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EPIDEMIOLOGY (COHORT STUDY OR CASE–CONTROL STUDY)

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Is there an association between depression and periodontitis? A birth cohort study

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Abstract

Aim: To investigate the association between depression and periodontitis among adults enrolled in the 1982 Pelotas Birth Cohort, Brazil.

Materials and methods: Major depressive episode (MDE) and severity of depressive symptoms obtained in 2012 were considered the exposure of this study. In 2013, periodontitis, the outcome of interest, was clinically assessed and two different case definitions were used: the CDC/AAP and a combination of clinical attachment loss (CAL) and bleeding on probing (BOP) simultaneously. Serum levels of C-reactive protein and frequency of dental flossing were defined as mediators while confounders comprised a set of variables collected throughout the life-course of the participants. The parametric g-formula was used to test the direct, indirect and total effects of depression on periodontitis.

Results: 539 participants were clinically examined. Individuals with depressive symptoms presented higher risk of periodontitis (risk ratio [RR] 1.19). The presence of depressive symptoms was also associated with moderate/severe periodontitis (total effect RR 1.18). None of the associations was mediated by flossing or C-reactive protein levels. Finally, neither the presence of depressive symptoms nor the presence of major depression was associated with the combination of CAL+BOP.

Conclusions: A positive association between depressive symptoms and periodontitis and moderate/severe periodontitis was found. MDE was not associated with periodontitis.

KEYWORDS
cohort studies, depressive symptoms, major depression, periodontal diseases

1 | INTRODUCTION

Depression, a frequently undiagnosed mood disorder, is a condition that may affect all age groups. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), it involves disturbances in emotional, cognitive, behavioural and somatic regulation and is characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration (APA, 1994). Especially when long-lasting and with moderate or severe intensity, depression may become a serious health condition. It can cause the affected person to suffer greatly and function poorly at work, at school and

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in the family (WHO, 2016). It is estimated that around 350 million people are affected worldwide (WHO, 2017). Besides, the global burden of mental illness accounts for 32.4% of years lived with disability and 13.0% of disability-adjusted life-years (Vigo, Thornicroft, & Atun, 2016).

It has been reported that depression and chronic stress could alter the host immune response. So, a variety of conditions have been associated with them, such as diabetes mellitus, stroke, hypertension, alcohol abuse, sleep disorders and renal disease (Hsu et al., 2015). Moreover, oral conditions such as temporo-mandibular joint disorders, oral lichen planus, burning mouth syndrome and periodontal diseases have also been related to depression (Cademartori, Gastal, Nascimento, Demarco, & Correa, 2018; Genco, Ho, Dunford, & Tedesco, 1999; Solis et al., 2004).

The idea about the influence of stress and depression on the body includes the adaptive response, which is essential to survival. It has been speculated that physical and psychological stressors induce peripheral and central responses so the homeostasis is maintained. The pattern and magnitude of these responses are determined by several factors as the duration of exposure (chronic or acute), and the kind of stress (physical or psychological) (Joels & Baram, 2009). Additionally, the alteration of the hypothalamic–pituitary–adrenal axis (HPA) has a pro-inflammatory or anti-inflammatory effect on tissues. Accordingly, there seems to be a meaningful association between environmental stressors, psychological factors and the immune system (Leresche & Dworkin, 2002). It is also believed that these hormonal and inflammatory changes may alter the development of other diseases such as diabetes, obesity and periodontitis (Nascimento et al., 2014; Renn, Feliciano, & Segal, 2011). Increased inflammatory responses stimulate bone resorption while immunological deficiencies lead to lower host responses (Delgado-Angulo et al., 2015).

Besides the biological component, behavioural changes related to depression may also take part in the aetiology of periodontal diseases. The relation between depression and poor oral health status has been examined in some studies (Delgado-Angulo et al., 2015; Genco et al., 1999; Marcenes & Sheiham, 1992; Marcenes et al., 2013). Psychological factors may affect reactions to stressful events and modify or induce certain behaviours such as neglected oral hygiene (AAP, 1999; Lindhe & Lang, 2015). Therefore, it seems reasonable that studies investigating the relationship between depression and periodontitis properly account for the mediating role played by systemic inflammation and oral hygiene habits.

Although a growing body of evidence indicates that mental disorders, mainly anxiety and depression, may be associated with periodontal diseases, the literature is still scarce and controversial. While a positive association between depression and periodontal outcomes has been claimed (Khambaty & Stewart, 2013; Park, Ko, Shin, Ha, & Kim, 2014; Peruzzo et al., 2007; Sundararajan, Muthukumar, & Rao, 2015), this relationship remains unclear (Ababneh, Al Shaar, & Taani, 2010; Delgado-Angulo et al., 2015; Persson et al., 2003; Viana, Castro, Pereira, Pereira, & Lopes, 2013). This discrepancy of results may be explained by methodological aspects, such as use of self-reported assessment of depression, different criteria to assess periodontitis, and the lack of proper adjustment for mediators. Irrespective of other methodological differences, most of studies published on the topic share the cross-sectional design, which precludes the establishment of temporal and causal relationships.

Clinical Relevance

Scientific rationale for the study: The association between depression and periodontal disease remains unclear in the literature. However, no study so far has evaluated such association in a population-based prospective longitudinal study.

Principal findings: A positive association between depressive symptoms and periodontitis and more severe forms of periodontitis was observed.

Practical implications: Depressive symptoms may be considered in the clinical setting as part of a more individualized periodontal diagnosis, treatment and supportive therapy.

The aim of the present study was to investigate the association between depression and periodontitis among young adults that have been prospectively followed since birth in a Southern Brazilian city. Additionally, to estimate whether and to what extent systemic inflammation and oral hygiene habits mediate this association.

2 | MATERIALS AND METHODS

2.1 | The 1982 Pelotas Birth Cohort

In 1982, the three maternity hospitals of Pelotas, a southern city of Brazil, were visited daily and all births identified. Those liveborn infants whose parents lived in the urban area of the city were examined (N = 5,914) and their mothers interviewed. Interviews covered aspects on socioeconomic conditions, dietary habits, smoking, alcohol consumption and health conditions. These individuals have been followed in several occasions during lifetime. More details can be found elsewhere (Horta et al., 2015; Loret De Mola et al., 2016).

In 1997, at the age of 15, a systematic random sample of 70 (27%) of the 259 census tracts located within the city limits was selected, all the households included in these tracts were visited, and 900 adolescents were selected for the Oral Health Study (OHS)-97. Of the 900 participants, 888 individuals (98.7%) were orally examined. In 2006, at the age of 24, participants of the OHS-97 were invited for a new oral health examination. A total of 720 (81.1%) were followed up. In 2013 (OHS-2013), at the age of 31, all study participants of the OHS-97 were again contacted for a third oral health assessment. Data used in this study come from the OHS-2013 study. Figure 1 illustrates the follow-ups of 1982 Pelotas Birth Cohort. Technical

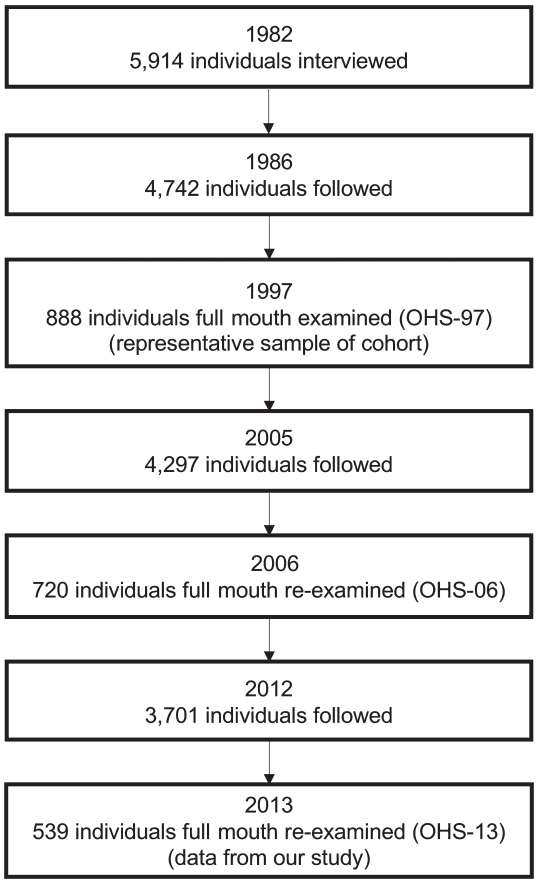

FIGURE 1 Flow chart of the 1982 Pelotas Birth Cohort and the Oral Health Studies

notes on the oral health studies in the 1982 Pelotas Birth Cohort can be found elsewhere (Peres et al., 2011).

All teeth were examined for the presence of periodontal disease (bleeding on probing—BOP, probing depth—PD, clinical attachment loss—CAL) and other oral conditions. Six previously calibrated dentists who underwent theoretical and practical training on 25 individuals performed the oral examination (Nascimento et al., 2017). The lowest intraclass correlation coefficient for pocket depth and CAL was 0.85. The Ethics Committee of the Federal University of Pelotas approved this study. Written informed consent was obtained from all enrolled individuals.

2.2 | Outcome

2.2.1 | Periodontitis

Clinical oral examination was carried out at the participants' home following the biosafety procedures recommended by the World Health Organization for epidemiological surveys, and a head-light, dental mirror and PCP2 periodontal probe with 2-mm banding were used (Hu-Friedy PCP-2, Rotterdam, the Netherlands). Periodontal examinations consisted of full-mouth probing at six sites per tooth. Two different case definition criteria were adopted for this study:

1. *American Academy of Periodontology and the Center for Diseases Control and Prevention:* Individuals were classified into four categories: healthy, mild, moderate or severe periodontitis (Eke, Page, Wei, Thornton-Evans, & Genco, 2012). After that, two different variables were created: the first variable was dichotomized and included all the individuals with any degree of periodontitis (mild or moderate/severe) compared to those considered healthy; the second variable was dichotomized into: individuals with moderate/severe periodontitis versus individuals with mild periodontitis and healthy individuals, which were considered as the reference category (Nascimento et al., 2017).

2. *Clinical attachment loss and bleeding on probing (CAL+BOP)*: Individuals presenting at least one site with simultaneous occurrence of CAL ≥4 mm and BOP were classified as having periodontitis (Baelum & López, 2012).

2.3 | Exposure

2.3.1 | Major depressive episode and depressive symptoms

In 2012, when individuals were aged 30, psychological interviews using the Mini-international psychiatric interview (MINI) V5.0 validated for Brazilian Portuguese (Amorim, 2000) was performed by four trained psychologists in order to assess the presence of a major depressive episode (MDE). The Beck Depression Inventory (BDI-II) validated for Brazilian Portuguese (Gomes-Oliveira, Gorenstein, Lotufo-Neto, Andrade, & Wang, 2012) was used to assess the presence of depressive symptoms. The BDI-II was self-administered, and the participant was alone in the room when filling out the form. The instrument consists of 21 symptoms of depression rated on a 4-point scale (0–3) within the time frame of the past 2 weeks, and it was used to evaluate the intensity of depressive symptoms. BDI-II scores were classified as: minimal/no depression: 0–13 points, mild depression: 14–19, moderate/severe: 20–63 (Beck, Steer, & Gk, 1996; Loret De Mola et al., 2016). For analytical purposes, the variable was dichotomized into: absence of depressive symptoms (reference category) versus presence of depressive symptoms (mild, moderate or severe). Hereafter, we use the term depression to refer to both major depression episode and depressive symptoms.

2.4 | Mediators and confounders

Based on the literature, we elaborated a conceptual framework, which is presented in Figure 2.

2.4.1 | Mediators

As depression seems to induce low-grade systemic inflammation, and to affect oral hygiene habits, we have included two mediators accordingly:

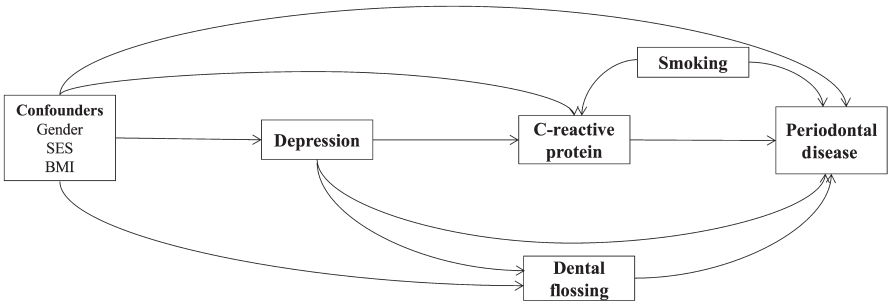

FIGURE 2 Direct acyclic graphic for the influence of depression on the occurrence of periodontitis

Level of C-reactive protein (2012): Serum level of C-reactive protein (Immulite; DPC/Siemens, Los Angeles, USA) was used as a proxy for systemic inflammation and presented as a continuous variable. For analytical purposes, the variable was categorized into tertiles and converted to a dichotomous variable in which the first and the second tertiles were grouped.

Dental flossing (2013): Frequency of dental flossing (never versus sometimes/always) was used as a proxy for oral hygiene habits.

2.4.2 | Confounders

The following variables in their respective years of collection were defined as confounders:

1982 (at birth): Sex, maternal schooling at birth (0–8 years; ≥9 years);
2012 (at age 30): Body mass index (obese/overweight: BMI ≥ 25 kg/m^2 or eutrophic: BMI < 25 kg/m^2); education at age 30 (0–8 years; ≥9 years); smoking status (current or former/never smoker).

2.5 | Analytical approach

Variables were described according to the outcome variables. STATA version 14 (Stata Corp., College Station, TX, USA) was used for data analysis.

In order to investigate the association between depression and periodontal disease, we applied the parametric g-formula ("mediation option") to estimate the total effect, the natural direct/indirect effects, and the controlled direct effect. The total effect is the difference between the potential outcome if all individuals were counterfactually exposed and unexposed. The natural direct effect is the difference between two potential outcomes: the first is the potential outcome if in the counterfactual scenario all individuals were exposed, keeping the mediators to their potential values under no exposure; the second is the potential outcome if all individuals were unexposed in the counterfactual scenario. The natural indirect effect is the difference between the total effect and the direct effect. Finally, the controlled direct effect is a comparison of the expected outcome while keeping the value of the mediators fixed ($M = 0$).

The Monte Carlo approach was used to estimate the effects. Bootstrap method was used to estimate the standard errors as well as the confidence interval of the estimated effects. For this later estimation, we used 1,000 resamples of size 10,000. Sensitivity analysis for unmeasured confounding was performed as recommended by VanderWeele (2010).

3 | RESULTS

Of the 888 participants of the OHS-97 (15 years), 539 individuals were interviewed in 2013 (61% of OHS-97). The flowchart of the 1982 Pelotas Birth Cohort is displayed in Figure 1. The prevalence of any type of periodontitis at age 31 was 37%, while the prevalence of mild and moderate/severe periodontitis was 23% and 14%, respectively. The prevalence of having at least one site with the combination of CAL+BOP was 15%. The prevalence of major depression was 6.1%. Table 1 describes sociodemographic and psychological characteristics of the sample in 1982 (at birth), 2012 (30 years) and the OHS-13 (31 years).

The risk of periodontitis was 19% higher among the individuals with depressive symptoms (risk ratio [RR] 1.19; 95% confidence interval [95% CI] 1.04–1.36). The indirect effect shows that this association was not mediated by flossing neither by C-reactive protein levels (RR 1.00; 95% CI 0.94–1.08). When mediators were fixed at $M = 0$, the controlled direct effect was similar to the total effect (RR 1.12; 95% CI 1.00; 1.28). However, such association was not noted when major depression was the main independent variable (Table 2).

Table 3 shows the association between moderate/severe periodontitis and the presence of depressive symptoms. The controlled direct effect of depressive symptoms on moderate/severe periodontitis was RR 1.13 (95% CI 1.00–1.30). Similar estimates were observed for the total effect (RR 1.18; 95% CI 1.03–1.35) and the natural direct effect (RR 1.20; 95% CI 1.05–1.37). Once more, the effect was not mediated by the oral hygiene habits or by systemic inflammation (RR 0.98; 95% CI 0.91–1.05). When major depression episode was the exposure of interest, no association was noted with moderate/severe periodontitis.

Finally, neither the presence of depressive symptoms nor the presence of major depression was associated with the combination of CAL+BOP, as demonstrated in Table 4. Results from the sensitivity analyses for unmeasured confounder are presented in Supporting Information Table S1. It is possible to note that the unmeasured confounder must be strongly associated with periodontitis and

TABLE 1 Comparison of demographic and socioeconomic characteristics between the original sample at birth and at the age of 30 years and those enrolled in the OHS-2013 at the age of 31. 1982 Pelotas Birth Cohort study, Brazil

	Total sample (1982 – birth) (*N* = 5,914)	Total sample (2012 – 30 years) (*N* = 4,026)	OHS-13 (2013 – 31 years) (*N* = 539)
Sociodemographic information			
Sex (1982)			
Male	3,037 (51.4)	1,980 (53.0)	273 (50.6)
Female	2,876 (48.6)	2,044 (47.0)	266 (49.4)
Maternal schooling experience (1982)			
0–8 years	4,414 (75.1)	3,063 (75.1)	122 (77.3)
9 years or more	1,493 (24.9)	929 (24.9)	416 (22.7)
Family income (1982) (in minimum wages)			
<1	1,288 (21.9)	851 (21.3)	93 (17.3)
1.1–3	2,789 (47.4)	1,963 (48.9)	282 (52.4)
>3	1,808 (30.7)	1,192 (29.7)	163 (30.3)
Smoking status (2012)			
Non-smoker	—	2,998 (76.4)	396 (80.4)
Smoker	—	949 (23.6)	96 (19.5)
Mental disorder			
Major depression episode (2012)			
Yes	—	350 (8.7)	29 (6.1)
No	—	3,676 (91.3)	451 (93.9)
Depressive symptoms (2012)			
Absence	—	3,068 (76.2)	381 (78.1)
Mild	—	403 (10.0)	52 (10.7)
Moderate/ severe	—	523 (13.0)	55 (11.3)

TABLE 2 Estimates from the parametric g-formula evaluating the association between mental health and any degree of severity of periodontitis (mild, moderate/severe). 1982 Pelotas Birth Cohort, 1982–2013, Pelotas, Brazil

	Periodontitis, RR (95% CI)			
Mental disorders	Total effects	Direct natural effect	Indirect natural effect	Controlled direct effect
BDI-II				
Absence	1.00	1.00	1.00	1.00
Presence	1.19 (1.04; 1.36)	1.18 (1.03; 1.36)	1.00 (0.94; 1.08)	1.12 (1.00; 1.28)
MINI				
Absence	1.00	1.00	1.00	1.00
Major depression	0.95 (0.80; 1.18)	0.99 (0.63; 1.23)	0.96 (0.89; 1.03)	0.91 (0.74; 1.12)

Note. RR: risk ratio; 95% CI: 95% confidence interval; BDI-II: Beck Depression Inventory; MINI: mini-international psychiatric interview.

unequally distributed among those with and without depression to nullify the association.

4 | DISCUSSION

This study evaluated the association between depression and periodontitis among 31-year-old adults from a birth cohort study. Our findings demonstrated that the association between depressive symptoms and periodontitis was not mediated by oral hygiene or systemic inflammation.

The association between depressive symptoms and periodontitis observed in this study corroborates with previous findings (Genco et al., 1999; Khambaty & Stewart, 2013; Park et al., 2014). There are two proposed pathways that can possibly explain this association. One behavioural, through neglected attitudes and at-risk health

TABLE 3 Estimates from the parametric g-formula evaluating the association between mental health and mild and moderate/severe periodontitis. 1982 Pelotas Birth Cohort, 1982–2013, Pelotas, Brazil

	Moderate/severe periodontitis, RR (95% CI)			
Mental disorders	Total effects	Direct natural effect	Indirect natural effect	Controlled direct effect
BDI-II				
Absence	1.00	1.00	1.00	1.00
Presence	1.18 (1.03; 1.35)	1.20 (1.05; 1.37)	0.98 (0.91; 1.05)	1.13 (1.00; 1.30)
MINI				
Absence	1.00	1.00	1.00	1.00
Major depression	0.99 (0.80; 1.22)	1.00 (0.81; 1.24)	0.98 (0.92; 1.06)	0.95 (0.77; 1.16)

Note. RR: risk ratio; 95% CI: 95% confidence interval; BDI-II: Beck Depression Inventory; MINI: mini-international psychiatric interview.

TABLE 4 Estimates from the parametric g-formula evaluating the association between mental health and the combination of CAL+BOP. 1982 Pelotas Birth Cohort, 1982–2013, Pelotas, Brazil

	CAL+BOP, RR (95% CI)			
Mental disorders	Total effects	Direct natural effect	Indirect natural effect	Controlled direct effect
BDI-II				
Absence	1.00	1.00	1.00	1.00
Presence	1.06 (0.93; 1.21)	1.10 (0.97; 1.25)	0.96 (0.90; 1.02)	1.06 (0.93; 1.18)
MINI				
Absence	1.00	1.00	1.00	1.00
Major depression	1.11 (0.89; 1.37)	1.13 (0.91; 1.39)	0.98 (0.91; 1.05)	1.08 (0.87; 1.33)

Note. RR: risk ratio; 95% CI: 95% confidence interval; BDI-II: Beck Depression Inventory; MINI: mini-international psychiatric interview.

behaviours, and another biological which is related to psychoneuroimmunologic changes. Moreover, a combination of both has also to be considered (Joels & Baram, 2009). The behavioural changes would lead to increased oral biofilm burden and decreased resistance of the periodontal tissues to inflammatory breakdown. This via suggests depression as a risk factor for poor oral health, since it affects oral hygiene habits and the use of oral health services (Okoro, Strine, Eke, Dhingra, & Balluz, 2012; Park et al., 2014). However, our findings revealed a controlled direct effect of depressive symptoms on periodontitis, even when the value of dental flossing, a proxy used for oral hygiene behaviour, was fixed in ($M = 0$). Johannsen and colleagues have found that individuals with stress-related depression had more biofilm accumulation and gingival inflammation than those without this disorder (Johannsen, Rylander, Söder, & Marie, 2006). Nevertheless, we were not able to test this hypothesis, since we did not collect information regarding plaque accumulation. One may speculate about the use of dental calculus as a proxy for dental biofilm accumulation. Even though dental calculus would be a useful measure in this context, we had to remove this variable from the analytical models, due to its high collinearity with the frequency of dental floss.

In the biological pathway, the effects of depression on periodontitis could be exerted through different mechanisms inducing systemic inflammation, such as C-reactive protein and cortisol. Despite the positive association between depression, C-reactive protein and periodontitis observed in previous studies (D'Aiuto et al., 2004; Wium-Andersen, Orsted, Nielsen, & Nordestgaard, 2013), our results demonstrated that systemic levels of C-reactive protein did not mediate the relationship between depressive symptoms and periodontitis. Even though C-reactive protein is considered a marker of systemic inflammation, there is lack of specificity related to the origin of its systemic commitment, what might have partially explained our results. On the other hand, cortisol, a glucocorticoid that reduces immunocompetence by inhibiting immunoglobulin A and G and neutrophil function (Engeland et al., 2016), has the ability to inhibit inflammatory responses, which may lead to destruction of periodontal tissues (Iacopino, 2009). Therefore, cortisol seems to be a more informative marker of the association between depression and periodontitis; however, information on cortisol was not available for this population, and therefore, future studies should investigate this potential mechanism.

Another aspect to be pointed out is the relationship between depressive symptoms and the severity of periodontal disease. Our

results have shown an association between depressive symptoms and moderate/severe periodontitis, corroborated by previous studies (Monteiro Da Silva, Oakley, Newman, Nohl, & Lloyd, 1996; Moss et al., 1996; Sundararajan et al., 2015). As longer episodes of depression may have greater impact on the immune response, a prolonged imbalance in the immune function might explain the dose–response relationship observed (Monteiro Da Silva et al., 1996; Moss et al., 1996).

The reason why major depression episode was not associated with any form of periodontitis might be related to the difference between the two instruments used to assess MDE and depressive symptoms. MINI, a semi-structured interview used for the standardized diagnosis of major depression, only takes into consideration the presence or absence of disease, without specifying its chronicity. On the other hand, the BDI-II is a scale to quantify depressive symptoms and their duration, but unable to detect depression itself (Wang & Gorestein, 2013). As the diagnosis of MDE does not consider its duration, the short follow-up between exposure and outcome might explain our findings (Persson et al., 2003).

Our study has key strengths that should be emphasized. First, the prospective longitudinal data originated from a population-based birth cohort provide robust information since early life, reducing the odds of recall bias. Furthermore, the sample remains representative of the entire cohort, as attrition was not observed. Periodontal examination was conducted in the full mouth and not only in index teeth, and thus, provided accurate information on the severity and extension of periodontal disease. In addition, the presence of depression and the severity of depressive symptoms were assessed by two validated, recognized and widely used instruments, whereas most of previous studies have used only self-reported information. Finally, we should emphasize the analytical approach employed in our study. The use of the parametric g-formula allowed us to test the association between depression and periodontitis using a counterfactual approach. It is of relevance for studying the effects of exposures that cannot be allocated in randomized clinical trials for ethical reasons. Although we have estimated total effects, natural direct/indirect effects and controlled direct effects, the latter has a more direct application in the public health context (Naimi, Kaufman, & MacLehose, 2014).

However, there are also limitations that should be examined. As the depression outcomes were measured in 2012, and periodontitis was assessed in 2013, it is possible to speculate that the effect of depression was underestimated due to the short follow-up time. In addition, it is suggested that this association may vary during life-course, since depression is a condition that may affect individuals since early life, while unfavourable periodontal outcomes are more evident in adulthood. Since both conditions present a chronic nature, further studies should rely on longer follow-up periods in order to evaluate the progression of both diseases over time. Another important limitation was the relatively low age of the studied sample which may have directly impacted on the prevalence of major depression. Given our limited sample size, and the low prevalence of major depression, we might have not had enough analytical power to detect an association between those conditions. Finally, we cannot rule out residual confounding, especially due to the low specificity of C-reactive protein as a marker of systemic inflammation, and the lack of adjustment for medications that could influence C-reactive protein values.

Irrespective of the limitations, our findings provide evidence on the association between depressive symptoms and periodontitis among young adults. Understanding that mental disorders may play a role in the onset and progression of periodontitis is of great value to provide an individual-based treatment plan and supportive therapy.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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