Brain, Behavior, & Immunity - Health 34 (2023) 100689

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Association between periodontitis and depression severity – A cross-sectional study of the older population in Hamburg

Carolin Walther [a,1], Berit Lieske [a,*,1], Katrin Borof [a], Simone Kühn [b], Martin Härter [c], Bernd Löwe [d], Thomas Beikler [a], Guido Heydecke [e], Piotr Kuta [f], Udo Seedorf [a], Kristin Spinler [a], Jürgen Gallinat [b,2], Ghazal Aarabi [a,2]

[a] Department of Periodontics, Preventive and Restorative Dentistry, Center for Dental and Oral Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[b] Department of Psychiatry and Psychotherapy, Center for Psychosocial Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[c] Department of Medical Psychology, Center for Psychosocial Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[d] Department of Psychosomatic Medicine and Psychotherapy, Center for Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[e] Department of Prosthetic Dentistry, Center for Dental and Oral Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[f] Institute of Clinical Chemistry and Laboratory Medicine, Center for Diagnostics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

ARTICLE INFO

Keywords:
Periodontitis
Oral health
Depressive disorders
Depression
Inflammation
Risk factor

ABSTRACT

The aim of the current study is to investigate the association between periodontitis (exposure variable) and depression severity (outcome variable) in an older German population. We evaluated data from 6,209 participants (median age 62 years) of the Hamburg City Health Study (HCHS). The HCHS is a prospective cohort study and is registered at ClinicalTrial.gov (NCT03934957). Depression severity were assessed with the 9-item Patient Health Questionnaire (PHQ-9). Periodontal examination included probing depth, gingival recession, plaque index, and bleeding on probing. Descriptive analyses were stratified by periodontitis severity. Multiple linear regression models were adjusted for age, sex, diabetes, education, smoking, and antidepressant medication. Linear regression analyses revealed a significant association between log-transformed depression severity and periodontitis when including the interaction term for periodontitis * age, even after adjusting for age, sex, diabetes, education, smoking and antidepressant medication. We identified a significant association between severe periodontitis and elevated depression severity, which interacts with age. Additionally, we performed a linear regression model for biomarker analyses, which revealed significant associations between depression severity and severe periodontitis with log-transformed inflammatory biomarkers interleukin 6 (IL-6) and high-sensitivity C-reactive protein (hsCRP). In order to identify new therapeutic strategies for patients with depression and periodontal disease, future prospective studies are needed to assess the physiological and psychosocial mechanisms behind this relationship and the causal directionality.

1. Introduction

Analyses of the Global Burden of Disease database revealed an incident increase of depression from 1990 to 2017 by 49.86% (Liu et al., 2020). In absolute numbers, this means about 322 million people worldwide suffer from depression (World Health, 2017; Wittchen et al., 2011). Depression is a well identified risk factor for general health, including cardiovascular health (Goldstein et al., 2015), cognitive dysfunction (MacQueen and Memedovich, 2017), insomnia (Murphy and Peterson, 2015), fatigue (Ghanean et al., 2018) and a weakened immune system (Gabbay et al., 2009).

Depression can also affect oral health. A recent published review demonstrated that depression increased the odds for dental caries (OR 1.27; 95% CI 1.13–1.44) and tooth loss (OR 1.31; 95% CI 1.24–1.37) (Cademartori et al., 2018).

Associations between depression and oral health might be explained

* Corresponding author. Department of Periodontics, Preventive and Restorative Dentistry Center for Dental and Oral Medicine University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246, Hamburg, Germany.
E-mail address: b.lieske@uke.de (B. Lieske).
[1] shared first authorship.
[2] *shared last authorship*.

https://doi.org/10.1016/j.bbih.2023.100689
Received 14 March 2023; Received in revised form 22 September 2023; Accepted 23 September 2023
Available online 25 September 2023

by behavioral patterns. For example, patients suffering from depression present different dietary habits (Molendijk et al., 2018) and tend to show insufficient oral health behavior (Park et al., 2014). In recent publications, however, an opposite direction of action has been discussed. Patients with major depressive disorder differed significantly in their pro-inflammatory cytokine levels, e.g. interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), high-sensitivity C-reactive protein (hsCRP), compared to matched controls (Liu et al., 2012). Periodontitis, characterized by chronic inflammation of the tooth surrounding tissue, is a significant source of systemic inflammatory molecules (Hashioka et al., 2018) and contributes to the overall inflammatory "pool" in the body. A second possible pathway is the direct invasion of periodontal pathogens and their inflammatory products into the brain through infection of the trigeminal and olfactory nerve (Dominy et al., 2019). Interestingly, patients with chronic apical periodontitis showed strong correlation between root canal endotoxin levels (lipopolysaccharides (LPS)) and depression severity (Gomes et al., 2018). High levels of LPS might be one possible link between periodontitis and depression (Hashioka et al., 2018). Yet, the association between oral health and depression in Germany has so far only been demonstrated in one longitudinal study with 310 patients with chronic and aggressive periodontitis (Ehrenthal et al., 2016). Higher tooth loss at the beginning of the examination was significantly associated with higher scores of depression severity. In light of the restricted knowledge, the aim of the current study is to investigate the association between periodontitis (exposure variable) and depression severity (outcome variable) in a large German population of older adults.

2. Materials and methods

2.1. Subjects, study design and setting

The Hamburg City Health Study (HCHS) is a prospective, long-term, population-based, cohort study conducted at the University Medical Center Hamburg-Eppendorf (UKE). The local ethics committee of the Medical Association of Hamburg approved the study protocol (PV5131) and it is registered at ClinicalTrial.gov (NCT03934957). The HCHS aims to collect health-related data from 45,000 citizens (aged 45–75 years) from the greater area of Hamburg to gather information regarding the disease burden of the older northern population (Jagodzinski et al., 2020). Available were the baseline-data from the first 10,000 participants recruited between February 2016 and November 2018. Of these, n = 6,209 subjects had received a full dental examination. Full depression screening was available for n = 8,888 subjects and hsCRP analysis was available for n = 9,395 subjects of the 10,000 screened participants. IL-6 analysis was performed for the first n = 5,000 HCHS participants and data was available for n = 4,949 subjects. In total, n = 5,591 participants presented full periodontal examination and depression screening and were selected for analysis. Exclusion criteria for the current study were: no periodontal examination (n = 3,791) and no documentation of the 9-item Patient Health Questionnaire (PHQ-9; n = 1,112) (Kroenke et al., 2001), which screens adult patients for the presence and severity of depression.

2.2. Assessment of dental variables

All participants received a full dental examination, performed by trained and calibrated study nurses under supervision of a trained dentist. Oral examination included: a full dental status, probing depth (mm, 6 sites per tooth), gingival recession (mm, 6 sites per tooth), determination of the plaque index (2 sites per tooth), and the bleeding on probing index (BOP-Index) (2 sites per tooth; PCP-12 probe). Subsequently, secondary variables were calculated, such as DMFT-Index (number of decayed, missing, filled teeth) and the clinical attachment loss (CAL) (sites/mouth CAL≥3 mm). All participants were then categorized in one out of three severity levels of periodontitis (Eke et al., 2012): (Liu et al., 2020) no periodontitis/mild periodontitis, (World Health, 2017) moderate periodontitis, and (Wittchen et al., 2011) severe periodontitis.

2.3. Assessment of depression severity

The 9-item Patient Health Questionnaire (PHQ-9) corresponds to the depression module of the PHQ-D and comprises nine items assessing the severity of depressive symptoms. It is a reliable and valid measure of depression severity and each item of the PHQ-9 captures one of the nine criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), for the diagnosis of "major depression" (Kroenke et al., 2001; Association, 2013). Based on participant response (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day), a total depression score ranging from 0 to 27 was obtained. Higher scores indicate increased depression severity. The PHQ-9 scores are divided into five categories of depression: none (<5); minimal (MacQueen and Memedovich, 2017; Murphy and Peterson, 2015; Ghanean et al., 2018; Gabbay et al., 2009; Cademartori et al., 2018); mild (10–14); moderate (15–19); and severe (>19) (Kroenke et al., 2001). The validated German version of the PHQ-9 was used to determine depression severity among the respondents (Löwe et al., 2004). It was self-completed by the patient in electronic or written form.

2.4. Assessment of biomarkers

Venous blood samples of all HCHS participants were obtained under fasting conditions. Samples were processed and stored at −80 °C until subsequent usage. IL-6 (mg/l) was measured in EDTA plasma using the Human IL-6 Quantikine HS ELISA Kit (R&D Systems) with an assay range of 0.2–10 pg/mL. Coefficient of variation (CV) were as follows: intra CV% 2,47, inter CV% 10.08. hsCRP (mg/l) was determined by immunoturbidimetric method with reagents of Siemens Healthcare Diagnostics on the Atellica CH Analyzer, Siemens Healthineers, Erlangen, Germany.

2.5. Assessment of additional variables

The following information on confounding variables were retrieved from the HCHS database for all participants: sex, age (in years), education (according to the International Standard Classification of Education-97 (ISCED-97) (Co-operation OfE, 1999)), body mass index (BMI) (in kg/m^2), smoking (current smoker), diabetes (positive self-declaration and/or taking medication of the A10 group (insulin and analogues), and/or fasting glucose >126 mg/dL, not fasting glucose >200 mg/dL), HBA1C (in %), alcohol consumption (in g per day), medication intake (yes), number of medication, and intake of antidepressant medication (yes), such as non-selective monoamine reuptake inhibitors or selective serotonin reuptake inhibitor.

2.6. Statistical analyses

Descriptive analyses were stratified by periodontitis severity (Table 1) and by depression severity (Table 2). Continuous variables are displayed as median and interquartile range [median (IQR)]. Categorical variables are displayed as absolute numbers and percentages [n (%)]. Within-group differences were calculated using the Chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. To determine the association between periodontitis (exposure) and depression severity (outcome), linear regression models were applied (Table 3). We used a log (1 + x) transformation for depression severity and adjusted for age, sex, diabetes, education, smoking, and antidepressant medication. Due to the opposite distribution of exposure and outcome, an interaction term (periodontitis * age) was used in the regression model. Lastly, we performed linear regression models for biomarker analyses (outcome = biomarkers IL-6 and hsCRP) (Table 4).

Table 1
Descriptive characteristics of periodontitis cohort.

Characteristics	Overall, N = 5,591[a]	Periodontitis			*P*-value[b]
		None/mild, N = 1,310[a]	Moderate, N = 3,239[a]	Severe, N = 1,042[a]	
Sociodemographics					
Sex					<0.001
Male	2,778 (50%)	535 (41%)	1,605 (50%)	638 (61%)	
Female	2,813 (50%)	775 (59%)	1,634 (50%)	404 (39%)	
Age	62.0 (55.0,69.0)	58.0 (52.0,66.0)	62.0 (55.0,69.0)	66.0 (59.0,71.0)	<0.001
Education					<0.001
Low	221 (4.1%)	36 (2.8%)	134 (4.3%)	51 (5.1%)	
Medium	2,641 (49%)	597 (47%)	1,519 (49%)	525 (53%)	
High	2,528 (47%)	639 (50%)	1,470 (47%)	419 (42%)	
Missing	201	38	116	47	
Risk factors					
BMI	26.0 (23.5,29.0)	25.6 (23.0,28.7)	26.0 (23.5,29.0)	26.4 (24.1,29.5)	<0.001
Missing	291	75	153	63	
Smoking	992 (18%)	208 (16%)	532 (17%)	252 (24%)	<0.001
Missing	30	5	19	6	
Diabetes	392 (7.6%)	73 (5.9%)	214 (7.2%)	105 (11%)	<0.001
Missing	426	66	275	85	
Alcohol consumption last 12 month					0.194
Never	362 (7.9%)	86 (7.7%)	200 (7.6%)	76 (9.3%)	
Once per month or less	794 (17%)	202 (18%)	450 (17%)	142 (17%)	
2–4 times/month	1,187 (26%)	282 (25%)	684 (26%)	221 (27%)	
2–3 times/week	1,226 (27%)	298 (27%)	741 (28%)	187 (23%)	
4 times/week or more	1,004 (22%)	246 (22%)	565 (21%)	193 (24%)	
Missing	1,018	196	599	223	
Alcohol consumption g/day	9.8 (2.8,23.3)	9.4 (2.7,21.6)	9.6 (2.8,23.2)	10.7 (2.9,27.0)	0.088
Missing	203	43	113	47	
Biomarkers					
HBA1C	5.50 (5.30,5.70)	5.50 (5.30,5.70)	5.50 (5.30,5.80)	5.60 (5.30,5.80)	<0.001
Missing	191	40	119	32	
IL6	1.56 (1.13,2.18)	1.44 (1.01,2.05)	1.55 (1.14,2.15)	1.73 (1.32,2.44)	<0.001
Missing	2,683	606	1,566	511	
hsCRP	0.11 (0.06,0.25)	0.10 (0.06,0.23)	0.11 (0.06,0.24)	0.13 (0.07,0.29)	<0.001
Missing	337	80	203	54	
Depression					
Depression severity (PHQ-9)					0.121
None	1,100 (20%)	227 (17%)	653 (20%)	220 (21%)	
Minimal	2,886 (52%)	673 (51%)	1,672 (52%)	541 (52%)	
Mild	1,280 (23%)	337 (26%)	717 (22%)	226 (22%)	
Moderate	254 (4.5%)	55 (4.2%)	156 (4.8%)	43 (4.1%)	
Severe	71 (1.3%)	18 (1.4%)	41 (1.3%)	12 (1.2%)	
Medication					
Medication intake	4,197 (79%)	993 (78%)	2,416 (78%)	788 (80%)	0.385
Missing	246	29	161	56	
Number of medication	5.0 (3.0,9.0)	4.0 (2.0,8.0)	5.0 (3.0,9.0)	6.0 (3.0,10.0)	0.003
Missing	1,410	324	831	255	
Antidepressant medication	311 (5.8%)	91 (7.1%)	173 (5.6%)	47 (4.8%)	0.048
Missing	246	29	161	56	
Dental parameters					
Number of missing teeth	2.0 (1.0,5.0)	2.0 (0.0,4.0)	2.0 (1.0,5.0)	4.0 (1.0,8.0)	<0.001
DMFT-Index	19.0 (15.0,23.0)	17.0 (14.0,21.0)	19.0 (16.0,23.0)	21.0 (17.0,24.0)	<0.001
Sites/mouth CAL $\geq$ 3 mm	36.3 (19.8,57.2)	12.5 (6.4,20.8)	38.1 (25.6,53.3)	68.5 (53.9,83.3)	<0.001
Missing	2	0	2	0	
BOP Index	7.7 (1.9,20.4)	2.1 (0.0,7.1)	8.3 (2.2,19.2)	21.2 (9.6,42.1)	<0.001
Missing	77	33	42	2	
Plaque Index	7.7 (0.0,27.3)	0.0 (0.0,11.1)	8.3 (0.0,27.3)	22.2 (5.6,55.9)	<0.001
Missing	78	8	51	19	

Abbreviations: BMI = Body-Mass-Index, BOP = Bleeding on Probing, CAL = Clinical attachment loss, hsCRP = high-sensitivity C-reactive proteine, DMFT = Decayed Missing Filled Teeth, IL-6 = Interleukin −6, PHQ-9 = 9-item Patient Health Questionnaire.
[a] n (%); Median (25%,75%).
[b] Pearson's Chi-squared test; Kruskal-Wallis rank sum test.

All statistical analyses were performed using the computing software R (Version 4.0.3) with standard p-value <.05 for statistical significance.

3. Results

3.1. Descriptive analyses

Table 1 displays descriptive characteristics of the periodontitis cohort (n = 6,209). 1,453 participants had either none or mild periodontitis, 3,580 had moderate and 1,176 presented severe periodontitis. When compared to participants to none/mild periodontitis, participants with severe periodontitis were more frequently older men (median age 59 vs. 66 years and 40% vs. 61% males), with more cardiovascular risk factors (BMI, smoking and diabetes), higher inflammatory biomarker levels (IL6 and hsCRP) and higher overall medication intake (Table 1). Participants with severe levels of depression were more frequently women (62% vs. 35%) and of younger age (58 vs. 65 years) when compared to participants with no depression (Table 2).

Table 2
Descriptive statistics for different levels of depression severity.

Characteristics	Overall, N = 5,591[a]	Depression severity (PHQ-9)					*P*-value[b]
		None, N = 1,100[a]	Minimal, N = 2,886[a]	Mild, N = 1,280[a]	Moderate, N = 254[a]	Severe, N = 71[a]	
Sociodemographics							
Sex							<0.001
Male	2,778 (50%)	715 (65%)	1,418 (49%)	524 (41%)	91 (36%)	30 (42%)	
Female	2,813 (50%)	385 (35%)	1,468 (51%)	756 (59%)	163 (64%)	41 (58%)	
Age	62.0 (55.0,69.0)	65.0 (57.0,70.0)	63.0 (55.0,69.0)	60.0 (54.0,68.0)	59.0 (55.0,65.0)	57.0 (53.5,62.0)	<0.001
Education							
Low	221 (4.1%)	31 (2.9%)	103 (3.7%)	66 (5.4%)	15 (6.4%)	6 (9.4%)	
Medium	2,641 (49%)	474 (44%)	1,369 (49%)	622 (51%)	138 (59%)	38 (59%)	
High	2,528 (47%)	563 (53%)	1,322 (47%)	541 (44%)	82 (35%)	20 (31%)	
Missing	201	32	92	51	19	7	

PHQ-9 = 9-item Patient Health Questionnaire.
[a] n (%); Median (25%,75%).
[b] Pearson's Chi-squared test; Kruskal-Wallis rank sum test.

3.2. Regression analyses

Linear regression analyses revealed a significant association between severe periodontitis and log-transformed depression severity ($\beta = 0.72$ *[0.21–1.23], p = .006*) when including the interaction term severe periodontitis * age ($\beta = -0.01$ *[−0.02—0.00], p = .006*) and adjusting for age, sex, diabetes, education, smoking and antidepressant medication (Table 3). Linear regression model for biomarker analyses revealed significant association between depression severity (β = 0.01 [0.01–0.02]; 0.02 [0.01–0.03]; both $p < .001$) and severe periodontitis (β = 0.12 [0.06–0.18]; 0.16 [0.07–0.24]; both $p < .001$) with log-transformed inflammatory biomarkers IL-6 and hsCRP (Table 4).

4. Discussion

4.1. Main findings

Severe periodontitis was more prevalent in older men, while depression severity was higher in woman compared to men. Our regression analyses demonstrated a significant association between severe periodontitis and log-transformed depression severity when including the interaction term periodontitis * age. Additionally, depression and periodontitis severity were significantly positively associated with the inflammatory biomarkers IL-6 and hsCRP.

4.2. Previous research and possible explanations

The results of the current study are in line with previously published cross-sectional data from the United States of America (Aldosari et al., 2020) and longitudinal data from Taiwan (Hsu et al., 2015). Both surveys revealed a significant association between periodontitis and depression severity, even after adjustments for several confounding factors (age, sex, race/ethnicity, education, income, cigarette smoking, heavy alcohol consumption, psychotherapeutic medications, diabetes, depression-associated comorbidities). Controversially, a systematic review and meta-analysis from 2016 assessed fifteen cross-sectional studies and could not confirm the association between periodontitis and depression (Araújo et al., 2016). This could be due to the high heterogeneity among the included studies, with different instruments used to assess depression severity and varying age groups. Furthermore, Nolde et al. (2022) aimed to clarify the shared genetic background between periodontitis and depression, using summary statistics from published genome wide associations studies (GWAS). The authors only found weak genetic correlation between depression and periodontitis and bidirectional causality of both entities could not be confirmed (Nolde et al., 2022).

Another possible reason for those mixed findings is the following. During the analyses of the data, we were facing a major difficulty: Depression severity and periodontitis among the participants were unequally distributed. This has already been reported in the literature: with higher prevalence rates of depression among younger females (Kuehner, 2003; Silverstein, 2002; Karger, 2014) and more prevalent cases of periodontitis among older males (Holde et al., 2017; Ju et al., 2021). Thus, the variable "age" seems to influence the relationship between periodontitis and depression. Consequently, we decided to apply an interaction term "periodontitis * age" in our regression models. The interaction term can be explained as follows: according to model 3 in Table 3 (adjusted for age and sex) the outcome variable (log-transformed depression severity) will increase by the factor 0.84 for participants with severe periodontitis compared to participants with none/mild periodontitis. Further, we have to consider the interaction term severe periodontitis * age = −0.01 * e.g. 55 years, which decreases the effect to 0.29 (result of subtracting 0.84–0.55). For participants of 45 years of age the difference between none/mild or severe periodontitis is 0.84–0.45 = 0.39. In summary, the older the person, the larger the interaction term and the smaller the subtraction of the two. Hence, the variable "age" presents a protective effect on depression severity in participants with severe periodontitis. To the best of our knowledge, this is the first study in this field of research applying this interaction term and therefore acknowledging the effect of age on the relationship between depression severity and periodontitis.

Two underlying mechanisms of this association have been discussed: Periodontal disease may increase the risk for depression severity through psychological effects (Dumitrescu, 2016; Hashioka et al., 2019). For example, periodontitis has been associated with poorer oral hygiene and oral halitosis (De Geest et al., 2016; Tsai et al., 2008), which in turn often leads to feelings of shame and embarrassment, which reduces the patient's quality of life (Dumitrescu, 2016; Bale et al., 2004; Durham et al., 2013). Additionally, tooth loss (the clinical endpoint of periodontal disease manifestation) (Kassebaum et al., 2014; Romandini et al., 2021) may impair the patient's body image and diminish self-esteem, which as a result may lead to isolation and loneliness (Nordenram et al., 2013) constituting risk factors for depression. The effect of tooth loss on depression severity seems to be greater in younger age groups. Older people might consider the loss of teeth as a naturally occurring change with ageing to which they have adapted (MacEntee et al., 1997; Matsuyama et al., 2021). Moreover, studies on the attitude of different age groups on the appearance of teeth show that dental aesthetics are not as important among older in comparison to younger patients (Vallittu et al., 1996; Strajnić et al., 2016). As shown in a study from the United Kingdom, older patients were more satisfied with their dental appearance than younger age groups (Alkhatib et al., 2005). Thus, these factors might explain the protective effect of age on depression severity and therefore the weaker psychological effects among older patients.

Another possible pathway is that periodontal disease may increase

Table 3
Linear regression for the association between periodontitis and depression severity (PHQ-9).

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	β	*p-value*	*β*	*p-value*	*β*	*p-value*	*β*	*p-value*	*β*	*p-value*	*β*	*p-value*	*β*	*p-value*	*β*	*p-value*
Moderate periodontitis	−0.05 (−0.10;0.00)	**.049**	0.01 (−0.04;0.06)	.766	0.30 (−0.06;0.66)	.098	0.36 (−0.02;0.73)	.060	0.29 (−0.09;0.66)	.130	0.27 (−0.11;0.64)	.166	0.30 (−0.07;0.67)	.111	0.37 (−0.05;0.80)	.083
Severe periodontitis	−0.08 (−0.14;-0.02)	**.015**	0.04 (−0.02;0.10)	.229	0.84 (0.35;1.32)	**.001**	0.91 (0.40;1.42)	**<.001**	0.76 (0.24;1.28)	**.004**	0.67 (0.15;1.19)	**.011**	0.72 (0.21;1.23)	**.006**	0.72 (0.13;1.31)	**.017**
Age			−0.01 (−0.01;-0.01)	**<.001**	−0.01 (−0.01;-0.00)	**.006**	−0.01 (−0.01;-0.00)	**.007**	−0.01 (−0.01;-0.00)	**.003**	−0.01 (−0.01;-0.00)	**.006**	−0.01 (−0.01;-0.00)	**.004**	−0.01 (−0.02;-0.01)	**<.001**
Female sex			0.27 (0.23;0.31)	**<.001**	0.27 (0.23;0.31)	**<.001**	0.28 (0.24;0.32)	**<.001**	0.26 (0.22;0.31)	**<.001**	0.27 (0.22;0.31)	**<.001**	0.24 (0.20;0.29)	**<.001**	0.23 (0.18;0.28)	**<.001**
Moderate periodontitis * Age					−0.00 (−0.01;0.00)	.098	−0.01 (−0.01;0.00)	.059	−0.00 (−0.01;0.00)	.120	−0.00 (−0.01;0.00)	.149	−0.00 (−0.01;0.00)	.112	−0.01 (−0.01;0.00)	.081
Severe periodontitis * Age					−0.01 (−0.02;-0.01)	**.001**	−0.01 (−0.02;-0.01)	**.001**	−0.01 (−0.02;-0.00)	**.004**	−0.01 (−0.02;-0.00)	**.009**	−0.01 (−0.02;-0.00)	**.006**	−0.01 (−0.02;-0.00)	**.016**
Diabetes							0.21 (0.13;0.29)	**<.001**	0.19 (0.11;0.27)	**<.001**	0.19 (0.11;0.27)	**<.001**	0.17 (0.09;0.25)	**<.001**	0.10 (0.01;0.18)	**.021**
Education high									−0.20 (−0.31;-0.09)	**<.001**	−0.19 (−0.30;-0.08)	**.001**	−0.17 (−0.28;-0.06)	**.002**	−0.18 (−0.30;-0.06)	**.003**
Smoking											0.11 (0.05;0.16)	**<.001**	0.09 (0.03;0.14)	**.002**	0.11 (0.04;0.17)	**.001**
Antidepressant medication													0.60 (0.51;0.69)	**<.001**	0.53 (0.44;0.62)	**<.001**

Linear regression model with outcome = depression severity. * = Interaction term periodontitis with age. Adjusted for: age, sex, diabetes, education, smoking and antidepressive medication. None/mild periodontitis, Male sex and low educational level serve as reference and are not displayed in the table. PHQ-9 = 9-item Patient Health Questionnaire.

Table 4
Linear regression for biomarker analyses.

Linear Model for Biomarkers				
	Outcome: log IL6		Outcome: log hsCRP	
	β	*p-value*	*β*	*p-value*
Age	0.02 (0.01;0.02)	**<.001**	0.01 (0.01;0.02)	**<.001**
Depression severity (PHQ-9)	0.01 (0.01;0.02)	**<.001**	0.02 (0.01;0.03)	**<.001**
Moderate periodontitis	0.04 (−0.01;0.08)	.106	0.04 (−0.03;0.11)	.242
Severe periodontitis	0.12 (0.06;0.18)	**<.001**	0.16 (0.07;0.24)	**<.001**
Female sex	−0.05 (−0.09;-0.01)	**.013**	0.02 (−0.04;0.07)	.513

Linear regression model with outcome = biomarker IL-6 and hsCRP. Adjusted for: age, depression severity, periodontitis and sex. None/mild periodontitis and male sex serve as reference and are not displayed in the table. PHQ-9 = 9-item Patient Health Questionnaire.

the risk for depression by being a significant source of systemic inflammatory molecules. In our linear regression model for biomarker analyses, we found a significant positive association between depression severity and severe periodontitis with log-transformed inflammatory biomarkers IL-6 and hsCRP. Patients with severe periodontitis and higher PHQ-9 scores demonstrated significantly higher IL-6 and hsCRP levels. This is in line with other research, showing elevated levels of inflammatory biomarkers among periodontitis patients (Bretz et al., 2005; Engebretson et al., 2007; Paraskevas et al., 2008). Moreover, other studies report an increase in inflammatory response among subjects with depression (Liu et al., 2012; Mac Giollabhui et al., 2021; Osimo et al., 2020). Periodontitis does not just cause local inflammation in the oral cavity, but through dissemination of inflammatory mediators and bacterial components may contribute to the inflammatory pool in the body, therefore contributing to extraoral diseases (Hoare et al., 2019). Findings suggest an association between systemic inflammation and a higher risk to be affected by depression (Frank et al., 2021; Milaneschi et al., 2021; Li et al., 2023). One hypothesis is that bacteria from the periodontal pocket - such as *Poryphyromonas gingivalis*, which has previously been associated with cognitive impairment in the elderly (Poole et al., 2013) - can gain access to the blood circulation, which results in the translocation of pathogenic products from the mouth to the brain through the blood-brain barrier (Kamer et al., 2008; Martínez et al., 2021). A recent published systematic review assessed biomarkers common for periodontitis and depression, in order to address the question on how oral (peripheral) inflammation can induce neuroimmune response. The authors confirmed the association between depression and periodontitis and also the inflammatory contribution to each disease. Nevertheless, they conclude that only limited evidence is available to acknowledge a causal pathway between depression and periodontitis (Neupane et al., 2022).

Vice versa, depression might also increase the risk for periodontitis. For example, depression has been associated with unhealthy dietary habits (Molendijk et al., 2018; Ljungberg et al., 2020; Lang et al., 2015; Paans et al., 2018; Kris-Etherton et al., 2021; Liu et al., 2007) as well as a lack of sufficient oral health behavior (Park et al., 2014; Kisely et al., 2016; Tiwari et al., 2021), which leads to an increased risk of periodontal disease.

4.3. Strengths and limitations

To our knowledge, this is the first study to introduce an interaction term (periodontitis * age), which takes the opposite distribution of exposure and outcome - severe periodontitis more frequently among older men and higher depressive severity among younger women – into account. However, since this is a cross-sectional study, we cannot establish the directionality of the association or confirm true causality. The validity of the PHQ-9 and adequacy for the general German population has been shown in previous publications (Martin et al., 2006; Reich et al., 2018; Spangenberg et al., 2012; Kocalevent et al., 2013). For instance, among a representative sample of the general population in Germany with 2,066 subjects that filled in the PHQ-9, results supported the construct validity of the depression scale (Martin et al., 2006). The HCHS cohort consists of middle-aged, mostly white Caucasian subjects. Thus, our findings cannot be generalized to a much younger population or other ethnicities.

5. Conclusion

We identified a significant association between severe periodontitis and depression severity. In order to identify new therapeutic strategies for patients with depression and periodontal disease, future prospective studies are needed to assess the physiological and psychosocial mechanisms behind this relationship.

Funding

The participating institutes and departments from the University Medical Center Hamburg-Eppendorf contribute all with individual and scaled budgets to the overall funding.

The HCHS is additionally funded by the euCanSHare grant agreement [Grant Number 825903-euCanSHare H2020]; the Joachim Herz Foundation, the Foundation Leducq [Grant Number 16 CVD 03] and the Innovative medicine initiative [Grant Number 116074]. The HCHS is further supported by Deutsche Gesetzliche Unfallversicherung (DGUV); Deutsches Krebsforschungszentrum (DKFZ); Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK); Deutsche Stiftung für Herzforschung; Seefried Stiftung; Bayer; Amgen, Novartis; Schiller; Siemens; Topcon, Unilever and by donations from the "Förderverein zur Förderung der HCHS e.V.", and TePe® (2014). Sponsor funding has in no way influenced the content or management of this study.

Ethical standards

The study protocol (PV5131) was approved by the local ethics committee of the Medical Association of Hamburg and registered at ClinicalTrial.gov (NCT03934957). Our study is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate

All persons gave their informed consent prior to their inclusion in the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100689.

References

Aldosari, M., Helmi, M., Kennedy, E.N., Badamia, R., Odani, S., Agaku, I., et al., 2020. Depression, periodontitis, caries and missing teeth in the USA, NHANES 2009-2014. Fam. Med. Commun.Health 8 (4).

Alkhatib, M.N., Holt, R., Bedi, R., 2005. Age and perception of dental appearance and tooth colour. Gerodontology 22 (1), 32–36.

Araújo, M.M., Martins, C.C., Costa, L.C.M., Cota, L.O.M., Faria, R.L.A.M., Cunha, F.A., et al., 2016. Association between depression and periodontitis: a systematic review and meta-analysis. J. Clin. Periodontol. 43 (3), 216–228.

Association, A.P., 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-5.

Bale, S., Tebbie, N., Price, P., 2004. A topical metronidazole gel used to treat malodorous wounds. Br. J. Nurs. 13 (11), S4–S11.

Bretz, W.A., Weyant, R.J., Corby, P.M., Ren, D., Weissfeld, L., Kritchevsky, S.B., et al., 2005. Systemic inflammatory markers, periodontal diseases, and periodontal infections in an elderly population. J. Am. Geriatr. Soc. 53 (9), 1532–1537.

Cademartori, M.G., Gastal, M.T., Nascimento, G.G., Demarco, F.F., Correa, M.B., 2018. Is depression associated with oral health outcomes in adults and elders? A systematic review and meta-analysis. Clin. Oral Invest. 22 (8), 2685–2702.

Co-operation OfE, Development, 1999. Classifying Educational Programmes: Manual for ISCED-97 Implementation in OECD Countries. Organisation for Economic Co-operation and Development.

De Geest, S., Laleman, I., Teughels, W., Dekeyser, C., Quirynen, M., 2016. Periodontal diseases as a source of halitosis: a review of the evidence and treatment approaches for dentists and dental hygienists. Periodontol. 2000 71 (1), 213–227.

Dominy, S.S., Lynch, C., Ermini, F., Benedyk, M., Marczyk, A., Konradi, A., et al., 2019. Porphyromonas gingivalis in Alzheimer's disease brains: evidence for disease causation and treatment with small-molecule inhibitors. Sci. Adv. 5 (1), eaau3333.

Dumitrescu, A.L., 2016. Depression and inflammatory periodontal disease considerations-an interdisciplinary approach. Front. Psychol. 7, 347.

Durham, J., Fraser, H.M., McCracken, G.I., Stone, K.M., John, M.T., Preshaw, P.M., 2013. Impact of periodontitis on oral health-related quality of life. J. Dent. 41 (4), 370–376.

Ehrenthal, J.C., Graetz, C., Plaumann, A., Dörfer, C.E., Herzog, W., 2016. Number of teeth predict depressive symptoms in a longitudinal study on patients with periodontal disease. J. Psychosom. Res. 89, 16–19.

Eke, P.I., Page, R.C., Wei, L., Thornton-Evans, G., Genco, R.J., 2012. Update of the case definitions for population-based surveillance of periodontitis. J. Periodontol. 83 (12), 1449–1454.

Engebretson, S., Chertog, R., Nichols, A., Hey-Hadavi, J., Celenti, R., Grbic, J., 2007. Plasma levels of tumour necrosis factor-alpha in patients with chronic periodontitis and type 2 diabetes. J. Clin. Periodontol. 34 (1), 18–24.

Frank, P., Jokela, M., Batty, G.D., Cadar, D., Steptoe, A., Kivimäki, M., 2021. Association between systemic inflammation and individual symptoms of depression: a pooled analysis of 15 population-based cohort studies. Am. J. Psychiatr. 178 (12), 1107–1118.

Gabbay, V., Klein, R.G., Alonso, C.M., Babb, J.S., Nishawala, M., De Jesus, G., et al., 2009. Immune system dysregulation in adolescent major depressive disorder. J. Affect. Disord. 115 (1–2), 177–182.

Ghanean, H., Ceniti, A.K., Kennedy, S.H., 2018. Fatigue in patients with major depressive disorder: prevalence, burden and pharmacological approaches to management. CNS Drugs 32 (1), 65–74.

Goldstein, B.I., Carnethon, M.R., Matthews, K.A., McIntyre, R.S., Miller, G.E., Raghuveer, G., et al., 2015. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American heart association. Circulation 132 (10), 965–986.

Gomes, C., Martinho, F.C., Barbosa, D.S., Antunes, L.S., Póvoa, H.C.C., Baltus, T.H.L., et al., 2018. Increased root canal endotoxin levels are associated with chronic apical periodontitis, increased oxidative and nitrosative stress, major depression, severity of depression, and a lowered quality of life. Mol. Neurobiol. 55 (4), 2814–2827.

Hashioka, S., Inoue, K., Hayashida, M., Wake, R., Oh-Nishi, A., Miyaoka, T., 2018. Implications of systemic inflammation and periodontitis for major depression. Front. Neurosci. 12, 483.

Hashioka, S., Inoue, K., Miyaoka, T., Hayashida, M., Wake, R., Oh-Nishi, A., et al., 2019. The possible causal link of periodontitis to neuropsychiatric disorders: more than psychosocial mechanisms. Int. J. Mol. Sci. 20 (15), 3723.

Hoare, A., Soto, C., Rojas-Celis, V., Bravo, D., 2019. Chronic inflammation as a link between periodontitis and carcinogenesis. Mediat. Inflamm. 2019, 1029857.

Holde, G.E., Oscarson, N., Trovik, T.A., Tillberg, A., Jönsson, B., 2017. Periodontitis prevalence and severity in adults: a cross-sectional study in Norwegian circumpolar communities. J. Periodontol. 88 (10), 1012–1022.

Hsu, C.C., Hsu, Y.C., Chen, H.J., Lin, C.C., Chang, K.H., Lee, C.Y., et al., 2015. Association of periodontitis and subsequent depression: a nationwide population-based study. Medicine (Baltim.) 94 (51), e2347.

Jagodzinski, A., Johansen, C., Koch-Gromus, U., Aarabi, G., Adam, G., Anders, S., et al., 2020. Rationale and design of the Hamburg city health study. Eur. J. Epidemiol. 35 (2), 169–181.

Ju, X., Harford, J., Luzzi, L., Jamieson, L.M., 2021. Prevalence, extent, and severity of periodontitis among Australian older adults: comparison of two generations. J. Periodontol.

Kamer, A.R., Craig, R.G., Dasanayake, A.P., Brys, M., Glodzik-Sobanska, L., de Leon, M. J., 2008. Inflammation and Alzheimer's disease: possible role of periodontal diseases. Alzheimers Dement 4 (4), 242–250.

Karger, A., 2014. Geschlechtsspezifische Aspekte bei depressiven Erkrankungen. Bundesgesundheitsblatt - Gesundheitsforsch. - Gesundheitsschutz 57 (9), 1092–1098.

Kassebaum, N.J., Bernabé, E., Dahiya, M., Bhandari, B., Murray, C.J.L., Marcenes, W., 2014. Global burden of severe tooth loss:A systematic review and meta-analysis. J. Dent. Res. 93 (7_Suppl. l), 20S-8S.

Kisely, S., Sawyer, E., Siskind, D., Lalloo, R., 2016. The oral health of people with anxiety and depressive disorders - a systematic review and meta-analysis. J. Affect. Disord. 200, 119–132.

Kocalevent, R.D., Hinz, A., Brähler, E., 2013. Standardization of the depression screener patient health questionnaire (PHQ-9) in the general population. Gen. Hosp. Psychiatr. 35 (5), 551–555.

Kris-Etherton, P.M., Petersen, K.S., Hibbeln, J.R., Hurley, D., Kolick, V., Peoples, S., et al., 2021. Nutrition and behavioral health disorders: depression and anxiety. Nutr. Rev. 79 (3), 247–260.

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613.

Kuehner, C., 2003. Gender differences in unipolar depression: an update of epidemiological findings and possible explanations. Acta Psychiatr. Scand. 108 (3), 163–174.

Lang, U.E., Beglinger, C., Schweinfurth, N., Walter, M., Borgwardt, S., 2015. Nutritional aspects of depression. Cell. Physiol. Biochem. 37 (3), 1029–1043.

Li, X., Huan, J., Lin, L., Hu, Y., 2023. Association of systemic inflammatory biomarkers with depression risk: results from national health and nutrition examination survey 2005-2018 analyses. Front. Psychiatr. 14, 1097196.

Liu, C., Xie, B., Chou, C.P., Koprowski, C., Zhou, D., Palmer, P., et al., 2007. Perceived stress, depression and food consumption frequency in the college students of China Seven Cities. Physiol. Behav. 92 (4), 748–754.

Liu, Y., Ho, R.C., Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J. Affect. Disord. 139 (3), 230–239.

Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., Lyu, J., 2020. Changes in the global burden of depression from 1990 to 2017: findings from the global burden of disease study. J. Psychiatr. Res. 126, 134–140.

Ljungberg, T., Bondza, E., Lethin, C., 2020. Evidence of the importance of dietary habits regarding depressive symptoms and depression. Int. J. Environ. Res. Publ. Health 17 (5).

Löwe, B., Kroenke, K., Herzog, W., Gräfe, K., 2004. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). J. Affect. Disord. 81 (1), 61–66.

Mac Giollabhui, N., Ng, T.H., Ellman, L.M., Alloy, L.B., 2021. The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. Mol. Psychiatr. 26 (7), 3302–3314.

MacEntee, M.I., Hole, R., Stolar, E., 1997. The significance of the mouth in old age. Soc. Sci. Med. 45 (9), 1449–1458.

MacQueen, G.M., Memedovich, K.A., 2017. Cognitive dysfunction in major depression and bipolar disorder: assessment and treatment options. Psychiatr. Clin. Neurosci. 71 (1), 18–27.

Martin, A., Rief, W., Klaiberg, A., Braehler, E., 2006. Validity of the brief patient health questionnaire mood scale (PHQ-9) in the general population. Gen. Hosp. Psychiatr. 28 (1), 71–77.

Martínez, M., Martín-Hernández, D., Virto, L., MacDowell, K.S., Montero, E., González-Bris, Á., et al., 2021. Periodontal diseases and depression: a pre-clinical in vivo study. J. Clin. Periodontol. 48 (4), 503–527.

Matsuyama, Y., Jürges, H., Dewey, M., Listl, S., 2021. Causal effect of tooth loss on depression: evidence from a population-wide natural experiment in the USA. Epidemiol. Psychiatr. Sci. 30, e38.

Milaneschi, Y., Kappelmann, N., Ye, Z., Lamers, F., Moser, S., Jones, P.B., et al., 2021. Association of inflammation with depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts. Mol. Psychiatr. 26 (12), 7393–7402.

Molendijk, M., Molero, P., Ortuño Sánchez-Pedreño, F., Van der Does, W., Angel Martínez-González, M., 2018. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. J. Affect. Disord. 226, 346–354.

Murphy, M.J., Peterson, M.J., 2015. Sleep disturbances in depression. Sleep Med Clin 10 (1), 17–23.

Neupane, S.P., Virtej, A., Myhren, L.E., Bull, V.H., 2022. Biomarkers common for inflammatory periodontal disease and depression: a systematic review. Brain, Behav. Immun.Health 21, 100450.

Nolde, M., Holtfreter, B., Kocher, T., Alayash, Z., Reckelkamm, S.L., Ehmke, B., et al., 2022. No bidirectional relationship between depression and periodontitis: a genetic correlation and Mendelian randomization study. Front. Immunol. 13.

Nordenram, G., Davidson, T., Gynther, G., Helgesson, G., Hultin, M., Jemt, T., et al., 2013. Qualitative studies of patients' perceptions of loss of teeth, the edentulous state and prosthetic rehabilitation: a systematic review with meta-synthesis. Acta Odontol. Scand. 71 (3–4), 937–951.

Osimo, E.F., Pillinger, T., Rodriguez, I.M., Khandaker, G.M., Pariante, C.M., Howes, O.D., 2020. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav. Immun. 87, 901–909.

Paans, N.P.G., Bot, M., van Strien, T., Brouwer, I.A., Visser, M., Penninx, B., 2018. Eating styles in major depressive disorder: results from a large-scale study. J. Psychiatr. Res. 97, 38–46.

Paraskevas, S., Huizinga, J.D., Loos, B.G., 2008. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J. Clin. Periodontol. 35 (4), 277–290.
Park, S.J., Ko, K.D., Shin, S.I., Ha, Y.J., Kim, G.Y., Kim, H.A., 2014. Association of oral health behaviors and status with depression: results from the Korean National Health and Nutrition Examination Survey, 2010. J. Publ. Health Dent. 74 (2), 127–138.
Poole, S., Singhrao, S.K., Kesavalu, L., Curtis, M.A., Crean, S., 2013. Determining the presence of periodontopathic virulence factors in short-term postmortem alzheimer's disease brain tissue. J. Alzheim. Dis. 36, 665–677.
Reich, H., Rief, W., Brähler, E., Mewes, R., 2018. Cross-cultural validation of the German and Turkish versions of the PHQ-9: an IRT approach. BMC Psychol. 6 (1), 26.
Romandini, M., Baima, G., Antonoglou, G., Bueno, J., Figuero, E., Sanz, M., 2021. Periodontitis, edentulism, and risk of mortality: a systematic review with meta-analyses. J. Dent. Res. 100 (1), 37–49.
Silverstein, B., 2002. Gender differences in the prevalence of somatic versus pure depression: a replication. Am. J. Psychiatr. 159 (6), 1051–1052.
Spangenberg, L., Brähler, E., Glaesmer, H., 2012. [Identifying depression in the general population - a comparison of PHQ-9, PHQ-8 and PHQ-2]. Z. Psychosom. Med. Psychother. 58 (1), 3–10.
Strajnić, L., Bulatović, D., Stančić, I., Živković, R., 2016. Self-perception and satisfaction with dental appearance and aesthetics with respect to patients' age, gender, and level of education. Srp. Arh. Celok. Lek. 144 (11–12), 580–589.
Tiwari, T., Kelly, A., Randall, C.L., Tranby, E., Franstve-Hawley, J., 2021. Association between mental health and oral health status and care utilization. Front Oral Health 2, 732882.
Tsai, C.-C., Chou, H.-H., Wu, T.-L., Yang, Y.-H., Ho, K.-Y., Wu, Y.-M., et al., 2008. The levels of volatile sulfur compounds in mouth air from patients with chronic periodontitis. J. Periodontal. Res. 43 (2), 186–193.
Vallittu, P.K., Vallittu, A.S., Lassila, V.P., 1996. Dental aesthetics–a survey of attitudes in different groups of patients. J. Dent. 24 (5), 335–338.
Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., et al., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol 21 (9), 655–679.
World Health, O., 2017. Depression and Other Common Mental Disorders: Global Health Estimates. World Health Organization, Geneva. Contract No.: WHO/MSD/MER/2017.2.