

Oral Health Status and Cardinal Symptoms of Depression in the Old Order Amish: a cross-sectional study

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Abstract

Background

Although results have been mixed, possibly owing to high confounding heterogeneity within and across studies, multiple efforts suggest that tooth loss and periodontitis are associated with depression.

Methods

We analyzed questionnaires on dental health and depression obtained as a component of a Wellness study in 4,288 Old Order Amish (mean age = 43.5 ± 16.8 years; 57% women), a population with relatively high genetic and lifestyle homogeneity. Specifically, we obtained questionnaires reporting the use of removable partial/complete dentures (false teeth) and cardinal symptoms of depression (dysphoria/hopelessness and anhedonia), and we analyzed their associations using multivariable logistic regression, with adjustment for age, sex, smoking status, and occupation (farmer vs. non-farmer).

Results

We report statistically significant associations between dentures and current (but not “ever”) depression symptom ratings ($p < 0.05$). The most robust associations were between current anhedonia AND dysphoria/hopelessness and the presence of any dentures (versus no dentures) (OR 1.760 [1.131, 2.737], $p = 0.012$), and the presence of complete dentures (versus partial or no dentures) (OR 1.794 [1.008, 3.193], $p = 0.047$).

Conclusions

In this relatively homogeneous population, denture use—particularly complete dentures—was associated with current anhedonia and dysphoria/hopelessness. A primary strength of the study is its relatively homogeneous population, with a low prevalence of smoking—an important confounding factor—and limited access to both prophylactic dental care and fluoridated water, which collectively enhance the reliability of the findings. Limitations include the cross-sectional design and reliance on self-reported data. These findings warrant replication in future longitudinal studies incorporating dental and clinical examinations, imaging, and laboratory biomarkers.

1. Introduction

Periodontal diseases are the most common dental plaque-induced inflammatory conditions localized to the gingiva or extending to the supporting structures of the teeth. Reversible inflammation of the gingiva without evidence of breakdown of the periodontium is characteristic of gingivitis [1–3] and, if untreated,

can progress to periodontitis [4]. The hallmark of periodontitis is the irreversible breakdown of the connective tissue attachment to the root of the tooth and resorption of the alveolar bone, both primarily attributable to the immune and inflammatory response to bacterial pathogens [2]. Progressive periodontal destruction results in tooth mobility (loose teeth) and tooth loss [5–7]. The estimated prevalence of periodontitis was 42% of adults (≥ 30 years old) in the United States (US) based on data from the National Health and Nutrition Examination Survey [8]. Moreover, the prevalence of severe periodontitis was 7.8%, most prevalent among adults aged 65 years or older, smokers, Mexican American persons, and non-Hispanic Black individuals [8].

Infection, and in particular, periodontal disease is the most common cause of tooth loss [5, 6, 9]. Tooth loss is positively associated with both cardiovascular [10–12] and all-cause mortality [12]. Tooth mobility is strongly correlated with the degree of alveolar bone loss in periodontitis [13]. Tooth loss, and its prosthetic replacement by removable partial or complete dentures, thus represents a readily ascertainable marker of cumulative oral disease burden, and is the focus of the present study.

There is an elevated risk of periodontal disease in psychiatric patients, both inpatients [14–16] and outpatients [17]. Multiple studies have reported associations between tooth loss and depression [18–34]; however, other studies have not reached the same results [35–45]. Heterogeneous risk factors among individuals in these studies may have contributed to these discrepancies. These factors include varying associations between specific depressive symptoms and infections, co-existing substance use disorders, psychological trauma, pregnancy, medical conditions, medications, genetic susceptibility to depression linked with particular pathogen serotypes, and lifestyle differences.

For instance, alcohol use and smoking have been reported to be risk factors for both depression [46–48] and periodontitis [49–54]. In the present study, we decreased the number of confounding factors by examining a relatively homogeneous population of the Old Order Amish (OOA), who have a low prevalence of alcohol use and smoking [55, 56] and relatively similar socioeconomic status and lifestyles [57], and, likely, poor access to and use of prophylactic dental care across the community. Prosthetic tooth replacement (e.g., removable partial or complete dentures/false teeth) serves as a surrogate variable for tooth loss. We hypothesized that using a removable dental appliance would be positively associated with cardinal symptoms of depression, specifically anhedonia and/or dysphoria/hopelessness. We focused on these two symptoms because, according to the DSM-5, the presence of at least one of them—depressed mood (dysphoria/hopelessness) or markedly diminished interest or pleasure (anhedonia)—is required for the diagnosis of a major depressive episode, unlike the remaining symptoms [58]; moreover, anhedonia [59] and hopelessness [60] are each, independently, recognized risk factors for suicidal behavior.

2. Methods

2.1 Recruitment

The Amish Wellness Study is a community-based program of cardio-metabolic health carried out in the Lancaster, Pennsylvania Amish community that included a broad panel of lifestyle factors collected from family and medical history questionnaires and sleep and mood questionnaires. Our recruitment and study procedures in the Amish Wellness Study and the use of a modified Patient Health Questionnaire-2 (PHQ-2) have been previously described [61]. The PHQ-2 provides ratings of current and ever dysphoria/hopelessness and anhedonia and has been reported to have high sensitivity (83%–89.3%) and specificity (75.9%–92%) [62–64]. Self-reported measures of dental health were also obtained. The questions included on the modified PHQ-2 were: “during the last month have you often been bothered by feeling down, depressed, or hopeless?”, which represented “current” dysphoria/hopelessness, and “during the last month have you had little feelings of interest or pleasure?”, which represented “current” anhedonia. Participants were categorized as currently experiencing dysphoria/hopelessness AND anhedonia if they answered “yes” to both questions, or dysphoria/hopelessness OR anhedonia if they responded yes to either of the two symptoms on the PHQ-2. The questionnaires also asked whether the participant had experienced either of these symptoms in the past. If participants experienced any of these symptoms currently or in the past, they were categorized as “ever.” If participants answered “no” to both items on the PHQ-2, they were classified as having “no depressive symptoms.”

The question related to dental health that we analyzed for this study was: “Do you have false teeth?” (answers were “yes-full”, “yes-partial”, “no”, and “don’t know”). Information about smoking and occupation was obtained from the Amish Wellness Study Medical and Social History Inventory. For smoking adjustment, we used “ever” (yes, in the past OR yes, current use) versus “never” use, and included the following modalities of tobacco use: cigarettes, cigars, pipe, snuff, and chewing tobacco. For occupation, we transformed the multiple occupational categories on the original response categories of the Amish Wellness Study Medical and Social History Inventory into binary categories, “farmer versus non-farmer.” These original categories included: (a) housekeeping, housewife (both denote home-based domestic work and fall under the non-farmer category); (b) farming (dairy, plant, tobacco), horse keeping, field worker, farmer’s wife; (c) shopkeeping, marketing, gardening, waitress, cook, cleaning, livestock auction, caring, cashier; (d) clerk work, needlework, quilting, teaching, order buyer at hale sales, craft making, municipal waste management, shoe repair; (e) carpenter, smith, woodwork, mason, mechanic, welder, painting, sawmill, fencing, house framer; (f) construction, contractor, mobile home builder; (g) retired; and (h) other. The questionnaires were vetted during several feedback sessions by representatives of the Amish community (Amish liaisons with the Amish Clinic of the University of Maryland staff) and received their unanimous approval. The University of Maryland Baltimore Institutional Review Board approved the study protocol. To participate, members of the Amish community had to provide written consent after a full explanation of the study and having sufficient time to have all their questions answered. The research was conducted in accordance with the Declaration of Helsinki [Clinical Trial Number: not applicable; this is an observational study].

There were 6,230 Old Order Amish individuals living in Lancaster County, Pennsylvania, aged ≥ 18 years (57% women), who were recruited into the “parent” Amish Wellness Study between 2010 and 2019. The last participants in this set had their Wellness visit completed on 08/26/2019. Among the 6,230

participants enrolled in the Wellness study at the time of analysis, 1,709 (27.4%) had neither dental nor PHQ-2 questionnaires, 167 (2.7%) had dental only, and 66 (1.1%) had PHQ-2 only. Participants responding “don’t know” were excluded from analysis. The analyzed sample included 4,288 (68.8%) participants with both dental and PHQ-2 questionnaires. Figure 1 shows the Wellness study, the completion percentage for the dental and depression questionnaires, and the analyzed sample.

2.2 Statistical analyses

Analyses were performed using logistic regression models with dental variables (partial denture, complete dentures, or any denture) included as independent variables and symptoms of depression as dependent variables. Age, sex, smoking status (ever smoker versus never smoker), and occupational status (farmer versus non-farmer) were included as covariates in these analyses. For the comparison of partial denture versus no denture, edentulous participants (i.e., those with complete dentures) were excluded. Results are presented as odds ratios with 95% confidence intervals, and statistical significance was assessed using two-tailed p-values with $\alpha = 0.05$. Statistical analyses were completed using the SAS 14.2 software package (Cary, NC, USA).

3. Results

The frequency of participants with depression symptoms according to the use of partial or complete dentures is provided in Table 1, and the associations between these variables, adjusted for age, sex, smoking status, and occupation, are presented in Table 2. A summary of these results is as follows:

Table 1

Frequency of participants with depression symptoms according to dental status (partial and complete dentures).

Variables	Final Sample (N = 4,288)	All teeth intact (n, % = 3,389, 76.1%)	Partial denture, present (n, % = 589, 14.8%)	Complete denture, present (n, % = 425, 9.9%)
Age, mean $\pm$ SD, years	43.5 $\pm$ 16.8	39.1 $\pm$ 14.4	54.1 $\pm$ 15.6	62.4 $\pm$ 14.8
Current dysphoria/hopelessness, present, n (%)	381 (9.0%)	281 (6.7%)	51 (9.3%)	37 (8.7%)
Current anhedonia, present, n (%)	219 (5.1%)	159 (3.8%)	33 (5.9%)	20 (4.6%)
Current anhedonia AND dysphoria/hopelessness, present, n (%)	158 (3.7%)	115 (2.7%)	22 (4.0%)	18 (4.1%)
Current anhedonia OR dysphoria/hopelessness, present, n (%)	442 (10.3%)	325 (7.7%)	62 (11.1%)	39 (8.9%)
Ever anhedonia OR dysphoria/hopelessness, present, n (%)	727 (17.0%)	536 (12.9%)	99 (18.2%)	71 (16.7%)

Percentages for the “All teeth intact,” “Partial denture,” and “Complete denture” columns are computed relative to the final sample (N = 4,288); symptom percentages within each column are computed relative to that column’s denominator.

3.1 Partial denture vs. no partial denture (excluding participants with complete dentures)

In these analyses, we excluded edentulous participants (those with complete dentures), and adjustment was done for the covariates age, sex, smoking, and occupational status. Individuals with a partial denture versus individuals with no dentures displayed a statistical trend toward higher odds of current anhedonia (OR 1.521, 95% CI [0.980, 2.361], $p = 0.062$), as well as ever anhedonia OR dysphoria/hopelessness (OR 1.262, 95% CI [0.964, 1.653], $p = 0.091$). There were no significant associations of partial denture with current dysphoria/hopelessness, current anhedonia AND dysphoria/hopelessness, or current anhedonia OR dysphoria/hopelessness (see Table 2).

3.2 Complete dentures vs. partial or no denture

In these analyses, covariates included age, sex, smoking, and occupational status. Individuals with complete dentures versus individuals with a partial or no denture had statistically significant higher odds

of having current anhedonia AND dysphoria/hopelessness (OR 1.794, 95% CI [1.008, 3.193], $p = 0.047$). However, there were no significant associations with other depression-related variables (see Table 2).

3.3 Any denture (including both complete and partial dentures) vs. no denture

In these analyses, covariates included age, sex, smoking, and occupational status. In the entire sample, individuals with any denture versus individuals with no dentures had statistically significant higher odds of reporting current anhedonia (OR 1.560, 95% CI [1.062, 2.292], $p = 0.024$), as well as current anhedonia AND dysphoria/hopelessness (OR 1.760, 95% CI [1.131, 2.737], $p = 0.012$). Additionally, a statistical trend was identified for the association between any denture and ever anhedonia OR dysphoria/hopelessness (OR 1.238, 95% CI [0.982, 1.562], $p = 0.071$). There were no significant associations of any denture with other mood variables (see Table 2).

Table 2

Associations between dentures (independent variables) and cardinal symptoms of depression (dependent variables), adjusted for age, sex, smoking status, and occupation (farmer versus non-farmer).

Variables	Partial denture vs. no denture – OR [95% CI]	Complete dentures vs. partial or no denture – OR [95% CI]	Any denture (complete and partial) vs. no denture – OR [95% CI]
Current dysphoria/hopelessness	1.259 [0.880, 1.801], $p = 0.208$	1.148 [0.754, 1.748], $p = 0.521$	1.281 [0.942, 1.742], $p = 0.115$
Current anhedonia	1.521 [0.980, 2.361], $p = 0.062$ [^]	1.269 [0.747, 2.157], $p = 0.379$	1.560 [1.062, 2.292], $p = 0.024$ *
Current anhedonia AND dysphoria/hopelessness	1.519 [0.896, 2.573], $p = 0.121$	1.794 [1.008, 3.193], $p = 0.047$ *	1.760 [1.131, 2.737], $p = 0.012$ *
Current anhedonia OR dysphoria/hopelessness	1.298 [0.934, 1.804], $p = 0.120$	1.001 [0.668, 1.499], $p = 0.997$	1.253 [0.940, 1.670], $p = 0.125$
Ever anhedonia OR dysphoria/hopelessness	1.262 [0.964, 1.653], $p = 0.091$ [^]	1.065 [0.777, 1.461], $p = 0.695$	1.238 [0.982, 1.562], $p = 0.071$ ^

Partial denture vs. no denture comparison excludes subjects with complete dentures. * Statistical significance ($p < 0.05$). ^ Statistical trend ($p < 0.10$).

4. Discussion

4.1 Summary of key findings

As hypothesized, when compared with individuals without any dentures, participants with dentures were significantly more likely to report current anhedonia and combined current anhedonia AND

dysphoria/hopelessness. When compared with participants without complete dentures (i.e., those with either no dentures or partial dentures), participants with complete dentures were significantly more likely to report current anhedonia AND dysphoria/hopelessness. A low-grade statistical trend was observed for individuals with partial dentures versus those with no dentures, and for those with any dentures versus those with no dentures, to endorse ever anhedonia OR dysphoria/hopelessness. Notably, the significant associations were confined to current, rather than “ever,” symptom ratings.

4.2 Strengths and limitations of the study

A primary strength of the study is its relatively homogeneous population. The OOA have a low prevalence of alcohol use and smoking [55, 56], relatively similar socioeconomic status and lifestyles [57], and limited access to prophylactic dental care and fluoridated water across the community, which collectively reduce confounding heterogeneity. In addition, the OOA are generally less exposed to the negative effects of intense evening light and low-wavelength light originating from televisions, computers, tablets, and mobile phone screens [65], and have a lower frequency of short sleepers [66]. However, in the Amish, current and lifetime stress levels do affect sleep [67], as do heritability (of wake-time [67], only after accounting for shared environment), chronotype [68], and seasonality [69]; these factors were not adjusted for in the present analyses.

Several limitations should be considered. The study is cross-sectional; therefore, we cannot ascertain a causal relationship between denture use and symptoms of depression. To measure symptoms of depression we did not use standardized structured diagnostic instruments, and for periodontal outcomes we did not corroborate responses with clinical notes, radiographs, or contemporaneous oral examinations. Data on sleep, diet, oral hygiene practices, and frequency of dental visits were not available. We also did not account for education and income; formal education is highly homogeneous in this population (schooling through the 8th grade for nearly all participants), and, while income may vary, lifestyle and healthcare access are relatively uniform owing to shared cultural norms. Importantly, we did not directly ask about tooth loss or its most common causes (periodontal disease, decay, and trauma), and dentures were used only as a surrogate for tooth loss. Consequently, “no denture” encompasses both individuals who have never lost teeth and those who lost teeth without replacement, which is a considerable shortcoming; this limitation is likely to blur differences in symptoms of depression between those with and without dentures, but is unlikely to create spuriously significant differences.

With respect to analysis and interpretation, the PHQ-2 is useful for screening and estimation but not for the clinical diagnosis of depression [63, 64]. Additionally, the expression of negative mood in the OOA is somewhat limited as a consequence of the OOA valuing gratitude and stoicism [57]. The OOA believe in accepting the hardships of daily life as God’s will (Gelassenheit), respond to adversity by yielding to divine providence, and often consider that divine intervention leads to the resolution of past symptoms [57]. Hence, the OOA are prone to underreport past symptoms once they are resolved, and a culturally based bias might have contributed to significant associations between dental status and current, but not past, symptoms of depression. Therefore, the generalizability of our findings to non-OOA populations may be limited. We expect that stronger effect sizes may emerge in less stoic populations, in particular

for past symptoms; on the other hand, the higher heterogeneity of lifestyle could increase confounding and decrease statistical power.

4.3 Interpretation and implications in the context of the totality of evidence

Our results are consistent with the majority trend in previous studies [18, 20–27]. A meta-analysis of 14 studies by Liu et al. (2018) [18] confirmed a significant association between chronic periodontitis and “emotional disorder” (including depression and anxiety) (OR = 1.54, 95% CI 1.27–1.86). In a prospective study, one of the first of its kind, the “dental-to-mental” direction of causality was examined in outpatients with chronic and aggressive periodontitis to assess the impact of tooth loss on future depressive symptoms [19]. Tooth status of 310 patients was determined initially, and they were followed for 13 years for the subsequent development of depressive symptoms using the PHQ-9. Even after controlling for several covariates, including smoking status, age at baseline, and comorbid somatic illnesses, fewer teeth at the beginning of treatment were related to higher depressive symptom scores, establishing that tooth loss may be a risk factor for developing depression in individuals with periodontitis [19]. Similarly, a large US study indicated that adults with current depression, lifetime diagnosed depression, and lifetime diagnosed anxiety were significantly more likely to have had at least one tooth removed relative to depression- and anxiety-free individuals [28]. Compared with individuals with 0 teeth removed, the adjusted odds of being in the all-teeth-removed, 6–31-teeth-removed, or 1–5-teeth-removed categories were increased for individuals with current depression (adjusted odds ratio [AOR] = 1.44, 95% CI 1.11–1.86; AOR = 1.83, 95% CI 1.51–2.22; and AOR = 1.35, 95% CI 1.14–1.59, respectively) [28].

In contrast, no significant associations between depression and periodontal disease were reported in a meta-analysis [35], nor in cohort [36], case-control [37, 38], and cross-sectional studies [32, 39–42, 70]. It is possible that the heterogeneous distribution of certain confounding variables (substance use disorders, tobacco use, socioeconomic status, occupation, living environment and cultural practices, access to mental health and dental care services, and various amounts and modalities of fluoride intake) across studies contributed to differences in outcome. By evaluating a relatively homogeneous population (i.e., the OOA), we have minimized these potential confounders.

What are the potential mechanisms underlying the reported associations? Although progressive periodontitis often accounts for the majority of cases, other pathological pathways could contribute to tooth loss. For instance, advanced dental caries (decay) can induce endodontic infection and pain, which may result in extraction of the offending teeth. When untreated, a late-stage endodontic infection leads to apical periodontitis, a chronic inflammatory state of the peri-radicular tissues. Apical periodontitis shares important similarities with the microbial spectrum and immune-inflammatory response of periodontitis [71]; for example, it is also associated with significant serum elevations in inflammatory mediators such as CRP, IL-1, and IL-6 [72], which have been identified as predictors of cardiovascular

events in humans [73]. However, a recent study using NHANES data found that depression is associated with tooth loss and periodontitis, but not with caries [74].

As noted earlier, tooth mobility and tooth loss exhibit a strong association with the severity of periodontitis, likely as a consequence of it [5–7, 13]. Periodontitis is associated with elevations in markers of inflammation [75], such as Type 1 cytokines, C-reactive protein [76–80], IL-6 [81], and IL-18 [78]. Furthermore, type 1 cytokines [IL-1 β , IL-6, and tumor necrosis factor- α (TNF)] can be induced by periodontal pathogens and their products [82, 83]. Increasing evidence also links inflammation to symptoms of depression [84–90], and multiple non-human animal studies point toward a causal relationship between inflammatory mediators and depressive-like symptoms [91–96]. Research further supports the potential role of inflammation as a key mediator of the periodontitis–depression link [97–99]. Alterations in the oral microbiome could also provide a link with depression [100–102], potentially via upregulation of inflammation and impairment of barrier function (intestinal and blood-brain barrier [BBB]).

Sleep disturbance is also associated with both depression and tooth loss. Specifically, tooth loss and periodontitis are negatively associated with sleep duration and positively associated with perceived sleep insufficiency [103], and more generally with multiple disturbances of sleep duration and quality (e.g., obstructive sleep apnea) [104]. A spectrum of sleep disturbances—including insomnia, obstructive sleep apnea, hypersomnia, restless legs syndrome, aberrant sleep duration (both short and long), and eveningness chronotype orientation—are also associated with depression, as demonstrated by a systematic review and meta-analysis of longitudinal studies [105].

Translocation of periodontal pathogens from the oral cavity to the systemic and cerebral circulation and the central nervous system is another pathway connecting periodontal disease and mental health. Periodontal bacteria and their products can gain access to the circulation [106, 107], resulting in systemic dissemination of both bacterial products and the bacteria themselves. Invasive periodontal treatment may induce a temporary increase in pro-thrombotic/inflammatory mediators [108] and endothelial dysfunction within 24 hours after treatment [109], likely mediated by transient bacteremia due to trauma during treatment [110]; these changes may last up to 4 weeks post-treatment [108], leading to an increased risk of cardiovascular events during this period [111]. Moreover, even minor trauma such as toothbrushing can precipitate bacteremia episodes in patients with periodontitis [106, 112, 113]. Consistently, animal models of oral infection with *Porphyromonas gingivalis*, a keystone periodontal pathogen with demonstrated capability to translocate, have shown that inflammatory reactions due to this infection may be promoted in atheromatous lesions distant from the oral cavity [114–116]. Furthermore, the BBB is broken down via abnormal activation of matrix metalloproteinases by systemic injection of LPS [117, 118], which may allow molecular inflammatory products and phagocytes to enter the brain directly, ultimately and potentially leading to depressive mood and behavioral changes [119].

Periodontal disease [120] may also affect the gut microbiota [121], which may further contribute to mental health symptoms [122] through the gut-brain connection, as evidenced by animal [123–129], clinical [130], and imaging studies [131].

Poor oral health, particularly associated with tooth loss, could also lead to difficulty with communication, affecting other psychological and social aspects of human life [132] and worsening quality of life through diminished self-esteem and social status, impaired body image, and loss of chewing functionality [133–135]. Ill-fitting and painful dentition or dentures can cause difficulties with eating and speaking, and psychogenic incompatibility of prosthodontic replacement or denture dissatisfaction could also contribute to depressive symptoms [136, 137]. It is possible that patients with periodontitis experience social stigma from the negative effects of tooth loss on facial contour and aesthetics, as well as halitosis [138], which could precipitate or perpetuate anhedonia and/or hopelessness/dysphoria, thereby contributing to syndromic depression [139].

It is important to acknowledge that we chose to examine only two symptoms of depression (anhedonia and dysphoria/hopelessness) mainly for feasibility reasons. The team even considered simplifying further by asking only a single question about ever dysphoria/hopelessness OR anhedonia, but prior data did not support this additional simplification: the sensitivity for estimating the presence of major depression using a solitary question related to dysphoria/hopelessness is approximately 85–90%, and this sensitivity increases to 95% when an additional question related to anhedonia is added [62]. Both anhedonia and dysphoria/hopelessness are cardinal symptoms of depression, with at least one required for a defined major depressive episode, and both are well-recognized individual risk factors for suicidal behavior [140], beyond the presence of depression itself. These symptoms also allow application of the Research Domain Criteria to depression and suicide research, as both anhedonia and hopelessness can be individually modeled in animals [141]. Furthermore, anhedonia carries an individual negative prognosis regarding psychological, social, and physical functioning [142] and is linked with a more refractory response to antidepressant treatment [143].

From a clinical standpoint, our results suggest that it will likely be beneficial to foster bidirectional dialogue and collaboration between dentists and mental health providers.

4.4 Controversies raised by this study

Several considerations temper a causal interpretation of our findings. Because the study is cross-sectional and denture use serves only as a surrogate for tooth loss, the direction of any causal relationship between oral health status and symptoms of depression cannot be established. Moreover, increased stress [97, 144–148] could precipitate, exacerbate, perpetuate, and reactivate both periodontitis and depression and, together with other risk factors, could represent hidden “upstream” variables that may create false promises of causal associations—specifically, the hope that therapeutically targeting one domain will improve the other. It therefore remains possible that denture use is a marker of cumulative biological and psychosocial burden rather than a contemporaneous cause of depressive symptoms.

4.5 Future research directions

These findings warrant replication in future longitudinal studies incorporating dental and clinical examinations, imaging, and laboratory biomarkers. The apparent predominance of anhedonia over dysphoria/hopelessness as a contributor to our results requires further investigation; if the causal inferences underlying our associations were confirmed, periodontal prophylactic approaches could have the potential to prevent treatment refractoriness in depression among vulnerable individuals. More broadly, studies are needed to investigate in depth the reciprocal interactions between mental illness and periodontal disease, their treatments, and their overlapping immune, metabolic, and vascular associations.

5. Conclusions

In this relatively homogeneous population—characterized by a low prevalence of smoking and limited access to both prophylactic dental care and fluoridated water—denture use, and particularly the use of complete dentures, was associated with current anhedonia and dysphoria/hopelessness. These findings support a clinically meaningful link between oral health status and cardinal symptoms of depression and underscore the potential value of bidirectional collaboration between dental and mental health care. Given the cross-sectional design and the reliance on self-reported measures, the results warrant replication in longitudinal studies incorporating clinical dental and psychiatric examinations, imaging, and laboratory biomarkers.

Abbreviations

CI: confidence interval; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; IRB: Institutional Review Board; MIRECC: Mental Illness Research, Education and Clinical Center; MVM-CoRE: Military and Veteran Microbiome: Consortium for Research and Education; NORC: Nutrition Obesity Research Center; OOA: Old Order Amish; OR: odds ratio; PHQ-2: Patient Health Questionnaire-2; SD: standard deviation; VISN: Veterans Integrated Service Network.

Declarations

Ethics approval and consent to participate: The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Maryland, Baltimore, MD. All participants were required to sign informed consent after a full explanation of the study, being encouraged to ask questions and having all their questions answered. Members of the Old Order Amish community (Amish liaisons to the University of Maryland School of Medicine) vetted the study and study questionnaires several months prior to the IRB submission and had their suggestions heard and questions answered on at least two occasions prior to the start of the questionnaire administration.

Consent for publication: All authors approved the publication of the final version of the manuscript. No other consents for publication were applicable. No material from other sources was used.

Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available due to the absence of Amish participant consent for data sharing. Summary and aggregate data rather than individual data could be made available upon reasonable request emailed to the corresponding author.

Competing interests: The authors declare that they have no competing interests. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Author contributions: T.T.P., A.W., and M.A.R. conceptualized the study, interpreted the data, and drafted the original and advanced drafts of the manuscript. M.L.D. led the data management and secondary analyses for the study, and K.A.R. performed the formal analysis of the data. A.D. and H.M. contributed to the acquisition of depression data. B.D.M. supervised the data collection and statistical analyses and provided leadership of the Amish Research Program and the Amish Research Clinic of the University of Maryland, Lancaster, PA, and J.A.K. interpreted results and provided critical feedback considering implications in light of diminished preventive dental services. L.A.B., A.J.H., S.M-M., and R.K.E. interpreted data with a focus on potential underlying neuroimmunology and microbiological implications; and J.V. contributed to the potential moderation/mediation of sleep in the denture use–depression symptom connections. T.T.P. and L.A.B. provided scholarly expertise in affective disorders, and M.A.R. in clinical periodontology. All authors have provided intellectual content, edited initial and/or middle drafts, and given approval for submission of the final version of the manuscript.

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References

1. Page RC, Schroeder HE. Periodontitis in man and other animals. A comparative review. Basel, Switzerland: S. Karger; 1982.
2. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol*. 1999;4(1):1-6.

3. Lang NP, Lindhe J. Clinical Periodontology and Implant Dentistry, 2 Volume Set. 6th ed. Chichester, United Kingdom: Wiley-Blackwell; 2015.
4. Mariotti A. Dental plaque-induced gingival diseases. *Ann Periodontol.* 1999;4(1):7-19.
5. Oliver RC, Brown LJ, Loe H. Periodontal diseases in the United States population. *J Periodontol.* 1998;69(2):269-78.
6. Thornton-Evans G, Eke P, Wei L, Palmer A, Moeti R, Hutchins S, et al. Periodontitis among adults aged ≥ 30 years - United States, 2009-2010. *MMWR Suppl.* 2013;62(3):129-35.
7. Hyde S, Dupuis V, Mariri BP, Dartevielle S. Prevention of tooth loss and dental pain for reducing the global burden of oral diseases. *Int Dent J.* 2017;67 Suppl 2:19-25.
8. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA, Genco RJ. Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009-2014. *J Am Dent Assoc (1939).* 2018;149(7):576-88.e6.
9. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global Burden of Severe Tooth Loss: A Systematic Review and Meta-analysis. *J Dent Res.* 2014;93(7 Suppl):20s-8s.
10. Heitmann BL, Gamborg M. Remaining teeth, cardiovascular morbidity and death among adult Danes. *Prev Med.* 2008;47(2):156-60.
11. Holmlund A, Holm G, Lind L. Number of teeth as a predictor of cardiovascular mortality in a cohort of 7,674 subjects followed for 12 years. *J Periodontol.* 2010;81(6):870-6.
12. Schwahn C, Polzer I, Haring R, Dorr M, Wallaschofski H, Kocher T, et al. Missing, unreplaced teeth and risk of all-cause and cardiovascular mortality. *Int J Cardiol.* 2013;167(4):1430-7.
13. Glass RL, Loftus ER, Kapur KK, Alman JE. Analyses of components of periodontal disease. *J Dent Res.* 1973;52(6):1238-44.
14. Angelillo IF, Nobile CG, Pavia M, De Fazio P, Puca M, Amati A. Dental health and treatment needs in institutionalized psychiatric patients in Italy. *Community Dent Oral Epidemiol.* 1995;23(6):360-4.
15. Rekha R, Hiremath SS. Oral health status and treatment requirements of confectionery workers in Bangalore city. A comparative study. *Indian J Dent Res.* 2002;13(3-4):161-5.
16. Tang WK, Sun FC, Ungvari GS, O'Donnell D. Oral health of psychiatric in-patients in Hong Kong. *Int J Soc Psychiatry.* 2004;50(2):186-91.
17. Burchell A, Fernbacher S, Lewis R, Neil A. "Dental as Anything" Inner South Community Health Service Dental Outreach to People with a Mental Illness. *Aust J Prim Health.* 2006;12(2):75-82.
18. Liu F, Wen YF, Zhou Y, Lei G, Guo QY, Dang YH. A meta-analysis of emotional disorders as possible risk factors for chronic periodontitis. *Medicine.* 2018;97(28):e11434.
19. Ehrental JC, Graetz C, Plaumann A, Dorfer CE, Herzog W. Number of teeth predict depressive symptoms in a longitudinal study on patients with periodontal disease. *J Psychosom Res.* 2016;89:16-9.
20. Johannsen A, Rylander G, Soder B, Asberg M. Dental plaque, gingival inflammation, and elevated levels of interleukin-6 and cortisol in gingival crevicular fluid from women with stress-related

- depression and exhaustion. *J Periodontol*. 2006;77(8):1403-9.
21. Johannsen A, Rydmark I, Soder B, Asberg M. Gingival inflammation, increased periodontal pocket depth and elevated interleukin-6 in gingival crevicular fluid of depressed women on long-term sick leave. *J Periodontol*. 2007;42(6):546-52.
 22. Ababneh KT, Taha AH, Abbadi MS, Karasneh JA, Khader YS. The association of aggressive and chronic periodontitis with systemic manifestations and dental anomalies in a Jordanian population: a case control study. *Head Face Med*. 2010;6:30.
 23. Luca M, Luca A, Grasso CM, Calandra C. Nothing to smile about. *Neuropsychiatr Dis Treat*. 2014;10:1999-2008.
 24. Laforgia A, Corsalini M, Stefanachi G, Pettini F, Di Venere D. Assessment of Psychopatologic Traits in a Group of Patients with Adult Chronic Periodontitis: Study on 108 Cases and Analysis of Compliance during and after Periodontal Treatment. *Int J Med Sci*. 2015;12(10):832-9.
 25. Genco RJ, Ho AW, Grossi SG, Dunford RG, Tedesco LA. Relationship of stress, distress and inadequate coping behaviors to periodontal disease. *J Periodontol*. 1999;70(7):711-23.
 26. Ng SK, Keung Leung W. A community study on the relationship between stress, coping, affective dispositions and periodontal attachment loss. *Community Dent Oral Epidemiol*. 2006;34(4):252-66.
 27. Rosania AE, Low KG, McCormick CM, Rosania DA. Stress, depression, cortisol, and periodontal disease. *J Periodontol*. 2009;80(2):260-6.
 28. Okoro CA, Strine TW, Eke PI, Dhingra SS, Balluz LS. The association between depression and anxiety and use of oral health services and tooth loss. *Community Dent Oral Epidemiol*. 2012;40(2):134-44.
 29. O'Neil A, Berk M, Venugopal K, Kim SW, Williams LJ, Jacka FN. The association between poor dental health and depression: findings from a large-scale, population-based study (the NHANES study). *Gen Hosp Psychiatry*. 2014;36(3):266-70.
 30. Saman DM, Lemieux A, Arevalo O, Lutfiyya MN. A population-based study of edentulism in the US: does depression and rural residency matter after controlling for potential confounders? *BMC Public Health*. 2014;14:65.
 31. Coles E, Chan K, Collins J, Humphris GM, Richards D, Williams B, et al. Decayed and missing teeth and oral-health-related factors: predicting depression in homeless people. *J Psychosom Res*. 2011;71(2):108-12.
 32. Persson GR, Persson RE, MacEntee CI, Wyatt CC, Hollender LG, Kiyak HA. Periodontitis and perceived risk for periodontitis in elders with evidence of depression. *J Clin Periodontol*. 2003;30(8):691-6.
 33. Singh H, Maharaj RG, Naidu R. Oral health among the elderly in 7 Latin American and Caribbean cities, 1999-2000: a cross-sectional study. *BMC Oral Health*. 2015;15:46.
 34. Urzua I, Mendoza C, Arteaga O, Rodriguez G, Cabello R, Faleiros S, et al. Dental caries prevalence and tooth loss in Chilean adult population: first national dental examination survey. *Int J Dent*. 2012;2012:810170.

35. Araujo MM, Martins CC, Costa LC, Cota LO, Faria RL, Cunha FA, et al. Association between depression and periodontitis: a systematic review and meta-analysis. *J Clin Periodontol*. 2016;43(3):216-28.
36. Moss ME, Beck JD, Kaplan BH, Offenbacher S, Weintraub JA, Koch GG, et al. Exploratory case-control analysis of psychosocial factors and adult periodontitis. *J Periodontol*. 1996;67(10 Suppl):1060-9.
37. Castro GD, Oppermann RV, Haas AN, Winter R, Alchieri JC. Association between psychosocial factors and periodontitis: a case-control study. *J Clin Periodontol*. 2006;33(2):109-14.
38. Solis AC, Marques AH, Pannuti CM, Lotufo RF, Lotufo-Neto F. Evaluation of periodontitis in hospital outpatients with major depressive disorder. *Journal of periodontal research*. 2014;49(1):77-84.
39. Solis AC, Lotufo RF, Pannuti CM, Brunheiro EC, Marques AH, Lotufo-Neto F. Association of periodontal disease to anxiety and depression symptoms, and psychosocial stress factors. *J Clin Periodontol*. 2004;31(8):633-8.
40. Ababneh KT, Al Shaar MB, Taani DQ. Depressive symptoms in relation to periodontal health in a Jordanian sample. *International journal of dental hygiene*. 2010;8(1):16-21.
41. Khambaty T, Stewart JC. Associations of depressive and anxiety disorders with periodontal disease prevalence in young adults: analysis of 1999-2004 National Health and Nutrition Examination Survey (NHANES) data. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*. 2013;45(3):393-7.
42. Mendes DC, Silva TF, Barros Lde O, de Oliveira MV, Vieira LT, Haikal DS, et al. Analysis of the normative conditions of oral health, depression and serotonin-transporter-linked promoter region polymorphisms in an elderly population. *Geriatrics & gerontology international*. 2013;13(1):98-106.
43. Peeran SW, Kumar NP, Azaruk FAA, Alsaid FM, Abdalla KA, Mugrabi MH, et al. Association between mental well-being, depression, and periodontal attachment level among young adults of the postwar Sebha city, Libya: A pilot study. *Journal of natural science, biology, and medicine*. 2014;5(2):308.
44. Silveira ML, Whitcomb BW, Pekow P, Carbone ET, Chasan-Taber L. Anxiety, depression, and oral health among US pregnant women: 2010 Behavioral Risk Factor Surveillance System. *Journal of public health dentistry*. 2016;76(1):56-64.
45. Okamoto N, Morikawa M, Okamoto K, Habu N, Iwamoto J, Tomioka K, et al. Relationship of tooth loss to mild memory impairment and cognitive impairment: findings from the Fujiwara-kyo study. *Behavioral and brain functions : BBF*. 2010;6:77.
46. Klimkiewicz A, Klimkiewicz J, Jakubczyk A, Kieres-Salomonski I, Wojnar M. [Comorbidity of alcohol dependence with other psychiatric disorders. Part I. Epidemiology of dual diagnosis]. *Psychiatria polska*. 2015;49(2):265-75.
47. Luger TM, Suls J, Vander Weg MW. How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models. *Addictive behaviors*. 2014;39(10):1418-29.

48. Paperwalla KN, Levin TT, Weiner J, Saravay SM. Smoking and depression. *The Medical clinics of North America*. 2004;88(6):1483-94, x-xi.
49. Tezal M, Grossi SG, Ho AW, Genco RJ. Alcohol consumption and periodontal disease. *The Third National Health and Nutrition Examination Survey*. *J Clin Periodontol*. 2004;31(7):484-8.
50. Pitiphat W, Merchant AT, Rimm EB, Joshipura KJ. Alcohol consumption increases periodontitis risk. *Journal of dental research*. 2003;82(7):509-13.
51. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. *Periodontology 2000*. 2013;62(1):59-94.
52. Chambrone L, Preshaw PM, Rosa EF, Heasman PA, Romito GA, Pannuti CM, et al. Effects of smoking cessation on the outcomes of non-surgical periodontal therapy: a systematic review and individual patient data meta-analysis. *J Clin Periodontol*. 2013;40(6):607-15.
53. Fiorini T, Musskopf ML, Oppermann RV, Susin C. Is there a positive effect of smoking cessation on periodontal health? A systematic review. *Journal of periodontology*. 2014;85(1):83-91.
54. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, et al. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *Journal of periodontology*. 1994;65(3):260-7.
55. Levinson RM, Fuchs JA, Stoddard RR, Jones DH, Mullet M. Behavioral risk factors in an Amish community. *Am J Prev Med*. 1989;5(3):150-6.
56. Reed RM, Dransfield MT, Eberlein M, Miller M, Netzer G, Pavlovich M, et al. Gender differences in first and secondhand smoke exposure, spirometric lung function and cardiometabolic health in the old order Amish: A novel population without female smoking. *PLoS One*. 2017;12(3):e0174354.
57. Kraybill D, Johnson-Weiner K, Nolt S. *The Amish*. Baltimore, Maryland: The John Hopkins University Press; 2013.
58. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
59. Ducasse D, Loas G, Dassa D, Gramaglia C, Zeppegno P, Guillaume S, et al. Anhedonia is associated with suicidal ideation independently of depression: a meta-analysis. *Depress Anxiety*. 2018;35(5):382-92.
60. Beck AT, Steer RA, Kovacs M, Garrison B. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *Am J Psychiatry*. 1985;142(5):559-63.
61. Wadhawan A, Dagdag A, Duffy A, Daue ML, Ryan KA, Brenner LA, et al. Positive association between *Toxoplasma gondii* IgG serointensity and current dysphoria/hopelessness scores in the Old Order Amish: a preliminary study. *Pteridines*. 2017;28(3-4):185-94.
62. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Medical care*. 2003;41(11):1284-92.
63. Gilbody S, Richards D, Brealey S, Hewitt C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. *J Gen Intern Med*.

2007;22(11):1596-602.

64. Mitchell AJ, Yadegarfar M, Gill J, Stubbs B. Case finding and screening clinical utility of the Patient Health Questionnaire (PHQ-9 and PHQ-2) for depression in primary care: a diagnostic meta-analysis of 40 studies. *BJPsych open*. 2016;2(2):127-38.
65. Lee EE, Amritwar A, Hong LE, Mohyuddin I, Brown T, Postolache TT. Daily and Seasonal Variation in Light Exposure among the Old Order Amish. *Int J Environ Res Public Health*. 2020;17(12).
66. Zhang M, Ryan KA, Wickwire E, Postolache TT, Xu H, Daue M, et al. Self-Reported Sleep Duration and Pattern in Old Order Amish and Non-Amish Adults. *J Clin Sleep Med*. 2019;15(9):1321-8.
67. Bruce HA, Kochunov P, Chiappelli J, Savransky A, Carino K, Sewell J, et al. Genetic versus stress and mood determinants of sleep in the Amish. *Am J Med Genet B Neuropsychiatr Genet*. 2021;186(2):113-21.
68. Zhang L, Evans DS, Raheja UK, Stephens SH, Stiller JW, Reeves GM, et al. Chronotype and seasonality: morningness is associated with lower seasonal mood and behavior changes in the Old Order Amish. *J Affect Disord*. 2015;174:209-14.
69. Raheja UK, Stephens SH, Mitchell BD, Rohan KJ, Vaswani D, Balis TG, et al. Seasonality of mood and behavior in the Old Order Amish. *J Affect Disord*. 2013;147(1-3):112-7.
70. Park H-E, Song HY, Han K, Cho K-H, Kim Y-H. Number of remaining teeth and health-related quality of life: the Korean National Health and Nutrition Examination Survey 2010-2012. *Health Qual Life Outcomes*. 2019;17(1):5-.
71. Rupf S, Kannengiesser S, Merte K, Pfister W, Sigusch B, Eschrich K. Comparison of profiles of key periodontal pathogens in periodontium and endodontium. *Endodontics & dental traumatology*. 2000;16(6):269-75.
72. Gomes MS, Blattner TC, Sant'Ana Filho M, Grecca FS, Hugo FN, Fouad AF, et al. Can apical periodontitis modify systemic levels of inflammatory markers? A systematic review and meta-analysis. *Journal of endodontics*. 2013;39(10):1205-17.
73. Gomes MS, Hugo FN, Hilgert JB, Sant'Ana Filho M, Padilha DM, Simonsick EM, et al. Apical periodontitis and incident cardiovascular events in the Baltimore Longitudinal Study of Ageing. *International endodontic journal*. 2016;49(4):334-42.
74. Aldosari M, Helmi M, Kennedy EN, Badamia R, Odani S, Agaku I, et al. Depression, periodontitis, caries and missing teeth in the USA, NHANES 2009-2014. *Fam Med Community Health*. 2020;8(4).
75. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nature reviews Immunology*. 2015;15(1):30-44.
76. Ebersole JL, Machen RL, Steffen MJ, Willmann DE. Systemic acute-phase reactants, C-reactive protein and haptoglobin, in adult periodontitis. *Clinical and experimental immunology*. 1997;107(2):347-52.
77. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E. Periodontal infections contribute to elevated systemic C-reactive protein level. *Journal of periodontology*. 2001;72(9):1221-7.

78. Buhlin K, Hultin M, Norderyd O, Persson L, Pockley AG, Rabe P, et al. Risk factors for atherosclerosis in cases with severe periodontitis. *J Clin Periodontol*. 2009;36(7):541-9.
79. Gomes-Filho IS, Freitas Coelho JM, da Cruz SS, Passos JS, Teixeira de Freitas CO, Aragao Farias NS, et al. Chronic periodontitis and C-reactive protein levels. *Journal of periodontology*. 2011;82(7):969-78.
80. Pejicic A, Kesic LJ, Milasin J. C-reactive protein as a systemic marker of inflammation in periodontitis. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. 2011;30(3):407-14.
81. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *Journal of periodontology*. 2000;71(10):1528-34.
82. Wu Z, Ni J, Liu Y, Teeling JL, Takayama F, Collicutt A, et al. Cathepsin B plays a critical role in inducing Alzheimer's disease-like phenotypes following chronic systemic exposure to lipopolysaccharide from *Porphyromonas gingivalis* in mice. *Brain, behavior, and immunity*. 2017;65:350-61.
83. Liu Y, Wu Z, Nakanishi Y, Ni J, Hayashi Y, Takayama F, et al. Infection of microglia with *Porphyromonas gingivalis* promotes cell migration and an inflammatory response through the gingipain-mediated activation of protease-activated receptor-2 in mice. *Scientific reports*. 2017;7(1):11759-.
84. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Progress in neuro-psychopharmacology & biological psychiatry*. 2011;35(3):664-75.
85. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Archives of general psychiatry*. 2001;58(5):445-52.
86. Raison CL, Borisov AS, Broadwell SD, Capuron L, Woolwine BJ, Jacobson IM, et al. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. *Journal of clinical psychiatry*. 2005;66(1):41.
87. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in immunology*. 2006;27(1):24-31.
88. Kohler-Forsberg O, Buttenschon HN, Tansey KE, Maier W, Hauser J, Dernovsek MZ, et al. Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. *Brain, behavior, and immunity*. 2017;62:344-50.
89. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. *Biological psychiatry*. 2010;67(5):446-57.
90. Luo Y, He H, Zhang M, Huang X, Fan N. Altered serum levels of TNF-alpha, IL-6 and IL-18 in manic, depressive, mixed state of bipolar disorder patients. *Psychiatry research*. 2016;244:19-23.
91. Bhatt S, Bhatt R, Zalcman SS, Siegel A. Role of IL-1 beta and 5-HT2 receptors in midbrain periaqueductal gray (PAG) in potentiating defensive rage behavior in cat. *Brain, behavior, and immunity*. 2008;22(2):224-33.

92. Bhatt S, Siegel A. Potentiating role of interleukin 2 (IL-2) receptors in the midbrain periaqueductal gray (PAG) upon defensive rage behavior in the cat: role of neurokinin NK(1) receptors. *Behavioral brain research*. 2006;167(2):251-60.
93. Dunn AJ. Effects of cytokines and infections on brain neurochemistry. *Clinical neuroscience research*. 2006;6(1-2):52-68.
94. Hassanain M, Zalcman S, Bhatt S, Siegel A. Interleukin-1 beta in the hypothalamus potentiates feline defensive rage: role of serotonin-2 receptors. *Neuroscience*. 2003;120(1):227-33.
95. Patel A, Siegel A, Zalcman SS. Lack of aggression and anxiolytic-like behavior in TNF receptor (TNF-R1 and TNF-R2) deficient mice. *Brain, behavior, and immunity*. 2010;24(8):1276-80.
96. Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, et al. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology*. 2013;38(9):1609.
97. Decker A, Askar H, Tattan M, Taichman R, Wang HL. The assessment of stress, depression, and inflammation as a collective risk factor for periodontal diseases: a systematic review. *Clin Oral Investig*. 2020;24(1):1-12.
98. Makkar H, Reynolds MA, Wadhawan A, Dagdag A, Merchant AT, Postolache TT. Periodontal, metabolic, and cardiovascular disease: Exploring the role of inflammation and mental health. *Pteridines*. 2018;29(1):124-63.
99. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, et al. Periodontitis and cardiovascular diseases: Consensus report. *J Clin Periodontol*. 2020;47(3):268-88.
100. Martínez M, Postolache TT, García-Bueno B, Leza JC, Figuero E, Lowry CA, et al. The Role of the Oral Microbiota Related to Periodontal Diseases in Anxiety, Mood and Trauma- and Stress-Related Disorders. *Front Psychiatry*. 2021;12:814177.
101. Malan-Müller S, Vidal R, O'Shea E, Montero E, Figuero E, Zorrilla I, et al. Probing the oral-brain connection: oral microbiome patterns in a large community cohort with anxiety, depression, and trauma symptoms, and periodontal outcomes. *Translational psychiatry*. 2024;14(1):419.
102. Neupane SP, Virtej A, Myhren LE, Bull VH. Biomarkers common for inflammatory periodontal disease and depression: A systematic review. *Brain Behav Immun Health*. 2022;21:100450.
103. Liu M, Wu Y, Song J, He W. Association of Sleep Duration with Tooth Loss and Periodontitis: Insights from the National Health and Nutrition Examination Surveys (2005-2020). *Sleep Breath*. 2024;28(2):1019-33.
104. Carra MC, Balagny P, Bouchard P. Sleep and periodontal health. *Periodontology 2000*. 2024;96(1):42-73.
105. Zhang MM, Ma Y, Du LT, Wang K, Li Z, Zhu W, et al. Sleep disorders and non-sleep circadian disorders predict depression: A systematic review and meta-analysis of longitudinal studies. *Neuroscience and biobehavioral reviews*. 2022;134:104532.
106. Sconyers JR, Crawford J, Moriarty J. Relationship of bacteremia to toothbrushing in patients with periodontitis. *Journal of the American Dental Association*. 1973;87(3):616-22.

107. Forner L, Larsen T, Kilian M, Holmstrup P. Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. *Journal of clinical periodontology*. 2006;33(6):401-7.
108. D'Aiuto F, Parkar M, Tonetti MS. Periodontal therapy: a novel acute inflammatory model. *Inflammation research : official journal of the European Histamine Research Society [et al]*. 2005;54(10):412-4.
109. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, et al. Treatment of periodontitis and endothelial function. *The New England journal of medicine*. 2007;356(9):911-20.
110. Tonetti MS, Van Dyke TE. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAPWorkshop on Periodontitis and Systemic Diseases. *Journal of periodontology*. 2013;84 Suppl 4S:S24-s9.
111. Minassian C, D'Aiuto F, Hingorani AD, Smeeth L. Invasive dental treatment and risk for vascular events: a self-controlled case series. *Annals of internal medicine*. 2010;153(8):499-506.
112. Lazansky JP, Robinson L, Rodofsky L. Factors influencing the incidence of bacteremias following surgical procedures in the oral cavity. *Journal of dental research*. 1949;28(6):533-43.
113. Tomas I, Diz P, Tobias A, Scully C, Donos N. Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis. *J Clin Periodontol*. 2012;39(3):213-28.
114. Hayashi C, Gudino CV, Gibson FC, 3rd, Genco CA. Review: Pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specific innate immune inflammatory pathways. *Molecular oral microbiology*. 2010;25(5):305-16.
115. Gibson FC, 3rd, Yumoto H, Takahashi Y, Chou HH, Genco CA. Innate immune signaling and *Porphyromonas gingivalis*-accelerated atherosclerosis. *Journal of dental research*. 2006;85(2):106-21.
116. Gibson FC, 3rd, Genco CA. *Porphyromonas gingivalis* mediated periodontal disease and atherosclerosis: disparate diseases with commonalities in pathogenesis through TLRs. *Current pharmaceutical design*. 2007;13(36):3665-75.
117. Frister A, Schmidt C, Schneble N, Brodhun M, Gonnert FA, Bauer M, et al. Phosphoinositide 3-kinase gamma affects LPS-induced disturbance of blood-brain barrier via lipid kinase-independent control of cAMP in microglial cells. *Neuromolecular medicine*. 2014;16(4):704-13.
118. Bohatschek M, Werner A, Raivich G. Systemic LPS injection leads to granulocyte influx into normal and injured brain: effects of ICAM-1 deficiency. *Experimental neurology*. 2001;172(1):137-52.
119. Hashioka S, Inoue K, Hayashida M, Wake R, Oh-Nishi A, Miyaoka T. Implications of Systemic Inflammation and Periodontitis for Major Depression. *Frontiers in neuroscience*. 2018;12:483-.
120. Ritchie CS, Kinane DF. Nutrition, inflammation, and periodontal disease. *Nutrition*. 2003;19(5):475.
121. Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. *Nature*. 2011;474(7351):327.

122. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front Cell Neurosci.* 2015;9:392.
123. Bercik P, Park AJ, Sinclair D, Khoshdel A, Lu J, Huang X, et al. The anxiolytic effect of *Bifidobacterium longum* NCC3001 involves vagal pathways for gut-brain communication. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society.* 2011;23(12):1132-9.
124. Lyte M, Li W, Opitz N, Gaykema RP, Goehler LE. Induction of anxiety-like behavior in mice during the initial stages of infection with the agent of murine colonic hyperplasia *Citrobacter rodentium*. *Physiol Behav.* 2006;89(3):350-7.
125. Zheng P, Zeng B, Zhou C, Liu M, Fang Z, Xu X, et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Mol Psychiatry.* 2016;21(6):786.
126. Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, et al. Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. *Biological psychiatry.* 2017;82(7):472-87.
127. Desbonnet L, Clarke G, Traplin A, O'Sullivan O, Crispie F, Moloney RD, et al. Gut microbiota depletion from early adolescence in mice: implications for brain and behaviour. *Brain Behav Immun.* 2015;48:165-73.
128. Diaz Heijtz R, Wang S, Anuar F, Qian Y, Bjorkholm B, Samuelsson A, et al. Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences of the United States of America.* 2011;108(7):3047-52.
129. Ait-Belgnaoui A, Colom A, Braniste V, Ramalho L, Marrot A, Cartier C, et al. Probiotic gut effect prevents the chronic psychological stress-induced brain activity abnormality in mice. *Neurogastroenterol Motil.* 2014;26(4):510-20.
130. Messaoudi M, Violle N, Bisson JF, Desor D, Javelot H, Rougeot C. Beneficial psychological effects of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in healthy human volunteers. *Gut microbes.* 2011;2(4):256-61.
131. Ong IM, Gonzalez JG, McIlwain SJ, Sawin EA, Schoen AJ, Adluru N, et al. Gut microbiome populations are associated with structure-specific changes in white matter architecture. *Translational psychiatry.* 2018;8(1):6.
132. Mirza I, Day R, Phelan M, Wulff-Cochrane V. Oral health of psychiatric in-patients: a point prevalence survey of an inner-city hospital. *Psychiatric Bulletin.* 2001;25(4):143-5.
133. Saintrain MV, de Souza EH. Impact of tooth loss on the quality of life. *Gerodontology.* 2012;29(2):e632-6.
134. Al-Harthi LS, Cullinan MP, Leichter JW, Thomson WM. The impact of periodontitis on oral health-related quality of life: a review of the evidence from observational studies. *Australian dental journal.* 2013;58(3):274-7; quiz 384.

135. Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NH. Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. *Health Qual Life Outcomes*. 2010;8:126.
136. Friedman N, Landesman HM, Wexler M. The influences of fear, anxiety, and depression on the patient's adaptive responses to complete dentures. Part I. *The Journal of prosthetic dentistry*. 1987;58(6):687-9.
137. John MT, Micheelis W, Steele JG. Depression as a risk factor for denture dissatisfaction. *Journal of dental research*. 2007;86(9):852-6.
138. O'Dowd LK, Durham J, McCracken GI, Preshaw PM. Patients' experiences of the impact of periodontal disease. *J Clin Periodontol*. 2010;37(4):334-9.
139. Beck AT. Cognitive therapy. A 30-year retrospective. *The American psychologist*. 1991;46(4):368-75.
140. Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, et al. Time-related predictors of suicide in major affective disorder. *The American journal of psychiatry*. 1990;147(9):1189-94.
141. Gould TD, Georgiou P, Brenner LA, Brundin L, Can A, Courtet P, et al. Animal models to improve our understanding and treatment of suicidal behavior. *Translational psychiatry*. 2017;7(4):e1092.
142. Wong S, Le GH, Phan L, Rhee TG, Ho R, Meshkat S, et al. Effects of anhedonia on health-related quality of life and functional outcomes in major depressive disorder: A systematic review and meta-analysis. *J Affect Disord*. 2024;356:684-98.
143. Luca A, Luca M, Kasper S, Pecorino B, Zohar J, Souery D, et al. Anhedonia is associated with a specific depression profile and poor antidepressant response. *Int J Neuropsychopharmacol*. 2024;27(12).
144. Aggarwal K, Gupta J, Kaur RK, Bansal D, Jain A. Effect of anxiety and psychologic stress on periodontal health: a systematic review and meta-analysis. *Quintessence Int*. 2022;53(2):144-54.
145. Badia II, Aparicio LC, Aranda MR, Illueca FA, Roldán AL. Assessment of Psychological Stress as a Risk Factor for Periodontal Disease: Systematic Review and Meta-Analysis. *Journal of International Dental and Medical Research*. 2022;15(3):1330-9.
146. Castro MML, Ferreira RO, Fagundes NCF, Almeida A, Maia LC, Lima RR. Association between Psychological Stress and Periodontitis: A Systematic Review. *Eur J Dent*. 2020;14(1):171-9.
147. Spector AM, Postolache TT, Akram F, Scott AJ, Wadhawan A, Reynolds MA. Psychological stress: a predisposing and exacerbating factor in periodontitis. *Current Oral Health Reports*. 2020;7:208-15.
148. Zheng DX, Kang XN, Wang YX, Huang YN, Pang CF, Chen YX, et al. Periodontal disease and emotional disorders: A meta-analysis. *J Clin Periodontol*. 2021;48(2):180-204.

Figures

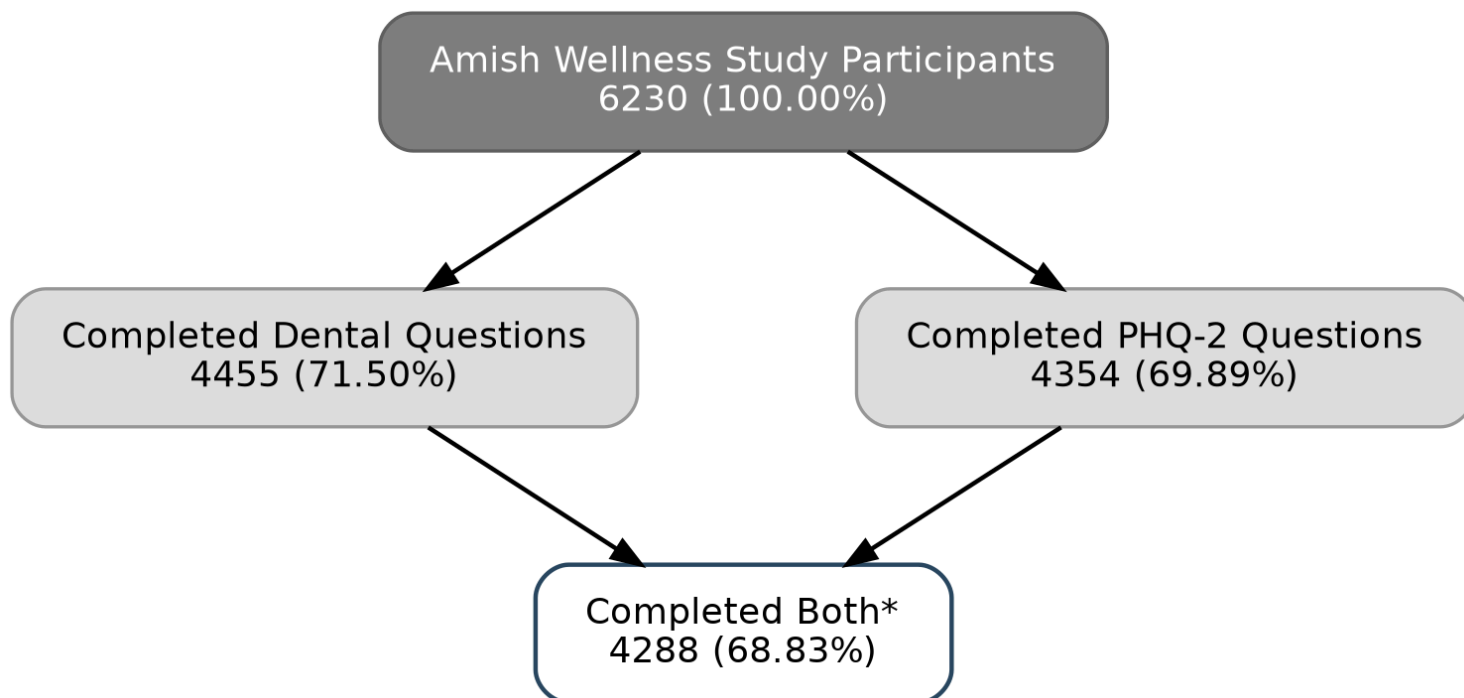


Figure 1

Wellness Study: completion percentage for the dental and depression questionnaires and the analyzed sample of completers of both questionnaires. Of 6,230 participants enrolled in the “parent” Wellness study at the time of the data freeze, 167 (2.7%) had dental questionnaires only, 66 (1.1%) had PHQ-2 questionnaires only, and 1,709 (27.4%) had neither dental nor PHQ-2 questionnaires. Our study included the 4,288 participants who completed both the PHQ-2 and dental questionnaires. *Indicates the study/analysis sample.

Supplementary Files

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- [SuprTable1b.docx](#)
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