The State of Oral Health Among Individuals with Schizophrenia and Alzheimer's Disease: A Hungarian Perspective

Ph.D. Thesis

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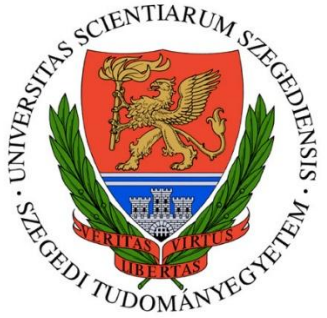

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PUBLICATIONS

I. Publications related to the subject of the thesis

1. **Aghasizadeh Sherbaf R,** Kaposvári GM, Nagy K, Álmos ZP, Baráth Z, Matusovits D. Oral Health Status and Factors Related to Oral Health in Patients with Schizophrenia: A Matched Case-Control Observational Study. *Journal of Clinical Medicine*. 2024; *13*(6):1584. https://doi.org/10.3390/jcm13061584

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2. **Aghasizadeh Sherbaf R**, Kaposvári GM, Nagy K, Pakáski M, Gajdács M, Matusovits D, Baráth Z. Oral Health Status and Factors Associated with Oral Health in Patients with Alzheimer's Disease: A Matched Case-Control Observational Study. *Journal of Clinical Medicine*. 2025; *14*(5):1412. https://doi.org/10.3390/jcm14051412

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II. Other publications related to the subject of the thesis

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III. Presentations related to the subject of the thesis

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2. **Aghasizadeh, Sherbaf Reza**; Gajdács, Mário; Kaposvári, George Michael; Pakáski, Magdolna; Matusovits, Danica; Baráth, Zoltán: Oral health status in patients with Alzheimer's: An age and gender-matched case-control observational study. In NÉPEGÉSZSÉGÜGY 101: 2 pp. 105-105. 2024. August 28-30. Pécs, Hungary.

LIST OF ABBREVIATIONS

- AD: Alzheimer's disease
- AL: attachment loss
- APA: American Psychiatric Association
- ApoE: apolipoprotein E
- APP: amyloid precursor protein
- BI: Barthel index
- BBB: Blood Brain Barrier
- BOP: Bleeding on probing
- BRPS: Brief Psychiatric Rating Scale
- CL: calculus index
- COPD: Chronic Obstructive Pulmonary Disease
- CPI: community periodontal index
- CT: Computed Tomography
- DI: debris index
- DMF-S: Decayed, missing and filled surfaces
- DMF-T: Decayed, missing and filled teeth
- DSM: Diagnostic and Statistical Manual
- GBD: Global Burden of Disease
- GDS: Geriatric Depression Scale
- GDS: Global Deterioration Scale
- MMSE: Mini-Mental State Examination
- MRI: Magnetic Resonance Imaging
- Mt: Missing teeth
- NHANES: National Health and Nutrition Examination Survey
- NIA: National Institute of Aging
- NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
- OHI: Oral Hygiene Index
- PANSS: Positive and Negative Syndrome Scale
- PD: pocket depths
- QoL: Quality of Life
- ROAG: Revised Oral Assessment Guide
- RT-PCR: Reverse Transcription-Polymerase Chain Reaction
- SCZ: Schizophrenia
- TFT: Thyroid Function Tests
- UN: United Nations
- WHO: World Health Organization

1. INTRODUCTION

1.1 Schizophrenia

Mental health is a fundamental aspect of overall well-being, encompassing our emotional, psychological, and social states. It influences how we think, feel, and act, playing a crucial role in our ability to handle stress, relate to others, and make choices. When mental health is compromised, it can lead to various conditions, with Schizophrenia (SCZ) being a particularly severe and chronic mental disorder. SCZ is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. It is characterized by distortions in thinking, perception, emotions, language, sense of self, and behavior. According to the World Health Organization (WHO), SCZ affects approximately 24 million people worldwide, or 1 in 300 people (0.32%), and this rate is 1 in 222 people (0.45%) among adults [1]. People with SCZ may seem as though they have lost touch with reality, which can be distressing for them and for their family and friends.

The exact causes of SCZ are not fully known, but research suggests a combination of genetic, environmental, and brain chemistry factors contribute to its development [2]. While there is no cure for SCZ, treatments such as antipsychotic medications, psychosocial therapies, and coordinated specialty care can help manage symptoms, reduce relapses, and improve quality of life, enabling many individuals to lead fulfilling lives [3]. Early diagnosis and intervention are crucial for improving outcomes.

1.1.1 Epidemiology and Disease Burden

Mental disorders constitute a considerable and increasing burden on global health, both from an epidemiological and economic context [4]; according to the Global Burden of Disease Study (GBD) 2019 estimates, they account for over >400 million disability-adjusted life years (DALYs; 16% of the global burden), and ~USD 5 trillion of overall economic costs [5]. Mental disorders include depressive, bipolar and anxiety disorders; substance abuse disorders; eating disorders; SCZ; and self-harm, among others, all of which are often associated with poor quality of life (QoL) [6,7]. SCZ is a complex mental disorder—which affects 0.45% (1:222) of the adult population—characterized, on one hand, by persistent hallucinations, delusions,

psychosis, disorganized behavior and agitation (i.e., positive symptoms) and, on the other hand, by social withdrawal, limited experience of emotions, passiveness, cognitive dysfunctions and slow movements (i.e., negative symptoms) [1,8]. SCZ patients are often affected by discrimination and stigma, further facilitating withdrawal from society and from performing everyday tasks [9]. Based on a recent meta-analysis, 24.2% (95% CI: 20.3–28.0%) of SCZ patients returned to previous functionality following treatment [10]; however, it has been estimated that the risk of relapse in SCZ is ~3.5%/month [11].

1.1.2 Comorbidities and Associated Health Issues

Many individuals affected by SCZ also suffer from various comorbid conditions, including cardiovascular diseases, chronic obstructive pulmonary disease (COPD), obesity, diabetes, endocrine disorders and other mental health conditions (e.g., mood disorders, panic disorders, substance abuse) [12,13]. Additionally, many reports highlight the disproportionately poor oral health outcomes (including higher incidence and severity of dental caries, periodontal disease and severe tooth loss) of SCZ patients, owing to a multidimensional set of factors [12,13]. Oral health is a critical aspect of an individual's overall health and QoL, having essential physiological (breathing, eating), social (communication) and psycho-social (confidence, well-being) dimensions [14,15]. Furthermore, the bidirectional relationship between mental health indicators and overall dental health status has also been noted previously [16,17]. A variety of factors may contribute to the poor oral health of SCZ patients: they may lack motivation to keep up adequate oral hygiene habits (due to negative symptoms or a relapse) [18], and they are often less likely to attend dental visits than their healthy counterparts [19]. SCZ patients often receive medications, including first- and second-generation antipsychotics, mood stabilizers, benzodiazepines and anti-Parkinson drugs (e.g., anticholinergics), all of which present with numerous adverse effects in the oral cavity [20]. Salivary gland hypofunction and xerostomia are notable consequences of these drugs, leading to increased incidence of (often severe) caries due to the reduced salivary flow rate [21]. Likewise, orofacial (or tardive) dyskinesia constitutes involuntary movements of the face, mouth and tongue, which hinders the individual's ability to perform oral hygiene practices effectively [22]. On the other hand, various lifestyle factors, such as tobacco consumption, alcohol use and poor dietary habits (i.e., high intake of simple sugars, low intake of fibers and vitamins), may further exacerbate the oral health (high rates of caries, poor periodontal status, experience of ulcers) of SCZ patients [23–25].

As individuals affected by mental disorders often receive suboptimal dental healthcare—especially in the case of hospitalized patients—many initiatives have been put forth aiming to recognize and highlight the vulnerability of specific psychiatric patient groups—including SCZ patients—to dental caries, deterioration in periodontal status, tooth loss and poor QoL [26]. As such, these patients may require a heightened focus on preventive oral hygiene interventions, or dental treatment for oral health rehabilitation. While there has been an increase in the number of clinical studies dealing with the oral health status of patients with SCZ [27,28], there are limited epidemiological data available comparing the dental and periodontal parameters of patients with SCZ to the general population.

1.2 Alzheimer's Disease

Dementia is a broad term describing a decline in cognitive function—affecting memory, thinking, language, judgment, and behavior—severe enough to interfere with daily life. It's not a specific disease itself but rather a collection of symptoms that can be caused by various underlying conditions. Alzheimer's Disease (AD) is the most common cause of dementia, accounting for a significant majority of cases. AD is a progressive neurodegenerative disorder that primarily affects older adults and is the most common cause of dementia, accounting for an estimated 60-80% of cases [29]. It is characterized by a gradual decline in memory, thinking, behavior, and social skills, which eventually interferes significantly with a person's ability to perform daily activities [30]. The disease process involves complex changes in the brain, including the abnormal buildup of proteins (amyloid plaques and tau tangles), leading to nerve cell damage and death, and brain shrinkage [31]. While age is the most significant known risk factor, AD is not a normal part of aging [30]. Currently, there is no cure for AD; however, available treatments can help manage symptoms, and research is ongoing to find better ways to treat, delay its onset, and prevent it from developing [29]. Early diagnosis is crucial for managing the condition and planning for the future.

1.2.1 Epidemiology and Disease Burden

Degenerative diseases, and pathologies with a delayed onset are expected to carry a rapidly increasing societal burden, due to the late stages of the epidemiological transition, the increase in life expectancy and the ageing of the global population [32,33]. According to recent projections, the share of the global population aged ≥65 years is expected to reach >16% by

2050 [34]. Of note, dementias—corresponding to a group of diseases with a heterogeneous pathophysiology, but similar clinical presentation—are noted as one of the most severe public health concerns of the 21st century [35,36]. Dementias include AD; corresponding to 50-75% of all dementia diagnoses and other forms of dementia, such as vascular dementia, frontotemporal, Lewy body dementia and mixed-form dementia [37,38]. Based on the estimates of the WHO for 2021, AD and other form of dementia were responsible for the deaths of ~1.8 million people, ranking as the seventh leading cause of death in both sexes, and raking fourth in developed countries [39]. Furthermore, based on Global Burden of Disease (GBD) estimates, the prevalence of dementia is expected to increase from 57.4 million cases (2019) to 152.8 million cases by 2050 [40]; during the same time-frame, dementia is projected to incur a cost of 14,513 billion international dollars (INT$, set at 2020 value), highlighting the sizable economic burden of disease, both for the caregivers and the healthcare systems [40,41].

The emergence of AD cases is bimodal: the overwhelming majority (>90%) of AD cases have an onset ≥65 years of age, and are considered sporadic; on the other hand, <10% of cases present <65 years of age ("early-onset AD", usually between 30-60 years), where there is a known familial history of the disease [42,43]. Based on disease severity, the illness may also be classified as mild, moderate and severe AD [44]. AD leads to progressive changes in the central nervous system, which may be broadly described as the "AD continuum": i) in the first, preclinical stage (which may last as long as 20 years), the biological onset of the illness and the various associated biomarkers may be detected, but the individual is symptom-free; ii) in the second stage, mild cognitive impairment may be noted by the individual or the close community around the individual (family members, friends), but these symptoms rarely interfere with the person's ability to handle daily tasks; iii) the later stages of AD are characterized by severely impaired cognitive abilities and memory—limiting patients in executive functions, performing everyday tasks, and not recognizing loved ones—compromised ability to communicate, erratic (or often aggressive) behaviors and a tendency to wandering off [45,46]. Due to the nature of the disease, AD patients are characterized by substantial disability and dependency, leading to significant decline in the quality of life (QoL) not only for AD patients, but also for their families and caregivers [47]; in severe cases, appropriate treatment of these individuals may only be insured in long term care facilities [48]. At present, the most well-established theory for the etiopathogenesis of AD is associated with the deposition of β-amyloid plaques and neurofibrillary tangles, composed of hyperphosphorylated tau (τ) protein, resulting in elevated intracellular Ca2+-concentrations

and an overall Ca2+-imbalance, consequently leading to the major loss of cholinergic neurons in basal part of the forebrain [49-51]. Nevertheless, novel theories on the pathogenesis of AD, including alternative pathways of neuroinflammation or the role of oxidative stress, are emerging [52,53].

1.2.2 Risk Factors and Associated Health Issues

Among non-modifiable risk factors, advanced age, female sex and various apolipoprotein E (ApoE) and amyloid precursor protein (APP) alleles have been associated with developing AD, while metabolic syndrome (i.e. hypertension, high fasting plasma glucose, elevated cholesterol, obesity) and associated atherosclerosis, inadequate physical activity, excessive alcohol consumption, hearing loss and other co-morbidities (e.g., depression) are among the modifiable risk factors for developing the disease [54,55]. The interplay between oral health and AD (and dementia more broadly) has been the subject of substantial attention [56]; on one hand, with the progression of the disease, AD patients are increasingly limited performing everyday tasks, such as keeping up appropriate oral hygiene practices (which may be compounded by the loss sensory and motor functions associated with physiological ageing), leading to substandard oral health outcomes and oral health-related QoL [57]. Furthermore, various medicines administered as adjunctive treatment (e.g., mood stabilizers, benzodiazepines, antipsychotics), or to target the cognitive symptoms of the patient may present with severe adverse events in the oral cavity, further exacerbating AD patients' oral health status [58,59]. Thus, the upkeep of AD is a crucial domain within the scope of gerodontology.

On the other hand, there is increasing awareness about the role of oral health as a risk factor for developing AD and other types of dementia; the link between severe tooth loss and edentulism, and cognitive impairment has been established by numerous epidemiological studies [60,61]. Additionally, the chronic and systemic inflammation caused by the dysbiosis in the oral cavity, due to the progression of periodontal disease, has also been associated with the pathogenesis of AD-associated cognitive impairment, and other neurodegenerative diseases [62,63]. Among *periodontopathogenic* bacteria, the role of *Porphyromonas gingivalis (P. gingivalis)*—and its virulence factors—is the most well-established, which are capable of passing though the blood brain barrier (BBB), contributing to direct neuronal damage, neuroinflammation and β-amyloid plaque formation [64]. Furthermore, a recent population-

based, data linkage study by the National Institute of Aging (NIA)—based on the National Health and Nutrition Examination Survey (NHANES) population—has shown a notable association with diagnoses of AD or other dementia, and AD-associated deaths and antibodies against *P. gingivalis.* Furthermore, the study found that the mortality risk increased if results are clustered with antibodies against other oral bacteria (including *Campylobacter rectus* and *Prevotella melaninogenica*), highlighting the role of bacteria implicated in periodontal disease in the pathogenesis of AD and cognitive decline [65]. Thus, health policy initiatives should focus on the delivery of the appropriate dental healthcare services as needed; initially, to reduce the risk and extent of chronic inflammatory processes via preventive interventions, furthermore, to ensure the best possible oral health outcomes and oral health-related QoL in patients affected by AD. Although numerous epidemiological studies have assessed the dental and periodontal indicators of AD patients alone [66,67], comparative analyses of their oral health status with members of the general population are scarce.

2. AIMS AND HYPOTHESES OF THE STUDIES

This thesis encompasses two primary studies focusing on the oral health status of vulnerable patient populations. The rationale for these studies is grounded in the recognized connection between oral health and overall well-being, particularly in individuals whose conditions may impair their ability to maintain oral hygiene. Both individuals with SCZ and AD experience conditions that can substantially hinder their capacity to carry out daily tasks, including maintaining proper oral hygiene. Despite differing underlying disease mechanisms, this thesis posits that patients with SCZ and AD are both at an elevated risk of deteriorating oral health because of condition-specific factors that can compromise their ability to perform effective oral self-care.

2.1 Study 1: Oral Health in Patients with SCZ

Aim: To compare the indicators of dental and periodontal health in patients with SCZ to those of non-affected healthy controls. Additionally, to assess the influence of various anamnestic factors and lifestyle habits on the oral health status of SCZ patients.

Hypotheses:

- (i) SCZ patients have worse dental status parameters compared to their healthy controls.
- (ii) SCZ patients have worse periodontal status parameters compared to their healthy controls.
- (iii) Lifestyle habits may have negative (i.e., tobacco consumption, alcohol consumption, coffee consumption) or positive (i.e., use of vitamin supplements) effects on dental and/or periodontal status.

2.2 Study 2: Oral Health in Patients with AD

Aim: To assess and compare the dental and periodontal health outcomes of patients with AD with those of non-affected healthy controls. Furthermore, to evaluate the potential impact of various anamnestic factors and lifestyle habits on the oral health outcomes of AD patients.

Hypotheses:

- (i) AD patients have worse dental status parameters compared to their healthy controls.
- (ii) AD patients have worse periodontal status parameters compared to their healthy controls.
- (iii) Dental and periodontal status parameters do not show differences on the basis of the participant's sex.
- (iv) Lifestyle factors (i.e., tobacco consumption, alcohol consumption, coffee consumption, vitamin supplement use) affect dental and/or periodontal status parameters.

3. METHODS

This research involved two distinct studies, hereafter referred to as Study 1 (SCZ Patient Group) and Study 2 (AD Patient Group). The methods for both studies are described together, with differences highlighted where relevant.

3.1 Study Design and Participants

Both studies employed a single-center case-control observational design and were conducted at the Albert Szent-Györgyi Health Centre, University of Szeged, a primary- and tertiary-care teaching hospital in the Southern Great Plain of Hungary. The studies were carried out between November 1st, 2016, and December 31st, 2021.

3.1.1 Study 1 (SCZ Patient Group):

- **Cases:**

  Individuals diagnosed with SCZ, treated as outpatients or inpatients at the Department of Psychiatry, University of Szeged. The diagnosis was based on Diagnostic and Statistical Manual (DSM) criteria of the American Psychiatric Association (APA) [68], including positive and negative symptoms, and social/occupational dysfunction. Patients were selected through random stratified sampling based on age and gender from the SCZ Ward or Rehabilitation Centre [69]. Only patients in a state of remission were included to ensure a consistent baseline [70].

- **Controls:**

  Generally healthy individuals without psychiatric disorders (and not taking psychiatric medications) or other severe systemic illnesses, seeking dental treatment at the Faculty of Dentistry, University of Szeged. Controls were matched to cases by age (±2 years) and gender [71].

- **Sample Size:**

A required sample size of n=50 participants per group was determined to identify changes of a magnitude of 1.5 in quantitative variables with 80% statistical power and α set at 5% [72].

3.1.2 Study 2 (AD Patient Group)

- **Cases:**

  Individuals diagnosed with AD, treated as outpatients or inpatients at the Department of Psychiatry, Albert Szent-Györgyi Health Centre, University of Szeged. Diagnosis was confirmed through comprehensive history, neurological and psychiatric examinations, psychometric tests (MMSE for cognitive impairment, GDS for depressive symptoms), brain Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), and routine laboratory work-ups including thyroid function tests. All participants met DSM-5 criteria and probable AD criteria according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Patients (ranging from mild to severe cases) were selected via random stratified sampling based on age and gender from the Department of Psychiatry.

- **Controls:**

  Generally healthy, cognitively normal individuals without neurodegenerative or psychiatric disorders (or related medications) or other severe systemic illnesses. Controls were sourced from individuals seeking dental treatment at the Faculty of Dentistry, University of Szeged, and from retirement homes in Kistelek and Szentlőrinc. Controls were matched to cases by age (±3 years) and gender.

- **Sample Size:**

  A required sample size of *n=40* participants per group was determined for a study of inter-observer agreement with two raters, with 80% statistical power and α set at 5% [72].

3.2 Assessment of Oral Health Status and Anamnestic Data

In both studies, oral health was assessed through a comprehensive full-mouth dental status and periodontal examination according to WHO criteria. The clinical oral examinations

for cases in both studies were conducted in a separate oral and maxillofacial department beside the Department of Psychiatry, University of Szeged, under the supervision of a psychiatric care physician. The oral cavity was illuminated with a penlight and evaluated visually using a dental mirror, tweezers, and a periodontal probe. Clinical examinations also included panoramic radiographs. To ensure uniformity, all dental examinations in both studies were performed by two operators, each with over five years of clinical experience at the time of the studies. After the oral examination, instructions on maintaining oral hygiene were provided. In Study 2, this specifically included counseling on the importance of mouth rinsing. Edentulous individuals and their controls were excluded from the analysis of periodontal status parameters in both studies.

The following indices were calculated in both studies:

- Decayed, missing and filled surfaces (DMF-S)
- Decayed, missing and filled teeth (DMF-T)
- Missing teeth (Mt; count of teeth missing)
- Plaque index (%)
- Bleeding on probing (BOP%)
- Mean pocket depth (mean PD)
- Mean attachment loss (mean AL)
- Severe tooth loss (having ≤8 remaining teeth)
- The number of crowns (count of individual crowns, including pontic and abutment crowns) was used as an estimate to ascertain a participant's agency over their oral health [73,74].

Data on anamnestic information and lifestyle habits that could impact oral health outcomes were collected through direct questions from the examiners in both studies.

Common data collected in both studies:

- Gender
- Age
- Tobacco consumption (cigarettes/day)
- Alcohol consumption (units/week)
- Coffee consumption (cups/day)

- Use of vitamin supplements (yes/no)

Medication data collected in Study 1 (SCZ Patient Group):

- Use of second-generation antipsychotic medications (e.g., olanzapine, risperidone)
- Use of benzodiazepines (e.g., clonazepam, alprazolam)
- Use of mood stabilizer medications (e.g., carbamazepine, sodium valproate)

Medication data collected in Study 2 (AD Patient Group):

- Use of mood stabilizer medications (i.e., citalopram, duloxetine)
- Use of drugs for the treatment of non-cognitive symptoms (behavioral and psychological, i.e., tiapride, risperidone)
- Use of drugs for the treatment of cognitive symptoms (i.e., donepezil, rivastigmine, piracetam, nicergoline)

3.3 Statistical Analysis

In both studies, continuous variables were expressed as means and standard deviations (mean ± SD), while categorical variables were expressed as frequencies (n) and percentages (%). Normality of variables was tested using the graphical method (Q-Q diagrams) and Shapiro-Wilk tests.

- **Study 1 (SCZ Patient Group):** The Fisher's exact test was used to detect differences between proportions (with Cramer's phi [φ] effect size measure), while Mann-Whitney U-tests were carried out for the comparison of continuous variables between groups of interest.
- **Study 2 (AD Patient Group):** The following univariate analyses were performed: i) to detect differences between proportions, the $\chi 2$-test and Fisher-exact tests were used (with a Cramér's phi [φ] effect size measure), ii) comparison of continuous variables between groups were performed using Mann-Whitney U-tests.

Statistical analyses for both studies were performed using SPSS Statistics version 26.0 (IBM Inc., Chicago, IL, USA). In both studies, p-values <0.05 were considered statistically significant.

3.4 Ethical Consideration

Both studies were conducted in accordance with the Declaration of Helsinki and national and institutional ethical standards. Ethical approval for the study protocols was obtained from the Human Institutional and Regional Biomedical Research Ethics Committee, University of Szeged, Hungary (reference number: 170/2016-SZTE [3867]), and the Hungarian Medical Research Council (ETT-TUKEB; reference number: IV/2426-2/2020/EKU). Written informed consent was obtained from all the participants involved in this study or their legal guardians. They were briefed about the research objectives, privacy, and confidentiality of their data, and they were made aware that their participation in the research was voluntary and that they may withdraw from the study at any time. During data collection, the anonymity of the patients and controls was preserved

4. RESULTS

This section of the dissertation presents the findings of the research. It begins by detailing the oral health status of individuals with SCZ compared to a control group. This includes a breakdown of demographic characteristics, anamnestic data (such as smoking, alcohol, and coffee consumption, and use of vitamin supplements), and specific dental and periodontal parameters. The results for the SCZ group are further analyzed based on gender and smoking habits. Subsequently, the section presents similar data for patients with AD and a corresponding control group, covering demographic and anamnestic information, as well as dental and periodontal health indicators. For the AD group, findings are also examined in relation to gender, smoking habits, alcohol consumption, coffee consumption, and vitamin supplement use. The section relies heavily on statistical comparisons between the patient groups and their respective controls, and within subgroups, to highlight significant differences and tendencies in oral health outcomes.

4.1. Oral Health in SCZ

4.1.1 Demographic Characteristics and Anamnestic Data

Fifty (n = 50) patients with SCZ were included in this study, along with fifty (n = 50) matched, healthy control subjects; demographic characteristics were the following for both groups: (*i*) Gender: 29 males [58.0%] and 21 females [42.0%]. (*ii*) Age: the mean age was 51.86 ± 13.28 years (range: 29–80), with the following distribution: <40 years: n = 9 (18.0%), 41–59 years n = 26 (52.0%), ≥60 years n = 15 (30.0%) (no significant differences were present between the two groups on the basis of age [p = 1.000] or gender [p = 1.000]). A summary of anamnestic and lifestyle characteristics corresponding to SCZ patients and controls is shown in Table 1; significant differences were observed in the context of tobacco consumption (p < 0.001, φ = 0.529), alcohol consumption (p = 0.038, φ = 0.261), coffee consumption (p = 0.004, φ = 0.358) and the use of vitamin supplements (p < 0.001, φ= 0.408), respectively. A total of 18.0% and 56.0% of SCZ patients and controls were nonsmokers, respectively. Among the SCZ patients, n = 37 (74.0%) patients received second-generation antipsychotic drugs, n = 40 (80.0%) received benzodiazepines, while n = 39 (78.0%) received mood stabilizers at the time of this study. During comparative analyses, the following subgroups were made: smoking: 0–

10 cigarettes/day vs. >10 cigarettes/day, alcohol consumption: 0–3 units/week vs. ≥4 units/week, coffee consumption: 0–1 cups/day vs. ≥2 cups/day, vitamin supplements: taking vs. not taking them.

Table 1. Anamnestic data corresponding to patients with SCZ and controls

	Patients with SCZ		Controls	
	n	%	*n*	%
Cigarettes/day				
0–5	11	22.0	37	74.0
6–10	20	40.0	9	18.0
11–20	15	30.0	3	6.0
≥20	4	8.0	1	2.0
Alcohol consumption (units/week)				
0	9	18.0	19	38.0
1–3	24	48.0	23	46.0
4–10	17	34.0	8	16.0
Coffee consumption (cups/day)				
0	3	6.0	13	26.0
1	16	32.0	22	44.0
2	20	40.0	9	18.0
≥3	11	22.0	6	12.0
Takes vitamin supplements				
No	40	80.0	20	40.0
Yes	10	20.0	30	60.0

4.1.2 Dental Status Parameters

The summary of dental status findings corresponding to SCZ patients and controls is presented in Table 2. Patients with SCZ had significantly higher DMF-S (81.30 ± 40.16 vs. 61.64 ± 40.56; $p = 0.010$), D (8.18 ± 7.73 vs. 4.18 ± 4.22; $p < 0.001$) and DMF-T (18.20 ± 8.36 vs. 14.42 ± 8.21; $p = 0.024$) scores but significantly lower F (1.84 ± 0.29 vs. 4.62 ± 3.98; $p < 0.001$) scores compared to the controls. Only numerical differences were shown for the number of crowns (1.76 ± 4.01 vs. 2.88 ± 4.56; $p = 0.059$) and M scores (8.18 ± 7.73 vs. 5.62 ± 6.61; $p = 0.071$), respectively (Table 2). $n = 42$ (84.0%) of SCZ patients and $n = 36$ (72.0%) of controls had at least one missing tooth, while $n = 26$ (52.0%) of SCZ patients and $n = 40$

(80.0%) of controls had at least one filled tooth, respectively. In addition, $n = 5$ (10.0%) of SCZ patients and $n = 2$ (4.0%) of controls had severe tooth loss, respectively. Male subjects had significantly lower DMF-S (74.52 ± 39.72 vs. 90.67 ± 39.1; $p = 0.020$) and DMF-T (16.52 ± 8.12 vs. 20.52 ± 8.32; $p = 0.031$) scores compared to females, while only numerical tendencies were shown for D (6.92 ± 2.33 vs. 8.78 ± 2.10; $p = 0.31$), M (7.45 ± 6.57 vs. 9.19 ± 7.45; $p = 0.43$) and F (4.12 ± 2.30 vs. 3.24 ± 2.62; $p = 0.54$) scores and the number of crowns, respectively (2.13 ± 3.31 vs. 2.53 ± 1.10; $p = 0.245$) (Table 2).

Table 2. Dental status parameters of patients with SCZ and controls

	Patients with SCZ					Controls				
	D	M	F	DMF-T	DMF-S	D	M	F	DMF-T	DMF-S
Total	8.18± 5.17	8.18 ± 7.73	1.84 ± 0.29	18.20 ± 8.36	81.30 ±40.16	4.18 ± 4.22	5.62 ± 6.61	4.62 ± 3.98	14.42 ±8.21	61.64 ± 40.56
Gender										
Male	7.44 ± 0.69	7.47 ± 1.38	1.62 ± 0.41	16.51± *1.51*	74.52 ±7.37	3.86 ± 0.81	4.10 ± 0.95	4.27 ± 0.66	12.31 ±1.51	50.62 ± 7.40
Female	9.19 ± 1.45	9.19 ± 1.78	2.14 ± 0.67	20.52 ± 1.82	90.66 ±8.69	4.61 ± 0.89	7.71 ± 1.72	5.09 ± 0.99	17.33±7.59	76.88 ± 37.24

D: decayed; M: missing; F: filled; DMF-T: decayed, missing and filled teeth; DMF-S: decayed, missing and filled surfaces.

In the context of female subjects, patients with SCZ had significantly higher D (9.19 ± 1.45 vs. 4.61 ± 0.89; $p = 0.009$) and significantly lower F (2.14 ± 0.67 vs. 5.09 ± 0.99; $p = 0.16$) scores, while only numerical differences were observed for DMF-S scores (90.66 ± 48.69 vs. 76.86 ± 37.24; $p = 0.174$), DMF-T scores (20.52 ± 1.82 vs. 17.33 ± 7.59; $p = 0.129$), M scores (9.19 ± 1.78 vs. 7.71 ± 1.72; $p = 0.66$) and the number of crowns (2.42 ± 1.18 vs. 2.76 ± 0.83; $p = 0.145$), respectively. For male subjects, patients with SCZ had significantly higher DMF-S (74.52 ± 7.38 vs. 50.62 ± 7.40; $p = 0.023$), D (7.44 ± 0.69 vs. 3.86 ± 0.81; $p < 0.001$), M (7.44 ± 1.38 vs. 4.10 ± 0.95; $p = 0.045$) and DMF-T (16.51 ± 1.51 vs. 12.31 ± 1.51; $p = 0.045$) scores but significantly lower F (1.62 ± 0.41 vs. 4.27 ± 0.66; $p = 0.002$) scores compared to the controls (Table 2.). Only numerical differences were shown for the number of crowns (1.27 ± 2.56 vs. 2.56 ± 5.10; $p = 0.21$).

In the context of smoking habits, DMF-S (64.10 ± 41.22 vs. 97.59 ± 29.25; $p < 0.001$), DMF-T (64.10 ± 41.22 vs. 97.59 ± 29.25; $p = 0.006$) and M (6.17 ± 6.28 vs. 9.48 ± 6.80; $p = 0.017$) scores were significantly higher in individuals who smoked >10 cigarettes/day. On the other hand, based on alcohol consumption (0–3 units/week vs. ≥4 units/week), coffee consumption (0–1 cups/day vs. ≥2 cups/day) and vitamin supplementation status (taking vs. not taking them), no significant differences were found for either of the dental status indices.

4.1.3 Periodontal Status Parameters

The summary of periodontal status findings corresponding to SCZ patients and controls is presented in Table 3. Patients with SCZ had significantly higher plaque indices (56.96 ± 23.19 vs. 27.44 ± 17.53; $p < 0.001$), BOP% (58.96 ± 22.89 vs. 23.56 ± 17.53; $p < 0.001$), PD (2.84 ± 0.67 vs. 2.19 ± 0.49; $p = 0.024$) and AL (3.39 ± 1.72 vs. 2.49 ± 0.76; $p < 0.001$) values compared to controls (Table 3). Similar findings were shown when comparing male (plaque indices: 53.86 ± 23.34 vs. 26.43 ± 15.25, $p < 0.001$; BOP%: 55.36 ± 22.08 vs. 23.61 ± 19.32, $p < 0.001$; PD: 3.02 ± 0.68 vs. 2.13 ± 0.53, $p = 0.009$; AL: 3.34 ± 1.39 vs. 2.35 ± 0.73, $p = 0.032$) and female SCZ patients and control subjects separately (plaque indices: 61.30 ± 22.91 vs. 28.85 ± 14.09, $p < 0.001$; BOP%: 64.00 ± 23.47 vs. 23.50 ± 15.85, $p < 0.001$; PD: 2.71 ± 0.65 vs. 2.29 ± 0.45, $p = 0.038$; AL: 3.34 ± 1.39 vs. 2.35 ± 0.73; $p = 0.012$)) (Table 3). Only numerical differences were shown for all periodontal status parameters when compared between male and female participants (plaque indices: $p = 0.600$; BOP%: $p = 0.875$; PD: $p = 0.196$; AL: $p = 0.116$).

Table 3. Periodontal status parameters of patients with SCZ and controls.

	Plaque Index (%)	BOP%	PD	AL	Plaque Index (%)	BOP%	PD	AL
Total	56.96 ± 23.19	58.96 ± 22.89	2.84 ± 0.67	3.39 ± 1.72	27.44 ± 17.53	23.56 ± 17.53	2.19 ± 0.49	2.49 ± 0.76
Gender								
Male	53.86 ± 23.34	55.36 ± 22.08	3.02 ± 0.68	3.34 ± 1.39	26.43 ± 15.25	23.61 ± 19.32	2.13 ± 0.53	2.35 ± 0.73
Female	61.30 ± 22.91	64.00 ± 23.47	2.71 ± 0.65	3.44 ± 2.15	28.85 ± 14.09	23.50 ± 15.85	2.29 ± 0.45	2.70 ± 0.78

BOP: bleeding on probing; PD: pocket depth; AL: attachment loss.

In the context of smoking habits, plaque indices (36.33 ± 20.85 vs. 61.91 ± 25.36; $p <$ 0.001), BOP% (35.37 ± 24.82 vs. 61.05 ± 24.74; $p < 0.001$), PD (2.37 ± 0.59 vs. 3.50 ± 0.14; $p < 0.001$) and AL (2.75 ± 1.11 vs. 3.59 ± 2.22; $p< 0.001$) were significantly higher in individuals who smoked >10 cigarettes/day. Subjects who consumed ≥4 units/week of alcohol also had significantly worse periodontal status parameters (plaque indices: 33.59 ± 20.79 vs. 51.17 ± 24.73, $p < 0.001$; BOP% (31.73 ± 23.51 vs. 51.19 ± 26.92; $p < 0.001$), PD (2.32 ± 0.59 vs. 2.71 ± 0.69; $p = 0.005$) and AL (2.68 ± 1.08 vs. 3.21 ± 0.23; $p= 0.008$)). In contrast, coffee consumption (0–1 cups/day vs. ≥2 cups/day) and vitamin supplementation status (taking vs. not taking them) had no significant effect on either of the periodontal status parameters.

4.2 Oral Health in AD

4.2.1 Demographic Characteristics and Anamnestic Data

Forty-one (n=41) patients with AD were included in the study, along with forty-one (n=41) matched control subjects without AD; the demographic characteristics of the subjects were the following: *i)* gender: 17 male [41.5%] and 24 female [58.5%], *ii)* age: the mean age was 83.32±7.82 years (range: 66-97), with the following distribution: 66-77 years n=11 (26.8%), 78-87 years n=17 (41.5%), 88-97 years n=13 (31.7%). On the basis of age or gender, no significant differences were present between the two groups (p=1.000 in both cases). A summary of anamnestic and lifestyle characteristics corresponding to patients with AD and controls is presented in Table 4.; no significant differences were observed in the context of tobacco use (p=0.676, φ=0.097), alcohol consumption (p=0.956, φ=0.03), coffee consumption (p=0.156, φ=0.173) and the reported use of vitamin supplements (p=0.085, φ=0.19), respectively. 56.1% and 46.3% of patients with AD and controls were non-smokers, respectively. At the time of the study, 51.2% (n=21), 68.3% (n=28) and 87.8% (n=36) of patients received mood stabilizers, drugs for their non-cognitive symptoms and cognitive symptoms, respectively. For the purposes of inferential statistics, the following dichotomous subgroups were made: *i)* smoking: *non-smoker* (0 cigarettes/day) vs. *smoker* (≥1 cigarettes/day), *ii)* alcohol consumption: *non-drinker* (0 units/week) vs. *drinker* (≥1 units/week), *iii)* coffee consumption: *0-1 cups/day* vs. *≥2 cups/day*, *iv)* vitamin supplements: *taking them* vs. *not taking them*.

Table 4. Anamnestic data corresponding to patients with AD and controls

	n	%	*n*	%
Gender				
Male	17	41.5%	17	41.5%
Female	24	58.5%	24	58.5%
Age				
66–77 years	11	26.8	11	26.8
78–87 years	17	41.5	17	41.5
88–97 years	13	31.7	13	31.7
Cigarettes/day				
0	23	56.1	19	46.3
1–4	13	31.7	16	39.0
≥5	5	12.3	6	14.7
Alcohol consumption (units/week)				
0	16	39.0	16	39.0
1–3	17	41.5	16	39.0
4–10	8	19.5	9	22.0
Coffee consumption (cups/day)				
0	8	19.5	11	26.8
1	21	51.2	25	60.9
≥2	12	29.3	5	12.3
Takes vitamin supplements				
No	8	19.5	26	63.4
Yes	33	80.5	15	36.6

4.2.2 Dental Status Parameters

The summary of dental status parameters corresponding to patients with AD and controls are presented in Table 5. No significant differences were shown between AD patients and controls corresponding to DMF-S (119.83±16.78 vs. 119.00±18.93; p=0.563), D (4.56±4.18 vs. 4.02±4.95; p=0.599), M (20.66±7.29 vs. 21.37±7.76; p=0.672), F (1.02±2.23 vs. 0.78±1.82; p=0.590), DMF-T values (26.24±3.58 vs. 26.15±4.29; p=0.911) and the number of crowns (3.61±5.23 vs. 3.76±5.51; p=0.903), respectively (Table 5). Severe tooth loss was observed in the case of n=18 (43.9%) of patients with AD, and n=23 (56.1%) of controls. In the context of gender, no significant differences were observed among male vs. female subjects with regards to D (3.83±4.45 vs. 4.94±4.74; p=0.284) and F (0.67±1.75 vs. 1.24±2.36; p=0.314) values and the number of crowns (3.23±4.99 vs. 4.32±5.94; p=0.314), while a

numerical tendency was seen for M (22.42±6.43 vs. 19.03±8.47; *p*=0.054), DMF-T (26.87±2.74 vs. 25.21±4.74; *p*=0.064) and DMF-S (122.46±13.09 vs. 115.12±22.36; *p*=0.065) values, which consistently showed higher values for females. Among female subjects, no significant differences were shown between patients with AD and controls, corresponding to DMF-S (121.21±15.96 vs. 123.71±9.61; *p*=0.549), D (4.67±4.65 vs. 3.00±4.48; *p*=0.198), M (21.45±7.05 vs. 23.38±5.74; *p*=0.307), F (0.38±1.50 vs. 0.95±2.23; p=0.251), DMF-T values (26.50±3.26 vs. 27.29±2.12; *p*=0.323) and the number of crowns (2.79±4.71 vs. 3.66±5.33; *p*=0.514), respectively (Table 5). Similarly, among male subjects, no significant differences were shown between patients with AD and controls corresponding to DMF-S (117.88±18.19 vs. 112.35±26.10; *p*=0.479), D (4.41±3.59 vs. 5.47±5.74; *p*=0.533), M (19.53±7.69 vs. 18.53±9.41; *p*=0.737) and DMF-T values (25.88±4.08 vs. 24.53±5.91; *p=0.443*) and the number of crowns (4.76±5.91 vs. 3.88±6.13; *p*=0.672), respectively; on the other hand, numerical tendency was seen in the case of F values (1.94±3.05 vs. 0.52±1.06*; p*=0.081), with higher values seen in AD patients. Based on smoking habits (non-smoker vs. smoker), alcohol consumption (non-drinker vs. drinker), coffee consumption (0-1 cups/day vs. ≥2 cups/day) and vitamin supplement use (taking them vs. not taking them), no significant differences were seen for any of the dental status indices studied (*p*>0.05 in all cases).

Table 5. Dental status parameters of patients with AD and controls

	D	M	F	DMF-T	DMF-S
Total	4.56 ± 4.18	20.66 ± 7.29	1.02 ± 2.23	26.24 ± 3.58	119.83 ± 16.78
Gender					
Male	4.41 ± 3.59	19.53 ± 7.69	1.94 ± 3.05	25.88 ± 4.08	117.88 ± 18.19
Female	4.67 ± 4.65	21.45 ± 7.05	0.38 ± 1.5	26.50 ± 3.26	121.21 ± 15.96
Controls					
	D	M	F	DMF-T	DMF-S
Total	4.02 ± 4.95	21.37 ± 7.76	0.78 ± 1.82	26.15 ± 4.29	119.00 ± 18.93
Gender					
Male	5.47 ± 5.74	18.53 ± 9.41	0.52 ± 1.06	24.53 ± 5.91	112.35 ± 26.14
Female	3.00 ± 4.18	23.38 ± 5.74	0.95 ± 2.23	27.29 ± 2.12	123.71 ± 9.61

D: decayed; M: missing; F: filled; DMF-T: decayed, missing and filled teeth; DMF-S: decayed, missing and filled surfaces.

4.2.3 Periodontal Status Parameters

The summary of periodontal status parameters corresponding to patients with AD and controls are presented in Table 6. AD patients had significantly higher plaque indices (59.06±15.45 vs. 41.35±7.97; p<0.001), BOP% (62.65±12.00 vs. 40.12±10.86; p<0.001), PD

(2.63±0.56 vs. 2.29±0.13; p=0.002) and AL (2.85±0.79 vs. 2.39±0.41; p=0.026) values, compared to controls (Table 3). Similar findings were observed when comparing male (plaque indices: 58.44±17.39 vs. 43.22±9.23, p<0.001; BOP%: 65.44±12.70 vs. 40.33±13.22, p<0.001; PD: 2.60±0.73 vs. 2.27±0.12, p=0.0015; AL: 2.73±0.97 vs. 2.24±0.73, p<0.001) and female (plaque indices: 59.75±14.11 vs. 39.25±6.21, p<0.001; BOP%: 59.50±11.11 vs. 39.88±8.42, p<0.001; PD: 2.68±0.32 vs. 2.32±0.15, p<0,001; AL: 2.98±0.53 vs. 2.53±0.46; p=0.015) AD patients and control subjects separately (Table 3). In the context of gender, no significant differences were observed among female and male subjects regarding plaque index (49.55±13.90 vs. 50.83±15.68; p=0.246), BOP% (49.69±13.90 vs. 52.89±18.03; p=0.303), PD (2.50±0.31 vs. 2.43±0.54; p=0.378) and AL (3.03±0.98 vs. 2.63±0.75; p=0.375) values, respectively. Based on smoking habits (non-smoker vs. smoker), plaque indices were significantly higher in smokers (51.40±13.23 vs. 56.28±12.36, p=0.038), while in case of BOP% (52.87±13.65 vs. 53.76±11.40; p=0.200), PD (2.45±0.37 vs. 2.56±0.55; p=0.423) and AL (2.61±0.41 vs. 2.71±0.84; p=0.370) values, no significant differences were seen. Based on alcohol consumption (non-drinker vs. drinker), plaque indices were significantly higher in individuals who consumed alcohol (54.78±14.86 vs. 58.68±9.86, p=0.040), while in case of BOP% (53.76±21.40 vs. 55.38±11.58; p=0.254), PD (2.46±0.53 vs. 2.55±0.34; p=0.567) and AL (2.69±0.81 vs. 2.62±0.39; p=0.502) values, no significant differences were seen. In contrast, according to coffee consumption (0-1 cups/day vs. ≥2 cups/day) and vitamin supplement use (taking them vs. not taking them), no significant differences were seen for any of the periodontal status indices studied (p>0.05 in all cases).

Table 6. Periodontal status parameters of patients with AD and controls

AD Patients				
	Plaque Index (%)	BOP%	PD	AL
Total	59.06 ± 15.45	62.65 ± 12.00	2.63 ± 0.56	2.85 ± 0.79
Gender				
Male	58.44 ± 17.39	65.44 ± 12.70	2.60 ± 0.73	2.73 ± 0.97
Female	59.75 ± 14.11	59.50 ± 11.11	2.68 ± 0.32	2.98 ± 0.52
Controls				
	Plaque Index (%)	BOP%	PD	AL
Total	41.35 ± 7.97	40.12 ± 10.86	2.29 ± 0.13	2.39 ± 0.41
Gender				
Male	43.22 ± 9.23	40.33 ± 13.22	2.27 ± 0.12	2.24 ± 0.73
Female	39.25 ± 6.21	39.88 ± 8.42	2.32 ± 0.15	2.53 ± 0.46

BOP: bleeding on probing; PD: pocket depth; AL: attachment loss.

5. DISCUSSION

This section provides a comprehensive interpretation of the research findings presented in this thesis. It begins by separately analyzing the results pertaining to the oral health status of patients with SCZ and those with AD, comparing these outcomes with existing literature and established knowledge in the respective fields. The discussion will delve into the potential implications of these findings, including underlying mechanisms, the clinical relevance for these vulnerable patient populations, and practical recommendations for dental healthcare. Finally, the section will address the methodological limitations of the conducted studies.

5.1 Interpreting Oral Health Findings in SCZ

Mental disorders are a heterogeneous group of illnesses, which have multidimensional impacts on an individual's health and well-being [75]. Psychiatric patients are considered a special-needs and vulnerable patient group, requiring tailored approaches from both general health and dental healthcare professionals [76]. SCZ patients are often hindered in the context of procuring oral healthcare; in addition, preventive dental services are often not a part of the care provided to institutionalized persons [77]. The systematic review and meta-analysis of Molstrom et al. described SCZ as an independent risk factor for poor dental health (i.e., higher D, M and DMF-T values but lower F values compared to the non-SCZ population) [78]. Patients in acute episodes or in relapse have irregular behaviors and activities, which limit them from paying attention to regular oral hygiene. Inversely, poor oral health may further aggravate the overall health status and QoL of SCZ patients [78,79]. If patients are capable of performing activities of daily living, attention to oral self-care (i.e., the use of fluoride-containing toothpaste) and professional preventive fluoridation strategies during the attendance of a dental visit, are crucial. However, due to the negative symptoms of SCZ, both self-cleaning practices and motivations to visit dental healthcare professionals are hindered considerably [80].

Our single-center observational study, the oral health status of fifty SCZ patients were comprehensively assessed and compared to age- and sex-matched healthy controls to offer valuable insights for tailored preventive and rehabilitative measures [81]. The majority (~80%) of patients received antipsychotic medication in addition to mood stabilizers and/or sedato-hypnotic drugs [82]. By reducing salivary flow rate, many pharmaceuticals, including

antipsychotic medications, antidepressants and benzodiazepines, contribute to disadvantageous shifts in the oral microbiota and to the development of dental caries [83]. The dose-response relationship between antipsychotics and the deterioration of oral health has been described previously [84]. Furthermore, as many SCZ patients may have various mental and/or physical comorbidities-especially in individuals ≥50 years of age many additional drugs (e.g., antihypertensives, parasympatholytics, antihistamines) may need to be taken, further exacerbating side effects through anticholinergic and anti-alpha-adrenergic receptor activities, such as hyposalivation and drowsiness [78,85]. On the other hand, maxillo-facial dystonia or tardive dyskinesia a major side effect of antipsychotic drugs-may further limit orofacial functionality in SCZ patients [80]. It has also been described that taking anti-SCZ drugs may lead to changes in the oral microbiota composition, which promote pro-inflammatory processes in the mouth, leading to worse periodontal disease outcomes [86]. Furthermore, as a cumulative consequence of drug adverse effects, poor oral hygiene, overgrowth of oral Candida spp. and the increasing prevalence of dysphagia with age, SCZ patients are at a higher risk of developing hospital-acquired/aspiration pneumonia, where members of the oral microbiota are often seen as important etiological factors [87].

In line with our initial hypothesis, the main dental status parameters (i.e., DMF-S, DMF-T) corresponding to caries experience were significantly higher among SCZ patients compared to controls. A high prevalence of participants affected by missing and filled teeth were observed in both groups (84.0% and 72.0%, and 52.0% and 80.0%, respectively), which is consistent with previous epidemiological studies (~80%) in psychiatric patients [88,89]. Interestingly, male participants overall had better dental status, which is in contrast to the findings of many previous studies [89,78]. No significant differences were shown for the number of crowns between SCZ patients and controls; this number was used as an empirical measure of an individual's control over their oral health versus having many decayed/filled teeth [59]. Similarly, SCZ patients presented with significantly worse clinical periodontal status parameters (i.e., plaque %, BOP%, PD and AL) compared to their matched controls, concurrent with our initial hypothesis [90]; on the other hand, statistical differentiation among the sexes was not observed in the context of periodontal health indicators [91].

High M and DMF-T scores may be explained by the dental care strategies often utilized for SCZ patients; often, tooth extraction is chosen as treatment due to convenience and the difficulties associated with their care, foregoing more work-intensive, tooth-conserving

methods, which would require the cooperation of the patients [86]. However, teeth loss is a major contributor to impaired mastication, oral functionality and QoL [84]; furthermore, the relationship between severe tooth loss and cognitive decline has also been highlighted [96]. The oral rehabilitation of these patients through restorative protocols is considerably more cost-intensive compared to the timely application of preventive measures [87]. In addition, due to the limited illness perception and adherence to medical advice in SCZ patients complicated by xerostomia and parafunctional habits (e.g., bruxism) the success rates of restorative treatments may be limited [89]. For example, the use of partial or total removable dentures may be impractical or even impossible [90].

This study also assessed the influence of several anamnestic parameters on oral health parameters; consequently, the deleterious effect of smoking >10 cigarettes/day was shown in our sample, leading to higher DMF-S, M and DMF-T values. Smokers also presented with significantly higher values in all measured periodontal status indicators. Tobacco use is a known contributor to xerostomia, and the detrimental effects of tobacco use on gingival health and on the progression of periodontal disease has also been described [90,91]. In addition, alcohol consumption of over 4 units/week also had a detrimental effect on periodontal health [78]; as SCZ patients may often use drinking as a coping strategy, this could inadvertently further exacerbate oral health [79]. The study of Tezal et al. assessed the periodontal status (expressed in AL) in the context of alcohol consumption and found a dose-response relationship between AL levels and 5, 10, 15 and 20 drinks/week using the data of the Third National Health and NHANES in the US [92]. On the other hand, our initial hypotheses were not confirmed regarding vitamin supplement use and coffee consumption habits, as variance in those regards did not lead to statistically significant differences in oral health parameters. Similar to our findings, the Mendelian randomization study of Liao et al. also failed to show a strong association between coffee-consuming behavior and periodontitis, indicating a risk increase of ~1% [93]. The study of Saleh et al. established the role of regular vitamin and supplement consumption on periodontal health in adults, using the "BigMouth" dental data repository: among the 21 supplements surveyed, only the consumption of multivitamins and iron showed substantial benefits for periodontal health [94]. Furthermore, the role of vitamin D in the maintenance of periodontal health both in the context of bone metabolism and as an anti-inflammatory agent-was described [95].

While there have been numerous publications reporting on the dental and periodontal health of SCZ patients worldwide, well-founded comparisons with our data are made difficult as studies from Central-Eastern Europe (and from similar healthcare settings) are scarce; this has been highlighted by the systematic review of Khokhar et al. (2016) [96] and the systematic review and meta-analysis of Kisely et al. (2018) [75]. A single-center, case-control study from Spain reported similar mean dental status parameters (D: 7.26, M: 9.10, F: 1.30, DMF-T: 17.74) and a correspondingly high prevalence of missing and filled teeth in SCZ patients, while no significant differences were noted on the basis of the patient's sex [72]. A Greek observational study reported considerably higher mean DMF-T scores (23.35±8.36), with a high burden of M teeth in SCZ patients, although a clear delineation was shown between outpatients and long-term inpatients [97]. Additionally, the authors noted strong and significant correlations between the negative symptom subscale of the Brief Psychiatric Rating Scale (BPRS) values, DMF-T scores and simplified Oral Hygiene Index (OHI-15), respectively [98]. In a cross-sectional study from China, the relationship of dental status with cognitive and mental status was assessed in inpatient SCZ patients >50 years of age, with a battery of neuropsychological scales [98]. Mean DMF-T values were 12.99±8.86 in their patient population (prevalence of caries and tooth loss: 83.1% and 83.3%), which were significantly higher in individuals who smoked or who used to smoke [99]; DMF-T values and M values showed significant negative correlation with the Mini-Mental State Examination Scale (MMSE) score, but significant positive correlation with age and the Global Deterioration Scale (GDSRANK) scores, respectively [100]. A Japanese observational study assessed the oral health status (using the DMF-T index, calculus index [CI], debris index [DI] and Revised Oral Assessment Guide [ROAG]) of hospitalized SCZ patients [54]; significant negative correlations were shown between DMF-T values (mean: 21.7±7.3 higher in males), chlorpromazine equivalents (CPZE) and Barthel index (BI) (denoting mental illness severity), while positive correlations were found with age and length of hospitalization [107]. Another Spanish case-control study compared the dental and periodontal health status among SCZ patients and controls without psychiatric illnesses: mean dental status indices (D: 4.39, M: 5.66, F: 3.53, DMF-T: 13.51) were lower compared to our study, while the mean periodontal health (expressed using the community periodontal index [CPI]) score was 2.32 [56]. SCZ patients had worse outcomes both in the case of caries and in periodontal status compared to control participants [57]. Their study also found significant correlations between DMF-T, CPI scores and the negative subscale of the Positive and Negative Syndrome Scale (PANSS) [108]. A comparative study from Taiwan involving SCZ patients in psychiatric long-term care institutions and individuals from

the general public assessed the dental and periodontal status (using CPI) of the subjects [109]. The study has showed that SCZ patients had significantly higher DMF-T values (13.94±8.48 vs. 8.39±7.01), edentulism (5.0% vs. 1.7%) and CPI indices (CPI=3 35.9% vs. 5.1%) and a lower number of remaining teeth (17.66±8.83 vs. 23.23±6.62) compared to the general population, while no significant differences were found based on the individual's sex [100]. A recent population-based cohort study in Taiwan involved over 3600 individuals with newly diagnosed SCZ who developed periodontal disease within a year of their diagnosis [101]. They showed a significant association between female sex (adjusted OR [aOR]: 2.24), receipt of first-generation (aOR: 1.89) and second-generation (aOR: 1.33) antipsychotics, blood pressure medications (aOR: 1.91), anticholinergics (aOR: 1.24) and the development of periodontal disease [102].

In addition to tooth loss, it was suggested that poor oral health may lead to cognitive impairment via another pathway: due to the progression of periodontal disease, a chronic and systemic inflammatory burden is present, predominantly due to the presence of *Porphyromonas gingivalis* virulence factors [103]. As a consequence, pro-inflammatory cytokines (IL-1, IL-6, TNF-a) are released, contributing to neuroinflammation [104]. Patients affected by SCZ should be considered as a priority group to receive dental healthcare services to improve and maintain their QoL, functionality, and societal integration [105]. This requires targeted interventions as a part of health policy initiatives, in addition to the heightened awareness of dentists directly interacting with these patients [105]. Furthermore, closer interprofessional collaboration is warranted between the providers of dental and psychiatric health services [105]. In the following, we provide a set of concise and practical recommendations to ensure the success of dental consultations and treatments for SCZ patients: (i) If a patient with a history of SCZ presents at the dental office, consultation with the psychiatrist managing the patient is recommended, with a special focus on reviewing medical history, medications and the current status of the patient. (ii) Dentists should be familiar with the possible drug-drug interactions between medicines commonly prescribed for SCZ patients and drugs used during dental treatments, as some drugs (e.g., lithium) may need to be temporarily suspended. (iii) An organized, consistent routine should be developed for present and future appointments, where individual steps are familiar for the patient. (iv) Initiatives should be put forth for a relaxing atmosphere in the treatment area by reducing stimulation of the patient (either by music, background noises or unnecessary contact) as much as possible. (v) The comfort level of the patients should continually be checked, with healthcare

professionals being mindful of akathisia (restlessness of the extremities) and avoiding arguing with or antagonizing the patient. (vi) If cooperation with the patient becomes difficult, involvement of the psychiatrist is recommended. (vii) If possible, the presence of a family member and/or caregiver in the treatment area is recommended. (viii) The patient's explanation of their oral hygiene practices should be surveyed and corrected as needed. (ix) Oral hygiene and self-care instructions should be explained in a way that is understandable at the patient's awareness level. (x) The patient's oral health status should be closely monitored, and in case of an exacerbation, interventions should be carried out rapidly to prevent further deterioration of periodontal status and tooth loss. (xi) Dentists should be aware of the characteristic findings to look for (e.g., complaints of xerostomia, ulcers, involuntary movements, dysphagia, candidiasis) during the assessment of SCZ patients. (xii) If the patient experiences severe orofacial dyskinesia, a bite block should be used. (xiii) Dental interventions should be controlled for possible bleeding. (xiv) Precautions should be taken to avoid postural hypotension, and equipment should be available to monitor vital signs. (xv) Special care should be taken to avoid the use of adrenaline-containing anesthetics (due to the risk of a hypertensive crisis) and atropine (due to the risk of severe anticholinergic effects) [78,79,20,105].

5.2 Interpreting Oral Health Findings in AD

The ageing of the global population is accelerating, with estimates from the United Nations (UN) projecting the elderly population to double by 2050 [106]; these demo-graphic changes are causing particular challenges for healthcare systems (costs of medical care) and for societies (social care costs) alike [34,107]. For this purpose, the UN has announced the "The Decade of Healthy Ageing" programme (2021-2030), with the aim of improving lives of the elderly and their caregivers, to maintain their health and dignity and to ensure sustainability on a global scale [108]. Patients with dementias - among which AD is the most common will have difficulties in performing activities of daily living, while in the late stages of the disease, they may require intensive, around-the-clock care for several years [109]. As the therapeutic options of AD - which are mostly limited to the management of symptoms are limited, all interventions targeting the reduction of AD-related disease burden are critical, both from an epidemiological and economic context [110]. In addition to age, many lifestyle factors and co-morbidities are associated with the increased risk of developing AD later in live [47,54,111]; of note, the relationship between oral health and AD has received considerable attention. Thus, health

policy considerations should strengthen the initiatives in support of integrating oral healthcare for ageing populations, both from the context of retained functionality and autonomy, and to reduce an important modifiable risk fac-tor for AD [112].

There is increasing evidence to support the bidirectional relationship between oral health and cognitive function, with severe tooth loss, edentulism and a decline in masticatory function in a similar fashion to hearing loss and vision impairment leads to a compounding loss in self-sufficiency in elderly people [113,114]. In a me-ta-analysis of longitudinal studies by Qi et al., a dose-response relationship was identified between tooth loss, cognitive impairment (1.48-times higher risk) and a diagnosis of dementia (1.28-times higher risk), even after controlling for other variables [115]; on the other hand, the association was not significant in individuals using dentures. This protective effect of denture use against the rate of cognitive decline was also demonstrated by other studies [116]. Furthermore, numerous studies underpin the relationship between periodontal disease and its clinical consequences (i.e. chronic inflammation, AL, increased PD and alveolar bone loss) and the pathomechanism of AD [117]; as the global prevalence of periodontitis is 30-50%-out of which ~19% of the world's population is affected by severe chronic periodontal disease this association carries considerable epidemiological relevance [118]. The oral microbiota consist of >700 distinct bacterial species, out of which, *P. gingivalis* has the most pronounced role in maintaining the chronic and destructive inflammatory processes leading to periodontal disease [31,119]. This pathogen has the ability to pass on through the BBB via the bloodstream, and possesses various virulence factors (i.e. lipopolysaccharide, gingipain, capsule, fimbriae, proteases for the cleavage of anti-inflammatory cytokines and outer mem-brane vesicles [OMVs]) to maintain a persistent, dysregulated, systemic inflammatory cascade [120,121].

The systematic review of Said-Sadier et al. performed the narrative synthesis of studies on the association between periodontitis and cognitive impairment/dementia and AD pathology [104]; their summary revealed two distinct, but interconnected mechanisms by which *P. gingivalis* contributes to dementia risk. Direct effects include the invasion of the brain by the pathogen via the BBB, impairing the function of nerve cells and glial cells by direct neurotoxicity (through gingipains secreted by the bacteria), neuroinflammation and contributing to plaque formation [119-121]. Other studies also highlighted that gingipains (i.e. cysteine proteases) may also have a role by increasing the permeability of human cerebral microvascular endothelial cells by affecting tight junctions - facilitating invasion [119,122]. Indirect effects include the release of pro-inflammatory (IL-1, IL-6, TNF-a) cytokines and

reduction of anti-inflammatory mediators (e.g., epidermal growth factor, interferon-induced protein 10 [CXCL10], monocyte chemoattractant protein-1) leading to a pathological immune response. Based on the narrative synthesis, the risk for dementia is higher in individuals affected by chronic periodontitis for ≥8 years [104].

In this part of the thesis, the dental and periodontal status of forty-one AD patients were surveyed and subsequently compared to cognitively healthy, age and sex-matched controls; our study aims to highlight the dental healthcare burden of this population with special dental care needs, and to showcase disparities in oral dis-ease burden between physiological ageing and AD. The study used standard method-ology to assess dental and periodontal health and mental status (the MMSE was the most commonly used test in the published literature to determine cognitive status [104]), and had a similar sample size and duration with other reports to allow for com-parison. In contrast to our initial hypothesis, no significant differences were shown among AD patients and the controls in our sample regarding the main caries status indicators (i.e. DMF-T and DMF-S) assessed, and the number of crowns (which was considered a proxy measure of an individual's health-seeking behavior). D, M and F teeth or the presence of crowns (70.7% vs 53.7%, 100.0% vs. 100.0%, 29.3% vs. 24.4% and 31.7% vs. 41.5%, respectively) were prevalent in both the AD patients' group and among controls. Our results are in agreement with the findings of a systematic review by Delwel et al., where they compared the dental status of older people with and without dementia [123]. Their summary found no relevant differences overall - high-lighting only one study, where dementia patients had significantly worse DMF-T and oral health index (OHI) values, compared to healthy individuals [124] while noting that root caries was more common in dementia. The M and DMF-T values from our participants were in the higher end (M without dementia: 19.7-26.1, M with dementia: 14.9-28.0, DMF-T without dementia: 10.2-27.3, DMF-T with dementia: 9.3-28.2) of values reported previously for both groups (our results being more homogeneous to studies from developing countries), especially for M teeth, even though the majority were in a similar age range [123]. Although a tendency for higher M values was shown in females, differentiation in dental status according to sex was not seen; likewise, the majority of related studies did not find or did not report sex-based differences in dental status [123], with the exception of one study based in nursing homes, where significantly more males were dentate [124].

In addition to advanced age, the strategies applied in the dental care of patients with dementia may explain the high number of M teeth and DMF-T values in our study and in the published literature [123]; in many instances, tooth-conserving methods (which are more labor-

intensive, and would require additional follow-ups and the adherence of the patients) are waived in exchange for the strategy to extract impacted teeth, due to the challenges in facilitating the effective dental treatment of AD patients [62].

In line with our initial hypothesis, AD patients presented with significantly worse periodontal status indicators (plaque index, BOP%, PD and AL), compared to control subjects [125]; this underscores the findings in the systematic review and meta-analysis by Maldonado et al., where the clinical periodontal status of older people with our with-out dementia were compared, collecting data on the same indicators as used in our study (i.e. plaque index, PD, BOP%, clinical AL and bleeding index) [125]. Quantitative analysis revealed a weighted mean difference of 35.72% (~22% in our study), 6.98%, 15.95% (~18% in our study), 2.53 mm, and 1.46 mm (~0.4 mm in our study) for BOP%, bleeding index, plaque index, clinical AL and PD, respectively. Compared to the above results, differences in periodontal status indicators between cases and controls were less pronounced in our sample, which may explained by differences in the diagnostic criteria used and the progression of the disease (mild vs. severe; which would inherently affect the executive functions of AD patients), the heterogeneity in the AD patients' age (ranging from 50-107 years), differences in sample sizes (ranging between 52-409), or the overall worse oral health condition of our controls [125]. Participants did not show relevant differences in their periodontal status parameters on the basis of gender, which also confirmed our working hypothesis; while one study showed significantly higher values for inflammatory markers (e.g., leukocytes, neutrophil counts, C-reactive protein) in male AD patients [126], neither this, or other related studies showed sex-based differences in the periodontal status indicators assessed. The systematic reviews of Delwel et al. [123] and Maldonado et al. [125] also showcased the limited number of studies on AD patients with a case-control study design from Central and Eastern European countries.

The study also assessed the potential effects of various lifestyle factors which were well-matched among AD cases and controls on oral health parameters: overall, smokers (vs. non-smokers) and individuals consuming alcohol (vs. non-drinkers) had comparatively worse plaque indices (%), but similar differences were not shown for other periodontal indicators [127]. Similarly, neither of the lifestyle factors had relevant effects for caries experience in our sample. Our findings correspond to the results of Panzarella et al., involving patients with AD and mild cognitive impairment [128]; while male sex and an AD diagnosis was associated with worse DMF-T indices and a higher microbial load of relevant periodontopathogens, similar differences in the con-text of smoking were not shown. Furthermore, the study of Calzada et

al. involving cognitively health individuals aged ≥60 years old - did not confirm smoking as a significant predictor for mandibular edentulism [129]. Likewise, Holmer et al. showed in a comparative study with sample of individuals with AD, varying levels of cognitive decline and healthy individuals - that while AD patients had significantly higher rates of deep periodontal pockets and BOP, differences in smoking habits (i.e. cur-rent-previous-never) did not affect clinical parameters and microbial alpha-diversity. Their results underlined that specific shifts in microbial composition, characteristic of periodontal disease, were observed in the subgingival microbiota of AD patients [130]. Tobacco consumption may also contribute to the progression of AD via the nexus of the oral microbiota, by leading to a shift towards high-risk *periodontopathogenic* bacteria in the oral cavity, and by increasing the expression of bacterial virulence factors. Furthermore, components of cigarette smoke impair the function of microvascular endothelial cells and damage tight junction proteins (facilitating invasion of oral bacteria through the systemic circulation), and they increase the risk of plaque deposition in the brain [131].

The evidence for alcohol consumption being an independent risk fac-tor for periodontal disease (by being a direct irritant to gingival tissues, affecting the immune response, leading to higher inflammatory marker levels, affecting decision-making and nutrition) is well-established, and is characterized by a linear dose-response relationship [132]. The meta-analysis of Yussof et al. also highlighted that alcohol consumption (focusing on binge drinking) contributes to the pathogenesis of AD via multiple pathways, inducing various signaling mechanisms and dysbiosis in the oral microbiota, altering BBB permeability [133].

Dental and periodontal health may also be markedly influenced by qualitative and quantitative aspects of one's nutrition, especially in context of elderly patients [111,134]. On one hand, a lack of appetite, reduced olfactory and gustatory capacities, a monotonous diet, severe limitations in activities of daily functioning or unnoticed orofacial pain may lead to various nutritional deficiencies such as protein-energy mal-nutrition, lack of minerals, vitamins- carrying considerable risks. The sufficient intake of vitamin C (acting as a co-factor for collagen synthesis, ensuring the appropriate functioning of the gingiva and periodontal ligaments) and D (described as having anti-inflammatory properties and essential to regulate mineral density of teeth) is especially important for AD patients [135]. In addition, the frequent consumption of food-stuffs (e.g., fruit juices, coffee) containing large quantities of acids, may lead to dental erosion [136]. Our study assessed whether coffee consumption and/or vitamin supplement use had any effect on oral health parameters, which showed no significant

differences. In a data-linkage study using the "BigMouth" dental data repository, Saleh et al. collected data on the consumption of 21 vitamin and supplements and periodontal health indicators: with the exception of iron supplements and multivitamins, the users of the majority of products did not observe significant benefits [137]. A systematic re-view and meta-analysis by Rhee et al.- based on available studies - has failed to show a significant association between coffee consumption and periodontal diseases [138]. These observations were confirmed by Liao et al., whose study employed a Mendelian randomization design, which also pointed to the lack of relationship between coffee-consuming behavior and the onset of periodontitis [139]. On the other hand, the hospital-based case-control study of Hou et al. has shown the protective effects of consuming ≥3 cups of coffee or tea per day against AD and vascular dementia, respectively; their study has also highlighted that this protective effect was more pronounced for hypertensive individuals and female patients [140].

From the standpoint of oral healthcare, elderly individuals represent a vulnerable patient population, with special treatment needs [141]; barriers to treatment and/or preventive services are further compounded in the case of individuals affected by dementia. AD leads to the progressive loss of cognitive functions and autonomy, with limited therapeutic options available at present. The aim of pharmacological treatments is to postpone or slow down the decline in cognitive function, to address the behavioral aspects of the disease, and to treat associated co-morbidities; these drugs are prescribed to ensure the best possible QoL for AD patients, and to decrease the burden for their caregivers [38,73]. Medicines used to treat modulate cognitive symptoms include cholinesterase inhibitors (donepezil, rivastigmine, galantamine, tacrine), the N-methyl-D-aspartate (NMDA) receptor antagonist memantine and nootropics (such as piracetam and nicergoline). Furthermore, additional drugs may be prescribed adjunctively to treat sleep disturbances (e.g., benzodiazepines, zolpidem), agitation with or without psychosis and delusions (e.g., risperidone, quetiapine, tiapride), depression (e.g., selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors) and apathy (e.g., methylphenidate) [46,53,54,58,59,142]. Over half of the AD patients in our study received mood stabilizers, while the majority were on neuroleptics and cholinesterase inhibitors, respectively. Adverse effects of the above drugs especially in relation to adjunctive treatments - may lead to xerostomia, involuntary movements, and a net decline in the density of beneficial bacteria in the oral cavity, further impairing the physiological functions of the mouth [143]. Recent advanced in AD pharmacology shifted towards targeting the pathomechanisms and progression of the disease: to this end, various monoclonal antibodies

(i.e. aducanumab, lecanemab, donanemab) have been studied, which act by inhibiting the formation of senile plaque via targeting APP [54,58,144]. However, the developments in this field were not without its challenges: the commercialization of aducanumab has been recently discontinued due to insufficient evidence towards its efficacy and frequent reports of notable ad-verse events (amyloid-related imaging abnormalities with edema or effusions), following an intensely scrutinized accelerated approval decision by the Food and Drug Administration [54,58,144,145].

As effective therapeutic alternatives of AD are still scarce, the societal value of providing preventive dental care services and controlling the burden of periodontitis, severe tooth loss and edetulism- being significant risk factors for its development - should not be underestimated in reducing the global dementia burden [40,108]. Further-more, as AD patients often receive suboptimal dental healthcare, tailored approaches should be facilitated to maintain the oral functionality, autonomy and dignity for as long as possible, which will also result in positive add-on effects for their families and caregivers [108,146]. As the disease progresses towards its moderate and severe stages, the upkeep or personal oral hygiene habits may become challenging to individuals: they may forget the goal and specific steps (e.g., toothbrushing with toothpaste, rinsing, flossing) of their oral hygiene routines, or have difficulties in performing them due to tremors or loss of motor coordination [57]. Motor and non-motor symptoms of AD will inevitably lead to significant impairment, affecting ordinary gestures and the individual's personal oral hygiene practices [147]. In case of patients wearing dentures, their appropriate upkeep and cleaning practices may also be neglected. Oral health often becomes less of a priority in case of patients requiring 24/7 care by their family or caregivers (as they are struggling with more urgent everyday concerns), in nursing homes (nursing staff and allied healthcare professionals are not qualified to perform it) or for patients institutionalized due to their behavioral symptoms or delusions (oral care is often not provided) [150,142]. The role of dental hygienists, as qualified healthcare professionals in administering competent and sensitive oral healthcare, in addition to supporting their physical and emotional well-being through flexibility and continuous follow-up [148]. The review of Marchini et al. identified five levels of barriers limiting oral healthcare in AD patients: i) personal level, i.e. the decline in executive function, resistance to assistance from others, aggression, and impaired ability to provide in-formed consent; ii) population/societal level, i.e. there are not enough dental healthcare professionals available for the growing number of patients with dementia; iii) professional level, i.e. many dental healthcare professionals do not feel comfortable or

competent to give treatment to dementia patients or to work in long-term care facilities; iv) institutional level, i.e. in many settings (e.g., nursing homes), they are unable to provide appropriate oral healthcare; v) healthcare system level, i.e. dental care is not included in the country's health insurance schemes, or limited reimbursement rates associated with domiciliary care [149].

A significant avenue for future research lies in the detailed examination of the oral microbiome. Scholars are encouraged to pursue this by collecting salivary samples, including those from tongue swabs and saliva, from patients with SCZ and AD. Subsequent analysis of these samples using advanced laboratory techniques, such as Reverse Transcription-Polymerase Chain Reaction (RT-PCR), would be invaluable for mapping out the oral microbiome. The insights gained from such studies hold the potential to pave the way for new targeted interventions and a deeper understanding of the interplay between systemic conditions and oral health, offering a rich area for further investigation by the scientific community.

5.3 Study Limitations

5.3.1 Study 1 (SCZ Patient Group)

The results concerning SCZ should be interpreted considering several limitations. This study utilized a relatively small sample size, potentially leading to false-negative and false-positive findings. Additionally, the sample originated from patients within a single clinical center, which restricts the generalizability of these results. The study might also be influenced by selection bias, a characteristic often found in epidemiological studies conducted in tertiary-care health facilities. Furthermore, significant socio-demographic details (such as socio-economic status, living conditions, highest education level, occupation history, and social support availability), specific medical information (including illness duration, symptom severity, relapse frequency, disease management characteristics, treatment adherence, other co-existing medical or psychiatric conditions, a full list of medications taken [beyond those with available qualitative data], and therapeutic drug levels), along with certain lifestyle information (like pre-instruction oral hygiene habits, diet, and risk-taking behaviors [excluding habits with available qualitative data]) were not assessed. These unassessed factors could act as confounders in observational epidemiological studies.

5.3.2 Study 2 (AD Patient Group)

Limitations related to the AD part of the study should be acknowledged, including the relatively small sample size and its single-center origin. The findings could also be affected by selection bias, as the cases were selected from patients treated at a specialized tertiary-care clinical center. Consequently, these points may limit the external validity and general applicability of the findings to other settings. Moreover, comprehensive information was not assessed for participants regarding various socio-demographic characteristics (like living standards, socio-economic stratification, highest educational level, and occupational hazard exposures), lifestyle factors, risk-taking behaviors, and co-morbidities, all of which could influence outcomes concerning AD disease stage and/or oral health. Additionally, information on the personal oral hygiene habits of the patients before they joined the study was not available.

6. NEW FINDINGS

- **Dental Status in Schizophrenia patients vs. controls**

Schizophrenia patients had worse dental status parameters (with higher DMF-T, DMF-S and lower F scores), compared to their matched controls, suggesting a greater tendency towards tooth extraction over restorative fillings; male patients had lower DMF-T and DMF-S scores.

- **Periodontal Status in Schizophrenia patients vs. controls**

Schizophrenia patients showed worse periodontal status parameters (with higher plaque indices, BOP%, PD, and AL values), compared to their matched controls.

- **Impact of Lifestyle Factors on oral health in Schizophrenia**

Schizophrenia patients who smoked >10 cigarettes/day had worse dental and periodontal health, while those who consumed ≥4 units/week of alcohol had worse periodontal health, respectively; on the other hand, vitamin supplement intake or coffee consumption did not affect dental or periodontal status in our sample.

- **Dental Status in Alzheimer's disease patients vs. controls**

No significant differences were found between Alzheimer's disease patients and controls regarding their dental status parameters; severe tooth loss was seen in 43.9% of Alzheimer's disease patients and 56.1% of controls, but overall dental status indices did not vary significantly between the groups.

- **Periodontal Status in Alzheimer's disease patients vs. controls**

Alzheimer's disease patients had worse periodontal status parameters with higher plaque indices, BOP%, PD, and AL values), compared to their matched controls.

- **Impact of Lifestyle Factors on oral health in Alzheimer's disease**

Most lifestyle factors did not affect dental or periodontal status in Alzheimer's disease patients. Smoking and alcohol consumption, however, were associated with higher plaque indices, though no similar effects were shown for dental status parameters. Coffee intake and vitamin supplement use had no significant effect on dental or periodontal status parameters.

7. SUMMARY

This thesis presents the findings of two distinct but interconnected observational studies investigating the oral health status of individuals with SCZ and AD in Hungary. The studies collectively highlight the significantly compromised oral health within these vulnerable populations compared to controls, underscoring the urgent need for targeted interventions and improved access to oral healthcare services. The SCZ study revealed that patients exhibited poor overall oral health, with smoking exacerbating dental issues and alcohol consumption negatively impacting both dental and periodontal health. Interestingly, male SCZ patients demonstrated better dental status parameters than females, a finding that contrasts with some existing epidemiological data. The AD study similarly demonstrated a substantial unmet need for dental and periodontal care among affected individuals. While the demographic factor of sex did not significantly influence oral health outcomes in the AD, mirroring previous research, smoking and alcohol use were identified as detrimental factors for periodontal health, a factor increasingly recognized for its potential role in AD pathogenesis. Taken together, these findings emphasize the profound impact of both SCZ and AD on oral health, highlighting the necessity for dentists and healthcare systems to adapt to the unique needs of these populations. This includes understanding the progression of both diseases, the limitations they impose on patients' ability to maintain oral hygiene, and the potential for oral discomfort to manifest as behavioral changes. The research strongly advocates for preventive strategies, specialized care protocols, and enhanced resources, particularly for institutionalized patients and those in nursing homes, to mitigate the oral health disparities faced by individuals with SCZ and AD.

Finally, merging the studies on SCZ and AD within a single thesis offers several synergistic benefits. Firstly, it allows for a broader and more impactful exploration of oral health disparities in vulnerable populations, demonstrating a pattern of neglect that extends beyond a single disease entity. This strengthens the overall argument for systemic change in healthcare provision. Secondly, comparing and contrasting the findings from both studies allows for a more nuanced understanding of the factors influencing oral health in each group. While both groups experience poor oral health, the specific risk factors and their impact differ, enriching the overall analysis and highlighting the complexity of the issue. Thirdly, showcasing these studies together underscores the shared challenges faced by individuals with cognitive and mental health impairments in accessing and maintaining adequate oral care. This unified approach amplifies the call to action for healthcare professionals, policymakers, and

researchers to develop and implement targeted strategies that address the unique needs of these often-overlooked populations, ultimately promoting health equity and improving the quality of life for individuals affected by both SCZ and AD.

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Finally, my sincere thanks go to **my mother, my sisters,** and **my brother** for their constant belief in me and their encouragement throughout my life and studies. I also wish to remember **my late father**. Though he is not here to see this completed, his memory, values, and the foundations he laid have been a constant source of inspiration.

10. APPENDIX

Appendix A: Regional Biomedical Research Ethics Committee University of Szeged's Permissions

SZEGEDI TUDOMÁNYEGYETEM
SZENT-GYÖRGYI ALBERT KLINIKAI KÖZPONT
REGIONÁLIS HUMÁN ORVOSBIOLÓGIAI TUDOMÁNYOS ÉS KUTATÁSETIKAI BIZOTTSÁGA
(6725 Szeged, Korányi fasor 8-10.
Tel/Fax: 62/545-997; E-mail: office.rkeb@med.u-szeged.hu)

Szakmai-etikai vélemény 959- XXVII-061 -20/2018.

Iktatószám: **170/2016-SZTE**

Elnök:
Dr. Wittmann Tibor
egyetemi tanár

Titkár:
Dr. Szendrényi Júlia
főorvos

Tagok:
Dr. Alexin Zoltán
egyetemi adjunktus
adatvédelmi felelős

Dr. Csukonyi Katalin
klinikai főgyógyszerész

Dr. Daru József
egyetemi docens

Dr. Esiobu Anayo Augustus
teológus

Dr. Forster Tamás
egyetemi tanár

Dr. Husz Sándor
egyetemi tanár

Dr. Julesz János
egyetemi tanár

Kálmán Ildikó
egészségügyi szakdolgozó

Dr. Kiss Zoltán
egyetemi magántanár

Dr. Nagymajtényi László
egyetemi tanár

Dr. Thurzó László
egyetemi tanár

Dr. Török Mária
Jogász

Dr. Virágos Kis Erzsébet
egyetemi adjunktus

Dr. Aghasizadeh Sherbaf Reza DDS rezidens orvos
Szegedi Tudományegyetem Fogorvostudományi Kar
Szájsebészeti Tanszék
(6720 Szeged, Tisza Lajos krt. 64-66.)

Pszichiátriai betegek szájhigiénés állapotának összehasonlító tanulmánya.

témájú beadványához.

Bizottságunk a **2016. 09. 16**-án érkezett fenti orvosbiológiai vizsgálatról szóló tervet kutatásetikai és orvosetikai szempontból értékelte és megállapította, hogy az abban foglaltak a 23/2002. EüM rendeletben valamint a 235/2009. (X.20.) Korm. rendeletben leírtaknak **megfelelnek**/nem felelnek meg*.

A részletes kutatáshoz, tervhez mellékelt vizsgálatba vett személyi adatlap mintát, a betegtájékoztatót és a beleegyezési nyilatkozatot etikai-szakmai szempontból **megfelelőnek** /kifogásolhatónak* találtuk.

Az engedélyt kérvényezőtől a vizsgálatba bevont személyek érdekeit képviselő, a kutatásban közvetlenül részt nem vevő kijelölt intézeti orvos láttamozásával a kutatás elkezdésétől számított **18 hónap múlva 1 oldalas jelentést kérünk** /csak a rendeletben foglaltak alapján* kérünk értesítést.

A vizsgálati program befejezését hasonló módon **kérjük**/nem kérjük* visszajelezni.

Az Etikai Bizottság a GCP és a hatályos jogszabályok szerint működik.

Szeged, 2016. október 17.

Dr. Wittmann Tibor
egyetemi tanár
.....
SZTE
Szent-Györgyi Albert
Klinikai Központ
Regionális Tudományos és
Kutatásetikai Bizottság elnöke

Szent-Györgyi Albert Orvos- és Gyógyszerészeti Tudományi Centrum
Regionális Humán Orvosbiológiai Kutatásetikai Bizottsága
ELNÖK
SZTE *

Dr. Julesz János
egyetemi tanár
.....
SZTE
Szent-Györgyi Albert
Klinikai Központ
Etikai Bizottság tagja

* aláhúzással jelezzük a megfelelő véleményt. Kifogás esetén észrevétel a túloldalon vagy melléklet formájában csatolva.

3867

Szegedi Tudományegyetem
Szent-Györgyi Albert Klinikai Központ

Human Investigation Review Board
University of Szeged
Albert Szent-Györgyi Clinical Centre

H-6701 Szeged
P.O.Box: 427

Hungary

The Human Investigation Review Board on its last meeting discussed the ethical relations of the research proposal to be carried out at the Department of

Dr. Aghasizadeh Sherbaf Reza DDS rezidens orvos
Szegedi Tudományegyetem Fogorvostudományi Kar
Szájsebészeti Tanszék
(6720 Szeged, Tisza Lajos krt. 64-66.)

The title of the proposed project is:

Pszichiátriai betegek szájhigiénés állapotának összehasonlító tanulmánya.

The scheme of the experiments complies with the ethics of research. It agrees with the declaration of the Medical Word Federation proclaimed in Helsinki in 1964, therefore, the Human Investigation Review Board does not raise any objection to it from ethical point of view and supports it.

Szeged, 17-Oct-2016

Szent-Györgyi Albert Orvos- és Gyógyszerészettudományi Centrum Orvosbiológiai Kutatásetikai Bizottsága ELNÖK SZTE

Dr. Wittmann Tibor
President of the
Human Investigation Review Board
University of Szeged
Hungary

Appendix B: Hungarian Medical Research Council Ethic

1

Egészségügyi Tudományos Tanács
Tudományos és Kutatásetikai Bizottság (ETT TUKEB)
Levelezési cím: H-1051 Budapest, Széchenyi István tér 7-8.
Székhely: Budapest 1054 Alkotmány u. 25.

Ügyiratszám: **IV/2426- 2 /2020/EKU**
Ügyintéző neve: **Dr. Kardon Tamás titkár**
Elérhetősége: **tukeb@emmi.gov.hu**
Telefon: **+(36) 1 795-1197**

Tárgy: Engedélyező határozat

Kutatóhely neve: Szegedi Tudományegyetem FOK Szájsebészeti Tanszék
Kutatóhely címe:
Szeged
Tisza Lajos körút 64.
6720

Kutatásvezető: Dr. Nagy Katalin részére

HATÁROZAT

A(z) Szegedi Tudományegyetem FOK Szájsebészeti Tanszék, mint megbízó (6720 Szeged Tisza Lajos körút 64.) képviseletében Prof. Dr. Minárovits János (6720 Szeged Tisza Lajos körút 64.) (továbbiakban: Kérelmező) "Pszichiátriai betegek szájhigiénés állapotának összehasonlító tanulmánya" című, beavatkozással nem járó vizsgálat engedélyezése iránt kérelmet nyújtott be az Egészségügyi Tudományos Tanács Tudományos és Kutatásetikai Bizottságához (az ETT TUKEB-hez).

Az ETT TUKEB, mint első fokú hatóság, a vizsgálat engedélyezése iránti kérelmet megvizsgálta és a következő, testületi véleményen alapuló döntést hozta:

Az ETT TUKEB a benyújtott kérelem szerinti, beavatkozással nem járó vizsgálatra

a szakmai-etikai engedélyt megadja.

Az eljárás során eljárási költség nem merült fel tekintettel arra, hogy a kérelmezett vizsgálat nem kereskedelmi vizsgálat.

A Bizottság döntése ellen a közlést követő 15 napon belül van helye fellebbezésnek az ETT Elnökségéhez. A fellebbezést az ETT TUKEB-hez kell benyújtani.

A fellebbezési eljárás illeték- és díjmentes.

INDOKOLÁS

A Kérelmező "Pszichiátriai betegek szájhigiénés állapotának összehasonlító tanulmánya" című, beavatkozással nem járó vizsgálat engedélyezése iránt kérelmet nyújtott be ETT TUKEB-hez, ami 2020. március 16-én érkezett meg a Bizottsághoz.
Az eljárás megindult, és a Bizottság az általános közigazgatási rendtartásról szóló 2016. évi CL. törvény (továbbiakban: Ákr.) 43.§ (1) - (3) bekezdéseinek megfelelően függő hatályú végzést bocsátott ki.

A Bizottság megvizsgálta és megtárgyalta a kérelmet és a csatolt dokumentumokat.

Ügyiratszám: IV/2426- 2 /2020/EKU

A tervezett, beavatkozással nem járó vizsgálat azonosító adatai:

A vizsgálat címe:
"Pszichiátriai betegek szájhigiénés állapotának összehasonlító tanulmánya"

Kutatásvezető, aki az egész vizsgálatot vezeti: Dr. Nagy Katalin

Megbízó neve és címe:
Szegedi Tudományegyetem FOK Szájsebészeti Tanszék
6720 Szeged, Tisza Lajos körút 64.

Megbízó képviselőjének a neve és címe:
Prof. Dr. Minárovits János
6720 Szeged, Tisza Lajos körút 64.

A vizsgálat tervezett időtartama: 2020.04.01 - 2022.04.01

A vizsgálatban résztvevő vizsgálóhelyek felsorolása, valamint az adott vizsgálóhelyen a vizsgálat vezetője:
Szegedi Tudományegyetem FOK Szájsebészeti Tanszék
Szegedi Tudományegyetem ÁOK Pszichiátriai Klinika

Az ETT TUKEB a kutatási engedély iránti kérelemről *az emberen végzett orvostudományi kutatások, az emberi felhasználásra kerülő vizsgálati készítmények klinikai vizsgálata, valamint az emberen történő alkalmazásra szolgáló, klinikai vizsgálatra szánt orvostechnikai eszközök klinikai vizsgálata engedélyezési eljárásának szabályairól szóló 235/2009. (X. 20.) Korm. rendelet* (a továbbiakban: *235/2009. Korm. rendelet*) 18. § (2) bekezdése alapján a következőket állapította meg:

a) A beadott kérelem tárgyául szolgáló vizsgálat valóban beavatkozással nem járó vizsgálat-e?
Igen

b1) A tervezett vizsgálat érdemi, szakmai tudományos kérdésfelvetéseket tartalmaz-e?
Igen

b2) A tervezett vizsgálat módszerei alkalmasak-e az érdemi, szakmai tudományos kérdésfelvetések megválaszolására?
Igen

c1) A betegtájékoztató és a beleegyező nyilatkozat tervezett szövege megfelel-e az emberen végzett orvostudományi kutatásokról szóló miniszteri rendeletben foglaltaknak?
Igen

c2) A toborzás tervezett szövege megfelel-e az emberen végzett orvostudományi kutatásokról szóló miniszteri rendeletben foglaltaknak?
Igen

Mindezek alapján a Bizottság a rendelkező résznek megfelelően határozott, és engedélyezte a kutatási engedély iránti kérelemben megjelölt beavatkozással nem járó vizsgálatot.

Felhívjuk figyelmét arra a jogszabályi kötelezettségére, mely szerint a beavatkozással nem járó vizsgálat befejezését követő kilencven napon belül értesítenie kell az ETT TUKEB-et a vizsgálat befejezéséről, a bevont betegek számáról, illetve köréről, továbbá a vizsgálat befejezését követő száznyolcvan napon belül értesítenie kell az ETT TUKEB-et a vizsgálat célkitűzésére adott válaszról. (Ezt az előírást *az emberen végzett orvostudományi kutatásokról szóló 23/2002. (V. 9.) EüM rendelet* (továbbiakban: *23/2002. (V. 9.) EüM rendelet*) 20/O. § tartalmazza.)

Ügyiratszám: IV/2426- 2 /2020/EKU

Kérjük, amennyiben a beavatkozással nem járó vizsgálat nem kezdődik el, vagy idő előtt lezárásra kerül, akkor erről - az indokok felsorolásával - e-mailen és levélben is tájékoztassa az ETT TUKEB-et. (Ezt a *23/2002. (V. 9.) EüM rendelet* 21. § (3) bekezdése írja elő.)

Az ETT TUKEB eljárása és határozata elsősorban *az egészségügyről szóló 1997. évi CLIV. törvény* (továbbiakban: *Eütv.*) 164/A. § (1) és (2).bekezdésein, a *235/2009. (X. 20.) Korm. rendelet* 17/A. § (1) - (4), a 18. § (1) és (2) bekezdésein, valamint *az általános közigazgatási rendtartásról szóló 2016. évi CL. törvény* (továbbiakban: *Ákr.*) 80. § (1) bekezdésén és az *Ákr.* 81. § (1) és (4) bekezdésein alapul.

A kutatás engedélyezési eljárásokban az *Eütv.* 164/B. § kimondja "Az orvostudományi kutatás, valamint a 164/A. § szerinti beavatkozással nem járó vizsgálat engedélyezési eljárásáért - az egészségügyért felelős miniszternek az adópolitikáért felelős miniszterrel egyetértésben kiadott rendeletében meghatározott - igazgatási szolgáltatási díjat kell fizetni."
A Kérelmező által kért vizsgálat azonban nem kereskedelmi vizsgálat a *23/2002. EüM. rend.* 20/B. § f) pontja alapján, ezért eljárási költség, és így igazgatási szolgáltatási díj fizetési kötelezettsége sem keletkezett a *23/2002. EüM. rend.* 15. §-a és 20/R. § (1) bekezdése szerint.

A Bizottság hatásköre és illetékessége az *Eütv.* 164/A. § (2) bekezdésén, valamint *235/2009. Korm. rend.* 16. § a) pontján, a 17. § (1) bek. a) pontja ab) alpontján alapul.

A fellebbezés lehetőségét az *Ákr.* 116. § (1) bekezdésének megfelelően az *Eütv.* 164/A. § (2) bekezdése mondja ki, mely szerint "A (3) és (5) bekezdésben nem említett beavatkozással nem járó vizsgálat esetében a szakmai-etikai engedélyről az emberen végzett orvostudományi kutatásokról szóló kormányrendelet szerinti kutatás-etikai bizottság a kérelem megérkezését követő naptól számított negyvenöt napon belül dönt. A döntés ellen fellebbezésnek van helye, a másodfokú eljárást az ETT elnöksége folytatja le."

A fellebbezési eljárás illetékmentességét *az illetékekről szóló 1990. évi XCIII. Törvény* 67. § (3)-(5) bekezdései alapján a *23/2002. EüM. rend.* 15. §-a és 20/R. § (1) bekezdése mondja ki, tekintettel arra, hogy a kérelmezett vizsgálat nem kereskedelmi vizsgálat a *23/2002. EüM. rend.* 20/B. § f) pontja alapján.

A fellebbezés előterjesztésére az *Ákr.* 118. § (3) bekezdése vonatkozik.

Budapest, 2020. április 1.

P.H.

Dr. Schaff Zsuzsa
akadémikus, egyetemi tanár,
az ETT TUKEB elnöke

EGÉSZSÉGÜGYI TUDOMÁNYOS TANÁCS
Tudományos és Kutatásetikai Bizottság
Budapest

Kapják:

1./ Kutatásvezető
2./ Intézetvezető
3./ Intézményvezető
4./ Irattár

Ügyiratszám: IV/2426- 2 /2020/EKU

Co-author certification

I, **Danica Matusovits, M.D., Ph.D. Habil.** as a corresponding author of the following publication declare that the authors have no conflict of interest, and **Reza Aghasizadeh Sherbaf D.M.D.,** Ph.D. candidate had significant contribution to the jointly published research(es). The results discussed in his thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

Szeged, 2025.05.14

.....

Danica Matusovits M.D., Ph.D. Habil.

The publication(s) relevant to the applicant's thesis:

Aghasizadeh Sherbaf R, Kaposvári GM, Nagy K, Álmos ZP, Baráth Z, Matusovits D. Oral Health Status and Factors Related to Oral Health in Patients with Schizophrenia: A Matched Case-Control Observational Study. *Journal of Clinical Medicine*. 2024; 13(6):1584. https://doi.org/10.3390/jcm13061584

Co-author certification

I, **Zoltán Lajos Baráth, D.M.D., Ph.D. Habil. Prof.** as a corresponding author of the following publication declare that the authors have no conflict of interest, and **Reza Aghasizadeh Sherbaf D.M.D.,** Ph.D. candidate had significant contribution to the jointly published research(es). The results discussed in his thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

Szeged, 2025.05.14 .....

Zoltán Lajos Baráth, D.M.D., Ph.D. Habil. Prof.

The publication(s) relevant to the applicant's thesis:

Aghasizadeh Sherbaf R, Kaposvári GM, Nagy K, Pakáski M, Gajdács M, Matusovits D, Baráth Z. Oral Health Status and Factors Associated with Oral Health in Patients with Alzheimer's Disease: A Matched Case-Control Observational Study. *Journal of Clinical Medicine*. 2025, 14(5), 1412; https://doi.org/10.3390/jcm14051412.