Chemosensory dysfunction in diabetes mellitus: A reason for higher consumption of sugar and salt? NHANES 2013-2014

Master's Thesis
Biomedical Engineering & Informatics, 2017
School of Medicine and Health, Aalborg University
Camilla Urup Noe Andersson

AALBORG UNIVERSITY
STUDENT REPORT

School of medicine and health
Biomedical Engineering and Informatics
Niels Jernes Vej 12, A5
9220 Aalborg East
Telephone 9940 8752
http://www.smh.aau.dk/

Title:
Chemosensory dysfunction in diabetes mellitus: A reason for higher consumption of sugar and salt? NHANES 2013-2014

Theme:
Master's thesis

Project period:
4. semester master Spring 2017

Project group:
17gr10403

Member:

Camilla Urup Noe Andersson

Supervisor:

Simon Lebech Cichosz

Pages: 82

Concluded: d. 07-06-2017

Synopsis:

Adults with diabetes mellitus (DM) reached 422 million in 2014. DM may cause chemosensory dysfunction. This study used data from NHANES to investigate if diabetic participants with chronic complications (e.g. retinopathy and nephropathy) would develop taste and smell impairment due to the chronic complications and if the impairment would create a higher craving for sugar and salt compared with controls. Participants were divided into three groups; 304 with non-complicated DM, 199 complicated DM and a 2702 in control group. DM was defined as $HbA1_c$ $\geq$6.5%. The study demonstrated that both non-complicated and complicated DM had a higher percentage of smell impairment (21.1-27.1%) vs. controls (15.5%). The study did not find relation between DM and taste impairment. The two DM groups consumed significant less of sugar and calories, though sodium levels was the same when compared to controls. To find predictors for a higher consumption of salt and sugar in DM, stepwise multiple linear regression was applied. The regression model found that (1) gender and age was the most significant predictors of food consumption, (2) if a participant had smell impairment, 359 less kcal was consumed. Further research is needed to address eating habits and food choices in patients with diabetes and in the general public to prevent an further epidemic growth of diabetes.

Resumé

Kemosensorisk dysfunktion i diabetes mellitus: En årsag til højere indtagelse af sukker og salt? NHANES 2013-2014
Igennem de seneste årtier er forekomsten af type 2-diabetes og fedme steget betydeligt. Omtrent 90% af alle type 2-diabetes tilfælde kan relateres til overvægt.
Diabetes og fedme er et globalt problem, hvor 13% af verdens voksne befolkning er overvægtige, og antallet af voksne med diabetes nåede 422 millioner i 2014.
Forekomsten af type 2-diabetes skyldes hovedsageligt udbredelsen af stillesiddende arbejde og livsstil samt et øget indtagelse af sukkerholdig og fed mad. Livsstilsfaktorer såsom forhøjet kolesterol, forhøjet blodtryk og nedsat fastende glukose overses ofte eller ignoreres og kan med tiden udvikle sig til type 2-diabetes eller hjerte-kar-sygdom.
Hvis diabetes ikke behandles korrekt, kan kroniske diabetiske komplikationer udvikle sig. Kroniske komplikationer ved diabetes kan være, diabetisk nefropati, retinopati og neuropati. Nefropati er den mest alvorlige sendiabetiske komplikation og hyppigste årsag til nyresvigt. Perifer neuropati kan forårsage fod sår og retinopati kan forårsage blindhed.

Visse sygdomme der iblandt personer med diabetes kan opleve forringelse af smag og lugtesans. Disse sanser er vigtige, når der skal smages eller duftes til mad. Et godt eksempel er smagen af sødt som er forbundet med en positiv sensorisk tilfredsstillelse.
En øget smagstærskel for sødt er rapporteret hos personer med forekomst af både type 2-diabetes og type 1-diabetes sammenlignet med raske personer. Dette kan muligvis være med til at skabe en ond cirkel hvor diabetespatienten udvikler en øget smagstærskel for salt og sukker, der resulterer i en forværring af sygdommen, der i den sidste ende forårsager hypertension og hyperglykæmi.
Nedsat smagssans er fundet hos 80% af dårligt kontrollerede diabetespatienter og hos 50% af de kontrollerede diabetiske deltagere sammenlignet med en rask kontrolgruppe.

National Health and Nutrition Examination Survey (NHANES) har indsamlet data angående smag- og lugtsans fra 2012 til 2014. NHANES er en open source database indeholdende en stor mængde data, der gør det muligt at undersøge diabetes, kostvaner og smag- og lugtesansen i flere retninger.

Baseret på nuværende viden om diabetes og kemosensorisk dysfunktion er følgende to formål identificeret.

Formål 1: Identificering af mulige forskelle i smag- og lugtfunktion hos deltagere med diabetes med eller uden komplikationer sammenlignet med kontrolgruppen og undersøge indvirkningen på indtagelse af salt og sukker.

Formål 2: Anvend en modelleringsteknik til at undersøge diabetes og mulige faktorer af et højere indtag af sukker, salt og kalorier.

Deltagerne i NHANES blevet delt op i tre grupper: (1) diabetes uden komplikationer med en $HbA1_c$ værdi $\geq$ 6.5%, (2) diabetes med komplikationer (nefropati, retinopati, hjertekramper, hjerteanfald og slagtilfælde) og $HbA1_c$ værdi på $\geq$ 6.5%, (3) kontrolgruppen med en $HbA1_c$ værdi $\leq$6.4%.

Resultatet af undersøgelsen i denne rapport var at både ikke-kompliceret diabetes og kompliceret diabetes havde en højere procentdel af manglende lugtesans henholdsvis 21,1% og 27,1% sammenlignet med kontrolgruppen uden diabetes på 18,4%.
Det skal bemærkes, at de to grupper med diabetes havde en højere alder sammenlignet med kon-

trolgruppen. Nedsat lugtsans ses hos over 50% af befolkningen over 65 år.
Undersøgelsen fandt ikke en sammenhæng mellem diabetes og nedsat smagssans.

En analyse af kostvaner, viste et andet resultat end et forventet højere indtag af salt, sukker og kalorier. De to grupper med diabetes indtog signifikant mindre sukker og kalorier som helhed, dog var natrium på samme niveau.
Dette står i kontrast til det signifikant højere BMI målt i gruppen med diabetes, som ellers må antage at spise mad med et højere kalorieindhold. Det lavere indtag af kalorier og sukker kan skyldes, at diabetespatienter er opmærksomme på konsekvensen af at spise for meget sukker. En del af deltagerne var også på kur under interviewet. I begge grupper med diabetes var omkring 32% på en diæt sammenlignet med kun 15,5% i kontrolgruppen. Dette kan gør det svært, at komme med et retvisende billede af indtagelse af sukker, salt og kalorier.

For at undersøge sammenhæng mellem manglende smags- og lugtesans og diabetes og hvordan det kan påvirke gruppens valg af mad blev der udført en multipel lineær regressions analyse.
Det generelle billede, baseret på de fremkomne resultater, er at køn har den højste indvirkning på kostvaner. Alder har ligeledes indflydelse på indtagelse af salt og kalorier. Des ældre deltagerne bliver jo mindre spiser de. Lugtesans testen har også en betydelig indflydelse på kalorieindtaget. En stigning i $HbA1_c$ ser ud til at have indflydelse på natriumindtaget.
For at udvide forståelsen af manglende smag- og lugtesans hos patienter med diabetes, kan der i fremtidige studier medtages yderligere faktorer som muligvis også kan fremkalde kemosensorisk dysfunktion. Det kunne være rygestatus, medicin og socioøkonomiske problemer.
Yderligere er det vigtig at undersøge kostvaner hos patienter med diabetes og i den generelle befolkning for at forhindre en yderligere epidemisk vækst af diabetes.

Preface

This master thesis has been written by Camilla Urup Noe Andersson (group 17gr10403) during the 4^{st} semester of the Master programme in Biomedical Engineering and Informatics at Aalborg University. The master thesis title is "Chemosensory dysfunction in diabetes mellitus: A reason for higher consumption of sugar and salt? NHANES 2013-2014".
The thesis has been supervised by Simon Lebech Cichosz.

Reading Guide

This thesis consists of 3 parts and 1 chapters, and 3 appendices. Figures and tables are numbered by chapter and section.

In chapter 1 the thesis' overall dilemma and the initial problem is presented. Part I contains 4 chapters. Chapter 2 contains information on the development of diabetes, diabetes types, and diabetic complications. Chapter 3 contains information about taste and smell senses and what may cause and impairment. Chapter 4 contains a literature search of current knowledge on diabetes and chemosensory dysfunction. Lastly chapter 5 that contains a summary.

Part II contains 4 chapters. Chapter 6 contains aim and method strategy for the study. Chapter 7 explained applied data. Methods and theory are presented in chapter 8 and results are found in chapter 9. Part III contains a discussion and conclusion.

In appendix A, a literature protocol provided. Table A.7 contains main findings in the found articles. Appendix B contains information about missing data i NHANES. Lastly appendix C contains used NHANES codes.

Applied literature is presented in alphabetical order in the bibliography. Literature will be specified by author, title, edition and publishing. Web pages are specified by, information about the author(s), title, URL address, and access data.
Literature references in this reports is structured by the Harvard method [Last name, year]. If a reference is set after a dot, the literature has been used for the previous section and if the reference is set before a dot the literature only concern the sentence.

Contents

Chapter 1

Introduction

The prevalence of type 2-diabetes along with obesity has increased substantially over the past several decades [Neiers et al., 2016]. 90% of developed type 2-diabetes is related to excess weight [Verma and Hussainb, 2017].
Diabetes and obesity affects globally, with 13% of the world's adult population being obese [WHO, 2016b] and the number of adults with diabetes reached 422 million in 2014 [WHO, 2016a].

The number of type 2-diabetes is increasing worldwide as well in Denmark. From 1996 to 2012, diabetes raised from 113,598 to 320,545 cases. [Det Nationale Diabetesregister, 2012] Given a prevalence of diabetes on 5.7% pr. 100,000 inhabitants in Denmark as illustrated in figure 1.1. It is estimated that 200,000 has diabetes without knowing it. [Eiken and Snorgaard, 2016]

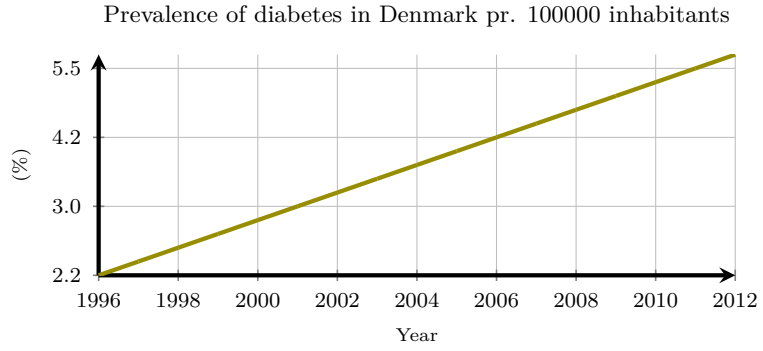


Figure 1.1: Prevalence of diabetes in Denmark from 1996 to 2012 [Det Nationale Diabetesregister, 2012].

One of the main contributors to these health issues are due to increased consumption of energy-dense foods containing high contents of sweet carbohydrates and saturated fat [Neiers et al., 2016]. The food choices are triggered by many factors; e.g. what the eyes see, smell, and memory of food. The anticipation for food is linked with activation of defined regions of the hypothalamus. [Leng et al., 2016] Taste perception plays a key role for our strong preference for sweet food and regulating the energy intake. Detection of sweet food in the oral cavity provides information on the calories and macronutrients of ingested food by generating a strong sensory comfort. [Neiers et al., 2016, Laffitte et al., 2014]

Various diseases including diabetes are affected by chemosensory dysfunction. The dysfunction covers gustatory (taste) and olfactory (smell) impairment. Several studies has described an increased sweet taste threshold in both patients with type 1-diabetes Khobragade et al. [2012] and type 2-diabetes Gondivkar et al. [2009], Wasalathanthri et al. [2014] compared with healthy controls. The reason for this dysfunction is not completely understood, and whether the taste and smell impairment is due to pathophysiological changes related to diabetes, its confounders e.g. obesity, or such as medicine intake, or a combination [Naka et al., 2010, Wasalathanthri et al., 2014].

Impaired taste and smell function in patients with diabetes is associated with a greater craving for high carbohydrate containing foods and thereby likely to consume more sugar compared to non-diabetics. The higher craving for carbohydrates may possibly reveal a vicious circle, where a higher consumption of sugar can exacerbate hyperglycemia. [Wasalathanthri et al., 2014]

Taste and smell impairment pose a threat to health in general e.g. food preferences, quality of life, and nutritional status are affected by the impairment [Liu et al., 2016]. Patients who have taste and smell impairment are not often aware of the problem when comparing self-assessment ratings with measurements of taste and smell that did not correlate. [Naka et al., 2010]

Approximately 14 million elderly in the U.S. may suffer from smell impairment. Less is known about taste [Liu et al., 2016]. The National Health and Nutrition Examination Survey (NHANES) have collected data on taste and smell from 2012 to 2014 to investigate different aspects of taste and smell impairment. E.g. physiologic variations of taste and smell correlated to nutritional and obesity data. [CDC and NCHS, 2013] Liu et al. [2016] found that the prevalence of diabetes with impairment was 21.2% for smell and 15.7% for taste in the NHANES taste and smell survey.

NHANES is an online open source database with a large amount of data that enables to study diabetes in multiple directions. Therefore, it could be interesting to investigate diabetes joined with taste and smell protocol, and dietary interview to find possible patterns of how diabetes are affected by taste and smell impairment and what this may do to eating habits. On this basis the initial problem has been formulated.

Initial problem

Diabetes mellitus, is a disease with a wide range of chronic complications. What consequence may chronic complications have on chemosensory dysfunction is the dysfunction affecting the taste and smell senses?

Part I

Background

Chapter 2

Pathogenesis of diabetes mellitus

To investigate relation between diabetes and impairment of taste and smell, knowledge about normal glucose tolerance and how diabetes develops and manifests in both type 1- and type 2- diabetes is important. Knowledge about diabetic complications is also essential. The development of either type 1- or type 2-diabetes is illustrated in figure 2.1. To understand why diabetes develop chemosensory dysfunction (taste and smell impairment) knowledge about the anatomy and physiology of the gustatory (taste) and olfactory (smell) senses and possible impairment are also explored. Lastly, a section with current knowledge about diabetes and the effect on taste and smell.

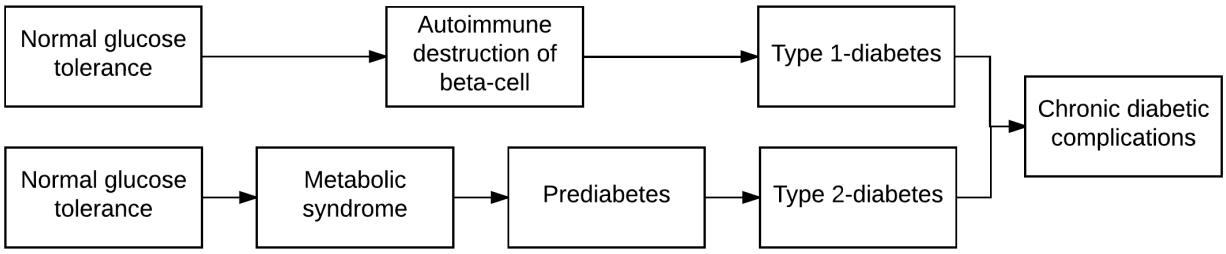


Figure 2.1: If the normal glucose tolerance is interrupted in some way, the end result could be the development type 1-diabetes or type 2-diabetes. The pathologic way is different for the two types but both can develop chronic diabetic complications. [Leahy, 2005, Sen et al., 2016]

2.1 Normal glucose tolerance

When humans consume food high in carbohydrates, like a cake, the glucose level in the blood rises and the body reacts by secreting the hormone insulin that works as transporter for glucose so that it can enter the cells to be used in combustion and/or storage, as illustrated in figure 2.2. Normal blood glucose levels are the result of an efficient pancreas secreting insulin when food is consumed. [Martini and Nath, 2009a]

The pancreas is a part of the endocrine system but it functions as both an endocrine and exocrine organ. 99% of the cells in the pancreas has an exocrine function that produces digestive enzymes. The endocrine part of the pancreas consists of small cell clusters. The clusters are called pancreatic islets. A normal pancreas contains roughly 2 million islets. The pancreatic islets are surrounded by a capillary network that sends the hormones into the bloodstream. Each islet contains four different cell types δ-, F-, α- and β-cells. β-cells produces and secretes insulin when blood glucose levels rises. Insulin lowers blood glucose levels by increasing the rate of glucose uptake and usage by most body cells. Insulin also increases glycogen synthesis in skeletal muscles and liver. α-cells produces and secretes the hormone glucagon. Opposite insulin, glucagon raises the blood glucose levels by stimulating the breakdown of glycogen and glucose release by the liver. [Martini and Nath, 2009a]

Figure 2.2 illustrates a healthy pancreas and how the β-cells produce insulin and afterwards the insulin is transported to bloodstream reaching the cells so that glucose can be absorbed into the cells.

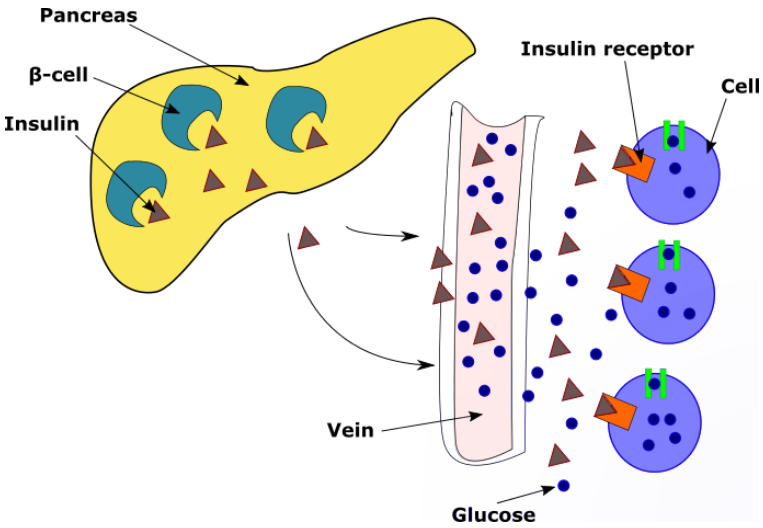


Figure 2.2: illustrates how healthy β-cells produce insulin (gray triangles) and afterwards it is transported to the bloodstream reaching cells so that glucose (blue circles) can be absorbed into the cells. [Martini and Nath, 2009a, Eiken and Snorgaard, 2016]

2.2 Diabetes mellitus

Diabetes mellitus (diabetes) covers a number of diseases with a changed glucose metabolism resulting in abnormally high blood glucose levels (hyperglycemia). Which type of diabetes (type 1- and type 2-diabetes, secondary etc.) the patient gets depends on ethology and pathogenesis. [Eiken and Snorgaard, 2016]

2.2.1 Type 1-diabetes

The vast majority of type 1-diabetes is caused by cell-mediated destruction of the β-cells in pancreas. This autoimmune effect will cause the pancreas to fail to produce insulin and thereby absolute insulin deficiency as illustrated in figure 2.3.

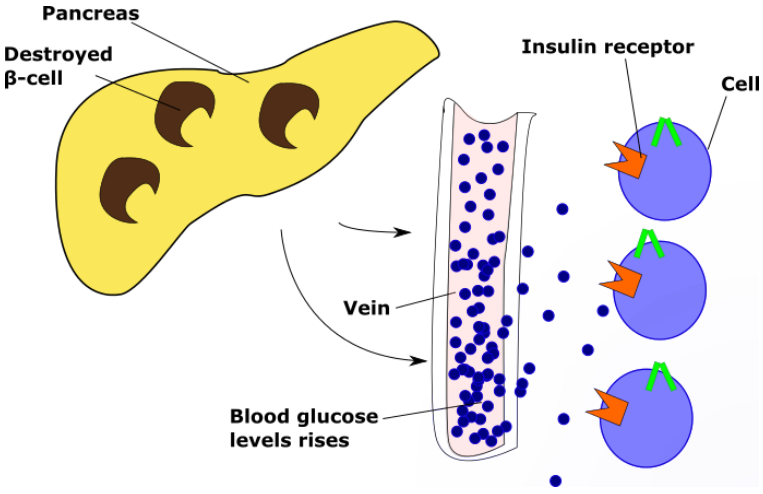


Figure 2.3: illustrates what happens if a patient has type 1-diabetes. The β-cells in the pancreas does not longer produce insulin due to an autoimmune defect where the immune system attacks the β-cells. [Martini and Nath, 2009a, Eiken and Snorgaard, 2016]

Lack of insulin leads to hyperglycemia and thereby lack of intracellular glucose which is necessary for cells metabolism and energy production. [Eiken and Snorgaard, 2016] This makes type 1-diabetes insulin-dependent. Type 1-diabetes normally occurs by age 20, though it can occur at any age and

the majority of patients that develops type 1-diabetes are not obese. [O'Keefe et al., 2009]

Symptoms of type 1-diabetes are e.g. thirst, polyuria, fatigue, dehydration, weight loss, infection, and nausea. There are approximately 30,000 patients with type 1-diabetes in Denmark. [Eiken and Snorgaard, 2016]

2.2.2 Metabolic syndrome and prediabetes

The normal body metabolism can become disrupted by different factors causing type 2-diabetes and cardiovascular disease if untreated. These factors are collectively known as the metabolic syndrome. The risk factors/symptoms are abdominal obesity, dyslipidemia (raised triglycerides and lowered high-density lipoprotein (HDL) cholesterol), raised blood pressure, and raised fasting glucose. [Fernández-García et al., 2013] The metabolic syndrome has become a serious health issue and its prevalence is increasing together with obesity and sedentary lifestyle. The factors/symptoms are often ignored or overlooked before type 2-diabetes evolves [O'Keefe et al., 2009]. When diagnosing metabolic syndrome, the limit values are:

- Abdominal obesity $\geq$94 cm for men and $\geq$80 cm for women
- Triglycerides $\geq$ 1.7 mmol/l
- HDL cholesterol $<$ 1.0 mmol/l for men and $<$ 1.3 mmol/l for women
- Blood pressure $\geq$ 130/85 mmHg
- Impaired fasting glucose (fasting glucose $\geq$ 5.6 mmol/l)

A group of patients will have a high glycated hemoglobin A1c $(HbA1)_c$ value in the normal range (over 6%) followed by one or more metabolic symptoms and a diagnosed with prediabetes. These patients have a 4 to 5 times the change of developing diabetes. [Eiken and Snorgaard, 2016]

2.2.3 Type 2-diabetes

Type 2-diabetes is normally a disease which develops slowly over several years. Type 2-diabetes accounts for 85-90% of all diabetic cases. The central pathogenesis in development of type 2-diabetes is abdominal obesity, insulin resistance, dyslipidemia, and hypertension.
Through the years the body has compensated for the insulin resistance by producing more insulin. When this function declines, blood glucose level rises. Figure 2.4, illustrates insulin resistance and thereby the increased blood glucose level which consequence is hyperglycemia. [Eiken and Snorgaard, 2016]

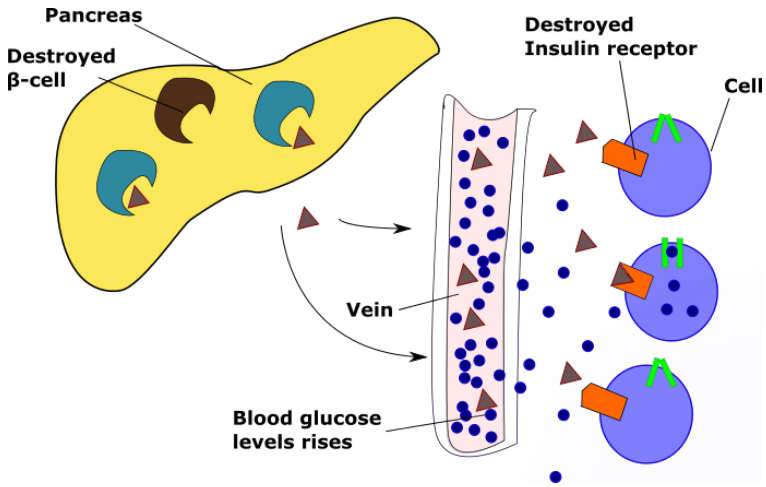


Figure 2.4: illustrates what happens if a patient develops type 2-diabetes. Here the pancreas produces more insulin due to cells insulin receptors become insulin resistant. β-cells will also be destroyed with time. [Martini and Nath, 2009a, Eiken and Snorgaard, 2016]

Symptoms of type 2-diabetes are fatigue and postprandial hypoglycemia. If type 2-diabetes is undetected for years, complications can be myocardial infarction, stroke, loss of vision, and peripheral neuropathy. About one-third of type 2-diabetes will at some point require insulin therapy. Diet, exercise, and weight loss can improve insulin resistance. Bariatric surgery can in approximatively 75% of the cases result in recovery from type 2-diabetes. [O'Keefe et al., 2009]

In recent decades, the prevalence of type 2-diabetes in Denmark and worldwide has been increasing due to our modern lifestyle with physical inactivity, excessive eating behavior causing an obesity epidemic. [Eiken and Snorgaard, 2016]

2.3 Identifying diabetes

If it is suspected that a patient has diabetes, a set of tests is performed to diagnose the patient as described below:

- Fasting plasma glucose $\geq$ 7.0 mmol/l measured twice on two separate days
- Diabetic symptoms and plasma glucose $\geq$ 11.1 mmol/l
- 2 hours after 75 g peroral glucose $\geq$ 11.1 mmol/l (OGTT = oral glucose tolerance test)

In Denmark, since 2012 the recommended standard has been the measurement of long-term blood glucose. When hemoglobin joins glucose it comes "glycated". By measuring glycated Hemoglobin A1c ($HbA1_c$), an overall picture of the patients average blood sugar levels can be measured over a period of 8-12 weeks. [Eiken and Snorgaard, 2016]
If $HbA1_c$ is $\geq$ 6.5% it indicates that the patient has diabetes [Dansk Selskab for Almen Medicin, 2012].

2.4 Chronic complications

If diabetes is untreated a range of chronic complications will develop with time. Chronic complications of diabetes are micro- and macroangiopathy. Microangiopathy is a disorder of the small vessels in the eyes, kidneys, and nerves. Macroangiopathy are cardiovascular disease and vascular stiffness in the heart, brain, and peripheral vessels. [Eiken and Snorgaard, 2016]

Diabetic nephropathy is the most severe long term complication and is the most common cause

of renal failure. Degenerative changes in the kidneys are caused by hyperglycemia and the condition is often worsened by presence of hypertension and neuropathy. [Eiken and Snorgaard, 2016]

Diabetic peripheral neuropathy and/or arterial insufficiency can cause problems with diabetic foot ulcers which ultimately may result in amputation of the foot. [Sen et al., 2016]

Diabetic retinopathy damages the eyes retina causing vision impairment and blindness. Diabetic retinopathy can be prevented by optimal glycemic control. [Sen et al., 2016]

Cardiovascular disease occurs more often in diabetic patients when compared with the general population. Hypertension and dyslipidemia increases the risk of cardiovascular disease. Smoking also increases the risk. Diabetic cardiovascular disease consists of coronary heart disease, cardiac insufficiency, arterial insufficiency, and cerebral ischemia (insufficient blood flow to the brain). [Eiken and Snorgaard, 2016]

Chapter 3

Chemosensory function and dysfunction

When food is consumed different chemosensory senses pick up the savors and odors. Nutrients, which the human organism need enters our body by the mouth and chemicals are detected by the nose as illustrated in figure 3.1. Taste receptors in the mouth and smell receptors in the nose can warn against of environmental hazards, but also determine the flavor of our foods and beverages, fulfilling the need for nutrients. [Doty, 2015a]

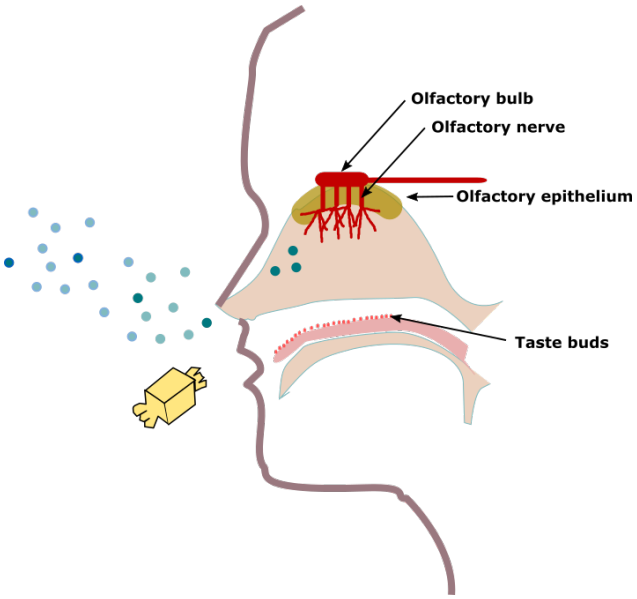


Figure 3.1: illustrates the chemosensory function in humans. When airborne particles reach the nose, smell receptors within the nasal cavity are stimulated and sends a signal to the cerebral cortex. Or if sweets are eaten, taste receptors on the tongue register sweetness. The illustration is developed on the basis of Martini and Nath [2009b].

3.1 Gustation - sense of taste

At birth a child has around 10,000 taste buds but as it gets older the number declines. An adult has about 5000 taste buds. Taste receptors are distributed over the superior surface of the tongue and in the pharynx and larynx. Taste sensitivity differs significantly among individuals. E.g. phenylthiocarbamide (PTC) tastes bitter to some, but is tasteless to others. [Martini and Nath, 2009b]
There are five fundamental taste modalities (sweet, salty, bitter, sour, and umami), which plays role in dietary choice. [Neiers et al., 2016]
E.g. the sweet taste perception has an ability to detect carbohydrates and to ensure energy-dense food intake. Sweetness is associated with a highly positive sensory pleasure. Sweet taste receptors is expressed in taste buds on the tongue. The receptors are also expressed in extra-oral tissues, including the pancreas, stomach, liver, gut, and brain. [Neiers et al., 2016]

A range of diseases and interventions e.g. surgery are associated with alterations of taste function. It could be the release of bad-tasting materials from oral medical conditions, excessive dryness of the oral cavity, damage to taste pores from a burn, destruction or loss of taste buds themselves.

Damage to the central nervous system caused by e.g. tumor, epilepsy or stroke. Lastly taste impairment can be cause by systemic disturbance of metabolism that presumably will affect the taste senses e.g. medications, diabetes, liver or kidney disease. [Bromley and Doty, 2015]

3.2 Olfaction - sense of smell

When air is inhaled through the nose, air swirls within the nasal cavity and brings airborne particles to the olfactory organs, see figure 3.1. Olfactory stimulation reaches the cerebral cortex directly. The sense of smell is mediated by olfactory (smell) receptor cells in the epithelium of the nasal cavity. Smell receptors, are directly exposed to the outside environment. The underlying layer consists of areolar tissue, numerous blood vessels, and nerves. Between 10 and 20 million smell receptors are packed into an area of roughly 5 cm^2. The total number of receptors declines with age, and those that remain become less sensitive. [Martini and Nath, 2009b]

Olfactory impairment is not uncommon, 1-2% of the population under the age of 65 years and >50% in the population older than 65 years are affected by smell impairment.
Many factors can have an implication on the impairment. Medication (e.g. antihistamines), endocrine and metabolic (e.g. diabetes or pregnancy), infections, cancer, neurological (e.g. Alzheimer's), and nutritional (e.g. alcoholism). The impairment may affect quality of life, change in appetite and body weight, or psychological well-being. [Doty, 2015b]

Chapter 4

Current knowledge of diabetes and the effect on chemosensory function

To investigate current knowledge about diabetes and chemosensory dysfunction a literature search was conducted, (see appendix A).
From section 3, it is clear that the development of taste and smell impairment can occur from several medical and the lifestyle factors, among them diabetes.

To find what triggers the taste and smell impairment, different angles to the problem will be investigated. Firstly, where in the stage of diabetes the impairment will occurs. Secondly, what are the consequences of the impairment and what other confounders that may affect the impairment and thirdly what can this discovery be used for in the prevention and treatment of diabetes.

Wasalathanthri et al. [2014] evaluated if there is an increased sweet sensitivity in prediabetes compared to diabetes and normoglycemic controls ($\leq$5.7 HbA1$_c$). The study did not find significant lower threshold for sweet sensitivity in prediabetes compared to the other groups but it confirmed previous findings of blunted taste response in diabetes. The study concluded that various factors could affect the sweet taste response e.g. weight loss, correction of hyperglycemia which indicates that sweet taste threshold is not static.
Altundag et al. [2017] evaluated the relationship between diabetic state and taste and smell impairment in type 1-diabetes and healthy controls. Comparison between the two groups revealed that there was no difference among them.

Neiers et al. [2016] found that the difference in sweet taste sensitivity may contribute to an increase in sugar intake, which may be a driving factor for diabetes. The consequence of taste and smell impairment may be that diabetic patients eat more than normal.
Yu et al. [2013] investigated if poorly controlled diabetes is associated with enhanced carbohydrate cravings. From the results it was strongly suggested that carbohydrate cravings is associated with poor glycemic control or hyperglycemia. Though, participants with diabetes had a less craving for high fat food comparing with participants without diabetes.

Gouveri et al. [2014] evaluated smell impairment in patients with type 2-diabetes and found that diabetic peripheral neuropathy and retinopathy are significantly associated with smell impairment. The study also found that hypertension seems to be an independent factor for smell impairment. They did not found a correlation between smell impairment and macrovascular disease or non-complicated diabetes which implies that microvascular disease could possibly explain smell impairment in type 2-diabetes. The study concludes that further work must be carried out to investigate if olfactory dysfunction is a manifestation of microvascular disease and whether a olfactory test could contribute to earlier detection of microvascular complications in type 2-diabetes.
The literature reveals that different factors may affect taste and smell senses and not only diabetes. Confounders as e.g. obesity, hypertension and age may have an influence, but it is also clear that there are variables that need to be further investigated. [Gondivkar et al., 2009, Gouveri et al., 2014, Naka et al., 2010]

The extent of the taste and smell impairment problem was demonstrated in Gondivkar et al. [2009]

where impaired taste sensation was found in 80% of poorly controlled diabetic patients and nearly 50% of the well controlled diabetic participants compared with controls. Malaty and Malaty [2013] estimates that 95% of taste disorders are caused by impairment of smell rather than gustatory loss.

Tsujimoto et al. [2016] investigated taste and smell impairment in NHANES data from 2011-2012. The study defined taste disorder as a condition in which the ability to taste was worse compared with when the participant was 25 years old. The study concluded that there is a connection between vascular complications and increased sugar intake in diabetic patients but that there is a need for further studies to reveal the association between sweet taste impairment and vascular complications. It is a limitation to the study that the study used self-reported questions about taste to reveal if a diabetic patient have taste impairment.

The literature search revealed that diabetes and the effect on taste and smell impairment is an area that needs to be further investigated. There is a need to find a clearer pattern of which diabetic complications and confounders that have the highest probability of developing impairment, and which consequence it has on food choices. The search also revealed that there is a need for studies that investigate larger samples of participants.

From the literature, factors that could possibly affect smell and taste was subtracted. Table 4.1 illustrates which factors that correlate with taste and smell impairment. Peripheral neuropathy and retinopathy seems to be a factor. While duration of diabetes and $HbA1_c$ do not seem to have an influence.
From table 4.1 it is hypothesized that taste and smell impairment evolve due to chronic diabetic complications. Therefore the figure from section 2 (Pathogenesis of diabetes mellitus) is expanded with a box illustrating taste and smell impairment that is drawn from chronic diabetic complications, see figure 4.1

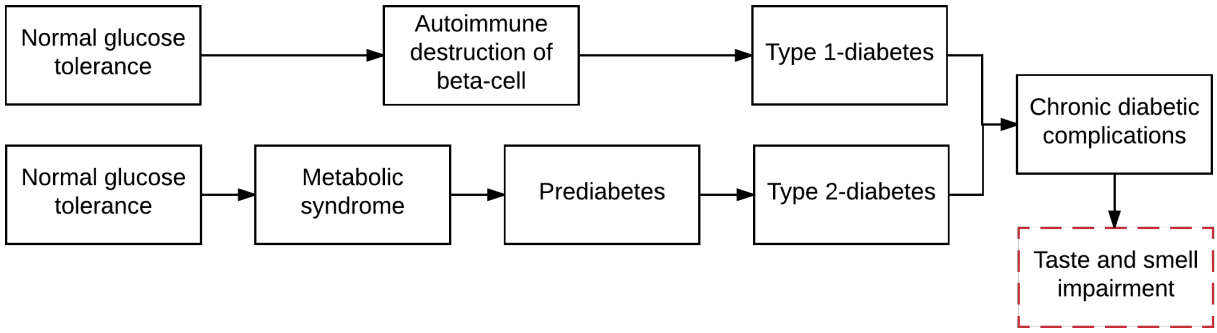


Figure 4.1: The figure from chapter 2 (Pathogenesis of diabetes mellitus) is expanded with a box from diabetic complications due to findings in literature of what may cause taste and smell impairment.

Table 4.1: From literature, a summation of which factors the studies found to correlate with taste and smell impairment.

Article	**n**	**Correlation with taste and smell impairment**	**No correlation**
Altundag et al. [2017]	70		Duration of diabetes $HbA1_c$ Non-complicated type 1-diabetes
Duda-Sobczak et al. [2017]	136	Peripheral neuropathy Retinopathy BMI	$HbA1_c$
Gouveri et al. [2014]	154	Peripheral neuropathy Retinopathy Type 2-diabetes (Independently associated) Hypertension (Independently associated)	$HbA1_c$ Macrovascular disease Nephropathy
Naka et al. [2010]	96	Complicating diseases Obesity	Non-complicated diabetes Duration of diabetes $HbA1_c$
Yu et al. [2013]	210	Type 2-diabetes Poorly controlled $HbA1_c$ = higher food cravings BMI	
Brady et al. [2013]	93	Neuropathic pain	
Yu et al. [2014]	200		Age BMI Duration of diabetes Hyperglycemia Medication $HbA1_c$
Wasalathanthri et al. [2014]	124	Diabetes Prediabetes	

n: number of participants in the study.

Chapter 5

Summary

Under normal conditions when food is consumed, the pancreas produces insulin to help maintain blood glucose levels. This may become disrupted if diabetes develops. Diabetes is classified after the pathogenesis. Type 1-diabetes is a genetic disease causing autoimmune destruction of the insulin producing β-cells. Type 2-diabetes is mainly caused by modern sedentary lifestyle and consumption of high energy-dense food. This have created an epidemic of obesity followed by type 2-diabetes.
Lifestyle factors such as high cholesterol, high blood pressure, and impaired fasting glucose are often overlooked or ignored. If these factors are ignored type 2-diabetes or cardiovascular disease may evolve with time.
Test of $HbA1_c$ gives an overall picture of the patients average blood sugar levels over a period of 8-12 weeks. If $HbA1_c$ is $\geq$6.5% the patient has by definition diabetes. If diabetes is not properly treated chronic diabetic complications will evolve. Peripheral neuropathy causing foot ulcers and retinopathy causing blindness are common.

Diseases such as diabetes may affect taste and smell senses causing impairment. These senses are important when savors enter the mouth or odors enter the nose. Smell receptors can warn against environmental hazards but also determine flavor of food. The taste buds of the tongue can detect five fundamental taste modalities (sweet, salty, bitter, sour, and umami). E.g. the sweet perception has the ability to detect carbohydrates to ensure energy dense food intake. Sweet perception is also associated with a highly positive sensory pleasure.
An increased sweet taste threshold perception have been reported in both type 2-diabetes, and in type 1-diabetes compared with healthy participants.
Sweet taste impairment may contribute to an increase in sugar intake, which may be a driving factor for further progress of diabetes. Impaired taste sensation has been found in 80% of poorly controlled diabetic patients and nearly 50% of the controlled diabetic participants compared with controls.

Current knowledge on diabetes and taste and smell impairment revealed that diabetes and the effect on taste and smell impairment is an area that needs to be further investigated. Firstly, which diabetic complications and confounders that have the highest probability of affecting taste and smell. Secondly which consequence does it have on food choices, and thirdly, there is a need for larger population size.
The literature also revealed a possible vicious circle where diabetic patients develop a higher craving for sugar or salt intake that result in a decline of the diabetic disease causing hypertension and hyperglycemia.

Part II

Problem solving

Chapter 6

Problem solving strategy

6.1 Problem statement

Based on current knowledge of diabetes and chemosensory dysfunction a problem statement was set:

> *How are diabetic participants from the NHANES study affected by chemosensory dysfunction and how will the dysfunction affect the consumption of salt or sugar?*

In order to answer the problem statement two aims was identified. The first aim was to investigate NHANES data to analyze if there was a statistical significant difference between participants with diabetes with or without complications compared to controls when investigating taste and smell impairment and dietary habits.

Aim 1: Identify possible differences in taste and smell function between diabetic participants with or without complications and controls and will the impairment cause a higher consumption of sugar and salt.

After identifying possible difference in taste and smell function, the second aim was to investigate the whole diabetes group to analyze their eating habits and to reveal possible significant predictors for consuming a higher amount of sugar, sodium, and calories.

Aim 2: Use a modeling technique to investigate diabetes and possible predictors' of a higher intake of sugar, sodium and calories.

6.2 Solution strategy

To answer the two aims, it was first investigated which data are contained in the NHANES in chapter 7. Next a methods and theory in chapter 8. To perform statistical analysis of the NHANES data, a three step method was applied. First a preliminary analysis in section 8.3.2 that will handle missing data, outliers, and determine if the data was normal distributed. Next, theory on statistical methods in section 8.2 and lastly a description of the model solution in section 8.3. See chapter references below.

- Chapter 7: Study data
  - Section 7.1: Data source and study population NHANES
- Chapter 8: Methods and theory
  - Section 8.3.2: Preliminary analysis
  - Section 8.2: Statistical analysis theory
  - Section 8.3: Model solution

Chapter 7

Study data

7.1 Data source and study population NHANES

The National Health and Nutrition Examination Survey (NHANES) are designed to evaluate the health and nutritional status of adults and children in the United States (U.S.). The NHANES program has been running since the early 1960s and focusing on different population groups or health topics through the years. The survey combines home-based health interviews and physical examinations. NHANES contains information about demographics, dietary intake, examination (e.g. taste and smell), laboratory answers, and questionnaires e.g. diabetes questionnaire. Participants are interviewed in their home and in a mobile examination center (MEC) for a physical examination, a 24-h dietary recall, and blood samples. NHANES examines 5,000 civilian of all ages (birth to >80 years) from 15 randomly-selected U.S. counties each year. [NCHS, 2014]

7.1.1 Dietary interview

The dietary interview contains detailed dietary intake information from NHANES participants. The dietary data are used to estimate the types and amounts of foods and beverages consumed during the 24-hour period prior to the interview. The total nutrient intake component estimates the total intake of energy and other food components. The first dietary interview is conducted at the MEC examination and the second interview via phone 3 to 10 days later. [National Center for Health Statistics, 2016]

7.1.2 Diabetes interview

The NHANES diabetes questionnaire provides data on e.g. diabetes, prediabetes, use of insulin or hypoglycemic medications, and self-reported awareness of risk factors, and knowledge of diabetic complications. [National Center for Health Statistics, 2014]

7.1.3 Taste and smell examination

For the first time in the NHANES history a taste and smell protocol was included. The protocol was included from 2012 to 2014. [Rawal et al., 2015] It was designed to estimate the taste and smell variation, and dysfunction in U.S. adults. Thereby determine associations between taste and smell function and other NHANES health measures. [CDC and NCHS, 2013] In NHANES 2013-2014, 3708 men and women were enrolled in the taste and smell examination. [NCHS, 2016]

Taste and smell protocol
The taste test included a tongue tip taste test and a whole-mouth taste test.
For the tongue tip test, a cotton swab was gently moved across tongue tip with quinine (bitter) or NaCl (salty). Participants were asked to identify the taste (salty, bitter, sour, something else, no taste) and rate the perceived intensity.

For the whole mouth test participants were asked to gently swish the solution in his/her mouth for 3 seconds, then spit it out. Participants were asked to identify the taste (salty, bitter, sour, something else, no taste) and rate the perceived intensity. [Liu et al., 2016].
Each participant was presented with three tastants in randomized orders: 0.32 M NaCl, 1 mM

quinine, 1M NaCl; or 1M NaCl, 1 mM quinine, 0.32 M NaCl.

For the smell test, 8 odors (chocolate, strawberry, smoke, leather, soap, grape, onion, and natural gas) were presented in a fixed order. Participants were forced to identify each odor from 4 alternative odors. [NCHS, 2016]

For the taste and smell examination the inclusion and exclusion criteria are:

Inclusion criteria

- $\geq$ 40 year

Exclusion criteria

- Pregnant or lactating
- Allergic to quinine (only excluded from quinine taste test)
- Unable to correctly rate the brightness of three lights in an LED luminescence panel. Excluded from taste testing not from smell test

Chapter 8

Methods and theory

8.1 Preliminary analysis

Before any statistical analysis can be performed. Data needs to be assessed for missing data, outliers and normality. This information is imported for choosing the correct statistical analysis.

Missing data
Missing data are a general issue in medical research [Donders et al., 2006]. To handle missing data, an analyze of data patterns will be performed in SPSS.

Outliers
The data will probably contain outliers, but is it due to a mistake that the number is high or is it a reasonable value. To test for outliers, box plots for each variable will be inspected. [Pallant, 2016]

Normal distribution
Normal distribution of data is a symmetrical, bell shaped curve, which has the greatest frequency of values and smaller frequencies towards the extremes. Normality can be assessed by kurtosis ("tails" in data) and skewness (asymmetry in data) and visual inspection by histogram and Q-Q plot. If data is not normally distributed non-parametric tests are preferable. [Pallant, 2016]

8.2 Statistical analysis theory

To interpret output of the NHANES data, information about applied statistical methods is essential. Section 8.2 will contain information about parametric test; Analysis Of Variance (ANOVA) and post hoc test, and multiple linear regression. The non-parametric test Kruskal-Willis and post hoc test. Statistical analysis will be conducted using IBM Statistical Package for the Social Sciences (SPSS), version 24.0 [IBM, 2017]. P-values <0.05 were considered statistically significant for all tests.

8.2.1 ANOVA

Analysis Of Variance (ANOVA) is a statistical method to determine if there are differences in mean values in more than two populations. It is an effective method for analyzing the data from medical experiments. ANOVA provides a statistical test of a null hypothesis that the means of three groups are identical. [Armstrong et al., 2000]

H_0: $\mu_0 = \mu_1 = \mu_2$

The alternative hypothesis:

H_A: the mean values are not the equal.

ANOVA is based on the evaluation of variance between the groups with the variance within the groups as illustrated in figure 8.1.

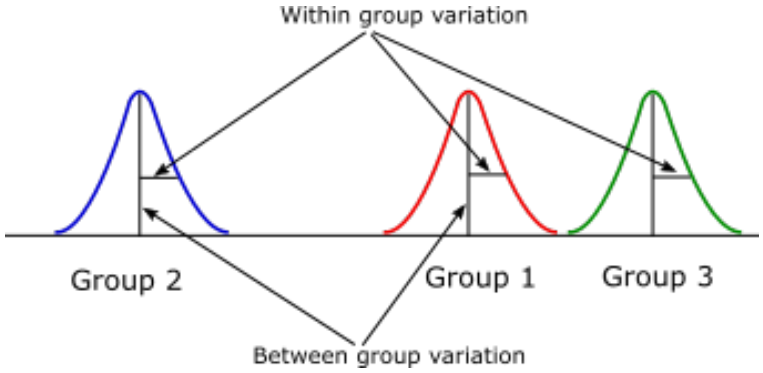


Figure 8.1: illustrates a dataset with 3 groups. ANOVA evaluates the variation of mean within the groups and between the groups.

Before an ANOVA analysis can be performed of the data, there are some assumptions that need to be addressed [Johansen, 2006].

- Normally distributed data
- Groups are independent
- Homogeneity of variance between the groups

Independence refers to if the mean value is either equal or different. If there is no significant difference between the groups mean, there will be no significant variation of these means from the overall mean. Homogeneity of variance assumes that the variance in each group is equal. [Pallant, 2016]

Calculation of ANOVA is done by evaluating the mean between the groups and within that is used to measure the total variation [Armstrong et al., 2000]:

$$\text{Total sum of squares} = \text{between groups sums of squares} + \text{within groups sums of squares} \quad \textbf{(8.1)}$$

When performing ANOVA in SPSS, a table will summarize the outcome, se figure 8.2

ANOVA

Time

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	215,333	2	107,666	(1) 179,667	(2) ,000
Within Groups	13,783	23	,599		
Total	229,115	25			

Figure 8.2: illustrates the outcome of ANOVA, (1) F indicates if the null hypothesis can be rejected, (2) if the Sig. (p-value) is <0.05, there is a significant difference among the mean score on the dependent variable for the 3 groups.

F-value

An calculated F-value tells if there is variance between the groups. The larger the variation between

the groups compared to variation within the groups, the larger F-value. A significant F indicates if the null hypothesis can be rejected. [Pallant, 2016]

$$\text{F-value} = \text{variation between sample means / variation within the sample} \quad \textbf{(8.2)}$$

When performing an ANOVA, and examination of the p-value is important to evaluate of there is a significant difference between the group means. [Pallant, 2016]
From the output of the performed ANOVA, the significance value is Sig. <0.05 (p = <0.05), therefore there is a significant difference between the different groups. But for now, it is not known which specific groups differ. [Pallant, 2016]

Post hoc test parametric
Next step is to perform a post-hoc test to evaluate difference between groups. There is a variety of post hoc tests; the individual tests vary in how effectively they address a particular statistical problem e.g. the possibility of making a type 1 error, rejecting the null hypothesis when it is true. [Armstrong et al., 2000]
To test for homogeneity of variances, a visual inspection is executed. This is due to the large amount of data. A test like Levine will not find homogeneity of variances for large data set. [Pallant, 2016]
To test for variance between the groups, the Bonferroni was selected. The Bonferroni correction is a very strict conservative multiple testing correction. It increase the number of false negatives (type 2 errors) failing to reject the null hypothesis when opposite rejecting the null hypothesis is correct. [Armstrong et al., 2000] The Bonferroni adjusted p-value is found by divide the original p-value by the number of comparisons on the dependent variable. [Cleophas and Zwinderman, 2012]

$$\text{Adjusted p-value} = \alpha/\text{comparisons} \quad \textbf{(8.3)}$$

α is mostly 0.05.

8.2.2 Pearson Chi-square test

Pearson Chi-square test of independence is a non-parametric test for categorical data such as gender (male or female). [Pallant, 2016]
Pearson Chi-square test assumes that the data should be categorical and that the variables consist of two or more categorical independent groups. [Pallant, 2016]
The Chi-square test gives a p-value to evaluate the statistical significance.

8.2.3 Kruskal-Wallis test

Kruskal-Wallis is the non-parametric alternative to ANOVA. The test converts scores into ranks and the mean rank for each group is compared. The test compare "between groups" so different participants must only be in one group. [Pallant, 2016]
The test gives a p-value and if this is significant a post hoc test can be executed to find different between pairs of groups [Pallant, 2016].

Post hoc test non-parametric
The Mann-Whitney U test will analyze "between pairs of groups". To control for type 1 errors, a Bonferroni adjustment to the α-value is applied. [Pallant, 2016]

8.2.4 Multiple linear regression

Multiple linear regression is a method that describes the relationship between one continuous variable and a number of independent variables as illustrated in figure 8.3. [Pallant, 2016]

When Y is linear dependent on more than one independent variable X_1, X_2, the value of α is the value of Y when both X_1 and X_2 are set to zero, see equation 8.4:

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_2 \tag{8.4}$$

β equals the slope of the line and α is where the line crosses the y-axis.

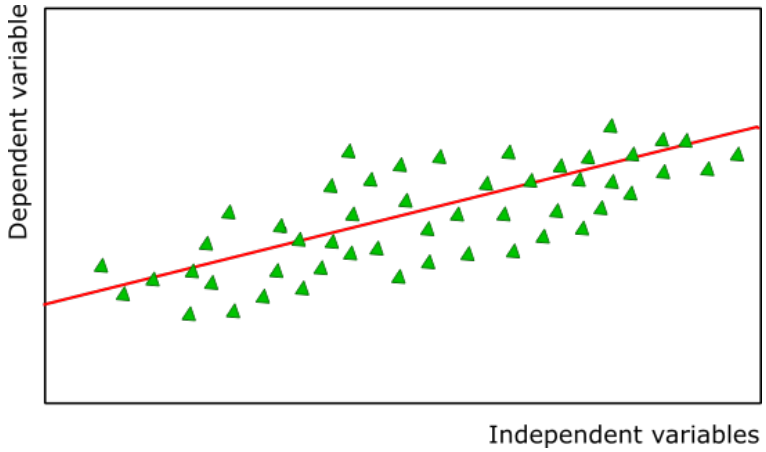


Figure 8.3: illustrates a dependent variable relationship to independent variables.

The degree of relation between the independent and dependent values is determined by a coefficient of determination (R square) $\mathbf{R}^2$. The coefficient tells how much variance in the dependent is explained i the model. Closer the $\mathbf{R}^2$ value is to 1, the better result. [Zar, 2014]

Before an multiple linear regression analysis can be performed, there are some assumptions that need to be addressed [Johansen, 2006].

- Multicollinearity and singularity
- Sample size
- Outliers
- Normality, linearity, homoscedasticity, independence of residuals

Multicollinearity and singularity refers to the relationship between independent variables. Multicollinearity is when the variables are highly correlated and singularity is when the variables is a sub-value of a total value and they both a included.
Multiple linear regression is very sensitive to outliers (very low and very high).
Relative to sample size, it depends on the independent variables and methods. For the stepwise regression, there should be around 40 cases per independent variable.
Assumption of the residuals can be checked from the residuals scatterplots, when performing the multiple regression analysis. [Zar, 2014]

Stepwise multiple linear regression

There is a need for eliminating not significant variables. To determine which independent variables that should be used in the multiple linear regression model stepwise regression was selected. Stepwise regression employs both addition and elimination of independent variables. Every time an X is added, the β associated with the each is examined for its "t" (β/standard error) value. The smallest

t is then eliminated at that step. Only one X is added or removed at each step. [Zar, 2014]

To explain the regression and get the needed data, examples of SPSS output, are explained in the following. Three tables was analyzed.
First model summary, to get the R^2 value, see figure 8.4.

Model Summary[d]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,284[a]	,081	,078	948,966
2	,420[b]	,176	,172	899,501
3	,446[c]	,199	,192	888,169

a. Predictors: (Constant), RIDAGEYR Age in years at screening

b. Predictors: (Constant), RIDAGEYR Age in years at screening, Gender_DV

c. Predictors: (Constant), RIDAGEYR Age in years at screening, Gender_DV, Smelltest_DV

d. Dependent Variable: DR1TKCAL Energy (kcal)

Figure 8.4: illustrates Model summary for the multiple linear regression. From SPSS.

The $R^2 = 0.199$. This means that the independent variables explain 19.9% of the variation in the dependent variable.

Next, an ANOVA table to check the p-value in third model, if it is significant, then the independent variable is a significant predictor, see figure 8.5

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	29194041,78	1	29194041,78	32,419	,000[b]
	Residual	333198395,7	370	900536,205		
	Total	362392437,4	371			
2	Regression	63833862,98	2	31916931,49	39,447	,000[c]
	Residual	298558574,5	369	809101,828		
	Total	362392437,4	371			
3	Regression	72097934,85	3	24032644,95	30,466	,000[d]
	Residual	290294502,6	368	788843,757		
	Total	362392437,4	371			

a. Dependent Variable: DR1TKCAL Energy (kcal)

b. Predictors: (Constant), RIDAGEYR Age in years at screening

c. Predictors: (Constant), RIDAGEYR Age in years at screening, Gender_DV

d. Predictors: (Constant), RIDAGEYR Age in years at screening, Gender_DV, Smelltest_DV

Figure 8.5: AVONA table for the multiple linear regression. From SPSS.

The p-value for F statistic is <0.001. This means that at least one independent variable is a significant predictor.

Lastly, a coefficients table, which different types of information, see figure 8.6

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	3494,107	280,688		12,448	,000		
	RIDAGEYR Age in years at screening	-25,393	4,460	-,284	-5,694	,000	1,000	1,000
2	(Constant)	3332,154	267,206		12,470	,000		
	RIDAGEYR Age in years at screening	-28,205	4,249	-,315	-6,638	,000	,990	1,010
	Gender_DV	616,027	94,149	,311	6,543	,000	,990	1,010
3	(Constant)	3257,388	264,849		12,299	,000		
	RIDAGEYR Age in years at screening	-25,747	4,264	-,288	-6,039	,000	,958	1,043
	Gender_DV	626,398	93,018	,316	6,734	,000	,989	1,012
	SmellTest_DV	-359,770	111,154	-,154	-3,237	,001	,966	1,036

a. Dependent Variable: DR1TKCAL Energy (kcal)

Figure 8.6: Coefficients table for the multiple linear regression. From SPSS.

Unstandardized coefficients β are used in the prediction and interpretation of the regression model. The Constant is the predicted value of the dependent variable when all of the independent variables have a value of zero. This means that the multiple regression model was:

$$\text{Energy (kcal)} = 3257.4 - 25.8(\text{Age}) + 626.4(\text{Gender}) - 359.8(\text{Smell test}) \quad \textbf{(8.5)}$$

Standardized coefficients Beta are used for comparing the effect of the independent variables and find the most significant one.

Variance inflation factor (VIF): analyzes data for multicollinearity problems, if VIF is > 10, it is a problem Pallant [2016].

8.3 Model solution

8.3.1 Data selection

To answer the aim, each participant needs to meet two requirements or the participants will be excluded from the analysis. The data should contain:

(a) A HbA1$_c$ value to define if the participant has diabetes. If it is ≥6.5%, a participant is said to have diabetes.

(b) Have been a part of the first dietary interview

Based on these requirements, three steps were performed to reduce the data. These are illustrated in figure 8.7.

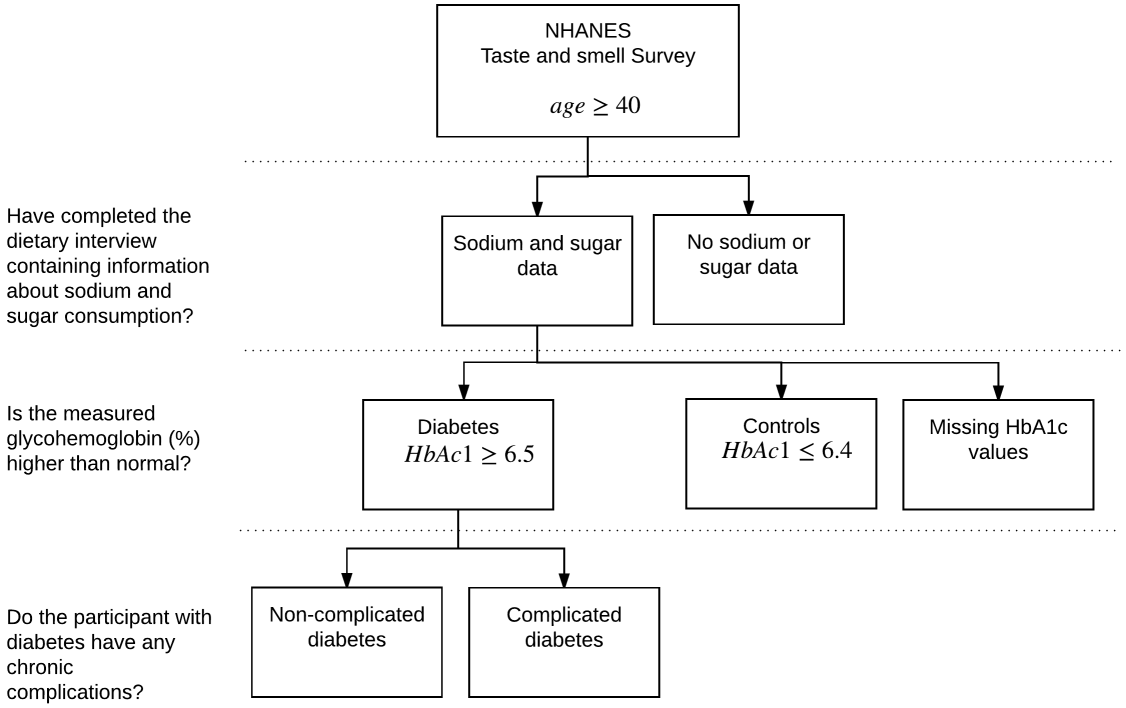


Figure 8.7: illustrates the selected of participants, based on the requirements.

The first step was to exclude all participants in the taste and smell survey that did not complete the first dietary interview. Next step was to divide participants based on their HbA1$_c$ value and exclude participants with no HbA1$_c$ value. The last step was to divide the diabetes group into two groups based on selected chronic diabetic complications.
3 groups was divided based on Tsujimoto et al. [2016]. Group 1 contained non-complicated diabetes meaning that the group was defined as well threated diabetes with none of the selected diabetic complications. Therefore, group 2 contained all diabetic participants with chronic diabetic complications which included diabetic nephropathy defined by urine albumin ≥300 mg/g. Diagnosis of retinopathy, myocardial infarction, angina pectoris, and/or stroke, defined by self-port questionnaire answers. Lastly, all other NHANES participants in the taste and smell survey was contained in group 3. Participants in group 3 all had a HbA1$_c$ value ≤6.4% but did include other exclusion criteria. The 3 groups are listed in table 8.1

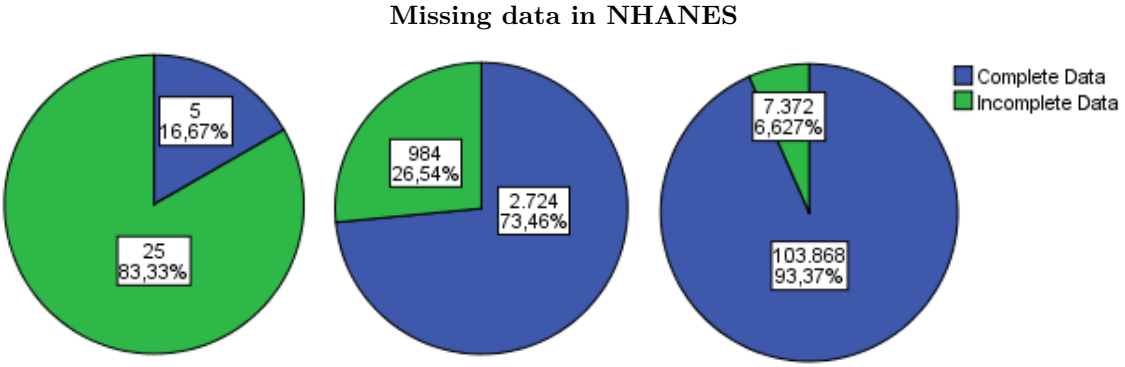
Table 8.1: Based on literature, 3 groups are formed. Group 1 contained all participants with well treated diabetes, group 2 contained participants with diabetes and whom has chronic diabetic complications. Lastly group 3 contained all other NHANES participants.

Groups	**HbA1$_c$ value**	**Defined by**
Group 1 Non-complicated diabetes	≥6.5%	The participants are assumed to have well treated diabetes with no chronic diabetic complications
Group 2 Complicated diabetes	≥6.5%	Complicated diabetes are determined as micro or macrovascular complications: • Diabetic nephropathy: -Urine albumin ≥300 mg/g Self-reported: • Retinopathy • Angina pectoris • Heart attack • Stroke
Group 3 Controls	≤6.4%	Contains all other participants in the NHANES taste and smell survey thats meets the requirements

8.3.2 Preliminary analysis

Missing data

Figure 8.8 represents the total data set and what data was missing. 25 of the variables had missing data, 73.5% of the cases had complete data. Overall 93.4% of the NHANES data was complete. From analysis, "Sodium" and "Total sugar" were missing 11.0%. Because this variable was used to test the hypothesis, imputations were not a solution. Therefore cases with no values for "Sodium" or "Total sugar" would be excluded.



(a) Variables (b) Cases (c) Values

Figure 8.8: Overall summary of missing data. The blue color represents complete data and the green color represents missing data. Extracted from SPSS.

A complete missing variable summary can be found in appendix B.
For the taste and smell examination, some data sets where missing in the taste testing e.g. quinine testing, this was due to participants not correctly rated three lights in the correct relative order on the general Labeled Magnitude Scale (gLMS) scale or had quinine allergy. And thereby data was missing in the taste variables and these participants were excluded from the taste examination but not from the smell examination.
For all variables that had missing values $\leq 5\%$ these values was calculated by the Expectation Maximization (EM) method in SPSS. E.g. BMI (kg/m^2) and albumin creatinine ratio (mg/g) had new values calculated. This solution was chosen due to the amount of missing data was under 5%, and thereby irrelevant for the end result. [Dong and Peng, 2013] In table 8.2 the variables are listed with the number of missing values, the missing values in % and the result of the EM.

Table 8.2: Variables from the selected NHANES data that have missing values. Expectation maximization (EM values) was calculated and was replaced with the missing values.

Variable	**Missing values**	**in pct.**	**EM**
BMI (kg/m^2)	60	1.6%	18.65 - 36.67 (kg/m^2)
Albumin creatinine ratio (mg/g)	92	2.5%	25.95 - 87.57 (mg/g)
Direct HDL-Cholesterol (mmol/L)	168	4.5%	0.63 - 1.58 (mmol/L)
Total Cholesterol (mmol/L)	168	4.5%	4.66 - 5.19 (mmol/L)

Outliers

A visual inspection of the NHANES data was performed, to check for outliers. The NHANES data had some obvious outliers, but when inspecting data, the values was reasonable. Some of the participants have a high weight and thereby a high BMI, see figure 8.9.

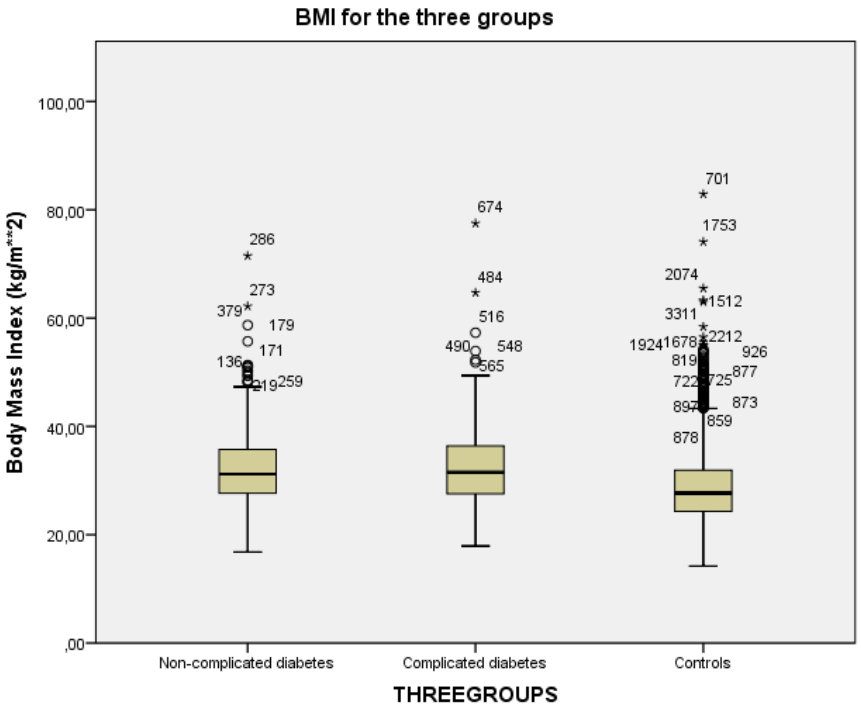


Figure 8.9: illustrates a box plot of the groups and BMI. When inspecting it is obvious that there are significant outliers.

Normal distribution

To handle normality, visual inspection by a histogram revealed that data was not normally distributed. It had a "tail" with data and by that definition not normally distributed, see figure 8.10.

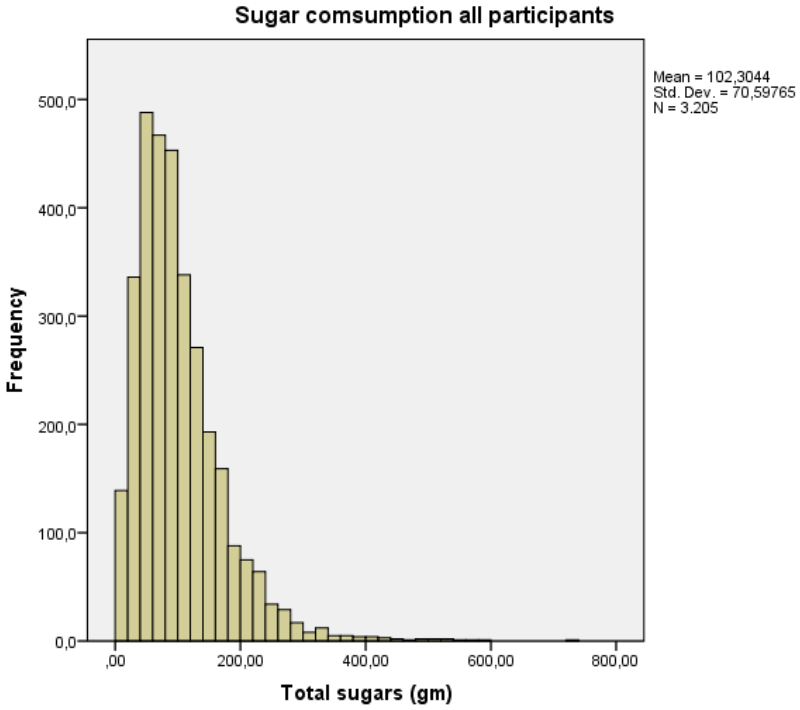


Figure 8.10: illustrates a histogram of the sugar values. When inspecting it is obvious that it has a “tail”, and by that definition it is not normal distributed.

8.3.3 Statistical analysis

From the preliminary analysis on NHANES data, it was obvious that most of the data was not normally distributed. Variables not following the normal distribution were analyzed by Kruskal-Wallis tests and if statistical significant post hoc tested by Mann-Whitney U. The result will be expressed by median plus interquartile range (25%-75%).
Normally distributed quantitative variables were analyzed by using 1-way analysis of variance (ANOVA) and if statistical significance post hoc by Bonferroni. The result was expressed at mean ± standard deviation (SD). Categorical variables were analyzed using Pearson Chi-square test.
For each analyze, used NHANES codes is found in appendix C.

The statistical analysis contained four elements:

1. Demographic data

Included in demographic analysis was:

- Age
- Gender
- $HbA1_c$
- Total Cholesterol(mmol/L)
- Direct HDL-Cholesterol (mmol/L)
- Duration of diabetes (years)
- Ever told you had high blood pressure - self reported

After preliminary analysis BMI, $HbA1_c$, duration of diabetes, total cholesterol and HDL-cholesterol was analyzed by Kruskal-Wallis, and if there was significance post hoc test with Mann-Whitney. Age was analyzed with ANOVA and gender and hypertension by Pearson Chi-square test.

2. Taste and smell examination

For the taste and smell examination was analyzed with Pearson Chi-square test.

Smell testing
The smell test was assessed by included an 8-item odors test. Smell impairment was defined as $\leq$ 5 odors and normal smell senses was $\geq$ 6 odors.

Taste testing
To assess taste impairment, test of whole mouth; quinine, 0.32 M NaCl, and 1 M NaCl was included. Both questions and ratings on and general Labeled Magnitude Scale (gLMS) were included. This gave four taste tests to analyze:

- (1) Ranking the two salty solutions 0.32 M and 1 M in the wrong order on the gLMS scale
- (2) Incorrect question answer to the salty solution 0.32 M NaCl
- (3) Incorrect question answer to the salty solution 1 M NaCl
- (4) Incorrect question answer to the bitter solution 1 mM quinine

This was due to no specific guidelines of how to assess taste impairment. Therefore 4 tests was included to analyze any difference in the results.

3. Sugar and sodium consumption

To investigate the participants eating habits an analysis af dietary variables was performed. The analyze was performed by Kruskal-Wallis test and post hoc with Mann-Whitney U due to the data not being normally distributed.
For each participant, the total nutrient intake was determined at the first interview, the second interview was not included due to a lot less participation answered the second interview by phone. From the dietary data three variables was selected; total amount of sugar, salt (sodium) and total energy in consumed food. Total energy was included to calculate how much percent of sugar that counts in total calories.

Diet data

To investigate the eating habits of the participants that might influence on the calorie intake, an analysis of which "diet" that the participants was on doing the dietary interview. To cover a range a diets, overall diet plans and 4 different types of diet was analyzed. The five types a listed below:

- On special diet
- Weight loss/Low calorie diet
- Low salt/Low sodium diet
- Sugar free/Low sugar diet
- Diabetic diet

4. Relation between diabetes and taste and smell impairment

To test if diabetes on its own was affecting the consumption of sugar, sodium and total calories a multiple linear regression analysis was conducted. A stepwise method was used to find significant predictors.

For the regression analysis, the odor test and one of the four taste test will be selected for analysis. Next significant demographic variables and values of sugar, sodium and total calories. This gives a total of six tests that was used in multiple linear regressions. Independent and dependent variables are following:

- Smell test or taste test (independent)
- Significant demographic variables (independent)
- sugar, sodium and total calories (dependent)

Chapter 9

Results

9.1 Study population

The selected NHANES data resulted in 304 participants with non-complicated diabetes, 199 participants with complicated diabetes and 2702 controls as illustrated in figure 9.1.

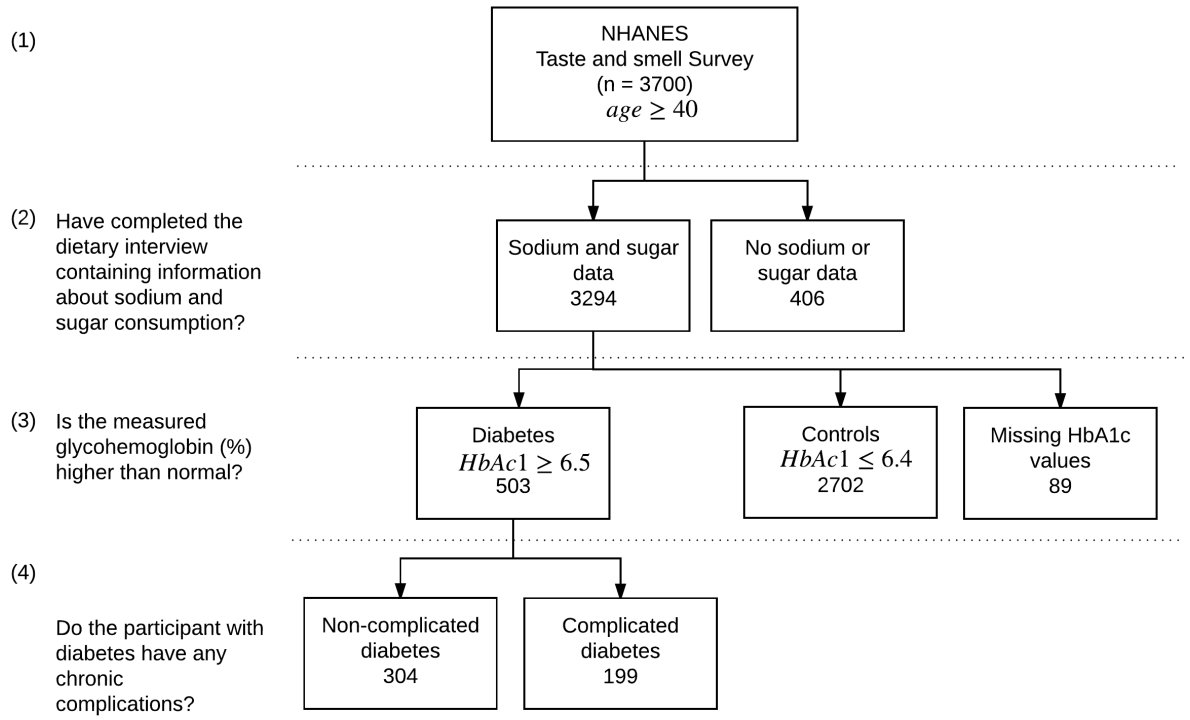


Figure 9.1: illustrates the distribution of participants over four steps: (1) Intervention group in taste and smell survey minus pregnant women. (2) completed the dietary interview? (3) Is the measured HbA1$_c$ (%) higher than 6.5%? (4) Do the participants with diabetes have any of the selected chronic diabetic complications?

9.2 Demographic characteristics

From these 3 groups, non-complicated diabetes, complicated diabetes and controls, the demographic characteristics was analyzed and the result is found in table 9.1.

Table 9.1: Demographic characteristics for study participants, NHANES 2013-2014.

Variable	Non-complicated diabetes (n = 304)	Complicated diabetes (n = 199)	Controls (n = 2702)	p-value
Age (years)	60.6 ± 11.30[b]	64.1 ± 10.9[b]	58.4 ± 12.0	<0.001
Gender [n, (female)]	146 (48.0)	80 (40.2)	1460 (54.0)	<0.001
BMI* (kg/m2)	31.3 (27.7-36.1)[a]	31.6 (27.8-38.0)[a]	27.8 (24.4-32.0)	<0.001
Hypertension [n, (yes)]	189 (62.2)	155 (77.9)	1236 (45.7)	<0.001
$HbA1_c$ (in %)	7.3 (6.8-8.3)[a]	7.5 (6.8-8.9)[a]	5.5 (5.3-5.8)	<0.001
T-Chol (mmol/L)	4.6 (3.9-5.4)[a]	4.5 (3.7-5.3)[a]	5.0 (4.3-5.7)	<0.001
HDL-Chol (mmol/L)	1.2 (1.0-1.4)[a]	1.1 (0.9-1.3)[a]	1.3 (1.1-1.7)	<0.001
Duration of diabetes (years)	10 (5-15)[b]	13 (7-20)	-	0.002

Data are represented as n (%) or mean ± standard deviation (SD) for age. Median (interquartile range) for BMI, $HbA1_c$, T-Chol, HDL-Chol, and duration of diabetes. [b]p<0.05 post hoc test non-complicated diabetes vs. complicated diabetes. [a]p<0.05 non-complicated- or complicated diabetes vs. controls. $HbA1_c$: percentage of glycated haemoglobin A1c; BMI: Body mass index; T-Chol: total cholesterol; HDL-Chol: Direct HDL-Cholesterol Hypertension: self-reported question.

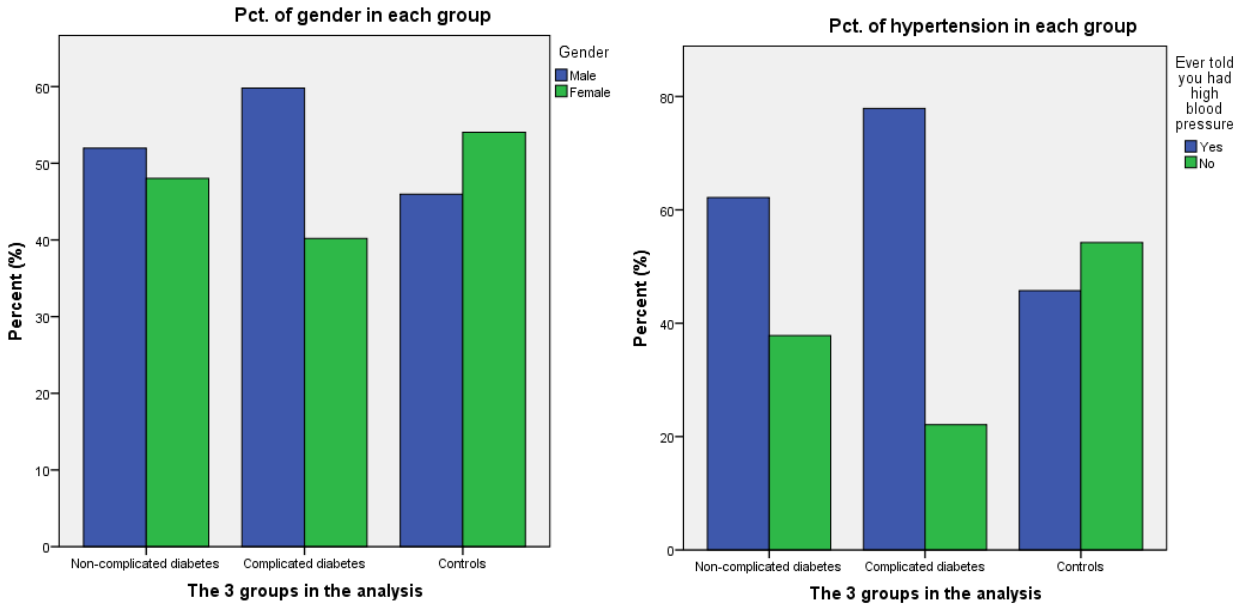
*According to World Health Organization (WHO), BMI is classified into three categories. Underweight, if BMI is ≤18.5, normal range between 18.5-24.99, if BMI is ≥25, it is classified as overweight, and Obesity ≥ 30. [World Health Organistation, 2016]

The demographic data shows a significant difference in age (p<0.001) between the three groups. Post hoc comparisons of age between non-complicated diabetes and complicated diabetes showed a statistically significantly difference.

There is significant difference between female and male in the non-complicated diabetes group and the complicated diabetes group. There is a higher percent of males in non-complicated and complicated diabetes as illustrated in graph 9.2a.

The $HbA1_c$ value among non-complicated and complicated diabetes, has the same level but are statistically significantly different when comparing to controls (p<0.001).

For the self-reported question about hypertension, it was statistically significant (p<0.001). A graph with the 3 groups is illustrated in figure 9.2b. It it clear that more participants are affected by hypertension in the diabetic groups and even more in the complicated diabetes group.



(a) (b)

Figure 9.2: (a) illustrates the connection between gender and the 3 groups. (b) illustrates the connection between hypertension and the 3 groups.

For T-Chol and HDL-Chol, the two diabetic groups had a statistically significant difference in values compared with controls. Treatment of dyslipidemia should be initiated when T-Chol is >4.5 mmol/l and HDL-Chol is <1 mmol/l for men and <1.2 mmol/l for women. [Dansk Selskab for Almen Medicin, 2012]

Lastly, duration of diabetes for the diabetic groups reveled that participants with complicated diabetes have had diabetes for a longer period (p=0.002). Respectively 13 years for complicated diabetes and 10 years for non-complicated diabetes.

9.3 Taste and smell examination

To analyze the participants degree of taste and smell impairment, analysis of the different taste tests was performed and the result is found in table 9.2. The smell analysis revealed a statistically significant difference between the two diabetic groups and controls (p=0.006).
Analysis of the taste impairment did not reveal any significant difference between the three groups. Though, for taste test (1), there is a almost significant difference (p = 0.058).

Table 9.2: Taste and smell examination of the three groups, NHANES 2013-2014.

	Non-complicated diabetes	Complicated diabetes	Controls	p-value
Smell impairment				
5 ≤ correct odors (%)	55 (18.6)[a]	48 (24.9)[a]	426 (16.2)	0.006
Taste impairment				
(1) gLMS 0.32 M > 1 M NaCl (%)	53 (17.4)	31 (15.6)	368 (13.6)	0.058
(2) Salty, 0.32 M NaCl (%)	25 (8.2)	25 (12.6)	254 (9.4)	0.096
(3) Salty, 1 M NaCl (%)	7 (2.3)	8 (4.0)	60 (2.2)	0.144
(4) Bitter, 1 mM quinine (%)	47 (15.5)	18 (9.0)	419 (15.5)	0.187

Data are represented as n (%). [a]p<0.05 post hoc test non-complicated and complicated diabetes vs. control.
(1) Ranking the two salty solutions 0.32 M and 1 M in the wrong order on the gLMS scale. (2) Incorrect question answer to the salty solution 0.32 M NaCl. (3) Incorrect question answer to the salty solution 1 M NaCl. (4) Incorrect question answer to the bitter solution 1 mM quinine. gLMS: general Labeled Magnitude Scale.

Due to exclusion criteria in the taste and smell protocol, participants in each test differ. In the smell test included participants are:

- non-complicated diabetes n=295, complicated diabetes=193, and controls 2630

For taste test (1-3):

- non-complicated diabetes n=270, complicated diabetes 160, and controls 2454

For taste test (4):

- non-complicated diabetes n=265, complicated diabetes 152, and controls 2380

9.4 Sugar and sodium consumption

For the three groups, sodium and sugar consumption, amount of total calorie content that comes from sugar, and total energy was calculated and listed in table 9.3.

Table 9.3: Dietary intake for the three groups.

Dietary variable	Non-complicated diabetes (n = 304)	Complicated diabetes (n = 199)	Controls (n = 2702)	p-value
Sodium (mg)	3095.0 (2148.3-4266.0)	2829.0 (2086.0-3992.0)	3010.5 (2159.8-4176.6)	0.472
Sugars (gm)	74.3 (41.7-124.1)	68.8 (40.2-107.7)[a]	90.5 (55.1-135.8)	<0.001
Sugar content (%)	18.1 (12.1-24.9)	17.4 (10.1-23.9)[a]	20.3 (14.2-27.0)	<0.001
Energy (kcal)	1807.5 (1290.0-2474.0)	1652.0 (1182.0-2236.0)[a]	1887.5 (1389.8-2480.0)	0.001

Data are represented as median (Interquartile range 25%-75%). [a] $p \leq 0.001$ complicated diabetes vs. controls. To calculate total calories of sugar, sugar was multiplied by 4.06. 2000 mg of sodium corresponds to 2.5 grams of salt.

The results shows that the two diabetic groups consume significant less sugar and calories than controls ($p<0.001$). In terms of total amount of sugar in calorie content it was also significant less than controls ($p<0.001$). For sodium consumption the level was the same ($p=0.472$).

9.4.1 Possible reason for lower calorie consumption

From table 9.3, the pattern is that controls has a higher sugar intake, compared with both non-complicated diabetes and complicated diabetes. Which is inconsistent with a higher BMI in the two diabetic groups. To investigate this issue diet data was analyzed for possibly influence in the result of the food consumption.

Table 9.4: Diet information on the three groups.

On a diet	Non-complicated diabetes (n = 304)	Complicated diabetes (n = 199)	Controls (n = 2702)	p-value
On special diet?	99 (32.6)	66 (33.2)[a]	418 (15.5)	<0.001
Weight loss/Low calorie diet	33 (10.9)	8 (4.0)	209 (7.7)	0.019
Low salt/Low sodium diet	9 (3.0)	14 (7.0)	70 (2.6)	0.002
Sugar free/Low sugar diet	4 (1.3)	3 (1.3)	18 (0.7)	0.230
Diabetic diet	53 (17.4)	39 (19.6)	36 (1.3)	<0.001

[a] $p<0.001$ complicated diabetes vs. controls.

Table 9.4 shows the relation between the groups and possible diet. The result is that about 32 percent in the two diabetic groups was on a diet compared to only 15.5 percent in the control group ($p<0.001$). More with complicated diabetes was on a "low salt" diet and both diabetic groups had high amount of participants that was on a diabetic diet.

9.5 Relation between diabetes and taste and smell impairment

The hypothesis was that participants with diabetes and with or without chronic complications would eat more sugar and salt than controls, but that was not the case. But it is still of interest how the whole diabetes group will behave on its own, towards dietary habits. A stepwise multiple linear regression was performed in SPSS, to find predictors that could have an influence on consumption of sugar, salt and total calories.

9.5.1 Smell impairment

Firstly, a relation between diabetes, smell impairment and sugar intake, see table 9.5.

Table 9.5: Stepwise multiple linear regression analysis of the variables affecting the amount of consumed sugar (gm).

Diabetes	Variable	Standardized coefficient β	p-value
Sugar (gm)	Smell test		0.100*
	Age (years)	-0.123	**<0.001**
	Gender		0.057*
	BMI (kg/m2)		0.089*
	Hypertension		0.885*
	$HbA1_c$ (%)		0.444*
	T-Chol (mmol/L)		0.925*
	HDL-Chol (mmol/L)		0.457*
	Duration of diabetes (years)		0.127*

$R^2 = 0.034$, $p<0.001$. * is excluded from the model.

For sugar there is only one significant predictor "Age" with a negative effect.
The result of the multiple regression is an R^2 of 0.034. This means that the independent variable explain 3.4% of the variation in the dependent variable. The p-value of the ANOVA is $p<0.001$ this means that at least one independent variable is a significant predictor.

Based on data from the regression analysis a regression model for sugar is set:

$$\text{Sugar (mg)} = 154.4 - 1.2(\text{Age}) \quad \textbf{(9.1)}$$

The Constant (154.4) is the predicted value of the dependent variable sugar (mg) when all of the independent variables have a value of zero. The result of the regression is that only significant variable was "Age". The model states that every time a person gets older, there is a decrease in sugar intake.

Next the relation between diabetes, smell impairment, and total calorie intake, see table 9.6.

Table 9.6: Stepwise multiple linear regression analysis of the variables affecting the total energy (kcal).

Diabetes	Variable	Standardized coefficient β	p-value
Energy (kcal)	Smell test	-0.154	**0.001**
	Age (years)	-0.288	**<0.001**
	Gender	0.316	**<0.001**
	BMI (kg/m2)		0.251*
	Hypertension		0.754*
	$HbA1_c$ (%)		0.805*
	T-Chol (mmol/L)		0.567*
	HDL-Chol (mmol/L)		0.143*
	Duration of diabetes (years)		0.652*

$R^2 = 0.199$, $p<0.001$. * is excluded from the model.

For energy there are three significant predictors. “Gender” being the most significant predictor followed by “Age”.

The result of the multiple regression is an R^2 of 0.199. This means that the independent variables explain 19.9% of the variation in the dependent variable. The p-value of the ANOVA $p<0.001$ this means that at least one independent variable is a significant predictor.

Next a regression model for energy:

$$\text{Energy (kcal)} = 3257.4 - 25.8(\text{Age}) + 626.4(\text{Gender}) - 359.8(\text{Smell test}) \quad \textbf{(9.2)}$$

The Constant (3257.4) is the predicted value of the dependent variable energy (kcal) when all of the independent variables have a value of zero.
The slope of “Gender” is 626.4. This means that, on average, predicted calorie intake for males are 626.4 higher than for females, after controlling for age and smell test”.
The slope of “Smell test” is -359.8 this means that on average, predicted calorie intake for participants with smell impairment consume 359.8 calories less then participants with no smell impairment after controlling for “Age” and “Gender”.

Lastly the relation between diabetes, smell impairment, and sodium intake, see table 9.7.

Table 9.7: Stepwise multiple linear regression analysis of the variables affecting the sodium (mg).

Diabetes	Variable	Standardized coefficient β	p-value
Sodium (mg)	Smell test	-0.162	**0.001**
	Age (years)	-0.279	**<0.001**
	Gender	0.330	**<0.001**
	BMI (kg/m2)		0.809*
	Hypertension		0.971*
	$HbA1_c$ (%)	0.115	**0.018**
	T-Chol (mmol/L)		0.434*
	HDL-Chol (mmol/L)		0.141*
	Duration of diabetes (years)		0.361*

$R^2 = 0.200$, $p<0.001$. * is excluded from the model.

For sodium there are four significant predictors: "Gender" being the most significant predictor followed by "Age"and "$HbA1_c$.

The result of the multiple regression is an R^2 of 0.200. This means that the independent variables explain 20.0% of the variation in the dependent variable. The p-value of the ANOVA is $p<0.001$ this means that at least one independent variable is a significant predictor.

Next a regression model for sodium:

$$\text{Sodium (mg)} = 4307.5 + 1229.6(\text{Gender}) - 38.6(\text{Age}) - 713.6(\text{Smell test}) + 120.7(HbA1_c) \quad \textbf{(9.3)}$$

The Constant (4307.5) is the predicted value of the dependent variable (sodium) when all of the independent variables have a value of zero.
The slope of "$HbA1_c$" is 120.7. This means that there is a increase in sodium intake if the $HbA1_c$ level increases.

9.5.2 Taste impairment

Next the relation between taste impairment and dietary was tested. From the four tests of taste, taste test number ((1) gLMS 0.32 M > 1M NaCl)) was chosen because of its p-value.

First the relation between diabetes, taste impairment, and total sugar intake, see table 9.8.

Table 9.8: Stepwise multiple linear regression analysis of the variables affecting the total sugar (gm).

Diabetes	Variable	Standardized coefficient β	p-value
Sugar (gm)	Taste test		0.317*
	Age (years)	-1.068	**0.003**
	Gender		0.102*
	BMI (kg/m2)		0.051*
	Hypertension		0.688*
	HbA1$_c$ (%)		0.892*
	T-Chol (mmol/L)		0.924*
	HDL-Chol (mmol/L)		0.513*
	Duration of diabetes (years)		0.150*

R^2 = 0.028, p=0.003. * is excluded from the model.

For sugar there is only one significant predictor "Age" with a negative effect.
The result of the multiple regression is an R^2 of 0.028. This means that the independent variables explain 2.8% of the variation in the dependent variable. The p-value of the ANOVA is p=0.003 this means that at least one independent variable is a significant predictor.

Next a regression model for sugar:

$$\text{Sugar (mg)} = 151.9 - 1.1(\text{Age}) \quad \textbf{(9.4)}$$

The Constant (151.9) is the predicted value of the dependent variable sugar (mg) when all of the independent variables have a value of zero. The result of the regression is that only variable was significant "Age". The model states that every time a person gets older, there is a decrease in sugar intake.

Next the relation between diabetes, taste impairment, and total calorie intake, see table 9.9.

Table 9.9: Stepwise multiple linear regression analysis of the variables affecting the total energy (kcal).

Diabetes	Variable	Standardized coefficient β	p-value
Energy (kcal)	Taste test		0.451*
	Age (years)	-0.288	**<0.001**
	Gender	0.315	**<0.001**
	BMI (kg/m2)		0.164*
	Hypertension		0.249*
	HbA1$_c$ (%)		0.695*
	T-Chol (mmol/L)		0.418*
	HDL-Chol (mmol/L)		0.163*
	Duration of diabetes (years)		0.691*

R^2 = 0.164, p<0.001.* is excluded from the model.

For energy there are two significant predictors: “Gender” being the most significant predictor followed by “Age”.
The result of the multiple regression is an R^2 of 0.164. This means that the independent variables explain 16.4% of the variation in the dependent variable. The p-value of the ANOVA is p<0.001 this means that at least one independent variable is a significant predictor.

Next a regression model for energy:

$$\text{Energy (kcal)} = 3235.5 - 630.2(\text{Gender}) - 26.4(\text{Age}) \quad \textbf{(9.5)}$$

The Constant (3235.5) is the predicted value of the dependent variable energy (kcal) when all of the independent variables have a value of zero.
The slope of “Gender” is 630.2. This means that, on average, predicted calorie intake for males are 626.4 higher than for females, after controlling for “Age”

Lastly the relation between diabetes, taste impairment, and sodium intake, see table 9.10.

Table 9.10: Stepwise multiple linear regression analysis of the variables affecting sodium (mg) consumption.

Diabetes	Variable	Standardized coefficient β	p-value
Sodium (mg)	Taste test		0.647*
	Age (years)	-0.233	**<0.001**
	Gender	0.332	**<0.001**
	BMI (kg/m2)		0.914*
	Hypertension		0.456*
	$HbA1_c$ (%)	0.111	**0.039**
	T-Chol (mmol/L)		0.283*
	HDL-Chol (mmol/L)		0.216*
	Duration of diabetes (years)		0.548*

$R^2 = 0.173$, p<0.001. * is excluded from the model.

For sodium there are three significant predictors: “‘Gender” being the most significant predictor followed by “Age” followed by $HbA1_1$
The result of the multiple regression is an R^2 of 0.173. This means that the independent variables explain 17.3% of the variation in the dependent variable. The p-value of the ANOVA is p<0.001 this means that at least one independent variable is a significant predictor.

Next a regression model for sodium:

$$\text{Sodium (mg)} = 4233.2 + 1254.9(\text{Gender}) - 40.2(\text{Age}) + 126.1(HbA1_c) \quad \textbf{(9.6)}$$

The Constant (4233.2) is the predicted value of the dependent variable sodium (mg) when all of the independent variables have a value of zero.
The slope of $HbA1_c$ is 126.1 this means that there is an increase in sodium intake if the $HbA1_c$ level increases.

9.6 Interpretation of results

To interpret the model, energy consumption affected by the smell test was calculated, see table 9.11:

Table 9.11: Calculation of energy (kcal).

	Smell impairment Age 42	No smell impairment Age 42	Smell impairment Age 70	No smell impairment Age 70
Male	2440 kcal	2800 kcal	1718 kcal	2077 kcal
Female	1814 kcal	2173 kcal	1091 kcal	1451 kcal

For interpretation of the multiple linear regression model, dichotomous variables was created:
Smell test: Impairment = 1, No impairment = 0
Gender: Male = 1 and female = 0

The result of the regression is that men that are 42 years and has no smell impairment consumes the highest amount of calories. Comparing to men at age 70 with no smell impairment consumes 522 less calories.
Women that are 42 years with smell impairment consumes less calories, then females in the same age range but with no smell impairment.

Part III

Synthesis

Chapter 10

Discussion

10.1 Chemosensory dysfunction affecting dietary habits

The study conducted in this report enables the assessment of olfactory (smell) and gustatory (taste) function in relation to diabetes and chronic diabetic complications.
First, it was demonstrated that both non-complicated diabetes and complicated diabetes had a higher percentage of smell impairment, respectively 21.1% and 27.1% compared to the control group with 18.4%. This is consistent with other studies [Gouveri et al., 2014, Naka et al., 2010, Duda-Sobczak et al., 2017] that also found a higher smell impairment in participants with diabetes.
That diabetic patients diagnosed with micro- or macro vascular complications gained lower smell scores compared to non-complicated diabetic patients demonstrates that there is a possible relation between smell impairment and chronic diabetic complications. It should be noticed that the two diabetic groups have a higher age compared to the control group and that smell impairment affects >50% of the population over 65 years. This should be accounted for when interpreting the result.
The current study did not find a relation between diabetes and taste impairment and the four analyzes of taste gave an inconsistent result with different percentage of participants in each test.

After analyzing the three group's dietary data, it showed a different result than stated in the aim that participants with diabetes and chemosensory dysfunction would consume more sugar, salt and calories. The result was that the two diabetic groups consumed statistically significant less of both sugar and calories in total, though sodium was at the same level.
Yu et al. [2014] found similar results of a lower preference for sweet taste despite a decreased sweet taste perception. This may be due to diabetic patients being aware of the consequence of eating too much sugar and this may repress the desire for sweet foods.
This is contrast to other studies that found the opposite result. [Yu et al., 2013, Tsujimoto et al., 2016, Gondivkar et al., 2009] analyzed diabetes and taste impairment. The studies found that participants with diabetes consumed more sugar then controls. In the current study a significantly higher BMI was found in the two diabetic groups when compared to controls which would assume that the two diabetic groups would consume food with higher calorie content.

An answer to less consumption of sugar and calories may be found in the NHANES participants' diet data. In both diabetic groups, about 32% of the participants was on a diet compared to only 15.5% in the control group. Moshfegh et al. [2008] states that dietary data are considered reliable in healthy normal BMI population opposite those with diabetes or overweight may tend to under-report food intake. It is also possible that adults, regardless of weight, may alter their eating habits the day before a dietary interview.

10.2 Regression model of diabetes and dietary habits

To address diabetes and the consequence of taste and smell impairment on eating habits a multiple linear regression model was analyzed. Main findings in the model were that gender was the most significant predictor followed by age and smell taste. Making gender,age and smell test an independent predictor of dietary habits. An increases in $HbA1_c$ values seem to have an influence on intake of sodium.
When calculating the energy (kcal) consumption, men with no smell impairment consumed whole

2800 kcal, vs. 2173 kcal for men with smell impairment. The recommended calories intake for men when aged 42 is to consume between (2200-2800 kcal per day) depending on activity levels. [Office of Disease Prevention and Health Promotion, 2015]. The result suggests that dietary information towards patients with diabetes must be deployed earlier in stage and even before diabetes evolves. It is better to prevent the development of diabetes.
There was no relation between the control of diabetes expressed by $HbA1_c$, sugar intake and smell impairment, which is in line with previous studies [Altundag et al., 2017, Duda-Sobczak et al., 2017, Gouveri et al., 2014] that investigating smell function and diabetes.
When analyzing the taste test and diabetes, the test was not found to be significant predictor.

10.3 Strength and weaknesses in current study and NHANES

To assess the participant's dietary habits, a 24-hour dietary recall was analyzed. Only one dietary recall was used to estimate nutrient intake, because a lot less participants answered the second dietary interview by phone. However, nutrient intake based on one recall can be a reliable measure in large populations. [Basiotis et al., 1987]

Diabetes was defined as value of $HbA1_c$ $\geq$6.5% and not by a self-reported question as used in other studies [Tsujimoto et al., 2016, Liu et al., 2016] to define diabetes. This method was selected to find undiagnosed diabetic participants and to get a more objective answer for the diagnosis of diabetes. $HbA1_c$ is only measured once in NHANES, but the American Diabetes Association recommends measurement of $HbA1_c$ 3-4 times per year for poorly controlled type 2-diabetes and type 1-diabetes, and 2 times per year for well-controlled type 2-diabetes [Mayo clinics and Mayo Medical Laboratories, 2017].
The consequence of using the $HbA1_c$ value alone was that the control group contained participants who answered "Yes" to the self-reported question about diabetes. The reason for this error may be due to the participant is diagnosed with diabetes, but still not reached an $HbA1_c$ level $\geq$ 6.5% or secondly that the participants general practitioner have told that the patient have symptoms of diabetes and then participant answered "Yes" to the question of having diabetes.
The control group was defined as all other participants with $\leq$6.4% of $HbA1_c$. When doing so, this will also include participants with prediabetes. This may contaminate the result of the control group, given a higher value of demographic data and the result of the taste and smell examination due to fact that prediabetes maybe also are having a taste and smell impairment as found in a study by Wasalathanthri et al. [2014] investigating the relation between prediabetes and sweet taste sensitivity.
To define complicated diabetes a definition by Tsujimoto et al. [2016] was applied. The study found a relation between diabetes, micro- and macro vascular complications and increased sugar intake in NHANES 2011-2012. This study took into account for nephropathy (macroalbuminuria), retinopathy, ischemic heart disease, and stroke. Tsujimoto et al. [2016] also calculated estimated glomerular filtration rate (eGFR), but this is not accounted for in the current study but would presumably have included more participants in the complicated diabetes group.
The taste and smell examination from 2012 was not included in this study due the assumption that the result would be the same [Liu et al., 2016].

NHANES is a cross-sectional study which limits the ability to find causal relationship between the risk factors and taste and smell impairment.
For the demographic profile, triglycerides and LDL cholesterol, was not included, due to only half of the participants had laboratory data for these two. This a limitation in understanding the participants issues with cholesterol
In the NHANES diabetes questionnaire there is no division between different types of diabetes, which is a limitation. The behaviors of the two types are different and that may have an effect on dietary habit and answer to the taste and smell test. E.g. type 2-diabetes is often undetected for years opposite patients with type 1-diabetes that is often quickly diagnosed and the patient is send

under treatment. Though approx. 10% has type 1-diabetes it may still have an influence on the result
The taste and smell examination provides taste tests of salt and bitter, but not sweet or sour which is a limitation. Therefore it was assumed that an incorrect answer to bitter (quinine) or salty (NaCl) also meant that the participant would have an incorrect answer to sugar. There is no universally accepted standards for defining taste impairment [Rawal et al., 2015], therefore in the evaluation of taste impairment, four tests of taste from the NHANES data was analyzed.

Liu et al. [2016] also suggested that the taste test used in NHANES was not sensitive enough to capture age-related declines due to the concentration of quinine and NaCl was too high. This resulted in a inverse association between age and the prevalence of taste impairment in the study.
The taste and smell protocol was only measured at one single occasion, but a study by Rawal et al. [2015] found the protocol to be moderate-to-good test-retest reliability after a 6 month retest.
In the taste and smell protocol, all participants <80 was given the same age, this was a limit in the data, because it gives a large portion of participants with the same age.

10.4 Data handling of NHANES data

When visually inspecting the NHANES data, it was clear that it contained outliers e.g. BMI, $HbA1_c$, sugar consumption, and total calories contained outliers. Though was these outliers considered to be realistic and therefore not removed. To handle not normally distributed data, non-parametric test was used.
Some of the NHANES variables had missing data. This was handled by, using the expectation maximization method to calculate new values [Do and Batzoglou, 2008]. This was considered the best method, due to the small amount (<5%) of missing data in the selected variables.
When analyzing the NHANES data, it was chosen to use unweighted data, because the NHANES survey contains data from 15 different counties each year this gives a general representative segment of the U.S. population. Not using unweighted has its limitations due to NHANES contains a larger population of Non-Hispanic white, and there are an oversampling of elder participants [NCHS, 2014]. In addition, certain ethnic groups such as non-Hispanic Blacks and Mexican Americans has a higher prevalence of smell impairment than White Americans [Liu et al., 2016].
To find predictors for eating habits among participants with diabetes a multiple linear regression analysis was applied. The method has some assumptions; firstly that the data should be normal distributed and secondly not contain significant outliers. Outliers were not removed in the current study. This was not account for and is a limit to the study but a possible sensitivity analysis of current result and new data without outliers and normalized data could perhaps change the result.

10.5 Screening diabetes for chemosensory dysfunction

Up to 50% percent of diabetic patients will experience diabetic peripheral neuropathy. This suggests that the higher percentage of smell impairment in the diabetic groups is caused by a widespread neurodegeneration.
Other neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, and multi-infarct dementia have been identified to have premonitory smell impairment that may even predict later development of these diseases [Brady et al., 2013].
This raises the question of where in the stage of diabetes that the development of chemosensory dysfunction occurs. Future studies of diabetes and chemosensory dysfunction is needed to discover if would be possible to develop a screening protocol for taste and smell in diabetes, that could help to reveal undiscovered diabetes, in treatment, and to avoid further progress of diabetes causing diabetic complications.

10.6 Future studies

For optimizing the regression model for diabetes relation to chemosensory dysfunction and dietary habits, further research is needed regarding other parameters that may influence on the chemosensory dysfunction in diabetes e.g. smoking status, medication, and socioeconomics. Secondly further research is needs to address eating habits and food choices in patients with diabetes and in the general public to prevent further epidemic growth of diabetes.

Chapter 11

Conclusion

The aim of this project was to analyze taste and smell impairment and the influence on dietary habits in participants with diabetes (defined as $HbA1_c$ $\geq$6.5%) from the National Health and Nutrition Examination Survey (NHANES).

It was demonstrated that participants with both non-complicated and complicated diabetes gained a significant worse smell scores when compared to controls. The taste test did not show any significant patterns of taste impairment.
On the contrary participants with diabetes with or without chronic complications seems to be consuming significant less of sugar and calories compared to the control group. Hence, salt levels were the same. This is to be seen in contrast to a significant higher BMI in the two diabetes groups.
A developed regression model demonstrated that gender, age and smell test are predictors of dietary habits. The smell test had a significant influence on the consumption of calories. An increase in $HbA1_c$ value seem to have an influence on intake of sodium.

Bibliography

A. Altundag, S. A. Ay, S. Hira, M. Salihoglu, K. Baskoy, F. Deniz, H. Tekeli, O. Kurt, A. Yonem, and T. Hummel. Olfactory and gustatory functions in patients with noncomplicated type 1 diabetes mellitus. *Eur. Arch. Otorhinolaryngol.*, pages 1–7, 2017.

R. A. Armstrong, S. V. Slade, and F. Eperjesi. An introduction to analysis of variance (anova) with special reference to data from clinical experiments in optometry. *Ophthal. Physiol. Opt.*, 20(3): 235–241, 2000.

P. P. Basiotis, S. O. Welsh, F. J. Cronin, J. L. Kelsay, and W. Mertz. Number of days of food intake records required to estimate individual and group nutrient intakes with defined confidence. *American Institute of Nutrition*, 1987.

S. Brady, P. Lalli, N. Midha, A. Chan, A. Garven, C. Chan, and C. Toth. Presence of neuropathic pain may explain poor performances on olfactory testing in diabetes mellitus patients. *Chem. Senses*, (38):497–507, 2013.

S. M. Bromley and R. L. Doty. *Clinical Disorders Affecting Taste: An Update*. John Wiley & Sons, Inc., 3 edition, 2015.

C. CDC and N. NCHS. *National Health and Nutrition Examination Survey (NHANES) Taste and Smell Examination Component Manual*. 2013.

T. J. Cleophas and A. H. Zwinderman. *Statistics Applied to Clinical Studies*. Springer, 5 edition, 2012.

D. Dansk Selskab for Almen Medicin. *type 2-diabetes - et metabolisk syndrom*. 2012.

D. Det Nationale Diabetesregister. Antal diabetikere (prævalens), 1996-2012, 2012. URL http://www.diabetes.dk/presse/diabetes-i-tal/det-nationale-diabetesregister.aspx. Accessed on: 2017-03-02.

C. B. Do and S. Batzoglou. What is the expectation maximization algoritm? *Nature Biotechnology*, 26(8), 2008.

A. R. T. Donders, G. J. van der Heijdenc, T. Stijnend, and K. G. Moonsc. Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol*, art. 59, 2006.

Y. Dong and C.-Y. J. Peng. Principled missing data methods for researchers. *SpringerPlus*, 2:222, 2013.

R. L. Doty. *Introduction and Historical Perspective*. John Wiley & Sons, Inc., 3 edition, 2015a.

R. L. Doty. *Clinical Disorders of Olfaction*. John Wiley & Sons, Inc., 3 edition, 2015b.

A. Duda-Sobczak, A. Araszkiewicz, M. Urbas, L. Borucki, K. Kulas, M. Chudzinski, A. Suwalska, and D. Zozulinska-Ziolkiewicz. Impaired olfactory function is related to the presence of neuropathy in adults with type 1 diabetes. *Diabetes & Vascular Disease Research*, 14(1):139–143, 2017.

P. Eiken and O. Snorgaard. *Endokrinologi - i klinisk praksis*. Munksgaard, 2016.

J. C. Fernández-García, F. Cardona, and F. J. Tinahones. Inflammation, oxidative stress and metabolic syndrome: Dietary modulation. *Current Vascular Pharmacology*, 11:906–919, 2013.

S. M. Gondivkar, A. Indurkar, S. Degwekar, and R. Bhowate. Evaluation of gustatory function in patients with diabetes mellitus type 2. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.*, 108(6):876–880, 2009.

E. Gouveri, M. Katotomichelakis, H. Gouveris, V. Danielides, E. Maltezos, and N. Papanas. Olfactory dysfunction in type 2 diabetes mellitus: An additional manifestation of microvascular disease? *Angiology*, 65(10):869–876, 2014.

IBM. Ibm spss statistics 24, October 2017. URL https://www.ibm.com/analytics/dk/da/technology/spss/. Accessed on: 2017-03-28.

K. Johansen. *Basal sundhedsvidenskabelig statistik - begreber og metode*. Munksgaard danmark, 2006.

R. S. Khobragade, S. L. Wakode, and A. H. Kale. Psysiological taste threshold in type 1 diabetes mellitus. *Indian J. Physiol. Pharmacol.*, 56(1):42–47, 2012.

A. Laffitte, F. Neiers, and L. Briand. Functional roles of the sweet taste receptor in oral and extraoral tissues. *Current Opinion in Clinical Nutrition and Metabolic Care*, 17:379–385, 2014.

J. L. Leahy. Pathogenesis of type 2 diabetes mellitus. *Archives of Medical Research*, art. 36, 2005.

G. Leng, R. A. H. Adan, M. Belot, J. M. Brunstrom, K. de Graaf, S. L. Dickson, T. Hare, S. Maier, J. Menzies, H. Preissl, L. A. Reisch, P. J. Rogers, and P. A. M. Smeets. The determinants of food choice. *Proceedings of the Nutrition Society*, 6:1–12, 2016.

G. Liu, G. Zong, R. L. Doty, and Q. Sun. Prevalence and risk factors of taste and smell impairment in a nationwide representative sample of the us population, a cross-sectional study. *BMJ Open*, 2016.

J. Malaty and I. A. C. Malaty. Smell and taste disorders in primary care. *Am. Fam. Physician*, 88 (12):852–859, 2013.

F. H. Martini and J. L. Nath. *Fundamentals of anatomy and physiology, chapter 18: The Endocrine System*. Pearson, 2009a.

F. H. Martini and J. L. Nath. *Fundamentals of anatomy and physiology, chapter 17: The special senses*. Pearson, 2009b.

Mayo clinics and Mayo Medical Laboratories. Hemoglobin a1c, blood, 2017. URL http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82080. Accessed on: 2017-06-04.

A. J. Moshfegh, D. G. Rhodes, D. J. Baer, T. Murayi, J. C. Clemens, W. V. Rumpler, D. R. Paul, R. S. Sebastian, K. J. Kuczynski, L. A. Ingwersen, R. C. Staples, and L. E. Cleveland. The us department of agriculture automated multiple-pass method reduces bias in the collection of energy intakes. *American Society for Nutrition*, 88:324–32, 2008.

A. Naka, M. Riedl, A. Luger, T. Hummel, and C. A. Mueller. Clinical significance of smell and taste disorders in patients with diabetes mellitus. *European Archives of Oto-Rhino-Laryngology*, 267:547–550, 2010.

N. National Center for Health Statistics. Nhanes 2013-2014 data documentation, codebook, and frequencies, diabetes (diq_h), 2014. URL https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DIQ_H.htm. Accessed on: 2017-03-22.

N. National Center for Health Statistics. Dietary interview - total nutrient intakes, first day (dr1tot_h), 2016. URL https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DIQ_H.htm. Accessed on: 2017-04-05.

N. NCHS. *National Health and Nutrition Examination Survey, 2013-2014 - Overview*. 2014.

N. NCHS. National health and nutrition examination survey 2013-2014 data documentation, codebook, and frequencies - taste & smell (csx_h), 2016. URL https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/CSX_H.htm. Accessed on: 2017-03-15.

F. Neiers, M.-C. Canivenc-Lavier, and L. Briand. What does diabetes taste like? *Current Diabetes Reports*, 16(6):49, 2016.

Office of Disease Prevention and Health Promotion. Dietary guidelines for americans 2015-2020, 2015. URL https://health.gov/dietaryguidelines/2015/guidelines/. Accessed on: 2017-05-10.

J. H. O'Keefe, D. S. H. Bell, and K. L. Wyne. *Diabetes essentials*. 2009.

J. Pallant. *SPSS survival manual*. 6 edition, 2016.

S. Rawal, H. J. Hoffman, M. Honda, T. B. Huedo-Medin, and V. B. Duffy. The taste and smell protocol in the 2011-2014 us national health and nutrition examination survey (nhanes): Test-retest reliability and validity testin. *Chemosens Percept.*, 8(3):138–148, 2015.

S. Sen, R. Chakraborty, and B. De. *Diabetes Mellitus in 21st Century*. Springer, 2016.

T. Tsujimoto, K. Imai, SayakaKanda, M. Kakei, H. Kajio, and T. Sugiyama. Sweet taste disorder and vascular complications in patients with abnormal glucose tolerance. *International Journal of Cardiology*, (221):637–641, 2016.

S. Verma and M. E. Hussainb. Obesity and diabetes: An update. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 11:73–79, 2017.

S. Wasalathanthri, P. Hettiarachchi, and S. Prathapan. Sweet taste sensitivity in pre-diabetics, diabetics and normoglycemic controls: a comparative cross sectional study. *BMC Endocrine Disorders*, 14:67, 2014.

W. WHO. *Global report on diabetes*. 2016a.

W. WHO. Obesity and overweight, June 2016b. URL http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed on: 2017-03-02.

W. World Health Organistation. Bmi classification, 2016. URL http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed on: 2017-03-15.

J. H. Yu, M. S. Shin, D. J. Kim, J. R. Lee, S.-Y. Yoon, S. G. Kim, E. H. Koh, W. J. Lee, J.-Y. Park, and M.-S. Kim. Enhanced carbohydrate craving in patients with poorly controlled type 2 diabetes mellitus. *Diabetic Medicine*, 30(9):1080–1086, 2013.

J. H. Yu, M.-S. Shin, J. R. Lee, J. H. Choi, E. H. Koh, W. J. Lee, J.-Y. Park, and M.-S. Kim. Decreased sucrose preference in patients with type 2 diabetes mellitus. *Diabetes Research and Clinical Practice*, (104):214–219, 2014.

J. H. Zar. *Biostatistical Analysis: Pearson New International Edition*. Pearson, 2014.

Appendix A

Literature Search

To find factors that can influence on the taste and smell impairment of diabetic patients a literature search concerning the topic was performed.

Search protocol

Initial problem:	How can diabetes mellitus affect the taste and smell perception, and which complications can this result in?

Database	Reasons for choosing
Pudmed	Contains biomedical and life sciences journal literature
Embase	Cover international biomedical literature
Cochrane	Contains systematic reviews

Table A.1: Pubmed

	AND		
OR	A Diabetes	B Smell sense	C Taste sense
	MesH	**MesH**	**MesH**
	Diabetes Mellitus	Olfactory Perception	Taste perception
	Diabetes Mellitus, type 1	Olfactory Nerve Diseases	Taste
	Diabetes Mellitus, type 2	Smell	Ageusia
	Diabetic complications	Olfaction Disorders	
	Free text	**Free text**	**Free text**
	Diabetes Mellitus	Olfactory Perception	Taste perception
	Diabetes Mellitus, type 1	Olfactory Nerve Diseases	Taste
	Diabetes Mellitus, type 2	Smell	Ageusia
	Diabetic complications	Olfaction Disorders	
	hits: 414,919	hits: 21,236	hits: 34,644

Table A.2: Pubmed

	search string	Indentified	**Relevant**
A AND B 82 hits	Search ((((((("Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Complications"[Mesh])) OR ("Diabetes Mellitus" OR "Diabetes Mellitus, Type 1" OR "Diabetes Complications"))) OR ((((("Diabetes Complications") OR "Diabetes Mellitus, Type 2")) OR (("Diabetes Complications"[Mesh]) OR "Diabetes Mellitus, Type 2"[Mesh]))))) AND (((((("Olfactory Perception" OR "Olfactory Nerve Diseases")) OR ("Smell" OR "Olfaction Disorders"))) OR ((("Olfactory Perception"[Mesh] OR "Olfactory Nerve Diseases"[Mesh])) OR ("Smell"[Mesh] OR "Olfaction Disorders"[Mesh]))))	10	7
A AND C 352 hits	Search ((((((("Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Complications"[Mesh])) OR ("Diabetes Mellitus" OR "Diabetes Mellitus, Type 1" OR "Diabetes Complications"))) OR ((((("Diabetes Complications") OR "Diabetes Mellitus, Type 2")) OR (("Diabetes Complications"[Mesh]) OR "Diabetes Mellitus, Type 2"[Mesh]))))) AND ((((("Ageusia"[Mesh]) OR ("Taste Perception"[Mesh] OR "Taste"[Mesh]))) OR (("Ageusia") OR ("Taste Perception" OR "Taste")))	5	2
A AND B AND C 28 hits	Search (((((((("Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Complications"[Mesh])) OR ("Diabetes Mellitus" OR "Diabetes Mellitus, Type 1" OR "Diabetes Complications"))) OR ((((("Diabetes Complications") OR "Diabetes Mellitus, Type 2")) OR (("Diabetes Complications"[Mesh]) OR "Diabetes Mellitus, Type 2"[Mesh]))))) AND (((((("Olfactory Perception" OR "Olfactory Nerve Diseases")) OR ("Smell" OR "Olfaction Disorders"))) OR ((("Olfactory Perception"[Mesh] OR "Olfactory Nerve Diseases"[Mesh])) OR ("Smell"[Mesh] OR "Olfaction Disorders"[Mesh])))) AND ((((("Ageusia"[Mesh]) OR ("Taste Perception"[Mesh] OR "Taste"[Mesh]))) OR (("Ageusia") OR ("Taste Perception" OR "Taste")))	6	5
			Total minus duplicates = 6

Table A.3: Embase

AND			
OR	A Diabetes	B Smell sense	C Taste sense
	Emtree	**Emtree**	**Emtree**
	Diabetes Mellitus	Odor	Taste
	Insulin dependent diabetes mellitus	Smelling	Taste discrimination
	Non insulin dependent diabetes mellitus	Smelling disorder	Ageusia
		Olfactory discrimination	Taste disorder
	Free text	**Free text**	**Free text**
	Diabetes Mellitus	Odor	Taste
	Insulin dependent diabetes mellitus	Smelling	Taste discrimination
	Non insulin dependent diabetes mellitus	Smelling disorder	Ageusia
		Olfactory discrimination	Taste disorder
	hits: 803,883	hits: 46,343	hits: 54,565

Table A.4: Embase

	Identified	Relevant
A AND B 454 hits	8	3
A AND C 1,463 hits	17	6
A AND B AND C 86 hits	10	2
		Total minus duplicates = 7

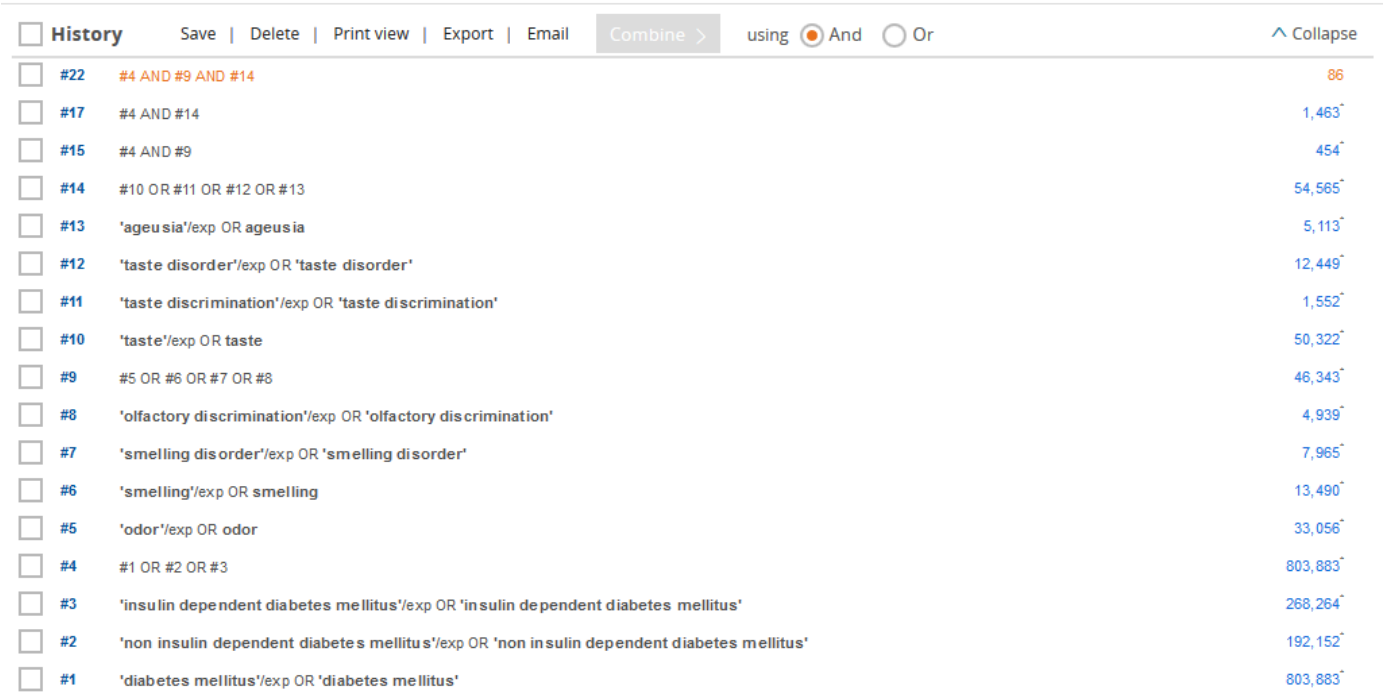


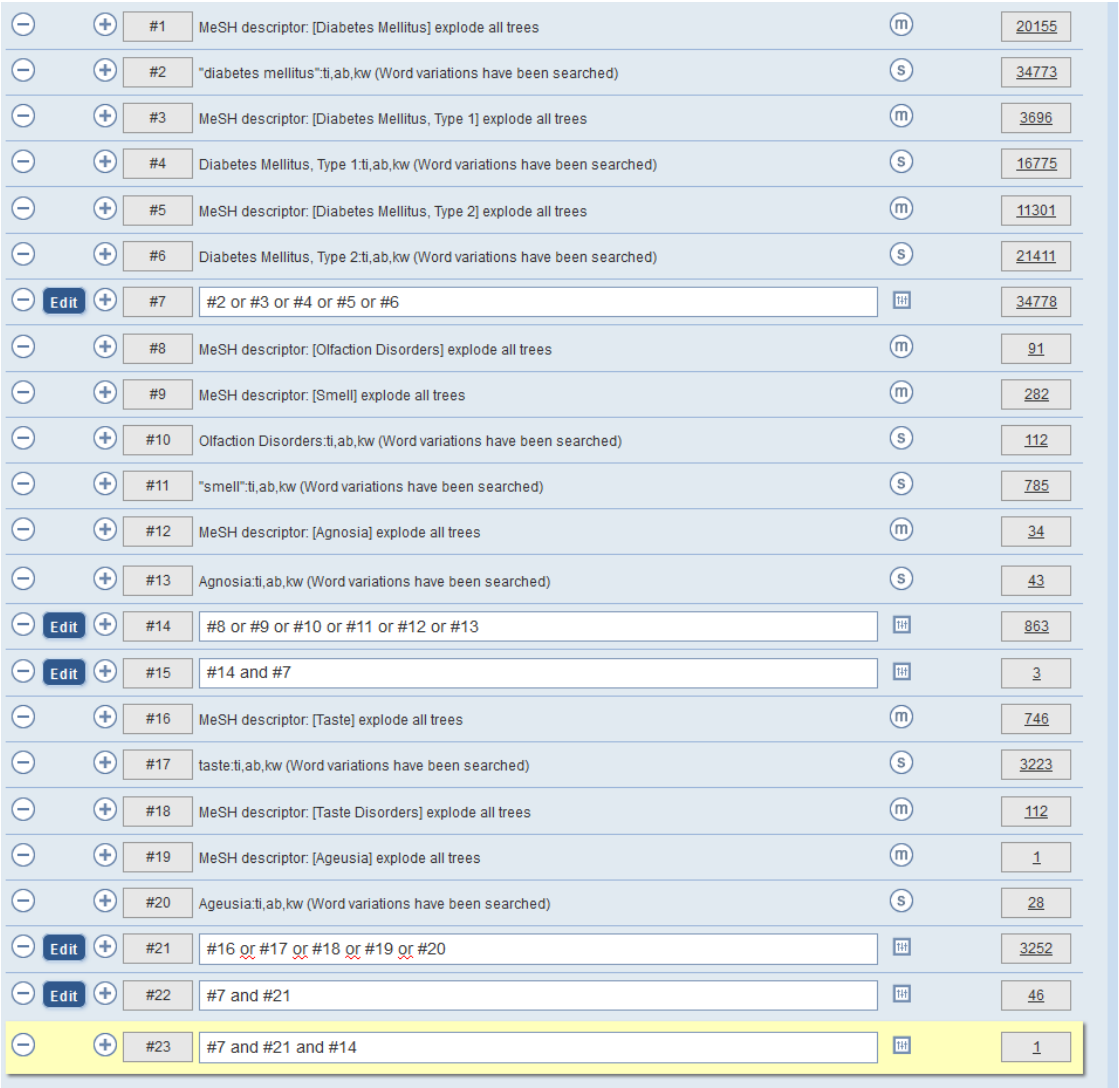
Figure A.1: Search tree in Embase.

Table A.5: Cochrane

	AND		
OR	A Diabetes	B Smell sense	C Taste sense
	MesH Diabetes Mellitus diabetes mellitus type 1 diabetes mellitus type 2 **Free text** Diabetes Mellitus diabetes mellitus type 1 diabetes mellitus type 2	**MesH** Smell Olfaction Disorders Agnosia **Free text** Smell Olfaction Disorders Agnosia	**MesH** Taste Taste disorder Ageusia **Free text** Taste Taste disorder Ageusia
	hits: 34,778	hits: 863	hits: 3,252

Table A.6: Cochrane

	Identified	Relevant
A AND B 3 hits	0	0
A AND C 45 hits	2	0
A AND B AND C 1 hits	0	0
		Total minus duplicates = 0



#1	MeSH descriptor: [Diabetes Mellitus] explode all trees	m	20155
#2	"diabetes mellitus":ti,ab,kw (Word variations have been searched)	s	34773
#3	MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees	m	3696
#4	Diabetes Mellitus, Type 1:ti,ab,kw (Word variations have been searched)	s	16775
#5	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees	m	11301
#6	Diabetes Mellitus, Type 2:ti,ab,kw (Word variations have been searched)	s	21411
Edit #7	#2 or #3 or #4 or #5 or #6		34778
#8	MeSH descriptor: [Olfaction Disorders] explode all trees	m	91
#9	MeSH descriptor: [Smell] explode all trees	m	282
#10	Olfaction Disorders:ti,ab,kw (Word variations have been searched)	s	112
#11	"smell":ti,ab,kw (Word variations have been searched)	s	785
#12	MeSH descriptor: [Agnosia] explode all trees	m	34
#13	Agnosia:ti,ab,kw (Word variations have been searched)	s	43
Edit #14	#8 or #9 or #10 or #11 or #12 or #13		863
Edit #15	#14 and #7		3
#16	MeSH descriptor: [Taste] explode all trees	m	746
#17	taste:ti,ab,kw (Word variations have been searched)	s	3223
#18	MeSH descriptor: [Taste Disorders] explode all trees	m	112
#19	MeSH descriptor: [Ageusia] explode all trees	m	1
#20	Ageusia:ti,ab,kw (Word variations have been searched)	s	28
Edit #21	#16 or #17 or #18 or #19 or #20		3252
Edit #22	#7 and #21		46
#23	#7 and #21 and #14		1

Figure A.2: Search tree in Cochrane.

Table A.7: Overview of articles concerning diabetes, and taste and smell. Sorted by year. DM: diabetes mellitus, T2DM: Type 2 DM, T1DM: Type 1 DM.

Article	**Impairment**	**Findings**
Duda-Sobczak et al. [2017]	Smell	Included 106 patients with T1DM and 30 healthy controls. Impaired smell is related to the presence of neuropathy in adults with T1DM.
Altundag et al. [2017]	Taste and smell	Included 39 patients with non-complicated DM and 31 healthy controls. T1DM non-complicated may not be associated with olfactory and gustatory dysfunction. Gustatory and olfactory functions may not be related with $HbA1_c$ values and disease duration in non-complicated T1DM.
Tsujimoto et al. [2016]	Sense of taste	Included 848 with diabetes and 849 with prediabetes who had sweet and salt taste disorders, NHANES 2011-2012. Patients with abnormal glucose tolerance is associated with increased sugar intake and vascular complications.
Neiers et al. [2016]	Sense of taste	A Sweet taste receptors and their physiological role of in taste perception and metabolic regulation with focus on their dysfunctions that leads to DM.
Gouveri et al. [2014]	Sense of smell	Included 154 adults of them 119 with T2DM. Among patients with T2DM, with microvascular disease has a particularly severe smell impairment. Hypertension seems to be an independent predictor of lower olfactory scores.
Yu et al. [2014]	Sense of taste	Included 100 T2DM patients and 100 matched controls.Participants with T2DM has a lower preference for sweet tastes than controls despite their decreased perception of sucrose. Reduced sucrose preference is not associated with better glycemic control in diabetic patients.
Wasalathanthri et al. [2014]	Sweet taste	Included 40 prediabetes, 40 T2DM and 34 normoglycemic controls. The study confirmed previous findings of blunted taste response in diabetics.
[Yu et al., 2013]	Food cravings	Included 105 with T2DM and 105 age-, sex- and BMI-matched controls. T2DM patients had a higher carbohydrate craving scores than control. Carbohydrates craving in DM patients were positively correlated with $HbA1_c$. Carbohydrate cravings declined in DM patients with improved glycemic control.
Brady et al. [2013]	Sense of smell	Included 74 participants 19 healthy control participants, 19 with non-complicated DM, 15 what DM with peripheral neuropathy but no pain and 21 with DM with peripheral neuropathy. Participants with diabetes had decreased olfactory sensitivity, impaired olfactory discrimination abilities, and reduced odor identification skills when compared with controls.
Khobragade et al. [2012]	Taste	Included 70 T1DM and 70 non-diabetics. A significant increase in taste threshold for sweet, salt, sour and bitter in T1DM was observed. The pathophysiology of taste disorders remains unclear in diabetes. Diabetic neuropathy and taste impairment has been associated but remain disputed. Drug used in T2DM have been thought to impair taste threshold.
Naka et al. [2010]	Taste and smell	Included 67 participants (T1DM, T2DM), divided into 3 groups, and 29 healthy controls. No significant differences in taste and smell function between patients with non-complicated diabetes and healthy controls. T2DM showed impaired smell function compared with type 1 patients.
Gondivkar et al. [2009]	Sense of taste	Included 40 controlled and 40 uncontrolled T2DM. T2DM patients had a blunted taste response mostly for sweet sensation followed by sour and salt tastes.

Appendix B

Missing data

Variable Summary[a,b]

	Missing		Valid N	Mean	Std. Deviation
	N	Percent			
CSXQUIST Whole Mouth 1 mM Quinine: What Was Taste	594	16,0%	3114		
CSXQUISG Whole Mouth Test: 1 mM Quinine gLMS	594	16,0%	3114	53,21	22,731
CSXSLTST Whole Mouth 1 M NaCl: What Was Taste?	491	13,2%	3217		
CSXSLTSG Whole Mouth Test: 1 M NaCl gLMS	491	13,2%	3217	52,06	22,566
CSXNAST Whole Mouth . 32 NaCl: What Was Taste?	490	13,2%	3218		
CSXNASG Whole Mouth Test: .32 M NaCl gLMS	490	13,2%	3218	33,08	19,413
DR1TSODI Sodium (mg)	407	11,0%	3301	3334,26	1787,782
DR1TSUGR Total sugars (gm)	407	11,0%	3301	102,5378	71,01286
DR1TKCAL Energy (kcal)	407	11,0%	3301	2009,21	953,348
CSQ490 High test light (1000 candelas/m2)	297	8,0%	3411	60,95	21,639
CSQ480 Low test light (4.3 candelas/m2)	297	8,0%	3411	11,46	10,198
CSQ470 Medium test light (193 candelas/m2)	296	8,0%	3412	29,80	16,673
CSXNGSOD Smell Test: Natural Gas Scent	189	5,1%	3519		
CSXONOD Smell Test: Onion Scent	189	5,1%	3519		
CSXGRAOD Smell Test: Grape Scent	189	5,1%	3519		
CSXSOAOD Smell Test: Soap Scent	188	5,1%	3520		
CSXLEAOD Smell Test: Leather Scent	188	5,1%	3520		
CSXSMKOD Smell Test: Smoke Scent	185	5,0%	3523		
CSXSBOD Smell Test: Strawberry Scent	183	4,9%	3525		
CSXCHOOD Smell Test: Chocolate Scent	181	4,9%	3527		
LBDHDDSI Direct HDL-Cholesterol (mmol/L)	168	4,5%	3540	1,3871	,42983

Variable Summary[a,b]

	Missing				
	N	Percent	Valid N	Mean	Std. Deviation
LBDTCSI Total Cholesterol(mmol/L)	168	4,5%	3540	4,9982	1,12153
LBXGH Glycohemoglobin (%)	131	3,5%	3577	5,9628	1,19148
URDACT Albumin creatinine ratio (mg/g)	92	2,5%	3616	64,9109	400,06184
BMXBMI Body Mass Index (kg/m**2)	60	1,6%	3648	29,3311	6,89127

a. Maximum number of variables shown: 100

b. Minimum percentage of missing values for variable to be included: 1,0%

Appendix C

NHANES codes

Definition of complicated diabetes

Table C.1: NHANES codes for demographic analysis.

Code	Explanation
URDACT	Urine albumin ≥300 mg/g
DIQ080	Retinopathy
MCQ160D	Angina pectoris
MCQ160E	Heart attack
MCQ160F	Stroke

Demographic data

Table C.2: NHANES codes for demographic analysis.

Code	Explanation
RIDAGEYR	Age in years at screening
RIAGENDR	Gender
BMXBMI	Body Mass Index (kg/m**2)
LBXGH	$HbA1_c$
LBDTCSI	Total Cholesterol(mmol/L)
LBDHDDSI	Direct HDL-Cholesterol (mmol/L)
DID040	Duration of diabetes
BPQ020	Ever told you had high blood pressure - self reported

Taste and smell examination

Smell testing

Table C.3: NHANES codes to define smell impairment.

Code	Explanation
CSXCHOOD	Smell Test: Chocolate Scent
CSXSBOD	Smell Test: Strawberry Scent
CSXSMKOD	Smell Test: Smoke Scent
CSXLEAOD	Smell Test: Leather Scent
CSXSOAOD	Smell Test: Soap Scent
CSXGRAOD	Smell Test: Grape Scent
CSXONOD	Smell Test: Onion Scent
CSXNGSOD	Smell Test: Natural Gas Scent

Taste testing

Table C.4: NHANES codes for defining taste impairment.

Code	Explanation
CSXSLTSG	Whole Mouth Test: 1 M NaCl gLMS
CSXNASG	Whole Mouth Test: 0.32 M NaCl gLMS
CSXQUIST	Whole Mouth 1 mM Quinine: What Was Taste?
CSXSLTST	Whole Mouth 1 M NaCl: What Was Taste?
CSXNAST	Whole Mouth 0.32 NaCl: What Was Taste?

Sugar and sodium consumption

Table C.5: NHANES codes for dietary intake analysis.

Code	Explanation
DR1TSUGR	Total sugars (gm)
DR1TSODI	Sodium (mg)
DR1TKCAL	Energy (kcal)

Diet data

Table C.6: NHANES codes for diet analysis.

Code	Explanation
DRQSDIET	On special diet? 100
DRQSDT1	Weight loss/Low calorie diet
DRQSDT3	Low salt/Low sodium diet
DRQSDT4	Sugar free/Low sugar diet
DRQSDT7	Diabetic diet