (thus giving them a threshold concentration of .0) and not having concentrations high enough for KD participant to detect, there was still no significant difference between groups for these thresholds. Variance in the thresholds as a result of the small sample size may also be preventing any significant results from occurring.

As a result of the small sample size, the inferential statistics may not be the best tool to use assessing the different in DTs between diseases. The following graphs (Figures 4.3 – 4.5) show the average predicted probability curves for all participants by odorant.

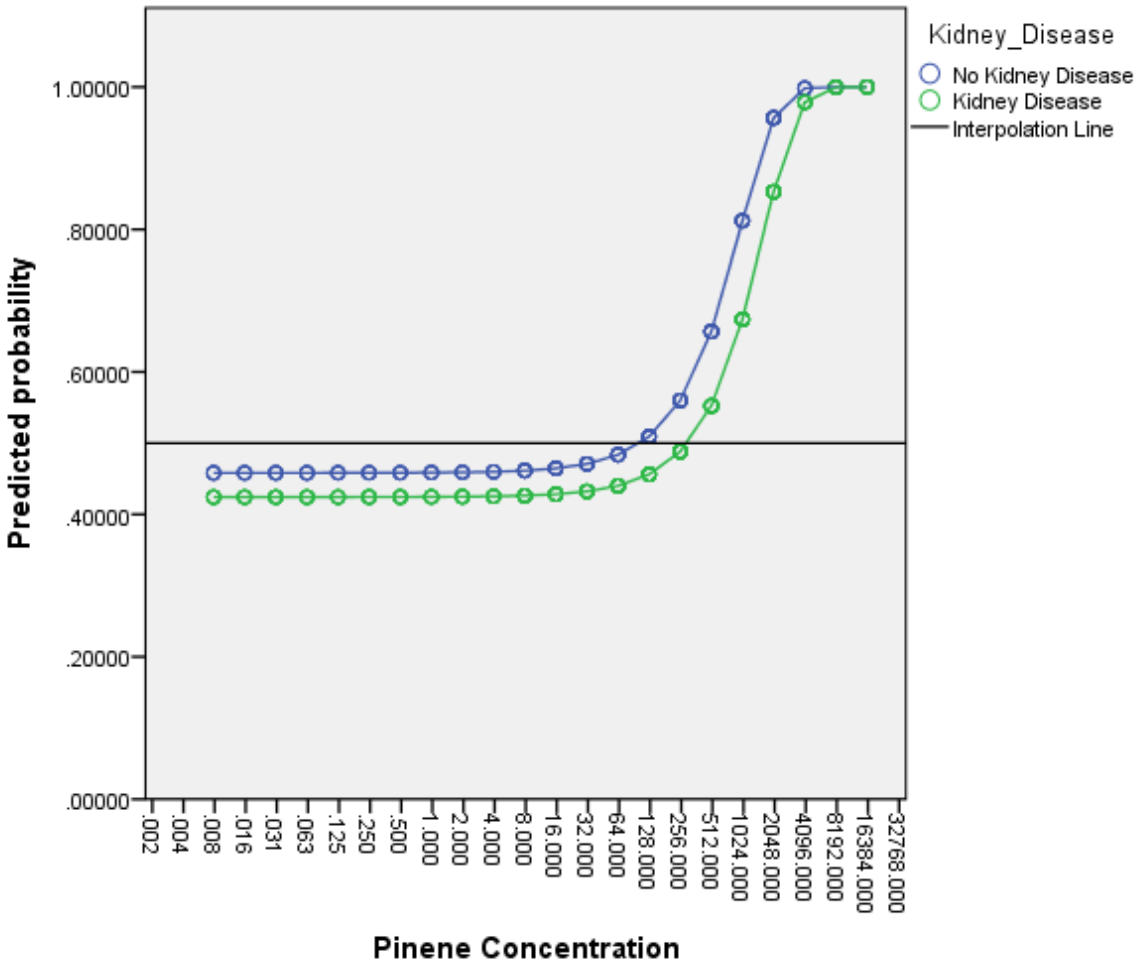

Figure 4.3 Predicted Probability Curve of Pinene by Group

The horizontal scale is graphed using a logarithmic scale to avoid skewness. Each point on the graph represents the probability of that concentration being detected with an ogival curve added for each group. The horizontal line depicts where the probability of .5 would intersect the probability curve. The corresponding concentration at the intersection of the horizontal line and probability curve is the estimated threshold.

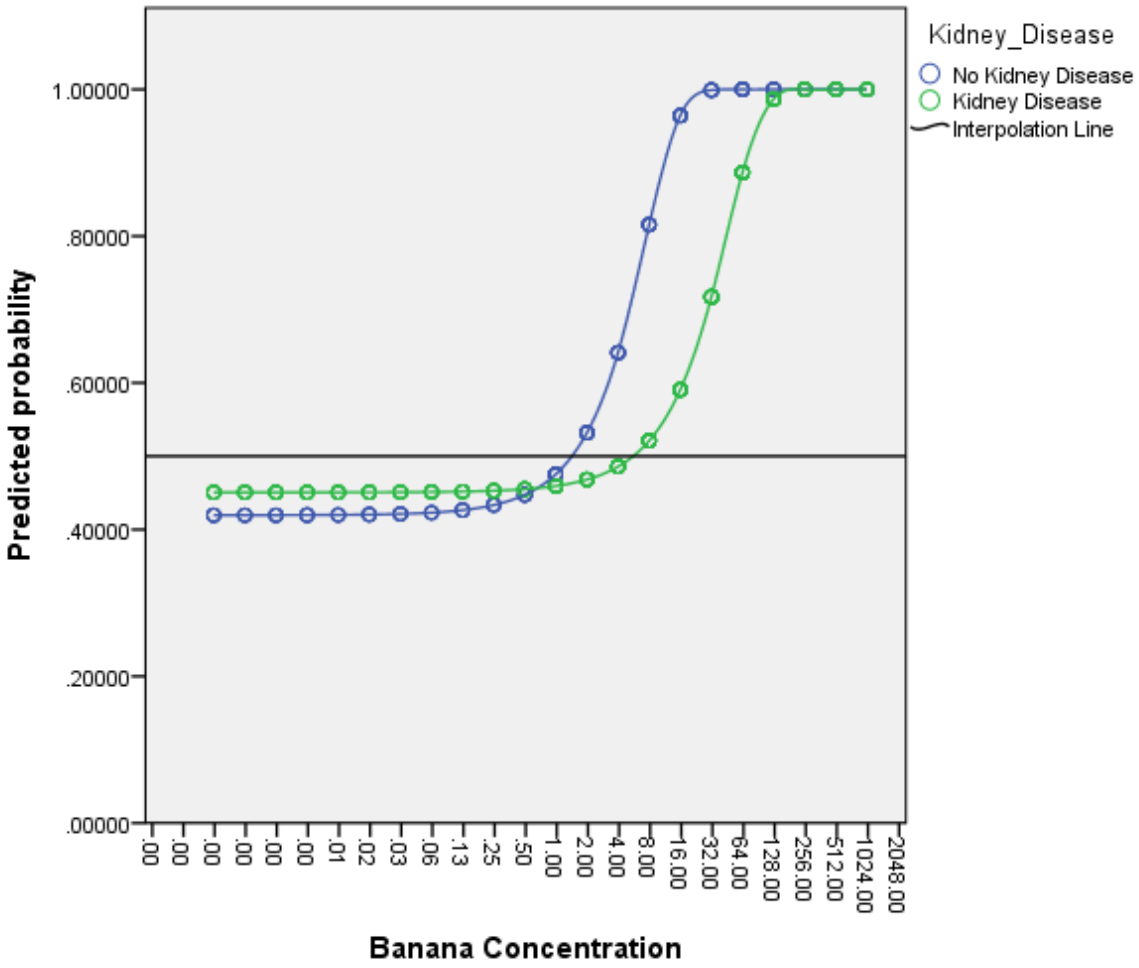

Figure 4.4 Predicted Probability Curve of Banana by Group

The horizontal scale is graphed using a logarithmic scale to avoid skewness. Each point on the graph represents the probability of that concentration being detected with an ogival curve added for each group. The horizontal line depicts where the probability of .5 would intersect the probability curve. The corresponding concentration at the intersection of the horizontal line and probability curve is the estimated threshold.

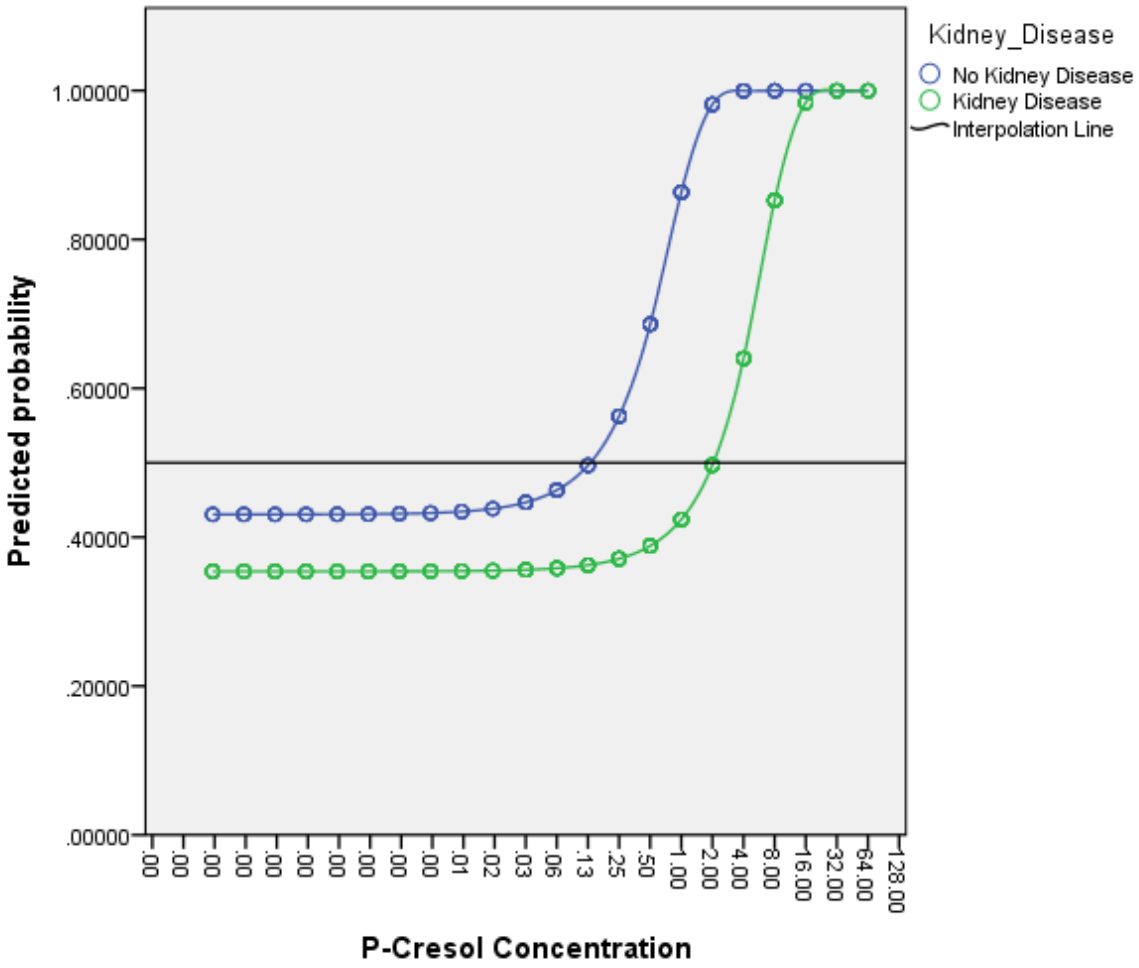

Figure 4.5 Predicted Probability Curve of p-Cresol by Group

The horizontal scale is graphed using a logarithmic scale to avoid skewness. Each point on the graph represents the probability of that concentration being detected with an ogival curve added for each group. The horizontal line depicts where the probability of .5 would intersect the probability curve. The corresponding concentration at the intersection of the horizontal line and probability curve is the estimated threshold.

As seen in the above figures (Figures 4.1 – 4.5), there appears to be performance differences based on odorant. It appears that there are very little differences in thresholds for KD participants compared to the controls in Pinene and Banana. However, there are large differences for the odorants Vanillin and Ethanol. The WUTC did not have a concentration low enough for the controls to detect on either odorant. Additionally, the WUTC did not contain a concentration

high enough for KD participants to detect. While no floor or ceiling effect was found for p-Cresol, the comparison of probability curves does appear to show poorer detection abilities for KD participants. This difference may also not be statistically significant as a result of the variability in the data. However, if significance is attained through a larger sample size, the decrease in DT for P-Cresol may be a result of some biological mechanism used in olfaction being blocked from the buildup of uremic toxins found in KD (McKinney, 2013) and may explain why the differences in sensitivity of P-Cresol were so close to significant in the small sample size. Another explanation for this difference in sensitivity may be a result of the KD participants being habituated to the odorant. Voss et al. (2005) found that KD patients do not smell their uremic odorant and their sweat contained high levels of uremic concentrations.

Limitations

As already discussed, the major limitation to the study was sample size. The criterion to meet in order to be eligible is a very long and specific list (See Appendix A for full list). This also made it very difficult for the recruitment of controls. Since controls had to be age and gender matched, recruitment could not be started until KD participants completed their participation. Further complicating this limitation was a result of having to omit participants from the already small dataset as a result of test performance. As stated in the introduction, any value of $A' \leq .5$ is due to an error in response confusion. Two individuals, one in each group, were removed from the analyses as a result of small A' values. Their A' values were indicative that these participants were guessing through the entire testing procedure. The guessing may have resulted from a total lack of olfactory ability.

B coefficients were obtained for every threshold analysis. Some coefficients were negative, indicating a decrease in predicted probability for detecting odorants as the concentrations increased. Anyone with an estimation of threshold with a negative *B* coefficient was not included in the analyses. The negative coefficients can actually be used for determinations of response confusion or possible guessing for participants. Surprisingly, this was only observed in the KD participants. No individual threshold was excluded from the controls as a result of response confusion. Given that response confusion was only found in KD participants, it may be indicative of an olfactory deficit.

However, there were a number of thresholds that were not able to be computed for the controls. These thresholds could not be obtained as a result of responding yes to every stimulus for an odorant. The logistic regression analysis will not compute predicted probabilities without the dependent variable assuming exactly two variables. This issue was only seen in the controls. This could be a result of response bias. Controls did have a higher response bias, indicating a higher tendency to say yes compared to the KD participants ($B'' = .194$, $B'' = -.346$, respectively). The non-significant difference in response bias could be the result of the small sample size, but it is more likely a result from the ranges used on the WUTC.

Another possible issue resulting from the small sample size is reliability. While Tewalt (2013) found reliability measures of > .8, the highest reliability observed in the present study was $K = .644$ (See table 4.1 for all observed reliability measures for each odorant). The reliability coefficient used was *K* to check for agreement in detection or no detection from the first presentation of a stimulus to its second presentation. Scores can range from -1 (no agreement) to +1 (high agreement).

Table 4.1 Observed Reliability Coefficients of the WUTC

Odorant	***Overall***	***KD***	***Controls***
Vanillin	.592	.581	.573
Pinene	.501	.335	.644
Ethanol	.449	.362	.429
Banana	.550	.524	.493
p-Cresol	.535	.377	.552

A statistically significant difference may not have been found as a result of the WUTC design. Although the WUTC includes the middle concentration reflective of the normative data on each odorant's threshold (Tewalt, 2013), the range may have been too restricted for the samples or populations being tested. The design of the test is restricting the range of sensitivity in that only half of the odorant containing stimuli is supposed to be detected. This restricted range may have also been a major cause in creating the ceiling and floor effects observed in the participants.

Direction of Future Research

The present study is a part of a much larger clinical drug trial that is still ongoing. The continuation of the study should alleviate the small sample size and reduce the variance. Olfactory measures may start to differentiate between KD participants and controls. Once the variance issue has been resolved, the analyses may become significant, given the trend of poorer olfactory performance in the KD participants. The larger study of which this study was a subset

of is also assessing the effectiveness of a drug supplementation which could be used to examine possible treatment effects like those seen in Landis et al. (2011) and Griep et al. (1997).

Adjusting the range of the odorants used in the WUTC is also necessary to analyze thresholds in both KD and control subjects. Extending the range of the concentrations may alleviate the presence of the ceiling and floor effects. One recommendation is to exclude two of the odorants currently in the WUTC. No ceiling or floor effects were found for Pinene or Banana, nor was there any indication of an obvious difference in probability curves. By eliminating these two odorants, the ranges can be extended three concentrations in each direction without adding to the length of the test. By extending the range and increasing the sample size, it may be possible to predict KD based on olfactory performance.

In addition to extending the ranges of concentrations in the WUTC, there should be a standardization of odorants used in testing olfactory performance in the KD population. Table 4.1 shows the results of previous studies and the odorants that were used when examining olfactory abilities in the KD population.

Table 4.2 Comparison of Results from Previous Olfactory Assessments of KD when Compared to Controls

OI tests used and the odorant(s) used in the study are reported in the parentheses.

Study	***Olfactory Identification***	***Detection Thresholds***
The Present Study	Non-significantly Lower (UPSIT)	Non-Significantly Higher (Vanillin, Pinene, Ethanol, Isoamyl Acetate, p-Cresol)
Landis et al. (2011)	Significantly Lower (Sniffin' Sticks)	Normal (*n*-Butanol) Elevated (Acetic Acid)
Frasnelli et al. (2002)	Significantly Lower (Sniffin' Sticks)	Normal (*n*-Butanol)
Griep et al. (1997)	-	Significantly Higher (Isoamyl Acetate)
Korytowska and Szmeja (1993)	Significantly Lower (Coffee and Lemon)	Normal (Coffee, Lemon Oil)

Only two odorants were used in more than one study, *n*-Butanol and Isoamyl Acetate, both of which have a banana smell. The reason the mixed results have been found in the DT literature may be a result of not using an odorant or odorants that are affected by the symptoms of the disease, like levels of uremic toxins in the blood.

Given the differences found with P-Cresol, both in sensitivity and thresholds, blood analyses should be done to determine if there is a relationship between P-Cresol blood levels and olfactory performance. McKinney (2013) found there was no P-Cresol in healthy individuals, which means P-Cresol may be the cause for the olfactory deficits. If there is an indication of a negative relationship, then further analyses can assess why P-Cresol may be hindering olfactory performance.

Conclusion

There has been conflicting data in regards to olfactory performance in KD. While there is a trend for deficits in OI, the results for DT are inconsistent. The prior results indicate poorer performance, no difference in performance, or varied performance between odorants when compared to healthy individuals. Further complicating the relationship of olfaction and KD is the increased prevalence of sleep disorders and depression. Both of these disorders have also been linked to declines in olfactory performance.

Although there were no statistically significant differences found in olfactory abilities between KD participants and controls, there does appear to be a trend for poorer olfactory abilities. The difference observed may not have been found significant as a result of the small sample size or as a result of the floor and ceiling effects found. Furthermore, the small sample size and large amount of variance may also have prevented any significant predictors of olfactory abilities and KD from being found.

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APPENDIX A

INCLUSION AND EXCLUSION CRITERIA FOR KIDNEY DISEASE PARTICIPANTS

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

1) Patient age > 18 and <85 years of age
2) Patients with CKD or ESRD with eGFR < 30 mls/min
3) If receiving hemodialysis, patients must be on treatment > 3 months
4) Normal healthy controls must be without a known history of CKD and be willing to have formal PSG test and plasma melatonin measurements

Exclusion Criteria:

1) Patients receiving outpatient hemodialysis for < 3 months
2) Patients with estimated GFR by Cockcroft Gault > 30 mls/min
3) Patients receiving beta blocker therapy within one month of randomization
4) Patients receiving Nifedipine therapy within one month randomization
5) Patients on peritoneal dialysis
6) Patient with chronic home oxygen supplementation
7) Patients receiving chronic home CPAP therapy
8) Patients actively receiving outpatient sleep medications
9) Patients with diabetic gastroparesis unresponsive to medication
10) Patients with known pregnancy or unwilling to use contraception during the course of the study
11) Patients with a functioning renal allograft
12) Patient currently receiving long-term immunosuppressive therapy. Patients receiving low dose prednisone (10mg or less per day) will not be excluded from this trial
13) Unable to give informed consent

APPENDIX B

DEMOGRAPHIC QUESTIONNAIRE FOR CONTROL SUBJECTS

Age (in years): _____

Gender (circle one); Male Female

If female, please answer the questions located on the next page. ***

Ethnicity (circle one): Caucasian African American Asian American Hispanic

Bi-Racial Other (please indicate): _____

Do you currently smoke (circle one): Yes No

If yes; How many cigarettes per day?_____; Cigars per day?____

What type of cigarettes do you smoke? _____

How many years have you smoked? _____

If not currently smoking, have you ever smoked? (Circle one): Yes No

If yes, how long ago did you stop?_____

How many cigarettes did you smoke per day?_____; Cigars per day?_____

Did your ability to smell change after you stopped smoking? (Circle one): Yes No

If yes; How?

_____

_____

What is your occupation: _____

Highest grade completed? (Circle only one number):

6 7 8 9 10 11 12 College 1 2 3 4 5 +

Please indicate if you have had past history of the following medical Illnesses. (Circle Yes or No):

High blood pressure	Yes	No	Diabetes	Yes	No
Arthritis	Yes	No	Heart disease	Yes	No
Thyroid disorder	Yes	No	Headaches	Yes	No
Lung trouble	Yes	No	Gout	Yes	No
Epilepsy	Yes	No	Circulation problems	Yes	No
Broken nose	Yes	No	Anemia	Yes	No
Strokes	Yes	No	Eye problems	Yes	No
Asthma	Yes	No	Cancer	Yes	No

Please indicate if you have had past history of the following medical Illnesses. (Circle Yes or No):

Hepatitis	Yes	No	Ulcer	Yes	No
Hiatal hernia	Yes	No	Kidney disease	Yes	No
Pelvic disease	Yes	No	Skin disease	Yes	No
Prostate problems	Yes	No	Infections	Yes	No
Bleeding/clotting disorder	Yes	No	HIV	Yes	No
TB	Yes	No	Neurological disease	Yes	No
Deviated septum	Yes	No	Sinus problems	Yes	No
Concussion/head trauma	Yes	No	Medical allergies	Yes	No
Food allergies	Yes	No	Seasonal allergies	Yes	No

Other: _____

Please indicate if you are currently taking any of the following types of medications. (Circle Yes or No):

Antibiotics	Yes	No	Antidepressants	Yes	No
Hormone replacements	Yes	No	Antihistamines	Yes	No
Antihypertensive	Yes	No	Antianxiety	Yes	No
Lithium	Yes	No			
Anti-inflammatory†	Yes	No			

†Including ibuprofen

Antineoplastic†† Yes No

††Examples of Antineoplastics are *Elspar* (asparaginase), *Alkeran* (melphalan), floxuridine, lomustine, procarbazine, thioguanine, thiotepa

Stimulant medications††† Yes No

†††Examples of Stimulant medications are *Adderall* and *Vyvanse*

Have you ever been diagnosed with Sleep Apnea? (Circle one): Yes No

***Females (optional, But VERY BENEFICIAL to answering research questions)**

If **FEMALE**; Are you currently on your menstrual cycle? (Circle one): Yes No

If **FEMALE**; Are you currently pregnant? (Circle one): Yes No

If **FEMALE**; Are you in menopause or post menopause? (Circle one): Yes No

APPENDIX C

UNIVERSITY OF PENNSYLVANIA SMELL

IDENTIFICATION KEY

UPSIT Key

1. B – Pizza
2. B – Bubble Gum
3. D – Menthol
4. D – Cherry
5. C – Motor Oil
6. B – Mint
7. A – Banana
8. B – Clove
9. C – Leather
10. B – Coconut
11. C – Onion
12. B – Fruit Punch
13. A – Licorice
14. D – Cheddar Cheese
15. B – Cinnamon
16. D – Gasoline
17. A – Strawberry
18. A – Cedar
19. B – Chocolate
20. C – Gingerbread
21. A – Lilac
22. A – Turpentine
23. B – Peach
24. A – Root Beer
25. B – Dill Pickle
26. C – Pineapple
27. D – Lime
28. B – Orange
29. B – Wintergreen
30. D – Watermelon
31. D – Paint Thinner
32. C – Grass
33. C – Smoke
34. A – Pine
35. D – Grape
36. D – Lemon
37. A – Soap
38. D – Natural Gas
39. B – Rose
40. A – Peanut

APPENDIX D

WUTC EXAMPLE SEQUENCE SHEET

Melatonin Threshold Sequence/Response Sheet

Name:_____ Date: _____

Admin: _____ Record: _____

Sequence	Remaining	Answer	First time	yes=1, no=0	Second time
6			[1]		[55]
39			[2]		[56]
43			[3]		[57]
50			[4]		[58]
35			[5]		[59]
48			[6]		[60]
10			[7]		[61]
31			[8]		[62]
44	100		[9]		[63]
34			[10]		[64]
5			[11]		[65]
41			[12]		[66]
16			[13]		[67]
22			[14]		[68]
51			[15]		[69]
52			[16]		[70]
47			[17]		[71]
40			[18]		[72]
46	90		[19]		[73]
11			[20]		[74]
32			[21]		[75]
42			[22]		[76]
36			[23]		[77]
20			[24]		[78]
22			[25]		[79]
53			[26]		[80]
25			[27]		[81]
25			[28]		[82]
14	80		[29]		[83]
1			[30]		[84]
1			[31]		[85]

49	
6	
48	
11	
52	
51	
54	
20	70
29	
45	
26	
26	
10	
18	
4	
13	
19	
54	60
7	
15	
35	
53	
2	
9	54
15	
30	
2	
33	50
21	
12	
4	
12	
38	
27	
24	
23	
9	
38	40
41	

[32]	[86]
[33]	[87]
[34]	[88]
[35]	[89]
[36]	[90]
[37]	[91]
[38]	[92]
[39]	[93]
[40]	[94]
[41]	[95]
[42]	[96]
[43]	[97]
[44]	[98]
[45]	[99]
[46]	[100]
[47]	[101]
[48]	[102]
[49]	[103]
[50]	[104]
[51]	[105]
[52]	[106]
[53]	[107]
[54]	[108]

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3	30
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40	10
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37	

APPENDIX E

CENTER FOR EPIDEMIOLOGIC STUDIES

DEPRESSION – REVISED SCALE

Place a check mark or "X" in the appropriate box. Only select one for each question.

Below is a list of the ways you might have felt or behaved. Please check the boxes to tell me how often you have felt this way in the past week or so.	Last Week				Nearly every day for 2 weeks
	Not at all *or* Less than 1 day	1-2 days	3-4 days	5-7 days	
1) My appetite was poor.					
2) I could not shake the blues.					
3) I had trouble keeping my mind on what I was doing.					
4) I felt depressed.					
5) My sleep was restless.					
6) I felt sad.					
7) I could not get going.					
8) Nothing made me happy.					
9) I felt like a bad person.					
10) I lost interest in my usual activities.					
11) I slept much more than usual.					
12) I felt that I was moving too slowly.					
13) I felt fidgety.					
14) I wished I were dead.					

Place a check mark or "X" in the appropriate box. Only select one for each question.

Below is a list of the ways you might have felt or behaved. Please check the boxes to tell me how often you have felt this way in the past week or so.	Last Week				Nearly every day for 2 weeks
	Not at all *or* Less than 1 day	1-2 days	3-4 days	5-7 days	
15) I wanted to hurt myself.					
16) I was tired all the time.					
17) I did not like myself.					
18) I lost a lot of weight without trying to.					
19) I had a lot of trouble getting to sleep.					
20) I could not focus on the important things.					

APPENDIX F

PITTSBURG SLEEP QUALITY INDEX

During the past month,

1. When have you usually gone to bed (what time)? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you…	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more time a week**
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loud				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity				
8. During the past month, how much of a problem has it been for you to keep your enthusiasm to get things done?				

	Very Good	**Fairly Good**	**Fairly Bad**	**Very Bad**
9. During the past month, how would you rate your sleep quality overall?				

APPENDIX G

IRB APPROVAL LETTER FOR KIDNEY DISEASE PATIENTS

MEMORANDUM

TO: Dr. Nicky Ozbek
Dr. James Tumlin

IRB # 12-196

FROM: Lindsay Pardue, Director of Research Integrity
Dr Bart Weathington, IRB Committee Chair

DATE: November 28, 2012

SUBJECT: IRB Application # 12-196: Olfactory Sensitivity and Depression in Dialysis Patients

The IRB Committee Chair has reviewed and approved your application and assigned you the IRB number listed above. You must include the following approval statement on research materials seen by participants and used in research reports:

The Institutional Review Board of the University of Tennessee at Chattanooga (FWA00004149) has approved this research project # 12-196.

Since your project has been deemed exempt, there is no further action needed on this proposal unless there is a significant change in the project that would require a new review. Changes that affect risk to human subjects would necessitate a new application to the IRB committee immediately.

Please remember to contact the IRB Committee immediately and submit a new project proposal for review if significant changes occur in your research design or in any instruments used in conducting the study. You should also contact the IRB Committee immediately if you encounter any adverse effects during your project that pose a risk to your subjects.

For any additional information, please consult our web page http://www.utc.edu/irb or email us at: instrb@utc.edu .

Best wishes for a successful research project.

APPENDIX H

IRB APPROVAL LETTER FOR CONTROL PARTICIPANTS

MEMORANDUM

TO: Joseph Jones **IRB #14-011**
Dr. Nicky Ozbek

FROM: Lindsay Pardue, Director of Research Integrity
Dr. Bart Weathington, IRB Committee Chair

DATE: January 16, 2014

SUBJECT: IRB #14-011: Olfactory Thresholds of Healthy Individuals

The IRB Committee Chair has reviewed and approved your application and assigned you the IRB number listed above. You must include the following approval statement on research materials seen by participants and used in research reports:

The Institutional Review Board of the University of Tennessee at Chattanooga (FWA00004149) has approved this research project #14-011.

Please remember that you must complete a Certification for Changes, Annual Review, or Project Termination/Completion Form when the project is completed or provide an annual report if the project takes over one year to complete. The IRB Committee will make every effort to remind you prior to your anniversary date; however, it is your responsibility to ensure that this additional step is satisfied.

Please remember to contact the IRB Committee immediately and submit a new project proposal for review if significant changes occur in your research design or in any instruments used in conducting the study. You should also contact the IRB Committee immediately if you encounter any adverse effects during your project that pose a risk to your subjects.

For any additional information, please consult our web page http://www.utc.edu/irb or email instrb@utc.edu

Best wishes for a successful research project.

APPENDIX I

INFORMED CONSENT FOR HEALTHY CONTROLS

Informed Consent Form

While we hope that you will complete the attached study, your participation is voluntary. You may elect not to participate at any time. In addition, if you do not feel comfortable answering any of the questions you may leave that question blank and continue with the rest of the study. The information you provide will be anonymous and we do not ask you to identify yourself in any way. Emotional and/or Psychological Stress, Boredom, Nasal Dryness, and/or an Allergic Reaction are possible risks associated with your participation in this project. You will not receive any direct benefit from participating in the study.

This first part of the study will ask you to respond to questions about sleeping, general health, and recent feelings or behaviors. The second part of the study will ask you to identify smells located on scratch and sniff booklets. The third part will ask you to respond whether or not you detected an odor in a tube. The last thing the study asks you to do is fill out a demographic page. The demographic information will ask about age, gender, ethnicity, occupation, education, smoking habits, and specific medical illnesses and medications. These questions will help us to interpret the results of the rest of the study.

The researcher will ask you for any allergies you may have. Depending on your allergies, you may be excluded from participating. If an allergic reaction does occur, you will be taken to the University Health Services for an allergy shot.

Some questions may cause emotional or psychological distress. If you experience either type of distress, please contact the University Counseling Center. They can be reached by phone or on site during walk-in hours.

Phone: 423-425-4438
Walk-in Hours: Monday – Friday, 9:00am-11:30am and 1:00pm-3:30pm

We expect that it will take approximately 1 hour to participate in this study.

Remember, this is an anonymous survey, so please do not write your name anywhere other than this page. You may also request a copy of this form for your records.

Who to Contact

If you have any questions or would like to obtain a report of this research study when the results have been completed, please contact Dr. Nicky Ozbek (423-425-4262), Department of Psychology, University of Tennessee at Chattanooga. This survey is being conducted as part of a Graduate Thesis. This project meets the requirements for approval by the UTC IRB and contact can be made to the UTC IRB through Director Lindsay Pardue (423-425-4443) and Chair Dr. Bart Weathington (423-425-4289).

By signing the consent, you are indicating that you are at least 18 years of age.

Thank you for participating in our research!

Name (Print) _____ Date_____

Signature _____ Date_____

VITA

Joe Jones was born in LaGrange, GA, to the parents of Jimmy and Susan Jones. He is the last born of his parent's children. He graduated from the University of Tennessee at Chattanooga with his Bachelors of Science degree in December 2011. It was during this time in which he discovered his enjoyment for Research. The following year, Joe accepted a Graduate Assistantship at the University of Tennessee at Chattanooga. Joe graduated with a Master of Science degree in Psychology in May 2014. Joe will continue his education in Psychology by pursuing a Ph.D. degree.