DOCTORADO EN
Epidemiología

“Tooth loss and depression: epidemiological evidence of causality from the Chilean population”

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1- Background

a) Depression: scope and definitions

Depression is considered a pathological alteration in which the sick person presents a decrease in mood that leads to sadness, a loss of the ability to be interested and enjoy things, a decrease in vitality that leads to a reduction in their activity level, and excessive fatigue, which appears even after minimal effort (1). The definition of depression as a disorder is based on symptoms forming a syndrome and causing functional impairment (1). It occurs at any life cycle stage and tends to manifest itself with several episodes throughout life. The onset of depression is usually gradual, depressive symptoms length varies considerably (1). Depression symptoms can be grouped into neurovegetative, emotional, and cognitive. Still, because they are commonly shared in other psychiatric disorders like anxiety disorder, schizophrenia, and medication side effects, the detection can be challenging (1). Screening tools have been developed for the early identification of depression in various clinical settings, and some self-report instruments can be used in a waiting room or online (2).

Prevalence worldwide

Major depressive disorder prevalence is similar between high-income countries (5.5%) and low-middle-income countries (5.9%) (3). Moreover, almost one in five people experience one episode at some point, and 40% occur in individuals younger than 20 (1). In Chile, according to the last national health survey (ENS 2016-2017), the prevalence of depression was 6.2%, with 10.1% in women and 2.1% in men (p-value <0.001). No statistically significant differences were observed according to age groups (p-value=0.248). The report of depression during the last 12 months was 6.2%; 36.1% of them answered currently being treated for depression through GES (Garantías Explícitas en Salud) program (4). Recently, mental health report estimated that the COVID-19 pandemic has led globally to an increase in the number of cases of depression during 2020, reaching 53.2 million (44.8 to 62.9) cases of major depressive disorder globally (an increase of 27.6% [25.1 to 30.3]) (5). Also, according to this report, women were affected more by pandemic than men for major depressive disorder and younger age groups were more affected than older age groups.

Pathophysiology of Depression

Currently, there is not a single mechanistic model to explain all aspects implicated in depression. Biological and psychosocial factors contributing to the pathology of depression are variable in different patients or even in separate episodes in the same patient at other times. Researchers have described depression causal models that include monoamine neurotransmitters, changes in the hypothalamic-pituitary-adrenal axis changes, inflammation mediated by peripheral cytokines, attenuation in neuroplasticity and neurogenesis, environmental milieu, genes, and gene-environment interactions have been described in depression causality models (1).

Biological and social determinants for depression

There is a consensus that depression is a multifactorial condition. Although social and cultural factors such as socioeconomic status can have a crucial role, genetic and other biological factors also drive this condition (1) The association between depression and stressful life events like chronic illness, financial problems, loss of employment, divorce, deprivation, or exposure to violence is robust and well documented (6). Moreover, exposure to sexual or physical abuse affects the severity and chronicity of depression (7). Depression's biological mechanisms include neurotransmitters, excessive stress-related cortisol release, brain changes, and inflammation (1). Peripherical cytokine concentrations can act directly on neurons, astrocytes, and microglia after trespassing the blood-brain barrier or via signals mediated by afferent pathways; these mechanisms could explain the association between severe infections and depression (8).

Depression risk is almost twice as frequent in women than men, and the peak in both genders occurs during the second or third decades of life (9). In this pattern, gender gap is related to biological or psychological susceptibility and environmental factors like socioeconomic and cultural conditions (10). However, limited evidence exists for gendered risk factors to be specific for depression (10). Depression onset, management, and symptoms are affected by life stages and exceptional circumstances, such as during the perinatal period (1).

Cohort studies have concluded that the oldest age groups have a two- or three-times higher likelihood of having a depression diagnosis, stating the role of age as a risk factor for depression in adulthood (11). Additionally, comorbidities and cognitive compromise are more pronounced with age, altering the clinical presentation of depression (12).

A higher educational level is associated with a reduced risk of depression, nevertheless, this protective effect varies across population subgroups (13) (14). In general, education has a more protective role for women than men and people growing up in families with limited socioeconomic resources (14). However, twin studies, concluded that common genetic pathways of education and depression might be a source of confounding factors (15). Evidence shows that education's protective role diminishes in people who are overqualified for their job (14). Furthermore, people with advantaged backgrounds may obtain a more significant protective effect from higher education (14). One of the pathways linking higher educational levels to lower depressive symptoms is connected to a successful career and higher wages (14).

Several studies have evaluated the association between educational level as a risk or protective factor for depression in different groups and backgrounds. Hoebel et al. (2017) reported that lower education increases the risk of depressive symptoms (OR 1.28, CI 95% 1.12;1.46) (16). Other studies found that the age of onset of major depression syndrome is likely to be later for those individuals with a higher number of years of education (17). Patients with low educational levels are significantly more likely to present neurovegetative or emotional symptoms and suicidal ideation (17). A prospective comparison of 23 European countries demonstrated that lower education was associated with an increased risk of depression at follow-up (18). The Canadian National Population Health Survey (NPHS) results showed that participants at a low educational level were likelier to have developed major depressive episodes than others, especially in the working population (19).

Occupation can affect mental health through exposure to psychosocial stressors related to lack of control at work, job strain, the imbalance between work-related effort and reward, and low occupational social prestige (16). The individual's perceptions of social disadvantage

may be associated with the pathogenesis of adult depression by psychosocial pathways. Finally, concerning social inequalities have implications for depression risk in different populations (16). Low socioeconomic status (SES) is generally associated with high psychiatric morbidity, more disability, and poorer access to health care. Lorant *et al.* (2002) indicated that socioeconomic inequality in depression is heterogeneous and varies according to the way psychiatric disorder is measured, to the definition and measurement of socioeconomic status, and to contextual features such as region and time (13)

Depression and smoking have been associated; smoking increases major depressive disorder risk in the population (HR 1.93, CI 95% 1.02;3.69) (20). In addition, prospective studies have shown a dose-response association. Flensborg-Madsen *et al.* (2011) found that the adjusted risk of depression among women smoking 11 - 20 g per day was 1.74 (CI 95% 1.33;2.27) and 2.17 (CI 95% 1.45; 3.26) among women smoking more than 20 g per day. There was an increased risk of depression for men who smoke more than 20 g per day (HR 1.90; CI 95% 1.05; 3.44)(21). Smoking may lead to depression through effects on an individual's neurocircuitry that increases susceptibility to environmental stressors.

The association between smoking and depression may also be bidirectional, with occasional smoking used to alleviate depressive symptoms but worsening them over time (22). A five-year longitudinal study showed that depression significantly increased the risk of progression to daily smoking (OR, 3.0, CI 95% 1.10; 8.20, p-value=0.01). A possible explanation of this association is the notion of self-medication, in which smokers use nicotine to medicate their depressed mood, and that reinforcing effects of nicotine's mood-altering characteristics are potent in depressed smokers (23).

Depression and obesity directional association remains unclear, although the literature indicates bidirectional pathways. The physiological mechanism that could link depression and obesity is the repeated activation of the hypothalamic-pituitary-adrenal (HPA) axis repeated activation (24). The chronic activation of the HPA axis is related to chronic inflammation and the glucocorticoid signaling pathway. It has been shown that glucocorticoids promote fat accumulation by impairing insulin activity; glucocorticoids also

support the differentiation and proliferation of human adipocytes (25). Nigatu *et al.* found that obesity was associated with the onset of recurrent major depressive disorder but not with single episodes of depression (OR 1.32, CI 95% 1.11;1.57) (25). In addition, diabetes mellitus II, included in metabolic syndrome, has been associated with an increased risk of depression attributable to systemic inflammation (26) (27). Also, other inflammatory diseases, such as cardiovascular, cancer, chronic infections, or autoimmune diseases, are associated with depression (27).

b) Oral diseases

Burden worldwide

Oral diseases are the most prevalent chronic conditions globally, representing a significant health problem due to the high prevalence and economic burden, especially in the adult population (28). The main chronic oral diseases are untreated caries and periodontitis, both irreversible and cumulative conditions that trigger tooth extraction, leading to edentulism (28). According to the last Global Burden of Disease 2017 Study (GBD 2017), the most economically developed countries have a lower burden of untreated caries and periodontitis. Also, these countries have a higher rate of tooth loss compared with the lower developed countries, which could relate with a higher access opportunity to dental care (29).

Oral diseases en Chile

The oral diseases rate in Chile is higher in women than men, considering all age groups. This difference is highly significant between the 45-59-year-old group, where edentulism is the third cause of disability-adjusted life years (DALYs) in women, with a load 2.8 times greater than in men (30). According to the last National Health Survey (ENS 2016-2017), in Chile, women had a 2.3 times greater risk for edentulism compared with men (OR 2.36, CI 95% 1.48;3.77) (4) (31). In Chile, subjects with less than eight years of studies (low educational level) had a higher risk of edentulism compared with those with more than 12 years of education (OR 9.69, CI 95% 4.24;22.19) (32).

In Chile, individuals aged 65 or older had 6.58 (CI 95% 3.90;11.11) times more risk of edentulism than those 45 to 64 years. Also, according to the last version of the National Health Survey (ENS 2016-2017), the perception of oral health as "very good" or "good" was 46.2% in both men and women; however, 15.6% of women perceived their oral health as "bad" or "very poor," whereas the proportion in men was 11.6%. In women, 50.8% had cavitated carious lesions, while this prevalence increased to 58.4% in men. Nevertheless, women had fewer teeth, with a prevalence of non-functional dentition of 31.0%, higher than that reported in men (22.9%) (p-value <0.001) (4).

Oral diseases pathophysiology

Oral diseases have a multifactorial origin, sharing risk factors with other chronic non-communicable diseases (NCDs), including tobacco consumption, harmful alcohol consumption, and unhealthy diet (33) (34). According to the National Health and Nutrition Examination Survey III (NHANES III), individuals exposed to Ambiental tobacco had 1.6 times greater odds of having periodontal disease than individuals not exposed to second-hand smoke. This association was observed after adjusting for age, gender, ethnicity, education, poverty index, history of diabetes, and dental visits in a study population of 6611 individuals 18 years or older who had never smoked (35).

In addition, numerous studies have shown the association between periodontitis, tooth loss, or caries with NCDs. These include diabetes mellitus II, cardiovascular diseases, cerebrovascular diseases, chronic obstructive pulmonary disease (COPD), dementia, psoriasis, and lung cancer (36). Tooth loss has been associated with systemic conditions such as coronary heart disease (37), metabolic syndrome (38), obesity (39), diabetes mellitus (40), and dementia (41), as well as with some types of cancer such as gastric cancer (42), liver cancer (43) and non-HPV related head and neck cancer (44).

According to the World Health Organization (WHO), oral health is essential for general health and quality of life. Oral health is defined as "state of being free from mouth and facial pain, oral and throat cancer, oral infection, and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit an individual's capacity in biting, chewing, speaking and psychosocial wellbeing (45). Oral health-related quality of life (OHRQoL) is part of general health and wellbeing. Oral disorders can affect at least three dimensions of quality of life: physical, emotional, and social welfare (45). One study showed that the oral health dimensions of quality of life were linked to well-known constructs such as anxiety and depression, as well as aggression, anger, and confusion. They found that the patient's perception of OHRQoL was related to an emotional spectrum, broader than usual, ranging from appropriately modulated mood to emotional dysregulation (46).

Oral health and depression: a bidirectional association

A significant association exists between the patient's perception of oral health and the experienced mood states, suggesting that psychological mechanisms are involved in treatment compliance (46). Additional factors influence that association, such as age and gender. Regarding gender, women had better oral health behavior than young men (47). At the same time, women perceive that oral health has a more significant impact on their quality of life and general health than men (46).

Common psychiatric conditions have also been associated with decreased oral health status. One of these disorders is depression, a condition that involves changes in emotional, cognitive, behavioral, and somatic regulation and is characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (48). The association between depression and oral health is explained by lifestyle changes, poor oral hygiene, and difficulties accessing dental care (49) (50).

A systematic review showed that the history of caries lesions was higher in individuals with depression, in comparison with those without depression. Also, the risk of tooth loss (OR 1.22, CI 95% 1.14;1.30) was higher in individuals with diagnosis of depression (51). Also, these authors reported that adults with current depression had a significantly higher prevalence of nonuse of oral health services in the past year without healthy individuals after adjustment for age, sex, ethnicity, education, and comorbidities (52).

Depression and periodontitis

A cohort study concluded that the risk of periodontitis was 19% higher in individuals with depressive symptoms (RR 1.19; CI 95% 1.04;1.36), independent of oral hygiene and systemic inflammation, in comparison with those with depression (53). Different mechanisms can explain this association: changes in behaviors about health management itself, psycho-immunological factors, or a combination of both pathways (54). Depression may alter the immune response of the individual, which is why it has been associated with conditions such as diabetes mellitus, arterial hypertension, alcohol abuse, sleep disorder, and kidney disease, as well as more specific requirements related to the stomatognathic system such as temporomandibular joint disorders, oral lichen planus, burning mouth syndrome, and periodontitis (53) (55).

Psychotropic medications, such as antidepressants, could further explain the increased incidence of caries (51). Antidepressants have been associated with xerostomia (dry mouth) through decreased salivary flow, which may offset the beneficial effects of fluorides (56). Some studies have reported an association between depressive symptoms and higher *Lactobacillus spp.* counts that may contribute to a higher risk for dental caries among individuals with depression (57). Other factors that could be intermediaries in the association between depression and poor oral health are unhealthy diet, smoking, and infrequent oral hygiene (58).

The association between periodontitis and depression has been reported in the literature. A population-based cohort study showed a higher incidence of depression in periodontal patients than healthy individuals, with a hazard ratio (HR) of 1.73 (CI 95% 1.58;1.89) adjusted by sex, age, and comorbidities (59). Both psychosocial and biological mechanisms explain this association. Periodontitis can increase the risk of depression through the psychosocial effects of halitosis, such as shame, loneliness, isolation, and decreased wellbeing (60).

One biological mechanism by which periodontitis may cause major depression is neuroinflammation. The neuroinflammation could be associated with increased proinflammatory cytokines in the central nervous system (CNS) induced by the systemic inflammation associated with periodontitis. Furthermore, neuroinflammation may be caused by the direct invasion of periodontal pathogens and their inflammatory products into the brain (61). One study reported that patients with periodontitis and depression had higher lipopolysaccharide (LPS) levels in the root canal than subjects with chronic periodontitis without depression (62). This study also showed a strong association between chronic periodontitis and the severity of depression (62).

The LPS induce proinflammatory cytokines such as Il-1β, IL-6, and TNF-α, which could enter the systemic circulation (63) (64). The systemic inflammation caused by periodontitis affects behavior and mood through possible communication pathways between the peripheral receptors and the brain, leading to neuroinflammation (61). Also, the systemic injection of LPS pass throughout the blood-brain barrier (BBB) by the abnormal activation of matrix metalloproteinase (65).

A study analyzed the burden of chronic diseases associated with periodontal diseases in a retrospective cohort study using UK primary care data. The authors found that at study entry, the exposed cohort (individuals with periodontal diseases, including gingivitis and periodontitis) had an increased likelihood of having a diagnosis of depression compared with the unexposed group (OR:1.69 CI 95%: 1.65; 1,73). During the follow-up of individuals

without pre-existing depression, the exposed group had an increased risk of developing depression (HR: 1.36 CI 95% 1.31; 1.41). In addition, the authors concluded that improving the understanding of the link between oral health and chronic diseases is essential, as cost-effective dental interventions are available, especially preventive care, that could reduce the public health burden of diseases (66).

d) Depression and tooth loss

Tooth loss is a complex but valuable indicator to measure the association between oral health outcomes, quality of life, and systemic diseases (67). Oral conditions such as tooth loss affect general health, including mental health status and health-related quality of life (OHRQoL) (68). Ehrenthal et al. discovered that tooth loss is a potential risk factor for the development of depression in patients with periodontal diseases, using regression analyses (69). One study showed that individuals with six or more teeth removed were at higher risk of depression alone (OR 1.64, CI 95%: 1.52;1.77) or with anxiety comorbidity (OR 1.91, CI 95%: 1.72; 2.11) (70).

Tyrovolas *et al*. (2016) concluded that edentulism was significantly associated with depression (OR 1.57, CI 95%: 1.23;2.00) in the younger group, with no significant associations in the older age group (71). Moreover, the consequences of missing teeth depend on the severity and intraoral location (72). In addition to the absolute number of missing teeth, the position is an important variable to consider when evaluating the effects of edentulism on health outcomes such as quality of life (68). Tooth loss effects should be measured quantitatively and in qualitatively, including the position in the mouth of missing teeth.

One recent study identified the causal effect of tooth loss on depression among U.S. adults in a natural experiment study, using instrumental analysis (the instrumental variable was exposure to drinking water fluoride) in 2006, 2008, or 2010 waves of the Behavioral Risk Factor Surveillance System (BRFSS).

Matsuyama et al. observed that for each additional tooth loss, depressive symptoms according to the eight-item Patient Health Questionnaire depression (PHQ-8) score increased by 0.146 (95% CI 0.008-0.284), and the probability of having clinical depression (PHQ-8 higher than 10) increased by 0.81 percentage points (95% CI -0.12 to 1.73) (73). These findings are consistent with Yamamoto et al.´ longitudinal study were showed that older adults in Japan with no teeth had a higher risk of depression (74). However, such association was not found in other cross-sectional study (75).

Anterior tooth loss, such as central incisors, lateral incisors, or canines, has a higher impact on the quality of life than the loss of premolars or molars (76). However, posterior tooth loss is more frequent (77). On the other hand, the need for prosthodontic interventions is higher in those subjects with anterior teeth, mainly for aesthetic reasons (68). Those needs are related to the absence of anterior teeth directly influencing the physical appearance and facial aesthetics. Both parameters affect social interaction at the same time (78). Furthermore, tooth loss can affect body image, self-esteem, and social status (79). However, there is a lack of studies evaluating the differential impact of anterior or posterior teeth (occlusal support) loss on depressive symptoms in adults.

Also, depression is a condition related to the risk of tooth loss. Okoro et al. (2012) found that the adjusted odds of being in the “1-5 teeth removed” or “6-31 teeth removed” categories versus “0 teeth removed” was also increased in adults with lifetime diagnosed depression versus those without this disorder (52). A recent study in Brazil, considering the National Health Survey (2013/2019), concluded that depression was statistically significant for tooth loss in all age groups except those aged 65 and over (80). Similarly, in a study conducted in Chile, including adults aged between 35 and 44, depression was a significant risk factor for fewer than 21 teeth, in addition to income, educational level, and age (81).

Removable prostheses are a standard treatment for patients with tooth loss, with suitable adaptation and satisfaction for some individuals. Nevertheless, it leads to emotional deterioration in other individuals since they have less capacity for psychological recovery or

adjustment to changes. Indeed, tooth loss could perpetuate emotional and psychological alteration in some patients, despite being successful users of removable prostheses wearers (82).

2- Problem, aim, and hypothesis

Previous studies have highlighted the challenges patients face with tooth loss, extending beyond mere physical discomfort. These individuals have diminished self-confidence and heightened emotional distress. However, it is essential to acknowledge that these studies may have some biases due to their selection of participants, and the reliability of the questionnaires used could be susceptible to measurement biases. It is crucial to exercise caution when interpreting the existing body of research, as many studies adopt cross-sectional designs that prevent establishing causal relationships. Moreover, the possibility of a spurious association between depression and tooth loss should not be dismissed, as different factors may confound the relationship. In addition, most of the studies regarding oral health impairment as a risk factor for depression have been conducted in individuals aged 65 years and older.

To achieve a more comprehensive understanding of the association between tooth loss and emotional wellbeing, there is a demanding need for additional research efforts. These endeavors should aim to develop tools capable of identifying and quantifying the impact of tooth loss on individuals while also recommending appropriate interventions when is necessary, recognizing that the link between depression and tooth loss as bidirectional. A scientific effort to understand the causal association between tooth loss and depression may contribute to redirect Dentistry towards prevention strategies, avoiding tooth extractions that could compromise the quality of life of individuals, especially those most vulnerable. Lastly, a deeper exploration of the role of anterior tooth loss versus posterior occlusal support loss, independent of periodontitis, is essential when studying the association between tooth loss and depression in adults.

Previous studies have found evidence supporting tooth loss as a risk factor for depression, mainly in observations made in older adults. However, this association has not been found in other studies, so the causal relationship between the number of teeth and depressive symptoms needs to be explored.

In this study we have considered the following questions: 1- What is the association between the number of remaining teeth in Chilean adults and the incidence or severity of depressive symptoms? 2- What is the role of the deterioration of oral functions related to tooth loss in the presence of depressive symptoms also considering the loss of anterior teeth? This research aimed to evaluate the causal association between tooth loss and depression, considering epidemiological data from different Chilean populations. We *hypothesized* a consistent association between fewer number of remaining teeth and an increased risk of onset and severity of depressive symptoms in adults, independent of educational level, age, and gender. We also *hypothesized* that the impairment of oral functions due to tooth loss, considering anterior missing teeth, significantly mediates the association between tooth loss and depression.

3- Methods

a) Design

We used different strategies and designs to answer the previous research questions. On the one hand, we considered a longitudinal design to determine the risk of developing depressive symptoms according to the number of teeth. On the other hand, we used the data framework of the third version of the Chile National Health Survey (ENS 2016-2017), which have a transversal design (4).

b) Population and sample

We considered the information of individuals enrolled in the Maule cohort (MAUCO) between 2014 and 2017 (83). MAUCO included individuals aged 38 to 74 (53.7, sd 9.8 at baseline) citizens of Molina for at least six months before the cohort enrolment. Molina is a small agricultural county with 42,859 inhabitants, 30.1% living in rural areas. In MAUCO, follow-up visits were planned at 2, 4, and 8 years after the enrolment, which is related to the longitudinal nature of the design (83). In MAUCO was identified the geographic distribution of eligible residents through a household census, which records their age and sex, as well as basic household data (water and electricity provision, housing construction materials) and coordinates (latitude-longitude coordinate´s format, WGS84). Based on census, a target population of 14 000 individuals and an expected response of 80% participation at baseline was included. The goal for enrollment was set at 10 000 participants (83).

The ENS 2016-2017 included participants over 15 years old, achieving a representative sample (n=6.233) of the Chilean population, including men and women who lived in rural and urban areas from all country regions. In the ENS 2016-2017, the sample size was calculated with a 20% relative error to estimate a national prevalence of over 3%. One participant per household was randomly selected using a computational Kish algorithm. A complex, stratified, multistage cluster sampling technique was used in this respect. The survey had a response rate of 67.0% from the eligible participants, whereas the rejection rate was 9.8%.

In our study, for both sample frameworks (MAUCO, ENS 2016-2017) we considered the individual as the unit of analysis.

c) Measuring depression

In MAUCO, depression was measured at baseline and follow-ups through the PHQ-9 instrument, a nine-item questionnaire, each rated from 0 to 3 on a Likert scale, where 0 is

"not all present", and 3 is "nearly every day", resulting in a total score that ranges from 0 to 27 (84) (85). The PHQ-9 was validated by Baader et al. (2012) in Chile by assessing 1327 patients in urban primary care practices in Valdivia County in southern Chile (86). The authors determined a cut-off score of 10 or higher on the PHQ-9 as positive for the presence of depression (86). Also, with PHQ-9, the severity of depression was ranged in this way: no (scores of 0-4), mild (scores of 5-9), moderate (scores of 10-14), moderately severe (scores of 15-19) and severe depression (scores of 20-27) (84).

ENS 2016-2017 measured depression through the self-report question: "Has a doctor or physician ever told you that you have or suffer from depression?" with possible answers "Yes" or "No". For the diagnosis of depression in a sample (n=3403) over 18 years, the CIDI (Composite International Diagnostic Interview) instrument was used, which was created for the WHO for population studies on mental health and adapted to the characteristics of the Chilean reality (ENS 2016-2017, F3) (87). We measured probable depression through the Composite International Diagnostic Interview – Short Form (CIDI SF) (ENS 2016-2017, F1) in individuals aged 15 years or over (88). The CIDI SF is a screening tool consisting of a structured interview with 31 questions, demonstrating adequate reliability and validity for major depressive episodes (88).

d) Measuring oral health and tooth loss

MAUCO study reported remaining teeth number at baseline categorizing individuals into four groups: "20 or more teeth", "10 to 19 teeth", "1 to 9 teeth", and "no natural teeth". Trained health technicians, using basic dental instruments and after asking the patient to remove their prosthesis, determined the number of remaining teeth registered in a clinical dental record (Odontogram). The ENS 2016-2017 determined the use of dental prostheses, number of remaining teeth (both jaws), anterior tooth loss, decayed teeth, and self-perception of oral health. For the remaining teeth, a nurse asked to brush their teeth previously and remove their prosthesis; then, they counted the participants' teeth in each dental arch.

In ENS 2016-2017, to assess anterior tooth loss, the nurses had to register the results by selecting one of the two response alternatives, "Yes" or "No," where "Yes" meant that at least one of the six anterior teeth in a dental arch was missing.

e) Confounding variables

We used a directed acyclic graph (DAGitty version 3.0) to structure the theoretical framework of each analysis and include potential confounders according to previous literature reports.

Regarding MAUCO, the data collected at the baseline for demographics, educational attainment and diabetes mellitus II was considered. Sex and age were included as demographic confounders. The educational level was determined by years of formal education: ≥12, 9-11 or ≤8 years. Also, diabetes mellitus II was defined by self-report or glycaemia ≥ 126 mg/dL or use of hypoglycemic drugs. Another variable included was stressful events at follow-up, which resulted from the presence (yes/no) of at least one of these conditions after baseline: 1-divorce or separation, 2- job loss or retirement. 3- business failure, 4- violent event, 5- major family problem, 6- recent health problem or accident, 7- death of spouse or partner, 8- illness or death of close relative, and 9- other major stress situation.

In the ENS 2016-2017 analysis we introduced these covariables: age (grouped as <65 years or ≥65 years), sex (female or male), educational level (<8 years, 8-12 years, or >12 years of education completed), smoking status (measured as "yes, one or more cigarettes per day," "yes, occasionally (less than one cigarette per day)," "no, I have quit smoking," or "no, I have never smoked"), and history of diabetes (captured through the question “Have you ever been told by a doctor, nurse, or other health care professional that you ever had diabetes? with possible answers "Yes" or "No".

f) Data analysis

Considering the MAUCO sample frame, a prospective longitudinal analysis was performed to determine the incidence of depression. Logistic regression was performed to calculate the odds ratios (OR) for the incidence of depression at 2- and 4-year follow-up. In this analysis, depression was a binary outcome: yes, a PHQ-9 ≥ 10 and not a PHQ-9 <10. A second approach was used to analyze depression severity utilizing multinomial logistic regressions. In all models, individuals with baseline depression (PHQ-9 ≥ 10) were excluded.

Regarding the ENS 2016-2017, the data was analyzed according to the cross-sectional nature of the design. Logistic regression models were performed to determine the association between oral health self-perception, number of teeth, number of teeth with cavitated caries, loss of at least one anterior tooth, denture use, and upper denture use with depression. Also, logistic regression models were used to associate variables related to oral function (tooth or denture discomfort when speaking, pain due to denture or dental origin, tooth or denture discomfort when eating, teeth or dentures interferences with activities and teeth or dentures interferences with social relationships) with depression (probable depression or diagnosis of depression in the past 12 month). This approach of analyzing association with cross-sectional data was a complement to those performed on MAUCO longitudinal data.

We performed a mediation analysis to estimate the contribution of oral functions impairment to the relationship between tooth loss and depression. The independent variable, corresponding to tooth loss, was measured in two ways: 1. number of teeth remaining in the mouth (≤19 versus ≥20 teeth) and 2. loss of anterior teeth, either upper or lower, regardless of the number of teeth lost. The mediating variables were determined by questions about how individuals felt in any of the five situations (figure 1). Each of the five situations could be answered with the alternatives "never", "almost never", "sometimes", "almost always", or "always", which for analysis purposes were dichotomized into 0:"never or almost never" and 1:"sometimes, almost always or always".

Figure 1. Questionnaire about oral functions (items=5). ENS 2016-2017, Chile.

1. Do my teeth or prosthesis feel uncomfortable when speaking?

2. Do my teeth or prosthesis cause me pain and suffering?

3. Do my teeth or prosthesis feel uncomfortable when eating?,

4. Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)?

5. Do my teeth or prosthesis interfere with my social relationships?

The causal mediation analysis was performed using the KHB package developed by Kohler & Karlson (89) to obtain three estimates: a. the indirect effect, corresponding to the effect given by the mediator in the relationship between exposure and outcome, b. the direct effect, corresponding to the unmediated effect, and c. the total effect, resulting from the sum of the two previous effects.

We performed logistic regression models and calculated odds ratios (OR) with their respective 95% confidence intervals (95% CI). The proportions mediated by the indirect effect were calculated by dividing the coefficient of the indirect impact and the total effect, multiplied by 100. All statistical analyses, considering both databases (MAUCO, ENS 2016-2017 F1 x F2, ENS 2016-2017 F1 x F2 x F3) were performed in Stata MP (Stata Corp., College Station, TX, USA). Interaction variables were not included in this analysis given the disposition in the databases.

g) Ethics approval

This study was conducted in accordance with the principles contained in the Declaration of Helsinki. In all the analyses, the privacy and dignity of the subjects were preserved, avoiding individualization of the subjects. Furthermore, regardless of the performance of secondary analyses in MAUCO or ENS 2016-2017, projects whose protocols were previously approved by scientific ethical committees, we also made additional requests for ethical and methodological evaluation based on the research objectives conceived for this study.

MAUCO protocol was approved by the ethics committees of Pontificia Universidad Católica de Chile and the Maule Regional Service of the Chilean Ministry of Health (83). The Scientific Ethics Committee of the Faculty of Medicine of Pontificia Universidad Católica de Chile approved the ENS 2016-2017 study (CEC-MEDUC, ID: 16-019). For the ENS analyses, the Ethical and safety unit at Pontificia Universidad Católica de Chile, considered this protocol exempt for ethical evaluation, according to the study scope (protocol ID 230915005).

4- Main Results

We estimated the risk of depression at follow-up 1 (n=3335) and follow-up 2 (n=2461) according to the number of teeth at baseline in MAUCO. We found that individuals with more teeth (10-19, ≥20) at baseline tended to be less depressive at follow-up, while those with no teeth were more severely depressed.

Table 1 shows the findings of the logistic regression analysis of the number of remaining teeth at the baseline and the incident depression at 2- and 4-year follow-ups inside the cohort. At follow-up 1, for both sexes, we observed higher odds of incident depression in the group with 10-19 teeth compared to more than 20 teeth. In the case of men, those with 10-19 teeth have 2.44 times higher odds of incident depression than those with 20 or more teeth at baseline (OR 2.44, CI 95% 1.33-4.50). Concerning 4-year follow-up, women with fewer teeth tended to have higher odds of being depressed compared to the reference group (≥20 teeth at baseline). Edentulous subjects (“none” teeth) at 4-year follow-up had 2.24 times higher odds of depression than those with more than 20 teeth in the mouth at baseline (OR 2.24 CI 95%1.35- 3.72). For them, the ORs (CI 95%) of incident depression were 2.56 (1.50-4.39), 1.56 (1.02- 2.40) and 1.27 (0.90- 1.81) for “none”, “1-9”, “10-19” respectively in compared to the reference group (≥20 teeth at baseline). This association was not verified in men, with OR values below 1, unlike those observed in this group at the first follow-up.

Table 2 shows the multinomial logistic regression analysis findings of the number of remaining teeth at the baseline and the depression severity for both follow-ups In edentulous individuals at baseline, the odds for each of the comparisons, "mild vs. no", "moderate vs. no", "moderately severe vs. no" and "severe vs. no" were above 1, at both follow-ups, but t95% CI around the ORs across comparisons include the null (not statistically significant). For the categories "1-9" or "10-19," the OR values were less consistent, with some values above 1 and some not. In edentulous individuals, the odds of "moderately severe" or "severe" depression were even higher at both follow-ups. For example, individuals without teeth at baseline had 3.43 times the odds of "moderately severe" depression at 4-year follow-up (OR 3.43, 95% CI 1.43-8.23).

Table 1: Depression incidence at 2-years and 4-years follow-up by number of remaining teeth at the baseline. MAUCO, Chile.

number of remaining teeth *(baseline)*	***Depression***	
	follow-up 1 (2 years)	
	Women (OR and CI 95%)	**Men** (OR and CI 95%)
none	0.93 (0.59-1.47)	2.16 (0.69-6.74)
1-9	1.01 (0.71-1.44)	2.07 (0.91-4.72)
10-19	1.12 (0.84-1.48)	2.44 (1.33-4.50)
≥20 (ref)	1	1
	follow-up 2 (4 years)	
none	2.56 (1.50- 4.39)	0.79 (0.15- 4.13)
1-9	1.56 (1.02- 2.40)	0.87 (0.29- 2.67)
10-19	1.27 (0.90- 1.81)	0.62 (0.25- 1.54)
≥20 (ref)	1	1

Logistic models were adjusted by age, sex, educational attainment, diabetes mellitus II and stressful events at follow-up. OR: odds ratio. CI: confidence interval. Ref: reference.

Table 2: Depression severity at 2-year and 4-yearsfollow-ups by number of remaining teeth at the baseline. MAUCO, Chile.

number of remaining teeth *(baseline)*	*follow-up 1 (2 years) Depression severity*			
	Mild *vs.* no (OR and CI 95%)	**Moderate *vs.* no** (OR and CI 95%)	**moderately severe *vs.* no** (OR and CI 95%)	**severe *vs.* no** (OR and CI 95%)
none	1.45 (1.01-2.09)	1.11 (0.65-1.93)	1.25 (0.58-2.67)	1.40 (0.52-3.76)
1-9	0.92 (0.69-1.23)	0.94 (0.62-1.43)	1.56 (0.91-2.70)	0.96 (0.41-2.22)
10-19	1.25 (1.01-1.57)	1.51 (1.11-2.05)	1.06 (0.65-1.74)	1.43 (0.73-2.78)
≥20	1	1	1	1
	follow-up 2 (4 years) Depression status			
none	1.03 (0.66-1.62)	1.91 (1.01-3.66)	3.43 (1.43-8.23)	1.86 (0.46-7.51)
1-9	0.90 (0.65-1.25)	1.45 (0.89-2.37)	1.60 (0.76-3.36)	0.78 (0.22-2.80)
10-19	0.87 (0.67-1.13)	1.05 (0.69-1.57)	1.47 (0.82-2.61)	0.76 (0.27-2.16)
≥20	1	1	1	1

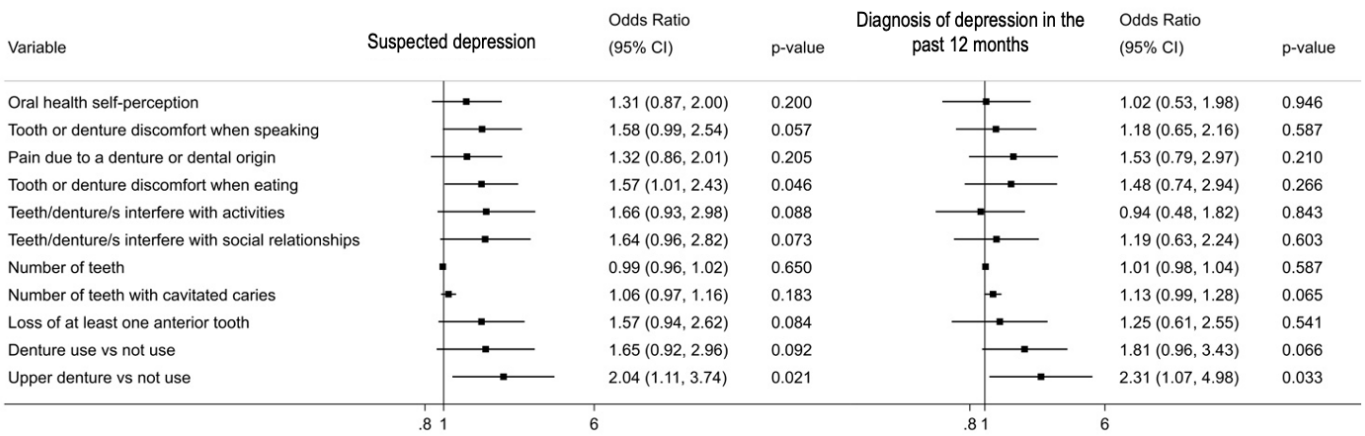
Multinomial logistic models were adjusted by age, sex, educational attainment, diabetes mellitus II and stressful events at follow-up. OR: odds ratio. CI: confidence interval.

In the first cross-sectional analysis considering ENS 2016-2017, 2953 individuals were included. Approximately 25% of women and 10.53% of men exhibited probable depression, while 9.84% of women and 2.39% of men had been diagnosed with depression in the past 12 months. Furthermore, the prevalence of a diagnosis of depression in the past 12 months was higher among individuals with higher levels of education (i.e., ≥13 years of schooling; 7.26%). Individuals exhibiting probable depression had a similar mean number of teeth (n=25), while those diagnosed with depression in the past 12 months exhibited a slightly lower mean number of teeth (n= 24) compared to those without depression.

Figure 2 shows the association between oral health and self-perception of oral health variables, with the risk of exhibiting probable depression or a diagnosis of depression in the last 12 months. The findings showed that patients experiencing difficulties while eating due to dental or prosthesis-related issues were at a higher risk of exhibiting probable depression (OR: 1.57; 95 CI%: 1.01–2.43) compared to those who did not experience these difficulties.

Patients undergoing frequent discomfort while speaking due to dental or prosthesis-related issues were also at a higher risk of exhibiting probable depression (OR: 1.58; 95% CI: 0.99–2.54) compared to those who did not experience this discomfort. In addition, we found a value of OR above one for patients who reported that their teeth or dentures frequently interfered with their social relationships in relation to probable depression (OR: 1.64; 95% CI: 0.96–2.82), in comparison to those who did not experience this interference, but this was not statically significant. Removable upper denture users were also at a higher risk of exhibiting probable depression (OR: 2.04; 95% CI: 1.11–3.74) or a diagnosis of depression in the past 12 months compared to those who did not use prostheses.

Figure 2. Association between self-perceived oral health, oral health status and depression. ENS 2016-2017, Chile.



*Logistic regression models were adjusted by sex, tobacco, and level of education.

In a second cross-sectional analysis, we included 5.383 participants, all with a valid CIDI SF questionnaire answered (ENS 2016-2017) (F1). According to the self-report, the prevalence of depression in our sample was 22,1%, while the suspicion of depression was 14,0%. In individuals with positive self-report of depressive symptoms, the proportion of ≤19 teeth in the mouth were 40,5%, while in those who responded no, it decreased to 35,9%.

This prevalence was very similar in individuals with positive or negative suspicion of depressive symptoms ("yes"=36,2%, "no"=37,1%). The prevalence of anterior tooth loss in individuals with positive self-reports of depression was 45,5%, while in those who said no, it decreased to 41,9%. On the other hand, in those with probable depression, the prevalence of anterior tooth loss was 40.7%, and in those with negative results, the value increased to 43.0%.

Table 3 shows the mediation analysis results, on the association between the number of remaining teeth and self-reported depression or probable depression. The total effect of fewer remaining (≤19) for self-reported depression was 1.21 (95% CI 1.02-1.44) and 1.09 (95% CI 0.90-1.33) for probable depression. Feeling uncomfortable when speaking (1.07, 95% CI 1.04-1.10, PM=35,0%, self-report of depression) (1.10, 95% CI 1.06-1.14, PM=118,9%, CIDI SF) or when eating (1.08, 95% CI 1.05-1.11, PM= 42,5%, self-report of depression) (1.10, 95% CI 1.07-1.14, PM= 117,5%, CIDI SF) significantly mediated the association between tooth loss and depression, being the two conditions that showed the greater mediation effect.

Also, in the other three variables related to pain and suffering, interference in daily activities and interference in social relationships, a statistically significant mediating effect was found, both when considering self-report or probable depression. Table 4 shows the mediation analysis results on the association between anterior tooth loss and depression. Regarding all five variables considered, a statistically significant indirect effect was found for the mediation. Again, the greater indirect effect was observed for “feeling uncomfortable when speaking” (1.07, 95% CI 1.04-1.10, PM=56,6%, self-report of depression) (1.10, 95% CI 1.07-1.14, PM=-270,51%, CIDI SH) and “feeling uncomfortable when eating” (1.08, 95% CI 1.05-1.11, PM= 64,3%, self-report of depression) (1.10, 95% CI 1.06-1.13, PM= -291,58%, CIDI SH).

Table 3: Mediating Effect of Oral Function and Impairment of Orofacial Appearance in the Relationship between the number of remaining teeth and Depression. (n=5.383).

Self-reported history of depression	**Do my teeth or prosthesis feel uncomfortable when speaking? OR (95% CI)**	**Do my teeth or prosthesis cause me pain and suffering? OR (95% CI)**	**Do my teeth or prosthesis feel uncomfortable when eating? OR (95% CI)**	**Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)? OR (95% CI)**	**Do my teeth or prosthesis interfere with my social relationships? OR (95% CI)**
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	1.13 (0.95-1.35)	1.17 (0.98-1.39)	1.12 (0.94-1.33)	1.16 (0.98-1.39)	1.15 (0.96-1.37)
Indirect effect	1.07 (1.04-1.10) *	1.04 (1.02-1.06) *	1.08 (1.05-1.11) *	1.04 (1.02-1.06)*	1.05 (1.03-1.07)*
Total effect	1.21 (1.01-1.44)*	1.21 (1.02-1.44)*	1.21 (1.02-1.44)*	1.21 (1.02-1.44)*	1.21 (1.01-1.44)*
Proportion mediated	35,0%	19,0%	42,3%	20,7%	26,1%
Probable Depression by CIDI Short Form					
Number of Remaining Teeth ≤19 (reference: ≥20 teeth)					
Direct effect	0.98 (0.80-1.21)	1.04 (0.85-1.27)	0.99 (0.80-1.21)	1.05 (0.86-1.28)	1.03 (0.84-1.26)
Indirect effect	1.10 (1.06-1.14)*	1.06 (1.03-1.08)*	1.10 (1.07-1.14)*	1.05 (1.02-1.07)*	1.06 (1.03-1.09)*
Total effect	1.09 (0.89-1.33)	1.10 (0.90-1.34)	1.09 (0.89-1.33)	1.10 (0.90-1.34)	1.09 (0.89-1.34)
Proportion mediated	118,9%	58,0%	117,5%	49,3%	67,6%

OR: Odds ratio, CI: Confidence interval.
The models were adjusted by age, sex, educational level, tobacco consumption, and history of diabetes.

Table 4: Mediating Effect of Oral Function and Impairment of Orofacial Appearance in the relationship between anterior tooth loss and depression (n=5,383).

Self-reported history of depression	**Do my teeth or prosthesis feel uncomfortable when speaking? OR (95% CI)**	**Do my teeth or prosthesis cause me pain and suffering? OR (95% CI)**	**Do my teeth or prosthesis feel uncomfortable when eating? OR (95% CI)**	**Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)? OR (95% CI)**	**Do my teeth or prosthesis interfere with my social relationships? OR (95% CI)**
Anterior Tooth Loss (reference: no)					
Direct effect	1.05 (0.89-1.24)	1.08 (0.91-1.27)	1.04 (0.88-1.23)	1.08 (0.91-1.27)	1.07 (0.91-1.26)
Indirect effect	1.07 (1.04-1.10)*	1.04 (1.02-1.06)*	1.08 (1.05-1.11)*	1.04 (1.02-1.06)*	1.05 (1.03-1.07)*
Total effect	1.12 (0.95-1.32)	1.12 (0.95-1.32)	1.12 (0.95-1.32)	1.12 (0.95-1.32)	1.12 (0.95-1.32)
Proportion mediated	56,6%	36,9%	64,3%	35,8%	42,7%
Probable Depression by CIDI Short Form					
Anterior Tooth Loss (reference: no)					
Direct effect	0.88 (0.72-1.06)	0.91 (0.76-1.10)	0.89 (0.73-1.07)	0.93 (0.77-1.12)	0.92 (0.76-1.11)
Indirect effect	1.10 (1.07-1.14)*	1.07 (1.04-1.09)*	1.10 (1.06-1.13)*	1.05 (1.03-1.08)*	1.06 (1.04-1.09)*
Total effect	0.97 (0.80-1.17)	0.97 (0.80-1.17)	0.97 (0.80-1.17)	0.97(0.80-1.17)	0.97 (0.80-1.17)
Proportion mediated	-270,5%	-248,2%	-291,6%	-205,2%	-208,1%

OR: Odds ratio, CI: Confidence interval
The models were adjusted by age, sex, educational level, tobacco consumption, and history of diabetes.

5- Discussion

This research aimed to evaluate the causal association between tooth loss and depression, considering epidemiological data from different Chilean populations. We hypothesized a consistent association between fewer number of remaining teeth and an increased risk of onset and severity of depressive symptoms in adults. In the longitudinal analysis (MAUCO), we found that individuals with less than 20 teeth, including those with total edentulism, showed higher odds of incident depression than those with 20 or more teeth. Still, this finding was not evident in all the groups. We observed heterogeneity in the association between the number of remaining teeth and the incidence of depression when considering gender subgroups. The findings in women were more consistent with our hypothesis that fewer remaining teeth may increase the risk of depression in Chilean adults.

According to the ENS 2016-2017 data, the association between the number of remaining teeth and depression was present but still weaker. Similar results were observed about anterior tooth loss as a risk factor for depression. However, we observed an increased risk of probable depression or a diagnosis of depression among individuals experiencing dental or prosthesis-related difficulties in eating, speaking, and social interactions. It is important considering that tooth loss *per se* is a cause of oral functions deterioration (68). Therefore, a mediation analysis was performed to evaluate the role of impairment of oral functions in the association between tooth loss and depression. After that, we found that feeling uncomfortable when speaking or eating, and interferences of dental condition on pain and suffering, daily activities such as working or studying, or in social relationships of individuals were mediators in the association between a lower number of remaining teeth and a higher risk of depression.

In the MAUCO cohort analysis, the individuals were aged 38 to 74 years, although the ENS 2016-2017, considered those with 15 years or more. Most previous studies about the association between tooth loss and prevalence or incident depression are limited to older persons (74) (90). Hence, this study contributed to understanding this phenomenon in the younger population.

Kusama et al. (2017) evaluated the role of difficulties in speaking, smiling, or chewing among older Japanese adults (65 years or over) as mediators in the association between the number of tooth loss and depression (91). In one of our analyses in the ENS 2016-2017 dataset, only individuals aged 18 years or older were considered because the CIDI instrument for depression diagnosis was applied according to this age criteria (ENS 2016-2017) (F3). However, in the mediation analysis, the individuals that were at least 15 years old were considered, as the CIDI-SF instrument and the self-report question about depression were applied to all individuals (ENS 2016-2017) (F1).

Concerning the association between oral health and depression, Yamamoto et al. 2017, in a prospective study that followed older people for three years (JAGES Project Longitudinal Study in Older Japanese), reported that edentulism may play a role in the development or worsening of depression (74). This study was similar to our analysis in MAUCO because it aimed to determine whether oral health predicts depressive symptoms by excluding participants with depression at baseline, using logistic regression models. However, in this study depression was evaluated with the Geriatric Depression Scale (GDS) and we employed the PHQ-9. At this point, it is relevant to consider that there are different instruments for depression in epidemiological studies, which may contribute to heterogeneity between the conclusions in the field.

Another longitudinal study conducted by Zhang et al. (2021) reported that older Chinese adults with fewer teeth (<20) and who were non-denture users were at higher risk of severe depressive symptoms (89). Moreover, in a Brazilian cohort, Kunrath & Ribeiro (2020) reported that older adults who experienced tooth loss between 2009 and 2015 (PR = 1.86; 95% CI: 1.01-3.53) were at greater risk of exhibiting depressive symptoms (92). Chu et al. found among middle-aged and older community dwellers, particularly men, a small number of teeth after the age of 40 was associated with the future incidence of depressive symptoms using generalized estimating equation (GEE) models (90). These authors employed GEEs, which enable the analysis of cumulative longitudinal data controlling for repeated observations and follow-up years within participants and allow the identification of a general pattern across the entire study period (90).

The design of these studies in different populations, such as Molina (Chile), implies the verification of hypotheses on association considering the prospective temporality and the exclusion of the event at the beginning of the follow-up, but they have limitations such as attrition.

Matsuyama et al. 2021, identified the effect of tooth loss on depression among U.S. adults using an instrumental variable for causal inference (73). The authors concluded that losing ten or more teeth had an impact comparable to adults with major depressive disorder not receiving antidepressant drugs (73). Also, the effect on depression seemed to be greater in people with higher incomes, young adults, and those with less dental care utilization (73). Moreover, a study using machine learning showed that socioeconomic factors were important in predicting future tooth loss in Japanese adults (93). In our MAUCO study, a differentiation by income was not possible due to the homogeneous low socioeconomic status of the participants in the cohort. In addition, age was an important variable because older people may consider tooth loss a natural process related to aging, and they could be adapted to it (94).

In MAUCO, we found differences in the magnitude of the association between tooth loss and incident depression when stratified by gender. In both follow-ups, women showed a higher risk of depression, when presented a lower number of teeth at baseline, including edentulous. Previous studies have shown that women perceive oral health as more relevant than men (95). However, our findings contrast with the report of Matsuyama et al. (2021), who observed that the effect of tooth loss on depressive symptoms was larger in men (73). Also, Chu et al. reported in a subgroup analysis that the effect of a small number of teeth on the future incidence of depressive symptoms was stronger in men than in women (90)There are different tooth loss trajectories in women and men, which might explain differences in the effect of tooth loss on depression in women and men of similar ages (73). Chu et al, mentioned that the gender differences were difficult to explain; however, one possible explanation was differences in smoking status in women and men, but this interaction was not evaluated and need to be included in future studies (90).

In Chile, according to the last National Health Survey (ENS 2016-2017), edentulousness was higher in women than men across most age groups (31). The mean number of teeth for women was 20.2 (sd 0.2), whereas, for men, it was 21.5 (sd 0.3) (31). Also, in MAUCO, the mean number of teeth was lower in women (18.0, sd 9.5) in comparison with men (19.4, sd 8.8) (96). These differences in the burden of oral damage measured as tooth loss may influence the magnitude and severity of depression, which should be further explored in future studies in Chile and the world. On the other hand, for example, according to the ENS 2016-2017, in the country, the use of removable prostheses was higher in women (29.1%) than in men (15.6%) (4). This intervention plays a role in the association between dental loss and depression pathway, that we have not captured at all in the studies and on which further epidemiological analyses are required.

In individuals enrolled in MAUCO and the 2016-2017 ENS, we evaluated the association between tooth loss and depression. Additionally, we determined possible variables related to this association beyond diet and inflammation. Therefore, based on the literature (91), we explored the role of mediators on the perception of oral health in daily activities (talking, chewing, pain, interacting with others) as a mechanism to approach the research problem based on the feasibility of having these measured variables in the ENS 2016-2017. We concluded that deterioration of oral functions had a mediator role in the association between tooth loss and depression. These findings are consistent with a cross-sectional study of Indian adults showing edentulism negatively affects older adults' psychological and subjective wellbeing (97). Similarly, in a study in Chilean 80-year-old individuals concluded that a functional dentition was associated with higher social participation frequency (98).

Abbas et al. 2022 concluded that tooth loss was the main predictor for social isolation at follow-up, while no dental prostheses use was an additional risk factor (99). In the same way Kusama et al. (2021) found that difficulty in speaking, smiling, or chewing among community-dwelling older adults was a mediator in the association between tooth loss and depression (91). Having difficulty in chewing showed a greater mediation effect (indirect effect of 1.05, 95% CI 1.02-1.09, PM=21,9%) (91), like our study (1.08, 95% CI 1.05-1.11, PM= 42,5%, self-report of depression) (1.10, 95% CI 1.07-1.14, PM= 117,5%, CIDI SF).

One study, using large-scale data of the elderly population from the KNHANES (Korean National Health and Nutrition Examination Survey) showed that the prevalence of depression in subjects with chewing problems was approximately two times higher than that in those with no chewing problems (100).

Our study also evaluated the mediating role considering anterior tooth loss as an independent variable, differentiating by position in the mouth and not only as number of remaining teeth. It is important if we consider that Tan et al. (2016) found that more missing anterior teeth are associated with low satisfaction levels and reduced oral health-related quality of life due to functional and aesthetic problems (101).

On the other hand, Kusama et al. (2021) (91) applied a mediation analysis with a longitudinal design closer to causal verification, in contrast with our cross-sectional approach. They conclude, as this study did, that other mediators should be considered in future studies to have a big picture of the indirect effect of third variables in the association between tooth loss and depression, for example using multiple mediators' models. Finally, the scope of our research did not only include aesthetic effects, although tooth loss also negatively affects multiple dimensions of life (68), with variables that mediate in complex models, which, among other consequences, lead to an increase in the risk or severity of depression in adults.

Our study involved a causal approach to the association between a lower number of teeth and the risk or severity of depression. We considered analyses suggesting direct and indirect pathways. One approach to how tooth loss affects depression through indirect pathways was the use of mediation analyses to explore the role of oral function impairment, beyond other more studied mediators such as inflammation or nutritional changes (102). Mediation analysis decomposes the total exposure-outcome effect into a direct effect and an indirect effect through a mediator variable (103). In fact, mediation analysis is an important statistical tool for gaining insight into the mechanisms of exposure-outcome effects, but to ensure a causal interpretation is crucial to assess the plausibility of the causal assumptions (104).

We measured the relative mediation size using the proportion mediated and interpreting the standardized indirect effect estimate in our models, according to recommendations in the literature (104).

Tooth loss is neither a sufficient nor a necessary cause for the presence of depressive symptoms, given the multifactorial complexity of this outcome (1), however we tried to open the door by considering several adjustment variables in the models and introducing different theorical frameworks. The MAUCO analysis had a longitudinal nature that allows causal verification; however, the design has limitations such as loss to follow-up or interval censoring (105). Regarding the strength of the association, we found confidence intervals with values that supported our hypotheses and at the same time this was less evident when showing the analyses by subgroups according to gender and age (supplementary material).

In our analysis in MAUCO we found a slight dose-response relationship in women, whereas tooth loss increased the risk of depression increased. Our findings have epidemiological plausibility and are a contribution to exploring the causal hypothesis in broader age groups and in populations with different characteristics than those included in previous literature (74). On the other hand, experimental evidence is scarce and preliminary, but interventions for prevention or treatment of edentulism may imply a change in the depression status of the subjects.

The mechanisms underlying the association between tooth loss and depression are multiple. A lower number of teeth implies a change in the diet, which affects, for example, the consumption of vitamins and minerals, which is related to the emotional state. A higher intake of dietary B vitamins is associated with a lower prevalence of depression, anxiety, and stress (90). Poor diet quality and higher intake of sweet and snack/fat food are also associated with depression among adults in Netherlands (106). A healthy dietary intake is crucial to preventing depression, whereas individual with fewer teeth have more difficulty in maintaining healthy dietary habits (107). In addition, the number of teeth is related with social participation in individuals, which is known factor related to emotional status (99) (108).

Chu et al found that participants with fewer than 10 teeth, after adjusting for social activity involvement, still had a higher risk of developing depressive symptoms (90). Another cross-sectional study in Japan found that participation in sport groups, neighborhood community associations, or hobby clubs was significantly associated with more teeth (109).

6- Strengths and Limitations

In this study it was possible to evaluate the hypothesized association between tooth loss and depression using different epidemiological strategies in two Chilean sample frames (MAUCO and ENS 2016-2017). This decision had strengths and limitations simultaneously, which should be considered when integrating the main findings.

First, we evaluated the association in a rural sample of a homogeneous socioeconomic profile (MAUCO), which limits external validity, but the sample size was high and representative for similar cohorts in the world.

Second, we analyzed the association between number of lost teeth and the occurrence of depressive symptoms in individuals of different socioeconomic and educational levels and a more comprehensive age range (ENS 2016-2017). At the same time, there were other limitations, such as using different instruments to determine depression, with different levels of sensitivity or specificity, but all the validated and previously employed in epidemiological studies. Regarding tooth loss, in both cases (MAUCO and ENS 2016-2017) was measured as the difference in the number of remaining teeth obtained by counting done by technicians and not by dentists, method which is considered the gold standard on oral health population-based studies (31).

Analyses in MAUCO framework, considering two follow-up periods, are a new contribution to the causal evidence ecosystem on the association between tooth loss and depression, considering that most of the previously published studies were cross-sectional. However, our results cannot be applied to other populations because they represent people living in a small agricultural county with low socioeconomic status in Central Chile. According to this limitation, a second strategy was employed to investigate the association between tooth loss

and depression in Chile, utilizing the last National Health Survey (ENS 2016-2017) dataset. This approach had as strengths the complex sample design, the high sample size, and the national representativeness of the Chilean population, but it was a cross-sectional framework as well.

In our study we considered several confounders, however the risk of unmeasured confounding will likely to affect our conclusions, given the complexity of the association. For example, we introduced diabetes mellitus in our models, however, other inflammatory conditions such as cancer, cardiovascular or autoimmune diseases are associated with tooth loss (107) and depression (27), which could be affecting our findings. A limitation of our study was not including sensitivity analyses; however, a strength was the use of evidence-based directed acyclic graphs (DAGs) for analysis decisions.

In addition, a strength of our study was to consider a cohort with a longitudinal analysis evaluating both the incidence and severity of depression. For this purpose, individuals with depression were excluded at baseline. Nevertheless, there were limitations, such as not considering the use of dentures, which may mitigate tooth loss, and on the contrary, this prosthodontic intervention could be associated with an increased risk of depressive symptoms (82).

A strength of our work was to include a mediation analysis which has been applied in many areas of research but remains scarce in observational or experimental studies related to oral health (104). This statistical analysis was performed only in ENS 2016-2017 because the variables defined for the oral functions construct were not available in MAUCO, which limited performing longitudinal mediation analysis. In the mediation analysis, the five questions employed included “teeth” and “prosthesis” simultaneously, making it challenging to discriminate how much of the response was associated only with teeth. In the ENS 2016-2017 sample, we evaluated the association between the use of dental prostheses and depression, but this refers only to the presence of the theses at the time of the examination by a calibrated nurse, but not to a clinical assessment in terms of functionality or occlusion.

In relation to our mediation analysis, we adjusted for measured confounders, but did not perform sensitivity analyses for unmeasured confounders and did not assess the presence of an exposure-mediator interaction.

In addition, in the cohort analysis, we captured exposure only at baseline, without assessing the tooth loss that may have occurred later. The study focused on the number of remaining teeth at baseline rather than tooth loss at follow-up to explain the incidence or severity of depression. Future studies may also assess the effect of becoming edentulous during follow-up or the time-varying tooth loss on subsequent changes in the levels of depression. About the depressive outcome, although we measured depressive events twice in the cohort analysis, this may not be accurate given the variability of depressive symptoms over time, unlike other health outcomes that are more robust, such as amputation or death.

In our longitudinal design, attrition was a problem, and due to the inherent nature of the outcome, those with more severe depression may have dropped out of the cohort, thus the reported findings may be underestimated. In both follow-ups, a cohort subgroup was not re-examined with the PHQ-9 questionnaire, corresponding to around 5% of the sample each time, which may introduce a selection bias. The above is related to the fact that this study was performed in a not primarily mental health cohort.

The main limitation of the ENS 2016-2017 is its cross-sectional design, which does not allow us to verify causality. Moreover, reverse causality could appear since studies have showed that depression affects oral health and may increase the risk of tooth loss due to lifestyle changes, poorer oral hygiene, and dental care access difficulties (50). A recent study concluded that depression was associated with a higher risk of tooth loss in all age groups except those aged 65 (80).

Mediation analyses assumes temporal precedence of the exposure, mediator, and outcome, which means that changes in the exposure are assumed to precede changes in the mediator, and that changes in the mediator are assumed to precede changes in the outcome (104). Concerning to exposure – mediator direction, in our study, it is less likely that the

deterioration of oral functions leads to tooth loss. However, outcome-mediator and outcome-exposure pathways are possible and difficult to measure in our design.

7- Opportunities for future research and policies

Future studies are required to understand the interactions of mechanisms in the association between tooth loss and depression, including systematic reviews about this topic to synthesize the evidence and evaluate clinical, statistical, or epidemiological heterogeneity.

While tooth loss is a complex measure of dental disease with multiple determinants (67), this is still a feasible and reasonable measurement for future epidemiological studies designed to evaluate the association, mediation, or interaction of oral health and other chronic noncommunicable diseases. For example, a recent study in Ireland evaluated the association between tooth loss and prevalent and incident diabetes, controlling for other covariates and with similar methods to our study (110). Also, clinical studies are necessary to verify the impact of oral interventions like dental prostheses on mental health outcomes and psychological diseases.

It is essential to consider the effect of dental interventions like removable prostheses since prosthodontic interventions aim to improve in perceived oral health rather than changes in "harder" disease-related outcomes (111). In a recent review based on clinical trials published between 2017 and 2021, the authors concluded that no significant evidence supports the impact of oral health interventions on mental health (50). Future studies may consider examining the relationship between oral health and depression considering other methods like salivary biomarkers analysis and simultaneous other variables related to diet, antidepressant intake and inflammation.

It is essential to evaluate the impact of dental interventions in national or regional programs, not only with clinical outcomes but also in aspects related to the patient's quality of life and general health. On the other hand, considering the high prevalence of depression in the general population and the negative consequences of this disorder on life (1), it is relevant to study whether dental programs can reverse or attenuate depressive symptoms.

Our findings indicate that preventing tooth loss may help to reduce the risk of depression. This reinforces the need for prevention at the individual and population levels in Chile and other countries. At the same time, this evidence is relevant for implementing and evaluating current plans, policies and programs that tend to be fragmented, for example, in primary health care in Chile. A focus on oral-mental disease comorbidity can reduce the burden of these conditions on the health system and improve people's quality of life. There are opportunities for this integration at the oral health level, based on evidence, considering the National Health Plan in Chile 2021-2030 (112)and Oral Health Action Plan 2023-2030(113).

8- Conclusions

This study provides new evidence of a positive association between tooth loss and prevalent and incident depression in the Chilean population. Previous studies in the country mainly have evaluated the presence of depression as a risk factor for a lower number of tooth loss. However, this study considered tooth loss, including anterior tooth loss, as exposure, using different methodological strategies and mixing designs in national populations with different socioeconomic and demographic backgrounds.

Beyond the limitations, the findings of this study provide evidence to consider the prevention of tooth loss as potentially reducing the risk or severity of depressive symptoms. It is strongly suggested that future national studies evaluate the results of dental health policies, programs or strategies with a preventive and oral health promotion focus on psychological aspects, wellbeing, and quality of life.

Additionally, efforts should be made to efficiently disseminate the results of our study to decision-makers and communities aware of the magnitude and trend of oral diseases and mental illnesses. Our findings should be considered by decision-makers in Chile and the world because the interventional approach that has persisted, including dental extractions, may perpetuate cumulative damage that affects more than the dimensions of the maxillofacial territory. The association between tooth loss and depression may also be higher in more

disadvantaged socioeconomic groups, which should be evaluated with future epidemiological and clinical studies that consider the interaction between these factors. Since the training of dental professionals in schools, an emphasis on avoiding tooth loss, training to prevent rather than treat, may lessen the psychological impact of losing teeth throughout the life course.

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Association between number of remaining teeth and incident depression in a rural Chilean cohort

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Abstract

Objectives Previous studies have established an association between tooth loss and depression. However, longitudinal evidence is scarce and needs to be verified in other populations. The aim of this study was to examine the longitudinal association between the number of remaining teeth and incident depression at 2- and 4-years follow-up in individuals enrolled in the Maule cohort (MAUCO) in Chile.

Methods This prospective study used the information of individuals, aged 38 to 74 years, excluding those with depression at baseline. The number of remaining teeth at baseline was determined in four groups: "20 or more teeth", "10 to 19 teeth", "1 to 9 teeth" and "no natural teeth". Depression was measured through the PHQ-9. Logistic regression was performed to calculate the odds ratios (OR) for incidence depression at both periods of follow-ups, adjusting for age, sex, educational attainment, diabetes mellitus II, and stressful events at follow-up. Also, we performed adjusted multinomial logistic models to analysis the association between the number of remaining teeth and depression severity.

Results In total individuals (n = 3335 at follow 1, n = 2461 at follow 2), all groups have ORs for incident depression above 1 considering 20 or more teeth as reference. In men, those with 10–19 teeth have 2.44 times higher odds of incident depression than those with 20 or more teeth (OR 2.44, CI 95% 1.33–4.50). Edentulous subjects at 4 years follow-up had 2.24 times higher odds of depression than those with more than 20 teeth (OR 2.24 CI 95%1.35–3.72). In women, the ORs (CI 95%) of incident depression were 2.56 (1.50–4.39), 1.56 (1.02–2.40) and 1.27 (0.90–1.81) for "none", "1–9", "10–19" respectively in comparison to the reference group. In edentulous individuals at baseline, the odds for each of the comparisons "mild vs no", "moderate vs no", "moderately severe vs no" and "severe vs no" were above 1, at both follow-ups.

Conclusion Individuals with less than 20 teeth in the mouth could had higher odds of incident depression at 2- and 4-years follow-up, with differences between men and women. Also, in our study, edentulism was associated with increased odds of incident depression at 4-years follow-up in women, and with higher levels of severity of depressive symptoms.

Keywords Cohort, MAUCO, Number of teeth, Oral health, Epidemiology, Depression

Abstract

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Conclusion: Individuals with less than 20 teeth in the mouth could had higher odds of incident depression at 2- and 4-years follow-up, with differences between men and women. Also, in our study, edentulism was associated with increased odds of incident depression at 4-years follow-up in women, and with higher levels of severity of depressive symptoms.

1. Background

Depression is a common illness that severely limits psychosocial functioning and diminishes the quality of life (1). It occurs at any stage of the life cycle and tends to manifest itself with the appearance of several episodes during life. The onset of depression is usually gradual, and the duration of depressive symptoms varies considerably (1). The symptoms of depression can be grouped into neurovegetative, emotional, and cognitive, and the detection can be challenging (1). Screening tools have been developed to identify depression in various clinical settings, and some self-report instruments can be used in a waiting room or online (2). The World Health Organization ranked depression as fifth among diseases with the highest burden, especially in developed countries (3). The 12-month prevalence of major depressive disorder varies considerably across countries but is approximately 6% overall (4). Also, due to COVID-19, there was an estimated globally increase in depression cases of 28% (95% CI=27.2–28.9) (5).

Oral diseases are another major public health issue affecting more than 3.5 billion people worldwide (6). According to cross-sectional studies, bidirectional associations between oral health and depression have been suggested. The relationship between depression and oral health could be explained by lifestyle changes, poor oral hygiene, and difficulties accessing dental care (7) (8) (9). A systematic review showed that the history of caries lesions was higher in individuals with depression, who had an odd of 2.8 (CI 95%=1.7-4.6) of having lost all their teeth than the general community (8). Okoro et al. (2012) found that the adjusted odds of being in the "1-5 teeth removed" or "6-31 teeth removed" groups compared to "0 teeth removed" was also increased for adults with lifetime diagnosed depression versus those without this disorder (10). Also, these authors reported that adults with current depression had a higher prevalence of nonuse of oral health services in the past year, considering age, sex, ethnicity, education, and chronic conditions like diabetes mellitus II (10). A cohort study concluded that the risk of periodontitis was 19% greater in individuals with depressive symptoms (RR 1.19; CI 95%=1.04-1.36), independent of oral hygiene and systemic inflammation (11). However, other studies did not find an association between depression and periodontitis. (12)

The presence of oral conditions such as tooth loss affects general health, including mental health status and health-related quality of life (13). One study showed that individuals with six or more teeth removed were at higher risk of depression alone (OR 1.64, CI 95%= 1.52-1.77) or with anxiety comorbidity (OR 1.91, CI 95%= 1.72-2.11) (14). Tyrovolas *et al*. (2016) concluded that edentulism was significantly associated with depression (OR 1.57, CI 95%= 1.23-2.00) in the younger group with no significant associations in the older age group (15). Additionally, the consequences of missing teeth depend on the severity and intraoral location (16). A recent study concluded that tooth loss causally increased depression among US adults, but the findings may not be directly transferrable to other countries or settings (17). The aim of this study was to examine the longitudinal association between the number of remaining teeth with incident depression at 2- and 4-years follow-up in individuals enrolled in the Maule cohort (MAUCO) in Chile. We hypothesized an association between a fewer number of remaining teeth with increased risk of incident depression in adults at both follow-ups.

2. Methods

2.1 Study Population

This longitudinal prospective study used the information of individuals, aged 38 to 74 years (53.5, sd 9.8 at baseline), enrolled in the Maule cohort (MAUCO) during 2014-2017. MAUCO is the first prospective population-based cohort of cardiovascular disease (CVD) and cancer in central Chile. The study protocol for the MAUCO was previously published (18). To be included in the cohort, participants had to meet the residency criteria and give informed consent. Individuals must have resided in Molina for at least 6 months prior to enrolment and not have plans to move from this town in the next 3 years. Molina is a small agricultural county with 42,859 inhabitants, 30.1% living in rural areas. Individuals who could not give informed consent autonomously or who has a terminal illness were excluded. Also, individuals without the completion of the Patient Health Questionnaire depression module (PHQ-9) or completed dental examination upon entry into the cohort were excluded. Accepting participants received the first interview about lifetime health information and physical examination in their homes or at the MAUCO study clinic. Contact was established in 70% of visited households, and in 95% of those, a resident agreed to respond to the survey. In MAUCO, follow-up visits were planned at 2,4 and 8 years after enrolment (18).

2.2 Outcome variable

Depression was measured at baseline and follow-ups in all subjects through the PHQ-9, a nine-item questionnaire, each rated from 0 to 3 on a Likert scale, where 0 is "not all present" and 3 is "nearly every day", resulting in a total score that ranges from 0 to 27 (19), (20). It is designed to measure severity of symptoms, where higher score means increased severity and a greater risk of major depressive disorder. The PHQ-9 was validated by Baader et al. (2012) in Chile by assessing 1327 patients in urban primary care practices in Valdivia County in southern Chile (21). Those investigators used a cut-off score of 10 or higher on the PHQ-9 as positive for the presence of depression, which is the cut-off score used in our study, so individuals with baseline depression (PHQ-9 $\geq$ 10) were excluded. Additionally, we considered the severity of depression as outcome according to the following PHQ-9 score levels: no (scores of 0-4), mild (scores of 5-9), moderate (scores of 10-14), moderately severe (scores of 15-19) and severe depression (scores of 20-27) (19). PHQ-9 was applied by trained health technicians either at the participant's home or at the MAUCO study clinic. Data entry, supervised by the data-manager, was done locally using REDCap™ (Research Electronic Data Capture) (18).

2.3 Independent variable

The number of remaining teeth at baseline was counted and categorized into the following four groups: "20 or more teeth", "10 to 19 teeth", "1 to 9 teeth" and "no natural teeth". Trained health technicians, using basic dental instruments and after asking the patient to remove their prosthesis, determined the number of remaining teeth, which was registered in an odontogram. Dental status was assessed using the standard diagnostic criteria of the World Health Organization (22). The health technicians wore gloves, a surgical mask, a head flashlight, tongue depressors, and flat mouth mirrors.

2.4 Confounders

A directed acyclic graph (DAGitty version 3.0) was performed to structure the theorical framework of this study (Figure 1). Following a conservative approach for selecting the confounders variables, the data collected at the baseline for demographics, educational attainment and diabetes mellitus II was considered in our DAG. Sex and age were considered as demographic confounders. Educational level was determined by years of formal

education: ≥12 years of formal Education, 9-11 years of formal Education ≤8 years of formal education. Also, diabetes mellitus II was defined by self-report or glycaemia ≥ 126 mg/dL or use of hypoglycemic drugs. Another variable included was stressful events at follow-up, which was the result of the presence (yes/no) of at least one of these conditions after baseline: 1-divorce or separation, 2- job loss or retirement. 3- business failure, 4- violent event 5- major family problem, 6- recent health problem or accident, 7- death of spouse or partner, 8- illness or death of close relative, and 9- other major stress situation.

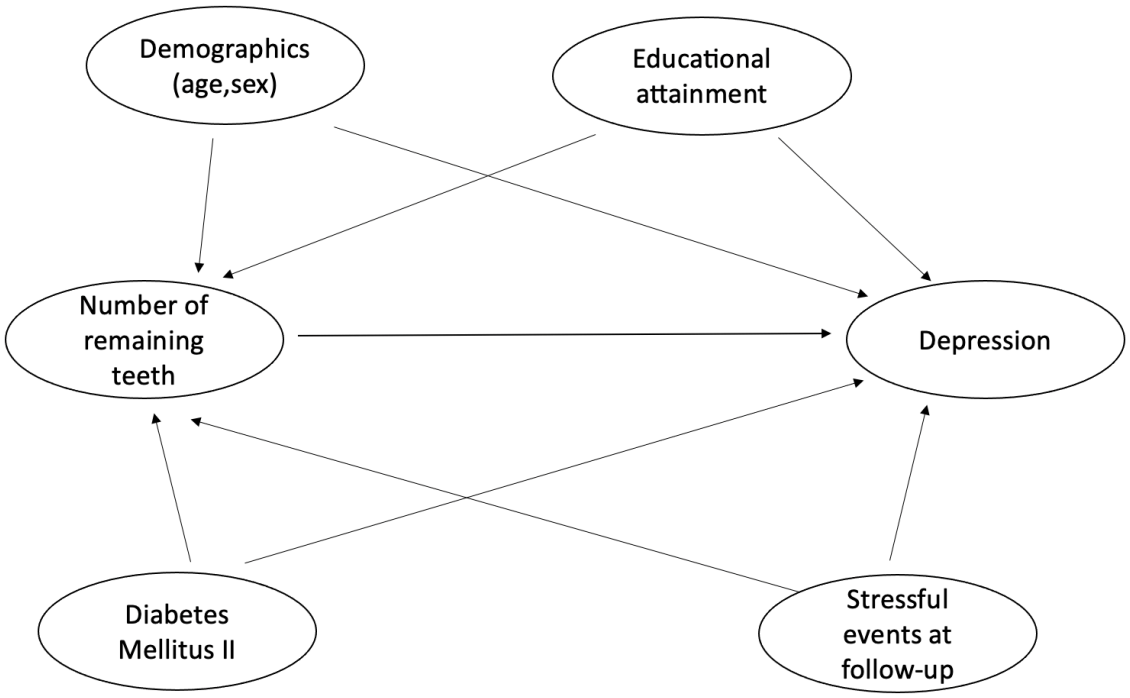


Figure 1. The hypothesized association between number of remaining teeth and depression, including the confounders. Demographics included sex and age. Stressful events at follow up included one of these conditions after baseline: 1-divorce or separation, 2- job loss or retirement. 3- business failure, 4- violent event 5- major family problem, 6- recent health problem or accident, 7- death of spouse or partner, 8- illness or death of close relative, and 9- other major stress situation. *DAGitty version 3.0*.

2.5 Statistical analysis

A descriptive analysis was used examine the baseline number of remaining teeth and the descriptive statistics of depression severity of individuals at 2- and 4-years follow-up. Logistic regression was performed to calculate the odds ratios (OR) and respective confidence intervals (95%) for incidence depression at both periods of follow-ups. In this analysis depression was a binary outcome, being yes, a PHQ-9 ≥ 10 and not a PHQ-9 <9. Logistic regressions were performed to obtain ORs of incident depression in women or men. A second approach was used to analysis depression severity utilizing multinomial logistic regressions. In all models, individuals with baseline depression (PHQ-9 ≥ 10) were excluded. We only showed fully adjusted models. Statistical Analyses were performed using Stata/SE 16 software from StataCorp LP, and the STROBE guidelines for cohort studies were followed by the authors.

2.6 Ethical approval:

The MAUCO protocol was approved by the ethics committees of Pontificia Universidad Católica de Chile and the Maule Regional Service of the Chilean Ministry of Health. Participants were notified that participation was voluntary. Informed consent was obtained from all subjects. The participants' privacy and data were protected throughout the study and individuals with abnormal results were informed and referred to their health care system accordingly (18).

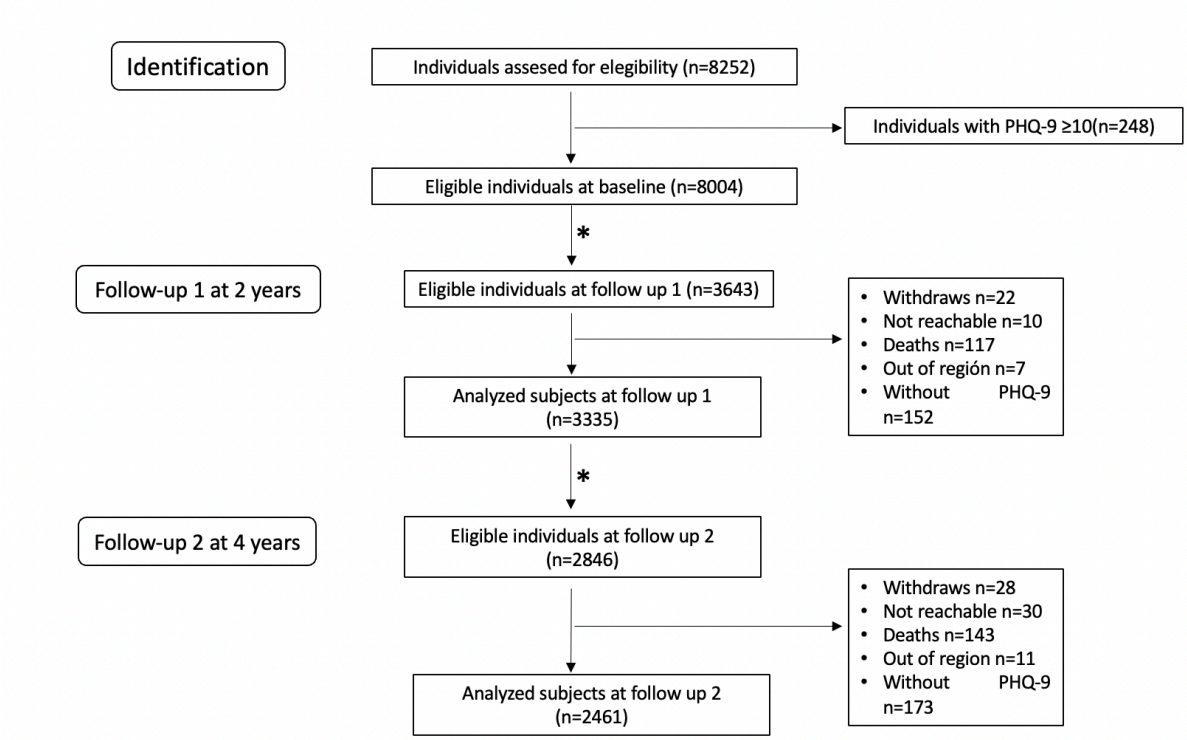
3. Results

Figure 2 shows the flow chart of the participant´s inclusion. Finally, 3 335 individuals were included at follow-up 1 (two years) and 2 461 at follow-up 2 (four years). Table 1 showed the descriptive statistics of the participants depression severity at 2- and 4-years follow-up, according to the number of remaining teeth at baseline. Those with higher number of teeth (10-19, ≥20) at baseline tended to be less depressive at follow up, while those with no teeth were more severely depressed.

Table 2 contained the findings of the logistic regression analysis of the number of remaining teeth at the baseline and the incident depression at 2- and 4-years follow-up of our cohort. For the first follow-up period for the total and both sexes, we observed higher odds of incident depression in the group with 10-19 teeth compared to more than 20 teeth. When considering total individuals, all groups have ORs for incident depression above 1 when considering 20 or more teeth at baseline, but these differences were not statistically significant for most groups. In the case of men, those with 10-19 teeth have 2.44 times higher odds of incident depression than those with 20 or more teeth at baseline (OR 2.44, CI 95% 1.33-4.50). In relation to 4-years follow-up, those who had fewer teeth tended to have higher odds of being depressed compared to the reference group (≥20 teeth at baseline), considering comparisons for total and women. Edentulous subjects ("none" teeth) at 4 years follow-up had 2.24 times higher odds of depression than those with more than 20 teeth in the mouth at baseline (OR 2.24 CI 95%1.35- 3.72). In women, the ORs (CI 95%) of incident depression were 2.56 (1.50-4.39), 1.56 (1.02- 2.40) and 1.27 (0.90- 1.81) for "none", "1-9", "10-19" respectively in compared to the reference group (≥20 teeth at baseline).

Table 3 showed the findings of the multinomial logistic regression analysis of the number of remaining teeth at the baseline and the depression severity for both follow-ups. In edentulous individuals at baseline, the odds for each of the comparisons "mild vs no", "moderate vs no", "moderately severe vs no" and "severe vs no" were above 1, at both follow-ups, but the 95% CI around the ORs across comparisons include the null (not statistically significant). For the categories "1-9" or "10-19" the OR values were less consistent, with some values above 1 and some not. In edentulous individuals, the odds of "moderately severe" or "severe" depression were even higher at both follow-ups. For example, individuals without any teeth at baseline had 3.43 times the odds of "moderately severe" depression at 4 years follow-up (OR 3.43, 95% CI 1.43-8.23).

Figure 2. The participants flowchart of analytic sample (n $_{follow\text{-}up\ 1}$ = 3335)(n $_{follow\text{-}up\ 2}$ = 2461).



*a subgroup of the cohort underwent complete examinations like baseline at follow up.

Table 1: Descriptive statistics of the number of remaining teeth at baseline and depression severity at follow up 1 (2 years) and follow up 2 (4 years), excluding individuals with depression at baseline (PHQ-9>10).

number of remaining teeth *(baseline)*	*follow-up 1 (2 years) Depression severity*					total
	no (n/ %)	Mild (n/ %)	Moderate (n/ %)	moderately severe (n/ %)	severe (n/ %)	
none	154/ 58.8	67/ 25.6	22/ 8.4	12/ 4.6	7/ 2.6	262
1-9	375/ 67.5	99/ 17.8	42/ 7.5	30/ 5.4	10/ 1.8	556
10-19	529/ 61.2	195/ 22.5	95/ 11.0	28/ 3,2	18/ 2.1	865
≥20	1 086/ 65.7	345/ 20.9	141/ 8.5	57/ 3.5	23 /1.4	1 652
total	2 144/ 64.3	706/ 21.2	300/ 9.0	127/ 3.8	58/ 1.7	3 335
	follow-up 2 (4 years) Depression severity					
none	118/ 62.5	38/ 20.1	18/ 9.5	11/ 5.8	4/ 2.1	189
1-9	299/ 68.6	82/ 18.8	37/ 8.5	14/ 3.2	4/ 0.9	436
10-19	469/ 69.3	130/ 19.2	47/ 6.9	25/ 3.7	6/ 0.9	677
≥20	775/ 66.9	253/ 21.8	84/ 7.3	34/ 2.9	13/ 1.1	1 159
total	1 661/ 67.5	503/ 20.4	186/ 7.6	84/ 3.4	27/ 1.1	2 461

Table 2: Summary of findings of the logistic regression analysis of the number of remaining teeth at the baseline and the incident depression follow-up 1 (2 years) and follow-up 2 (4 years).

number of remaining teeth *(baseline)*	*follow-up 1 (2 years) Incident Depression*		
	Total (OR and CI 95%)	Women (OR and CI 95%)	Men (OR and CI 95%)
none	1.06 (0.70-1.62)	0.93 (0.59-1.47)	2.16 (0.69-6.74)
1-9	1.13 (0.82-1.56)	1.01 (0.71-1.44)	2.07 (0.91-4.72)
10-19	1.29 (1.00-1.66)	1.12 (0.84-1.48)	2.44 (1.33-4.50)
≥20	1	1	1
	follow-up 2 (4 years) Incident Depression		
none	2.24 (1.35- 3.72)	2.56 (1.50- 4.39)	0.79 (0.15- 4.13)
1-9	1.45 (0.97- 2.17)	1.56 (1.02- 2.40)	0.87 (0.29- 2.67)
10-19	1.16 (0.84-1.61)	1.27 (0.90- 1.81)	0.62 (0.25- 1.54)
≥20	1	1	1

The model was adjusted for age, sex, educational attainment, diabetes mellitus II and stressful event at follow-up. OR: odds ratio. CI: confidence interval.

Table 3: Summary of findings of the multinomial logistic regression analysis of the number of remaining teeth at the baseline and the depression severity at follow-up 1 (2 years) and follow-up 2 (4 years).

number of remaining teeth *(baseline)*	*follow-up 1 (2 years) Depression severity*			
	Mild *vs.* no (OR and CI 95%)	Moderate *vs.* no (OR and CI 95%)	moderately severe *vs.* no (OR and CI 95%)	severe *vs.* no (OR and CI 95%)
none	1.45 (1.01-2.09)	1.11 (0.65-1.93)	1.25 (0.58-2.67)	1.40 (0.52-3.76)
1-9	0.92 (0.69-1.23)	0.94 (0.62-1.43)	1.56 (0.91-2.70)	0.96 (0.41-2.22)
10-19	1.25 (1.01-1.57)	1.51 (1.11-2.05)	1.06 (0.65-1.74)	1.43 (0.73-2.78)
≥20	1	1	1	1
	follow-up 2 (4 years) Depression status			
none	1.03 (0.66-1.62)	1.91 (1.01-3.66)	3.43 (1.43-8.23)	1.86 (0.46-7.51)
1-9	0.90 (0.65-1.25)	1.45 (0.89-2.37)	1.60 (0.76-3.36)	0.78 (0.22-2.80)
10-19	0.87 (0.67-1.13)	1.05 (0.69-1.57)	1.47 (0.82-2.61)	0.76 (0.27-2.16)
≥20	1	1	1	1

The model was adjusted for age, sex, educational attainment, diabetes mellitus II and stressful event at follow-up. OR: odds ratio. CI: confidence interval.

4. Discussion

In this longitudinal prospective cohort study, individuals with less than 20 teeth in the mouth showed higher odds of incident depression at 2- and 4-years follow-up but is important to notice that most of these values were not statistically significant. Also, edentulism could be associated with increased odds of incident depression at 4-years follow-up and with higher levels of severity of depressive symptoms, which followed an increasing gradient. The findings of this study were consistent with previous studies estimating the association between oral health and depressive symptoms. Yamamoto et al. 2017, in a Japanese longitudinal study, reported that having no teeth and oral health problems may play a role in the development or worsening of depressive symptoms (23). Zhang et al. (2021), in a

longitudinal study with 4 years of follow up, reported that Chinese older adults with fewer teeth left (<20) and those who were non-denture users were associated with severe depressive symptoms (24). Also, Kunrath & Ribeiro (2020), reported that Brazilian older adults who experienced tooth loss were more likely to exhibit depressive symptoms (25). Furthermore, Matsuyama et al. 2021, identified the causal effect of tooth loss on depression among U.S. adults in a natural experiment study, using instrumental analysis (instrumental variable was exposure to drinking water fluoride) in 2006, 2008 or 2010 waves of the Behavioral Risk Factor Surveillance System (BRFSS). They found that for each additional tooth loss, depressive symptoms according to the eight-item Patient Health Questionnaire depression (PHQ-8) score increased by 0.146 (95% CI 0.008-0.284) and the probability of having clinical depression (PHQ-8 higher than 10) increased by 0.81 percentage points (95% CI -0.12 to 1.73). Also, losing ten or more teeth was comparable to adults with major depressive disorder not receiving anti-depressant drugs (17). Additionally, an Indian cross-sectional study reported that edentulism was associated with poor self-rated health and low psychological and subjective well-being among older adults (26).

Deciphering the potential pathways between oral and mental health outcomes is important to prevent and treat these conditions and for the public health agenda to prioritize mental and oral health. From oral diseases to subsequent depression, it has been hypothesized that neuroinflammation due to past periodontal inflammation or autonomic nerve imbalance due to oral pain, stress and discomfort increases depressive symptoms (27). On the other hand, although an association between depression and poor oral health habits has been observed, the mechanism of this relationship is not well determined. Also, different mechanisms have been proposed, including changes in behaviors regarding psycho-immunological changes, health management itself, or even a combination of both mechanisms (28). Depression may affect oral health status, self-perceived oral health, dental attendance, and acquisition and reinforcement of poor oral health behaviors, decreasing the frequency of tooth brushing and flossing (27). Concerning the biological component, an association between depression and reduction in salivary flow, subjective oral dryness, and downregulation of the immune system

has been reported. Consequently, hyposalivation and induced changes in salivary immunity increase the risk of developing oral diseases, especially dental caries, or periodontal disease (27).

Our study found heterogeneity in the association between the number of remaining teeth and the incidence of depression when considering men versus women, within and between both follow-ups. The findings in women are more consistent with the hypothesis that fewer number of teeth may increase the risk of depression. Our proposed difference for gender is under evidence that women perceive oral health to be generally more relevant than men (29). However, our point contrasts with findings of Matsuyama et al. (2021), who observed that the effect of tooth loss on depressive symptoms was larger in men than in women (17). In addition, other studies have found heterogeneity according to the levels of tooth loss. Zhang et al. (2021), found that the depressive symptom scores of men were higher than those of women concerning to people with nine teeth or less, and the scores of women were higher than those of men for participants with 10-19 teeth (24). In Chile, according to the last National Health Survey (ENS 2016-2017), the median number of teeth was lower, and the prevalence of depression was higher in women, which also occurred in rural populations like the one included in this cohort (30). Differences in the trajectories of tooth loss between men and women, which are not fully addressed in this study, may influence the incidence of depression. Finally, regarding the gender gap in depression, there are factors related to susceptibility (biological and psychological) and environmental factors that operate on both the micro and macrolevel (31).

Our findings should be interpreted with caution because there were some limitations. Firstly, the external validity of MAUCO´s findings are limited, since this cohort represents an agricultural population from a small city in the country. Secondly, even we used several confounders including variables at baseline and follow-ups, the risk of residual confounding is likely to affect our conclusions given the complexity of the association under study. For example, in our models, we have considered the variable Diabetes Mellitus II because evidence supports that individuals with diabetes mellitus II have an increased risk of periodontitis or caries, conditions that lead to tooth loss (6). In addition, diabetes mellitus II,

included in metabolic syndrome, has been associated with an increased risk of depression attributable to systemic inflammation (32-33). However, there are other inflammatory diseases such as cardiovascular or autoimmune diseases associated with depression (33) that could be affecting our findings and whose complex pathways need to be addressed in future research. Also, the effect of prosthetics or others dental interventions were not captured in our analysis, in fact any potential oral rehabilitation effort received by the participants from the baseline observation to outcome assessment was not determined. Thirdly, there are subjects who were not included in both follow-ups due to lack of information on the depression variable, given the absence of the PHQ-9 register, which may result in selection bias. Fourthly, the number of subjects with "moderately severe" or "severe" depression was around 5% at both follow-ups, which may limit the power of the analyses, despite our sample size was relatively large. Fifthly, the dental examination was performed by dental technicians instead dental professionals which is considered the gold standard. Additionally, by the inherent nature of the outcome, those with more severe depression may have dropped out of the cohort, so the reported findings may be underestimated. Another limitation is that in both follow-ups, a subgroup of the cohort was not re-examined with the PHQ-9 questionnaire, corresponding to around a 5% of the sample in each time, which may introduce a selection bias. The above is related to the fact that our study was nested in a cohort whose objective was the follow-up of multiple noncommunicable diseases (NCDs), focusing on biomedical outcomes and not being primarily a mental health cohort. Finally, we focused on the number of remaining teeth at baseline rather than tooth loss at follow-up to explain the incidence or severity of depression. Future studies may also assess the effect of becoming edentulous during follow-up or the time-varying tooth loss on subsequent changes in the levels of depression. Despite these limitations, the main strength of this study was the longitudinal design, which allow to verify temporal relationship between baseline number of remaining teeth and incident depression over a 2- or 4-years follow-up period. The prospective nature allowed the exclusion of individuals with depression at baseline, which means outcome-free cohort analysis. Future studies should consider other variables, such as the use of antidepressants, from two scientific perspectives. On the one hand, in terms of the association presented in this study, these drugs are designed to decrease depressive symptoms and those,

may affect the impact of tooth loss on depression. On the other hand, previous studies have indicated that the use of some antidepressants decreases salivary flow rate, which could increase the risk of caries and thus tooth loss. Both hypotheses have not been measured in our study (27). Finally, additional investigations may evaluate the role of dental interventions as dental prostheses in the association between the number of the remaining teeth and subsequent depression risk.

5. Conclusion

Individuals with less than 20 teeth in the mouth could had higher odds of incident depression at 2- and 4-years follow-up, with differences between men and women. Also, in our study, edentulism was associated with increased odds of incident depression at 4-years follow-up in women, and with higher levels of severity of depressive symptoms. Prevention of tooth loss may potentially reduce the risk or severity of depression in adults.

Declarations

Ethics approval and consent to participate.

The MAUCO protocol and current study were approved by the ethics committees of Pontificia Universidad Católica de Chile (file number 14-141) and the Maule Regional Service of the Chilean Ministry of Health. Participants were notified that participation was voluntary. Informed consent was obtained from all subjects. The participants' privacy and data were protected throughout the study and individuals with abnormal results were informed and referred to their health care system accordingly. This study followed the principles of Declaration of Helsinki of 1975, as revised in 2013.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the Advanced Center for chronic Diseases (ACCDiS) Directorate in accordance with the local institutional review board authorization, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of cferrec@med.puc.cl or by contacting the corresponding author Duniel Ortuño at drortuno@uc.cl. Applications for data usage are accepted online from the MAUCO website: www.mauco.org. Additional information can be requested at contacto@mauco.org or by contacting the corresponding author Duniel Ortuño at drortuno@uc.cl.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Dr. Duniel Ortuño: Conceptualization, Methodology, Analysis, Writing – Original Draft, Edition and Visualization. **Dra. Constanza Martinez:** Conceptualization, Methodology, Review and Edition, Supervision. **Dra. Constanza Caneo:** Conceptualization, Methodology, Review and Edition. All the authors gave their final approval and agreed to be accountable for all aspects of the work.

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Supplementary Material

Supplementary table 1 (S.1): Baseline characteristics of the analytical sample.

	Depression				
	Yes		No		
	N	%	N	%	Total
Number of teeth					
≥20 teeth	762	14.1	4630	85.9	5392
10-19 teeth	368	16.4	1870	83.6	2238
1-9 teeth	215	16.8	1061	83.2	1276
0 teeth	99	18.3	443	81.7	542
Sex					
Men	363	8.4	3933	91.6	4296
Women	1081	20.9	4071	79,1	5152
Age					
38-45 Years	366	15.2	2036	84.8	2402
46-53 Years	416	16.3	2134	83.7	2550
54-61 Years	366	15.8	1945	84.2	2311
62-69 Years	214	13.3	1389	86.7	1603
≥70 Years	82	14.1	500	85.9	582
Education attainment					
≥12 years of formal Education	737	16.6	3693	83.4	4430
9-11 years of formal Education	602	14.6	3508	85.4	4110
≤8 years of formal Education	91	10.6	761	89.4	852
Diabetes Mellitus II					
Yes	213	19.6	869	80.4	1082
No	1231	14.7	7135	85.3	8366

*56 individuals not reported education attainment at baseline.

Supplementary table 2 (S.2): Descriptive statistics of the number of remaining teeth at baseline and depression severity at follow up 1 (2 years) and follow up 2 (4 years) in women, excluding individuals with depression at baseline (PHQ-9>10).

number of remaining teeth *(baseline)*	*follow-up 1 (2 years) Depression severity*					total
	no (n/ %)	Mild (n/ %)	Moderate (n/ %)	moderately severe (n/ %)	severe (n/ %)	
none	112/ 54.4	59/ 28.6	19/ 9.2	9/ 4.4	7/ 3.4	206
1-9	261/ 64.3	75/ 18.5	37/ 9.1	26/ 6.4	7/ 1.7	406
10-19	317/ 54.8	152/ 26.3	73/ 12.6	21/ 3.6	16/ 2.7	579
≥20	670/ 59.3	265/ 23.5	121/ 10.7	53/ 4.7	20/ 1.8	1 129
total	1 360/ 58.6	551/ 23.8	250/ 10.8	109/ 4.7	50/ 2.1	2 320
	follow-up 2 (4 years) Depression severity					
none	91/ 59.5	31/ 20.3	17/ 11.1	10/ 6.5	4/ 2.6	153
1-9	218/ 65.2	67/ 20.1	31/ 9.3	14/ 4.2	4/ 1.2	334
10-19	308/ 64.3	102/ 21.3	39/ 8.1	24/ 5.0	6/ 1.3	479
≥20	537/ 62.3	212/ 24.6	71/ 8.2	29/ 3.4	13/ 1.5	862
total	1 154/ 63.1	412/ 22.6	158/ 8.6	77/ 4.2	27/ 1.5	1 828

Supplementary table 3 (S.3): Descriptive statistics of the number of remaining teeth at baseline and depression severity at follow up 1 (2 years) and follow up 2 (4 years) in men, excluding individuals with depression at baseline (PHQ-9>10).

number of remaining teeth *(baseline)*	*follow-up 1 (2 years) Depression severity*					total
	no (n/ %)	Mild (n/ %)	Moderate (n/ %)	moderately severe (n/ %)	severe (n/ %)	
none	42/ 75.0	8/ 14.2	3/ 5.4	3/ 5.4	0/ 0.0	56
1-9	114/ 76.0	24/ 16.0	5/ 3.3	4/ 2.7	3/ 2.0	150
10-19	212/ 74.1	43/ 15.0	22/ 7.7	7/ 2.5	2/ 0.7	286
≥20	416/ 79.5	80/ 15.3	20/ 3.8	4/ 0.8	3/ 0.6	523
total	784/ 77.2	155/ 15.3	50/ 4.9	18/ 1.8	8/ 0.8	1 015
	follow-up 2 (4 years) Depression severity					
none	27/ 75.0	7/ 19.4	1/ 2.8	1/ 2.8	0/ 0.0	36
1-9	81/ 79.4	15/ 14.7	6/ 5.9	0/ 0.0	0/ 0.0	102
10-19	161/ 81.3	28/ 14.2	8/ 4.0	1/ 0.5	0/ 0.0	198
≥20	238/ 80.1	41/ 13.8	13/ 4.4	5/ 1.7	0/ 0.0	297
total	507/ 80.1	91/ 14.4	28/ 4.4	7/ 1.1	0/ 0.0	633

Supplementary table 4 (S.4): Summary of findings of the multinomial logistic regression analysis of the number of remaining teeth at the baseline and the depression severity at follow-up 1 (2 years) and follow-up 2 (4 years), in women.

number of remaining teeth	*follow-up 1 (2 years) Depression severity*			
	Mild *vs.* no (OR and CI 95%)	Moderate *vs.* no (OR and CI 95%)	moderately severe *vs.* no (OR and CI 95%)	severe *vs.* no (OR and CI 95%)
none	1.49 (1.01-2.23)	0.96 (0.53-1.74)	1.01 (0.44-2.32)	1.75 (0.63-4.88)
1-9	0.82 (0.58-1.14)	0.83 (0.53-1.30)	1.33 (0.74-2.39)	0.80 (0.30-2.12)
10-19	1.27 (0.99-1,66)	1.31 (0.93-1.85)	0.84 (0.48-1.46)	1.57 (0.77-3.21)
≥20	1	1	1	1
	follow-up 2 (4 years) Depression severity			
none	0.92 (0.56-1.53)	2.10 (1.06-4.19)	4.08 (1.62-10.33)	1.83 (0.45-7.44)
1-9	0.84 (0.58-1.21)	1.43 (0.84-2.46)	2.04 (0.95-4.40)	0.77 (0.22-2.78)
10-19	0.83 (0.62-1.13)	1.07 (0.68-1.67)	1.80 (0.98-3.31)	0.77 (0.27-2.17)
≥20	1	1	1	1

The model was adjusted for age, sex, educational attainment, diabetes mellitus II and stressful event at follow-up. OR: odds ratio. CI: confidence interval.

Supplementary table 5 (S.5): Summary of findings of the multinomial logistic regression analysis of the number of remaining teeth at the baseline and the depression severity at follow-up 1 (2 years) and follow-up 2 (4 years), in men.

number of remaining teeth	*follow-up 1 (2 years) Depression severity*			
	Mild *vs.* no (OR and CI 95%)	Moderate *vs.* no (OR and CI 95%)	moderately severe *vs.* no (OR and CI 95%)	severe *vs.* no (OR and CI 95%)
none	1.15 (0.48-2.74)	2.50 (0.60-10.47)	5.54 (0.76-40.89)	-
1-9	1.29 (0.73-2.29)	1.60 (0.51-4.96)	4.46 (0.88-22.69)	1.47 (0.23-9.27)
10-19	1.12 (0.72-1.76)	2.82 (1.37-5.84)	3.68 (0.95-14.30)	0.66 (0.10-4.47)
≥20	1	1	1	1
	follow-up 2 (4 years) Depression severity			
none	1.77 (0.64-4.90)	0.73 (0.08-6.71)	1.01 (0.07-13.29)	-
1-9	1.20 (0.57-2.56)	1.44 (0.43-4.78)	-	-
10-19	1.05 (0.59-1.88)	0.87 (0.32-2.36)	0.16 (0.02-1.54)	-
≥20	1	1	1	1

The model was adjusted for age, sex, educational attainment, diabetes mellitus II and stressful event at follow-up. OR: odds ratio. CI: confidence interval.

11- Manuscript 2: "Tooth Loss and Depression in Chilean Participants of the National Health Survey 2016-2017: Oral functions mediation analysis".

Abstract:

Objective: Previous studies have indicated the association between poor oral health and depression in adults, but more evidence is required. This study evaluated oral functions´ contribution to the association between tooth loss and the presence of depressive symptoms in Chilean individuals.

Methods: We used data from the third version of the Chilean National Health Survey (ENS 2016-2017), which included participants over 15-year-old. The number of remaining teeth (≤19 versus ≥20 teeth) and anterior tooth losses were the exposure variables. The outcome was depression, measured through a self-report question and with the Composite International Diagnostic Interview – Short Form (CIDI SF). The mediating variables were determined by five questions, including problems regarding "speaking", "pain and suffering", "eating", "daily activities", and "social relationships". We performed logistic regression models including age, sex, educational level, tobacco consumption, and history of diabetes as confounders variables. Finally, it was calculated indirect, direct effect, total effect, and the proportion mediated (PM) effects of dental loss by the deterioration of oral functions.

Results: We included 5383 participants. The self-reported depression and probable depression prevalence were 22,1% and 14,0% respectively. The total effect of fewer remaining teeth (≤19) on self-reported depression was 1.21 (95% CI 1.02-1.44), and 1.09 (95% CI 0.90-1.33) for probable depression. All five variables of oral functions significantly mediated the association between tooth loss and depression. Feeling uncomfortable when speaking (self-reported depression: OR 1.07, CI 1.04-1.10) (probable depression: OR1.10, CI 1.06-1.14) or eating discomfort (self-reported depression: OR 1.08, CI 1.05-1.11) (probable depression: OR 1.10, CI 1.07-1.14) were the most significant mediators.

Conclusions: Deterioration of oral functions was a significant mediator in the association between tooth loss and depression, in particular feeling uncomfortable when speaking or eating. This mechanism should be considered in interventions to improve mental health.

1. Background

Depression is a common illness that severely limits psychosocial functioning and diminishes the quality of life in young individuals and adults (1). The 12-month prevalence of major depressive disorder varies across populations but is approximately 6% overall, with similar values in high and low-middle-income countries (2). A recent mental health report has indicated that the COVID-19 pandemic has led globally to an increase in the number of cases of depression during 2020 (3). Depression is almost twice as common in women than men. The gender gap is related to biological and psychological susceptibility, and with cultural or environmental factors (1) (4). In the general population, depression is the most prevalent psychiatric disorder and the most frequent psychiatric comorbidity in non-psychiatric illnesses (5). Understanding the causes of depression is challenging because of multifactorial origin (1). Several biological and psychosocial factors have been associated with the onset or severity of depression, but the contributions from these factors are variable (1).

Identifying risk factors for depression is crucial for effective interventions. In this line, previous studies have indicated the association between a lower number of remaining teeth and the incidence of depressive symptoms (6) (7). According to Matsuyama *et al.* (2021), the effect size of losing 10 or more teeth was comparable to adults with major depressive disorder not receiving antidepressant drugs (7). Also, the authors concluded that the effect of teeth on depression seemed to be greater in young adults, men, people with higher income and those with less dental care utilization (7). One study showed that individuals with six or more teeth removed had a higher risk of depression (OR 1.64, 95% CI 1.52-1.77) (8). Tyrovolas *et al*. (2016) concluded that edentulism was significantly associated with depression (OR 1.57, 95% CI 1.23-2.00) only in the younger individuals (9). On the other hand, Yamamoto *et al.* (2017) found that being edentulous was a risk factor for developing depression in older people (6).

In a global situation where, oral diseases affect more than 3.5 billion people, knowing the mechanisms between tooth loss and mental health disorders is relevant to preventing and treating both conditions (10). Some pathways as neuroinflammation due to past periodontal

and autonomic nerve imbalance attributed to oral-related pain, have been hypothesized in the relationship between tooth loss and incident depression, with sex and age differences (11). Glick *et al.* (2017) defined social aspects of oral health like speaking, smiling, or enjoying meals with others, may affect mental health (12). People with fewer teeth might be less likely to communicate with others because of the problem of eating, speaking, or smiling, which might affect mental health outcomes (7). Rouxel *et al.* (2017) concluded that declines in social interactions due to poor oral health might also affect the association between tooth loss and the severity of depressive symptoms (13).

The role of inflammation or malnutrition has been more reported in the literature in linking oral and other noncommunicable diseases (14). In contrast, the mechanisms related to the deterioration of social activities attributed to detrimental oral health have been less emphasized. Kusama *et al.* (2021) found that diminished oral function and orofacial appearance mediated in more than 50% of the association between tooth loss as an oral structural impairment and the incidence of depressive symptoms (15). This study highlighted the importance of considering the social functions of oral health. Still, it was limited to 65 years and older individuals and only included three oral functions and orofacial appearance-related social activities as the mediators (difficulty in speaking, smiling, and chewing). Also, the authors evaluated tooth loss only quantitatively. To explore the impact of tooth loss on health outcomes as depression, it should consider the position and not only the number of missing teeth. Although the loss of posterior teeth is a more common event (16), a lower number of anterior teeth may affect physical appearance and facial aesthetics more. So, we hypothesized that the mediator role of measures of oral functions in the association between tooth loss and depression might be affected not only by the number of teeth but also by position in the mouth. This study aimed to evaluate oral functions contribution to the association between tooth loss, considering anterior losses, and the presence of depressive symptoms in Chilean individuals.

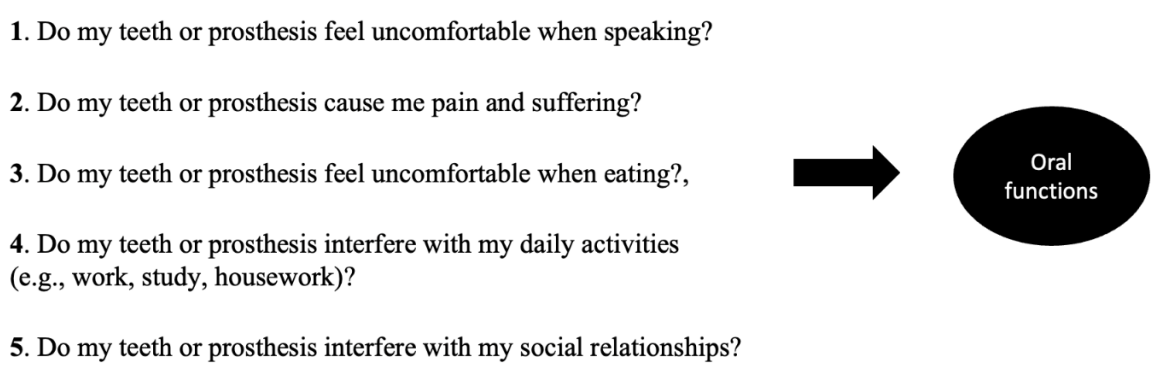
2. Methods

Our study was based on the third version of the Chilean National Health Survey (ENS 2016-2017), which included participants who were 15 years or over. In the ENS 2016-2017, the sample size was calculated with a 20% relative error to estimate a national prevalence of over 3%. One participant per household was randomly selected using a computational Kish algorithm. The sample was representative of the Chilean population, including men and women who lived in rural or urban areas from all country regions. A complex, stratified, multistage cluster sampling technique was used in this respect. The survey had a response rate of 67.0% from the eligible participants, whereas the rejection rate was 9.8%.

Oral health was measured using questionnaires and an intraoral examination performed by trained nurses following the WHO STEPwise approach to chronic disease surveillance (17). Also, dental status was assessed using the standard diagnostic criteria of the World Health Organization (18). The nurses were trained by nine dentists associated with the Ministry of Health of Chile (MINSAL). Also, MINSAL provided the nurses with a handbook for conducting dental assessments called "The Nurse Manual." This handbook is available in the national repository of population-based surveys (http://epi.minsal.cl/encuestas-poblacionales/). According to the pilot study of the ENS 2003, the nurses' sensitivity to detect tooth loss was over 70% (19), and the inter-examiner reliability was significant (kappa 0.75, p-value<0.001). As to the ENS 2016-2017, the inter-examiner reliability relating to the assessment of anterior tooth loss was almost perfect and significant (kappa 0.85, p-value<0.01) (20). The nurses wore gloves, surgical masks, head flashlights, tongue depressors, and flat mouth mirrors. Clinical examination was carried out while the participant was sitting in a straight back chair in front of the light from the head flashlight. To determine the number of remaining teeth, a nurse asked to brush their teeth previously and remove their prosthesis; then, they counted the participants' teeth in each dental arch. To assess anterior tooth loss, the nurses had to register the results by selecting one of the two response alternatives, "Yes" or "No," where "Yes" meant that at least one of the six anterior teeth in a dental arch was missing. This data was collected using an electronic tablet and then submitted and validated according to the national survey protocols.

We performed a mediation analysis to estimate the contribution of oral functions impairment to the relationship between tooth loss and depression. The independent variable, corresponding to tooth loss, was measured in two ways: 1. number of teeth remaining in the mouth (≤19 versus ≥20 teeth) and 2. loss of anterior teeth, either upper or lower, regardless of the number of teeth lost. The mediating variables were determined by questions about how individuals felt in any of five situations (figure 1). Each of the five situations could be answered with the alternatives "never", "almost never", "sometimes", "almost always", or "always", which for analysis purposes were dichotomized into 0:"never or almost never" and 1:"sometimes, almost always or always".

Figure 1. Questionnaire about oral functions (items=5). ENS 2016-2017, Chile.

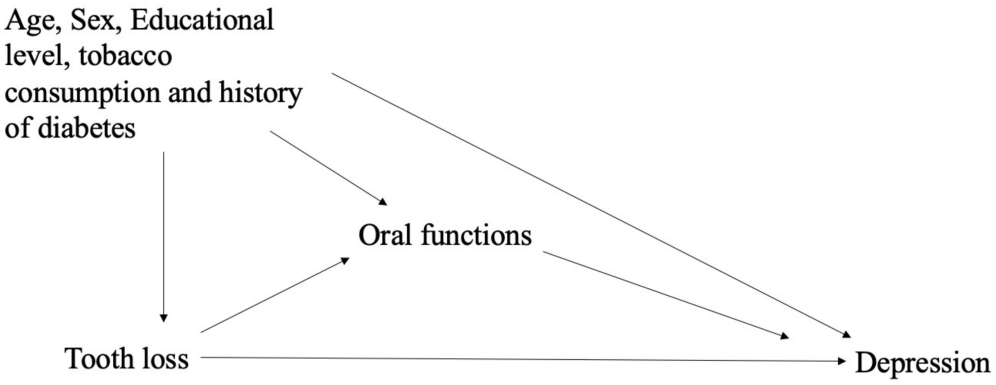


We considered the dependent variable in two ways: the first, through the self-report question "Has a doctor or physician ever told you that you have or suffer from depression?" with possible answers "Yes" or "No"; and the second, through the Composite International Diagnostic Interview – Short Form (CIDI SF) for probable depression (21). The CIDI SF is a screening tool consisting of a structured interview with 31 questions, demonstrating adequate reliability and validity for major depressive episodes. For the suspicion of depression, it is necessary to present dysphoria or lack of interest, as well as four or more of the following symptoms: fatigue, changes in weight, sleep problems, difficulty concentrating, feelings of worthlessness, and thoughts of death (22).

The causal mediation analysis was performed using the KHB package developed by Kohler & Karlson (23) to obtain three estimates: a. the indirect effect, corresponding to the effect given by the mediator in the relationship between exposure and outcome, b. the direct effect, corresponding to the unmediated effect, and c. the total effect, resulting from the sum of the two previous effects. We preformed logistic regression models and calculated odds ratios (OR) with their respective 95% confidence intervals (95% CI). The proportions mediated by the indirect effect were calculated by the division between the coefficient of the indirect effect by the total effect, multiplied by 100.

A directed acyclic graph (DAGitty version 3.0) was performed to structure the theoretical framework of this study (Figure 2). Based on evidence we introduced possible confounders as covariates with a conservative approach. We adjusted our regression models by age (grouped as <65 years or ≥65 years), sex (female or male), educational level (<8 years, 8-12 years, or >12 years of education completed), smoking status (measured as "yes, one or more cigarettes per day," "yes, occasionally (less than one cigarette per day)," "no, I have quit smoking," or "no, I have never smoked"), and history of diabetes (captured through the question “Have you ever been told by a doctor, nurse, or other health care professional that you ever had diabetes? with possible answers "Yes" or "No". All analyses were performed in Stata MP version 17 (Stata Corp., College Station, TX, USA).

Figure 2. The directed acyclic graph (DAG) of the variables considered in the present study. DAGitty version 3.0 (24).



The Scientific Ethics Committee of the Faculty of Medicine of Pontificia Universidad Católica de Chile approved this study (CEC-MEDUC, ID: 16-019). In the ENS 2016-22017, informed consent was obtained from all individuals. For participants under 16 years, written informed consent was obtained from their parents or guardians. Our study followed the principles of the Declaration of Helsinki of 1975, as revised in 2013.

3. Results

Figure 3 shows the flow chart of this cross-sectional study. We included 5.383 participants in the analysis. All participants had valid responses to the questions used as mediators. Table 1 contains the characteristics of the participants. According to the self-report, the prevalence of depression in our sample was 22,1%, while the CIDI SF questionnaire showed a suspicion of depression of 14,0%. In individuals with positive self-report of depressive symptoms, the proportion of ≤19 teeth in the mouth were 40,5%, while in those who responded no, it decreased to 35,9%. This prevalence was very similar in individuals with positive or negative suspicion of depressive symptoms when we considered CIDI SF ("yes"=36,2%, "no"=37,1%). As for the prevalence of anterior tooth loss, in individuals with positive self-report of depression, the value was 45,5%, while in those who said no, it decreased to 41,9%. On the other hand, according to the CIDI SF, in those with the presence of probable depression, the prevalence of anterior tooth loss was 40.7%, and in those with negative results, the value increased to 43.0%.

Figure 3: Determination of the number of participants for analysis (n=5.383)

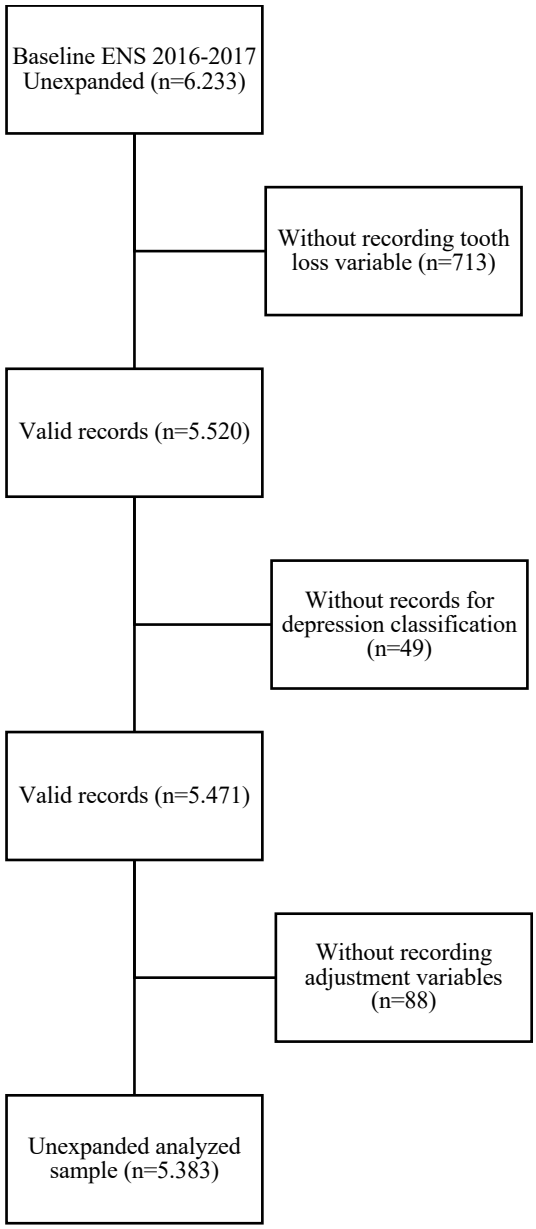


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Table 1: Characteristics of the participants according to variables of interest. National Health Survey 2016-2017 (n=5.383).

			Have you ever been told by a doctor or physician that you have or suffer from depression?				CIDI Short Form Positive			
	Total (n=5.383)		No (n=4.196)		Yes (n=1.187)		No (n=4.631)		Yes (n=752)	
Characteristics	n	%	n	%	n	%	n	%	n	%
Number of remaining teeth										
≥20	3.394	63,0	2.688	64,1	706	59,5	2.914	62,9	480	63,8
≤19	1.989	36,9	1.508	35,9	481	40,5	1.717	37,1	272	36,2
Anterior tooth loss										
No	3.084	57,3	2.437	58,1	647	54,5	2.638	57,0	446	59,3
Sí	2.299	42,7	1.759	41,9	540	45,5	1.993	43,0	306	40,7
Use of removable prosthesis										
No	3.695	68,6	2.964	70,6	731	61,6	3.178	68,6	517	68,8
Sí	1.688	31,4	1.232	29,4	456	38,4	1.453	31,4	235	31,2
Do my teeth or prosthesis feel uncomfortable when speaking?										
Never or rarely	4.686	87,1	3.713	88,5	973	82,0	4.090	88,3	596	79,3
Sometimes, very often or always	697	12,9	483	11,5	214	18,0	541	11,7	156	20,7
Do my teeth or prosthesis cause me pain and suffering?										
Never or rarely	4.499	83,6	3.589	85,5	910	76,7	3.956	85,4	543	72,2
Sometimes, very often or always	884	16,4	607	14,5	277	23,3	675	14,6	209	27,8
Do my teeth or prosthesis feel uncomfortable when eating										
Never or rarely	4.451	82,7	3.568	85,0	883	74,4	3.912	84,5	539	71,7
Sometimes, very often or always	932	17,3	628	15,0	304	25,6	719	15,5	213	28,3
Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)?										
Never or rarely	4.958	92,1	3.903	93,0	1.055	88,9	4.298	92,8	660	87,8
Sometimes, very often or always	425	7,9	293	7,0	132	11,1	333	7,2	92	12,2
Do my teeth or prosthesis interfere with my social relationships?										
Never or rarely	4.926	91,5	3.892	92,8	1.034	87,1	4.284	92,5	642	85,4
Sometimes, very often or always	457	8,5	304	7,2	153	12,9	347	7,5	110	14,6
Gender										

Male	1.974	36,7	1.791	42,7	183	15,4	1.800	38,9	174	23,1
Female	3.409	63,3	2.405	57,3	1.004	84,6	2.831	61,1	578	76,9
Age										
≤64 years	4.069	75,6	3.174	75,6	895	75,4	3.445	74,4	624	83,0
≥65 years	1.314	24,4	1.022	24,4	292	24,6	1.186	25,6	128	17,0
Years of study completed										
<8 years	1.294	24,0	1.007	24,0	287	24,2	1.121	24,2	173	23,0
8-12 years	2.909	54,1	2.277	54,3	632	53,2	2.489	53,8	420	55,9
>12 years	1.180	21,9	912	21,7	268	22,6	1.021	22,0	159	21,1
Do you currently smoke cigarettes?										
Yes, one or more cigarettes per day.	1.159	21,6	854	20,4	305	25,7	951	20,5	208	27,7
Yes, occasionally (less than one cigarette per day).	372	6,9	305	7,3	67	5,6	319	6,9	53	7,0
No, I have quit smoking.	1.289	23,9	961	22,8	328	27,6	1.093	23,6	196	26,1
No, I have never smoked.	2.563	47,6	2.076	49,5	487	41,1	2.268	49,0	295	39,2
Has a healthcare professional ever told you that you have diabetes?										
No	4.588	85,2	3.655	87,1	933	78,6	3.978	85,9	610	81,1
Yes	795	14,8	541	12,9	254	21,4	653	14,1	142	18,9

Table 2 show the mediation analysis results on the association between the number of remaining teeth and self-reported depression or probable depression. The total effect of fewer remaining (≤19) on depression was 1.21 (95% CI 1.02-1.44), considering self-reported, and 1.09 (95% CI 0.90-1.33) for probable depression. Feeling uncomfortable when speaking (indirect effect of 1.07, 95% CI 1.04-1.10, PM=35,0%, self-report of depression) (indirect effect of 1.10, 95% CI 1.06-1.14, PM=118,9%, CIDI SF) or when eating (indirect effect of 1.08, 95% CI 1.05-1.11, PM= 42,5%, self-report of depression) (indirect effect of 1.10, 95% CI 1.07-1.14, PM= 117,5%, CIDI SF) significantly mediated the association between tooth loss and depression, being the two conditions that showed the greater mediation effect compared to that of the others. Also, in the other three variables related to pain and suffering, interference in daily activities and interference in social relationships, a statistically significant mediating effect was found, both when considering self-report of depression and the CIDI SF instrument for probable depressive symptoms.

Table 2: Mediating Effect of Oral Function and Impairment of Orofacial Appearance in the Relationship between the number of remaining teeth and Depression. (n=5.383).

Self-reported history of depression	**Do my teeth or prosthesis feel uncomfortable when speaking? OR (95% CI)**	**Do my teeth or prosthesis cause me pain and suffering? OR (95% CI)**	**Do my teeth or prosthesis feel uncomfortable when eating? OR (95% CI)**	**Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)? OR (95% CI)**	**Do my teeth or prosthesis interfere with my social relationships? OR (95% CI)**
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	1.13 (0.95-1.35)	1.17 (0.98-1.39)	1.12 (0.94-1.33)	1.16 (0.98-1.39)	1.15 (0.96-1.37)
Indirect effect	1.07 (1.04-1.10) *	1.04 (1.02-1.06) *	1.08 (1.05-1.11) *	1.04 (1.02-1.06)*	1.05 (1.03-1.07)*
Total effect	1.21 (1.01-1.44)*	1.21 (1.02-1.44)*	1.21 (1.02-1.44)*	1.21 (1.02-1.44)*	1.21 (1.01-1.44)*
Proportion mediated	35,0%	19,0%	42,3%	20,7%	26,1%
Probable Depression by CIDI Short Form					
Number of Remaining Teeth ≤19 (reference: ≥20 teeth)					
Direct effect	0.98 (0.80-1.21)	1.04 (0.85-1.27)	0.99 (0.80-1.21)	1.05 (0.86-1.28)	1.03 (0.84-1.26)
Indirect effect	1.10 (1.06-1.14)*	1.06 (1.03-1.08)*	1.10 (1.07-1.14)*	1.05 (1.02-1.07)*	1.06 (1.03-1.09)*
Total effect	1.09 (0.89-1.33)	1.10 (0.90-1.34)	1.09 (0.89-1.33)	1.10 (0.90-1.34)	1.09 (0.89-1.34)
Proportion mediated	118,9%	58,0%	117,5%	49,3%	67,6%

OR: Odds ratio, CI: Confidence interval.
The models were adjusted by age, sex, educational level, tobacco consumption, and history of diabetes.

Table 3 show the mediation analysis results on the association between the presence of anterior tooth loss and self-reported depression or probable depression. The total effect of anterior tooth loss on depression was 1.12 (95% CI 0.95-1.32), considering self-reported, and 0.97 (95% CI 0.80-1.17) for probable depression. Concerning all five variables considered, a statistically significant indirect effect was found for the mediation between anterior tooth loss and depressive symptoms. Again, the greater indirect effect was observed for "feeling uncomfortable when speaking" (indirect effect of 1.07, 95% CI 1.04-1.10, PM=56,6%, self-report of depression) (indirect effect of 1.10, 95% CI 1.07-1.14, PM=-270,51%, CIDI SF) and "feeling uncomfortable when eating" (indirect effect of 1.08, 95% CI 1.05-1.11, PM= 64,3%, self-report of depression) (indirect effect of 1.10, 95% CI 1.06-1.13, PM= -291,58%, CIDI SF).

Table 3: Mediating Effect of Oral Function and Impairment of Orofacial Appearance in the Relationship between anterior tooth loss and depression (n=5,383).

Self-reported history of depression	**Do my teeth or prosthesis feel uncomfortable when speaking? OR (95% CI)**	**Do my teeth or prosthesis cause me pain and suffering? OR (95% CI)**	**Do my teeth or prosthesis feel uncomfortable when eating? OR (95% CI)**	**Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)? OR (95% CI)**	**Do my teeth or prosthesis interfere with my social relationships? OR (95% CI)**
Anterior Tooth Loss (reference: no)					
Direct effect	1.05 (0.89-1.24)	1.08 (0.91-1.27)	1.04 (0.88-1.23)	1.08 (0.91-1.27)	1.07 (0.91-1.26)
Indirect effect	1.07 (1.04-1.10)*	1.04 (1.02-1.06)*	1.08 (1.05-1.11)*	1.04 (1.02-1.06)*	1.05 (1.03-1.07)*
Total effect	1.12 (0.95-1.32)	1.12 (0.95-1.32)	1.12 (0.95-1.32)	1.12 (0.95-1.32)	1.12 (0.95-1.32)
Proportion mediated	56,6%	36,9%	64,3%	35,8%	42,7%
Probable Depression by CIDI Short Form					
Anterior Tooth Loss (reference: no)					
Direct effect	0.88 (0.72-1.06)	0.91 (0.76-1.10)	0.89 (0.73-1.07)	0.93 (0.77-1.12)	0.92 (0.76-1.11)
Indirect effect	1.10 (1.07-1.14)*	1.07 (1.04-1.09)*	1.10 (1.06-1.13)*	1.05 (1.03-1.08)*	1.06 (1.04-1.09)*
Total effect	0.97 (0.80-1.17)	0.97 (0.80-1.17)	0.97 (0.80-1.17)	0.97(0.80-1.17)	0.97 (0.80-1.17)
Proportion mediated	-270,5%	-248,2%	-291,6%	-205,2%	-208,1%

OR: Odds ratio, CI: Confidence interval
The models were adjusted by age, sex, educational level, tobacco consumption, and history of diabetes.

4. Discussion

In the present study, we found a mediator role in the impairment of oral functions in the association between tooth loss and depression. We also identified this role when analyzed anterior tooth loss as a risk factor for depression, verifying our initial hypothesis. Our results confirmed that a lower number of remaining teeth was associated with a higher risk of depression. The affectation of oral function significantly explained this association regarding feeling uncomfortable when speaking or eating, and with interferences of dental condition on pain and suffering, daily activities such as working or studying, or in social relationships of individuals. Also, feeling uncomfortable when speaking or eating achieved the greater mediated proportion.

Our results are consistent with previous studies where a lower number of remaining teeth was associated with a higher risk for onset or severity of depressive symptoms (6) (25) (26). Zhang *et al.* (2021) showed that having less than 20 teeth (nonfunctional dentition) or non-denture use were factors related to severe depressive symptoms (26). Most of these studies are limited to addressing the role of poorer oral health on older persons' mental health. This study contributes to the understanding of this phenomenon in a younger population as well as confirming previous findings in older people. Matsuyama *et al.* 2021, identified the causal effect of tooth loss on depression among U.S. adults in a natural experiment study using an instrumental analysis framework (7). They found that for each additional tooth loss, depressive symptoms score increased by 0.146 (95% CI 0.01-0.28) (7). A cross-sectional study of Indian adults concluded that edentulism negatively affected psychological and subjective well-being among older adults (27). Our results agreed with Kusama et al. (2021), because they found that difficulty in speaking, smiling, or chewing among community-dwelling older adults were a mediator in the association between tooth loss and depression (15). Having difficulty in chewing showed a greater mediation effect (indirect effect of 1.05, 95% CI 1.02-1.09, PM=21,9%), like our study (15). They suggested incorporating other mediators, such as discomfort or pain, for additional explanations of the proposed mechanism, which is partially considered in our analysis (15).

Previously published evidence supported that tooth loss deteriorates oral functions (28). Having fewer teeth alters the functional capacity of individuals and negatively affects the quality of life (28). It has been reported that the oral health aspect which has the highest impact on daily life is chewing capacity (29). Tooth loss also leads to diet modification due to decreased functional chewing units, which has repercussions at the level of the oral cavity and systemic level due to changes in dietary patterns (30). Beyond that, previous meta-analyses verified that nutritional habits affect the risk of depression (31) (32). Thus, a reduced chewing capacity may become difficult eating with other individuals, declining social interaction, and increasing feelings of isolation, which is directly related to a higher risk of depression (1).

In the present study, together with difficulty in eating, the other situation with the highest mediation proportion between tooth loss and depression was discomfort when speaking. These findings could be related to the role of anterior teeth in the emission of phonemes and the capacity to pronounce words correctly (33). The diminution of communication may affect social relationships and thus elevate the risk of depression, as previously mentioned by Kusama *et al.* (2021) (15). Tan *et al.* (2016) found that more missing anterior teeth are associated with low satisfaction levels and reduced oral health-related quality of life due to aesthetic problems (30). Aesthetic consequences of tooth loss cause lower self-esteem, lowered self-confidence, avoidance of laughing in public, and even social isolation (28), all conditions likely to increase the risk of depression.

Beyond discomfort when talking or eating as a mechanism in the association between fewer teeth and depression, we found that other consequences of tooth loss, such as pain and suffering, and interference in daily activities or social relationships, also mediated significantly. Previous studies have shown an association between poor oral health and lower social activities in older adults (13) (34). Ohara *et al.* (2020) found a significant association between eating alone and oral frailty in a general population of older Japanese adults (34). A recent study among Chilean 80-year-old individuals, concluded that a functional dentition was associated with higher social participation frequency (35).

The findings of our study highlight the relevance of the social functions of oral health on mental health beyond biological or inflammatory pathways. Future studies are required to understand the interactions of mechanisms in the association between tooth loss with depression. Also, clinical studies are necessary to verify the impact of oral interventions on mental health outcomes and psychological diseases. In a recent review based on clinical trials published between 2017 and 2021, the authors concluded that no significant evidence supports the impact of oral health interventions on mental health, which is inconsistent with the observational evidence in favor of the causal role of poorer oral health in mental health (36).

One limitation of our study is the transversal design which does not allow verification causality, so the inferences should be cautiously made. Also, reverse causality could appear since studies have demonstrated that depression affects oral health by lifestyle changes, poorer oral hygiene, and difficulties in accessing dental care (37). Okoro *et al.* (2012) found that the adjusted odds of being in the "1-5 teeth removed" or "6-31 teeth removed" categories versus "0 teeth removed" was increased for adults with lifetime diagnosed depression (38). A recent study in Brazil considering the National Health Survey (2013/2019) concluded that depression was statistically significant for tooth loss in all age groups, except for those aged 65 years and over (39). Finally, in relation to exposure – mediator direction, in our study it is less likely that the deterioration of oral functions leads to tooth loss. Another limitation is that the five questions employed for the mediation analysis included the terms "teeth" and "prosthesis" simultaneously. Therefore, it is challenging to discriminate how much of the response is associated with only teeth. In addition, we used a non-validated cut-off for those questions, which may lead to a bias toward null association, but we confirmed a clear association. Reporting the number of remaining teeth instead of the number of occluding pairs can also be considered a limitation. Anterior tooth loss was measured only as a binary variable without considering the number or type of anterior missing teeth. Losing upper anterior teeth may have different consequences compared to missing lower anterior teeth regarding oral functions such as speaking, given the role of the upper incisors in phonetics.

In relation to residual confounding, it would likely affect our conclusions, given the complexity of the association.

Our study has strengths related to the use of a representative sample of the Chilean population, participation of young adults, and that is one of the first studies in Chile to address the association between tooth loss and depression. Also, this study has important implications for the design of new national health programs considering oral and mental health disorders at the same time, currently limited in most of the countries worldwide. In future health surveys in Chile, the clinical examination should be performed by dentists instead of nurses, an assessment considered the gold standard in dentistry. Finally, other mediators and indirect pathways should be included in epidemiological models further to elucidate the role of tooth loss in depression.

5. Conclusions

Deterioration of oral functions had a mediator role in the association between tooth loss and depression. Difficulties regarding speaking or eating, interferences of teeth on pain and suffering, daily activities, and social relationships significatively mediated in that association. The greater effect was observed in feeling uncomfortable when speaking or eating. The role of oral functions should be more considered in interventions to improve oral and mental health. In addition, trying to provide scientific mechanisms for this route of association, we observed that oral functional impairment, mainly speech or eating problems attributable to tooth loss, had a mediating role in triggering depression.

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Supplementary materials

Table S1: Mediating Effect of Oral Function and Impairment of Orofacial Appearance in the Relationship between the number of remaining teeth and Self-reported history of Depression, by sex (n=5.383).

Women	Do my teeth or prosthesis feel uncomfortable when speaking? OR (95% CI)	Do my teeth or prosthesis cause me pain and suffering? OR (95% CI)	Do my teeth or prosthesis feel uncomfortable when eating? OR (95% CI)	Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)? OR (95% CI)	Do my teeth or prosthesis interfere with my social relationships? OR (95% CI)
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	1.19 (0.97-1.44)	1.24 (1.02-1.51)*	1.18 (0.97-1.43)	1.23 (1.01-1.50)*	1.21 (0.99-1.47)
Indirect effect	1.07 (1.04-1.11)*	1.03 (1.01-1.05)*	1.08 (1.04-1.11)*	1.03 (1.01-1.05)*	1.05 (1.02-1.08)*
Total effect	1.27 (1.05-1.54)*	1.27 (1.05-1.55)*	1.27 (1.04-1.54)*	1.27 (1.05-1.54)*	1.27 (1.05-1.54)*
Proportion mediated	28.48%	10.67%	31.22%	13.22%	20.95%
Men					
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	0.93 (0.61-1.40)	0.91 (0.61-1.37)	0.88 (0.59-1.33)	0.89 (0.59-1.35)	0.93 (0.62-1.40)
Indirect effect	1.04 (0.96-1.12)	1.05 (0.99-1.10)	1.08 (1.01-1.15)*	1.06 (1.01-1.13)*	1.03 (0.98-1.09)
Total effect	0.96 (0.64-1.44)	0.96 (0.64-1.43)	0.95 (0.64-1.43)	0.95 (0.63-1.42)	0.96 (0.64-1.44)
Proportion mediated	-85.24%	-108.85%	-157.48%	-122.14%	-76.23%

OR: Odds ratio, CI: Confidence interval.
The models were adjusted by age, sex, educational level, tobacco consumption, and history of diabetes.

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Table S2: Mediating Effect of Oral Function and Impairment of Orofacial Appearance in the Relationship between the number of remaining teeth and Probable Depression by CIDI Short Form, by sex (n=5.383).

Women	Do my teeth or prosthesis feel uncomfortable when speaking? OR (95% CI)	Do my teeth or prosthesis cause me pain and suffering? OR (95% CI)	Do my teeth or prosthesis feel uncomfortable when eating? OR (95% CI)	Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)? OR (95% CI)	Do my teeth or prosthesis interfere with my social relationships? OR (95% CI)
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	0.97 (0.77-1.23)	1.04 (0.83-1.32)	0.98 (0.78-1.24)	1.04 (0.83-1.32)	1.01 (0.80-1.28)
Indirect effect	1.10 (1.06-1.15)*	1.04 (1.01-1.07)*	1.09 (1.05-1.13)*	1.04 (1.01-1.07)*	1.07 (1.03-1.10)*
Total effect	1.07 (0.85-1.35)	1.08 (0.86-1.37)	1.07 (0.85-1.35)	1.09 (0.86-1.37)	1.08 (0.85-1.36)
Proportion mediated	140.53%	45.43%	122.87%	48.69%	85.37%
Men					
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	1.03 (0.68-1.56)	1.03 (0.68-1.54)	0.98 (0.65-1.49)	1.07 (0.71-1.61)	1.10 (0.74-1.65)
Indirect effect	1.08 (1.01-1.17)*	1.09 (1.03-1.15)*	1.13 (1.05-1.21)*	1.05 (0.99-1.12)	1.03 (0.97-1.09)
Total effect	1.12 (0.75-1.67)	1.11 (0.75-1.66)	1.11 (0.74-1.66)	1.13 (0.75-1.68)	1.13 (0.76-1.69)
Proportion mediated	70.68%	77.06%	115.34%	43.06%	20.82%

OR: Odds ratio, CI: Confidence interval.
The models were adjusted by age, sex, educational level, tobacco consumption, and history of diabetes.

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Table S3: Mediating Effect of Oral Function and Impairment of Orofacial Appearance in the Relationship between the number of remaining teeth and Self-reported history of Depression, by age (n=5.383).

≤64 years	Do my teeth or prosthesis feel uncomfortable when speaking? OR (95% CI)	Do my teeth or prosthesis cause me pain and suffering? OR (95% CI)	Do my teeth or prosthesis feel uncomfortable when eating? OR (95% CI)	Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)? OR (95% CI)	Do my teeth or prosthesis interfere with my social relationships? OR (95% CI)
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	1.28 (1.05-1.56)*	1.31 (1.08-1.59)*	1.25 (1.03-1.52)*	1.31 (1.08-1.59)*	1.29 (1.06-1.57)*
Indirect effect	1.06 (1.02-1.10)*	1.05 (1.02-1.07)*	1.09 (1.05-1.13)*	1.04 (1.01-1.07)*	1.05 (1.02-1.08)*
Total effect	1.36 (1.12-1.65)*	1.37 (1.13-1.66)*	1.36 (1.12-1.65)*	1.36 (1.12-1.65)*	1.36 (1.12-1.65)*
Proportion mediated	19.26%	14.38%	27.87%	13.55%	17.25%
≥65 years					
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	0.69 (0.47-0.99)*	0.72 (0.50-1.04)	0.70 (0.48-1.01)	0.70 (0.49-1.02)	0.70 (0.48-1.01)
Indirect effect	1.06 (1.01-1.10)*	1.01 (0.99-1.03)	1.05 (1.01-1.10)*	1.03 (0.99-1.07)	1.04 (1.01-1.07)*
Total effect	0.73 (0.50-1.05)	0.73 (0.50-1.05)	0.73 (0.51-1.06)	0.73 (0.50-1.05)	0.72 (0.50-1.04)
Proportion mediated	-17.12%	-3.14%	-14.83%	-9.58%	-10.71%

OR: Odds ratio, CI: Confidence interval.
The models were adjusted by age, sex, educational level, tobacco consumption, and history of diabetes.

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Table 4S: Mediating Effect of Oral Function and Impairment of Orofacial Appearance in the Relationship between the number of remaining teeth and Probable Depression by CIDI Short Form, by age (n=5.383).

≤64 years	Do my teeth or prosthesis feel uncomfortable when speaking? OR (95% CI)	Do my teeth or prosthesis cause me pain and suffering? OR (95% CI)	Do my teeth or prosthesis feel uncomfortable when eating? OR (95% CI)	Do my teeth or prosthesis interfere with my daily activities (e.g., work, study, housework)? OR (95% CI)	Do my teeth or prosthesis interfere with my social relationships? OR (95% CI)
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	0.97 (0.78-1.21)	1.02 (0.82-1.27)	0.95 (0.76-1.19)	1.03 (0.82-1.28)	0.99 (0.80-1.25)
Indirect effect	1.12 (1.07-1.17)*	1.07 (1.04-1.11)*	1.14 (1.09-1.19)*	1.07 (1.03-1.10)*	1.08 (1.05-1.12)*
Total effect	1.08 (0.87-1.35)	1.10 (0.88-1.36)	1.08 (0.87-1.35)	1.09 (0.88-1.36)	1.08 (0.87-1.35)
Proportion mediated	137.65%	75.06%	164.36%	71.26%	100.04%
≥65 years					
Number of Remaining teeth ≤19 (ref: ≥20 teeth)					
Direct effect	1.08 (0.62-1.87)	1.14 (0.66-1.97)	1.12 (0.65-1.93)	1.14 (0.66-1.97)	1.14 (0.66-1.98)
Indirect effect	1.06 (1.01-1.11)*	1.01 (0.98-1.04)	1.02 (0.99-1.06)	1.01 (0.96-1.04)	0.99 (0.96-1.04)
Total effect	1.14 (0.66-1.98)	1.15 (0.67-1.99)	1.14 (0.66-1.98)	1.14 (0.66-1.97)	1.14 (0.66-1.97)
Proportion mediated	42.01%	8.78%	17.17%	0.23%	-2.65%

OR: Odds ratio, CI: Confidence interval.
The models were adjusted by age, sex, educational level, tobacco consumption, and history of diabetes.

12- Manuscript 3: "Association between oral health and depression: data from the National Health Survey 2016-2017"

Abstract

Objective: To evaluate the relationship between oral health status, self-perception of oral health, and depression.

Methods: This cross-sectional study included 2953 individuals that were ≥18 years of age and participated in the third Chilean National Health Survey (NHS 2016-2017). Information on oral, dental, and mental health, and the presence or absence of depressive symptoms was collected. Secondary data analysis was carried out using STATA and included logistic regression models adjusted for age, sex, educational level, and tobacco consumption.

Results: Participants experiencing dental or prosthesis-related discomfort while eating (odds ratios (OR): 1.58; 95% confidence intervals (CI): 0.99–2.54) or speaking (OR: 1.57; 95% CI: 1.01–2.43) were at a higher risk of probable depression compared to those who did not experience these difficulties. The odds (OR: 1.18; 95% CI: 0.65–2.16) of having been diagnosed with depression in the past 12 months were also higher among participants experiencing frequent dental or prosthesis-related discomfort. Removable upper denture users were at a higher risk of exhibiting probable depression (OR: 2.04; 95% CI: 1.11–3.74) compared to those that did not use them. Participants diagnosed with depression in the past 12 months had a slightly lower number of teeth (median=24) compared to those without depression (median=25), although this difference was not statistically significant (OR: 0.99; 95% CI: 0.96–1.02).

Conclusion: Experiencing dental or prosthesis-related difficulties in eating, speaking, and social interactions was associated with an increased risk of probable depression or a diagnosis of depression. These findings highlight the importance of developing comprehensive healthcare approaches that consider mental health in the context of oral health.

1. Background

In 2019, approximately 970 million people were diagnosed with a mental health disorder (1). The most common diagnoses were anxiety disorders, affecting 4% of the population, followed by depressive disorders (1). Neuropsychiatric conditions constitute a significant proportion of the disease burden in Chile, accounting for approximately 23.2% of years of healthy life lost due to disability (YLDs) (2). Despite rapid progresses in research and access to mental health services, the prevalence of substance abuse and anxiety disorders remain relatively high in the Chilean population (3). A recent longitudinal study conducted in Chile found that approximately 22.6% and 27.0% of study participants reported moderate to severe anxiety and depressive symptoms in the first and second waves of the COVID-19 pandemic, respectively, suggesting that the levels of mental distress increased between these two time periods (4).

On the other hand, according to the 2019 Global Burden of Diseases report, approximately 3.5 billion people globally live with untreated oral diseases including dental caries, severe periodontal diseases, tooth loss, and edentulism. Oral diseases also rank first and third in terms of prevalence and incidence, respectively, and are the tenth most common cause of moderate disability (5). Similar trends have also been observed in Chile, with the prevalence of oral diseases such as dental caries and periodontal diseases being high in the population (6).

Evidence suggests that individuals diagnosed with mental health disorders are at a higher risk of developing comorbidities due to difficulties associated with seeking and adhering to appropriate treatment plans (7). Depression is an important risk factor for many systemic conditions including obesity and sleeping disorders. It also plays a significant role in oral health through various biological and behavioral mechanisms, with adoption of risky behaviors such as frequent alcohol consumption, smoking, high fat and sugar intake, and sedentary lifestyles having a negative effect on the patient's oral health status. Furthermore, the patient's self-perception of oral health and their frequency of attendance at a dental clinic may also be affected. Previous studies have also reported potential biological mechanisms

including an association between depression and reduced salivary flow, xerostomia, and dysregulation of the immune system and salivary immunity. These, in turn, increase the risk of developing oral diseases such as dental caries and periodontal diseases. As a result, individuals diagnosed with depression typically tend to exhibit a higher prevalence of caries, loss of teeth, and edentulousness (8). At the same time, poor oral health could be related with higher risk of onset and severity of depression in adults. Few studies have evaluated the relationship between the oral health status, self-perception of oral health, and depression. We aimed to address this gap in knowledge using data from the Chilean National Health Survey (NHS 2016-2017).

2. Methods

This cross-sectional study used data from the third Chilean NHS 2016-2017; (Department of Epidemiology, Ministry of Health, Chile); which collected information about 72 health problems (6). The study sample was representative of the Chilean population over 15 years and included men and women from both rural and urban parts of the country. Pregnant women and individuals who refused to participate in the survey during the home visit were excluded. The survey was carried out using a complex multi-stage clustered, stratified, randomized oversampling technique, and had overall response and rejection rates of 67% and 9.8%, respectively. Data collection included home interviews carried out between August 2016 and March 2017 by interviewers and previously calibrated nurses (kappa: 0.85, p-value < 0,01).

The survey had 6233 respondents, of which 5520 underwent oral examination. The first, second, and third visits included interviews (Form F1); anthropometric measurement and testing (including oral examination) carried out by a trained nurse (Form 2); and application of an expanded mental health section to a sub-sample of participants by a trained interviewer (Form F3), respectively. The oral examination (Form F2) included evaluation of the following items: total number of remaining teeth (both jaws); absence of anterior teeth (yes/no); the total number of teeth with cavitated carious lesions (both jaws); and effective resolution of anterior edentulousness using removable dentures (yes/no; both jaws).

In form F3, selected sub-sections (screening of mental problems, depression, social phobia, agoraphobia, alcohol abuse and dependence, suicidality, mania, psychosis, and use of mental health services) of the Composite International Diagnostic Interview (CIDI), a mental health diagnostic tool developed by the World Health Organization, were applied to a sub-sample of participants (n = 3403) that were ≥18 years of age by a trained interviewer (9). Older adults that exhibited cognitive impairment during the first visit were excluded.

The final study sample included 2953 survey participants that were ≥18 years of age. The exclusion criteria were as follows: missing data on the oral health item of interest; failure to undergo oral examination; missing data on the extended mental health section (CIDI); and missing data in the depressive symptoms section. Probable depression was determined using an abbreviated version of the CIDI instrument (CIDI Short form; CIDI-SF) containing 31 questions focusing on the presence of dysphoria (sadness symptoms) and anhedonia (lack of interest or ability to enjoy), and a depression risk score was calculated if the patient met at least five out of seven complementary criteria (Diagnostic and Statistical Manual of Mental Disorders or DSM-IV minor criteria for depression).

The participants were diagnosed with depression (as per the CIDI-DSM IV criteria) if they exhibited [1] depressed mood and [2] reduction or loss of interest or pleasure for at least 2 weeks and met ≥3 of the following criteria: [1] significant increase or decrease in appetite resulting in substantial changes in weight; [2] suicidal ideation; [3] significant sleep disturbances; [4] psychomotor agitation or motor slow-down; [5] fatigue or loss of energy; [6] feelings of worthlessness or guilt; and [7] decreased concentration. Of these, the last five symptoms must have been experienced all day or almost every day for at least two weeks to be considered in the score. Furthermore, these symptoms must have caused clinically significant discomfort and impairment of social, occupational, and other important aspects of the individual's life. Therefore, a diagnosis of depression was made if the participant met at least five criteria. Participants with symptoms caused by substance abuse, drugs, medications, and grief or loss of a loved one were excluded.

The independent variables included use of dental prosthesis; number of remaining teeth (both jaws); anterior tooth loss; number of decayed teeth; and self-perception of oral health (Table 1) measured through one general question (GQ) and five specific questions (SQ), while the dependent variables were probable depression and diagnosis of depression in the last 12 months. The analysis models were adjusted for age, level of education, sex, and tobacco consumption.

Table 1. Chilean National Health Survey, 2016-2017: Self-perception of oral health.

Code	Question	Five-point ordinal scale
GQ	How would you rate your overall oral health?	0 = very poor, 1 = poor, 2 = neutral, 3 = good, 4 = excellent
SQ1	Do your teeth or prostheses cause discomfort when speaking?	0 = never, 1 = rarely, 2 = sometimes, 3 = very often, 4 = always
SQ2	Do your teeth or prostheses cause pain and suffering?	
SQ3	Do your teeth or prostheses cause discomfort when eating?	
SQ4	Do your teeth or prostheses interfere with your daily activities (e.g., work, study, housework)?	
SQ5	Do your teeth or prostheses interfere with your social relationships?	

GQ: general question; NHS SQ: NHS-specific question

Descriptive statistics, including proportions for categorical variables and mean and standard deviations for numerical variables, were generated. Logistic regression models were used to estimate OR and 95% CI. Relationship matrixes (heat plots) were used to examine the association between the variables and outcome measures. The models examining the

association between probable depression and self-perception of oral health were adjusted for sex, level of education, and age, while those exploring the relationship between prosthesis use and the number of remaining teeth were adjusted for the same factors as well as tobacco use. Potential confounding factors considered when examining a diagnosis of depression in the past 12 months as an outcome measure included sex, tobacco, and education, generating open backdoor paths if they do not condition them. The analysis carried out in this study respected the complex sampling method and the expansion factors used, which is represented in the results through frequencies and expanded sample sizes. All analyses were performed using the statistical software STATA version 16.1 (Windows; STATA Corp. 2019. College Station, TX: StataCorp LLC.).

The NHS 2016-2017 survey was approved by the Scientific Ethics Committee, Faculty of Medicine, Pontificia Universidad Católica de Chile, and informed consent was obtained from all participants. An anonymized version of the database of volunteers has been made available for use for research purposes on the Chilean Ministry of Health website.

3. Results

The study sample included 2953 individuals who participated in the Chilean NHS 2016-2017. Table 2 summarizes individuals characteristics by the presence of probable or diagnosed depression. Approximately 25% of women and 10.53% of men exhibited probable depression, while 9.84% of women and 2.39% of men had been diagnosed with depression in the past 12 months. Furthermore, the prevalence of a diagnosis of depression in the past 12 months was higher among individuals with higher levels of education (i.e., ≥13 years of schooling; 7.26%). Individuals exhibiting probable depression had a similar mean number of teeth (n=25) while those diagnosed with depression in the past 12 months exhibited a slightly lower mean number of teeth (n= 24) compared to those without depression.

Table 2. Patient demographics by presence of probable depression or a diagnosis of depression in the past 12 months (n = 2953).

Variable	Probable depression			Diagnosis of depression in the past 12 months		
	No	Yes	p-value	No	Yes	p-value
Age (years)	43 (30)	44 (25)	0.1306	43 (28)	48 (26)	0.9284
Sex						
Female	75.00%	25.00%	<0.0001	90.16%	9.84%	<0.0001
Male	89.47%	10.53%		97.61%	2.39%	
Educational level (years)						
Less than 8	85.73%	14.27%	0.4954	92.74%	7.26%	0.3337
8 to 12	81.84%	18.16%		93.29%	6.71%	
13 or more	81.00%	19.00%		95.83%	4.17%	
Zone						
Rural	82.52%	17.48%	0.9529	92.84%	7.16%	0.5932
Urban	82.30%	17.70%		94.07%	5.93%	
Smoking						
No	83.80%	16.20%	0.1360	94.64%	5.36%	0.2382
Yes	79.11%	20.89%		92.39%	7.61%	
How would you rate your overall oral health?						
Very good/good	84.06%	15.94%	0.2853	94.47%	5.53%	0.5740
Regular/Bad/Very bad	80.86%	19.14%		93.47%	6.53%	
Do your teeth or prostheses cause discomfort when speaking?						
Never/almost never/sometimes	83.34%	16.66%	0.0398	94.27%	5.73%	0.1671
Almost always/always	75.30%	24.70%		91.60%	8.40%	
Do your teeth or prostheses cause pain and suffering?						
Never/almost never/sometimes	83.27%	16.73%	0.1547	94.69%	5.31%	0.0838
Almost always/always	78.43%	21.57%		90.8%	9.20%	
Do your teeth or prostheses cause discomfort when eating?						
Never/almost never/sometimes	83.59%	16.41%	0.0343	94.62%	5.38%	0.0764
Almost always/always	76.24%	23.76%		90.64%	9.36%	
Do your teeth or prostheses interfere with your daily activities (e.g., work, study, housework)?						
Never/almost never/sometimes	83.00%	17.00%	0.0910	93.98%	6.03%	0.7977
Almost always/always	74.71%	25.29%		93.46%	6.54%	
Do your teeth or prostheses interfere with your social relationships?						
Never/almost never/sometimes	83.15%	16.85%	0.0438	94.15%	5.85%	0.2499
Almost always/always	73.98%	26.02%		91.72%	8.28%	

Number of teeth	25 (9)	25 (9)	0.7776	25 (9)	24 (10)	0.4825
Number of teeth with cavitated caries	1 (2)	1 (2)	0.4336	1 (2)	1 (2)	
Loss of at least one anterior tooth						
No	83.25%	16.75%	0.3599	94.68%	5.32%	0.2301
Yes	80.49%	19.51%		92.43%	7.57%	
Denture use						
No	83.34%	16.66%	0.2273	95.18%	4.82%	0.0158
Upper	74.12%	25.88%	0.0360	87.79%	12.21%	0.0148
Lower	89.22%	10.78%		92.90%	7.10%	
Upper and lower	86.84%	13.16%		93.75%	6.25%	

Data shown as frequencies expanded (percentages) or medians (interquartile range).

Figure 1 shows the association between oral health and self-perception of oral health variables, with the risk of exhibiting probable depression or a diagnosis of depression in the last 12 months. Adjustments were made based on the DAG evaluation, and the relationship matrix has been shown in Figure 2. The findings showed that patients experiencing difficulties while eating due to dental or prosthesis-related issues were at a higher risk of exhibiting probable depression (OR: 1.57; 95 CI%: 1.01–2.43) compared to those who did not experience these difficulties. Patients experiencing frequent discomfort while speaking due to dental or prosthesis-related issues were also at a higher risk of exhibiting probable depression (OR: 1.58; 95% CI: 0.99–2.54) or a diagnosis of depression in the last 12 months (OR: 1.18; 95% CI: 0.65–2.16) compared to those who did not experience this discomfort. In addition, patients who reported that their teeth or dentures frequently interfered with their social relationships were at a higher risk of exhibiting probable depression (OR: 1.64; 95% CI: 0.96–2.82) compared to those who did not experience this interference. Removable upper denture users were also at a higher risk of exhibiting probable depression (OR: 2.04; 95% CI: 1.11–3.74) or a diagnosis of depression in the past 12 months when compared to those who did not use prostheses.

Figure 1. Association between self-perceived oral health, oral health status and depression. *Logistic regression models. CI: confidence intervals.

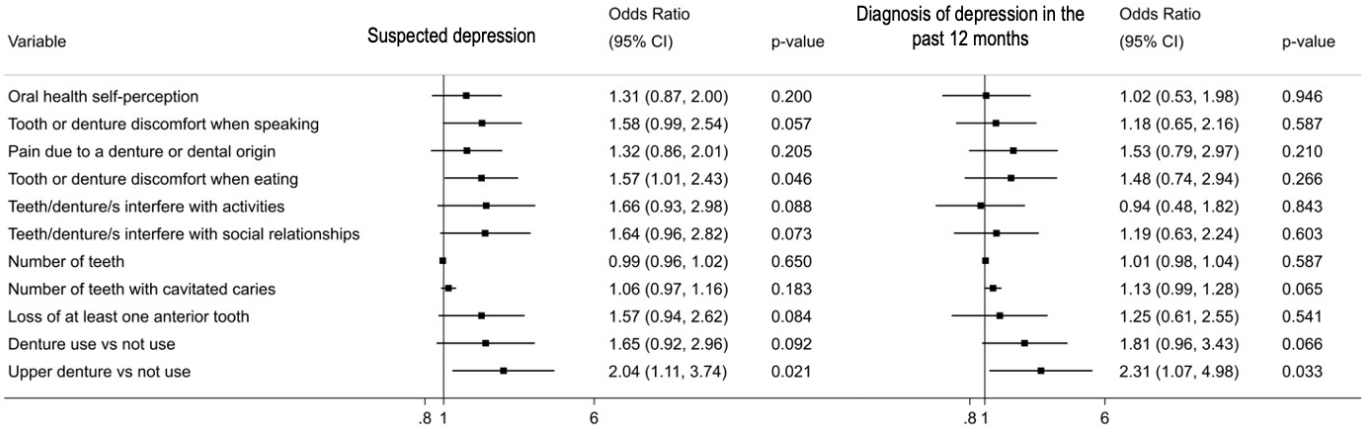
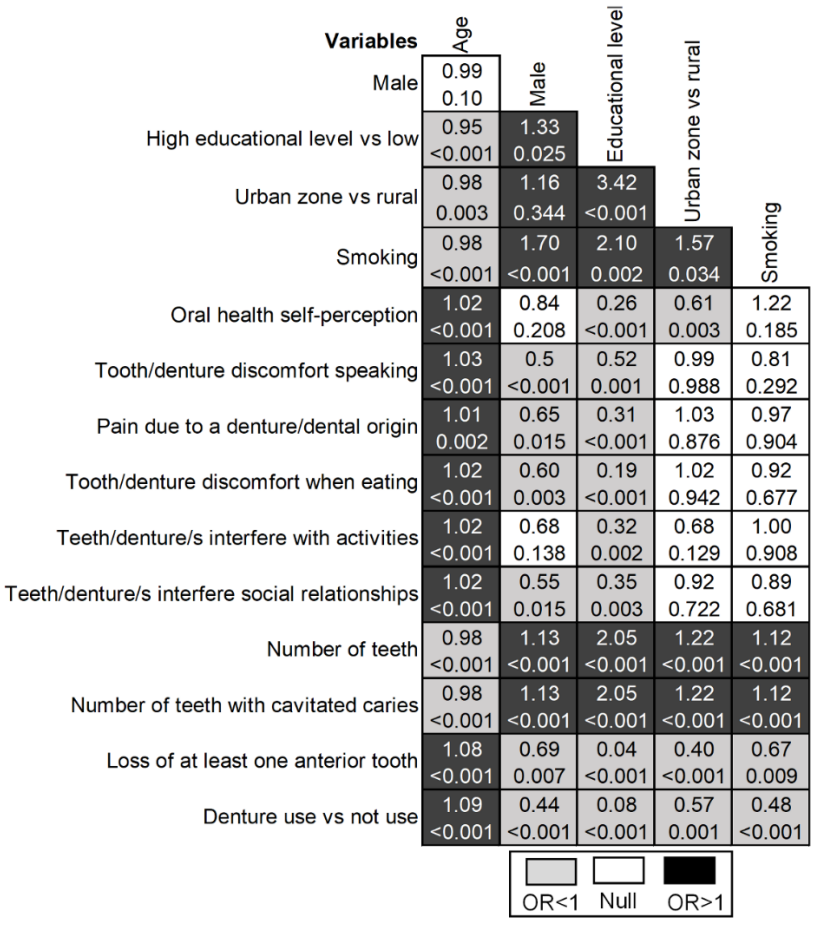


Figure 2. Association between variables for identifying factors that contribute to confusion.



4. Discussion

The current study observed an increased risk of probable depression or a diagnosis of depression among individuals experiencing dental or prosthesis-related difficulties in eating, speaking, and social interactions. Furthermore, participants using removable upper dentures also exhibited a higher risk of probable depression or a diagnosis of depression in the past 12 months.

The association between the number of remaining teeth and depression was weaker. This contrasted with previous studies that reported observing a significant and strong association between tooth loss and depression, with individuals with fewer remaining teeth being more likely to experience depression. For example, a longitudinal study in the Japanese population found that older adults with fewer teeth were at an increased risk of being diagnosed with depression, potentially due to changes in self-esteem and social support (10). Another study found that older adults with a higher number of missing teeth were at an greater risk of exhibiting depressive symptoms (11), while Matsuyama et al. (12) showed that losing even one tooth increased the risk of exhibiting depressive symptoms or being diagnosed with major depression. It has been suggested that social factors and oral health mediated this association, with declines in oral function and appearance playing a significant role (13).

When considered self-perception of oral health as variables in relation to depression or depressive symptoms, our association was still present but weak and not statistically significant. About this, Kim et al. (14) concluded that the incidence of depression was higher among individuals who evaluated their oral health using terms such as "poor" or "bad". Barbosa et al. (15) observed significantly higher risk of developing depression among individuals with negative self-perceptions of their oral health when compared to those with more positive perceptions (OR: 1.55; 95% CI: 1.05–2.28).

The current study also found that frequent dental or prosthesis-related discomfort while speaking or eating was associated with a higher risk of probable depression or a diagnosis of depression in the past 12 months. Park et al. (16) evaluated data from the Korean National Health and Nutrition Examination Survey and found that participants experiencing greater discomfort while eating exhibited a higher risk of depressive symptoms (OR: 1.25; 95% CI: 1.05–1.50) compared to those that did not experience such discomfort. Mariño et al. (17) using data from the Melbourne Longitudinal Study on Healthy Aging, found that older Australian adults experiencing oral or dental-related difficulties in eating exhibited significantly higher risk of depressive symptoms (p-value < 0.001) compared to those that did not experience these difficulties. Also, Kim et al. (14) showed that greater discomfort while chewing or eating was significantly associated with stress, depression, and suicidal ideation. However, discomfort while speaking was only associated with stress but not depression.

Previous studies have also examined the association between denture use and depression. Seenivasan et al. (18) demonstrated that older adults with dentures were more likely to experience depression. Jang (19) compared patients who did and did not use removable dentures and found that the prevalence of depression was 1.07 times higher (p-value < 0.001) in the former group. This could potentially be attributed to emotional and psychological alterations as a consequence of loss of teeth or an inability to adapt to the changes associated with the use of removable prostheses (20). Tooth loss can trigger depression in vulnerable individuals in particular, and the level of satisfaction with removable prostheses is often determined by certain personality traits (21,22).

Poor oral health has been shown to be associated with systemic diseases such as depression, with previous studies proposing various underlying biological mechanisms. Oral health problems, particularly those that cause pain, can lead to poor quality of life, stress, anxiety, and depression (23). Chronic inflammation caused by oral infections, such as periodontitis can also cause alterations in hormonal and neurotransmitter levels in the brain, leading to depression (24). Finally, poor oral health and tooth loss are often associated with unhealthy

dietary habits, reduced nutritional intake, and difficulties while eating, which increases the risk of various mental disorders (25).

This study has several limitations. First, the cross-sectional study design prevented elucidation of causality, with reverse causation remaining a possibility. Second, the study primarily included secondary data analysis which may have affected the results as the data was not collected specifically for this purpose. Third, the oral health examinations were carried out by nurses instead of dentists; however, provision of appropriate training and subsequent calibration ensured high levels of agreement inter-examiners, as evidenced in the pilot studies (kappa: 0.85, p-value < 0.01) (26). Fourthly, the CIDI-SF instrument does not rule out the possibility of false positives such as chronic diseases, other psychiatric diagnoses including dysthymia, bipolar disorder, or substance abuse. Finally, most oral health variables included in this study were self-reported. Future studies may consider examining the relationship between oral health and depression considering other methods like salivary biomarkers analysis. The key strength of this study was the use of a large study sample that was representative of the Chilean population, ensuring external validity, generalizability, higher statistical power, and reliability of the findings. Finally, the good replicability demonstrated reinforces the robustness of its findings.

5. Conclusion

The findings of this study suggest that poor oral health and a negative self-perception of oral health in adults may be associated with an increased risk of depression. However, further research is necessary to elucidate the direction of this association, understand the underlying mechanisms involved, and develop effective interventions that adopt a comorbid approach toward improving oral and mental health outcomes.

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Supplementary material

Supplementary table. Adjusted generalized linear regression model (GLM) showing the relationship (Prevalence ratio) between self-perceived oral health, oral health status, probable depression, and a diagnosis of depression in the past 12 months and sensitivity analyses comparing with odds ratio from logistic regression model.

Variable	Outcome									
	Probable depression					Diagnosis of depression in the past 12 months				
	PR	LB	UB	p-value	Comparison p-value	PR	LB	UB	p-value	Comparison p-value
Oral health self-perception	1.25	0.9	1.73	0.189	0.2861	1.02	0.56	1.88	0.939	0.9498
Tooth or denture discomfort when speaking	1.47	1.03	2.1	0.036	0.2282	1.16	0.68	1.97	0.596	0.5556
Pain due to a denture or dental origin	1.23	0.89	1.71	0.204	0.2473	1.46	0.81	2.63	0.205	0.2856
Tooth or denture discomfort when eating	1.43	1.03	1.99	0.034	0.1377	1.42	0.78	2.61	0.253	0.3982
Teeth/denture/s interfere with activities	1.49	0.96	2.31	0.073	0.2156	0.94	0.52	1.72	0.850	0.8015
Teeth/denture/s interfere with social relationships	1.48	0.98	2.23	0.061	0.1954	1.16	0.66	2.05	0.602	0.6440
Number of teeth	0.99	0.97	1.02	0.597	0.8597	1.01	0.98	1.03	0.547	0.8968
Number of teeth with cavitated caries	1.04	0.99	1.11	0.145	0.3120	1.10	1.01	1.2	0.030	0.2604
Loss of at least one anterior tooth	1.44	0.99	2.11	0.060	0.2672	1.22	0.64	2.32	0.546	0.5227
Denture use vs does not use	1.55	0.97	2.47	0.065	0.3809	1.67	0.95	2.94	0.073	0.0672
Upper denture vs does not use	1.72	1.09	2.7	0.020	0.1920	1.99	1.05	3.78	0.035	0.0623

PR: Prevalence ratio; LB and UP: Lower and upper bound 95% confidence interval; p-value: GLM model; Comparison p-value: adjusted Wald test