J Clin Periodontol 2015; 42: 333–341 doi: 10.1111/jcpe.12380

Journal of Clinical Periodontology

# Association between low-dose aspirin and periodontal disease: results from the continuous national health and nutrition examination survey (NHANES) 2011–2012

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*Kotsakis GA, Thai A, Ioannou AL, Demmer RT, Michalowicz BS. Association between low-dose aspirin and periodontal disease: results from the continuous national health and nutrition examination survey (NHANES) 2011–2012. J Clin Periodontol 2015; 42: 333–341. doi: 10.1111/jcpe.12380*

***Abstract***

**Aim:** Low-dose aspirin has been hypothesized as being a potential host modulatory agent for periodontitis treatment. We investigated the relationship between low-dose aspirin use and periodontitis prevalence in the continuous National Health and Nutrition Examination Survey, 2011–2012.

**Methods:** We analysed $n = 2335$ adult men and women who received a full-mouth periodontal examination and responded to an aspirin use questionnaire. Periodontal disease was defined as severe, moderate or mild according to established case definitions. Mean full-mouth probing depth, attachment loss and tooth loss were also considered. Low-dose aspirin was defined by any self-reported, physician prescribed aspirin use of ≤162 mg/day.

**Results:** Participants had mean age (SE) 55.8 years (0.42). The prevalences of periodontitis and low-dose aspirin use were 49.5% and 25% respectively. In multivariable logistic regression models controlling for age, sex, race, socioeconomic variables and comorbidities, the odds ratios [95%CI] for moderate or severe periodontitis among low-dose aspirin users (versus non-users) were: 0.91 [0.56–1.50] and 1.06 [0.74–1.50] respectively. Results were unchanged among participants without diabetes or coronary heart disease.

**Conclusions:** Within the limitations of this cross-sectional study we conclude that low-dose aspirin is not associated with prevalent periodontal status in a nationally representative sample of US adults.

Key words: aspirin; epidemiology; host modulation therapy; national health and nutrition examination survey; periodontal diseases; periodontitis

Accepted for publication 7 February 2015

**Conflict of interest and source of funding statement**

All authors report no conflict of interest related to this study.Dr. Demmer was supported by NIH grant R00 DE018739.

Periodontal disease is highly prevalent in adults and can significantly impair oral health-related quality of life (Eke et al. 2012a, Durham et al. 2013). Most periodontal disease prevention and treatment strategies target pathogens within the microbiota (Axelsson et al. 2004, Lopez et al. 2006). Yet, periodontal disease is known to be a multifactorial disease influenced by host responses to bacterial antigens (Pihlstrom et al. 2005).

Variations in host susceptibility to microbial challenge result in distinct clinical responses ranging from chronic gingivitis to aggressive periodontal tissue destruction (Johnson et al. 1988).

Host modulatory agents have been advocated as a means of mitigating deleterious host responses that lead to periodontal tissue loss (Hasturk et al. 2012). Aspirin, or acetylsalicylic acid, is one such commonly used agent. The two leading biological hypotheses concerning the role of aspirin use in the treatment of periodontitis focus on either the anti-inflammatory or the anti-platelet effects of aspirin.

Aspirin may protect against inflammation and subsequent periodontitis because it irreversibly inhibits cyclooxygenase-2 that interferes with the synthesis of prostaglandin E2 (PGE2) (Drouganis & Hirsch 2001). PGE2 plays a crucial role in the inflammatory cascade that leads to periodontal destruction (Offenbacher et al. 1993, Taxman et al. 2012) and levels in saliva correlate with periodontal disease severity (Sanchez et al. 2013). Aspirin has been also shown to reduce interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) levels in the gingiva of rodents, although this effect was induced by very high doses of aspirin (30 mg/kg) over a 2-week period (Coimbra et al. 2011). Based on these actions, researchers have tested low-dose aspirin as a complement to host modulatory treatment regimens for use as an adjunct to mechanical periodontal treatment (El-Sharkawy et al. 2010, Elkhouli 2011).

In addition to its anti-inflammatory effects, aspirin also has an anti-platelet effect that might increase gingival bleeding (Schrodi et al. 2002, Gurbel et al. 2007). It has been suggested that low-dose aspirin can significantly increase bleeding on probing in persons with pre-existing gingivitis (Royzman et al. 2004). However, the work of Coimbra et al. (2011) has provided preliminary in vivo evidence to suggest that aspirin's platelet-inhibitory effect may provide an additional and independent protective effect against periodontal destruction (Coimbra et al. 2011). Whether aspirin's anti-platelet and anti-inflammatory effects will altogether protect the host against periodontal destruction has not been investigated (Royzman et al. 2004).

We hypothesized that the prevalence of periodontal disease is lower in individuals taking preventive, low-dose aspirin compared to individuals not taking low-dose aspirin. We tested this hypothesis using data from the US National Health and Nutrition Examination Survey (NHANES) 2011–2012.

## Materials and Methods

Data from the continuous National Health and Nutrition Examination Survey 2011–2012 were analysed. The NHANES is a cross-sectional survey that combines interviews and physical examinations to investigate the overall health and nutritional status of the US non-institutionalized population in the 50 states and the District of Columbia. The NHANES utilizes a multistage, probability sampling design to provide a representative sample of the US population. The 2011–2012 NHANES enrolled 9756 participants, 4365 of whom were eligible for the periodontal evaluation. The 2011–2012 survey was the first one to question participants about their use of low-dose preventive aspirin. The present analysis included adults who received a periodontal examination and completed the aspirin use questionnaire.

### Low-dose aspirin assessment

Questions investigating the use of aspirin to prevent heart attacks, strokes or cancer were asked by trained interviewers using the Computer-Assisted Personal Interviewing (CAPI) system to 3603 individuals. Participants were asked about low-dose aspirin use and about frequency and dosage. We defined low-dose aspirin for preventive reasons as doses not exceeding 162 mg a day, which is consistent with levels proposed in the current combined position statements of the American Diabetes Association, American Heart Association, and American College of Cardiology Foundation (ADA/AHA/ACCF) (Pignone et al. 2010). For the primary analyses, we excluded individuals taking aspirin doses greater than 162 mg and those with missing data. Individuals taking aspirin less than every other day were also excluded. Data from participants taking more than 162 mg of aspirin and up to 500 mg of aspirin per day or per alternate day ($n = 95$) were utilized to test for a dose-effect by comparing higher strength aspirin users against non-users.

### Periodontitis case definitions

Calibrated examiners performed full-mouth, six-site per tooth assessments for all eligible participants. Probing depth (PD) and gingival recession (GR) were recorded and attachment loss (AL) was calculated by subtracting GR from PD. A three-level definition of periodontitis was utilized in the primary analyses based on the 2003 case definitions proposed by an American Academy of Periodontology (AAP) and the Centers for Disease Control and Prevention (CDC) workgroup (Page & Eke 2007). A four-level case definition was also employed which included a separate category for mild periodontitis (Eke et al. 2012b). (Table S1) Participants with no or mild periodontitis were the referent group when using the three-level definitions. Those with no periodontitis served as the referent group when using the four-level classification.

Mean full-mouth probing depth (PD) and attachment loss (AL) also were computed for each participant as continuous measures of periodontal disease. We also explored the association between aspirin use and tooth loss.

### Risk factor assessment

We utilized a comprehensive data set available in NHANES to consider multiple risk factors relevant to both periodontitis and indications for low-dose aspirin as previously described (Arora et al. 2014). These included the demographic variables age, race/ethnicity, sex, education (<high school, high school, associate or technical, college or graduate) and poverty-income ratio (calculated by dividing family income by the poverty guidelines, specific to family size, as well as the appropriate year and state according to Department of Health and Human Services

guidelines). Assessed behaviours included physical activity (none, low, moderate or vigorous according to the Metabolic Equivalent of Task (MET) definitions, which are based on occupational and recreational physical activities performed in a typical week), and cigarette smoking duration and intensity (Thai et al. 2014). Trained NHANES personnel performed height, weight and blood pressure measures according to standardized protocols. Body Mass Index (BMI) was calculated as weight (kilograms)/height (meters$^2$) and participants were categorized as underweight/normal weight (<25 kg/m$^2$), overweight (25–29.9 kg/m$^2$) or obese (≥30 kg/m$^2$). Total and HDL cholesterol were measured from fasting blood samples and total/HDL ratio was calculated. Hypertension was defined as mean systolic blood pressure ≥140 mmHg, mean diastolic blood pressure ≥90 mmHg, taking hypertension medication, or physician-diagnosed hypertension. Participants were considered to have diabetes if they had a glycohaemoglobin level ≥6.5% or reported a physician diagnosis. Coronary heart disease status was ascertained using Rose angina questionnaire criteria (Rose & Blackburn 1968).

#### Statistical analysis

Survey procedures in SAS version 9.3 SAS Institute Inc. Cary, NC, USA were used for all analyses to account for the complex survey design and to generate the correct variance estimates. Sampling weights provided by NHANES were used in all analyses to account for oversampling, non-response and post-stratification; doing so allows generalization of finding to the US population. *p*-values presented in descriptive tables were derived from *t*-tests or chi-square statistics. Multivariable polytomous logistic regression was used to model the association between low-dose aspirin use (defined above) and the odds of CDC/AAP defined mild, moderate and severe periodontitis. 95% confidence intervals (CI) obtained from logistic regression models were reported as were *p*-values derived from Wald chi-square tests corresponding to any difference in the odds of periodontitis across levels of low-dose aspirin use. Linear regression models were used to evaluate continuous measures of periodontal disease by comparing mean full-mouth PD, AL and the number of missing teeth in aspirin users and non-users. A series of multivariable models are presented to demonstrate the influence of potential confounders. In an attempt to minimize confounding by indication, we performed subgroup analyses according to diabetes and angina status. Additional subgroup analyses based on age and sex also were performed to address confounding by these important variables using restriction rather than regression-based methods. The present report was conducted in compliance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (Table S2).

## Results

The primary analyses included 2335 participants after excluding participants who were either missing clinical periodontal data, were aspirin users who did not satisfy our definition of low-dose aspirin use, or who did not complete the preventive aspirin use questionnaire (Fig. S1). Participant characteristics are summarized in Table 1. Participants had a mean (SE) age of 55.8 years (0.42); 52.6% were female. Mean (SE) PD and AL were 1.44 mm (0.03) and 1.84 mm (0.06) respectively. The prevalence of several comorbidities, including diabetes, hypercholesterolaemia and hypertension, differed significantly between aspirin users and non-users (Table 1).

#### Aspirin use and periodontitis

Overall, 10.5% of participants had severe periodontitis and 35.4% had moderate periodontitis. In unadjusted analysis the odds ratios (OR) [95% CI] for moderate and severe periodontitis among low-dose aspirin users versus non-users were 1.39 [1.00–1.93] and 1.27 [0.99–1.63] (Table 2, model 1). Results were generally consistent across multiple levels of confounder adjustment, and in fully adjusted regression models the ORs for moderate and severe periodontitis were 0.91 [0.56–1.50] and 1.06 [0.74–1.50] respectively (Table 2, model 5). Results were consistent when comparing high-dose aspirin users versus non users (Table S3).

#### Aspirin use and probing depth, attachment loss or tooth loss

Low-dose aspirin users and non-users did not differ significantly in terms of mean PD or AL in the multivariable analysis (Table 3, Fig. 1). In unadjusted analysis, mean attachment loss was greater in low-dose aspirin users when compared with non-users ($p = 0.0038$, Table 1). The adjusted mean (SE) AL values in low-dose aspirin users and non-users were 1.91 mm (0.06) and 1.86 mm (0.05), respectively, ($p$-value = 0.46, Table 3, model 5). No differences were found between low-dose aspirin users and non-users among subgroups according to age, sex, diabetic status or coronary artery disease status (Figs 2, S2–S4).

In multivariable analyses, the number of missing teeth did not differ significantly between the two groups in any adjusted model (all *p*-values >0.2, Table 4, models 2–5). Users of high-dose aspirin (163–500 mg) had more missing teeth compared to non-users in the unadjusted model, but the differences did not remain significant in adjusted analyses (Table 4).

Known periodontitis risk factors (e.g. age, gender, race, education level and smoking status) were consistently associated with prevalent periodontitis in this sample population regardless of the periodontitis case definition used or the covariables included in the analysis. (Table S4).

## Discussion

We found that low-dose aspirin use (daily or every other day) was not associated with periodontitis prevalence in a nationally representative sample of US adults. The prevalence of severe periodontitis was similar among aspirin users and non-users (11% vs. 10%). Our findings also showed no association between low-dose aspirin and other clinical measures of either historic or current periodontal disease, including tooth loss, AL and PD. In addition to including potential confounders in multivariable analyses, we also analysed subgroups defined by age, gender, diabetes status or angina to minimize the strong potential for confounding by these important characteristics.

*Table 1.* General characteristics of participants overall and according to aspirin use. The continuous national health and nutrition examination survey 2011–2012

| | Overall* | No aspirin use* | Low-dose aspirin use* | *p*-value** |
|---|---|---|---|---|
| CDC/AAP case definitions for periodontitis, *N* (%) | | | | |
| Severe | 371 (10.5) | 274 (10.2) | 97 (11.3) | 0.1958 |
| Moderate | 977 (35.4) | 701 (33.7) | 276 (40.4) | |
| Mild | 58 (3.6) | 48 (3.6) | 10 (3.4) | |
| No | 929 (50.5) | 726 (52.4) | 203 (44.9) | |
| Probing depth in mm (SE) | 1.44 (0.03) | 1.44 (0.03) | 1.42 (0.03) | 0.4376 |
| Attachment loss in mm (SE) | 1.84 (0.06) | 1.79 (0.006) | 1.98 (0.07) | 0.0038 |
| Number of Sites with PD ≥4 mm (SE) | 1.96 (0.12) | 2.05 (0.13) | 1.66 (0.19) | 0.0635 |
| Number of Sites with AL ≥3 mm (SE) | 7.90 (0.38) | 7.85 (0.39) | 8.06 (0.45) | 0.5093 |
| Number of missing teeth (SE) | 7.27 (0.19) | 6.78 (0.22) | 8.76 (0.31) | <0.0001 |
| Age in years (SE) | 55.83 (0.42) | 53.47 (0.38) | 62.90 (0.73) | <0.0001 |
| Gender, *N* (%) | | | | |
| Male | 1134 (47.3) | 845 (47.4) | 289 (47.2) | 0.9332 |
| Female | 1201 (52.6) | 904 (52.6) | 297 (52.8) | |
| Ethnicity, *N* (%) | | | | |
| Other | 372 (7.1) | 316 (7.9) | 56 (4.6) | <0.0001 |
| Black | 650 (10.5) | 470 (10.6) | 180 (10.1) | |
| Hispanic or Mexican | 487 (11.6) | 378 (12.8) | 109 (8.1) | |
| Non Hispanic White | 826 (70.8) | 585 (68.6) | 241 (77.3) | |
| Educational level, *N* (%) | | | | |
| College or graduate | 634 (33.7) | 489 (33.6) | 145 (34.2) | 0.8505 |
| Associate or technical | 644 (30.4) | 481 (30.6) | 163 (29.9) | |
| Highschool | 503 (20.9) | 372 (20.4) | 131 (22.2) | |
| Less than highschool | 552 (15.0) | 406 (15.4) | 146 (13.7) | |
| Income Poverty Ratio (SE) | 3.21 (0.09) | 3.16 (0.11) | 3.38 (0.08) | 0.009 |
| Smoking status, *N* (%) | | | | |
| Current | 395 (17.2) | 316 (18.9) | 79 (12.1) | <0.0001 |
| Former | 611 (28.1) | 415 (25.7) | 196 (35.3) | |
| Never | 1326 (54.6) | 1015 (55.3) | 311 (52.6) | |
| BMI, *N* (%) | | | | |
| Obese (BMI ≥30) | 869 (36.3) | 620 (35.3) | 249 (39.2) | 0.2043 |
| Overweight (25 ≤ BMI <30) | 816 (37.0) | 614 (36.8) | 202 (37.7) | |
| Normal/Underweight (BMI <25) | 631 (26.0) | 501 (27.3) | 130 (22.2) | |
| Total/HDL Cholesterol (mg/dL) (SE) | 4.03 (0.04) | 12.02 (2.01) | 109.93 (2.47) | 0.0017 |
| Hypertension, *N* (%) | | | | |
| Yes | 1183 (45.6) | 742 (38.2) | 441 (67.5) | <0.0001 |
| No | 1152 (54.4) | 1007 (61.8) | 145 (32.5) | |
| Diabetic Status, *N* (%) | | | | |
| Yes | 460 (13.2) | 249 (9.9) | 211 (22.9) | <0.0001 |
| No | 1875 (86.8) | 1500 (90.1) | 375 (77.1) | |
| History of angina, *N* (%) | | | | |
| Grade 2 | 19 (0.5) | 13 (0.6) | 6 (0.4) | 0.3764 |
| Grade 1 | 49 (1.4) | 33 (1.3) | 16 (1.9) | |
| None | 2203 (96.0) | 1670 (96.7) | 533 (94.0) | |
| MET min/week, *N* (%) | | | | |
| High | 365 (17.7) | 292 (19.0) | 73 (13.9) | 0.4046 |
| Moderate | 311 (14.1) | 242 (13.9) | 69 (14.9) | |
| Low | 1027 (44.2) | 761 (44.2) | 266 (44.0) | |
| None | 632 (24.0) | 454 (23.0) | 178 (27.3) | |
| Last Dental visit, *N* (%) | | | | |
| Within past year | 1400 (66.8) | 1010 (63.3) | 390 (77.2) | 0.0001 |
| >1 year ago | 932 (33.1) | 738 (36.6) | 194 (22.7) | |

*Overall: $n$ = 101,271,551; No aspirin use: $n$ = 75,903,599; Low-dose aspirin use: $n$ = 25,367,953.
$n$ is the weighted population size for each group. Percentages presented in this table are also weighted.
**Pair-wise comparison between low-dose aspirin users vs. non-users.

When we further explored the association between aspirin use and periodontitis in these subgroups, results remained unchanged.

These findings contradict previously published studies that have suggested that low-dose aspirin may have a protective effect against periodontitis (Feldman et al. 1983, Drouganis & Hirsch 2001, Faizuddin et al. 2012). Some key differences between our current analysis of the NHANES sample and previous reports are outlined below and focus on three key scientific design features including: (i) inclusion/exclusion criteria and generalizability; (ii) level of adjustment for potential confounders; (iii) duration of aspirin use.

To our knowledge, this study is the first analysis of a large nationally

*Table 2.* Odds ratios summarizing the association between low dose aspirin use and periodontitis among $n = 2335$ participants enrolled in The Continuous National Health and Nutrition Examination Survey (NHANES) 2011–2012

| | Model 1* | | Model 2* | | Model 3* | | Model 4* | | Model 5* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Three-level definition of periodontitis | | | | | | | | | | |
| Severe | 1.27 | 0.99–1.63 | 1.17 | 0.81–1.68 | 1.17 | 0.81–1.68 | 1.11 | 0.77–1.59 | 1.06 | 0.74–1.50 |
| Moderate | 1.39 | 1.00–1.93 | 0.99 | 0.63–1.56 | 0.99 | 0.63–1.56 | 0.94 | 0.58–1.50 | 0.91 | 0.56–1.50 |
| No/Mild | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Four-level definition of periodontitis | | | | | | | | | | |
| Severe | 1.28 | 1.00–1.63 | 1.11 | 0.79–1.54 | 1.21 | 0.86–1.71 | 1.16 | 0.82–1.63 | 1.12 | 0.79–1.58 |
| Moderate | 1.4 | 1.02–1.92 | 0.96 | 0.63–1.48 | 1.03 | 0.67–1.58 | 0.97 | 0.62–1.52 | 0.96 | 0.60–1.54 |
| Mild | 1.1 | 0.44–2.77 | 1.67 | 0.60–4.65 | 1.61 | 0.57–4.51 | 1.66 | 0.60–4.59 | 1.59 | 0.59–4.28 |
| None | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Participants | $n = 2335$ | | $n = 2129$ | | $n = 2112$ | | $n = 1983$ | | $n = 1933$ | |

Additional information on the ORs for each of the covariables is presented in Table S4.
*Model 1: crude; Model 2: adjusted for age, sex, race, education and poverty-income ratio; Model 3: Model 2 & smoking and BMI; Model 4: Model 3 & total/HDL cholesterol and hypertension; Model 5: Model 4 & diabetes, angina, physical activity.

*Table 3.* Comparison of mean probing depth and attachment loss in aspirin users versus low-dose users and high-dose users among $n = 2430$ participants enrolled in The Continuous National Health and Nutrition Examination Survey (NHANES) 2011–2012

| | | No aspirin use | Low-dose aspirin (25–162 mg) | | Aspirin dosage >162 mg | |
|---|---|---|---|---|---|---|
| | | Mean (SE) | Mean (SE) | *p*-value** | Mean (SE) | *p*-value*** |
| Model 1* | Probing depth (mm) | 1.44 (0.03) | 1.42 (0.03) | 0.4378 | 1.52 (0.09) | 0.4170 |
| | Attachment loss (mm) | 1.79 (0.06) | 1.98 (0.07) | 0.0039 | 2.09 (0.22) | 0.1653 |
| | $n = 2430$ | | | | | |
| Model 2* | Probing depth (mm) | 1.46 (0.02) | 1.46 (0.04) | 0.9583 | 1.51 (0.10) | 0.6551 |
| | Attachment loss (mm) | 1.90 (0.05) | 1.95 (0.06) | 0.4462 | 1.99 (0.24) | 0.7145 |
| | $n = 2222$ | | | | | |
| Model 3* | Probing depth (mm) | 1.46 (0.02) | 1.47 (0.03) | 0.6935 | 1.50 (0.10) | 0.6412 |
| | Attachment loss (mm) | 1.88 (0.05) | 1.96 (0.06) | 0.2366 | 2.00 (0.23) | 0.6226 |
| | $n = 2202$ | | | | | |
| Model 4* | Probing depth (mm) | 1.45 (0.02) | 1.45 (0.03) | 0.8648 | 1.50 (0.11) | 0.6946 |
| | Attachment loss (mm) | 1.87 (0.05) | 1.93 (0.06) | 0.2982 | 1.98 (0.24) | 0.6386 |
| | $n = 2071$ | | | | | |
| Model 5* | Probing depth (mm) | 1.45 (0.02) | 1.44 (0.04) | 0.7799 | 1.50 (0.12) | 0.6925 |
| | Attachment loss (mm) | 1.86 (0.05) | 1.91 (0.06) | 0.4609 | 1.99 (0.27) | 0.627 |
| | $n = 2020$ | | | | | |

*Model 1: crude; Model 2: adjusted for age, sex, race, education and poverty-income ratio; Model 3: Model 2 & smoking and BMI; Model 4: Model 3 & total/HDL cholesterol and hypertension; Model 5: Model 4 & diabetes, angina, physical activity.
**Pair-wise comparison between low-dose aspirin users vs. non-users.
***Pair-wise comparison between aspirin users taking >162 mg vs. non-users.

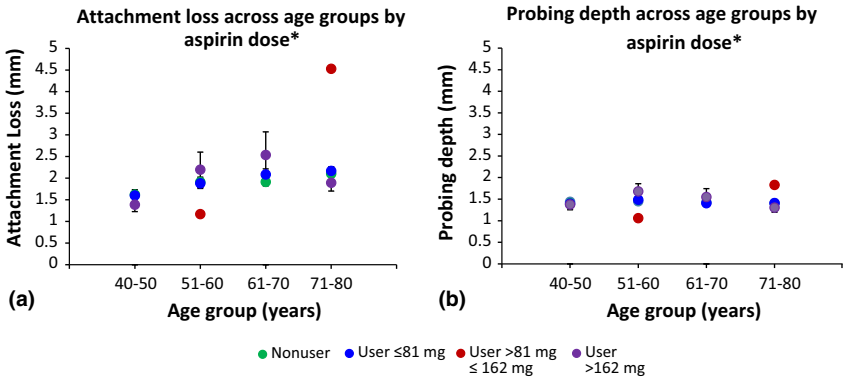


*Fig. 1.* (a) Depicts mean (SE) attachment loss stratified by age group. No significant association was found in this model. (b) shows mean (SE) for probing depth stratified by age group. No significant association was found in this model. *Least squares means adjusted for age.

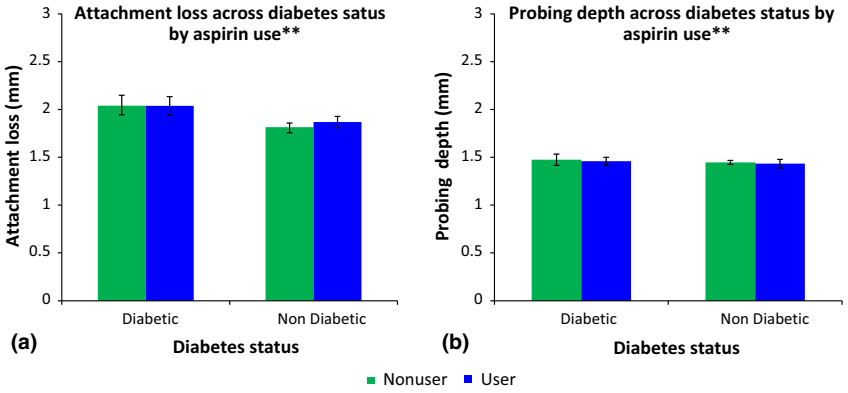


*Fig. 2.* (a) Depicts mean (SE) attachment loss stratified by *diabetes status*. No significant association was found in this model. (b) depicts mean (SE) probing depth stratified by *diabetes status*. No significant association was found in this model. *Least squares means (SE) adjusted for age, sex, race, education and poverty-income ratio, smoking and BMI, total/HDL cholesterol and hypertension, diabetes, angina, physical activity.

*Table 4.* Mean tooth loss levels across categories of aspirin use among $n = 2430$ participants enrolled in The Continuous National Health and Nutrition Examination Survey (NHANES) 2011–2012

| | No aspirin use | Low-dose aspirin (25–162 mg) | | Aspirin dosage >162 mg | |
|---|---|---|---|---|---|
| | Mean ± SE | Mean ± SE | *p*-value** | Mean ± SE | *p*-value*** |
| Model 1* | 6.78 (0.22) | 8.76 (0.31) | <.0001 $n = 2430$ | 8.57 (0.71) | 0.03 |
| Model 2* | 7.64 (0.21) | 8.06 (0.30) | 0.26 $n = 2222$ | 8.06 (0.77) | 0.59 |
| Model 3 * | 7.58 (0.22) | 8.04 (0.32) | 0.25 $n = 2202$ | 7.89 (0.70) | 0.66 |
| Model 4* | 7.46 (0.21) | 7.81 (0.33) | 0.39 $n = 2071$ | 7.71 (0.73) | 0.74 |
| Model 5* | 7.45 (0.20) | 7.79 (0.40) | 0.48 $n = 2020$ | 7.63 (0.67) | 0.80 |

*Model 1: crude; Model 2: adjusted for age, sex, race, education and poverty-income ratio; Model 3: Model 2 & smoking and BMI; Model 4: Model 3 & total/HDL cholesterol and hypertension; Model 5: Model 4 & diabetes, angina, physical activity.
**Pair-wise comparison between low-dose aspirin users vs. non-users.
***Pair-wise comparison between aspirin users taking >162 mg vs. non-users.

representative sample of adults in comparison to previous studies that were restricted to self-selected male non-smoker participants (Drouganis & Hirsch 2001), non-smoker, non-diabetic cardiology outpatients (Faizuddin et al. 2012), or US Veterans with arthritis from a VA outpatient clinic (Feldman et al. 1983). While the sample characteristics of previous studies do not necessary invalidate their conclusions, they do limit the interpretation of results in terms of the population level impact of aspirin use on periodontitis prevalence. This study, in contrast, was the first nationally representative report from the US that included data from more than 2000 individuals with diverse ethnic backgrounds utilizing a sampling strategy that was constructed to produce an unbiased national estimate (Eke et al. 2012a).

Another strength of this study is the inclusion of subgroup analyses as well as comprehensive confounder adjustment including age, sex, socioeconomic status, smoking, diabetes status, obesity, activity levels and cardiovascular disease risk factors including cholesterol and hypertension in the analysis. Prior studies only adjusted for a limited number of potential confounders, therefore it cannot be excluded that spurious associations between aspirin use and periodontitis were identified in these studies (Feldman et al. 1983, Drouganis & Hirsch 2001, Faizuddin et al. 2012). In the studies by Drouganis and Hirsch and Faizuddin et al., the analysis included limited risk factor adjustment, namely age, sex and smoking status, and age, diabetes status and smoking, respectively (Drouganis & Hirsch 2001, Faizuddin et al. 2012). Also, in the study by Feldman et al. important confounders related to socioeconomic status, education and other comorbidities were not included in their analyses (Feldman et al. 1983). Moreover, the additional use of indomethacin by some of the aspirin users among the US Veterans rheumatology outpatients included in their study was not adjusted for in the analyses (Feldman et al. 1983). A synergistic protective effect between aspirin and indomethacin could be speculated, although Feldman et al. did not separately report results in aspirin users with or without additional indomethacin intake (Feldman et al. 1983).

Since the adjustments in these studies (Feldman et al. 1983, Drouganis & Hirsch 2001, Faizuddin et al. 2012) were not as extensive as in this study, it is possible that the previously observed differences may be due to residual or unmeasured confounding. For example, in our analyses, when compared to the unadjusted (crude) OR, the addition of age, sex, race and socioeconomic covariables to the model negated the association between low dose aspirin and moderate periodontitis from a significant OR of 1.40 to a non-significant OR of 0.96 in the adjusted model (Table 2).

An important limitation of the NHANES data is the lack of information on duration of aspirin use. As the hypothesized benefits of aspirin use are likely to aggregate over time, analyses that group recently initiated users with long-time users would likely bias findings towards the null. Two previous reports have considered inclusion thresholds for duration of aspirin use. Drouganis and Hirsch only considered participants that had been using aspirin for

at least 2 years, whereas in Feldman et al., users were taking aspirin for at least 5 years prior to assessment (Feldman et al. 1983, Drouganis & Hirsch 2001). The NHANES preventive aspirin questionnaire that was utilized in this study included details on the frequency and dosage of aspirin, but not on the duration. It is possible that the differences in the results among this study and previous reports may be partially attributable to the duration of aspirin use. However, although a cumulative inhibitory effect of low-dose aspirin on several pro-inflammatory mediators has indeed been shown, the inhibitory effect seems to reach a plateau within weeks following initiation of the aspirin regimen (Patrignani et al. 1982). Whether or not the duration of aspirin's protective effect influenced the severity of periodontal disease observed in this study could only be determined through prospective studies in carefully selected cohorts, or by the addition of relevant questions in the NHANES "preventive aspirin use" questionnaire in future study cycles.

The main limitation of this study is the cross-sectional design that limits the strength of causal inference as compared to longitudinal studies. Although the cross-sectional design of the NHANES precluded any inference regarding the temporality of the relationship between aspirin use and periodontal disease, no significant differences were observed between aspirin users and non-users even when mean PD was evaluated in our study (Table 3). While tooth loss and AL provide information on the history of periodontal disease, PD can be considered as a surrogate measure for current periodontal status. Thus, if a significant protective effect of aspirin indeed existed, aspirin users should demonstrate reduced mean PD compared to non-users. However, our analysis showed no difference for mean PD in aspirin users versus non-users. (1.44 mm vs. 1.45 mm respectively; Table 3, model 5). Radiographic assessment of bone loss could be an additional surrogate for periodontal tissue destruction and would allow direct comparison to other studies that reported the progression of periodontal bone loss following use of NSAIDs (Williams et al. 1989). The question of the rate of bone resorption in aspirin users is essentially coupled to the question of whether duration of dosage is a key determinant of aspirin's therapeutic efficacy due to the slow metabolic rate of the alveolar bone (Coimbra et al. 2011). Recent in vivo data collected from animal studies have suggested effects of aspirin on various molecular pathways that combat chronic inflammation in the periodontium and may prevent or contain bone destruction in periodontics. Such examples are the anti-platelet effect of aspirin on the gingival levels of thromboxane A2 (Coimbra et al. 2011) and the function of resolvins as anti-inflammatory molecules against periodontal bone destruction (Hasturk et al. 2006). Due to the cross-sectional design of this study the effect of long-term low-dose aspirin on periodontal bone destruction could not be addressed, thus this question should be investigated in longitudinal studies that should also assess the effect of aspirin dosage and duration.

Our results are in general agreement with earlier studies on the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on periodontal disease. Williams and colleagues reported that ibuprofen, naproxen and flurbiprofen inhibited crevicular pro-inflammatory mediators and hypothesized that the use of these anti-inflammatory agents could be useful adjuncts in the treatment of periodontal disease (Williams et al. 1984, 1985, Offenbacher et al. 1992). A series of pre-clinical studies by the same research group revealed a protective effect of NSAIDs, namely flurbiprofen, against alveolar bone loss in beagle dogs (Williams et al. 1985, 1987, 1988). Although promising, this finding was not reproduced in subsequent human studies that found no significant clinical effect of flurbiprofen in both treated and untreated periodontal patients (Williams et al. 1989, Bragger et al. 1997).

In summary, this study has several notable strengths. The robust sample selection and data collection processes allowed us to perform subgroup analyses by overall cardiometabolic health status, which substantially reduced the potential for confounding by indication. In addition, the breadth and completeness of the NHANES data sets allowed us to consider various additional confounders in the adjusted analyses. Indeed, several covariables, such as ethnicity and income poverty ratio, differed significantly across aspirin use and were significantly associated with periodontitis in the adjusted analyses. In contrast, none of these variables had been considered in previous cross-sectional studies that reported on the association between aspirin use and periodontitis. On the basis of the results of this study, we report no association between frequent low dose aspirin use and periodontal disease in a nationally representative sample of US adults. However, due to the potential for confounding by indication in this sample, future intervention studies that can more directly assess the influence of aspirin therapy on periodontal outcomes are warranted.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Case definitions for periodontal disease based on CDC/AAP guidelines

**Table S2.** STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

**Table S3.** Odds Ratios for Severe vs. No/Mild periodontitis and Moderate vs. No/Mild periodontitis in individuals taking more than 162 mg and up to 500 mg of aspirin

**Table S4.** Odds ratios for various covariables included in adjusted models (Models 2–5)

**Figure S1.** Flowchart showing participant selection process according to STROBE guidelines.

**Figure S2**. Mean AL and PD per age subgroups.

**Figure S3**. Mean AL and PD per sex subgroups.

**Figure S4**. Mean AL and PD per history of angina status.

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**Clinical Relevance**

*Scientific rationale for the study*: Host modulatory agents, including aspirin, have been proposed for the treatment of periodontitis. We hypothesized that low-dose aspirin use would be associated with lower prevalence of periodontitis among US adults.

*Principal findings*: Low-dose aspirin use is not associated with reduced prevalence of periodontitis in a nationally representative sample of US adults.

*Practical implications*: Our results conflict with previous reports. More research is justified to better understand the possible role of aspirin in periodontitis treatment and to understand which persons might realize periodontal benefit from aspirin therapy.