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Eating and Swallowing, Oral Health, and Saliva Production

Rebecca H. Affoo
The University of Western Ontario

Supervisor
Dr. Ruth Martin
The University of Western Ontario

Graduate Program in Health and Rehabilitation Sciences
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EATING AND SWALLOWING, ORAL HEALTH, AND SALIVA PRODUCTION
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by

Rebecca Hannah Affoo

Graduate Program in Health and Rehabilitation Sciences
Speech and Language Sciences

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The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

Abstract

Eating and maintaining optimal nutrition are essential to health and quality of life. In both health and disease, eating is influenced by multiple factors including swallowing, oral health, and saliva production. Perturbations to any, or all, of these inter-related factors may result in consequences that negatively affect the health and wellness of an individual. Eating and swallowing impairment are common symptoms of neurodegenerative diseases such as dementia, and these symptoms are associated with a host of negative sequelae such as malnutrition, dehydration, aspiration pneumonia, and reduced quality of life. The studies reported in this dissertation explored elements of eating and swallowing, saliva production, and saliva modulation in healthy individuals and in persons with Alzheimer's disease (AD).

This dissertation is composed of three studies. First, a scoping review methodology was used to examine literature that addressed autonomic nervous system and/or swallowing dysfunction in individuals with AD. Then, systematic review and meta-analysis methodologies were used to examine a potential effect of aging on saliva production. Finally, a within-subjects methodology was used to examine the modulation of salivary flow by tooth brushing in healthy older adults.

In the first study, swallowing dysfunction and autonomic nervous system dysfunction, including salivary flow dysfunction, were found to occur in persons with AD. In the second study, salivary flow was found to be reduced in adults aged 60 years and older who were free of major systemic disease. In the third and final study, the use of manual and electric tooth brushing was found to increase whole salivary flow rates in adults aged 60 years of age and older who were free of major systemic disease.

The results of this dissertation have very important implications for the future research and management of eating and swallowing, oral health, and saliva production in a variety of populations, including aging individuals and persons with AD.

Keywords

The following could be used to describe a thesis entitled “Eating and Swallowing, Oral Health, and Saliva Production”: eating, swallowing, dysphagia, deglutition disorders, Alzheimer’s disease, dementia, autonomic nervous system, saliva, salivary flow, oral health, oral cavity stimulation, aging, older adults, tooth brushing.

Co-Authorship Statement

A version of the study presented in Chapter 2, entitled "Swallowing Dysfunction and Autonomic Nervous System Dysfunction in Alzheimer's Disease: A Scoping Review of the Evidence" was published in the Journal of the American Geriatrics Society in December 2013 and was co-authored by Ms. Norine Foley, Dr. John Rosenbek, Dr. Kevin Shoemaker, and Dr. Ruth Martin.

Rebecca Affoo made substantial contributions in the areas of data acquisition, analysis and interpretation of data, drafting and revising the article, and final approval of the version to be published. Norine Foley made substantial contributions in the areas of methodological review and consultation, revising the article, and final approval of the version to be published. Dr. John Rosenbek made substantial contribution in the areas of expert review and consultation of the content addressing dysphagia, revising the article, and final approval of the version to be published. Dr. Kevin Shoemaker made substantial contribution in the areas of expert review and consultation of the content addressing autonomic nervous system, revising the article, and final approval of the version to be published. Dr. Ruth Martin made substantial contributions in the areas of analysis and interpretation of data, drafting and revising the article, and final approval of the version to be published.

A version of the study presented in Chapter 3, entitled "A Meta-Analysis of Salivary Flow Rates in Healthy Young and Older Adults" was accepted for publication in the Journal of the American Geriatrics Society in Feburary 2015 and was co-authored by Ms. Norine Foley, Ms. Rushlee Garrick, Dr. Walter Siqueira, and Dr. Ruth Martin.

Rebecca Affoo made substantial contributions in the areas of study conceptualization and design, data acquisition, analysis and interpretation of data, drafting and revising the article, and final approval of the version to be published. Norine Foley made substantial contributions in the areas of methodological review and consultation, revising the article, and final approval of the version to be published. Rushlee Garrick made substantial contribution in the areas of data acquisition and data analysis. Dr. Walter Siqueira made substantial contribution in the areas of expert review and consultation of the content, revising the article, and final approval of the version to be published. Dr. Ruth Martin made substantial

contributions in the areas of study conceptualization and design, analysis and interpretation of data, drafting and revising the article, and final approval of the version to be published.

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Chapter 1

1 Introduction

1.1 Eating

The ability to eat in order to meet one's metabolic requirements is a basic human need (Maslow, 1954), an integral part of homeostatic regulation (Langhans & Geary, 2010), and fundamental to survival. Eating and maintaining optimal nutrition are essential to health (Waxman & World Health Assembly, 2004) and quality of life (Vailas, Nitzke, Becker, & Gast, 1998). Being unable to eat results in dietary imbalances, which are known to contribute to disease (Waxman & World Health Assembly, 2004), as well as malnutrition, which can result in physical, mental, and social disability (La Rue et al., 1997; Muhlethaler, Stuck, Minder, & Frey, 1995). The inability to eat often results in an individual receiving nutrition via another route, such as parenterally (intravenous nutrition) or enterally (tube feeding). Even when other routes are used to provide nutrition, however, the inability to eat significantly detracts from an individual's quality of life (Winkler, 2005).

Eating disability, or the inability to eat, may occur as a symptom of many neurologic (Bakke, Moller, Thomsen, Dalager, & Werdelin, 2007; Benfer et al., 2014), anatomic (Patterson, McColl, Wilson, Carding, & Rapley, 2015), or psychological conditions and diseases (Baijens, Koetsenruijter, & Pilz, 2013). Eating impairment is a common symptom of neurodegenerative conditions such as dementia (Affoo, Foley, Rosenbek, Shoemaker, & Martin, 2013) and may be characterized by distraction during meals, refusal to eat, agitation/aggression at mealtimes, using food as nonfood play objects, expectorating food/refusing to swallow, inability to masticate, choking, or aspiration (Durnbaugh, Haley, & Roberts, 1996; Morris, Hope, & Fairburn, 1989; Priefer & Robbins, 1997).

There are several physiological components that are fundamental to eating. Eating involves transportation of food and fluid to the mouth, salivary secretion in order to lubricate the mouth and initiate chemical digestion of starches, preparation of the material

in the oral cavity such as mastication of solid food material, and swallowing to transport food or fluid from the mouth to the stomach (Miller, 2013).

1.2 Swallowing

Swallowing is a fundamental component of eating and is the process by which saliva, food, and fluid is safely transported from the mouth to the stomach. Swallowing involves the integration of volitional and sensorimotor events. The process begins with the preparation and softening of food or fluid into a bolus through mastication and manipulation in the oral cavity. During this process, the salivary glands secrete saliva into the oral cavity, which initiates the process of chemical digestion. Once formed, the bolus is propelled through the oral cavity towards the pharynx and the ascending sensory information associated with preparing and transporting the bolus trigger the pharyngeal phase of swallowing. A complex and coordinated series of muscular contractions results in airway closure and movement of the bolus through the pharynx and into the esophagus, where it is eventually transported to the stomach (Matsuo, 2013).

1.3 Dysphagia

The term dysphagia refers to deficits in transporting saliva, food, or fluid from the mouth to the stomach (Logemann, 1998). Dysphagia is a symptom of many congenital abnormalities, acquired neurologic or physical dysfunctions, progressive degeneration, and psychiatric disorders (Murry, 1999) and often contributes to impaired eating in these populations. A host of negative physiological consequences are associated with dysphagia, such as dehydration (Whelan, 2001), and malnutrition (Namasivayam & Steele, 2015). Dysphagia may lead to aspiration, which is the misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract. Aspiration is associated with aspiration pneumonia, which occurs when bacteria colonize the misdirected contents and infect the lung (Marik, 2001), and results in suboptimal patient outcomes and increased mortality (Foley, Affoo, & Martin, 2014). Dysphagia and eating impairment often lead to an increased sense of isolation and loss of self-esteem, avoidance of social eating situations, and anxiety or panic during mealtimes (Ekberg,

Hamdy, Woisard, Wuttge-Hannig, & Ortega, 2002), all of which negatively impact a person's social and psychological well being, and quality of life.

Estimates of the prevalence of dysphagia vary by setting, population, disease state, country, and manner in which dysphagia is assessed. The prevalence of self-reported dysphagia in primary care patients has been found to be 22% (Wilkins, Gillies, Thomas, & Wagner, 2007). Dysphagia prevalence has been reported anywhere from 0.35% to 55% in the acute care in-patient setting (Altman, Yu, & Schaefer, 2010; Cabre et al., 2010) and 68% in long-term care (Steele, Greenwood, Ens, Robertson, & Seidman-Carlson, 1997). Up to 78% of individuals experience dysphagia after a stroke (Martino et al., 2005), between 35% and 82% of persons with Parkinson's disease have dysphagia (Kalf, de Swart, Bloem, & Munneke, 2012), and the prevalence of dysphagia in individuals with Alzheimer's disease is anywhere from 45% to 93% (Affoo et al., 2013).

1.4 Oral Health

The oral health of an individual is defined as "a state of being free of mouth and facial pain, oral and throat cancer, oral infection and sores, birth defects such as cleft lip and palate, periodontal disease, tooth decay and tooth loss, and other disease and disorders that limit an individual's capacity in biting, chewing, smiling, speaking, and psychological wellbeing" (WHO, 1992). The relationship between oral health and overall health is complex, however, links between poor oral health and oral preparatory and oral stage dysphagia (Liedberg & Owall, 1991), malnutrition (Daly, Elsner, Allen, & Burke, 2003; Poisson, Laffond, Campos, Dupuis, & Bourdel-Marchasson, 2014), aspiration pneumonia (Langmore et al., 1998), and increased mortality from pneumonia (Awano et al., 2008) have been documented.

1.5 Saliva

One essential component necessary for adequate oral health is salivary flow. Saliva is important for maintaining oral and general health (Mandel, 1989) and has many and varied functions including protection against mechanical, thermal and chemical irritation, reducing demineralization and facilitating remineralization of the teeth, facilitating

antimicrobial actions and clearance of bacteria, initiating chemical digestion, and facilitating taste (Whelton, 2004).

Saliva production is often limited by disease or pharmaceutical use (Sreebny, 2000). Reduced saliva production results in rapid deterioration of oral health and increased bacterial colonization in the oral cavity. Many of the diseases and disorders associated with dysphagia may also be associated with reduced salivary flow. Additionally, individuals with reduced salivary flow may experience dysphagia (Poisson et al., 2014).

In an individual experiencing hyposalivation and associated increased bacterial colonization and oral pathology, the co-occurrence of dysphagia may increase the risk of the individual aspirating bacteria-rich oral contents and developing aspiration pneumonia (Ortega et al., 2014). Aspiration pneumonia is associated with increased risk of mortality in certain populations (Foley et al., 2014). Thus, there appears to be a critical relationship between factors associated with eating and swallowing function, oral health, and saliva production. Perturbations to any, or all, of these factors may result in consequences that negatively affect the health and wellness of an individual (Figure 1).

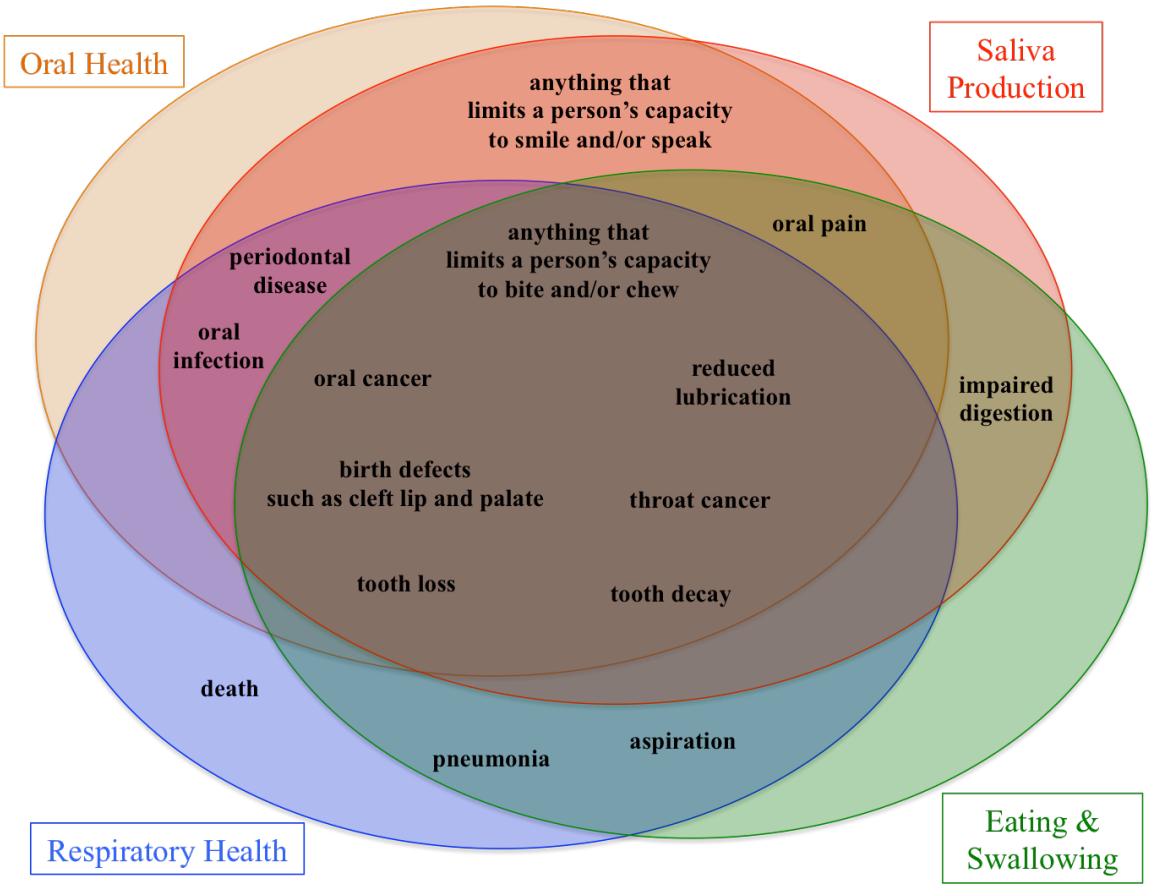

Figure 1. Inter-Related Factors Associated with Impaired Eating and Swallowing, Oral Health, Saliva Production, and Respiratory Health

1.6 Alzheimer's Disease

Alzheimer's disease (AD) and other dementias are a growing epidemic in Canada. Alzheimer's disease currently affects approximately 747,000 Canadians. This number is expected to nearly double to 14 million Canadians by 2031 (Alzheimer Society of Canada, 2012). Dysphagia (Affoo et al., 2013), poor oral health (Foley, Affoo, Siqueira, & Martin, 2015 unpublished), and reduced saliva production (Ship, DeCarli, Friedland, & Baum, 1990; Ship & Puckett, 1994) have been reported in individuals with AD. There is also evidence to suggest that this population is at increased risk of pneumonia-associated mortality (Foley et al., 2014), and it is well documented that pneumonia is the primary cause of mortality in AD (Beard et al., 1996). Therefore, in individuals with AD, it appears that impairments in eating and swallowing, oral health, and saliva production

together increase the risk of morbidity, including aspiration pneumonia, as well as suboptimal health outcomes and mortality (Figure 2).

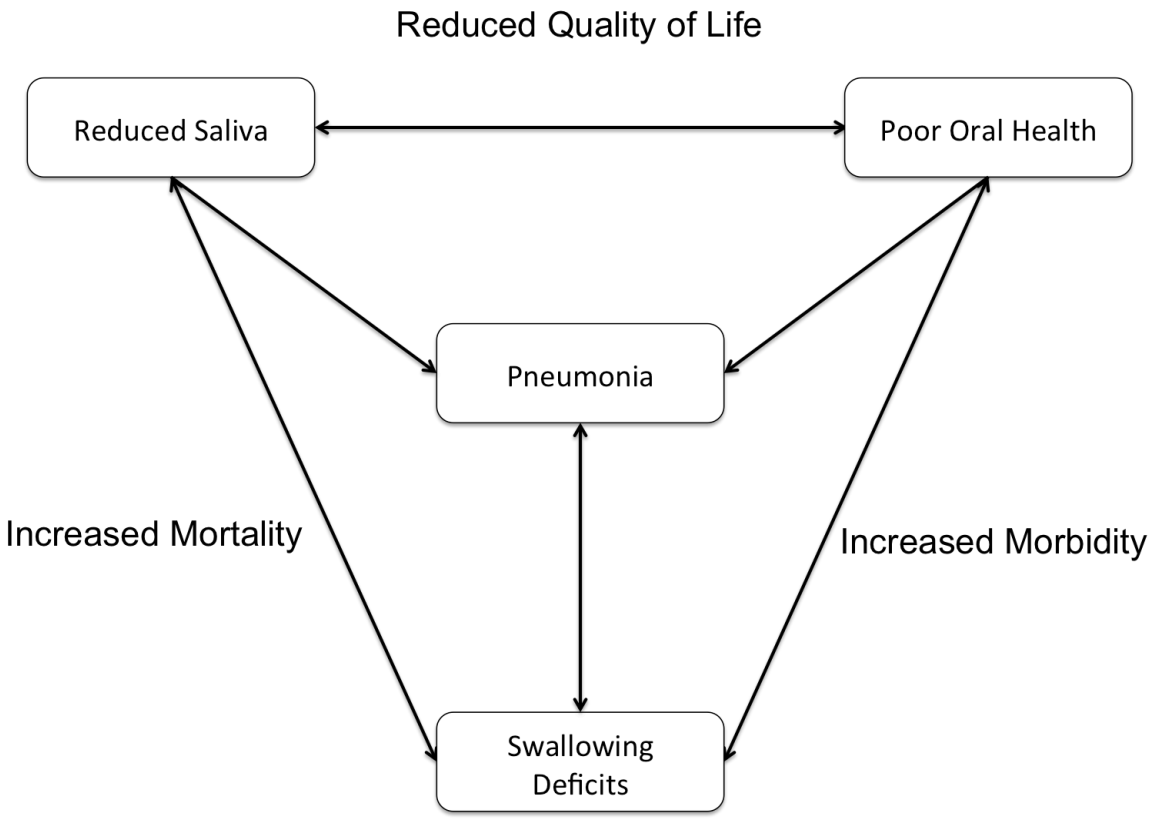

Figure 2: Proposed Model of the Relationship between Reduced Salivary Flow, Poor Oral Health, Dysphagia, and Suboptimal Outcomes

1.7 Eating and Swallowing, Oral Health, and Saliva Production

Eating and swallowing, oral health, and saliva production are crucial factors for maintaining a person's overall health and an optimal quality of life (Sreebny & Vissink, 2010; Vailas et al., 1998; Waxman & World Health Assembly, 2004; WHO, 1992). While published evidence suggests that these factors are inter-related in both health and disease, there is a paucity of evidence that has explored these factors and their potential relationships. Generating new knowledge of these factors and the relationships between them has the potential to positively impact health care provision for a variety of patient populations, including older adults and persons with dementia. Thus, the goal of the

present research was to broaden current understanding of eating and swallowing function and dysfunction, saliva production, and saliva modulation.

Three studies were conducted as part of this dissertation. In the first, eating and swallowing dysfunction and autonomic nervous system dysfunction, including salivary flow dysfunction, were examined in individuals with AD through a scoping review. In addition to gaining a better understanding of the current knowledge on eating and swallowing impairment and autonomic nervous system impairment in individuals with AD, the study identified gaps in the literature. One gap that was identified pertained to the rate of saliva production, or salivary flow rate, in individuals with AD. Saliva, a secretion crucial for maintaining oral homeostasis and for completing the oral preparatory and oral phases of swallowing, may be reduced as part of the disease process. This finding led us to question whether salivary flow rate is reduced as a function of aging.

In the second study in this dissertation, published literature examining salivary flow rate in adults of different ages was reviewed, described, and meta-analyzed in order to determine whether aging is associated with a change in saliva production. We found that, despite conflicting findings previously recorded in the literature, unstimulated and stimulated whole and submandibular/sublingual salivary flow rates were decreased in adults aged 60 years and older compared with younger adults aged 18 to 40 years.

Given that saliva is important for maintaining oral and general health (Mandel, 1989) and salivary flow rates have been found to be decreased in older adults compared with younger adults, it would be beneficial to elucidate whether salivary flow rates in older individuals can be modulated. One approach to modulating salivary flow rates is to use sensory stimulation. Previous studies examining the effects of sensory stimulation in the oral cavity have found that oral stimulation is associated with increased salivary flow rates (Karami Nogourani, Janghorbani, Kowsari Isfahan, & Hosseini Beheshti, 2012; Ligtenberg, Brand, Bots, & Nieuw Amerongen, 2006; Papas et al., 2006). Therefore, in the third study in this dissertation, the potential effects of manual and electric tooth brushing on whole salivary flow rates were examined in adults 60 years of age and older who were free of major systemic disease. We found that tooth brushing stimulates saliva

production for up to 5 minutes. A moderate, positive correlation was observed between age and maximum salivary flow rate increase associated with tooth brushing.

The knowledge generated from the three studies presented in this dissertation has the potential to improve the current understanding of oral physiology and inform the design of future research. It also has important implications for preventative, acute, and rehabilitative care for a number of patient populations, including aging individuals and individuals with dementia.

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Chapter 2

2 Swallowing Dysfunction and Autonomic Nervous System Dysfunction in Alzheimer's Disease: A Scoping Review of the Evidence

This scoping review aims to describe, synthesize, and interpret literature on swallowing impairment (dysphagia) and autonomic nervous system (ANS) dysfunction in Alzheimer's disease (AD), and to identify gaps in the existing literature[*].

2.1 Introduction

Alzheimer's disease (AD) is a neurodegenerative condition marked by cognitive and behavioural decline (Wimo et al., 2013). Currently, AD affects more than 3.4 million North Americans and its incidence is expected to exceed 5.5 million by 2030 (Alzheimer's Association, 2013; *Rising tide: The impact of dementia on Canadian society*, 2010). People with AD experience significant eating problems, particularly as the disease progresses (Njegovan, Hing, Mitchell, & Molnar, 2001). Although these eating problems arise from deficits across a range of dimensions, swallowing impairment (dysphagia) may be a critical factor; however, its impact is unknown. Understanding the contribution of dysphagia to altered eating in AD is especially important since the risk of AD increases with age and dysphagia in the elderly is associated with increased morbidity, including pneumonia (Loeb, McGeer, McArthur, Walter, & Simor, 1999) and malnutrition (Serra-Prat et al., 2012), and mortality (Groher & Crary, 2010).

Swallowing is regulated by both the somatic-voluntary nervous system and the autonomic nervous system (ANS) (Jean, 2001; Miller, 1999). The somatic-voluntary nervous system plays a fundamental role in the voluntary oral preparatory and oral stages of swallowing, during which ingested material is formed into a bolus and transported posteriorly across the tongue surface (Miller, 1999). The somatic-voluntary and ANS

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[*] A version of this chapter has been published (Affoo et al., 2013)

mediate the semi-automatic pharyngeal stage, during which the bolus is transported through the pharynx as the airway closes to protect against entry of material into the lower respiratory tract (Miller, 1999). The ANS then regulates contraction of the smooth muscle esophagus during the esophageal stage of swallowing (Miller, 1999). However, both animal and human studies have documented ANS involvement in *all* stages of swallowing, including salivary secretion required for the oral breakdown and lubrication of ingested material (Stuchell & Mandel, 1988), sensory processing of laryngeal and esophageal inputs necessary for swallowing (Aziz et al., 2000; Kalia & Mesulam, 1980), and esophageal peristalsis (Camilleri, 2004).

The AD literature has focused primarily on the voluntary nervous system, as documented by several systematic reviews (Marlatt & Lucassen, 2010; Nordberg, Rinne, Kadir, & Langstrom, 2010). Nevertheless, ANS dysfunction in AD has been reported, although systematic reviews are lacking (Lampe et al., 1989; Otsuka et al., 1990).

Given (i) the probability that swallowing impairment contributes to eating problems in AD, (ii) that ANS mechanisms play a fundamental role in swallowing regulation, and (iii) ANS dysfunction occurs in AD, a broad literature review examining dysphagia and ANS dysfunction in AD could provide important insights into these deficits and their potential associations.

The objectives of this study were to (i) describe, synthesize, and interpret literature on dysphagia/ANS dysfunction in AD, and (ii) identify gaps in the existing literature, utilizing a scoping review, a technique aimed at mapping relevant literature in a broad field of interest where several study designs may be represented (Arksey & O'Malley, 2005; Landa, 2011).

2.2 Methodology

Relevant studies were identified through a literature search encompassing the years 1978 to July 2012. Three searches of the PubMed, EBSCOhost, PsychINFO, Cochrane, EMBASE, and Scopus databases were conducted to identify studies of (i) dysphagia in AD, (search terms: dementia, Alzheimer’s disease, swallowing, deglutition disorders,

aspiration pneumonia, choking, and dysphagia) (ii) ANS dysfunction in AD, (search terms: dementia, Alzheimer's disease, autonomic nervous system, parasympathetic nervous system, sympathetic nervous system), and (iii) dysphagia *and* ANS dysfunction in AD, combining the search terms above. Reference lists of the retrieved articles were manually searched.

The inclusion criteria were: (i) clinical studies, (ii) physiological reports (including neuroanatomical studies) wherein any portion of the sample met the study author's criteria for having AD, and ANS dysfunction or dysphagia was examined; (iii) reviews, (iv) commentaries, or (v) case studies of dysphagia or ANS dysfunction in AD, and (vi) English language studies. Animal studies, human trials examining pharmacological treatment effects on dysphagia/ANS dysfunction, and studies on cerebral hemodynamics were excluded. Two reviewers (RA and RM) evaluated the surviving literature.

Clinical and physiological reports were evaluated using the Oxford Centre for Evidence-Based Medicine Levels of Evidence[†] ("CEBM Levels of Evidence," 2009) (OCEBM) criteria. Where possible, studies were classified as: treatment/prevention, prognosis, diagnosis, prevalence, or decision making/economic evaluation. Following categorization, the literature was synthesized and interpreted by the same two reviewers in order to form conclusions and identify knowledge gaps. Results were categorized and analyzed according to topics identified post hoc.

One expert in each of the fields of dysphagia, ANS physiology, and epidemiology was then consulted to verify the completeness of the literature retained for final review, to identify references that were not captured in the searches, and to comment on the appropriateness of the literature synthesis, interpretation, and gap identification.

2.3 Results

The initial search returned 7,422 results of which 95 met the study criteria and were reviewed (Figure 3). Summaries of all the included articles can be found in Appendix A –

[†] CEBM Levels of Evidence 2009 (online). Available at http://www.cebm.net/index.aspx?o=1025

D. Thirty-one studies examined dysphagia in AD, 64 examined ANS dysfunction in AD. No studies were identified that examined both dysphagia and ANS dysfunction in AD.

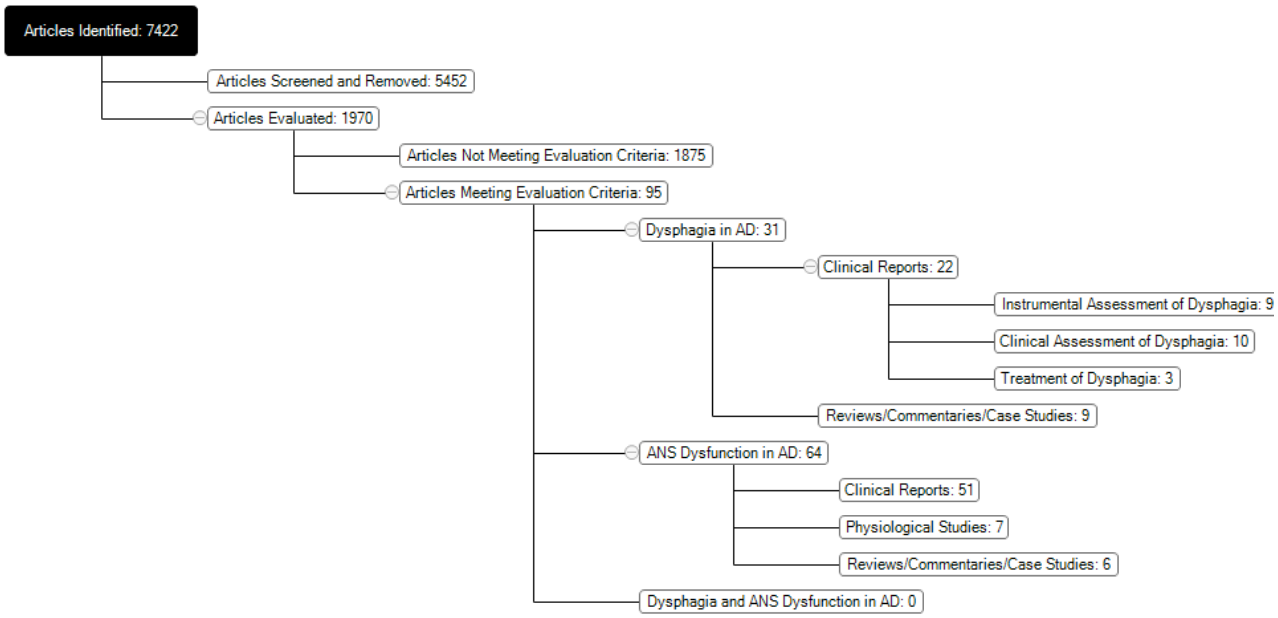

Figure 3. Flow Chart of Scoping Review

2.3.1 Diagnosis of Alzheimer's Disease

Eighty clinical reports addressed either dysphagia or ANS dysfunction in AD. In 56 of these, the diagnosis of AD was based on (i) the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ARDRA) diagnostic criteria (Algotsson, Nordberg, Almkvist, & Winblad, 1995; Algotsson, Viitanen, Winblad, & Solders, 1995; L. Allan, McKeith, Ballard, & Kenny, 2006; L. M. Allan et al., 2007; L. M. Allan, Ballard, Rowan, & Kenny, 2009; L. M. Allan et al., 2005; Andersson, Hansson, Minthon, Ballard, & Londos, 2008; Benedetti et al., 2004; Durnbaugh et al., 1996; Elmstahl et al., 1992; Elmstahl & Winge, 1993; Fotiou et al., 2009; Franceschi, Ferini-Strambi, Minicucci, Sferrazza-Papa, & Smirne, 1986; Horner, Alberts, Dawson, & Cook, 1994; Idiaquez, Alvarez, Villagra, & San Martin, 1994; Idiaquez, Rios, & Sandoval, 1997; Idiaquez, Sandoval, & Seguel, 2002; Ikeda, Brown, Holland, Fukuhara, & Hodges, 2002; Pascualy et al., 2000; Rainero, Vighetti, Bergamasco, Pinessi, & Benedetti, 2000; Ransmayr et al.,

2008; Shinagawa et al., 2009; Ship et al., 1990; Taki, Yoshita, Yamada, & Tonami, 2004; Vitiello et al., 1993; Wada et al., 2001; Watanabe et al., 2001; Zakrzewska-Pniewska, Gawel, Szmidt-Salkowska, Kepczynska, & Nojszewska, 2012), (ii) the Diagnostic and Statistical Manual of Mental Disorders (DSM) III or IV criteria (Borson, Barnes, Veith, Halter, & Raskind, 1989; Davidson, Borrie, & Crilly, 1991; Del-Ser, Munoz, & Hachinski, 1996; Guo, Viitanen, Fratiglioni, & Winbland, 1998; Lampe et al., 1989; Morris et al., 1989; Raskind, Peskind, Halter, & Jimerson, 1984), (iii) both the NINCDS-ARDRA and DSM-III/IV criteria (Aharon-Peretz, Harel, Revach, & Ben-Haim, 1992; Ahlskog et al., 1996; de Vilhena Toledo & Junqueira, 2008; Jhee, Sramek, Wardle, & Cutler, 1995; Mehrabian et al., 2010; Passant, Warkentin, & Gustafson, 1997; Peskind et al., 1998; Peskind et al., 1995; Toledo & Junqueira, 2010; Volicer et al., 1989; S. J. Wang et al., 1994; Zulli et al., 2005), or (iv) neuropathology (Andin, Passant, Gustafson, & Englund, 2007; Bonthius, Solodkin, & Van Hoesen, 2005; Burke, Coronado, Schmitt, Gillespie, & Chung, 1994; Chu, Tranel, Damasio, & Van Hoesen, 1997; Orimo et al., 2005; Rub et al., 2001; Shankle et al., 1993; Wakabayashi et al., 1999). Five (5) of the studies used the NINCDS-ARDRA criteria as well as a score of < 5 on Hachinski's Index to rule out vascular pathology (Hornqvist, Henriksson, Back, Bucht, & Winblad, 1987; Humbert et al., 2010; Humbert, McLaren, Malandraki, Johnson, & Robbins, 2011; Otsuka et al., 1990; Priefer & Robbins, 1997). The remaining nineteen (19) studies reported physician-specific diagnostic criteria (Bautmans, Demarteau, Cruts, Lemper, & Mets, 2008; Chouinard, Lavigne, & Villeneuve, 1998; Edahiro et al., 2012; Eisdorfer & Cohen, 1978; Feinberg, Ekberg, Segall, & Tully, 1992; Logemann et al., 2008; Robbins et al., 2008; Suh, Kim, & Na, 2009) or did not report diagnostic criteria (Bordier, Colsy, Robert, & Bourenane, 2007; Burge, 1994; Choi, Kim, & Kim, 2009; Correia, 2010; Garon, Sierzant, & Ormiston, 2009; Grunberger et al., 1999; Khurana & Garcia, 1981; Mizushima, 2005; Suski & Nielsen, 1989; Szili-Torok et al., 2001).

2.3.2 Dysphagia in Alzheimer's Disease

Thirty-one studies addressed dysphagia in AD, including identification of dysphagia (n=11), descriptions of swallowing difficulties (n=22), and treatment (n=3) (Figure 3). Of 22 clinical reports, nine employed an instrumental assessment of swallowing in

individuals with AD. Seven studies used videofluoroscopic swallow studies (VFSS) (Feinberg et al., 1992; Garon et al., 2009; Horner et al., 1994; Humbert et al., 2010; Humbert et al., 2011; Priefer & Robbins, 1997; Suh et al., 2009) and two used electromyography (EMG) following water injection into the pharynx (Mizushima, 2005; Wada et al., 2001). In contrast, 10 clinical reports employed a clinical evaluation of dysphagia or feeding difficulties (Burge, 1994; Chouinard et al., 1998; Correia, 2010; Durnbaugh et al., 1996; Edahiro et al., 2012; Ikeda et al., 2002; Morris et al., 1989; Shinagawa et al., 2009; Suski & Nielsen, 1989; Volicer et al., 1989) including observation at mealtimes, caregiver interview, and questionnaire. Three studies examined the treatment of dysphagia in AD (Bautmans et al., 2008; Logemann et al., 2008; Robbins et al., 2008).

2.3.2.1 Dysphagia in Alzheimer's Disease: Oxford Centre for Evidence-Based Medicine Levels of Evidence (OCEBM)

Classification using the OCEBM system was possible for eight studies of dysphagia in AD (Tables 1–3).

2.3.2.2 Studies Employing Instrumental Assessment of Swallowing in Alzheimer's Disease

The nine studies (Feinberg et al., 1992; Garon et al., 2009; Horner et al., 1994; Humbert et al., 2010; Humbert et al., 2011; Mizushima, 2005; Priefer & Robbins, 1997; Suh et al., 2009; Wada et al., 2001) that employed instrumental assessment of swallowing in AD provide preliminary evidence to support the following conclusions:

1. The prevalence of dysphagia in moderate-to-severe AD is 84% (Horner et al., 1994) to 93% (Feinberg et al., 1992). Only one study failed to identify significant swallowing dysfunction in AD (Mizushima, 2005); it examined swallow-related and cough-related EMG responses to graded volumes of water injected into the pharynx through a nasal catheter.

2. Dysphagia may occur early in AD. Three studies using VFSS documented swallowing alterations in small groups of patients with mild AD, compared with healthy age-matched controls (Humbert et al., 2010; Humbert et al., 2011; Priefer & Robbins, 1997).

3. Dysphagia occurring early in AD may be associated with functional changes in the cortical swallowing network (i.e., pre- and post-central gyrus, and frontal and Rolandic operculum) as measured with functional magnetic resonance imaging (fMRI) (Humbert et al., 2010; Humbert et al., 2011; Priefer & Robbins, 1997).

4. The oral and pharyngeal stages of swallowing may be affected in AD (Feinberg et al., 1992; Garon et al., 2009; Horner et al., 1994; Humbert et al., 2010; Humbert et al., 2011; Priefer & Robbins, 1997; Suh et al., 2009; Wada et al., 2001). Oral deficits include prolonged bolus preparation and oral transit times. Pharyngeal deficits include delayed pharyngeal swallow initiation, reduced hyo-laryngeal excursion, laryngeal penetration, tracheal aspiration, and pharyngeal residue post swallow.

5. Dysphagia severity and AD severity may be associated. One study (Wada et al., 2001) reported that subjects with severe AD demonstrated greater pharyngeal swallow delay than patients with mild and moderate AD. Another study (Horner et al., 1994) identified a non-significant trend wherein subjects with lower Mini-Mental State Examination (MMSE) scores had more severe dysphagia.

Table 1. Clinical Reports Employing Instrumental Assessment of Swallowing in Alzheimer's Disease (AD)

Conclusion	Supporting Studies	Study Description	Level of Evidence
Prevalence of dysphagia in AD	Horner et al. 1994	Prospective Case Series	4
	Feinberg et al. 1992	Retrospective Cohort	2b
	Mizushima et al. 2005	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	NA

Dysphagia occurs early in AD	Humbert et al. 2010	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	NA
	Priefer & Robbins 1997		
	Humbert et al. 2011		
Dysphagia in early AD may be associated with functional change of the cortical swallowing network	Humbert et al. 2010	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	NA
	Humbert et al. 2011		
Dysphagia occurs in both the oral and pharyngeal phases of swallowing	Garon et al. 2009	Retrospective Cohort	2b
	Horner et al. 1994	Prospective Case Series	4
	Suh et al. 2009	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	NA
	Wada et al. 2001		
	Priefer & Robbins 1997		
	Humbert et al. 2010		
Disease severity	Wada et al. 2001	Described/characterized dysphagia in AD	NA

may be associated with dysphagia severity		through comparison of two or more groups of individuals	
	Horner et al. 1994	Prospective Case Series	4

NA = not applicable. See Appendix A for more details.

2.3.2.3 Studies Employing Subjective Assessment of Swallowing in Alzheimer's Disease

Eleven studies (Burge, 1994; Chouinard et al., 1998; Correia, 2010; Durnbaugh et al., 1996; Edahiro et al., 2012; Ikeda et al., 2002; Morris et al., 1989; Priefer & Robbins, 1997; Shinagawa et al., 2009; Suski & Nielsen, 1989; Volicer et al., 1989) assessed eating or swallowing in AD through clinical assessments, including one clinical report that also used an instrumental swallowing evaluation. These studies provide preliminary support for the following conclusions:

1. Prevalence estimates of dysphagia in AD based on clinical assessments are lower than estimates based on instrumental swallowing assessments. One study reported that 32% of residents with AD living in a long-term care facility were observed to choke on food and drink (Volicer et al., 1989). Another group (Chouinard et al., 1998) reviewed the health records of 47 institutionalized patients with dementia (45% AD) who had died over a two-year period and reported that 45% of the entire dementia sample had dysphagia, which was correlated with death from pneumonia.

2. Dysphagia occurs in all stages of AD and may be a marker of disease severity. One study (Correia, 2010) reported delayed swallowing and difficulty with ingestion of specific consistencies in moderate to severe AD. Another study (Edahiro et al., 2012) found signs of dysphagia in all stages of AD, although the frequency of signs increased in the advanced stages.

3. Behavioural eating difficulties occur in all stages of AD. Individuals with mild AD required and received significantly more cueing during a meal assessment compared to

controls (Priefer & Robbins, 1997) and demonstrated problematic mealtime behaviors such as attempting to eat pieces of food too big for the oral cavity (Durnbaugh et al., 1996; Morris et al., 1989). Difficulty initiating a meal, as well as severity of AD, significantly predicted eating dependence (Edahiro et al., 2012) and individuals with severe AD in long-term care facilities tended to receive mechanically altered diets and feeding assistance (Burge, 1994; Suski & Nielsen, 1989).

4. Eating and swallowing difficulties are less severe in AD than in other types of dementia. Two studies compared caregiver perceptions of eating and swallowing difficulties in AD, frontotemporal lobe dementia (Ikeda et al., 2002) and Lewy body dementia (Shinagawa et al., 2009) at similar stages. Both reported that AD caregivers perceived fewer abnormal eating and swallowing behaviours; however, AD caregivers also reported that eating and swallowing problems appear to develop earlier in AD progression.

Table 2. Clinical Reports Employing Clinical Assessment of Swallowing in Alzheimer's Disease (AD)

Conclusion	Supporting Studies	Study Description	Level of Evidence
Prevalence of dysphagia in AD	Volicer et al. 1989	Described/characterized an aspect of eating or swallowing dysfunction through the examination of a single group of patients with AD	NA
	Chouinard et al. 1998	Retrospective Cohort	2b
Dysphagia may occur in all stages of AD	Correia et al. 2010	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	NA
	Edahiro et al. 2012	Prospective Cohort Study	2b

Behavioural eating difficulties may occur in all stages of AD	Priefer & Robbins, 1997	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	NA
	Edahiro et al. 2012	Prospective Cohort Study	2b
	Durnbaugh et al. 1996	Described/characterized an aspect of eating or swallowing dysfunction through the examination of a single group of patients with AD	NA
	Morris et al. 1989		
	Burge 1994		
	Suski & Nielsen 1989		
Dysphagia and eating difficulties in AD may be less severe than in other types of dementia	Ikeda et al. 2002	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	NA
	Shinagawa et al. 2009		

NA = not applicable. See Appendix B for more details.

2.3.2.4 Treatment of Dysphagia in Alzheimer's Disease

Three randomized trials assessed the efficacy of intervention strategies on outcomes related to dysphagia in individuals with dementia (Bautmans et al., 2008; Logemann et al., 2008; Robbins et al., 2008). These studies provide support for the following conclusions:

1. Providing honey-thickened liquids to individuals with AD may eliminate thin liquid

aspiration; however, this intervention may not reduce long-term morbidity or mortality. One study (Logemann et al., 2008) compared the effects of chin-down posture during swallowing, honey-thickened liquids, and nectar-thickened liquids, on thin liquid aspiration during VFSS in patients with dementia (15% AD), Parkinson's disease (PD), or PD with dementia. Aspiration was most successfully eliminated through use of the honey-thickened liquids for each diagnostic category. In a second study, the same authors also reported a non-significant trend towards reduced incidence of pneumonia favouring patients drinking nectar-thickened liquids compared to those drinking honey-thickened liquids, as well as a longer median length of hospital stay for participants randomly assigned to the honey-thickened liquid intervention who developed pneumonia (Robbins et al., 2008).

2. A physiotherapist-administered cervical spine mobilization protocol may improve "dysphagia limit" (defined as the maximum bolus of water that can be swallowed in a single movement) in individuals with severe AD and altered neck posture, based on a single crossover design randomized controlled trial (Bautmans et al., 2008). Dysphagia limit improved significantly following one treatment session and remained improved one week following the intervention.

Table 3. Clinical Reports Examining the Treatment of Dysphagia in Alzheimer's Disease (AD)

Conclusion	Supporting Studies	Study Description	Level of Evidence
Thickening liquids to a honey-thickened consistency may eliminate thin liquid aspiration in individuals with	Logemann et al. 2008	Randomized Clinical Trial	2b
	Robbins et al. 2008	Randomized Clinical Trial	2b

AD, however this intervention may not affect long-term morbidity and mortality			
A physiotherapist administered cervical spine mobilization protocol may improve "dysphagia limit" in individuals with severe AD and altered neck posture	Bautmans et al. 2008	Randomized Controlled Crossover Trial	2b

See Appendix C for more details.

2.3.2.5 Reviews

One narrative review (Chouinard, 2000) and one systematic review (Alagiakrishnan, Bhanji, & Kurian, 2013) were identified. While published 12 years apart, these reviews came to similar conclusions: dysphagia may occur early in AD, however, studies investigating prevalence, assessment, management and treatment of dysphagia in individuals with dementia are lacking; the existing literature is heterogeneous in design, methodology, type of assessment, and outcomes (Alagiakrishnan et al., 2013; Chouinard, 2000).

2.3.2.6 Commentaries

Four commentaries (Brush, Slominski, & Boczko, 2006; Clibbens, 1996; Kalia, 2003; Sumer, Sumer, & Sumer, 2005) covered a wide array of topics associated with dysphagia

and support the following conclusions:

1. The ethical issues surrounding eating and feeding in the final stages of AD are complex. One author (Clibbens, 1996) suggested that evidence-based decision-making is vital when providing clinical care to individuals with AD.

2. Dysphagia, aspiration pneumonia, and oral care are important issues when caring for individuals with AD. One author (Kalia, 2003) reported that dysphagia and aspiration pneumonia are severe and growing issues in the AD population. One group (Brush et al., 2006) cited mealtime strategies and caregiver education as useful management strategies for AD. Another group (Sumer et al., 2005) noted that diminishing cognitive function results in neglect of oral hygiene leading to increased prevalence of dental problems; reduced submandibular salivary flow, increased the risk of gingivitis, tooth decay, oral infections, as well as dysfunctional speech, chewing, and swallowing.

2.3.2.7 Case Studies

Three (3) case studies (Asplund, Norberg, & Adolfsson, 1991; Barratt, 2000; Yamaguchi, Maki, & Maki, 2010) described treatments for eating and swallowing impairments in five individuals with AD:

1. One group (Asplund et al., 1991) examined sucking behaviour in two patients with severe AD. Patients were observed to suck at different rates and pressures, and one demonstrated improved sucking over time. The authors concluded that the sucking method could be of value for end-of-life nutritional care in severe AD patients.

2. One case report (Barratt, 2000) described a 70-year-old woman with AD who exhibited eating deficits and severe dysphagia yet minimal communication and mobility deficits. She was treated with a percutaneous endoscopic gastrostomy for non-oral feeding, the most ethical choice given the patient's level of function.

3. Another group (Yamaguchi et al., 2010) reported 3 cases of concurrent dementia and dysphagia, two of which had late-stage AD and severe dysphagia. Treatment with dopamine agonists and angiotensin-converting enzyme inhibitors (ACEIs) resulted in

positive outcomes in swallowing and feeding, with associated prolonged oral intake and weight maintenance.

2.3.3 Autonomic Nervous System Dysfunction in Alzheimer's Disease

The review identified 64 studies that investigated autonomic function in AD (Figure 3).

2.3.3.1 Autonomic Nervous System Dysfunction in Alzheimer's Disease: Oxford Centre for Evidence-Based Medicine Levels of Evidence (OCEBM)

Two studies met the OCEBM criteria for classification (Table 4).

2.3.3.2 Autonomic Nervous System Dysfunction in Alzheimer's Disease

Of the 51 clinical reports and seven physiological studies, 49 studies identified at least one variable reflecting ANS dysfunction in AD (Aharon-Peretz et al., 1992; Ahlskog et al., 1996; Algotsson, Nordberg, et al., 1995; Algotsson, Viitanen, et al., 1995; L. Allan et al., 2006; L. M. Allan et al., 2007; L. M. Allan et al., 2009; Andersson et al., 2008; Andin et al., 2007; Benedetti et al., 2004; Bonthius et al., 2005; Bordier et al., 2007; Borson et al., 1989; Burke et al., 1994; Chu et al., 1997; Davidson et al., 1991; de Vilhena Toledo & Junqueira, 2008; Del-Ser et al., 1996; Eisdorfer & Cohen, 1978; Elmstahl et al., 1992; Elmstahl & Winge, 1993; Fotiou et al., 2009; Franceschi et al., 1986; Grunberger et al., 1999; Guo et al., 1998; Hornqvist et al., 1987; Idiaquez et al., 1994; Idiaquez et al., 1997; Idiaquez et al., 2002; Jhee et al., 1995; Kalman et al., 2002; Lampe et al., 1989; Mehrabian et al., 2010; Otsuka et al., 1990; Pascualy et al., 2000; Passant et al., 1997; Peskind et al., 1998; Peskind et al., 1995; Rainero et al., 2000; Ransmayr et al., 2008; Raskind et al., 1984; Rub et al., 2001; Ship et al., 1990; Szili-Torok et al., 2001; Vitiello et al., 1993; S. J. Wang et al., 1994; Zakrzewska-Pniewska et al., 2012; Zulli et al., 2005). These included measurements of blood pressure, heart rate, baroreflex sensitivity, vasomotor function, plasma norepinephrine levels, pupillary dilation, skin responses, urinary incontinence, constipation, blood pressure and heart rate responses to pain stimuli, and salivary flow. The remaining nine controlled studies failed to find significant

differences in autonomic function in individuals with AD compared with controls or patients with other types of dementia (L. M. Allan et al., 2005; Choi et al., 2009; Khurana & Garcia, 1981; Orimo et al., 2005; Raskind, Peskind, Holmes, & Goldstein, 1999; Shankle et al., 1993; Taki et al., 2004; Wakabayashi et al., 1999; Watanabe et al., 2001).

Twenty-eight studies were identified that provide evidence for the occurrence of cardiovascular ANS dysfunction in AD, supporting the following conclusions:

1. Individuals with AD demonstrate blood pressure differences compared with controls (Bordier et al., 2007; Burke et al., 1994; Elmstahl et al., 1992; Guo et al., 1998; Idiaquez et al., 1997; Kalman et al., 2002; Lampe et al., 1989; Otsuka et al., 1990). These include blunted diastolic pressor responses to thyrotropin stimulating hormone (Lampe et al., 1989), higher baseline systolic blood pressure in bedridden patients with advanced AD (Otsuka et al., 1990) and, in contrast, lower baseline systolic and diastolic blood pressure was documented in mild to moderate AD (Elmstahl et al., 1992). Yearly systolic, diastolic, and mean arterial blood pressures decreased in 3 AD subjects every year following diagnosis (Burke et al., 1994) and lower systolic and diastolic blood pressures were associated with greater AD severity and shorter survival (Guo et al., 1998).

2. AD patients exhibit orthostatic hypotension, that is, significant decreases in blood pressure when transitioning from supine to standing position (L. M. Allan et al., 2007; L. M. Allan et al., 2009; Andersson et al., 2008; Andin et al., 2007; Jhee et al., 1995; Mehrabian et al., 2010; Passant et al., 1997; Vitiello et al., 1993; S. J. Wang et al., 1994; Zakrzewska-Pniewska et al., 2012), which may contribute to the risk of falls (L. M. Allan et al., 2009). Compared with controls, AD patients showed greater increases in heart rate, and greater decreases in mean systolic blood pressure in response to a tilting test (Elmstahl et al., 1992) and reduced change in diastolic blood pressure during an isometric handgrip exercise (Kalman et al., 2002).

3. Resting heart rate variability is significantly reduced in AD (Aharon-Peretz et al., 1992; Algotsson, Viitanen, et al., 1995; de Vilhena Toledo & Junqueira, 2008; Franceschi et al., 1986; Idiaquez et al., 2002; Szili-Torok et al., 2001; Toledo & Junqueira, 2010; Zulli et al., 2005). Although the interpretation of heart rate variability as a marker of sympathetic

nervous system (SNS) function is debated (Eckberg, 1997), some studies reported increased SNS activation (Aharon-Peretz et al., 1992; de Vilhena Toledo & Junqueira, 2008; Toledo & Junqueira, 2010) and decreased parasympathetic nervous system (PNS) activation (Aharon-Peretz et al., 1992; de Vilhena Toledo & Junqueira, 2008), whereas others reported decreased SNS and PNS activation in relation to heart rate variability (Algotsson, Viitanen, et al., 1995; Franceschi et al., 1986).

4. Blood pressure and heart rate responses to pre-stimulus pain and stimuli delivered at just above the pain threshold are blunted in AD (Rainero et al., 2000). Autonomic responses to pain appear to be related to the severity of cognitive impairment, as measured by the MMSE (Benedetti et al., 2004).

Twenty studies were identified that examined other aspects of ANS function in AD, supporting the following conclusions:

1. ANS dysfunction in AD may be subtle compared with other types of dementia such as Parkinson's disease dementia or Lewy body dementia. Clinical complaints of ANS dysfunction are less common among AD patients (L. Allan et al., 2006; L. M. Allan et al., 2007).

2. Baseline plasma norepinephrine levels are significantly higher in severe AD patients compared with moderate AD patients and controls (Pascualy et al., 2000; Raskind et al., 1984). Basal plasma norephinephrine levels and plasma norepinephrine levels in response to an alpha-2 adrenergic antagonist may be increased in AD, potentially indicating increased SNS activation (Peskind et al., 1998; Peskind et al., 1995), however decreased SNS activation in response to thyrotropin stimulating hormone has also been reported (Lampe et al., 1989). Modulation of plasma norepinephrine levels following stimulation with a cognitive task may be blunted in early AD (Borson et al., 1989).

3. Vasomotor function may be reduced in AD (Algotsson, Nordberg, et al., 1995; Hornqvist et al., 1987; Kalman et al., 2002) in response to vasodilating substances, adrenergic agonists, and maximal contraction. Skin vessel vasodilation in response to iontophoresis of acetylcholine and isoprenaline was significantly reduced in AD (Algotsson, Nordberg,

et al., 1995; Hornqvist et al., 1987). Decreased skin blood flow and increased change in cutaneous vascular resistance was reported in AD subjects compared to age-matched controls following an isometric handgrip exercise (Kalman et al., 2002).

4. Individuals with AD demonstrate anhydrosis (impaired sweating) (Elmstahl & Winge, 1993) following stimulation with a receptor agonist. Estimated mean sweat sodium concentration was significantly higher among women with AD compared with healthy controls and significantly more AD patients (27%) did not demonstrate a sweat response following stimulation (Elmstahl & Winge, 1993).

5. Increased pupillary sensitivity to a parasympathomimetic receptor agonist and a sympathomimetic receptor antagonist are seen in AD (Fotiou et al., 2009; Grunberger et al., 1999; Idiaquez et al., 1994). Pupillary dilatation following application of acetylcholine was greater in AD subjects at all measurement points (Grunberger et al., 1999; Idiaquez et al., 1994), indicating AD-induced changes in post-junctional receptor function. Functional stimulation with a pupil light reflex evaluation which engages the integrated reflex response, revealed a significantly slower reflex among AD patients compared to controls (Fotiou et al., 2009).

6. AD patients may experience constipation (Zakrzewska-Pniewska et al., 2012) and urinary incontinence (Davidson et al., 1991; Del-Ser et al., 1996; Ransmayr et al., 2008), indicating PNS dysfunction.

7. Individuals with AD may experience heightened cardiovascular arousal during learning (Eisdorfer & Cohen, 1978).

8. Resting and stimulated submandibular salivary flow is reduced in AD (Ship et al., 1990). Forty-six percent of a sample of AD patients had flow rates below the 10^{th} percentile compared to 11% of a control group.

Four studies examined AD neuropathology, supporting the following conclusions:

1. AD neuropathology may infiltrate central ANS structures, including the ventromedial frontal cortex (Chu et al., 1997), pons (Rub et al., 2001) medial parabrachial nucleus,

subpeduncular pigmented nucleus, and intermediate zone of the brainstem medullary reticular formation (Burke et al., 1994).

2. Telencephalic structures such as the insula may also be affected (Bonthius et al., 2005).

Table 4. Clinical/Physiological Reports Examining Autonomic Nervous System (ANS) Dysfunction in Alzheimer's Disease (AD)

Conclusion	Supporting Studies	Study Description	Level of Evidence
Individuals with AD demonstrate blood pressure differences at baseline and following stimulation, as compared with controls	Lampe et al., 1989	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Otsuka et al. 1990		
	Elmstahl et al. 1992		
	Burke et al. 1994	Retrospective chart review and neuroanatomical analysis of 3 postmortem AD subjects and characterization of an aspect of ANS dysfunction in AD through comparison of two or more groups of individuals, one or more of these groups being comprised of AD patients	NA
	Idiaquez et al. 1997	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Guo et al. 1998	Prospective cohort study	2b
	Kalman et al.	Described/characterized ANS dysfunction	NA

	2002	in AD through comparison of two or more groups of individuals	
	Bordier et al. 2007		
Individuals with AD demonstrate significantly greater falls in blood pressure (particularly systolic) when transitioning from supine to standing (orthostatic hypotension) compared with healthy age-matched controls	Elmstahl et al. 1992	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Vitiello et al. 1993		
	Wang et al. 1994		
	Jhee et al. 1995	Retrospective description of ANS dysfunction in AD through examination of a single group of AD subjects	NA
	Passant et al. 1997	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Kalman et al. 2002		
	Andin et al. 2007		
	Allan et al. 2007		
	Andersson et al. 2008		
	Allan et al. 2009	Prospective Cohort Study	2b
	Mehrabian et al. 2010	Described/characterized ANS dysfunction in AD through comparison of two or more	NA

	Zakrzewska-Pniewska et al. 2012	groups of individuals	
Significantly less heart rate variability has been reported in individuals with AD	Franceschi et al. 1986	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Aharon-Peretz et al. 1992		
	Algotsson et al. 1995 a		
	Szili-Torok et al. 2001		
	Idiaquez et al. 2002		
	Zulli et al. 2005		
	Zakrzewska-Pniewska et al. 2012		
	Toledo and Junqueira Jr, 2008		
	Toledo and Junqueira Jr. 2010	Described/characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	NA
Individuals with	Rainero et al.	Described/characterized ANS dysfunction	NA

AD also demonstrate altered blood pressure and heart rate responses to pain stimuli	2000	in AD through comparison of two or more groups of individuals	
	Benedetti et al. 2004	Described/characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	NA
Autonomic nervous system dysfunction appears to be subtle in patients with AD when compared with other types of dementia	Allan et al. 2007	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Allan et al. 2006		
Plasma norepinephrine levels may be altered in AD	Borson et al. 1989	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Raskind et al. 1984		
	Lampe et al. 1989		
	Peskind et al. 1995		
	Ahlskog et al. 1996		
	Peskind et al. 1998		

	Pascualy et al. 2000		
Vasomotor function may be reduced in individuals with AD	Algotsson et al. 1995	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Kalman et al. 2002		
	Hornqvist et al. 1987		
Individuals with AD may demonstrate an impaired sweat response	Elmstahl and Winge 1993	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
Pupillary responses in AD are altered in AD	Idiaquez et al., 1994	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Grunberger et al. 1999		
	Fotiou et al. 2009		
Constipation and urinary incontinence may occur in AD	Davidson et al. 1991	Described/characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	NA
	Del-Ser et al. 1996	Described/characterized ANS dysfunction in AD through comparison of two or more	NA

	Ransmayr et al. 2008 Zakrzewska-Pniewska et al. 2012	groups of individuals	
Heightened arousal during learning may occur in AD	Eisdorfer and Cohen in 1978	Described/characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	NA
Salivary flow is decreased in AD	Ship et al. 1990	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
The neuropathology of AD may affect central ANS control mediated by the ventromedial frontal cortex	Chu et al. 1997	Neuroanatomical and Described/ characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
The neuropathology of AD may affect central ANS central control mediated by the pontine regions of	Rub et al. 2000	Neuroanatomical and Described/ characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	NA

the brainstem			
The neuropathology of AD may affect the insula	Bonthius et al. 2005	Neuroanatomical and Described/ characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	NA
The neuropathology of AD may affect the C-1 neurons of the rostral ventrolateral reticular nucleus	Burke et al. in 1994	See Above	See Above
No significant differences between individuals with AD and controls	Khurana and Garcia 1981	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Shankle et al. 1993	Neuroanatomical and Described/ characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Wakabayashi et al. 1999		
	Taki et al. 2001	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Allen et al. 2004		
	Orimo et al. 2005	Neuroanatomical and Described/ characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA

	Choi et al. in 2009	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	NA
	Watanabe et al. 2001		
	Raskind et al. 1999		

NA = not applicable. See Appendix D for more details.

2.3.3.3 Reviews

Four non-systematic, narrative reviews (Borson et al., 1989; Idiaquez & Roman, 2011; Kenny, Kalaria, & Ballard, 2002; Royall, 2008) were identified.

One review (Borson et al., 1989) described studies of ANS function in AD that were published between 1978 and 1990 and concluded that:

1. SNS over-arousal may be a feature of advanced AD, whereas SNS arousal in mild to moderate AD appears to be significantly reduced.
2. Studies of heart-rate variability in AD have indicated reduced SNS activity, as well as SNS and PNS dysfunction.
3. Disordered vascular skin reactivity and reduced basal and stimulated salivary flow may occur in AD.

One narrative review described “neurocardiovascular instability” among patients with dementia, including AD, and suggested that this disorder may result in autonomic dysregulation (Kenny et al., 2002). Another review reported on the association of right cerebral hemisphere dysfunction, insular pathology, and mortality secondary to cardiovascular and autonomic dysregulation in AD (Royall, 2008). One further review suggested that dysautonomia is mild in AD and primarily manifests as cardiovascular and urinary dysfunction (Idiaquez & Roman, 2011).

2.3.3.4 Case Studies

Two case studies addressed ANS dysfunction in AD (Diamond & Diamond, 1991; Novak, Novak, Li, & Remillard, 1994). One described a patient with AD who developed thermoregulatory dysfunction (Diamond & Diamond, 1991). The other described an AD patient in whom spontaneous hypotension, accompanied by cardio-acceleration, occurred repeatedly in the supine position and/or during applied hyperventilation (Novak et al., 1994).

2.3.4 Dysphagia and Autonomic Nervous System Dysfunction in Alzheimer's Disease

The literature search did not identify any studies that directly examined *both* dysphagia *and* ANS dysfunction in AD. While one clinical report identified significantly decreased submandibular salivary flow in AD (Ship et al., 1990), its potential impact on swallowing was not examined. One commentary on oral health in AD suggested that reduced salivary flow might result in dysfunctional swallowing (Sumer et al., 2005).

2.3.5 Gap Analysis

2.3.5.1 Dysphagia in Alzheimer's Disease

1. Demographics – While there is preliminary evidence that dysphagia occurs in AD, few studies have examined its prevalence, or variations in prevalence as a function of disease progression.

2. Nature of dysphagia – While the evidence indicates that both the oral and pharyngeal stages of swallowing may be affected in AD, studies examining the esophageal stage of swallowing in AD are lacking.

3. Contribution of dysphagia to eating problems – The functional significance of dysphagia to eating problems in AD has not been elucidated.

4. Assessment of dysphagia – A variety of assessment approaches have been employed to examine dysphagia in AD. However, an optimized swallowing assessment, contextualized with respect to the manifestations of AD, has not been examined.

5. Treatment of dysphagia –Three studies have examined interventions for dysphagia in AD patients. The treatment paradigms were limited and long-term outcomes were either not measured or not identified. Sensory stimulation, or motor training approaches, to dysphagia treatment that have been examined in other neurodegenerative conditions, have not been examined in AD.

6. Relationship of dysphagia to other manifestations of AD – While there is preliminary evidence suggesting that dysphagia severity may be related to overall AD severity, or cognitive or executive dysfunction, associations between dysphagia and other signs of AD, such as independence in activities of daily living (ADL), have not been elucidated.

7. Neural mechanisms underlying dysphagia – A small number of studies have shown that changes in the cortical swallowing network occur early in AD and may be correlated with early functional changes in swallowing. However, the neuropathophysiology of dysphagia in AD is unclear.

2.3.5.2 Autonomic Nervous System Dysfunction in Alzheimer's Disease

1. Demographics – While a substantial literature has identified ANS dysfunction in AD, its prevalence remains unclear.

2. Relationships between ANS functions – The relative extent of impairment across a range of ANS functions in AD is not understood.

3. Functional significance of ANS dysfunction – The functional significance of ANS dysfunction in AD in terms of, for example, ability to perform ADLs, including eating, is unclear.

4. Neuropathophysiology of ANS dysfunction – The neural mechanisms that contribute to ANS dysfunction, how they relate to the disease process, and whether the severity changes as the disease progresses, remain unclear.

2.3.5.3 Dysphagia and Autonomic Nervous System Dysfunction in Alzheimer's Disease

Although it is known that ANS function is important in regulating swallowing, the relationship between oropharyngeal dysphagia and ANS dysfunction in AD has not been examined directly. No study has examined oropharyngeal dysphagia in relation to swallow-related ANS functions such as salivary flow, or esophageal smooth muscle function.

2.4 Discussion

This scoping review was undertaken to (i) describe, synthesize, and interpret literature on dysphagia and/or ANS dysfunction in AD, and (ii) identify gaps in the existing literature.

The review identified an emergent literature on dysphagia in AD, with 31 articles matching our search criteria. These articles provide preliminary evidence on the prevalence, nature, and treatment of dysphagia in AD. The available prevalence data suggest that oropharyngeal dysphagia may be a significant problem in AD, even early in the disease progression. However, knowledge gaps were also identified with respect to demographics, nature of dysphagia including the potential of an esophageal component, significance in relation to eating problems, assessment, treatment, and underlying mechanisms of dysphagia in AD.

The review identified 64 articles that examined ANS dysfunction in AD. While the literature on ANS dysfunction in AD is larger and broader than the literature on dysphagia in AD, there are inconsistent findings regarding the presence, severity, and nature of ANS dysfunction. Current evidence suggests that a variety of ANS functions, particularly cardiovascular regulation, may be impaired in AD, but the impact of dysfunction among multiple ANS systems remains unknown. Knowledge gaps were identified with respect to demographics, functional significance, relationships between ANS functions, and underlying neural mechanisms. No systematic reviews of ANS dysfunction in AD have been published previously.

No studies were identified that examined both dysphagia *and* ANS dysfunction in AD. Given the, albeit limited, evidence that salivary flow is reduced in AD, a relationship between oropharyngeal dysphagia and ANS dysfunction might be expected.

2.5 Conclusions

A scoping review of the literature revealed that dysphagia, as well as ANS dysfunction, may occur in AD. However, the potential relationship between dysphagia and ANS dysfunction in AD has not been explored. Moreover, the functional significance of dysphagia and eating-related ANS dysfunction, for example, reduced saliva, to eating problems in AD is not clear.

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Chapter 3

3 A Meta-Analysis of Salivary Flow Rates in Young and Older Adults

This meta-analysis aims to determine whether salivary flow decreases as a function of aging[‡].

3.1 Introduction

Saliva plays a vital role in maintaining oral homeostasis (Mandel, 1989). Saliva is a clear, slightly acidic oral fluid composed of more than 99% water. The remaining 1% is composed of a variety of electrolytes including sodium and potassium, proteins, and nitrogenous products such as urea and ammonia (Humphrey & Williamson, 2001). The electrolytes and proteins in saliva modulate pH levels in the oral cavity. Proteins contribute to cleaning the oral cavity and metabolizing dental plaque (i.e., oral biofilm). Calcium, phosphate and proteins combine to interfere in demineralization and promote remineralization of the teeth. Immoglobulins and proteins combine to provide antibacterial protection (Humphrey & Williamson, 2001). Decreased salivary flow, or hyposalivation, leads to drying of the oral mucosa, inefficient food bolus formation and transport, demineralization of dentition, mucosal ulceration, altered oral flora, dysphonia, impaired taste and smell while eating, and discomfort (Baum, 1989).

Saliva is secreted from three pair of major salivary glands: the parotid, submandibular, and sublingual glands, as well as numerous minor salivary glands. Another constituent of saliva is an exudate called gingival crevicular fluid (Sreebny & Vissink, 2010). The combination of all these fluids, as well as oral bacteria, and their products, is referred to as whole saliva. Glandular saliva is secreted in response to neurotransmitter stimulation from innervating sympathetic and parasympathetic nerves. The minor salivary glands function continuously day and night (Eliasson & Carlen, 2010) during wake and sleep.

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‡ A version of this chapter has been published (Affoo, Foley, Garrick, Siqueira, & Martin, 2015).

The major salivary glands, in contrast, secrete in response to low-grade mechanical stimulation associated with movements of the tongue and lips, and in response to mucosal dryness to lubricate and protect the oral cavity (Baum, 1987; Ekstrom, Khosravani, Castagnola, & Messana, 2012). Although this major salivary gland basal, or resting secretion is produced in response to nervous activity, it is known as "unstimulated salivary flow rate" (Ekberg, 2012; Ekstrom et al., 2012). Approximately 75% of unstimulated, whole saliva is derived from the submandibular/sublingual glands, about 15-20% from the parotid, and 5-8% from the minor salivary glands (Edgar, 1992; Humphrey & Williamson, 2001; Sreebny, 2000). At mealtimes, in response to taste, smell, visual, and mechanical stimuli, salivary flow rates increase by 5 to 50 times. The percentage contribution from the parotid gland increases to more than 50% of total salivary secretions. This increased flow rate is referred to as "stimulated salivary flow rate".

Age-related degenerative changes in the cellular structure of the submandibular and the parotid salivary glands have been previously identified (Scott, 1977; Scott, Flower, & Burns, 1987). A 20-40% decrease in the volume of cells responsible for saliva secretion and a corresponding increase by fatty and fibrous tissue in the glandular area has been reported (Baum, 1989; Scott, 1977; Scott et al., 1987; Sreebny, 2000). Comparable changes have been described for the labial minor glands (Drummond & Chisholm, 1984; Syrjanen, 1984). This evidence of age-related salivary gland degeneration suggests that functional reductions of salivary flow may also occur. Many studies have examined salivary flow rates in the context of aging. The results, however, are conflicting. Some authors have reported significantly decreased salivary flow with age (Ben-Aryeh, Miron, Szargel, & Gutman, 1984; Billings, Proskin, & Moss, 1996; Chang, Chang, Kim, Lee, & Kho, 2011; Cowman, Frisch, Lasseter, & Scarpace, 1994; Fenoll-Palomares et al., 2004; Flink, Bergdahl, Tegelberg, Rosenblad, & Lagerlof, 2008; Ghezzi, Lange, & Ship, 2000; Ghezzi & Ship, 2003; Gutman & Ben-Aryeh, 1974; Hershkovich, Shafat, & Nagler, 2007; Johnson, Yeh, & Dodds, 2000; Marotta et al., 2012; Meurman & Rantonen, 1994; Moritsuka et al., 2006; Nagler & Hershkovich, 2005a, 2005b; Navazesh, Mulligan, Kipnis, Denny, & Denny, 1992; Pedersen, Schubert, Izutsu, Mersai, & Truelove, 1985; Percival, Challacombe, & Marsh, 1994; Sawair, Ryalat, Shayyab, & Saku, 2009; Smith et

al., 2013; Streckfus, Bigler, & O'Bryan, 2002; Tanida et al., 2001; Toida et al., 2010; X. P. Wang et al., 2012; Yaegaki, Ogura, Kameyama, & Sujaku, 1985; Yeh, Johnson, & Dodds, 1998; Yeh et al., 2000), while others have not (Bakke et al., 2004; Baum, 1981; Baum, Costa, & Izutsu, 1984; Ben-Aryeh et al., 1986; Bourdiol, Mioche, & Monier, 2004; Chauncey, Feller, & Kapur, 1987; Eliasson, Birkhed, Heyden, & Stromberg, 1996; Fischer & Ship, 1997, 1999; Gandara, Izutsu, Truelove, Ensign, & Somers, 1985; Heft & Baum, 1984; Malhotra, Wood, & Sachse, 2009; Ogura et al., 1983; Parvinen & Larmas, 1982; Salvolini et al., 2000; Shern, Fox, & Li, 1993; Ship & Baum, 1990; Ship & Fischer, 1997; Sonnenberg et al., 1982; Takada, Suzuki, Okada, Nakashima, & Ohsuzu, 2006; Tylenda, Ship, Fox, & Baum, 1988; Yoshikawa et al., 2012). Variations in study designs, saliva collection methods, and selection of outcome measures may account for the lack of consistent findings among studies. This variation has been acknowledged in several narrative reviews, which themselves have drawn conflicting conclusions (Baum, Ship, & Wu, 1992; de Almeida Pdel, Gregio, Machado, de Lima, & Azevedo, 2008; Dodds, Johnson, & Yeh, 2005; Ekstrom et al., 2012; Eliasson & Carlen, 2010; Sreebny, 2000). The results from some reviews suggest that the flow of unstimulated whole saliva and unstimulated and stimulated submandibular/sublingual saliva (Dodds et al., 2005; Sreebny, 2000) decreases with increasing age. Other reviews have suggested that no age-related decreases in either unstimulated or stimulated parotid saliva occur. (Baum et al., 1992) Still other reviews have reported no age-related effects on any type of salivary flow (de Almeida Pdel et al., 2008; Ekstrom et al., 2012). To date, the issue remains unresolved, in part, because no pooled analyses have been undertaken. Therefore, the objective of this study was to determine whether there is an effect of age on salivary flow rates, using a meta-analytic approach. We hypothesized that salivary flow rates decrease with advancing age.

3.2 Methodology

Potentially relevant studies that examined salivary flow rate in adults of different ages were identified through literature searches of the PubMed, EBSCOhost, Web of Science, Cochrane, EMBASE, Dissertations and Theses, and Scopus databases, published from the inception of the databases through June 2013. Although search terms varied slightly

across databases, the terms “saliva” and “salivation” or “secretion” and “aged” or “aging” and “normal” or “disease-free” were used as MeSH terms, key words, or subject headings (Appendix E). Hand searching of the bibliographies of the included studies was conducted to identify potentially relevant articles not recovered using the search terms.

Inclusion/Exclusion Criteria: Our inclusion criteria were intentionally broad to capture as many studies as possible. Studies were included if saliva had been collected on at least one occasion, among participants aged 18 to 60 + years who had been classified in some manner to form “younger” and “older” groups. Additional inclusions were a sample size of at least 6 participants, studies published in the English language and sufficient reporting detail to enable extraction (or calculation) of data needed for pooled analysis. Studies that examined salivary flow rates from any/all sources (whole, parotid, submandibular/sublingual, and/or minor glands), in either physiological condition (stimulated and/or unstimulated condition), and using any established collection method (draining, expectoration, cotton rolls, suction, Carlson Crittenden/Curby/Lashley cup, mastication stimulated, or gustatory stimulated) were included. Studies that examined a therapy or medication were used if baseline measures of salivary flow rates were conducted prior to the introduction of the intervention, and reported. Normal aging was not defined *a priori;* instead studies were included if the participants were described as “healthy” by the authors, or if the participants were free of major systemic diseases. Reviews, commentaries, opinion pieces, case reports, case series, studies examining salivary flow in individuals with disease, and animal studies were excluded.

Two authors (RA and RG) independently reviewed titles and abstracts to determine initial eligibility. If an abstract was in question by either reviewer, the full article was retrieved and reviewed. Following this initial screen, the same authors reviewed the full text of the remaining articles to determine final eligibility. A third author (NF) resolved discrepancies. The degree of agreement between the two independent reviewers was calculated using a kappa value.

One author (RA) extracted data on trial design, sample sizes, participant characteristics, salivary flow rate (volume/collection time) for each of the salivary sources of interest

under unstimulated and stimulated conditions for the young and the older groups, as well as method of saliva collection, health status, and medication use from each study, and a second reviewer verified them for accuracy.

To enable comparisons of young and older subjects, the age groups operationally defined in individual studies were used. The two comparison groups were: (i) subjects closest in age to 18 – 40 years (i.e., young); and (ii) subjects closest to ≥60 years (i.e., old). Studies where little separation between age data occurred (e.g. young subjects were aged 18 to 64 years, and old subjects were aged 65 years and older) were excluded. Differences in salivary flow rates between age groups were calculated for each salivary source and condition and the results pooled using the software Comprehensive Meta-Analysis (version 2, Biostat Inc., 2007)[§]. This software enables the calculation of a pooled estimate of a treatment effect using differing forms of summary level data. Standardized mean differences (SMDs), standard errors (SEs), and 95% confidence interval (CIs) was calculated using the reported means and standard deviations of the two groups, or using the formula (Standardized Difference equals 2 times the correlation divided by the square root of 1, minus the correlation squared) for conversion when a Pearson's correlation co-efficient for salivary flow rates across the age continuum was reported. Separate analyses were conducted for each salivary source and condition, with subgroup analyses completed for collection method, gender, and health status, providing at least four studies were available for analysis. A separate analysis including subjects from studies where authors excluded those taking prescription and/or nonprescription medication was also conducted. The younger subject group data were used as the basis of comparison; therefore, differences between the younger and older subject groups observed to be greater than zero indicated that younger subjects had greater salivary flow rates than the older subjects. Cohen has suggested the following guide to interpretation of effect sizes: 0.80 = large; 0.50 = moderate; 0.20 = small (Cohen, 1988). A Cohen's d value of zero indicates no effect. Where possible, the effect size was also converted to more clinically interpretable measurement (mL/min) using a standard technique (Lipsey & Wilson,

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[§] Suppliers Version 2; Biostat Inc, 14 N. Dean St, Englewood, NJ 07631.

2001). A random effects model was used to address two sources of potential variance: within-study error in estimating the effect in each study, as well as the variation in the true effects across studies (Borenstein, 2009). In order to examine the observed dispersion in true effect sizes, and to estimate both the true variance and random error within the observed dispersion, a standardized weighted sum of squares (Q) was calculated and compared with the expected weighted sum of squares in order to yield a test of the null. Heterogeneity was considered statistically significant if $p < 0.05$. An estimate of the variance (T^2), the standard deviation (T), and confidence intervals of the true effects were calculated. Additionally, the proportion of true variance found within the observed variance was also calculated (I^2) (Borenstein, 2009). A rough guide to the interpretation of the I^2 statistic is: 0 to 40% may not be important, 30 to 60% may represent moderate heterogeneity, 50 to 90% may represent substantial heterogeneity, 75 to 100% considerable heterogeneity (Higgins et al., 2011).

3.3 Results

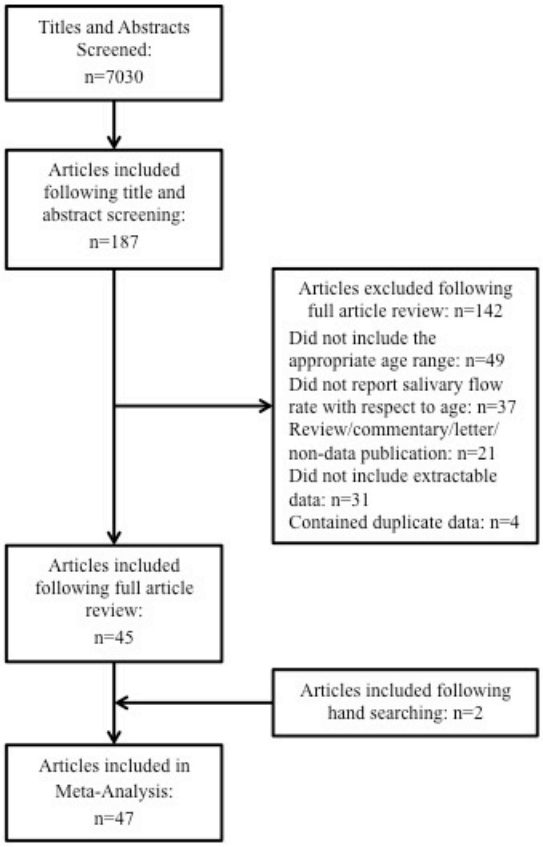

Figure 4. Flow Chart of Meta-Analysis

The initial search returned 7,030 results, of which 187 were selected for full review (Figure 4). After elimination of an additional 138 articles, 51 studies remained, four of which reported duplicate data. Forty-seven studies met the inclusion criteria and were included (Bakke et al., 2004; Baum, 1981; Baum et al., 1984; Ben-Aryeh et al., 1984; Ben-Aryeh et al., 1986; Billings et al., 1996; Bourdiol et al., 2004; Chang et al., 2011; Chauncey et al., 1987; Cowman et al., 1994; Eliasson et al., 1996; Fenoll-Palomares et al., 2004; Fischer & Ship, 1997, 1999; Flink et al., 2008; Gandara et al., 1985; Ghezzi et al., 2000; Ghezzi & Ship, 2003; Gutman & Ben-Aryeh, 1974; Heft & Baum, 1984; Henkin, Velicu, & Papathanassiu, 2007; Hershkovich et al., 2007; Johnson et al., 2000; Malhotra et al., 2009; Marotta et al., 2012; Meurman & Rantonen, 1994; Moritsuka et al., 2006; Nagler & Hershkovich, 2005a, 2005b; Navazesh et al., 1992; Ogura et al., 1983; Parvinen & Larmas, 1982; Pedersen et al., 1985; Percival et al., 1994; Salvolini et al.,

2000; Sawair et al., 2009; Shern et al., 1993; Ship & Baum, 1990; Ship & Fischer, 1997; Smith et al., 2013; Sonnenberg et al., 1982; Streckfus et al., 2002; Takada et al., 2006; Tanida et al., 2001; Toida et al., 2010; Tylenda et al., 1988; X. P. Wang et al., 2012; Yaegaki et al., 1985; Yeh et al., 1998; Yeh et al., 2000; Yoshikawa et al., 2012). Agreement between raters as to which studies should be retained was good to excellent (kappa: κ=0.836, SE=0.420).

The details of all studies included in the analyses are presented in Appendix F and summarized in Table 5. The 47 studies included sample sizes ranging from 15 to 1427 participants, arranged into two to seven age groupings. Young subjects ranged in age from 15 to 59 years and elderly subjects ranged in age from 60 to 97 years. Twenty-four studies examined the salivary flow rates of males and females separately.

Thirty-five studies described the included participants as “healthy” or “generally healthy”, or included a healthy control group, or reported excluding participants with health problems that could affect salivary flow, such as history of treatment for cancer, or systemic disease. Other studies reported that participants with common illnesses such as hypertension and compensated diabetes were not excluded, while other studies reported using data from cohorts of community-dwelling volunteers, or recruiting participants from dental clinic registries where older individuals appeared to be free of major systemic disease, but may have had some common age-related conditions.

Twenty-six studies excluded subjects taking certain medications. Some studies reported excluding subjects taking any medications, while others excluded subjects taking prescription medications and antihistamines or any saliva-affecting medications, but not hormone replacement therapy or birth control. We referred to participants in these studies, who were taking either no medications or minimal medications, as being “medication-free”. Twenty-one studies reported that individuals taking routine medications were included in the study or did not report the medication status of the participants.

The 47 studies included 33 trials examining unstimulated whole salivary flow rates; 23 trials examining stimulated whole salivary flow rates; eight trials examining unstimulated

parotid salivary flow rates; 19 trials examining stimulated parotid salivary flow rates; six trials examining unstimulated submandibular/sublingual (SMSL) salivary flow rates; seven trials examining stimulated SMSL salivary flow rates; and four each examining unstimulated minor buccal salivary flow rates, unstimulated minor palatal salivary flow rates, and unstimulated minor labial salivary flow rates. Some studies included more than one trial.

Of all studies included in the meta-analysis (N=47), 21 reported no significant differences in mean salivary flow between younger and older subjects, 15 reported age-related declines in salivary flow, one reported both age-related decreases and increases in salivary flow, and 10 studies reported equivocal results (i.e. in studies in which more than one result was reported, significant and nonsignificant results were reported in the same study).

Separate analyses for each of the salivary sources are presented below.

3.3.1 Whole Salivary Flow Rate

Whole salivary flow rate (Figure 5) was significantly reduced in the elderly group (SMD = 0.551, SE = 0.056, 95% CI = 0.423–0.678, $p < 0.001$). In subgroup analysis including the results from 33 studies, whole salivary flow rate in the unstimulated condition was significantly lower in the elderly group (SMD = 0.611, SE = 0.075, 95% CI = 0.464–0.758, $p < 0.001$). Similarly, subgroup analyses examining stimulated whole salivary flow rate (n = 23) revealed significantly lower flow rate in the elderly group (SMD = 0.367, SE = 0.131, 95% CI = 0.110–0.625, $p = 0.005$). Moderate and small effect sizes were identified, respectively.

Heterogeneity:

The results of the heterogeneity analysis indicated that the included studies did not share a common effect size (Q = 277.4, $p < 0.001$). The variance and standard deviation of the true difference between the whole salivary flow rates of young and older individuals indicated that the range of true differences crossed the no difference line, despite the summary effect being statistically significant ($T^2 = 0.187$, T = 0.432, 95% CI = -0.296 –

1.398). Eighty percent of the observed variance was found to be true variance of the effect size (I^2 = 80.17%).

The results of the heterogeneity analysis for whole salivary flow rate in the unstimulated condition indicated significant heterogeneity (Q = 80.70, $p < 0.001$). The range of true effects, although wider than the confidence interval of the summary interval, did not cross the no difference line (T^2 = 0.091, T = 0.301, 95% CI = 0.021 – 1.201). Sixty percent of the observed variance was found to be true variance of the effect size (I^2 = 60.35%).

The results of the heterogeneity analysis for whole salivary flow rate in the stimulated condition also indicated significant heterogeneity (Q = 195.37, $p < 0.001$). The range of true effects was observed to cross the no difference line, despite the summary effect being statistically significant (T^2 = 0.303, T = 0.551, 95% CI = -0.713 – 1.447). Eighty-eight percent of the observed variance was found to be true variance of the effect size (I^2 = 88.74%).

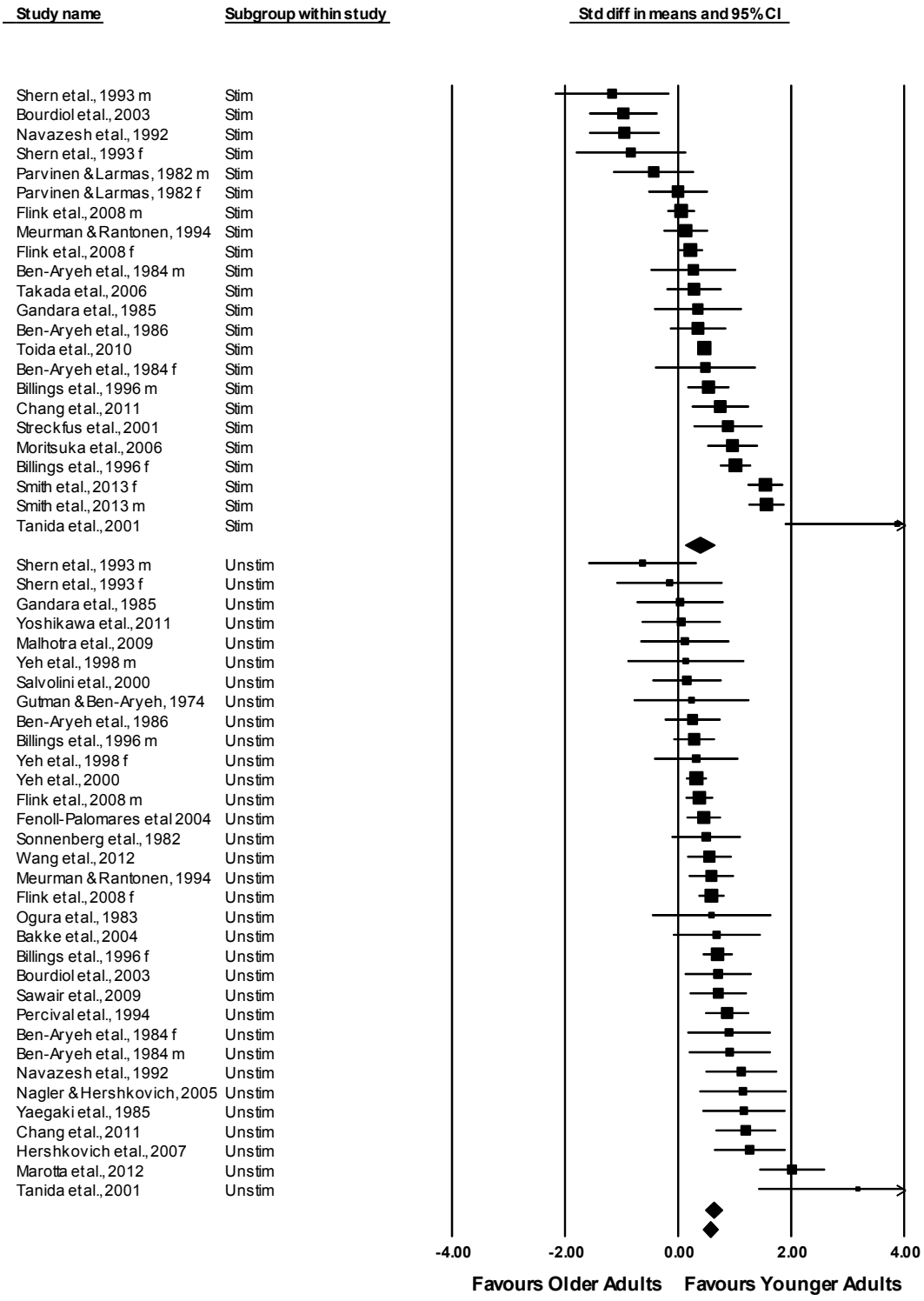

Figure 5: Forest Plot of the Difference in Whole Salivary Flow Rate Between Older and Younger Subjects

The first (left) column lists studies by primary author and publication date. An "f" or "m" following the primary author and date of publication indicates data that were reported separately for males and females in the same study. The second column indicates the subgrouping by condition (stimulated and unstimulated). The forest plot is illustrated in the right column. The solid squares illustrate the standardized mean difference (SMD) and the lines represent the 95% confidence intervals (CI). The younger subject group data were used as the basis of comparison, therefore, differences between younger and older subject groups observed to be greater than zero are represented on the right hand side of the line-of-no-difference, and indicate that younger subjects had greater salivary flow rates than the older subjects. The solid diamonds represent the pooled SMD and 95% CI.

3.3.2 SMSL Salivary Flow Rate

SMSL salivary flow rate (Figure 6) was significantly reduced in the elderly group (SMD = 0.582, SE = 0.123, 95% CI = 0.341–0.823, $p < 0.001$). Subgroup analyses indicated that both unstimulated (n = 6) and stimulated (n = 7) SMSL salivary flow rates were significantly reduced in the elderly group (unstimulated: SMD = 0.569, SE = 0.159, 95% CI = 0.257–0.881, $p < 0.001$; and stimulated: SMD = 0.600, SE = 0.193, 95% CI = 0.222–0.978, $p = 0.002$). Moderate effect sizes were identified.

Heterogeneity:

The results of the heterogeneity analysis indicated that the included studies did not share a common effect size (Q = 31.12, $p = 0.002$). The variance and standard deviation of the true difference between the SMSL salivary flow rates of young and older individuals indicated that the range of true effects, although wider than the confidence interval of the summary interval, did not cross the no difference line ($T^2 = 0.084$, T = 0.290, 95% CI = 0.014 – 1.150). Sixty-one percent of the observed variance was found to be true variance of the effect size ($I^2 = 61.44\%$).

The results of the heterogeneity analysis for SMSL salivary flow rate in the unstimulated condition did not reveal significant heterogeneity (Q = 10.51, $p = 0.062$). The range of

true effects, although wider than the confidence interval of the summary interval, did not cross the no difference line (T^2 = 0.073, T = 0.290, 95% CI = 0.014 – 1.150). Fifty-two percent of the observed variance was found to be true variance of the effect size (I^2 = 52.41%).

The results of the heterogeneity analysis for SMSL salivary flow rate in the stimulated condition indicated significant heterogeneity (Q = 20.45, *p* = 0.002). The range of true effects was observed to cross the no difference line, despite the summary effect being statistically significant (T^2 = 0.169, T = 0.411, 95% CI = -0.206 – 1.406). Seventy percent of the observed variance was found to be true variance of the effect size (I^2 = 70.66%).

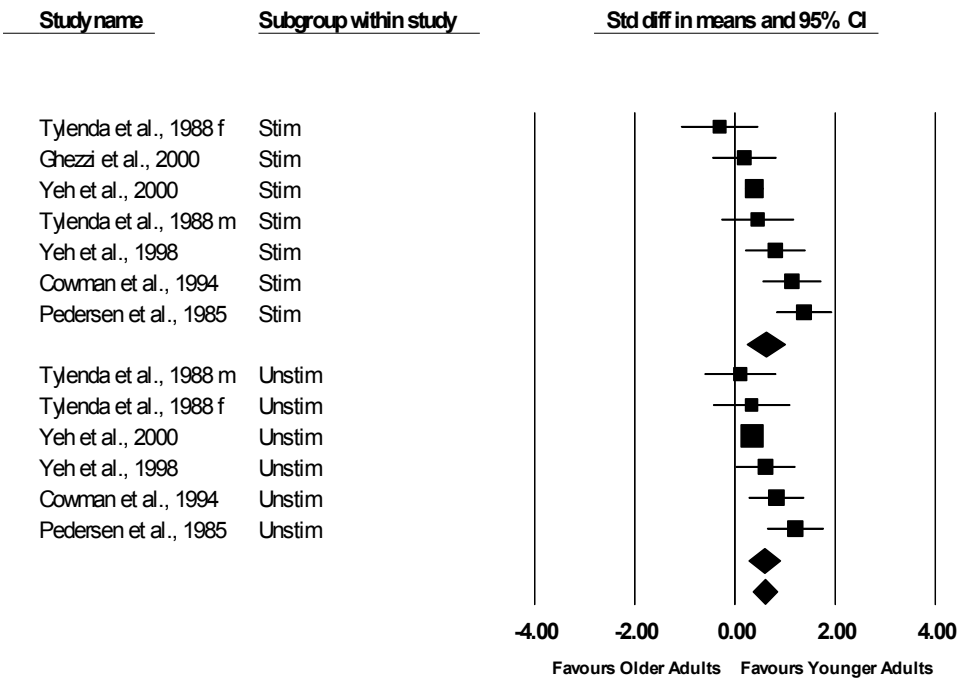

Figure 6: Forest Plot of the Difference in Submandibular/Sublingual Salivary Flow Rate Between Older and Younger Subjects

3.3.3 Parotid Gland Salivary Flow Rate

Parotid gland salivary rate was not significantly reduced in the elderly group (SMD = 0.023, SE = 0.063, 95% CI = -0.099–0.146, *p* = 0.71).

Heterogeneity:

The results of the heterogeneity analysis for parotid salivary flow rate did not reveal significant heterogeneity (Q = 37.31, $p = 0.07$). The variance and standard deviation of the true difference between the parotid salivary flow rates of young and older individuals indicated that the range of true differences crossed the no difference line ($T^2 = 0.029$, T = 0.169, 95% CI = -0.101 – 0.561). Thirty percent of the observed variance was found to be true variance of the effect size ($I^2 = 30.32\%$).

3.3.4 Minor Gland Salivary Flow Rate

Only unstimulated, minor gland salivary flow rate was analyzed because an insufficient number of studies examining stimulated minor gland flow rates were identified.

Unstimulated buccal (n = 4, SMD = -0.143, SE = 0.392, 95% CI = -0.912–0.626, $p = 0.715$), labial (n = 4, SMD = 0.069, SE = 0.213, 95% CI = -0.348–0.485, $p = 0.747$), and palatal (n = 4, SMD = 0.250, SE = 0.416, 95% CI = -0.566–1.065, $p = 0.548$) minor gland salivary flow rates were not significantly reduced in the elderly group.

Heterogeneity:

The results of the heterogeneity analysis for unstimulated buccal salivary flow rate indicated that the included studies did not share a common effect size (Q = 10.47, $p = 0.015$). The variance and standard deviation of the true difference between the buccal salivary flow rates of young and older individuals indicated that the range of true differences crossed the no difference line ($T^2 = 0.436$, T = 0.660, 95% CI = -1.437 – 1.151). Seventy-one percent of the observed variance was found to be true variance of the effect size ($I^2 = 71.34\%$).

The results of the heterogeneity analysis for unstimulated labial salivary flow rate did not reveal significant heterogeneity (Q = 3.288, $p = 0.349$). The variance and standard deviation of the true difference between the labial salivary flow rates of young and older individuals indicated that the range of true differences crossed the no difference line (T^2

= 0.016, T = 0.127, 95% CI = -0.180 – 0.318). Eight percent of the observed variance was found to be true variance of the effect size (I^2 = 8.77%).

The results of the heterogeneity analysis for unstimulated palatal salivary flow rate indicated that the included studies did not share a common effect size (Q = 8.506, *p* = 0.037). The variance and standard deviation of the true difference between the palatal salivary flow rates of young and older individuals indicated that the range of true differences crossed the no difference line (T^2 = 0.438, T = 0.662, 95% CI = -1.048 – 1.548). Sixty-four percent of the observed variance was found to be true variance of the effect size (I^2 = 64.73%).

3.3.5 Analysis of "Medication-Free" Subjects

When the analysis was limited to studies that excluded subjects taking medications (n = 26), a moderate effect size was observed for unstimulated whole salivary flow rate (n = 17, SMD = 0.641, SE = 0.155, 95% CI = 0.388–0.944, $p < 0.001$) (Figure 7). Similarly, moderate effect sizes were observed for unstimulated (n = 5, SMD = 0.668, SE = 0.189, 95% CI = 0.297–1.039, $p < 0.001$) and stimulated (n = 6, SMD = 0.646, SE = 0.249, 95% CI = 0.158–1.133, $p = 0.01$) SMSL salivary flow rates (Figure 8).

Heterogeneity:

The results of the heterogeneity analysis for whole salivary flow rate in the unstimulated condition indicated significant heterogeneity (Q = 48.88, $p < 0.001$). The range of true effects was observed to cross the no difference line, despite the summary effect being statistically significant (T^2 = 0.212, T = 0.460, 95% CI = -0.261 – 1.543). Sixty-seven percent of the observed variance was found to be true variance of the effect size (I^2 = 67.27%).

The results of the heterogeneity analysis for SMSL salivary flow rate in the unstimulated condition did not reveal significant heterogeneity (Q = 6.587, $p = 0.159$). The range of true effects, although wider than the confidence interval of the summary interval, did not cross the no difference line (T^2 = 0.070, T = 0.264, 95% CI = 0.151 – 1.185). Thirty-nine

percent of the observed variance was found to be true variance of the effect size (I^2 = 39.28%).

The results of the heterogeneity analysis for SMSL salivary flow rate in the stimulated condition indicated significant heterogeneity (Q = 16.61, p = 0.005). The range of true effects was observed to cross the no difference line, despite the summary effect being statistically significant (T^2 = 0.258, T = 0.508, 95% CI = -0.350 – 1.642). Sixty-nine percent of the observed variance was found to be true variance of the effect size (I^2 = 69.89%).

Stimulated whole salivary flow rate (Figure 7), and unstimulated and stimulated parotid salivary flow rates (data not shown), were not significantly different between groups. The analysis could not be completed for unstimulated minor gland salivary flow rate due to small sample sizes (n < 4).

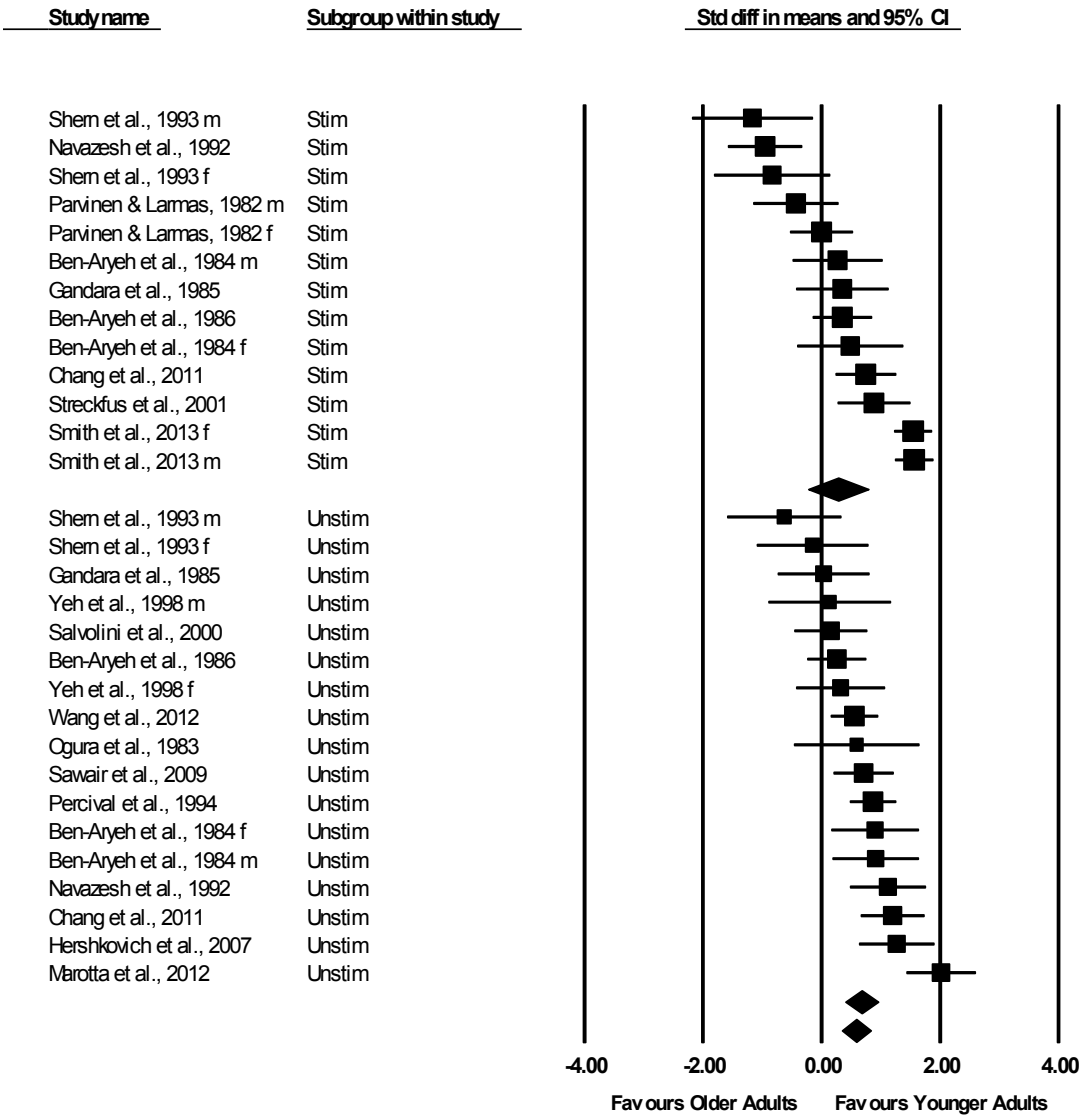

Figure 7: Forest Plot of the Difference in Whole Salivary Flow Rate Between "Medication-Free" Older and Younger Subjects

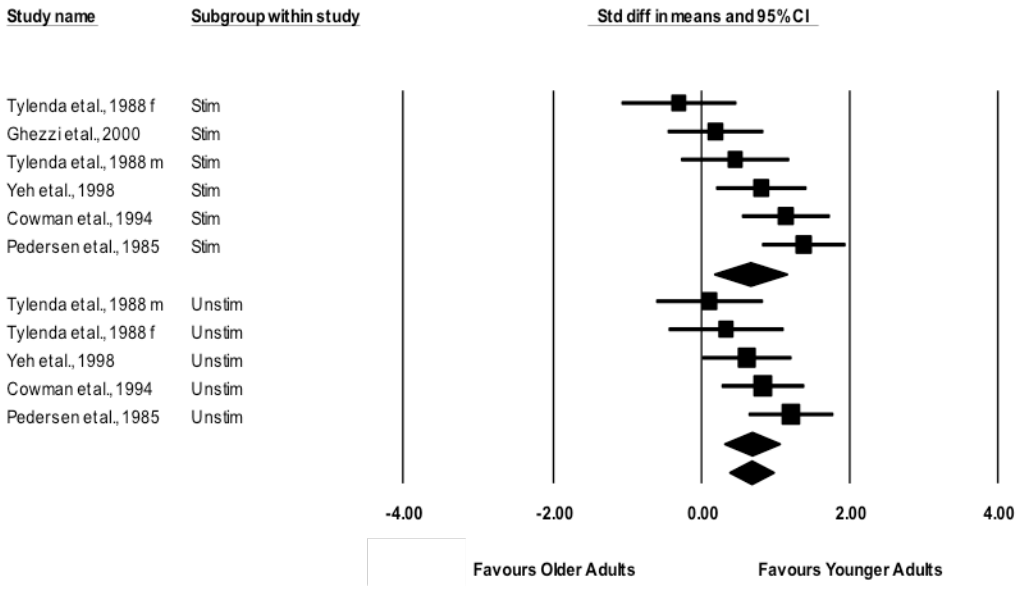

Figure 8: Forest Plot of the Difference in SMSL Salivary Flow Rate Between "Medication-Free" Older and Younger Subjects

Table 5: Summary of Results

					Effect Size
Source	Condition	Trials n	Subjects in Analysis n	Collection Method	Standardized Mean Difference, 95% Confidence Interval
Whole Salivary Flow	All	56	5870		0.551, 95% CI 0.423 – 0.678*
	Un-stimulated Whole	33	2687	Draining Method: (Bakke et al., 2004; Flink et al., 2008; Navazesh et al., 1992; Sonnenberg et al., 1982; X. P. Wang et al., 2012)	0.611, 95% CI 0.464 – 0.758*

				Spitting Method: (Ben-Aryeh et al., 1984; Ben-Aryeh et al., 1986; Chang et al., 2011; Fenoll-Palomares et al., 2004; Gandara et al., 1985; Gutman & Ben-Aryeh, 1974; Hershkovich et al., 2007; Marotta et al., 2012; Meurman & Rantonen, 1994; Nagler & Hershkovich, 2005b; Percival et al., 1994; Salvolini et al., 2000; Sawair et al., 2009; Yaegaki et al., 1985; Yeh et al., 1998; Yeh et al., 2000)	
				Cotton Rolls or the Saxon Test: (Bourdiol et al., 2004; Malhotra et al., 2009; Ogura et al., 1983; Takada et al., 2006; Tanida et al., 2001; Yoshikawa et al., 2012)	
				Suction Method of Bertram: (Billings et al., 1996)	
	Stimulated Whole	23	3183	Mastication: (Bourdiol et al., 2004; Chang et al., 2011; Flink et al., 2008; Gandara et al., 1985;	0.367, 95% CI 0.110 – 0.625*

				Meurman & Rantonen, 1994; Moritsuka et al., 2006; Navazesh et al., 1992; Parvinen & Larmas, 1982; Shern et al., 1993; Smith et al., 2013; Streckfus et al., 2002; Takada et al., 2006; Toida et al., 2010)	
				Gustatory Stimulus: (Ben-Aryeh et al., 1984; Ben-Aryeh et al., 1986; Billings et al., 1996; Tanida et al., 2001).	
Whole Salivary Flow – "Medication-Free" Participants	Un-stimulated Whole	17	899		0.641, 95% CI 0.338 – 0.944*
	Stimulated Whole	13	850		0.268, 95% CI -0.239 – 0.775
Submandibular/Sublingual Salivary Flow	All	13	1314		0.582, 95% CI 0.341 – 0.823*
	Un-stimulated SMSL	6	637	SMSL saliva was collected with a micropipette and light suction (Cowman et al., 1994; Ghezzi et al., 2000; Johnson et al., 2000;	0.569, 95% CI 0.257 – 0.881*

				Tylenda et al., 1988; Yeh et al., 1998; Yeh et al., 2000), or with an originally designed collection device fitted with a micropipette and dropper bulb (Pedersen et al., 1985)	
	Stimulated SMSL	7	677	Gustatory Stimulus: (Cowman et al., 1994; Ghezzi et al., 2000; Johnson et al., 2000; Pedersen et al., 1985; Tylenda et al., 1988; Yeh et al., 1998; Yeh et al., 2000)	0.600, 95% CI 0.222 – 0.978*
Sub-mandibular/Sub-lingual Salivary Flow – "Med-ication-Free" Partici-pants	Un-stimulated SMSL	5	238		0.668, 95% CI 0.297 – 1.039*
	Stimulated SMSL	6	278		0.646, 95% CI 0.158 – 1.133*
Parotid Salivary Flow	All	27	1856		0.023, 95% CI -0.099 – 0.146
	Un-	8	433	Parotid saliva was collected	0.045, 95% CI -

	stimulated Parotid			with a modified Carlson Crittenden, Curby, or Lashley cup (Ben-Aryeh et al., 1986; Bourdiol et al., 2004; Cowman et al., 1994; Fischer & Ship, 1999; Heft & Baum, 1984; Yeh et al., 1998)	0.161 – 0.250
	Stimulated Parotid	19	1423	Gustatory Stimulus: (Baum, 1981; Baum et al., 1984; Ben-Aryeh et al., 1986; Bourdiol et al., 2004; Chauncey et al., 1987; Cowman et al., 1994; Fischer & Ship, 1999; Gandara et al., 1985; Ghezzi et al., 2000; Heft & Baum, 1984; Johnson et al., 2000; Percival et al., 1994; Ship & Baum, 1990; Sonnenberg et al., 1982; Yeh et al., 1998; Yeh et al., 2000)	0.011, 95% CI - 0.142 – 0.165
Parotid Salivary Flow – Med-ication-Free	Un-stimulated Parotid	5	197		0.101, 95% CI - 0.266 – 0.468
	Stimulated Parotid	10	535		0.103, 95% CI - 0.075 – 0.280

Partici-pants					
Minor Gland Salivary Flow	Un-stimulated Palatal	4	77	Minor gland saliva was collected via the Periotron method or with chromatography paper	0.250, 95% CI -0.566 – 1.065
	Un-stimulated Labial	4	105		0.069, 95% CI -0.348 – 0.485
	Un-stimulated Buccal	4	105		-0.143, 95% CI -0.912 – 0.626

(*$p < 0.05$)

3.3.6 Translating Effect Size to the Original Metric

When converted to a traditional metric, the mean differences in salivary flow rates between young and old subjects were: 0.168 mL/min for unstimulated whole salivary flow rate; 0.293 mL/min for stimulated whole salivary flow rate; 0.015 mL/min for unstimulated SMSL salivary flow rate; and 0.040 mL/min for stimulated SMSL salivary flow rate. These rates represent a 40% reduction in flow rate for older participants for unstimulated whole saliva; a 15% reduction for stimulated whole saliva; an 11% reduction for unstimulated SMSL saliva; and a 9% reduction for stimulated SMSL saliva.

3.4 Discussion

The results from the present meta-analysis suggest that salivary flow decreases with age. Although this effect was evident for whole saliva, not all subcomponents of saliva showed decreased flow. Specifically, SMSL salivary flow rates in both the unstimulated and stimulated conditions were lower in older adults, whereas parotid gland and minor gland salivary flow rates were not different in young and older adults. These findings are consistent with the view that aging is associated with decreased salivary flow in a gland-

specific manner. Moreover, the age-related decrease in salivary flow was not fully explained on the basis of medication or disease.

3.4.1 Mechanisms

Both unstimulated and stimulated whole mean salivary flow rates were significantly lower in older adults compared to younger adults. The difference in *unstimulated* whole salivary flow rate was approximately 66% greater than the difference in *stimulated* whole salivary flow rate. This finding of greater reduction of unstimulated whole salivary flow rate associated with age is consistent with the present finding of decreased SMSL salivary flow. The SMSL salivary glands contribute 70% of the overall volume of unstimulated whole saliva, but less than 50% of stimulated whole saliva. The present finding of a lack of an age effect for parotid salivary flow rate would be consistent with this supposition.

A decline in the functional output of the SMSL glands in elderly subjects could be related to degenerative changes in their cellular structure, as has been reported previously, (Baum, 1989; Scott, 1977) although these anatomical changes do not explain why age-related decreases in parotid gland salivary flow rates were not found in the present study. The differential effects of age on SMSL and parotid flow rates may be due to inherent neuroanatomical and physiological differences between the glands. It has been speculated that specific age-related neuroanatomical changes may result in differential gland dysfunction (Baum, 1987). The secretory reserve hypothesis, which proposes that younger persons may possess an excess of salivary secreting cells beyond what is required for normal function, (Scott et al., 1987) may explain the relative age-related stability of parotid gland salivary flow in that age-related degeneration of these “reserve” cells may result in a decrease in saliva production without functional changes in salivary flow rate.

Although the difference in unstimulated whole salivary flow rate was greater than the difference in stimulated whole salivary flow rate, stimulated flow was found to decrease with age. Age related changes to oral motor function may result in reduced bite strength (Mioche, Bourdiol, Monier, Martin, & Cormier, 2004), potentially resulting in reduced

stimulation and reduced salivary flow rate during masticatory stimulated salivary collection (Baum, 1979). This mechanism may have influenced any significant decreases in salivary flow rates for older adults observed following mastication stimulation.

3.4.2 Contributions of Effect Modifiers

Potential sources of heterogeneity among studies, which may have affected effect size estimates, included the collection method, gender, medication use, and health status. Where feasible, we examined the SMDs between younger and older participants grouped by collection method, by gender, and by health status. Despite the fact that substantial heterogeneity was observed for the differences in whole, SMSL, and buccal and palatal minor gland salivary flow rates between young and older adults, and moderate heterogeneity was observed for the differences in parotid and labial minor gland salivary flow rates between young and older adults, little variability could be attributed to any of these potential sources of variability using this technique, given the overlapping CIs among the subgroups (data not shown). Certain salivary collection methods are associated with less reliability and greater variability in flow rate (Navazesh & Christensen, 1982). There is also evidence to suggest that women have lower mean salivary flow rates than men (Inoue et al., 2006; Percival et al., 1994), which may be related to smaller gland sizes in women (Inoue et al., 2006). However, the present analysis examined the salivary flow rates between age groups, so it can only be stated that the age-related decline was proportional between the sexes. Medication use did not appear to explain the difference in SMSL and unstimulated whole salivary flow rates between the young and older adults. This was an unexpected finding, given that many medications, such as antidepressants, diuretics, analgesics, antihistamines, anti-hypertensives, anti-anxiety medications, and appetite suppressants are known to reduce salivary flow. Polypharmacy is also more common with increasing age.

Other potential sources of variability that could not be explored in the present study due to lack of reporting details included timing of salivary collection, and interval between gustatory stimulation and collection. Salivary flow rates are known to vary with circadian rhythm (Aps & Martens, 2005). Given that the majority of studies included in this meta-analysis reported that saliva was collected within a specific temporal window (e.g.

between 8:00-11:00 am), timing of collection was not considered to be a major source of variability. Variation in the time of year when salivary collection occurred may have contributed to variability in effect sizes across studies. This information was not generally reported and could not be explored. There is evidence to suggest that the timing of the interval between stimulus presentation and collection may affect salivary flow rates in older adults. Wu and colleagues (1995) reported that older adults demonstrated reduced SMSL salivary flow rates when increasing periods of time were observed between stimulation and collection (Wu, Baum, & Ship, 1995). If researchers did not employ a standard protocol of saliva collection post stimulation, differences specific to the elderly group could have contaminated the results. The majority of studies included in this meta-analysis, however, reported that saliva was collected immediately post stimulation, or during stimulation, for all participants.

3.4.3 Limitations and Strengths

A variety of age ranges, and age groupings, were used in the included studies, which prevented us from developing an *a priori* definition of younger and older participants and distinct age groups. Although we were often able to form young and older groups based on ages 18 to 40 years, and >60 years, respectively, this group assembly was not always possible (Ben-Aryeh et al., 1986; Chauncey et al., 1987; Gandara et al., 1985; Johnson et al., 2000; Yeh et al., 1998).

A relative strength of this work is the number of studies included in each pooled analysis. Identification and inclusion of many relevant studies allowed us to pool the data for a large number of participants allowing us to identify a more precise estimate of the effect size.

A post-hoc sensitivity analysis was conducted after noting the results from a single study examining unstimulated and stimulated whole saliva were almost 4 standard deviations above the pooled mean (Tanida et al., 2001). Removal of the outlier resulted in an 11% reduction of the effect size for unstimulated whole salivary flow and a 3% reduction of the effect size for stimulated whole salivary flow, although the overall effect sizes

remained significant in both cases. An explanation for the inflated effect size was not obvious after reviewing the study's inclusion criteria and methods.

We excluded a study with insufficient separation between age groups (e.g. "young" subjects were aged 18 to 64 years and "elderly" subjects were aged 65 years and older) to reduce the risk of underestimating of effect sizes.

3.4.4 Future Directions

The results of the present study suggest that older adults have reduced salivary flow rates compared to younger adults. This new evidence provides a strong rationale for future longitudinal studies to confirm that the aging process may contribute to the decline in whole and glandular salivary flow rates. Further investigation into the mechanisms underlying the declines in SMSL salivary flow rates, and the relative stability of parotid gland salivary flow, with age would be beneficial in the understanding of the neurophysiologic correlates of salivary gland aging and in exploring potential treatment options. Saliva plays many important roles in maintaining oral homeostasis. The optimal volume of saliva to maintain function may not be equivalent across roles. Future research should focus on identifying the minimal volumes necessary to maintain the vital functions that saliva performs.

3.4.5 Clinical Significance

A difference between the whole and SMSL salivary flow rates of older and younger adults was identified and quantified. A moderate decrease of 0.168 mL/min was identified for unstimulated whole salivary flow rate, a small decrease of 0.293 mL/min was identified for stimulated whole salivary flow rate, a moderate decrease of 0.015 mL/min was identified for unstimulated SMSL salivary flow rate, and a moderate decrease of 0.040 mL/min was identified for stimulated SMSL salivary flow rate. Researchers can use these values to determine sample size calculations for future studies.

The heterogeneity analysis revealed that the studies included in this analysis did not share a common effect size and the magnitude of dispersion of the true effect of age on salivary flow rate was observed to be large. This perceived variability suggests that not all adults

will experience a clinically significant reduction in salivary flow rate as they age. The reasons for this heterogeneity may be related to factors such as gender, diet, and health status. Variability in the results of the studies examined here may also have been related to the different salivary collection methods employed.

The clinical relevance of the current finding that whole and SMSL salivary flow rates are decreased with increasing age remains unknown. While it is known that SMSL salivary flow protects the oral tissues, primarily during non-alimentary functions at rest through salivary mucins and other constituents (Prakobphol, Levine, Tabak, & Reddy, 1982; Wong, 2008), it is not known at what point reductions in the level of production affect function. Theoretically, age-related decreases of whole and SMSL salivary flow rates could contribute to oral infection, inflammation, and mechanical oral wear (Tabak, 1995). In contrast, no age-related reductions in parotid or minor gland salivary flow, which are integral for rinsing the oral cavity, neutralizing acids, forming the biofilm found on enamel, and digestion, (Dawes & Wood, 1973; Siqueira, Salih, Wan, Helmerhorst, & Oppenheim, 2008; Wong, 2008) were found. This finding suggests that older adults may tend to experience preserved digestive salivary functions.

3.5 Conclusion

Despite conflicting findings previously reported in the literature, unstimulated and stimulated whole and SMSL salivary flow rates are decreased in older adults compared with younger adults. In contrast, parotid gland and minor gland salivary flow rates do not appear to be significantly reduced in older subjects. Medication effects do not fully explain the age-related reduction in SMSL and unstimulated whole salivary flow rates. These findings have important clinical implications for maintaining optimal oral health in older adults.

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Chapter 4

4 The Effects of Oral Stimulation Associated with Manual and Electric Tooth Brushing on Whole Salivary Flow Rates in Healthy Older Adults

This study aims to examine the effects of manual and electric tooth brushing on salivary flow in older adults free of major systemic disease.

4.1 Introduction

Decreased salivary flow, or hyposalivation, results in profound deterioration of oral homeostasis. Increased susceptibility to dental caries and infections, decreased regulation and control of the oral microflora, and impaired swallowing may occur (Sreebny & Vissink, 2010). Salivary gland hypofunction can be caused by developmental or congenital disorders (Eveson, 2008), increased medication usage (Sreebny & Schwartz, 1997), systemic disorders such as Sjögren's syndrome (Fox, Stern, & Michelson, 2000), radiotherapy-induced damage to salivary acinar tissue (Henson, Inglehart, Eisbruch, & Ship, 2001), and anxiety (Bergdahl & Bergdahl, 2000). A recent meta-analysis demonstrated that aging is associated with decreased whole salivary flow rate in healthy older adults (Affoo et al., 2015). It also showed that, while unstimulated and stimulated submandibular/sublingual (SMSL) salivary flow rates were significantly decreased in healthy older adults compared with healthy young adults, parotid gland flow rate did not differ across age groups. Thus, decreased SMSL salivary flow appeared to underlie the reduction in whole salivary flow rates (Affoo et al., 2015). Decreased SMSL and parotid salivary gland flow rates have been reported in the context of certain diseases, such as Alzheimer's disease (Ship et al., 1990; Ship & Puckett, 1994).

The paired parotid salivary glands, submandibular salivary glands, and sublingual salivary glands are the major routes through which saliva is secreted into the oral cavity. The parotid salivary glands are located opposite the maxillary first molars, and the submandibular and sublingual glands are located in the floor of the mouth. Humans also

have numerous minor salivary glands located in the lower lip, tongue, palate, cheeks, and pharynx (Roth & Calmes, 1981).

There are three types of salivary secretion: spontaneous, resting, and stimulated secretion. The minor salivary glands spontaneously secrete saliva in the absence of exogenous stimuli, however, these glands are innervated and secretion rates increase in response to afferent stimuli (Emmelin, 1967). The oral tissues are among the most richly innervated of any in the human body, in terms of the number and variety of peripheral receptors that they contain (Haggard & de Boer, 2014). Both slowly and rapidly adapting sensory receptors in the tongue, periodontal ligament, gingiva, and palate convey an extensive range of sensory information including touch, pressure, vibration, proprioception, pain, and temperature (Dong, Shiwaku, Kawakami, & Chudler, 1993; Nordin & Hagbarth, 1989; Trulsson & Johansson, 2002). Resting and stimulated salivary secretion are nerve-mediated reflexes (Proctor & Carpenter, 2007). Information from mechanical afferent stimulation associated with oral rest conditions, such as contact between different surfaces in the mouth, and stimulated conditions, such as mastication, is conveyed by the sensory branches of the trigeminal and glossopharyngeal cranial nerves to the trigeminal sensory nuclei within the medulla. The salivatory nuclei are also located in the medulla and receive central information from areas of the brain such as the hypothalamus, as well as the incoming sensory information from the periphery. The superior salivatory nucleus contains the preganglionic autonomic motor neurons of the facial nerve, which sends secretomotor input to the submandibular, sublingual, and minor salivary glands, whereas the inferior salivatory nucleus contains the preganglionic autonomic motor neurons of the glossophyarngeal nerve, which sends secretomotor input to the parotid glands (Wilson-Pauwels, 2010). In response to the sensory stimuli, efferent parasympathetic and sympathetic secretomotor nerves conduct excitatory signals to the salivary glands resulting in secretion (Proctor & Carpenter, 2007) (Figure 9). Some studies have documented that increased oral cavity stimulation is associated with increased salivary secretion. Salivary secretion increases with the hardness and the size of an object being chewed, as well as the forces generated by the chewing muscles (Anderson & Hector, 1987; Hector & Linden, 1987; Rosenhek, Macpherson, & Dawes, 1993; Yeh et al., 2000). Increased saliva secretion has also been reported following the application of vibration

stimuli to the facial skin overlying the bilateral belly of the masseter muscles, possibly due to the tonic vibration reflex resulting in contraction of the masseter muscles and/or the vibration activating various types of mechanoreceptors through the skin and mucosa (Hiraba, Yamaoka, Fukano, Fujiwara, & Ueda, 2008). Thus it appears that mechanical stimulation involving stretch, pressure and vibration of the oral cavity have the capacity to stimulate saliva production.

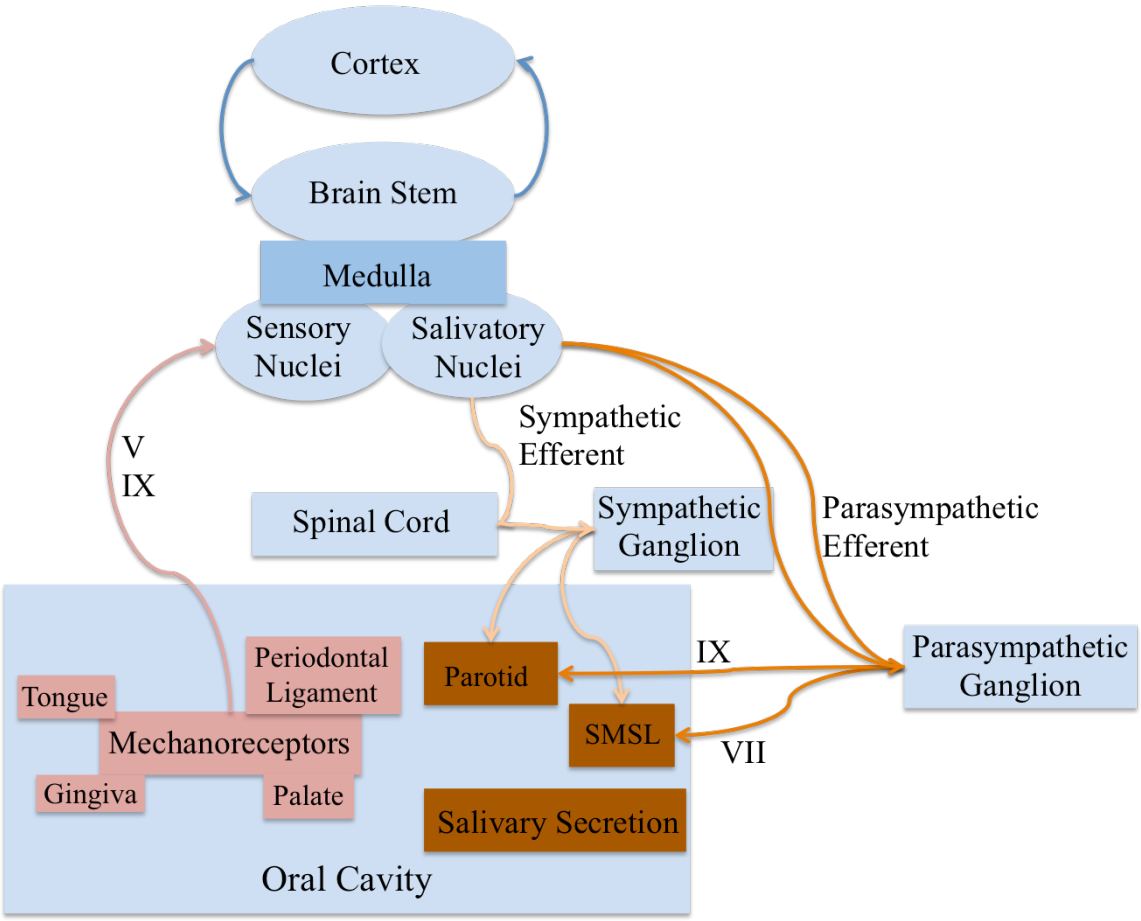

Figure 9: Salivation in Response to Mechanical Stimuli.

Peripheral sensory information is transduced by oral mechanoreceptors located in the tongue, periodontal ligament, gingiva, and palate. Sensory information from the face, tongue, teeth, and oral cavity is conveyed through the sensory component of the trigeminal cranial nerve (V) and sensory information from the posterior third of the tongue, tonsil, soft palate, fauces, and uvula is conveyed through the sensory

component of the glossopharyngeal cranial nerve (IX). Afferent information is conveyed to the trigeminal sensory nuclei within the medulla. The salivatory nuclei are also located in the medulla and receive central information from areas of the brain such as the hypothalamus as well as the incoming sensory information. The superior salivatory nucleus contains the preganglionic autonomic motor neurons of the facial nerve, which sends secretomotor input to the submandibular, sublingual and minor salivary glands, whereas the inferior salivatory nucleus contains the preganglionic autonomic motor neurons of the glossophyarngeal nerve, which sends secretomotor input to the parotid glands. Cortex mediated efferent signals are conveyed through the sympathetic and parasympathetic pathways to stimulate the parotid and submandibular and sublingual glands resulting in salivary secretion.

The use of tooth brushing as a mechanical form of whole salivary flow stimulation has been examined previously in healthy young adults (Hoek, Brand, Veerman, & Amerongen, 2002; Ligtenberg et al., 2006) and in older adults with clinically significant hyposalivation (Papas et al., 2006). Hoek and colleagues (2002) examined 14 healthy adults (Mean age = 32 years, SD = 11 years) to determine whether the volume and/or composition of saliva were altered by the mechanical stimulation associated with manual tooth brushing. A transient increase in salivary flow rate in the initial 5 minutes immediately following the mechanical stimulation was identified. Ligtenberg et al. (2006) examined the effects of tooth brushing among 80 healthy student volunteers who brushed their teeth with a manual toothbrush and water or dentifrice. Salivary flow rates increased significantly following tooth brushing with water and after brushing with toothpaste, and remained increased for 60 minutes post stimulation. In older adults with clinically significant hyposalivation, Papas et al. (2006) examined electric and manual tooth brushing as a technique for salivary stimulation in a longitudinal study design and reported that an electric toothbrush tended to stimulate greater salivary flow rates up to 45 minutes post stimulation.

Salivary flow rate has been reported to be decreased in healthy older adults compared to younger adults (Affoo et al., 2015). Disease and medication use are also associated with reduced salivary flow (Fox et al., 2000; Sreebny & Schwartz, 1997). Given the

detrimental effects of decreased salivary flow on oral and overall health, it would be beneficial to examine a non-invasive, low-cost, and non-pharmacologic method of stimulating salivary flow. As discussed above, mechanical stimulation is an effective way to stimulate salivary secretion. Tooth brushing has the capacity to produce pressure, stretch, and vibratory mechanical stimulation on the tongue, periodontal ligament (through pressure on the teeth), gingiva, and palate. Tooth brushing is an inexpensive and simple technique that stimulates the oral cavity and cleanses it at the same time. At this time however, the literature examining tooth brushing as a form of saliva stimulation is limited and the results are conflicting with regard to the duration of the increased salivary flow rate post stimulation. A clearer understanding of the effects of tooth brushing on salivary flow would inform consideration of the feasibility of this form of stimulation as an oral health intervention. In addition, differing study designs have been used previously, and no study has examined the salivary responses to tooth brushing in older adults without clinically significant hyposalivation.

Therefore, the present study aimed to: (i) examine whether manual and electric tooth, tongue, and palate brushing modulates whole salivary flow rates in older adults free of major systemic disease; (ii) ascertain the duration of the tooth/tongue/palate-brushing-related modulation in salivary flow rates; (iii) compare the salivary flow rate modulation associated with manual and electric tooth brushing; and (iv) examine the perceived acceptability and comfort of tooth brushing in older adults. We hypothesized that tooth, tongue, and palate brushing would result in a salivary flow rate increase. The duration of this increase was anticipated to last between 5 to 30 minutes post tooth brushing, based on the studies completed by Hoek et al. (2002), Ligtenberg et al. (2006), and Papas et al. (2006). We hypothesized that the modulation of salivary flow rates would be greater for the electric toothbrush intervention compared to the manual toothbrush intervention due to increased vibration and associated greater afferent stimulation. Additionally, we hypothesized that the maximum salivary flow rate increase in response to stimulation would decrease with increasing age.

4.2 Methodology

4.2.1 Participants

Twenty-one non-smoking adults who were free of major systemic disease volunteered as subjects. Volunteers were recruited through advertisements at a walking group for retired seniors. Candidates were excluded if they had less than 20 natural teeth, complained of xerostomia or dry mouth, or had been to the dentist in the seven days immediately prior to the experimental session. A sample size power calculation indicated that a sample of 20 subjects was sufficient to detect a difference of one standard deviation (d = 1.0), or a large effect, of a two-level, within-subjects independent variable 80.8% of the time, using a 0.01 alpha level and assuming a within-subject correlation of 0.30.

The effects of two tooth brushing interventions on salivary flow rate were examined in the present study: manual tooth brushing and electric tooth brushing. The order of the two interventions was counterbalanced, with participants randomly assigned to one of two groups. Group one used the manual toothbrush in the first experimental session and the electric toothbrush in the second experimental session. Group two used the electric toothbrush in the first experimental session and the manual toothbrush in the second experimental session. Each subject completed the two sessions a minimum of one day apart and a maximum of three weeks apart.

Relevant subject data relating to age, medical history, and dental history was collected during a brief interview prior to the experimental session (Appendix I). The participants were instructed to eat a typical breakfast and complete their morning oral hygiene routine (including tooth brushing) by 8:00 am and to refrain from eating or drinking prior to the study session. Each session commenced at 9:00 am and lasted approximately 120 minutes. Each subject gave written, informed consent before participating in the study, which was approved by the Western University Research Ethics Board for Health Sciences research involving human subjects (Appendix F).

4.2.2 Materials

Tooth brushing interventions were completed with a Colgate Sensitive Pro-Relief manual toothbrush and a Colgate Sonic Power electric toothbrush.

4.2.3 Protocol

For the duration of the experimental session, the subjects sat in a chair (approximately 45 cm in height) that was stationed in front of a table (approximately 41 cm in height). At the beginning of the experimental session, a brief visual inspection of the oral cavity was completed to ensure there were no gross anatomic abnormalities and to ensure each participant had at least 20 natural teeth. Participants then rinsed their mouths with distilled water and expectorated into a receptacle.

Three transducers were positioned on the subject: belt-mounted movement sensors positioned around the subject's neck (Model 1585, CT2 Pediatric Piezo Respiratory Effort Sensor, Pro-Tech Services, Inc., License No. 69444) and upper abdomen (Model 1582, CT2 Adult Piezo Respiratory Effort Sensor, Pro-Tech Services, Inc., License No. 69444), recorded neck and respiratory movements, respectively. An omnidirectional electret microphone (F-SM Snore Electret Microphone, Pro-Tech Services, Inc., License No. 69446) affixed to the subject's neck with medical tape, monitored the acoustic signal arising from the upper airway through the tissues of the neck. These physiologic signals were recorded continuously throughout the experimental session using an AS40 Comet Series PSG/EEG Portable System (Astro-Med Inc., License No. 65827). A video recording in the lateral plane at a camera-to-subject distance of approximately 120 cm was also made. These video images included the subject's head, facial profile, neck, shoulders, and chest. The video images and physiologic signals enabled the researchers to observe whether participants swallowed during the saliva collection periods. The use of physiologic signals to identify swallowing events is a validated method that has been used previously in the literature (Lowell et al., 2013). The addition of video images to identify swallowing events has also been used previously in the literature (Abe et al., 2014)

Each of the two study sessions was comprised of a habituation period, a control condition, an experimental condition, a washout period, and 11 salivary collection periods (Figure 10). During the 5-minute habituation period, the subjects sat quietly making minimal orofacial movements as video recordings and neck movement, respiratory, and acoustic data were collected.

Subjects provided saliva samples using the previously validated draining method (Navazesh & Christensen, 1982; Navazesh, 1993), as follows. While seated comfortably in a chair with eyes open and head tilted slightly forward, subjects swallowed to clear their mouths of residual saliva and then allowed their saliva to drain into a pre-weighed autoclaved beaker for 5 minutes while making minimal orofacial movements. After 5 minutes, subjects were instructed to collect any remaining saliva in the mouth and expectorate it into the beaker. Beakers containing saliva were immediately weighed after each saliva-draining period and whole salivary flow rates were calculated in grams per minute. Saliva was assumed to have a constant density of approximately $0.978 kg/m^3$(Lamey & Nolan, 1994). The subjects were instructed not to swallow their saliva during the draining period. Following the study, the video and physiologic signals were reviewed by RHA for evidence of swallow-related respiratory and laryngeal movement patterns and swallowing events to verify that swallowing did not occur during saliva collection. Five-minute saliva-draining collections were collected at baseline following the habituation period, and at 0 to 5 minutes, 10 to 15 minutes, 20 to 25 minutes, and 30 to 35 minutes following the control condition and experimental intervention.

Participants completed the control condition by placing either the manual or electric toothbrush in the oral cavity (without dentifrice, bristles down touching the superior surface of the tongue) and holding it unmoving for 2 minutes. The experimental stimulation condition involved the participant actively brushing his or her teeth, tongue, and palate (without dentifrice) for 2 minutes. Subjects were instructed not to swallow their saliva during the control and experimental tooth brushing conditions. Immediately following both conditions, subjects expectorated their saliva into a pre-weighed beaker. These salivary collections will be referred to as the salivary flow rates collected “during”

the control and experimental conditions. Participants sat quietly for a 5-minute washout period between the control condition and the experimental intervention.

Participants were instructed to use a standardized tooth brushing protocol when completing each 2-minute oral cavity stimulation intervention with either the manual or electric toothbrush. For the manual toothbrush intervention, participants were instructed to use a modified Bass technique (Bass, 1954) and systematically brush the outer, inner, and chewing surfaces of each quadrant of the mouth for 25-seconds each. On the inner and outer surfaces of the molars, subjects were directed to place the toothbrush at the gum margin at a 45-degree angle and use circular brushing motions followed by rolling the toothbrush down and away from the gums. Participants were instructed to use a back-and-forth brushing motion on the inner surfaces of the incisors and on the chewing surfaces of the molars. The final 10 seconds of the intervention was spent gently brushing the tongue and palate. The electric toothbrush intervention was similar to the manual toothbrush intervention except, instead of active brushing, participants were instructed to hold the bristles against the teeth and move from tooth to tooth slowly. The instructions for each of the standardized tooth brushing protocols were presented in an instructional video immediately prior to the experimental intervention.

A paper-and-pencil 10 cm visual analog scale (VAS) assessment of mouth comfort was presented to the participants at six different times during the experimental session (Appendix G and Figure 10). The VAS scale was anchored with the terms “normal comfort level” at 5 cm, “less comfortable” at 0 cm, and “more comfortable” at 10 cm.

At the end of the experimental session, each participant completed a questionnaire focusing on the ease of use of the tooth brushing protocol and the feasibility of implementing the protocol in the participant’s daily oral hygiene routine (Appendix H).

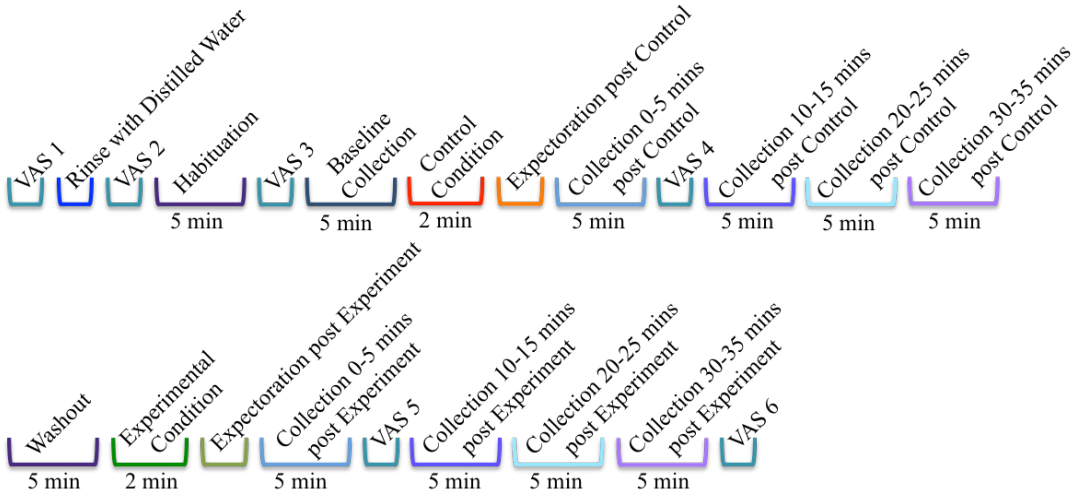

Figure 10: Experimental Protocol

4.2.4 Data Analysis

Relevant subject data relating to age, medical history, and dental history was analyzed by RHA.

All beakers were weighed immediately prior to the experiment and immediately following each saliva-draining period. Whole salivary flow rate at 0 to 5 minutes, 10 to 15 minutes, 20 to 25 minutes, and 30 to 35 minutes following the control condition and experimental intervention were calculated by dividing the weight of the saliva in grams by the 5-minute timeframe. Whole salivary flow rate during the control and experimental conditions were calculated by finding the weight in grams of the amount expectorated immediately following either the control, or experimental, condition and dividing that weight by the 2-minute timeframe.

A research assistant (RA) scored each of the VAS forms by measuring the length in centimeters between the far left of the VAS (0 cm) and the point where the participant had placed the mark indicating current mouth comfort. The length in centimeters represented the VAS score, with higher scores representing greater mouth comfort. VAS scores were analyzed by RHA.

Subject questionnaires were analyzed by RHA.

4.2.5 Statistical Analysis

Whole salivary flow rates were calculated for each collection period in g/min. Planned contrasts were completed using paired samples t-tests and a Holm-Bonferroni sequential procedure to correct for familywise error (p_{corr}<0.0045) (Holm, 1979). The comparisons of interest included: i) baseline rates compared to the flow rates during the control and experimental conditions; ii) baseline rates compared to the flow rates from 0 to 5 minutes, 10 to 15 minutes, 20 to 25 minutes, and 30 to 35 minutes after the experimental condition; and iii) flow rates during the control condition compared to the flow rates during the experimental condition, and from 0 to 5 minutes, 10 to 15 minutes, 20 to 25 minutes, and 30 to 35 minutes after the experimental condition, for both the manual and electric toothbrush experimental protocols. The effects of the control and treatment conditions on salivary flow rate were estimated using Cohen's d.

Potential differences between the effects of the manual and the electric toothbrush were examined through descriptive comparisons of the effect sizes (Cohen's d) calculated for the manual and electric toothbrush stimulation. Additionally, the maximum salivary flow rate change (i.e., the difference between salivary flow rate during tooth brushing and baseline flow rate) associated with the two types of tooth brushing were compared using a paired samples t-test ($p < 0.05$). A potential relationship between the maximum salivary flow rate change associated with the manual and electric tooth brushing interventions was also examined using a Pearson's correlation coefficient ($p < 0.05$).

The influence of age on the maximum salivary flow rate change was examined using Pearson's correlation coefficient ($p < 0.05$). Medication use was explored using descriptive statistics, as well as a chi-square test ($p < 0.05$) to determine whether equal numbers of participants were taking no, one, two, or three or more medications.

The effects of the control and experimental conditions on mouth comfort, measured using the VAS, were examined using a repeated measures ANOVA. The results of the feasibility questionnaire were examined for trends and are reported descriptively.

Statistical analyses were completed using SPSS (SPSS 2012) and Microsoft Excel.

4.3 Results

4.3.1 Subject Characteristics

Twenty-one subjects participated in the study (62–83 years of age, M = 71.33 years, SD = 6.46 years; 11 female). All participants had at least 20 natural teeth (Range = 22–28, M = 25.67, SD = 1.93). No participants were observed to swallow during the salivary collection periods. Using Sreebny and Vissink's "Classification of Xerogenic Drugs" (Sreebny & Vissink, 2010), 7 of the 21 subjects reported taking no medications with potential xerogenic effects and 14 of the 21 subjects were observed to be taking xerogenic medications (Range of xerogenic medications= 0–4, M = 1.25, SD = 1.11) (Figure 11). The results of a chi square test ($\chi^2 = 3.19$, $p = 0.36$) indicated that the numbers of participants in each category (no, one, two, or three or more xerogenic medications) were not significantly different. Xerogenic medications taken by the study participants included antihyperlipidemic agents, anti-ulcer agents, antihypertensive agents, and anti-inflammatory agents.

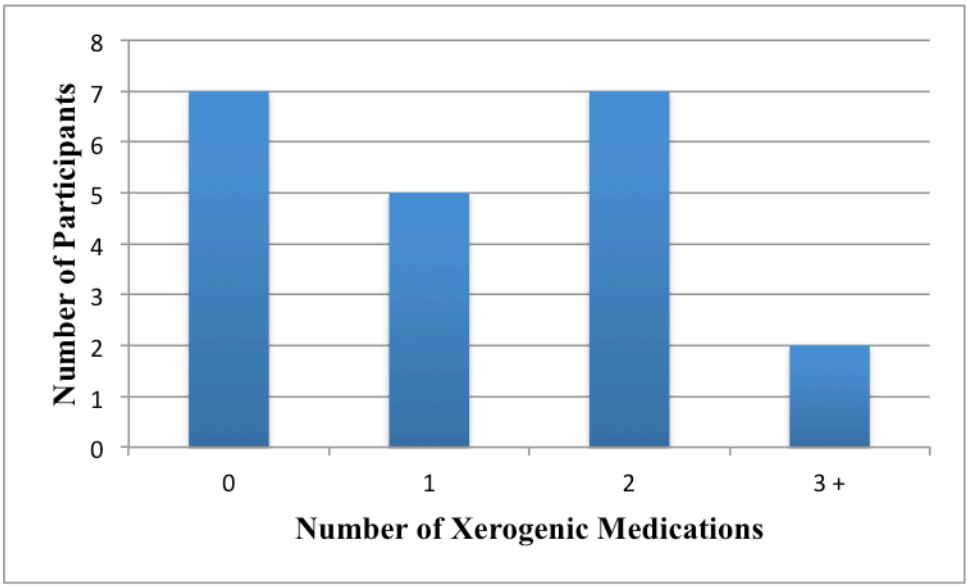

Figure 11: The Numbers of Study Participants Taking Different Numbers of Xerogenic Medications at the Time of the Study

The mean ages of participants taking no, one, two, or three or more xerogenic medications were similar (Figure 12).

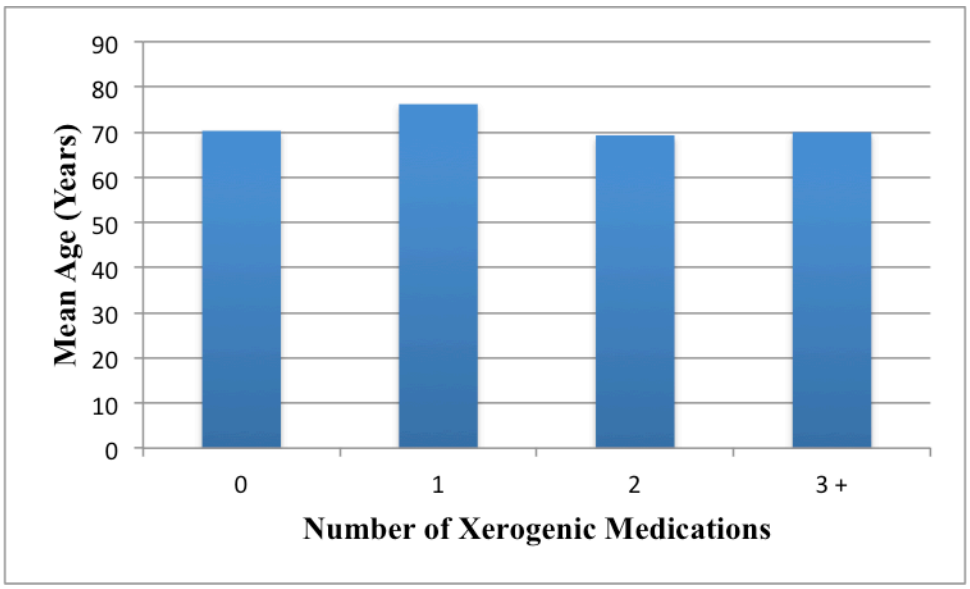

Figure 12: The Mean Age (in years) of Study Participants Taking Different Numbers of Xerogenic Medications at the Time of the Study

4.3.2 Effects of Manual and Electric Tooth Brushing on Whole Salivary Flow Rate

The mean whole salivary flow rates for each collection period are presented for the experiment using the manual toothbrush (Figure 13) and using the electric toothbrush (Figure 14).

Planned contrasts were completed using paired samples t-tests. The Holm-Bonferroni sequential procedure was used to correct for familywise error ($p_{corr} < 0.0045$) (Table 6). Of the 22 completed planned comparisons, the data associated with four comparisons were not normally distributed as assessed by the Shapiro-Wilk's test ($p < 0.05$); these were the comparison between baseline rates and the flow rates during the manual toothbrush control condition; between baseline rates and the flow rates from 0 to 5 minutes and 10 to 15 minutes after the manual toothbrush experimental condition; and between the flow rates during the electric toothbrush control condition and the flow rates from 30 to 35 minutes after the electric toothbrush experimental condition. Nevertheless, a paired samples t-test was used, as this test is robust to violations of normality (Herrendorfer, Rasch, & K.D., 1983; Posten, 1979; Rasch & Guiard, 2004).

4.3.2.1 Effects of Manual Tooth Brushing on Whole Salivary Flow Rate

There was a significant, large increase (d = 2.50) in salivary flow rates collected during the 2 minutes of manual tooth brushing compared with baseline salivary flow rate (M = 0.63, SD = 0.34, $p < 0.0045$) and compared with the salivary flow rate collected during the control condition (M = 0.58, SD = 0.33, $p < 0.005$). Although the salivary flow rate was observed to decrease immediately following the manual tooth brushing, the salivary flow rate collected from zero to five minutes post manual tooth brushing was found to be significantly, moderately increased (d = 0.661) compared with baseline salivary flow rate (M = 0.07, SD = 0.07, $p < 0.0055$).

Salivary flow rates collected during the periods 10 to 15 minutes, 20 to 25 minutes, and 30 to 35 minutes after manual tooth brushing were not significantly different from baseline flow rates. Similarly, salivary flow rates collected during the periods 0 to 5 minutes, 10 to 15 minutes, 20 to 25 minutes, and 30 to 35 minutes after manual tooth brushing were not significantly different compared with salivary flow rates collected during the manual tooth brushing control condition.

4.3.2.2 Effects of Electric Tooth Brushing on Whole Salivary Flow Rate

There was a significant, moderate increase (d = 0.672) in salivary flow rate during the 2-minute control condition compared with baseline salivary flow rate during the electric toothbrush protocol (M = 0.07, SD = 0.08, $p < 0.006$). There was a significant, large increase (d = 2.54) in salivary flow rates collected during the 2 minutes of electric tooth brushing compared with baseline salivary flow rate (M = 0.78,SD = 0.37, $p < 0.0045$) and compared with the salivary flow rate collected during the control condition (M = 0.71,SD = 0.35, $p < 0.005$). Although the salivary flow rate was observed to decrease immediately following electric tooth brushing, the salivary flow rate collected from 0 to 5 minutes post electric tooth brushing was found to be significantly, moderately increased (d = 0.681) compared with baseline salivary flow rate (M = 0.08, SD = 0.08, $p < 0.0055$).

Salivary flow rates collected during the periods 10 to 15 minutes, 20 to 25 minutes, and 30 to 35 minutes after electric tooth brushing were not significantly different from baseline flow rates. Similarly, salivary flow rates collected during the periods 0 to 5 minutes, 10 to 15 minutes, 20 to 25 minutes, and 30 to 35 minutes after electric tooth brushing were not significantly different compared with salivary flow rates collected during the electric tooth brushing control condition.

Table 6: Significant Salivary Flow Rate Comparisons and the Holm-Adjusted *p* Values

Comparison	Mean Difference	Holm-Adjusted *p*
Manual Toothbrush		
Baseline – During Brushing	0.63	0.0045
During Control – During Brushing	0.58	0.0050
Baseline – 0 to 5 Minutes Post Brushing	0.07	0.0055
Electric Toothbrush		
Baseline – During Brushing	0.78	0.0045
During Control – During Brushing	0.71	0.0050
Baseline – 0 to 5 Minutes Post Brushing	0.08	0.0055
Baseline – During Control	0.07	0.0060

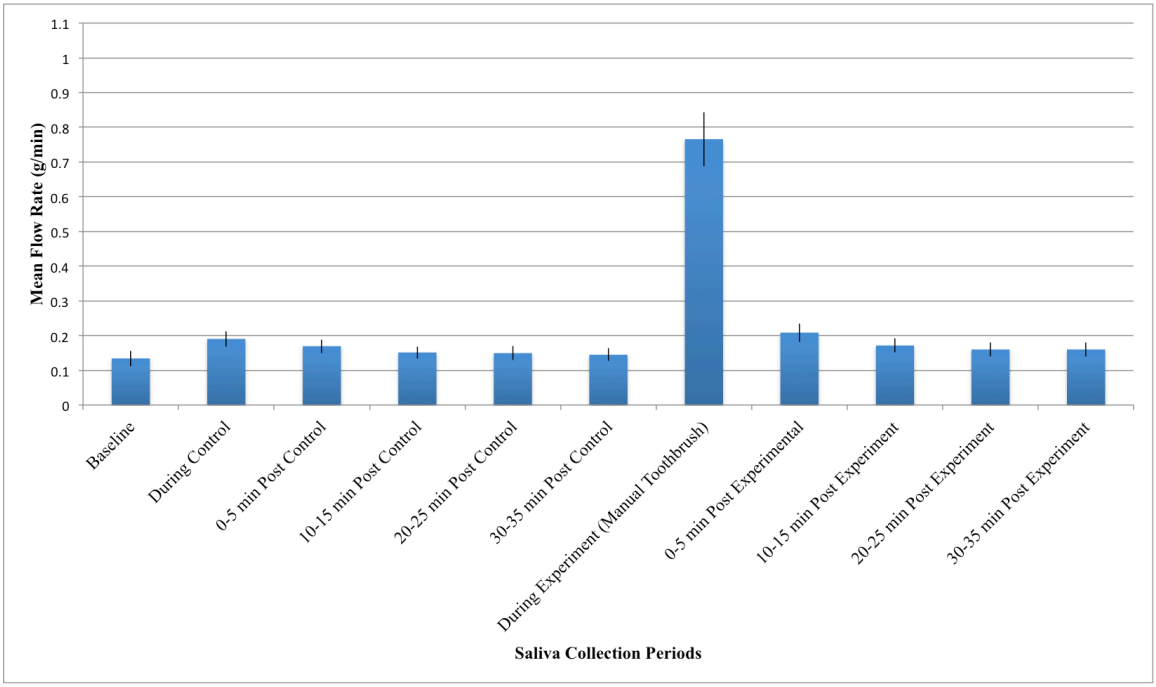

Figure 13: Mean Whole Salivary Flow Rate Collected at 11 Different Time Points Before, During, and Following Control and Manual Tooth Brushing Conditions

Mean flow rate (g/min) is represented by the bars and the error bars indicate SE.

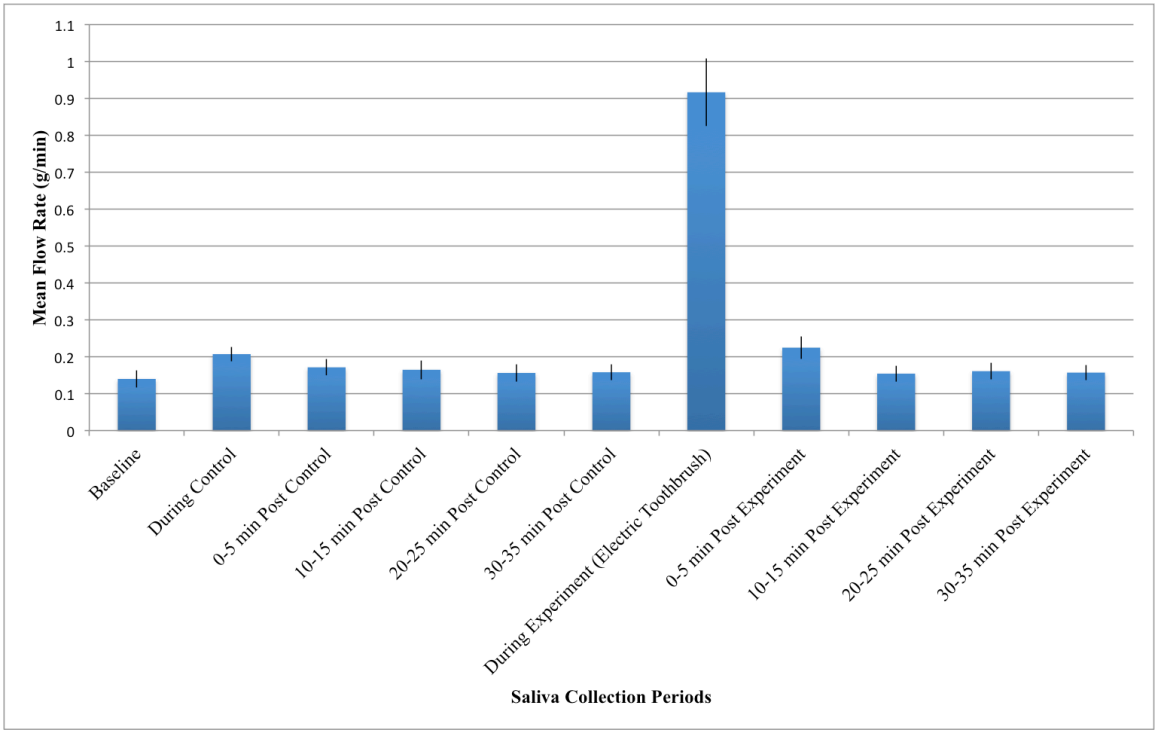

Figure 14: Mean Whole Salivary Flow Rate Collected at 11 Different Time Points Before, During, and Following Control and Electric Tooth Brushing Conditions

Mean flow rate (g/min) is represented by the bars and the error bars indicate SE.

4.3.3 Manual Compared to Electric Tooth Brushing

The salivary flow rates collected during the manual and electric tooth brushing protocols were compared using descriptive comparisons of their respective effect sizes (manual: d = 2.40; electric: d = 2.54). This analysis indicated that the effect sizes were similar. The maximum salivary flow rate change (i.e., difference between salivary flow rate during tooth brushing and baseline flow rate) associated with the two types of tooth brushing were also not significantly different (M = 0.15, SD = 0.42, $p = 0.129$). There was a small correlation between the maximum salivary rate changes associated with the manual and electric tooth brushing protocols (r (19) = 0.30, $p = 0.184$).

4.3.4 Age and Salivary Flow Rate

The influence of age on baseline salivary flow rate was examined. Baseline salivary flow rate data for the manual toothbrush protocol were not normally distributed, as assessed by

Shapiro-Wilk's test ($p = 0.001$), however baseline data for the electric toothbrush protocol were normally distributed ($p > 0.05$). Therefore, a Spearman rank-order correlation was completed with the manual toothbrush data and a Pearson's correlation coefficient was completed with the electric toothbrush data. Age was not significantly correlated with baseline salivary flow rate for the manual $r_s\,(19) = 0.05$, $p = 0.84$ or electric toothbrush protocols $r\,(19) = 0.1$, $p = 0.68$.

The influence of age on maximum salivary flow rate change (i.e., the difference between salivary flow rate during tooth brushing and baseline flow rate) was examined using a Pearson's correlation coefficient. Age and the maximum salivary flow rate change associated with manual tooth brushing was normally distributed, as assessed by Shapiro-Wilk's test ($p > 0.05$). Age was moderately correlated with the maximum salivary flow rate change ($r\,(19) = 0.55$, $p = 0.01$) for the manual toothbrush condition (Figure 15).

The influence of age on maximum salivary flow rate change associated with electric tooth brushing was also normally distributed, as assessed by Shapiro-Wilk's test ($p > 0.05$). A small, non-significant correlation was observed ($r\,(19) = 0.18$, $p = 0.44$) for the electric toothbrush condition (Figure 16).

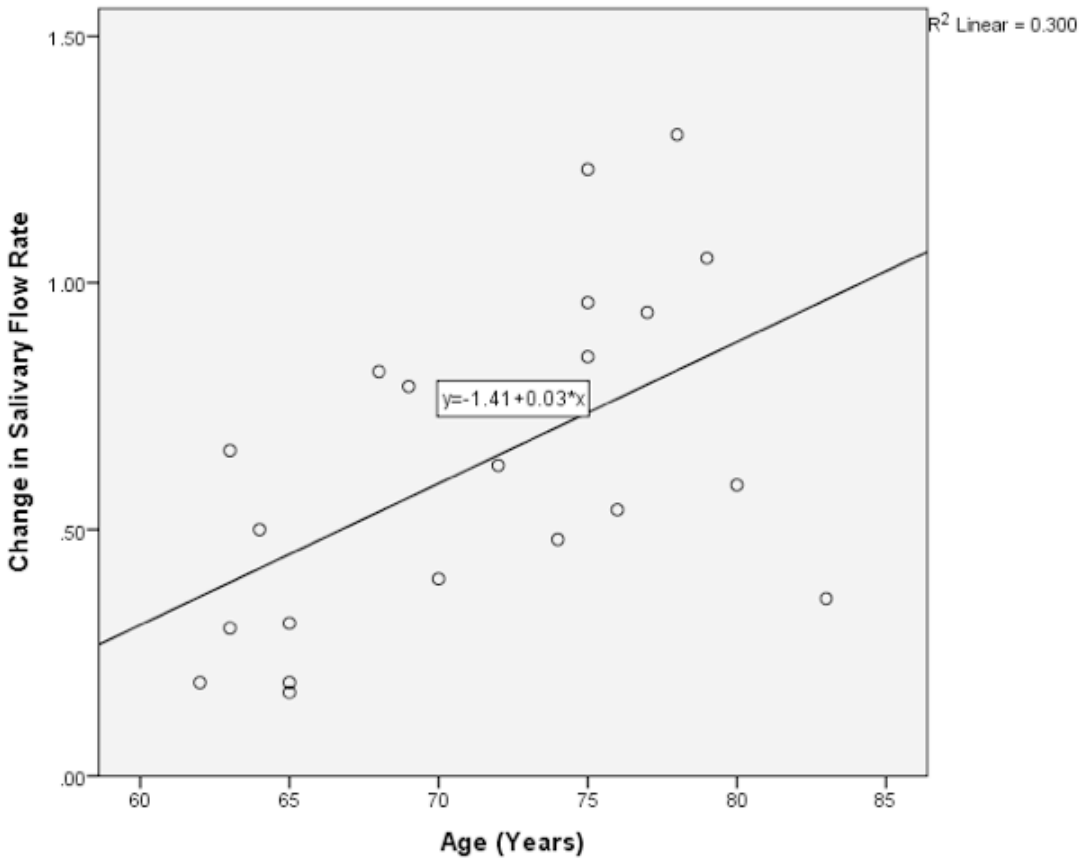

Figure 15: Scatterplot Illustrating the Correlation Between Age (in years) and the Maximum Salivary Change Associated with Manual Tooth Brushing

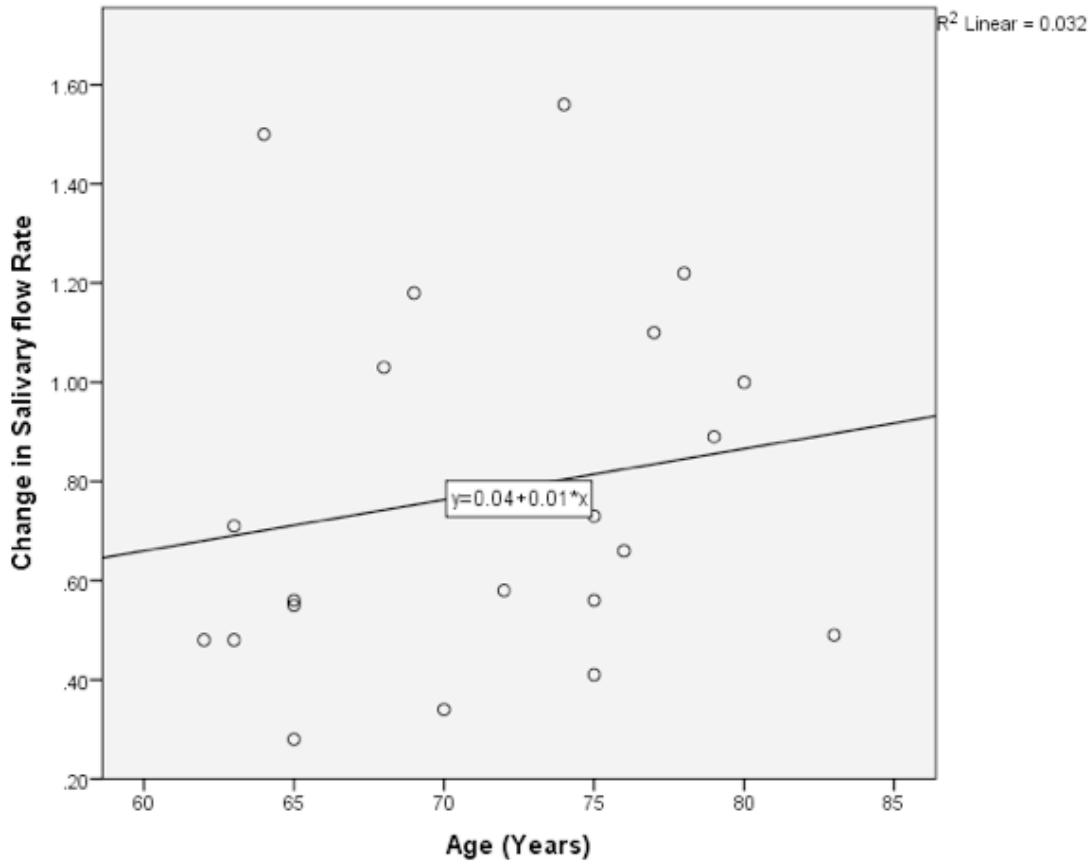

Figure 16: Scatterplot Illustrating the Correlation Between Age (in years) and the Maximum Salivary Change Associated with Electric Tooth Brushing

4.3.5 Mouth Comfort and Feasibility

Mouth comfort data, as measured by the VAS, were not normally distributed, as assessed by Shapiro-Wilk's test ($p < 0.05$). Outliers were observed, as assessed by inspection of a boxplot. In addition, Mauchly's Test of Sphericity indicated that the data violated the assumption of sphericity (manual: χ^2 (2) = 53.81, $p < 0.001$; electric: χ^2 (2) = 129.46, $p < 0.001$). Despite the fact that the data violated these assumptions, a one-way repeated measures ANOVA was used to examine mouth comfort scores throughout the manual and electric toothbrush experiments due its robustness to violations of normality (Glass, Peckham, & Sanders, 1972). No significant differences in mouth comfort were detected for either the manual or electric toothbrush experiments.

The responses to the feasibility questionnaires suggested that 95% of the participants reported that the instructions for both the manual and electric tooth brushing methods were easy to understand and the methods themselves were easy to complete. Ninety percent of the participants reported being amenable to incorporating the standardized tooth brushing method, with either the manual or electric toothbrush, into their daily oral hygiene routine. Ten percent of the respondents reported being resistant to change their oral hygiene routine at this point in their lives.

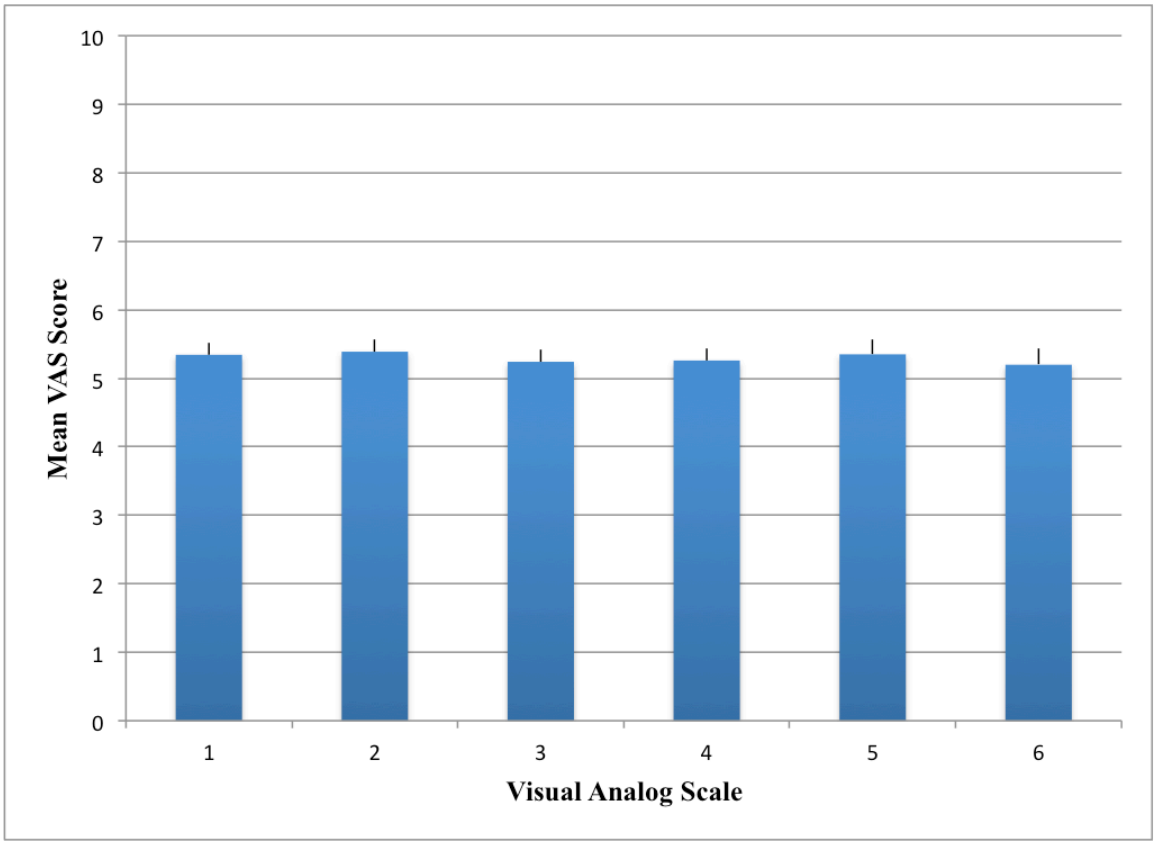

Figure 17: VAS Scores Recorded at 6 Different Time Points During the Manual Toothbrush Experiment

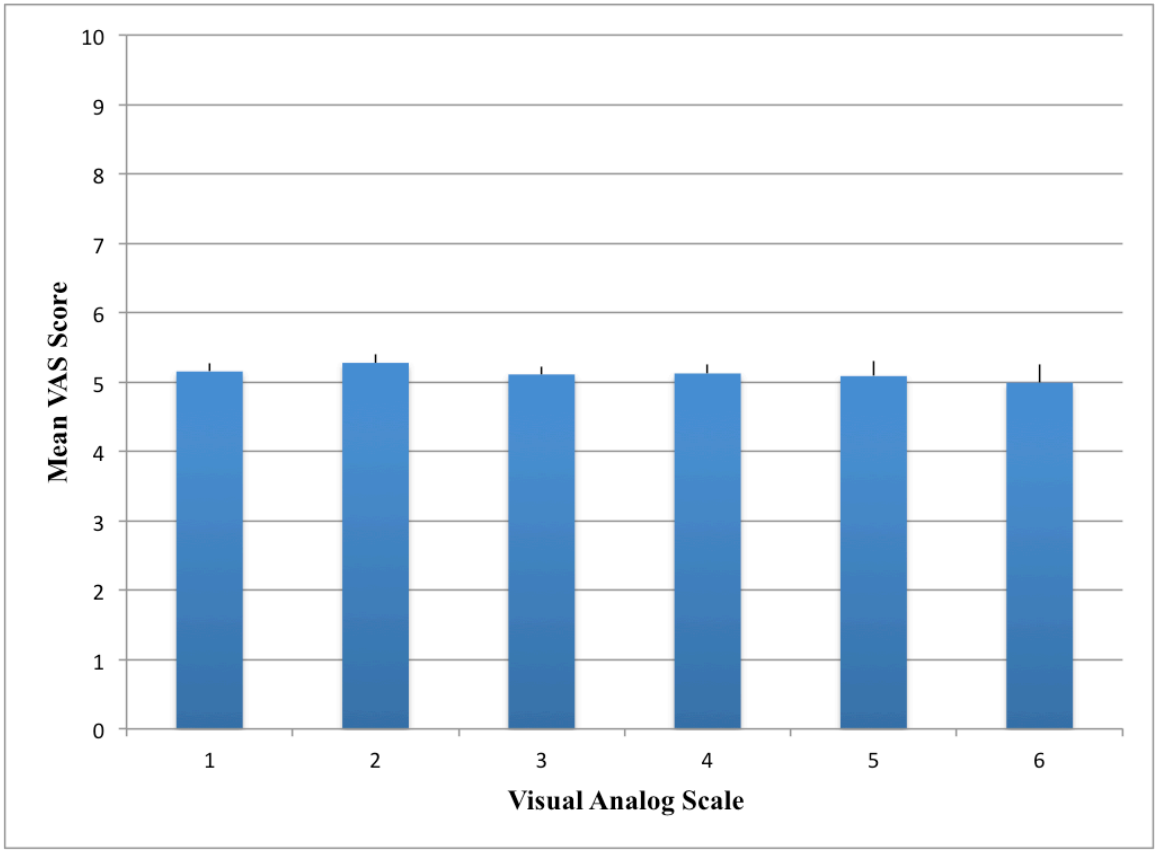

Figure 18: VAS Scores Recorded at 6 Different Time Points During the Electric Toothbrush Experiment

4.4 Discussion

The results of the current study suggest that oral cavity stimulation with a manual or electric toothbrush temporarily increases whole salivary flow rates in older adults. Specifically, we found that whole salivary flow rates were increased significantly for up to 5 minutes following either manual, or electric brushing of the teeth, tongue, and palate in healthy adults aged 60 years and older. The increase in salivary flow rate immediately following the 2-minute brushing period was large, whereas the increase in salivary flow rate 5 minutes following brushing was moderate. The present study also found that holding a de-activated electric toothbrush in a stationary position in the oral cavity resulted in an immediate, transient increase in whole salivary flow rate.

These results are similar to those of Hoek et al. (2002), who reported that brushing the teeth without dentifrice induced an increase in the saliva flow rate during the initial 5 minutes after tooth brushing, which was following by a decrease after 15 minutes. Our results are not consistent with those of Ligtenberg et al. (2006), however, who reported that, after brushing with water, the salivary secretion rate increased significantly for 60 minutes. Secretion rates were also significantly increased after brushing with toothpaste. This inconsistency may be because the stimulation protocol used by Ligtenberg and colleagues (2006) required subjects brush their teeth with water or dentifrice, either of which could have caused gustatory or temperature stimulation in addition to the mechanical stimulation associated with tooth brushing. This additional stimulation could have influenced the duration of increased salivary flow rates post stimulation.

In the present study, the greatest increase in salivary flow rate was observed immediately following manual or electric tooth brushing. We observed a mean salivary increase of 0.63 g/min (SD = 0.34 g/min) immediately following manual tooth brushing and a mean increase of 0.78 g/min (SD = 0.37 g/min) immediately following electric tooth brushing.

Previous studies have documented that increased oral cavity stimulation is associated with increased salivary secretion. Salivary secretion increases with the hardness and the size of an object being chewed, as well as with the forces generated by the chewing muscles (Anderson & Hector, 1987; Hector & Linden, 1987; Rosenhek et al., 1993; Yeh et al., 2000). Additionally, Papas et al., (2006) reported that Sonicare electric toothbrush users tended to have increased salivary flow rates at each 15-minute interval collection period up to 45 minutes post stimulation compared with manual toothbrush users. In contrast, Hiraba et al. (2008) found that increasing the frequency of vibratory stimuli applied to the facial skin overlying the belly of the masseter muscles bilaterally did not result in greater salivation possibly because individual mechanoreceptors differ in their threshold sensitivity to vibration.

We hypothesized that the modulation of whole salivary flow rates would be greater for electric tooth brushing compared with manual tooth brushing due to increased vibration and associated greater afferent stimulation. We found no significant differences,

however, between the two tooth brushing protocols with regard to increasing whole salivary flow rate. Although it is possible that other brands of electric toothbrushes might result in greater salivary stimulation compared with manual tooth brushing, our findings appear to suggest that the increased vibration associated with electric toothbrushes compared with manual toothbrushes may not result in a greater salivary response.

In our post hoc analysis, we examined a potential relationship between age and the maximum salivary flow rate change (i.e., the maximum difference between salivary flow rate during baseline and tooth brushing conditions). We hypothesized that, given that older adults have lower unstimulated whole salivary flow rates and lower stimulated and unstimulated SMSL salivary flow rates (Affoo et al., 2015) compared with younger adults, we would observe that, as age increased, maximum salivary flow rate change would decrease. This, however, was not the case. A moderate, positive correlation was observed between age and maximum salivary flow rate change. That is, as age increased, so too did the maximum salivary flow rate increase observed during tooth brushing. The positive relationship between age and maximum salivary flow rate change was found to be moderate for manual tooth brushing but small for electric tooth brushing. In order to explain this phenomenon, we hypothesized that the older participants experienced reduced baseline salivary flow rates compared with the younger participants. A lower baseline salivary flow rate might increase the potential for response to stimulation, resulting in a stimulated salivary flow rate similar to the younger participants. However, when the relationship between age and baseline salivary flow rates was examined, no significant correlations were identified. It appears, therefore, that the oldest adults in our sample demonstrated a more robust salivary response to tooth brushing than did the younger subjects. While reports confirm that parotid and minor salivary flow rates do not decline with increasing age (Affoo et al., 2015) and aspects of somatosensation, such as two-point discrimination, also do not decline with advancing age, (Calhoun, Gibson, Hartley, Minton, & Hokanson, 1992; Fukunaga, Uematsu, & Sugimoto, 2005) this does not explain why we observed a positive relationship between age and maximum salivary flow rate change. Older subjects were not observed to have more teeth than younger subjects (data not shown), younger subjects were not observed to be taking more xerogenic medications than older subjects, and males and females were found to be

equally distributed with regards to age (data not shown). It is currently unclear why we observed a positive relationship between age and maximum salivary flow rate change.

With regards to the finding that the degree of correlation between age and maximum salivary flow increase was different for the manual and electric toothbrushes, this is a provocative finding given that comparison of the salivary flow rate increases associated with the two types of brushing revealed no statistically significant differences. When the relationship between maximum salivary flow rate changes associated with manual and electric tooth brushing was explored, a small correlation was identified. These findings suggest, that while there appears to be similarity between the two types of brushing, there are also differences between the two types of brushing resulting in differences in the physiological salivary response.

Mouth comfort remained relatively consistent throughout the experimental protocols using the electric and manual toothbrushes. These results are consistent with those of Papas et al. (2006) who reported that 96.4% of participants felt that the Sonicare electric toothbrush was comfortable to use. Ninety percent of the participants in the present study were amenable to incorporating a standardized brushing protocol, with either a manual or electric toothbrush, into their daily oral hygiene routine suggesting that participants found this method of stimulation to be acceptable for daily use.

4.4.1 Strengths and Limitations

Epithelial cells are continually being shed from the oral mucosa into saliva and it has been estimated that the surface cells stay attached for only about three hours before being desquamated (Dawes, 2003). Participants in our study reported completing their early morning oral hygiene routine at least one hour prior to the experiment and all participants rinsed their oral cavities with distilled water immediately prior to participating. The elements of the present experimental protocol reduce the likelihood of epithelial cells making a significant contribution to the salivary collection and adding to the weight of the saliva samples. Nevertheless, it is possible that epithelial cells as well as plaque and residual food debris in the mouth, displaced by tooth brushing, may have contributed to the weight of the saliva samples.

One limitation of this study is that we did not complete a comprehensive dental exam on participants prior to study enrollment. We do not therefore have detailed information regarding the periodontal status of our participants.

Participants were mainly recruited from an exercise program, introducing a potential bias in that the participants may have been more health-conscious than the general population.

The electric toothbrush used in the experiment had a brush shaped similarly to the manual toothbrush and was not circular in shape. A circular brush is a popular shape among name brand electric toothbrushes. Therefore, we may not have employed a representative electric toothbrush.

Glandular saliva was not collected in the present study. Thus, it is unclear which glands contributed more saliva to the increased flow rates in response to the tooth brushing. Based on previous work in this area, however, showing that the percentage contribution from the parotid gland increases to more than 50% of total salivary secretions during stimulation (Edgar, 1992; Humphrey & Williamson, 2001; Sreebny, 2000), we would predict that that the parotid glands contributed the greatest percentage of saliva to the increased flow rates observed.

We observed limited response variability on the VAS scale measuring mouth comfort. Additionally, 40% of participants commented that they felt completing the VAS scale was the most difficult component of the experiment, possibly due to the complex and abstract nature of conceptualizing mouth comfort in individuals who do not experience oral discomfort on a regular basis. It is possible that the design of the VAS scale may have limited the response variability and in the future we may need to pilot VAS scales using different anchor terminology.

4.4.2 Clinical implications:

In the present study, we showed that tooth brushing is associated with an increase in salivary flow for up to 5 min post stimulation among adults aged 60 years and older who have at least 20 teeth and who do not complain of dry mouth or xerostomia. Although we

identified only a transient increase in salivary flow rates, this increase would be expected to contribute to reducing the bacterial load in the mouth and increasing oral lubrication.

Saliva is present throughout the oral cavity as a very thin film known as a biofilm. According to Collins et al. (1987), given an average volume of saliva in the mouth of about 1 ml, and given that the surface area of the adult mouth is just over 200 cm^2, saliva must be present as a film averaging about 0.1 mm or less in thickness between adjacent surfaces (Collins & Dawes, 1987). We observed a mean increase in whole salivary flow rates of 0.63 g/min (SD = 0.34 g/min) during manual tooth brushing and a mean increase of 0.78 g/min (SD = 0.37 g/min) during electric tooth brushing. These volumes could contribute substantially to the oral biofilm in the mouth, promoting optimal oral homeostasis, and potentially increasing oral comfort.

Increasing salivary volume also may affect salivary clearance in that the volume of oral saliva contributes to triggering of the pharyngeal stage of swallowing (Dawes, 1983) in addition to increasing the rate of swallowing (Lagerlof & Dawes, 1984). Swallowing of secreted saliva reduces the concentration of exogenous substances in the oral cavity. A rapid salivary clearance of harmful substances is beneficial for oral health (Dawes, 2004). An increase in salivary volume, stimulating increased salivary clearance in an individual with harmful substances (such as cariogenic substances) in the oral cavity, could have beneficial effects on oral and overall health.

We observed a moderate, positive correlation between age and maximum salivary flow rate increase, suggesting that the older adults in our sample tended to have greater salivary responses to stimulation. This finding suggests that older adults aged approximately 75 years and older could potentially benefit from tooth brushing more than their younger counterparts. This finding could have important implications for future studies examining saliva stimulation interventions.

4.4.3 Future Directions

In order to continue to broaden our understanding of oral physiology for eating and swallowing management and rehabilitation, future work in this field should focus on the

use of oral stimulation as a means of modulating salivary flow in a large sample of older adults. Examining the effects of increased saliva in the oral cavity on outcomes such as swallowing efficiency and safety would provide important clinical information. A study powered to compare salivary responses in age stratifications from 60 years of age to 90 years and older would be helpful to replicate the results presented here with regard to the moderate, positive correlation observed between age and maximum salivary flow rate change. This study would also be beneficial for determining whether the effect continues into the older age groups (84 years of age and older) that were not examined in the present study.

Future research should investigate the relative salivary contributions from each major salivary gland during tooth brushing. Additionally, examining other brands of electric toothbrushes to explore whether different brands result in different salivary stimulation profiles would provide practical information in terms of clinical translation.

Further research exploring the physiology of saliva secretion and the nerve-mediated reflex pathway in response to manual and electrical tooth-brushing stimulation would be beneficial as our results suggest the potential for some stimulatory differences between the two different types of tooth brushing.

4.5 Conclusion

The present study suggests that tooth brushing stimulates saliva production for up to 5 minutes in adults aged 60 years and older who are free of systemic disease. Older participants had a more robust salivary response to the tooth brushing compared with younger participants, suggesting that older adults may particularly benefit from tooth brushing to stimulate salivary secretion. Given that aging is associated with reduced salivary flow (Affoo et al., 2015) and reduced salivary flow may lead to impaired oral health (Baum, 1989), older adults are at greater risk of developing poor oral health. The ability to increase salivary secretions has important clinical implications with regard to improving the oral health of older adults.

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Chapter 5

5 Conclusion

In this dissertation, we used a scoping review technique to examine swallowing dysfunction and autonomic system dysfunction, including salivary flow dysfunction, in individuals with AD. We found that no studies have directly examined the effect of reduced salivary flow on swallowing function in AD despite the fact that salivary flow is crucial for optimal oral preparatory and oral phase swallowing (Matsuo, 2013) and may be reduced as part of the disease process (Ship et al., 1990; Ship & Puckett, 1994).

Salivary flow may be reduced in people with AD (Ship et al., 1990; Ship & Puckett, 1994). Previous research on the effect of aging on saliva production, however, is conflicting. As a result, we performed the second study of this dissertation to examine the effect of aging on saliva production, and we found that whole and SMSL salivary flow rates were reduced in older adults compared with younger adults.

In the third and final study in this dissertation, in order to examine the potential for modulating salivary flow rates in older adults, we examined the effects of manual and electric tooth brushing on whole salivary flow rates in adults 60 years of age and older who were free of major systemic disease. We found that tooth brushing is associated with increased salivary flow rates for up to 5 minutes. The older participants had a more robust salivary response to the mechanical stimulation compared with the younger participants.

Eating, swallowing, and maintaining optimal nutrition is essential to health (Waxman & World Health Assembly, 2004) and quality of life (Vailas et al., 1998). There appears to be a critical relationship between factors associated with eating and swallowing function, oral health, and saliva production. The studies reported in this dissertation were aimed at broadening the current understanding of these inter-related factors, both in healthy individuals and in individuals with AD. The results provide foundational information about eating and swallowing, saliva production, and saliva modulation and may incite future research, in many different patient populations, examining each of these individual elements and the critical relationship between them.

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Appendices

Appendix A: Clinical Reports Employing Instrumental Assessment of Swallowing in Alzheimer's Disease (AD)

Conclusion	Supporting Studies	Study Description	Type of Dementia	Method of Assessment	Results	Level of Evid-ence
Prevalence of dysphagia in AD	Horner et al. 1994	Prospective Case Series	Alzheimer's Disease (Moderate and Severe)	Video-fluoroscopy	Investigators examined the frequency of swallowing abnormalities and the incidence of aspiration in a group of 25 AD subjects with moderate or severe AD Swallowing impairment, characterized by impaired oral preparatory stage and delayed pharyngeal	4

					swallow, was observed in 21 of 25 (84%) individuals with moderate or severe AD Aspiration was observed in 6 of the 25 individuals (28.6%) Abnormal position of the bolus head at pharyngeal swallow initiation was also observed	
	Feinberg et al. 1992	Retro-spective Cohort	Alzheimer's Disease (Moderate and Severe), Multi-Infarct Dementia, and Parkinson's Disease Dementia	Video-fluoroscopy	Oral and pharyngeal function was examined in 131 individuals with advanced dementia (74 with AD) Swallowing	2b

					impairments were observed in 93% individuals (results not specific to dementia type) Oral-stage dysfunction was observed in 93 of 131 (71%) individuals, pharyngeal dysfunction in 56 of 131 (43%) individuals, and multiple stage dysfunction was observed in 55 of 131 individuals Major aspiration was observed in 31 (24%) individuals and minor	

					aspiration was observed in 66 (50%) individuals	
	Mizushima et al. 2005	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	Alzheimer's Disease and Vascular Dementia (Stage not specified)	Nasal Catheter to Inject Water into the Pharynx and EMG to Record the Swallow	Cough/swallowing reflexes were investigated in 30 patients with dementia (20 with AD) The swallowing water reflex was induced by a bolus injection of water into the pharynx through a nasal catheter and the reflex was evaluated by the volume injected that elicited a response within 4 sec following the injection	NA

					The cough reflex was evaluated following inhalation of capsaicin There were no statistically significant differences in these reflexes between dementia and control groups and between vascular and Alzheimer types	
Dysphagia occurs early in AD	Humbert et al. 2010	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	Alzheimer's Disease (Early and Mild)	Video-fluoroscopy & fMRI	Investigators examined whether functional changes in the cortical control of swallowing are evident in early AD On VFSS	NA

					(prone position), AD subjects demonstrated longer laryngeal vestibule closure, reduced hyo-larnygeal excursion, and decreased laryngeal elevation Significantly lower BOLD response was identified in many cortical areas that are traditionally involved in normal swallowing	
	Priefer & Robbins 1997	Described/characterized dysphagia in AD through comparison	Alzheimer's Disease (Mild)	Video-fluoroscopy	Investigators explored swallowing durations and self-feeding dependency in	NA

		of two or more groups of individuals			normal elderly and early stage AD Individuals with early AD demonstrated impaired oral preparatory stage, delay of the initiation of the pharyngeal swallow, and prolonged overall swallow duration No subjects demonstrated aspiration during VFSS	
	Humbert et al. 2011	See Above	See Above	See Above	See Above	See Above
Dysphagia in early AD may be associated with functional	Humbert et al. 2010	See Above	See Above	See Above	See Above	See Above
	Humbert et al. 2011	Described/characterized dysphagia in AD	Alzheimer's Disease (Mild)	fMRI	Investigators examined the frontal cortical activation in	NA

change of the cortical swallowing network		through comparison of two or more groups of individuals			response to a "Do Not Swallow" task In response to a "Do Not Swallow" instruction, the AD group had a significantly greater BOLD response in the insula/operculum as compared to healthy age-matched controls	
Dysphagia occurs in both the oral and pharyngeal phases of swallowing	Humbert et al. 2010	See Above	See Above	See Above	See Above	4
	Garon et al. 2009	Retro-spective Cohort	Alzheimer's Disease (Stage Not Specified) and General Dementia	Video-fluoroscopy	Of 106 individuals with dementia and complaints of dysphagia, 68% had tracheal aspiration during imaging69% of those who	2b

					had tracheal aspiration demonstrated silent tracheal aspiration	
	Suh et al. 2009	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	Alzheimer's Disease (Moderate) and Vascular Dementia	Video-fluoroscopy	Investigators examined swallowing in two dementia groups using VFSS and observed that individuals with AD demonstrated the following: Prolonged oral transit, delayed initiation of the pharyngeal swallow, laryngeal penetration, and pharyngeal residue post swallow Investigators	NA

					observed that individuals with vascular dementia demonstrated the following: Delayed initiation of the pharyngeal swallow, reduced hyo-laryngeal excursion, and pharyngeal residue post swallow	
	Wada et al. 2001	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	Alzheimer's Disease (Mild, Moderate, and Severe)	Nasal Catheter to Inject Water into the Pharynx and EMG to Record the Swallow	The mean latency of the "swallowing reflex" was examined in individuals with AD In the severe AD group, latency of the reflex was significantly longer	NA

					compared to the mild-moderate AD group No significant difference was observed between the mild and the moderate AD group	
	Priefer & Robbins 1997	See Above	See Above	See Above	See Above	See Above
	Horner et al. 1994	See Above	See Above	See Above	See Above	See Above
Disease severity may be associated with dysphagia severity	Wada et al. 2001	See Above	See Above	See Above	See Above	See Above
	Horner et al. 1994	See Above	See Above	See Above	See Above	See Above

Appendix B: Clinical Reports Employing Clinical Assessment of Swallowing in Alzheimer's Disease (AD)

Conclusion	Supporting	Study	Type of	Method of	Results	Level

	Studies	Description	Dementia	Assessment		of Evid-ence
Prevalence of dysphagia in AD	Volicer et al. 1989	Described/ characterized an aspect of eating or swallowing dysfunction through the examination of a single group of patients with AD	Alzheimer's Disease (Stage Not Specified)	Quest-ionnaire completed by care staff	Investigators examined eating difficulties in a group of AD patients in a long-term care facility 23 (32.4%) of the residents were observed to choke on food or drink, some of these were also known to refuse food	NA
	Chouinard et al. 1998	Retro-spective Cohort	Alzheimer's, Disease (Severe), Multi-Infarct Dementia, Other/Non-Specified	Chart review	Investigators completed retrospective chart review of individuals with advanced dementia who died of pneumonia	2b

					21 of 47 patients had Alzheimer's disease (45%). 21 of 47 patients had significant swallowing abnormalities (45%). Swallowing abnormalities were described as: difficulty taking liquids, presence of coughing/choking, poor tongue control, forgetting to swallow, and absence of chewing. The presence of swallowing disorders tended to correlate with	

					death from pneumonia	
Dysphagia may occur in all stages of AD	Correia et al. 2010	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	Alzheimer's Disease (Moderate and Severe)	Quest-ionnaire completed by caregiver and meal assessment using the Swallowing Rating Scale	Swallowing and feeding problems were characterized in a group with AD subjects with moderate or severe AD The moderate AD group demonstrated passivity, distraction, and refusal to eat. The severe AD group demonstrated distraction, passivity, and inappropriate feeding velocity 5 of the 18 subjects with moderate AD (27.8%) and	NA

					23 of the 32 individuals with severe AD (71.9%) had difficulty with the ingestion of specific consistencies 12 individuals with severe AD (37.5%) with delayed swallowing Severe swallowing problems were observed in 7 of the individuals from the severe AD group (21.87%)	
	Edahiro et al. 2012	Prospective Cohort	Alzheimer's Disease (Mild, Moderate, and Severe)	Meal Assessments completed by researchers	Factors affecting self-feeding in elderly subjects with	2b

					AD were examined Signs of dysphagia and behavioural eating deficits were observed in individuals with mild, moderate and severe AD Logistic regression identified the following factors as predictors of decreased eating independence: difficulty beginning a meal, presence of dysphagia signs, and the severity of dementia	
Behavioural eating	Priefer & Robbins,	Described/characterize	Alzheimer's Disease	Meal Assessment	Investigators examined	NA

difficulties may occur in all stages of AD	1997	d dysphagia in AD through comparison of two or more groups of individuals	(Mild)	s completed by researchers	swallowing durations and self-feeding dependency in healthy elderly and early stage AD 16 partner-initiated cued behaviours and/or assistance were directed at 4 subjects with AD 8 subject-initiated cued behaviours were completed by 7 subjects with AD Both partner-initiated cues and subject-initiated cues occurred significantly more	

					frequently compared to controls	
	Durnbaugh et al. 1996	Described/characterized an aspect of eating or swallowing dysfunction through the examination of a single group of patients with AD	Alzheimer's Disease (Mid-Stage)	Feeding Behaviour Inventory completed by nursing staff	Feeding behavior was examined in 20 subjects with AD 11 of the 20 (55%) subjects were on mechanically altered diets The most common mealtime behavioral problems were: distraction at meals, eating non-finger food with hands, playing with food, eating pieces that are too big, preference for sweet	NA

					foods, incorrect use of utensils, staring without eating, impatient behaviours demonstrated during or prior to mealtime, eating other residents' food, refusing meals	
	Morris et al. 1989	Described/characterized an aspect of eating or swallowing dysfunction through the examination of a single group of patients with AD	Alzheimer's Disease (mild, moderate, and severe), Multi-Infarct Dementia, and Mixed Dementia	Caregiver semi-structured interview	Investigators evaluated the eating habits of 33 patients with dementia (27 having AD) 63% of the sample demonstrated reduced food intake, 26% demonstrated increased food intake, 37% showed	NA

					changed food preferences, 60% demonstrated abnormal utensil use, and 26% demonstrated aberrant oral eating behaviour such as eating inappropriate non-food items.	
	Edahiro et al. 2012	See Above	See Above	See Above	See Above	See Above
	Burge 1994	Described/characterized an aspect of eating or swallowing dysfunction through the examination of a single group of patients with AD	Alzheimer's Disease (Severe) and Vascular Dementia	Meal time observations	Eating behavior was examined in a group of individuals with dementia Slightly less than half of 150 patients received some form of a texture	NA

					modified diet 22% of all patients were totally dependent for feeding and, of these patients, all received a modified diet regardless of the presence of a swallowing problem	
	Suski & Nielsen 1989	Described/characterized an aspect of eating or swallowing dysfunction through the examination of a single group of patients with AD	Alzheimer's Disease (Severe)	Comprehensive nutritional assessment	Nutritional intake and feeding difficulties were recorded in 19 women with advanced AD 19 of the 19 subjects (100%) required diet modifications	NA
Dysphagia and eating	Ikeda et al. 2002	Described/characterize	Fronto temporal	Quest-ionnaire	Frequency and characteristics	NA

difficulties in AD may be less severe than in other types of dementia		d dysphagia in AD through comparison of two or more groups of individuals	Lobe Dementia and Alzheimer's Disease (Mild, Moderate, and Severe)	completed by caregiver	of eating problems were recorded through caregiver questionnaires Caregivers of AD patients reported lower frequencies of swallowing problems, appetite changes, food preferences, and eating habits as compared to the caregivers of patients with frontotemporal lobe dementia. AD caregivers reported that 58.1% of the AD patients demonstrated at least one symptom of	

					eating and swallowing difficulties AD caregivers report that swallowing problems appear early in the disease process	
	Shinagawa et al. 2009	Described/characterized dysphagia in AD through comparison of two or more groups of individuals	Lewy Body Dementia and Alzheimer's Disease (Mild and Moderate)	Quest-ionnaire completed by caregiver	Frequency and characteristics of eating problems were recorded through caregiver questionnaires Caregivers of patients with Lewy body dementia reported significantly greater/more severe eating and swallowing difficulties	NA

					compared with caregivers of AD patients The AD caregivers reported a number of eating and swallowing abnormalities	

Appendix C: Clinical Reports Examining the Treatment of Dysphagia in Alzheimer's Disease (AD)

Conclusion	Supporting Studies	Study Description	Dementia Studied	Method	Results	Level of Evid-ence
Thickening liquids to a honey-thickened consistency may eliminate thin liquid aspiration in individuals	Logemann et al. 2008	Prospective Randomized Clinical Trial	Dementia with Alzheimer's disease, Dementia due to single or multistroke, Dementia (general), Parkinson's	711 thin liquid aspirators (confirmed during VFSS) were included in the study and received 3 intervention	Immediate elimination of aspiration on thin liquids occurred most often with honey-thickened liquids for patients in each	2b

with AD, however this intervention may not affect long-term morbidity and mortality			disease, and Parkinson's disease with dementia	s (chin-down posture, nectar-thickened liquids, or honey-thickened liquids) in a random order, during VFSS	diagnostic category This intervention was least preferred by the patients	
	Robbins et al. 2008	Prospective Randomized Clinical Trial	Dementia with Alzheimer's disease, Dementia due to single or multistroke, Dementia (general), Parkinson's disease, and Parkinson's disease with dementia	504 thin liquid aspirators (confirmed during VFSS) were randomly assigned 1 of 3 interventions (chin-down posture, nectar-thickened liquids, or honey-	No statistically significant differences in outcome were identified following the use of the three interventions	2b

				thickened liquids) and followed until death or four months		
A physiotherapist administered cervical spine mobilization protocol may improve "dysphagia limit" in individuals with severe AD and altered neck posture	Bautmans et al. 2008	Prospective Randomized Controlled Trial with Cross-Over Design	Alzheimer's Disease (Severe)	15 nursing home residents were randomized to participate in either an intervention condition (cervical spine mobilization) followed by a wash-out period followed by a control condition, or a control period followed by a washout period	Following the treatment paradigm the subjects demonstrated improved "dysphagia limit" (the maximum sized bolus of water that can be swallowed in a single movement)	2b

				followed by a treatment condition		

Appendix D: Clinical Reports Examining Autonomic Nervous System (ANS) Dysfunction in Alzheimer's Disease (AD)

Conclusion	Supporting Studies	Study Description	Results	Level of Evid-ence
Individuals with AD demonstrate blood pressure differences at baseline and following stimulation, as compared with controls	Lampe et al., 1989	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined changes in blood pressure, plasma norepinephrine (NE), serum prolactin, luteinizing hormone, and follicle-stimulating hormone associated with infusions of 2 thyrotropin-releasing doses in 10 men with early onset AD and in 9 age-matched controls Diastolic pressor responses to thyrotropin-releasing hormone (TRH) were substantially blunted in AD subjects relative to controls, even at the higher dose of TRH	NA

			There was a trend towards attenuation of the systolic and plasma NE response as well	
	Otsuka et al. 1990	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Blood pressure and heart rate measurements were recorded in 31 elderly hospitalized patients, who were classified into 4 groups: group D comprised 8 bedridden patients with AD; group R comprised 7 bedridden patients that did not have dementia; group N comprised 9 normotensive, ambulatory patients; and group H comprised 7 hypertensive, ambulatory patients For group D, mean systolic blood pressure over a 24-hour period was statistically higher compared with group R Also, in group D, the circadian rhythm of blood pressure was abnormal, showing no nocturnal	NA

			decrease as compared to the control groups	
	Elmstahl et al. 1992	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators studied 24 women with late-onset AD and 54 age-matched healthy controls using tilting and breathing tasks AD patients had lower baseline mean systolic and diastolic blood pressure compared with control patients After tilting, the AD patients had a greater increase in heart rate, and the mean systolic blood pressure fell significantly compared with the controls Acceleration indices were significantly higher in the AD patients and brake indices were significantly lower	NA
	Burke et al. 1994	Retrospective chart review and neuroanatomical analysis of 3 postmortem AD	Chart review of 3 patients with autopsy-confirmed AD indicated that yearly systolic, diastolic, and mean arterial blood pressures	NA

		subjects and characterization of an aspect of ANS dysfunction in AD through comparison of two or more groups of individuals, one or more of these groups being comprised of AD patients	decreased in all patients following the year of diagnosis Up to 30% of C-1 neurons were atrophied in sections from the same AD patients The number of C-1 neurons correlated strongly with mean arterial pressure and systolic blood pressure Hypothalamic phenylethanolamine N-methyl-transferase activity was significantly decreased in 5 AD patients compared with controls Neuropathology analysis documented neurofibrillary tangles in the paraventricular nucleus of an individual with Alzheimer's disease but not in a control subject	
	Idiaquez et al. 1997	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators studied 7 AD subjects and 23 controls before and after a meal to identify the presence/degree of postprandial hypotension	NA

			in AD 70% of 10 AD patients experienced postprandial hypotension compared to 26% of 23 controls.	
	Guo et al. 1998	Prospective cohort study	Investigators examined a relationship between low blood pressure and increased mortality in 202 patients with dementia (112 with AD) There was a positive linear relationship between blood pressure and Mini Mental State Exam score (every 10 mm Hg increase in systolic pressure was related to a 0.6 unit increase in score) for the total sample of individuals with dementia (results are not specific to dementia type, individuals with AD comprised 55.4% of the sample) Patients with moderate and severe dementia had significantly lower systolic and diastolic blood pressure	2b

			than did those with questionable and mild dementia When the sample was examined as a whole, patients with low blood pressures had shorter survival time than did those with higher blood pressures	
	Kalman et al. 2002	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Cutaneous active vasodilation was assessed in 22 patients with AD and 20 age-matched controls using an isometric handgrip exercise A significantly smaller reduction of R wave intervals (i.e., a measure of heart rate) was observed in the AD group Static exercise was associated with increased variation in both systolic blood pressure and diastolic blood pressure in both groups, but the systolic blood pressure change was significantly smaller in AD	NA

			patients Significantly higher cutaneous vascular resistance and decreased skin blood flow were observed following the stimulus in the AD group The resting R wave interval was significantly correlated with the Mini Mental State Exam score and a highly significant negative correlation was calculated for the resting skin blood flow and age for all AD subjects	
	Bordier et al. 2007	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	10 (30%) of AD subjects had positive carotid sinus massage, with prolonged ventricular standstill in two subjects (6.7%) The response to carotid sinus massage did not predict increased risk in bradycardia-mediated syncope Syncope was identified in 3 AD subjects during follow-	NA

			up (10%)	
Individuals with AD demonstrate significantly greater falls in blood pressure (particularly systolic) when transitioning from supine to standing (orthostatic hypotension) compared with healthy age-matched controls	Elmstahl et al. 1992	See Above	See Above	See Above
	Vitiello et al. 1993	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators measured the autonomic nervous system in AD using lying and standing blood pressure, pulse and plasma epinephrine and norepinephrine in 60 AD subjects and 20 normal elderly controls Following a supine to standing task, mean systolic BP decreased in the subjects with AD but increased in the controls In AD patients with depression, during orthostasis, systolic BP was significantly decreased compared to AD patients with no signs of depression The non-depressed AD patients had significantly lower systolic BP during orthostasis as compared to the controls	NA

			Subjects with AD demonstrated no differences in basal or standing plasma levels of norepinephrine and epinephrine	
	Wang et al. 1994	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Authors investigated cardiovascular autonomic function in 23 AD subjects and 23 age-matched controls Subjects with AD had significantly lower systolic and mean blood pressure levels in the supine position and 3 min after standing compared with controls There was a tendency toward lower systolic blood pressure in the patients with more severe disease	NA
	Jhee et al. 1995	Retrospective description of ANS dysfunction in AD through examination of a single group of AD subjects	Authors conducted a retrospective analysis of blood pressures and heart rates of 31 patients with AD Significant mean decreases in systolic and diastolic blood pressures were noted	NA

			in AD patients While the investigators report that these decreases were noted to be significantly different from baseline pressures, there was no comparison with healthy controls The mean decreases are consistent with other clinical reports that demonstrated significantly greater pressure drops in AD patients as compared to controls, when transitioning from sitting to standing	
	Passant et al. 1997	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined the prevalence of orthostatic hypotension, low blood pressure, dizziness, falls and fractures in patients with dementia (46 with AD) The mean supine/resting systolic blood pressure was generally lower than in normal healthy aged population (i.e., compared to norms as there was no	NA

			control group in this study) 18 of the 46 AD patients demonstrated orthostatic hypotension (a blood pressure decrease of 20 mm Hg or more) Only 39% of the AD patients with orthostatic hypotension experienced clinical symptoms of dizziness; 50-56% of those AD patients with orthostatic hypotension had experienced falls and more than one fracture 53% of the patients with AD and orthostatic hypotension experienced blood pressure falls after 3 min of standing or later, however, 27% didn't experience the maximum blood pressure drop until after 10 min of standing All AD patients demonstrated highly significant heart rate increases from supine to	

			standing position	
	Kalman et al. 2002	See Above	See Above	See Above
	Andin et al. 2007	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators retrospectively studied 22 AD cases with white matter disease and 22 AD cases without white matter disease, both based on neuropathology analysis Reports of hypertension, orthostatic hypotension, and dizziness/unsteadiness were significantly more frequent in the AD group with white matter disease compared with the AD group without white matter disease	NA
	Allan et al. 2007	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators compared cardiovascular autonomic function in subjects with AD (39), vascular dementia, Lewy body dementia, Parkinson's disease dementia, and controls AD patients demonstrated a significantly greater mean	NA

			fall in systolic blood pressure on standing when compared to an age matched group These AD patients also demonstrated a significantly greater prevalence of sustained orthostatic hypotension as well as a greater median time for return of systolic blood pressure to baseline AD patients were also more likely to have an autonomic neuropathy and severe, definite and atypical autonomic neuropathy, using the Ewing classification, as compared to controls Individuals with AD demonstrated the least amount of autonomic dysfunction as compared to individuals with other types of dementia	
	Andersson et al. 2008	Described/characterized ANS dysfunction in AD	Investigators aimed to determine whether	NA

		through comparison of two or more groups of individuals	orthostatic hypotension is more common in patients with dementia (235 having AD) as compared to 62 elderly controls Orthostatic hypotension occurred in 42% of the AD patients compared with only 13% of the controls	
	Allan et al. 2009	Prospective Cohort	Investigators aimed to identify potentially modifiable predictors of falls in older people with mild-moderate dementia (38 with AD) compared to 39 controls Univariate predictors of falls in dementia, stratified by diagnosis, were noted to include duration of dementia, history of falls or recurrent falls in the preceding 12 months, use of cardioactive medication, autonomic symptom scale greater than 7 and time taken for blood pressure to return to baseline on standing	2b

			Multivariate predictors of falls in dementia, stratified by diagnosis, were noted to be symptomatic orthostatic hypotension, and use of cardioactive medications Physical activity was noted to be protective in both models	
	Mehrabian et al. 2010	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined the relationship between orthostatic hypotension and cognitive function in a group of 495 consecutive elderly made up of those with normal cognitive function, mild cognitive impairment, AD, or vascular dementia Orthostatic hypotension was identified in 15% of the sample of 233 AD patients There was a significant relationship between orthostatic hypotension and cognitive status. Greater mean fall in systolic blood pressure after standing was	NA

			observed in patients with vascular dementia or AD as compared to those with normal cognitive function	
	Zakrzewska-Pniewska et al. 2012	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators evaluated clinical dysautonomia in 54 AD patients and 37 healthy age-matched controls using clinical autonomic assessment, functional assessment, the sympathetic skin response and the R-R interval variation test Clinical symptoms of dysautonomia were found in 66% of a group of 54 AD patients but were relatively mild In AD patients, orthostatic hypotension was observed in 34.5%, constipation in 17.2%, and urinary incontinence in 13.8 Sympathetic skin response was abnormal in 27% of AD patients and heart rate variability was abnormal in 88% of cases as compared	NA

			with controls	
Significantly less heart rate variability has been reported in individuals with AD	Franceschi et al. 1986	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Study examined cardiac ANS function during sleep in 16 AD patients compared with 7 healthy controls The mean body movement ratio (body movement related heart rate variation) during non-REM and REM sleep was significantly lower for AD patients compared with the controls	NA
	Aharon-Peretz et al. 1992[70]	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined heart rate variability in AD A group of 20 AD patients demonstrated significant differences in power spectrum density of echocardiogram as compared to 7 volunteer controls AD patients demonstrated a relatively hypersympathetic, hypoparasympathetic state with regard to heart rate, both when standing and supine	NA

			The peak-to-peak amplitude of the tachogram in a normal subject was about 3 times greater than the peak-to-peak amplitude of the tachogram of the patient with AD	
	Algotsson et al. 1995	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators measured heart rate variability and sympathetic skin response to electrical stimulation in order to assess parasympathetic and sympathetic ANS function in 29 AD patients and 15 controls Very few patients or caregivers reported symptoms of ANS dysfunction AD patients had significantly lower heart rate reactions to passive tilting and the Valsalva maneuver and a significantly greater reduction of finger pulse amplitude during the	NA

			Valsalva maneuver AD patients also demonstrated a decreased response the sympathetic skin response test The AD patients showed signs suggesting autonomic dysfunction affecting both parasympathethic and vasomotor sympathetic functions At one-year follow up, there was a slight deterioration for relative beat-to-beat variations during deep breathing but there was a slight improvement in heart reactions to the tilt test	
	Szili-Torok et al. 2001	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	A group 24 AD patients demonstrated significantly shorter R-R interval length on echocardiogram recordings as compared to a group of 22 controls Baroreflex sensitivity was also markedly reduced in AD patients as compared to	NA

			controls Patients with AD showed significantly higher basal heart rate and decreased R-R interval oscillation and increased systolic arterial blood pressure oscillation as compared to controls	
	Idiaquez et al. 2002	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined the association between specific neuropsychiatric deficits and autonomic dysfunction in patients with AD Measures of heart rate variation to deep breathing were consistently reduced in a group of 20 AD patients compared to a group of 20 age-matched controls In those AD patients who demonstrated abnormal heart rate variation, there were significant abnormalities in the Blessed score and in the apathy, delusions, and aberrant	NA

			motor behavior items of the neuropsychiatric inventory	
	Zulli et al. 2005	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	A group of 33 AD patients demonstrated significantly greater QT dispersion (i.e. an index of ventricular repolarization inhomogeneity) as compared to a group of 29 controls These subjects also demonstrated significantly decreased heart rate variability compared to the control group Investigators reported a positive linear correlation between the Mini Mental State Exam and Alzheimer's Disease Assessment Scale – cognitive subscale scores, and the measures of QT dispersion, QT corrected dispersion, low-frequency power, and high frequency power	NA
	Toledo and	Described/characterized	Investigators measured	NA

	Junqueira Jr, 2008	ANS dysfunction in AD through comparison of two or more groups of individuals	cardiac autonomic modulation and sympathovagal balance in the supine and active standing positions based on short-term time- and frequency-domain heart interval variability analysis in 22 AD patients as compared to 24 controls The mean high frequency power showed a significant, borderline reduction in the supine posture and was significantly reduced after standing in AD Sympathovagal balance (as measured by short-term time and frequency domain heart interval variability) was significantly altered towards relative depression of parasympathetic and enhancement of sympathetic modulation in the supine but not the standing posture AD patients demonstrated subtle, absolute and relative	

			parasympathetic depression and relative sympathetic exacerbation	
	Toledo and Junqueira Jr, 2010	Described/characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	Investigators examined the relationship between measures of cardiac sympathogvagal modulation of heart interval variability and the cognitive part of the Cambridge Examination for Mental Disorders of the Elderly (CAMCOG) and the Mini Mental State Exam (MMSE) in 22 AD subjects There was a significant positive correlation, in both supine and standing, between the cognitive performance and cardiac autonomic modulation of 5 min heart interval variability evaluated by time-and frequency-domain indexes (parasympathetic modulation) in 22 AD patients Negative trend correlation	NA

			was observed between absolute sympathetic modulations in supine posture Individuals with higher cognitive deficiency showed significantly lower cardiac parasympathetic modulation and trend for sympathetic over activity	
	Zakrzewska-Pniewska et al. 2012	See Above	See Above	See Above
Individuals with AD also demonstrate altered blood pressure and heart rate responses to pain stimuli	Rainero et al. 2000	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators analyzed the effects of electrical noxious stimulation on the ANS of 20 AD subjects compared with 20 healthy subjects Following presentation of threshold pain stimulation, there was a dramatic increase in heart rate in controls but only a slight increase in AD patients and the peak heart rate was significantly less pronounced for the AD patients	NA

			Heart rates increased in expectation of the pain stimuli and this was significantly less pronounced in the AD patients The changes in blood pressure paralleled the changes in heart rate but were not statistically significant AD patients reported experiencing the same pain intensity as the controls when the stimulation was at the pain threshold and just above the pain threshold. However, AD patients reported experiencing significantly less pain intensity in response to stimulation at twice pain threshold, Linear regression showed that pain rating of the twice pain-threshold stimulus was closely related to the severity of AD, as assessed	

			by the Mini Mental State Exam.	
	Benedetti et al. 2004	Described/characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	Neither stimulus detection nor pain threshold was correlated with cognitive status or brain electrical activity decline There was a correlation between heart rate responses and deterioration of both cognitive functions and brain electrical activity This correlation was also found for the anticipatory heart rate increases preceding pain stimulation.	NA
Autonomic nervous system dysfunction appears to be subtle in patients with AD when compared with other types of dementia	Allan et al. 2007	See Above	See Above	See Above
	Allan et al. 2006	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined the presence and severity of autonomic symptoms in patients with different subtypes of dementia (40 with AD) compared to healthy controls Individuals with AD had significantly lower activity	NA

			scores and significantly worse ADL scores compared to controls Individuals with AD scored similar to controls with respect to a self-reported autonomic symptoms scale All other subtypes of dementia scored higher on the self-reported autonomic symptoms scale	
Plasma norepinephrine levels may be altered in AD	Borson et al. 1989	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Indicators of SNS function were examined in 10 college educated males with AD and 7 education-matched, healthy controls Normal older subjects responded to mental effort with a rise in plasma norepinephrine, plasma epinephrine, mean arterial pressure, and heart rate AD patients responded to cognitive challenge with a significant but un-sustained rise in plasma epinephrine There were clear	NA

			differences between groups on 3 measures of sympathetic nervous system activity during cognitive effort, with AD subjects showing a blunted response as compared to controls	
	Raskind et al. 1984	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators measured CNS and peripheral noradrenergic function by measuring norepinephrine and 3-methoxy-4-hydroxyphenylglcol levels in CSF and plasma Norepinephrine and 3-methoxy-4-hydroxyphenylglcol levels were significantly higher in both CSF and plasma in patients with advanced AD as compared to individuals with moderate AD or controls Heart rate was higher in the patients with advanced AD compared with the other two groups and there was a tendency for mean arterial blood pressure to be higher	NA

			in patients with advanced AD	
	Lampe et al. 1989	See Above	See Above	See Above
	Peskind et al. 1995	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Cerebrospinal fluid and plasma norepinephrine concentrations were examined in response to an alpha-2 adrenergic antagonist in individuals with AD, healthy older controls, and healthy young controls Plasma norepinephrine concentrations in the placebo treatment condition was significantly higher in normal older and AD subjects compared with young subjects Mean arterial pressure in the placebo treatment condition was higher both normal older and AD subjects compared with young subjects	NA
	Ahlskog et al. 1996	Described/characterized ANS dysfunction in AD	Investigators evaluated plasma catechols in 15	NA

		through comparison of two or more groups of individuals	patients with Parkinson's disease, 12 AD subjects, and 15 controls A non-significant trend towards greater median plasma norephinephrine concentrations in the AD group compared with controls was reported	
	Peskind et al. 1998	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Resting CNS adrenergic activity was evaluated in AD and normal aging by measuring cerebrospinal and plasma epinephrine concentration, as well as heart rate and blood pressure in individuals with AD, healthy older controls, and healthy young controls The effects of AD and aging on the responsiveness of the CNS adrenergic systems were measured by evaluating the changes in cerebrospinal epinephrine following administration of an alpha-2 adrenergic receptor antagonist and an alpha-2 agonist	NA

			Plasma epinephrine was significantly higher in AD than normal older or normal younger subjects Blood pressure was affected by aging but not AD Higher heart rates were observed in the AD group as compared to the normal older and normal younger subjects Systolic and diastolic blood pressure measurements were significantly higher in the alpha-2 adrenoreceptor agonist condition in both older and AD subjects	
	Pascualy et al. 2000	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Plasma adrenocorticotropic hormone, cortisol, norepinephrine, and epinephrine responses to a one-minute cold pressor test were measured in 9 AD subjects and 9 age-matched controls Cortisol response was increased in the AD group	NA

			but the plasma adrenocorticotropic hormone response did not differ Basal norepinephrine concentrations were higher in the AD group, but norepinephrine responses to the cold pressor test did not differ between groups The blood pressure response to the cold pressor test was higher in the AD subjects, however there were no significant differences in heart rate	
Vasomotor function may be reduced in individuals with AD	Hornqvist et al. 1987	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Peripheral reactivity to an alpha1-agonist, a beta-agonist, and cholinergic agonist was examined in 12 AD subjects as compared to 16 controls A reduced response towards the adrenergic agonists and for the beta-agonist was seen in the AD patients The response to the cholinergic agonist did not	NA

			differ between individuals with AD and healthy controls Increasing age did not significantly influence the cutaneous responses in the controls	
	Algotsson et al. 1995	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators studied skin vessel reactivity in response to three vasodilating substances in 15 AD subjects as compared to 16 age-matched controls Skin vascular responses of the AD subjects to acetylcholine and isoprenaline (but not nitroprusside) were greatly attenuated compared with controls	NA
	Kalman et al. 2002	See Above	See Above	See Above
Individuals with AD may demonstrate an impaired sweat response	Elmstahl and Winge 1993	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators evaluated sweat electrolyte concentrations following pilocarpine iontophoresis stimulation in 15 females with AD compared to 29	NA

			healthy female controls Mean sweat sodium concentration was significantly higher among the AD subjects There was a higher proportion of non-responders among the AD women than among the controls	
Pupillary responses in AD are altered in AD	Idiaquez et al., 1994	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators studied cholinergic dysfunction in the iris in 26 subjects with AD and 23 healthy controls AD patients demonstrated significantly increased sensitivity to a parasympathetic agent (greater change in pupillary constriction) compared to controls	NA
	Grunberger et al. 1999	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined pupillary dilatation after application of an acetylcholine transmission antagonist in 29 AD patients and 29 controls	NA

			Initial pupillary diameters of the AD patients were significantly smaller than those of the controls Both AD patients and controls responded to the acetycholine agonist with pupillary dilation Patients with AD showed a larger relative change of pupillary diameter than the controls	
	Fotiou et al. 2009	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Central cholinergic dysfunction was examined with pupillometry in 23 patients with AD and in 22 patients with PD (11 with cognitive impairment and 11 without) compared with 23 normal controls AD patients had significantly lower levels of maximum constriction velocity, maximum constriction acceleration, amplitude, and percentage amplitude compared with controls	NA

			AD patients had significantly higher levels of percentage recovery – redilatation, latency, time for maximum velocity, and time for maximum constriction compared with controls	
AD patients may experience constipation and urinary incontinence	Davidson et al. 1991	Described/characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	Subjects with AD and incontinence scored significantly lower on a cube copying task than those demonstrating continence Qualitative analysis revealed that the drawings by incontinent patients showed features comparable with those observed in the drawings by patients with right-sided parietal lesions, in particular, poor representation of perspective and spatial orientation	NA
	Del-Ser et al. 1996	Described/characterized ANS dysfunction in AD	Investigators followed 73 patients with dementia (29	NA

		through comparison of two or more groups of individuals	autopsy confirmed cases of AD) for 5.6 ± 2.5 years and recorded the date of onset of urinary incontinence Loss of continence was associated with severe cognitive decline in pure AD but tended to precede severe cognitive decline in Lewy Body dementia	
	Ransmayr et al. 2008	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators evaluated frequency, urgency, incontinence, and nocturia, without major bladder outflow obstruction in 31 patients with dementia (16 with AD) Urge episodes and urge incontinence were observed in 12% of the AD patients and detrusor over activity occurred in 40% of the AD patients	NA
	Zakrzewska-Pniewska et al. 2012	See Above	See Above	See Above
Heightened arousal during	Eisdorfer and Cohen	Described/characterized an aspect of ANS	A pilot investigation with 13 AD patients compared	NA

learning may occur in AD	in 1978	dysfunction through the examination of a single group of patients with AD	data against pre-existing literature on normative values for a number of autonomic function measures AD patients demonstrated heightened ANS activity during learning situations that would induce minimal arousal in normal elderly males	
Salivary flow is reduced in AD	Ship et al. 1990	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Saliva production from the major salivary glands was evaluated in 28 unmedicated patients with early AD and 35 age-matched controls Submandibular salivary flow rates (resting and stimulated) were significantly lower among the AD patients compared with controls	NA
The neuropathology of AD may affect central ANS control	Chu et al. 1997	Neuroanatomical Described/characterized ANS dysfunction in AD through comparison of two or more groups of	Investigators examined the brains of 20 AD compared with 7 age-compatible healthy controls In all cortical regions, the	NA

mediated by the ventromedial frontal cortex		individuals	laminar pattern of neurofibrillary tangle involvement showed a predilection for layers III and V Layer V was most severely affected with neurofibrillary tangles, followed by layer III and then layer VI Layers II and VI contained few neurofibrillary tangles There were significant differences between mesocortex and granular cortex in all 3 layers The posteromedial autonomic-related cortical regions were most severely affected The patterns of regional distribution were consistent in all AD subjects with duration of dementia ranging from 3-15 years In neuropathologically less severe cases, pathological changes involved	

			predominantly autonomic-related cortex regions and spared granular areas entirely.	
The neuropathology of AD may affect central ANS central control mediated by the pontine regions of the brainstem	Rub et al. 2000	Neuroanatomical Described/characterized an aspect of ANS dysfunction through the examination of a single group of patients with AD	Investigators examined three nuclei of the pontine parabrachial region in 27 autopsy confirmed cases of AD Cytoskeletal anomalies emerged early in the nuclei of the pontine parabrachial region and in the intermediate zone of the medullary reticular formation The development of the neurofibrillary pathology was found in the medial parabrachial nucleus, subpeduncular pigmented nucleus, and intermediate zone of the medullary reticular formation commences already in cortical stage I and in the lateral parabrachial nucleus in cortical stage II	NA

			At all four sites, the progression of the lesions correlated linearly with the neurofibrillary tangles cortical staging sequence I-VI Investigators concluded that neurofibrillary tangles stages I-VI most probably reflect not only the progress of the AD related cytoskeletal pathology in cortical areas but also its evolution in specific subcortical sites. It is conceivable that a progressive deterioration of cardiovascular and respiratory functions occurs with advancing cortical neurofibrillary tangles stages	
The neuropathology of AD may affect the insula	Bonthius et al. 2005	Neuroanatomical Described/characterized an aspect of ANS dysfunction through comparison of two or more groups of	Insular pathology was examined in 17 autopsy confirmed cases of AD compared with 5 controls Investigators observed evidence of AD pathology	NA

		individuals	in the insular cortex in all 17 cases of AD The control cases had no neuritic plaques and only very rare and isolated neurofibrillary tangles Density of insular neurofibrillary tangles, but not neuritic plaques correlated with years of clinical dementia AD related pathology in the insula increased as pathology in the entorhinal cortex increased The human insula contains 3 distinct architectonic areas and severity of AD pathology varies among the insula's cytoarchitectonic regions	
The neuropathology of AD may affect the C-1 neurons of the rostral ventrolateral	Burke et al. in 1994	See Above	See Above	See Above

reticular nucleus				
No significant differences between individuals with AD and controls	Khurana and Garcia 1981	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators measured ANS function in 2 patients with subacute spongigorm encephalopathy compared with 2 patients with AD and 2 patients with Huntington's disease Individuals with subacute spongiform encephalopathy exhibited autonomic dysfunctions but the AD patients did not Measures included evaluation of lacrimation, pupillary responses to topically applied autonomic drugs, pulse rate in response to cold face test and atropine administration, and blood pressure in response to the cold pressor test	NA
	Shankle et al. 1993	Neuroanatomical Described/characterized ANS dysfunction in AD through comparison of	Investigators measured enteric neurons in the myenteric plexus of the esophagus, stomach, small	NA

		two or more groups of individuals	intestine, colon, and rectum in 18 AD subjects, 8 with other types of dementia, and 4 non-demented elderly control subjects There was age-related loss of enteric neurons and of plexus mass in the Auerbach plexus The size of the Auerbach plexus did not differ from control values for elderly patients with AD, suggesting that the neurons of the enteric nervous system are not affected by the degenerative processes of AD	
	Wakabayashi et al. 1999	Neuroanatomical Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined neurofibrillary tangle formation in the peripheral nervous system and central nervous systems in 20 AD subjects, 8 with progressive supranuclear palsy, and 100 elderly, non-demented individuals Neurofibrillary tangles were	NA

			not identified in the sympathetic or spinal ganglia in patients with AD	
	Taki et al. 2001	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators examined whether meta-iodobenzylguanidine mysocardial scintigraphic study could be used to explore the contribution of myocardial accumulation of meta-iodobenzylguanidine to the differential diagnosis between AD and Lewy body dementia AD patients demonstrated successful cardiac uptake of meta-iodobenzylguanidine in both early and delayed images, as compared to patients with Lewy body dementia who demonstrated reduced cardiac accumulation	NA
	Allen et al. 2004	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators evaluated ANS function in 14 AD subjects, 80 controls, and 20 subjects with vascular dementia, using power spectral analysis of heart	NA

			rate variability There were no differences in heart rate variability in patients with AD as compared with controls	
	Orimo et al. 2005	Neuroanatomical Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Investigators evaluated whether cardiac sympathetic denervation might account for the decreased uptake of meta-iodobenzylguanidine on meta-iodobenzylguanidine myocardial scintigraphy in Parkinson's disease and Lewy body disease Examined frequency and pattern of cardiac sympathetic nerve involvement in 10 subjects with pure AD AD patients did not show depletion of the cardiac sympathetic nerves	NA
	Choi et al. in 2009	Described/ characterized ANS dysfunction in AD through comparison of	Investigators reported no differences between AD patients (N=23) and controls (N=24) on a variety of measures of	NA

		two or more groups of individuals	cardiovascular autonomic function including heart rate responses to standing and deep breathing, and Valsava ratio	
	Watanabe et al. 2001	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	Heart/mediastinum ratio of meta-iodobenzylguanidine uptake in 10 patients with AD was indistinguishable from that in 10 control subjects	NA
	Raskind et al. 1999	Described/characterized ANS dysfunction in AD through comparison of two or more groups of individuals	The effects of normal aging and AD on cerebrospinal fluid and plasma catechols were assessed using high-performance liquid chromatography No plasma norepinephrine differences were found between groups Cerebrospinal 3,4-dihydroxyphenylalanine following an alpha-2 adrenoreceptor agonist, was higher in older and AD than in young subjects Cerebrospinal 3,4-dihydroxyphenylglycol did	NA

			not differ among groups Plasma 3,4-dihydroxyphenylalanine following an alpha-2 adrenoreceptor agonist, was higher in AD than in young subjects		

Appendix E: Meta-Analysis Search Terms

((((((((((Saliva)) OR (Salivation)) OR (Salivary proteins and peptides)) OR (salivary duct)) OR (salivary gland)) OR (Parotid gland)) OR (submandibular gland)) OR (sublingual gland))) AND (healthy OR normal OR "disease free")) AND (aged OR aging)) AND (flow OR production OR secretion OR secret* OR produc* OR secretory rate)

Appendix F: Summary of Studies Included in Meta-Analysis Arranged Chronologically

Study	Salivary Source & Condition	Participants* *(Groups included in analysis are in bold)	Method of Salivary Collection	Medication Use	Results* = No difference - Increased saliva with increasing age + Decreasing

					saliva with increasing age
Gutman & Ben-Aryeh, 1974	Unstim Whole	N=22, 12 Females 10 Males Children: n=7 Younger adults (15-21 years): n=6 Older adults (60-76 years): n=9 Examined the salivary flow rates of males and females separately	Unstim whole: spitting method	Medication use not reported Participants described as "healthy" or "generally healthy"	+
Baum, 1981	Stim Parotid	N=208, 85 Females 123 Males Younger Group (20-39 years): n=29 Middle-Aged Group (40-59	Modified Carlsson-Crittenden cup with 2% citric acid as stimulus	95 men were non-medicated and 48 women were non-medicated. Reported using data from cohorts of community-	=

		years): n=35 Older Group, Non-medicated (60-88 years): n=31 Older Group, Medicated (60-88 years): n=19 Examined the salivary flow rates of males and females separately		dwelling volunteers	
Parvinen & Larmas, 1982	Stim Whole	N=642, 316 Females 326 Males 30-34 years: n=145 35-39 years: n=116 40-44 years: n=93 45-49 years: n=77 50-54 years:	Paraffin mastication	All subjects were reportedly unmedicated. Reported excluding participants with health problems that could affect salivary flow	=

		n=60 55-59 years: n=40 60-64 years: n=46 65-69 years: n=41 ≥ 70 years: n=24 Examined the salivary flow rates of males and females separately			
Sonnenberg et al., 1982	Unstim Whole & Stim Parotid	N=132 (total) n=40* 14 Females 26 Males *Used the control group for data extraction Younger Group (mean age 28 ± 3 years): n=20	Unstim whole: draining method Stim parotid: double chamber suction capsule (similar to Lashley capsule) with sublingual perfusion of 2 % citric acid	Medication use was not reported	=

		Older Group (mean age 55 ± 7 years): n=20			
Ogura et al., 1983	Unstim Whole	N=14 All males Younger Group (mean age 22.7 years): n=7 Older Group (mean age 70.6 years): n=7 Examined the salivary flow rates of males and females separately	Peck's method	No medication use 2 weeks prior to study. Reported excluding participants with health problems that could affect salivary flow	=
Baum et al., 1984	Stim Parotid	N=202, 79 Females 23 Males Younger Group (20-39 years): n=38M, 28F Middle-aged	Modified Carlson-Crittenden cup with 2% citric acid as stimulus	No participants were taking prescription medications. Participants described as "healthy" or "generally healthy"	=

		Group (40-59 years): n=44M, 24F Older Group (60-88 years): n=41M, 27F Examined the salivary flow rates of males and females separately			
Ben-Aryeh et al., 1984	Unstim & Stim Whole	N=61, 30 Females 31 Males Younger Group (mean age 26 ± 2 years): n=31 Older Group (mean age 69 ± 5 F, 68 ± 3 M): n=30 Examined the salivary flow rates of males and females separately	Unstim whole: spitting method Stim whole: 2 % citric acid	Participants were reported to be unmedicated. Participants described as "healthy" or "generally healthy"	+ unstim whole = stim whole

Heft & Baum, 1984	Unstim & Stim Parotid	N=58, 39 Females 46 Males Age Range: 23-81 years Younger Group (20-39 years): n=13M, 17F Middle-aged Group (40-59 years): n=14M Older Group (≥ 60 years): n=19M, 22F Examined the salivary flow rates of males and females separately	Unstim parotid: modified Carlson-Crittenden cup over Stenson's duct Stim parotid: 2% citric acid to dorsal surface of tongue	No participants were taking any medications on a regular basis. Participants described as "healthy" or "generally healthy"	=
Gandara et al., 1985	Unstim Whole & Stim Whole & Parotid	N=50 (total), n=25* *Used the control group for data extraction	Unstim whole: spitting method Stim whole: paraffin mastication	No participants were taking any medications on a regular basis. Reported excluding	=

		Younger Group (mean age 44 years): n=12 Older Group (mean age 68 years): n=13	Stim parotid: via sour lemon drops stimulation	participants with health problems that could affect salivary flow	
Pedersen et al., 1985	Unstim & Stim SMSL	N=54 Age Range: 18-91 years Younger Group (mean age 25.7 years): n=28 Older Group (mean age 81.4 years): n=26 Examined the salivary flow rates of males and females separately	Unstim SMSL: novel collection device (Drummond micropipette holder, 2 ml amber latex rubber bulb for suction, 50 microliter Van-Lab micropipette collection chamber) over Wharton's duct Stim SMSL: 3 minutes of a lemon drop stimulus and then collection	No participants were taking medications known to affect salivation. Participants described as “healthy” or “generally healthy”	+

Yaegaki et al., 1985	Unstim Whole	N=32, 15 Females 17 Males Age Range: 20-83 years Younger Group (20-35 years): n=17 Older Group (50+ years): n=15	Spitting method	Medication use was not reported Participants described as "healthy" or "generally healthy"	+
Ben-Aryeh et al., 1986	Unstim & Stim Whole & Parotid	N=63, 31 Females 32 Males Younger Group (mean age 37 ± 10.5 years): n=39 Older Group (mean age 66 ± 3.3 years): n=24	Unstim whole: spitting method Unstim parotid: Curby cup Stim whole and parotid: 2% citric acid	Participants were reported to be unmedicated. Participants described as "healthy" or "generally healthy"	=
Chauncey et al., 1987	Unstim & Stim Parotid	N=203, All male Age Range: 39-64 years	Unstim parotid: vacuum-maintained metal	Medication use not reported. Participants described as	=

		<45 years: n=48 45-49 years: n=40 50-54 years: n=31 55-59 years: n=53 60+ years: n=41	collection device positioned over Stensen's duct Stim parotid: sour lemon-flavored lozenge	"healthy" or "generally healthy"	
Tylenda et al., 1988	Unstim & Stim SMSL	N=90 Age Range: 29-93 years Younger Group: n=22 Middle aged Group: n=32 Older Group: n=35 Examined the salivary flow rates of males and females separately	Unstim SMSL: Wharton's duct was isolated with cotton gauze and saliva collected from the duct orifice by use of a micropipette under light suction	Participants were not taking any prescription medications. Reported using data from cohorts of community-dwelling volunteers	+

Ship & Baum, 1990	Stim Parotid	N=50, 23 Females 27 Males Longitudinal Study (over 7-12 years, mean 9.7 years, 1.2 (SD)) Age Range: 29-72 years	2% citric acid from a single gland	Some medication use but 24 were not taking medication. Participants described as "healthy" or "generally healthy"	=
Navazesh et al., 1992	Unstim & Stim Whole	N=42, 18 Females 24 Males Younger Group (mean age 25.4 years): n=21 Older Group (mean age 71.7 years): n=21	Unstim whole: draining method Stim whole: gum base mastication	No participants were taking medication with xerogenic effects. Participants described as "healthy" or "generally healthy"	+ unstim whole - stim whole
Shern et al., 1993	Unstim & Stim Minor	N=51 26 Females 25 Males Age	Minor: strips cut from chromatograph	No participants were taking medications	= labial and buccal + palatal

		Range: 21-93 years Younger Group (< 41 years): n=17 Older Group (>60 years): n=18 Examined the salivary flow rates of males and females separately	y paper at labial, buccal, and palatal sites Stim whole: Parafilm mastication	that would influence with oral secretion. Participants described as "healthy" or "generally healthy"	- stim whole = unstim whole
Cowman et al., 1994	Unstim & Stim Parotid & SMSL	N=85 (total), n= 60* 32 Females 28 Males Age Range: 20-81 years *Used the control group for data extraction Younger Group (20-39 years): n=23	Parotid: modified Carlsson-Crittenden cup SMSL: cotton rolls isolate Wharton's duct & saliva collected by micropipette with light suction Stim parotid & SMSL: sterile	Participants were not using any medication with possible salivary gland effects (control group only)	+ unstim and stim SMSL and unstim parotid = stim parotid

		Middle-aged Group (40-59 years): n=15 Older Group (>60 years): n=22	2% citric acid solution to dorsal face of tongue at 30-sec intervals		
Meurman & Rantonen, 1994	Unstim & Stim Whole	N=187 Age Range: 20-60+ years Younger Group (20-40 years): n=36 Middle aged Group (41-60 years): n=88 Older Group (>60 years): n=63 Examined the salivary flow rates of males and females separately	Unstim whole: draining Stim whole: paraffin wax mastication	Typical population with regular medication use. Reported recruiting participants from dental clinic registries where older individuals appeared to be free of major systemic disease, but may have had some common age-related conditions.	+ unstim whole = stim whole
Percival et al., 1994	Unstim Whole &	N=116, 61 Females 55	Unstim whole: spitting	Participants were	+ unstim whole

	Stim Parotid	Males mean age 26.7± 1.06 years: n=29 mean age 50.4 ± 1.08 years: n=30 mean age 71.7 ± 1.07 years: n=28 mean age 84.03 ± 0.61 years: n=29	method Stim parotid: Lashley cup with 2% citric acid stimulation	reportedly unmedicated. Participants described as "healthy" or "generally healthy"	= stim parotid
Billings et al., 1996	Unstim & Stim Whole	N=710, 484 Females 226 Males Age Range: 19-88 years <30 years: n=55M, 99F 30-49 years: n=59M, 166F 50-69 years: n=61M, 110F 70+ years: n=51M, 109F	Unstim whole: Suction method of Bertram Stim whole: 2% citric acid	Older subjects were observed to take medications	=

		Examined the salivary flow rates of males and females separately			
Eliasson et al., 1996	Unstim Minor (Palatal, Buccal, and Labial)	N=127, 61 Females 66 Males Age Range: 22-89 years Younger Group (<40 years): n=14M, 12F Middle-aged Group (40-65 years): n=32M, 25F Older Group (>65 years): n=11M, 13F Examined the salivary flow rates of males and females separately	Periotron 6000 model 2 with standard filter paper	Some medication use. Reported using data from cohorts of community-dwelling volunteers	=
Fischer &	Unstim &	N=28, 14	Unstim	No participants	=

Ship, 1997; Fischer & Ship, 1999; Ship & Fischer, 1997	Stim Parotid	Females 14 Males Younger Group (20-35 years): n=14 Older Group (64-74 years): n=14	parotid: modified Carlson-Crittenden cup over Stenson's duct-parotid Stim parotid: 2% citric acid to dorsal lateral surface of tongue	were being treated for any systemic disease or taking any prescription or non-prescription medication. Participants described as "healthy" or "generally healthy"	
Yeh et al., 1998	Unstim Whole & Unstim & Stim Parotid & SMSL	N=1006 (total) n=247* 562 Females 444 Males *Used the nonmedicated group for Unstim Whole and Unstim & Stim SMSL *35-44 years: n=116 45-54 years: n=198	Unstim whole: spitting method Stim parotid & SMSL: citrate Unstim parotid: modified Carlson-Crittenden cup Unstim SMSL: micropipette connected to mini-vacuum	Participants were taking some medications in the whole population. Participants reported taking no prescribed or over the counter medications in the unmedicated subgroup.	+ unstim whole = unstim parotid + stim parotid + unstim & stim SMSL

		55-64 years: n=222 70-74 years: n=97 *>75 years: n=75 nonmedicated 35-44 years: n=55 45-54 years: n=58 55-64 years: n=50 65-69 years: n=41 70-74 years: n=30 >75 years: n=13 Examined the salivary flow rates of males and females separately	pump held over Wharton's duct	Reported using data from cohorts of community-dwelling volunteers	

Ghezzi et al., 2000;Ghezzi & Ship, 2003	Stim Parotid & SMSL	N=36, 18 Females 18 Males Younger Group (mean age 24.3 years): n=18 Older Group (mean age 69.9 years): n=18	Stim parotid: Modified Carlson-Crittenden cup over orifice of one gland with 2% citric acid applied to the dorsal surface of the tongue Stim SMSL: collected by light suction with 2% citric acid applied to the dorsal surface of the tongue	No prescription medications (other than HRT and birth control, and no non prescription antihistamines within 7 days). Participants described as "healthy" or "generally healthy"	=
Johnson et al., 2000	Stim Parotid & SMSL	N=80, 38 Females 42 Males Age Range: 35-76 years 35-44 years: n=19 45-54 years:	Stim parotid: mastication and gustatory stimulation - 0.1M citric acid was applied to the lateral surfaces of the tongue	No participants were taking medications. Reported using data from cohorts of community-dwelling volunteers	+ stim SMSL = stim parotid

		n=20 55-64 years: n=19 65-75 years: n=22	Stim SMSL: 0.1M citric acid was applied to the lateral surfaces of the tongue		
Salvolini et al., 2000	Unstim Whole	N=169, 95 Females 59 Males Age Range: 10-77 years 10-24 years: n=38 25-39 years: n=52 40-54 years: n=40 55-69 years: n=27 >70 years: n=12	Spitting method	No participants were taking any medication that would interfere with salivary secretion. Participants described as “healthy” or “generally healthy”	=
Yeh et al., 2000	Unstim Whole, Stim Parotid, & Unstim & Stim SMSL	N=399, 215 Females 184 Males Age Range:	Unstim whole: spitting method Unstim	Normal population with medication use.	+ unstim whole = stim parotid

		34-64 years Mean Age: 62.8 ± 0.6 years Examined the salivary flow rates of males and females separately	parotid: modified Carlson-Crittenden cup Unstim SMSL: micropipette over orifices of Wharton's duct and connected to mini-vacuum pump Stim parotid & SMSL: 2% citric acid swabbed over the lateral surfaces of the tongue	Reported using data from cohorts of community-dwelling volunteers	+ unstim & stim SMSL
Tanida et al., 2001	Unstim & Stim Whole	N=105 Healthy controls Age Range: 26-89 years 3rd decade: n=3 4th decade: n=5 5th decade: n=5	Unstim whole: Cotton rolls for saliva absorption Stim whole: ascorbic acid	Medication use was not reported	+

		6th decade: n=11 7th decade: n=10 8th decade: n=5 9th decade: n=6			
Streckfus et al., 2002	Stim Whole	N=50 Females only Age Range: 20-90 years	Mastication of a gum base	Participants were not taking any prescription medications. Participants described as "healthy" or "generally healthy"	+
Bakke et al., 2004	Unstim Whole	N=26 Females Younger Group (mean age 24 ± 3 years): n=13 Older Group (mean age 62 ± 4 years): n=13 Examined the	Draining Method	5 of the subjects took prescribed medications (birth control, hormones, NSAIDs). Participants described as	=

		salivary flow rates of males and females separately		"healthy" or "generally healthy"	
Bourdiol et al., 2004	Unstim & Stim Whole & Parotid	N=45, 22 Females 23 Males Younger Group (mean age 27.4 ± 2.3 years): n=25 Older Group (mean age 71.2 ± 2.1 years): n=20	Unstim whole & parotid: Cotton rolls for saliva absorption Stim parotid: Cotton rolls and parafilm chewing Stim whole: meat mastication	Medication use not reported. Participants described as "healthy" or "generally healthy".	=
Fenoll-Palomares et al., 2004	Unstim Whole	N=159, 107 Females 52 Males Age Range: 18-75 years Mean Age: 44.16 ± 14.23 years	Spitting method	Medication use not reported. Reported excluding participants with health problems that could affect salivary flow	+
Nagler & Hershkovich,	Unstim Whole	N=43, 22 Females 21	Unstim whole: spitting	Standard age-related	+

2005a, 2005b		Males Younger Group (mean age 21.2 ± 1.8 years): n=15 Older Group (mean age 75.8 ± 8.2 years): n=28	method	medication use, but no participant was using antidepressants or anticholinergics. Reported excluding participants with health problems that could affect salivary flow	
Moritsuka et al., 2006	Stim Whole	N=117, 84 Females 33 Males Younger Group (20-29 years): n=40 Middle aged Group (30-59 years): n=37 Older Group (60-88 years): n=40	Paraffin wax mastication	Some medication use for 18 subjects in the elderly group. Reported using data from cohorts of community-dwelling volunteers and recruiting participants from dental	+

				clinic registries where older individuals appeared to be free of major systemic disease, but may have had some common age-related conditions.	
Takada et al., 2006	Stim Whole	N=185 (total) n= 65* All female *Used the control group for data extraction Mean Age: 50.3 ± 12 years	Saxon Test	Medication use was not reported	=
Henkin et al., 2007	Stim Parotid	N=61, 21 Females 40 Males Age Range: 18-75 years <20 years: n=5 21-30 years:	Modified Lashley cup with lemon juice stimulation on the tongue	Participants were not taking any medication. Participants described as "healthy" or "generally	=

		n=15 31-40 years: n=23 41-50 years: n=46 51-60 years: n=46 61-70 years: n=37 >70 years: n=30		healthy”	
Hershkovich et al., 2007	Unstim Whole	N=44 Age Range: 20-80 years Younger Group (20-25 years): n=22 Older Group (70-80 years): n=22	Spitting method	No participants were taking saliva affecting drugs (e.g. anti-cholinergics or antidepressants) Participants described as “healthy” or “generally healthy”	+
Flink et al., 2008	Unstim & Stim Whole	N=1427, 758 Females 669	Unstim whole: draining	No exclusions based on	+ unstim whole

		Males 22-29 years: n=90M, 110F 30-39 years: n=120M, 157F 40-49 years: n=139M, 161F 50-59 years: n=155M, 158F 60-69 years: n=165M, 172F Examined the salivary flow rates of males and females separately	method Stim whole: paraffin mastication	medication use. Reported using data from cohorts of community-dwelling volunteers and recruiting participants from dental clinic registries where older individuals appeared to be free of major systemic disease, but may have had some common age-related conditions.	= stim whole
Malhotra et al., 2009	Unstim Whole	N=48 Age Range: 18-77 years Younger Group (18-40 years): n=16M	Cotton rolls for saliva absorption	Medication use not reported. Participants described as “healthy” or “generally healthy”	=

		Older Group (>65 years): n=16M, 16F Examined the salivary flow rates of males and females separately			
Sawair et al., 2009	Unstim Whole	N=244, 134 Females 110 Males Age Range: 15-76 years 15-19 years: n=32 20-29 years: n=106 30-39 years: n=32 40-49 years: n=28 50-59 years: n=29 ≥ 60 years: n=17	Spitting method	No participants were taking any medication that would interfere with salivary flow. Participants described as “healthy” or “generally healthy”.	+

Toida et al., 2010	Stim Whole	N=1188, 815 Females 373 Males Age Range: 20-90 years Mean Age: 51.4 ± 20.0 years Examined the salivary flow rates of males and females separately	Modified Saxon Test	Medication use was not reported. Reported using data from cohorts of community-dwelling volunteers	+
Chang et al., 2011	Unstim & Stim Whole	N=60, 30 Females 30 Males Younger Group (mean age 26.4 ± 2.4 years): n=30 Older Group (mean age 71.1 ± 4.6 years): n=30 Examined the salivary flow	Unstim whole: spitting method Stim whole: gum base mastication	No participants were taking psychiatric/neurologic medication or antihistamines. Reported excluding participants with health problems that could affect salivary flow	+ unstim whole M/F + stim whole M = stim whole F

		rates of males and females separately			
Marotta et al., 2012	Unstim Whole	N=90 Age Range: 20-65+ years Younger Group (20-40 years): n=30 Middle aged Group (41-65 years): n=30 Older Group (>65 years): n=30	Spitting method	No participants were taking inhaled, topical, or systemic corticosteroids or other immune modulating meds. Reported that participants with common illnesses such as hypertension and compensated diabetes were NOT excluded	+
Wang et al., 2012	Unstim Whole	N=191, 95 Females 96 Males 18-30 years (mean age 26 ±	Draining method	No participants were using medications that affects salivary production.	+

		3 years): n=48 31-40 years: n=48 41-50 years: n=48 51-75 years (mean age 56 ± 4 years): n=47		Reported excluding participants with health problems that could affect salivary flow	
Yoshikawa et al., 2012	Unstim & Stim Whole	N=70*, 19 Females 21 Males Age Range 42-79 years * Used healthy control group n=30 Younger (mean age 28.9 years): n=15 Older (mean age 68.2 years): n=15	Saxon test	Medication use was not reported	=
Smith et al., 2013	Stim Whole	N=540, 270 Females 270 Males	Gauze mastication	No participants were taking medications known to	+

		Younger Group (mean age 24.0 ± 3.1 years): n=180 Middle Aged Group (40-50 years): n=180 Older Group (mean age 75.2 ± 5.5 years):n= 180 Examined the salivary flow rates of males and females separately		affect salivation. Reported excluding participants with health problems that could affect salivary flow	

Appendix G: Ethics Approval

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Ruth Martin
Department & Institution: Health Sciences\Communication Sciences & Disorders,Western University

HSREB File Number: 105595
Study Title: Examination of Potential Salivary Effects of Oral Sensory Stimulation Substudy 3: The Effects of Oral Stimulation Associated with Manual and Electric Tooth Brushing on Whole Salivary Flow Rates in Healthy Older Adults
Sponsor:

HSREB Amendment Approval Date: November 26, 2014
HSREB Expiry Date: May 31, 2015

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Study title (Removed "Submandibular/Sublingual"), Study visits (from 4 to 2), Exclusion criteria (min. 20 natural teeth), Control activity added, Data sensors and videography added, Additional Instruments (comfort & difficulty of brushing), Additional items in questionnaires (dental history), updated poster	2014/10/08
Advertisement	Poster	2014/10/10
Revised Letter of Information & Consent		2014/10/08
Data Collection Form/Case Report Form	Revised Subject Questionnaire	2014/10/08
Instruments	Mouth Comfort Assessment	2014/10/08
Data Collection Form/Case Report Form	Data Collection Form	2014/10/08
Recruitment Items	Presentation Script	2014/10/10
Recruitment Items	Email Script	2014/10/10
Instruments	Questionnaire - Ease-of-Use	2014/10/08

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Amendment Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review. If an Updated Approval Notice is required prior to the HSREB Expiry Date, the Principal Investigator is responsible for completing and submitting an HSREB Updated Approval Form in a timely fashion.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Ruth Martin
Department & Institution: Health Sciences\Communication Sciences & Disorders,Western University

HSREB File Number: 105595
Study Title: Examination of Potential Salivary Effects of Oral Sensory Stimulation Substudy 3: The Effects of Oral Stimulation Associated with Manual and Electric Tooth Brushing on Whole Salivary Flow Rates in Healthy Older Adults
Sponsor:

HSREB Amendment Approval Date: January 05, 2015
HSREB Expiry Date: September 25, 2015

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Letter of Information & Consent	LOI and Consent PDF	2014/12/17
Revised Western University Protocol	Amended REB Application PDF	2014/12/17

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Amendment Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review. If an Updated Approval Notice is required prior to the HSREB Expiry Date, the Principal Investigator is responsible for completing and submitting an HSREB Updated Approval Form in a timely fashion.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

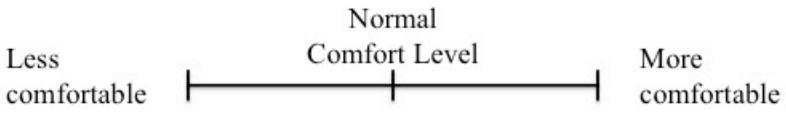
Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Appendix H: Visual Analog Scale (VAS) for Rating Mouth Comfort

Examination of Potential Salivary Effects of Oral Sensory Stimulation
Sub study 3: The Effects of Oral Stimulation Associated with Manual and Electric Tooth Brushing on Whole Salivary Flow Rates in Healthy Older Adults

How would you rate the comfort of your mouth at this moment?



Alphanumeric Identifier:

Date of Examination:

Form #:

Appendix I: Ease of Use Questionnaire

Examination of Potential Salivary Effects of Oral Sensory Stimulation

Sub study 3: The Effects of Oral Stimulation Associated with Manual and Electric Tooth Brushing on Whole Salivary Flow Rates in Healthy Older Adults

Alphanumeric Identifier:

Date of Examination:

Thank you for participating in our study. We have a few final questions we would like you to answer before you go.

1. Overall, the instructions I received for the tooth-brushing method and procedure were very easy to understand.

- o Strongly disagree
- o Somewhat disagree
- o Neither agree nor disagree
- o Somewhat agree
- o Strongly agree

2. The tooth-brushing procedure was very easy to complete.

- o Strongly disagree
- o Somewhat disagree
- o Neither agree nor disagree
- o Somewhat agree
- o Strongly agree

3. Would you use this tooth-brushing procedure in your daily routine? Yes or No
   Why or Why not

_____

_____

Appendix J: Medical and Dental History Questionnaire

PI: Dr. Ruth Martin

Examination of Potential Salivary Effects of Oral Sensory Stimulation

Sub study 3: The Effects of Oral Stimulation Associated with Manual and Electric Tooth Brushing on Whole Salivary Flow Rates in Healthy Older Adults

Subject Questionnaire

Alphanumeric Identifier:

Date of Examination:

1. Do you have any health conditions or illnesses? (e. g, diabetes, a heart condition, Sjogren's syndrome, high blood pressure)
2. Have you had any surgeries? (If so, what surgeries?)
3. Have you had teeth extracted? (If so, how many and when?)
4. Do you currently take any medicine? (If so, what medications and dosage?)
5. Do you have any allergies? (If so, what?)
6. Do you drink any alcohol? (If yes, how much do you drink a day?)
7. Do you smoke cigarettes? Have you ever smoked cigarettes? When did you quit?
8. Did you take any food, or drink, suck any candy, or brush your teeth after 8:00 am today?
9. Do you have dentures (complete or partial denture)?
10. Have you had any orthodontic treatment in the past? Do you have orthodontic appliances in your mouth?
11. Have you had any dental work in the last week? Do you have dry mouth?
12. Have you experienced any change in your sense of taste?
13. Do you have any condition or illness that affects your mouth?

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Curriculum Vitae

Personal Information

Name: Rebecca Hannah Affoo, MClSc, PhD (Candidate)

Main Affiliation: The Graduate Program of Health and Rehabilitation Sciences

Speech and Language Sciences

Western University

Education

2011–2015 Doctor of Philosophy

The Graduate Program of Health and Rehabilitation Sciences

Speech and Language Sciences

Western University, London, Ontario, Canada

Supervisor: Dr. Ruth Martin

PhD Thesis: "EATING AND SWALLOWING, ORAL HEALTH, AND SALIVA PRODUCTION ”

2006–2008 Master of Clinical Science

School of Communication Sciences and Disorders

Western University, London, Ontario, Canada

2002–2006	Bachelor of Health Science
	Faculty of Health Sciences
	Western University, London, Ontario, Canada

Teaching Experience

January 2014–May 2015	Limited Duties Lecturer
	Western University
	Faculty of Health Sciences
	Communication Sciences and Disorders 9643: Clinical Applications in Swallowing and Dysphagia
	Design and implement curriculum, lectures/lesson plans, and assessments.
	Present lectures and other learning materials.
	Facilitate discussion, critical thinking, problem solving.

Clinical Experience

2008–2015	Speech-Language Pathologist
	London Health Sciences Centre
	800 Commissioners Road East
	London, Ontario, Canada
	Perform speech, language, and swallowing assessment, management, treatment, counselling, and education with a variety of patient populations within the acute hospital setting.
	Perform the above duties within a team-based culture involving daily innovation, communication, collaboration, organization, and planning with other care team members.
	Supervise clinical Speech-Language Pathology students.

Research Experience

2011–Present	Researcher in Dr. Ruth Martin's Swallowing Laboratory
	Western University
	Perform academic duties such as contributing to research program development, contributing and collaborating on grant applications, researching ethics applications, and researching manuscripts and posters.
	Perform managerial tasks such as directing and planning research projects and collaborating, communicating, and organizing with other laboratory members.

Awards

2014–2015	Ontario Graduate Scholarship $15,000 for the 2014/15 academic year Awarded to the most accomplished students based on merit in all disciplines of graduate study at Western University.
2014	American Geriatrics Society Scientist-In-Training Award Awarded to a pre-doctoral candidate who submitted the most outstanding abstract for the 2014 AGS Annual Meeting.
2014	Canadian Institutes of Health Research Institute Community Support Travel Award through the Institute of Aging Awarded to applicants who demonstrated excellence in health research with a focus on aging.
2012–2013	Alzheimer Foundation London and Middlesex Doctoral Scholarship in Alzheimer Related Research $25,000 awarded over two years Awarded to one PhD student conducting Alzheimer's disease or related dementia research at Western University.

Publications

Refereed Journal Publications

Affoo, R.H., Foley, N., Garrick, R., Siqueira, W.L., & Martin, R.E. (2015). A Meta-Analysis of Salivary Flow Rates in Healthy Young and Elderly Adults. *Journal of the American Geriatrics Society. 63*(10), 2142-51.

Foley, N., **Affoo, R.H.**, & Martin, R.E. (2014). A Systematic Review and Meta-Analysis Examining Pneumonia-Associated Mortality in Dementia. *Dementia and Geriatric Cognitive Disorders. 39*, 52-67.

Abe, K., Weisz, S.E.M., Dunn, R.L., DiGioacchino, M.C., Nyentap, J.A., Stanbouly, S., Theurer, J.A., Bureau, Y., **Affoo, R.H.**, & Martin, R.E. (2014). Occurrences of Yawn and Swallow are Temporally Related. *Dysphagia. 30*(1), 57-66.

Affoo, R.H., Foley, N., Rosenbek, J., Shoemaker, J.K., & Martin, R.E. (2013). Swallowing Dysfunction and Autonomic Nervous System Dysfunction in Alzheimer's Disease: A Scoping Review of the Evidence. *Journal of the American Geriatrics Society. 61*(12), 2203-2213.

Affoo, R.H., Dasgupta, M., & Martin R.E. (2012). Dysphagia in Delirium. Two Case Studies [letter to the editor]. *Journal of the American Geriatrics Society. 60*(10), 1975-6.

Refereed Presentations

Foley, N., **Affoo, R.H.**, Siqueira, W.L., & Martin, R.E. A Systematic Review Examining the Oral Health Status of Persons with Dementia. Poster Presentation, *American Geriatrics Society Meeting,* National Harbor, Maryland, USA, May 15-17, 2015.

Foley, N., **Affoo, R.H.**, Siqueira, W.L., & Martin, R.E. A Systematic Review Examining the Oral Health Status of Persons with Dementia. Poster Presentation, *Dysphagia Research Society Meeting*, Chicago, Illinois, USA, March 11-14, 2015.

Affoo, R.H., Foley, N., Garrick, R., & Martin, R.E. A Meta-Analysis of Salivary Flow Rates in Young and Older Healthy Adults. Poster Presentation, *Canadian Association on Gerontology Annual Meeting*, Niagara Falls, Canada, October 16-18, 2014.

Felfeli, T., Foley, N., **Affoo, R.H**., & Martin, R.E. Weight Loss in Alzheimer's Disease Patients: A Meta-Analysis. Poster Presentation, *Canadian Association on Gerontology Annual Meeting*, Niagara Falls, Canada, October 16-18, 2014.

Affoo, R.H., Foley, N., Garrick, R. & Martin, R.E. Meta-analysis of the Effects of Age on Whole Salivary Flow. Poster Presentation, *The International Association of Dental Research General Session*, Cape Town, South Africa, June 25-28, 2014.

Affoo, R.H., Foley, N., Garrick, R. & Martin, R.E. Age-Related Changes in Salivary Flow: A Systematic Review and Meta-Analysis. Poster Presentation, *The American Geriatrics Society 2014 Annual Scientific Meeting*, Orlando, Florida, May 15-17, 2014.

Foley, N., **Affoo, R.H**., & Martin, R.E. A Systematic Review and Meta-Analysis Examining Pneumonia-Associated Mortality in Dementia. Poster Presentation, *The American Geriatrics Society 2014 Annual Scientific Meeting*, Orlando, Florida, May 15-17, 2014.

Affoo, R.H. & Martin R.E. A Systematic Review of Dysphagia in Individuals with Dementia. Poster Presentation, *Dysphagia Research Society Annual Meeting*, Seattle, Washington, March 14-16, 2013.

Affoo, R.H. & Martin R.E. Swallowing Deficits in Dementia: What do we know? Oral Presentation, *CASLPO – OSLA "Energized by Excellence" Conference*, Toronto, Canada, October 18, 2013.

Affoo, R.H. & Martin R.E. Dysphagia in Individuals with Dementia: A Systematic Review of the Evidence. Poster Presentation, *Canadian Association on Gerontology Meeting*, Vancouver, Canada, October 18-20, 2012.

Affoo, R.H. & Martin R.E. Dysphagia in Individuals with Alzheimer's disease: A Systematic Review of the Evidence. Poster Presentation, *Alzheimer's Association International Conference*, Vancouver, Canada, July 14-19, 2012.

Affoo, R.H., Dasgupta, M., & Martin R.E. Dysphagia in Delirium. Two Cases. Poster Presentation, *Canadian Geriatric Society Annual Meeting*, Quebec City, Canada, April 20-21, 2012.

Invited Articles

Affoo, R.H. (2014) Dysphagia Care for individuals with Dementia. Invited article for Dysphagia Café Website http://www.dysphagiacafe.com/2014/10/01/dysphagia-care-for-individuals-with-dementia/

Presentations

Non-Refereed Presentations

Affoo, R.H., Foley, N., Garrick, R. & Martin, R.E. Meta-Analysis of Salivary Flow Rates in Healthy Young and Elderly Adults. Oral Presentation, Western Research Forum, London, Canada, March 18, 2014.

Affoo, R.H., Foley, N., Garrick, R., & Martin, R.E. A Meta-Analysis of Salivary Flow Rates in Young and Older Healthy Adults. Poster Presentation, Aging, Rehabilitation and Geriatric Care of the Lawson Health Research Institute/Faculty of Health Sciences Research Symposium, London Canada, February 7, 2014.

Affoo, R.H. & Martin R.E. Dysphagia in Individuals with Alzheimer's disease: A Systematic Review of the Evidence. Oral Presentation, Western University Health and Rehabilitation Science Graduate Research Forum, London, Canada, February 6, 2013.

Affoo, R.H. & Martin R.E. A Systematic Review of Dysphagia in Individuals with Dementia. Poster Presentation. Poster Presentation, Aging, Rehabilitation and Geriatric Care of the Lawson Health Research Institute/Faculty of Health Sciences Research Symposium, London Canada, February 1, 2013.

Affoo, R.H., Dasgupta, M., & Martin R.E. Dysphagia in Delirium. Two Cases. Poster Presentation, Aging, Rehabilitation and Geriatric Care of the Lawson Health Research Institute/Faculty of Health Sciences Research Symposium, London Canada, February 3, 2012.