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The clinical and inflammatory relationships between periodontitis and chronic obstructive pulmonary disease

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Abstract

Aim: To investigate associations between periodontitis and chronic obstructive pulmonary disease (COPD) with and without alpha-1 antitrypsin deficiency (AATD), including neutrophil functions implicated in tissue damage.

Methods: The presence and severity of periodontitis (using two international criteria) and lung disease were assessed in 156 COPD patients with and without AATD accounting for common confounding factors. Saliva and systemic inflammatory markers were measured by ELISA together with neutrophil migration.

Results: COPD and AATD patients exhibited higher prevalence of periodontitis (COPD 95%; AATD 88%) than reported in unselected community-dwelling populations even when risk factors (age, smoking history, socio-economic status and dental habits) were considered. Periodontitis severity associated with lung disease severity (AATD, periodontitis versus no periodontitis; FEV1 = 56% versus 99% predicted; TLCO = 59% versus 81% predicted, $p < .0001$ for both). Neutrophil migratory accuracy declined in stage II–IV periodontitis patients with COPD or AATD compared to COPD or AATD with no or stage I periodontitis. Improved dental habits appeared to be associated with a reduction in exacerbation frequency in COPD.

Conclusion: The results support shared pathophysiology between periodontitis and COPD, especially when associated with AATD. This may reflect an amplification of neutrophilic inflammation and altered neutrophil functions, already described in periodontitis, COPD and AATD.

KEYWORDS

co-morbidity, inflammation, neutrophil biology, physiology

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1 | INTRODUCTION

Multi-morbidity (the presence of two or more chronic diseases) is common, accounting for sixty per cent of global deaths (Rizzuto, Melis, Angleman, Qiu, & Marengoni, 2017). Multi-morbid diseases do not randomly co-occur; common clusters have been described with some illnesses appearing central within the clusters. Chronic obstructive pulmonary disease (COPD) and periodontitis are such diseases, acting as central hubs in a number of chronic disease networks (Divo et al., 2015; Zhao, Zhen, Pelekos, Yiu, & Jin, 2019).

COPD affects ten per cent of adults over forty years of age worldwide (Buist et al., 2007) and will become the third leading cause of death by 2030 (WHO). It is characterized by airflow limitation and lung inflammation caused most commonly by smoking cigarettes. COPD is associated with co-morbidities that share risk factors such as age, chronic cigarette smoking, lower socio-economic status and sedentary lifestyles. However, these co-morbidities are still more prevalent than expected, even when common risk factors are accounted for (Mannino, Thorn, Swensen, & Holguin, 2008). Studies have proposed mechanistic links between COPD and co-morbid conditions (Gomez-Cabrero et al., 2016), and shared mechanisms support the concept of integrated therapeutic strategies. Alpha-1 antitrypsin deficiency (AATD) is the only robustly proven genetic risk factor for COPD, associated with a lack of functional alpha-1 antitrypsin, which would usually inhibit neutrophil proteinases on a one-to-one molar basis (Stockley & Turner, 2014). It is considered a rare disease, with a prevalence of 1 per every 2,000–5,000 people (Blanco et al., 2017).

The neutrophil is of central importance in COPD, related to disease severity and decline (Di Stefano et al., 1998). Neutrophil responses appear dysregulated in COPD with evidence of increased neutrophil proteinase activity and altered migratory dynamics (Sapey et al., 2011). This pathogenic relationship is even more direct in AATD. Here, the functional deficiency of alpha-1 antitrypsin (AAT) increases the susceptibility of lung tissue to degradation by neutrophil proteinases. Lung damage is seen at a younger age and with less or no cigarette smoke exposure compared to patients with non-AATD-related COPD. Neutrophils are now considered an immunotherapeutic target in AATD and COPD (Walton et al., 2016), and this may be true in other diseases.

Periodontitis is a destructive chronic inflammatory condition that leads to tooth loss, reduced nutrition, lower self-esteem and quality of life, and premature mortality (Garcia, Krall, & Vokonas, 1998). It affects 45%–50% of adults and in its most severe form impacts between 7.4% and 11.2% of adults worldwide (Kassebaum et al., 2014). In 2015, severe periodontitis incurred $54billion in indirect costs to the global economy (productivity losses; (Listl, Galloway, Mossey, & Marcenes, 2015)), and more years are lost to disability to periodontitis alongside dental caries than any other human disease. Its pathogenesis involves the recruitment and activation of neutrophils, which drives clinical attachment loss due to connective tissue destruction (Meyle & Chapple, 2015). Hyper-responsivity in peripheral blood neutrophils has been demonstrated for reactive oxygen species production (Matthews et al., 2007), proteinase release (Figueredo, Gustafsson, Åsman, & Bergström, 2000) and cytokine release (Ling, Chapple, & Matthews, 2015), and defects in chemotactic accuracy are also reported (Roberts et al., 2015). However, periodontitis is preventable and treatable and successful periodontal therapy has been shown to improve outcomes in other chronic co-morbidities (Sanz et al., 2018; Tonetti & Sanz, 2019).

Epidemiological studies consistently report an association between the prevalence of COPD and periodontitis, but these have had limitations (reviewed by (Hobbins, Chapple, Sapey, & Stockley, 2017)). Some reflect a secondary analysis of existing data sets using disparate definitions of periodontitis, as highlighted in systematic reviews (Garcia, Nunn, & Vokonas, 2001; Linden, Lyons, & Scannapieco, 2013). Others have not included contemporary gold standard definitions of COPD (Scannapieco & Ho, 2001) or involved a significant delay between the measurement of lung function and periodontal health (Barros, Suruki, Loewy, Beck, & Offenbacher, 2013; Offenbacher, Beck, Barros, Suruki, & Loewy, 2012). Frequently, there is no assessment of potential shared mechanisms of tissue damage or any comparison of markers of salivary and systemic inflammation (Deo, Bhongade, Ansari, Ramesh, & Chavan, 2009; Prasanna, 2011; Wang et al., 2009). Although both conditions are characterized by neutrophilic inflammation and neutrophil dysfunction (Roberts et al., 2015; Sapey et al., 2011), studies have not compared cellular functions between diseases.

Clinical Relevance

Scientific rationale for study: There is increasing recognition that multi-morbidity in chronic inflammatory diseases may reflect shared pathological mechanisms and thus shared putative therapeutic targets. Chronic obstructive pulmonary disease (COPD) and periodontitis frequently co-occur and share features of aberrant neutrophil responses, but this may reflect common risk factors of disease (smoking, age and socio-economic status) rather than shared pathophysiology.

Principal findings: Patients with COPD had poor dental habits prior to periodontal assessment and education. COPD and alpha-1 antitrypsin deficiency (a disease associated with heightened neutrophilic inflammation and COPD) had a high burden of periodontitis even after common risk factors were considered. This was associated with altered neutrophil functions implicated in both lung and periodontal tissue damage. Improving dental habits appeared to be associated with a reduction in COPD exacerbations.

Practical implications: Assessment and education can improve oral care in COPD, where the burden of periodontitis is high. Altered neutrophil functions are implicated in both disease processes. Importantly, improving oral care may reduce the frequency of COPD exacerbations and should be considered as part of patient management.

While there is considerable interest in potential mechanistic links between periodontitis and COPD, with a particular focus on neutrophils and proteinases, in COPD, there is also a high burden of lifestyle factors which could contribute to both conditions (poor dental health and hygiene, lower socio-economic status, increased smoking (Gaeckle, Heyman, Criner, & Criner, 2018; Gershon, Dolmage, Stephenson, & Jackson, 2012)) as well as confounding factors such as age (Winning, Patterson, Cullen, Kee, & Linden, 2019) and co-morbidities such as diabetes and cardiovascular disease (Cavaillès et al., 2013). These might blunt our ability to identify mechanistic relationships. Neutrophilic inflammation and proteinase-related damage are higher in AATD than in non-AATD COPD (Stone, McNab, Wood, Stockley, & Sapey, 2012), and this might allow any relationships between neutrophilic inflammation, lung disease and periodontitis to be amplified and more readily examined.

Our consortium of respiratory physicians, periodontologists and neutrophil biologists hypothesized that periodontitis and COPD would share aspects of neutrophil dysfunction as a mechanism of disease and that an association between COPD and periodontitis would remain once confounding factors were accounted for. We hypothesized that this relationship would be stronger in AATD, as unopposed neutrophil proteinase activity would increase both lung and periodontal tissue damage. Further, we hypothesized that improving oral health would impact on clinically important outcomes in COPD.

The current study had five aims:

- To characterize the presence and severity of periodontitis in COPD/AATD
- To describe relationships between periodontitis and lung disease
- To determine whether periodontitis was associated with an enhanced burden of local or systemic inflammation in COPD/AATD
- To determine whether neutrophil responses (migration) differed in COPD and AATD patients with and without periodontitis.
- To determine whether an oral health review with brief advice would impact on oral health behaviours and respiratory infections in the subsequent year.

2 | METHODS

AATD and COPD patients were recruited from the NIHR-supported West Midlands COPD and AATD cohorts at the Queen Elizabeth Hospital Birmingham, between 2014 and 2017, with follow-up completed in 2018. Ethical approval was granted by the National Research Ethics Service (REC13/WM/0044), and all participants provided informed consent. This study is reported in keeping with STROBE guidelines.

2.1 | Patient characterization

COPD was diagnosed and staged by GOLD criteria (Global Initiative for Chronic Obstructive Lung Disease, 2019). The AATD patients included only those with the PiZZ and PiZ0 null genotypes (confirmed by Heredilab, Salt Lake City, USA). Patients were excluded if they had any medical condition precluding an oral examination, were unable to perform lung function tests to ERS/ATS standards (ARTP Handbook, 2003) or had significant alternative lung diseases. All patients were exacerbation-free and free from overt oral infections for at least six weeks prior to the study. Socio-economic data were determined using the English Index of Multiple Deprivation (IMD, 2015) score and the National Statistics Socio-economic Classification (NS-SEC) score (Government 2015; Statistics, 2010).

Respiratory symptom burden was assessed using the modified Medical Research Council scale (mMRC scale) (Hajiro et al., 1998). Bronchitis was defined as self-reported cough and sputum production for at least three months of the year over two consecutive years. A full lung function assessment was conducted including post-bronchodilator spirometry, lung volumes and measures of gas transfer (TLco and Kco) and corrected for age, sex, height and ethnicity using GLI reference ranges (Cooper et al., 2017). Exacerbation frequency (defined as an acute worsening of respiratory symptoms that resulted in additional therapy (Global Initiative for Chronic Obstructive Lung Disease, 2019)) was confirmed as documented by primary care physicians.

Patients' oral habits were recorded, and all patients underwent an oral examination by a trained dental surgeon. Internal consistency of periodontal reporting was checked as part of study set-up. Measurements were carried out on all teeth using the UB-WHO-CF15 constant force periodontal probe (Implantium.co.uk) as described in the online supplement. Definitions of periodontitis were the Centers for Disease Control and Prevention–American Association of Periodontology (CDC-AAP) criteria (Eke, Page, Wei, Thornton-Evans, & Genco, 2012) (where periodontitis was classified as >2 inter-proximal sites with CAL > 4 mm (not on same tooth) or >2 inter-proximal sites with PD > 5 mm (not on same tooth)) and the consensus report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Papapanou et al., 2018), termed WWP (staged as I, II, III and IV—see online supplementary material—Periodontal Measurements). Patients were informed of the presence of periodontitis, dental habits were discussed, and modifications were suggested where needed. Patients were advised to see their own dentist for subsequent ongoing treatment and review.

Periodontal prevalence data in non-AATD COPD and AATD patients were compared to two different national dental health surveys of community-dwelling adults: first, the NHANES 2009–2012 dental health study in the United States, in which 7,066 individuals were screened for periodontitis and 45.9% of all adults, 52.7% of adults aged 50–64 and 68% of adults aged over 65 years were affected (Eke et al., 2015); second, the Adult Dental Health Survey (ADHS) of a UK dentate population in England and Wales, which took place in 2009 and included 11,380 adults aged 16 or over. Here, 45% of the total population and 60% of 65- to 84-year-olds had evidence of periodontitis (Adult Dental health Survey, 2009).

Twelve months following inclusion in the study, participants and their primary care physician were contacted to assess changes in oral health practices after inclusion in the study and brief advice, along with reported respiratory exacerbations (primary care confirmed).

2.2 | Blood samples

30 mL peripheral venous blood was taken from each patient using the BD Vacutainer system® (Becton, Dickinson and Company, Plymouth, UK) and plasma prepared.

2.3 | Saliva samples

Patients were asked to not eat, drink, smoke or brush their teeth for four hours prior to the sampling appointment. Saliva collection, processing and storage were as previously described (Chapple et al., 1997).

2.4 | Inflammatory mediators

See online supplement for details. The kits used were plasma high-sensitivity C-reactive protein (hsCRP) (Cambridge BioScience, Cambridge, UK), saliva CXCL8 (R&D Systems Ltd, Abingdon, UK) and saliva CRP (Salimetrics Europe, Newmarket, UK), all as per manufacturer's instructions.

2.5 | Neutrophil studies

Neutrophils were isolated from the whole blood of a subgroup of patients, and chemotaxis was assessed using an Insall Chamber (Weber Scientific International Ltd, Teddington, UK) as described previously (Sapey et al., 2011) and in the online supplement. Migration was assessed using two parameters:

- Average *speed* of cell movement. This was measured as the distance travelled between frames, in any direction, over time and is reported as μm/minute.
- Average *velocity* of cell movement. This was measured as the speed in a consistent direction towards the chemoattractant, also measured in μm/minute.

2.6 | Statistical analysis

Data were analysed using Stata version 14.2 (StataCorp LLC, USA). Tests are stated in the results. Due to low sample size, overfitting of logistic regression models was considered and non-parametric bootstrapping (replication 1,000) was used. The Holm–Bonferroni correction was applied for multiple comparisons to avoid a type 1 error. Power calculations are given in the online supplement.

3 | RESULTS

156 dentate (presence of ≥2 natural teeth) patients (88 COPD and 68 AATD) were recruited. Baseline characteristics and the prevalence of periodontitis are summarized in Table 1. Non-AATD COPD patients were significantly older with a greater smoking history, poorer socio-economic background and fewer remaining teeth. They were also more symptomatic and had worse lung function, more COPD exacerbations, an increased prevalence of vascular disease and a higher use of inhaled corticosteroids.

3.1 | Patients with non-AATD COPD had poor dental habits

At baseline assessment, the non-AATD COPD patients had poorer dental habits than patients with AATD, with only 35% being registered with a dentist, 26% having visited a dentist in the past year and 10% reporting using floss (compared to 95%, 76% and 73% in the AATD group, respectively). Compared to the ADHS 2009, a lower percentage of patients with COPD self-reported visiting the dentist annually (COPD 21% versus ADHS 71%, $p < .0001$), brushed their teeth twice a day (COPD 40% versus ADHS 75%, $p < .0001$) or flossed (COPD 10% versus ADHS 21%, $p = .049$). Using the same ADHS data, a similar percentage of patients with AATD self-reported visiting a dentist annually (AATD 76% versus ADHS 71%, $p = .52$) and brushed their teeth twice a day (AATD 78% versus ADHS 75%, $p = .72$), but a greater per cent reported using floss (AATD 73% versus ADHS 21%, $p < .0001$); Fisher's exact test for all.

Twelve months after their baseline assessment, there was no change in dental habits for patients with AATD, which remained good, but patients with non-AATD COPD described an overall improvement in dental habits, although these still remained poorer than the AATD group for all activities except toothbrushing frequency (Table 2).

3.2 | Periodontitis is highly prevalent in non-AATD COPD and AATD

The prevalence of periodontitis was high in both COPD and AATD (Table 1). The prevalence was higher in the COPD group compared with the CDC-AAP results quoted in the NHANES 2009–2012 study (Eke et al., 2015) when the whole adult per cent was used either for NHANES (NHANES 45.9% versus COPD 92.9%, Fisher's exact test, $p < .0001$) or for adults aged >65 (NHANES 68%, Fisher's exact test, $p < .0001$). This was also the case when comparing to the ADHS data (Adult Dental health Survey, 2009; Fisher's exact test $p < .0001$ compared to both all adults and adults aged over 65). In AATD,

TABLE 1 Baseline characteristics of non-AATD COPD (COPD) and AATD groups and prevalence of periodontitis

	COPD	AATD	*p* value
N	88	68	
Male participants, *n* (%)	62 (70.5%)	39 (57.4%)	.09
Age, years (Range)	68.6 (49 – 82)	55.3 (31 – 77)	**<.001**
BMI (*SD*)	27.8 (6.2)	26.0 (5.1)	.06
Current and ex-smokers, *n* (%)	88 (100%)	43 (63.2%)	**<.001**
Smoking PYH (*SD*)	56.0 (42.4)	12.6 (19.3)	**<.001**
Current smokers	53 (61%)	2 (3%)	**<.0001**
Number of teeth (*SD*)	17.1 (7.5)	24.4 (5.4)	**<.001**
Median IMD Score (range)	5 (1–5)	2 (1–5)	**<.001**
Age (years) when left education (*SD*)	15.7 (2.5)	18.6 (3.6)	**<.001**
Median NS-SEC (range)	5 (2–6)	2 (1–7)	**<.001**
Median GOLD stage (range)	2 (1–4)	2 (0–4)	
GOLD stage 1 (*n*, %)	15 (17%)	30 (44%)	**<.001**
GOLD stage 2 (*n*, %)	33 (38%)	17 (25%)	
GOLD stage 3 (*n*, %)	29 (33%)	18 (26%)	
GOLD stage 4 (*n*, %)	11 (12%)	3 (5%)	
Median mMRC (range)	3 (1–5)	2 (1–5)	**<.001**
Exacerbations per year (*SD*)	2.8 (3.0)	1.2 (1.2)	**<.001**
Frequent exacerbators[a] (*n*, %)	47 (53%)	21 (31%)	**.0058**
Bronchitis *n* (%)	37 (42.5%)	24 (35.3%)	.360
Radiological emphysema on CT (%)	76.3%	77.8%	.838
Diabetes *n* (%)	9 (10.2%)	1 (1.5%)	.044
Vascular disease, *n* (%)	26 (29.5%)	1 (1.5%)	**<.001**
Hypertension, *n* (%)	22 (25%)	9 (13.2%)	.068
Use of ICS, *n* (%)	75 (85.2%)	36 (52.9%)	**<.001**
% Predicted FEV_1 (*SD*)	54.4 (22.2)	70.8 (28.1)	**<.001**
FEV_1:FVC ratio (*SD*)	44.6 (13.9)	53.0 (19.3)	.011
% Predicted TLco (*SD*)	51.3 (16.4)	64.4 (19.8)	**<.001**
% Predicted Kco (*SD*)	67.6 (21.3)	67.7 (18.4)	.980
CDC-AAP. *n* (% moderate and severe)	79 (92.9)	49 (72.1)	**.0001**
WWP (*n*, %)			
No periodontitis	4 (4.7)	8 (11.8)	.065
Any periodontitis	84 (95.3)	60 (88.2)	
Mild (stage I)	40 (47.1)	40 (58.8)	
Moderate (stage II)	17 (19.3)	11 (16.2)	
Severe (stages III and IV)	27 (31.8)	9 (13.2)	

Note: Data are presented as mean with corresponding standard deviation or median and range depending on the distribution.

Exacerbations were self-reported and confirmed with primary healthcare provider as the number of episodes of respiratory deterioration requiring increased or additional treatment in the previous year (Burge & Wedzicha, 2003). Definitions are as follows: CDC-AAP, Centers for Disease Control and Prevention–American Association of Periodontology. CDC-AAP = ≥2 inter-proximal sites with CAL ≥ 4 mm (not on same tooth) or ≥2 inter-proximal sites with PD ≥ 5 mm (not on same tooth). WWP—a definition based on the consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Papapanou et al., 2018), where stage 1 (mild) periodontitis was inter-dental CAL at the site of greatest loss of 1–2 mm and maximal PPD ≤ 4 mm; stage 2 (moderate) periodontitis was inter-dental CAL at the site of greatest loss of 3–4 mm and maximal PPD ≤ 5 mm; and stage 3 disease or greater (severe periodontitis) was inter-dental CAL at the site of greatest loss of ≥5 mm and maximal PPD ≥ 6 mm. Data are presented as number of patients affected and corresponding percentage of the group. COPD and AATD groups were compared using Fisher's exact tests. Values in bold typeface remained statistically significant after Holm–Bonferroni correction.

Abbreviations: ICS, inhaled corticosteroid; IMD, Index of Multiple Deprivation, a score of deprivation based on postcode; NS-SEC, National Statistics Socio-economic Classification, the primary social classification system used in UK based on occupation; PYH, smoking pack-year history.

[a]Frequent exacerbators were those with two or more exacerbations per year (Global Initiative for Chronic Obstructive Lung Disease, 2019).

TABLE 2 Baseline and 12-month dental habits of COPD and AATD groups

	Baseline			12 months		
	COPD	AATD	*p* value	COPD	AATD	*p* value
N	88	68		86	68	
Is registered with a dentist (Yes, *n*, %)	31 (35%)	63 (95%)	**<.0001**	48 (56%) [**0.009**]	64 (98%) [0.691]	**<.0001**
Visited dentist in last year (Yes, *n*, %)	23 (26%)	50 (76%)	**<.0001**	37 (43%) [0.023]	55 (84%) [0.999]	**<.0001**
Number of times usually brush teeth per day, median (range)	1 (0–2)	2 (0–2)	**.0018**	2 (1–2) [**0.002**]	2 (1–2) [0.250]	.314
Used floss or mouthwash in past year (*n*, %)	9 (10%)	48 (73%)	**<.0001**	19 (22%) [0.039]	54 (83%) [0.206]	**<.0001**

Note: Data are presented as number (per cent) except where stated. Patients were asked if they were registered with a dentist (yes or no response); if they had undergone a dental examination in the past year (yes or no response); how many times a day they usually brushed their teeth; and if they had used mouthwash or dental floss in the preceding year (yes or no response). Binary responses were assessed using a Fisher exact test and number of toothbrushing compared using a Mann–Whitney test when comparing AATD to COPD and a Wilcoxon test when comparing change in habits in the same group. *p* values in separate column compare COPD to AATD group. Values in [] are *p* values comparing change in habits in the 12 months excluding the baseline assessment. Values in bold typeface remained statistically significant after Holm–Bonferroni correction.

TABLE 3 Odds Ratio for periodontitis in non-deficient COPD patients compared to AATD

Periodontitis definition	Odds ratio (OR) for Non-AATD COPD patients	95% CI	*p*-value
CDC-AAP criteria	**5.1**	**1.7–15.0**	**.003**
WWP	2.5	1.4–4.7	**.003**
CDC-AAP criteria	Adjusted 3.1	0.7–14.1	.135
WWP	Adjusted 1.3	0.5–3.6	.549

Note: Binary logistic regression was used to assess the OR for each binary outcome measure (periodontitis definition) individually. Both criteria remained significant after Holm–Bonferroni correction. Non-parametric bootstrapping was used. For adjusted odds ratios (adjusted for smoking, age and IMD score of deprivation and CDC-AAP was also adjusted for pack-year history of smoking), non-parametric bootstrapping was used (1,000 bootstrap replications) were applied to reduce the risk of overfitting the model.

the prevalence was higher than described in the NHANES study, when either the whole adult per cent was used (Fisher's exact test, $p = .0003$) or for adults aged 50 – 64 (NHANES 52.7% versus AATD 72.1%, Fisher's exact test, $p = .0084$). This was also the case when compared to the UK ADHS data (Fisher's exact test, $p = .0002$ for all adults and $p = .018$ for adults aged 50 – 64(Adult Dental health Survey, 2009).

3.3 | Periodontitis is equally associated with non-AATD COPD and AATD once age, smoking and social deprivation are accounted for

Binary logistic regression suggested the odds ratio (OR) for periodontitis was greater for the non-AATD COPD group compared to the AATD group. However, there was a significant difference in age, smoking history and IMD score between the non-AATD COPD and AATD groups. As these variables are recognized risk factors for periodontitis, they were included in a further multivariable regression model. After adjusting for age, smoking status and IMD score, there was no difference in the prevalence of periodontitis between non-AATD COPD and AATD patients despite the better dental habits of the AATD group and the reduced prevalence of other risk factors for periodontitis; see Table 3.

Univariate analyses revealed other variables as important risk factors for periodontitis in non-AATD COPD. These included age when leaving education, NS-SEC score, presence of vascular disease, use of inhaled corticosteroids and brushing teeth less than twice daily (all $p < .001$). These confounding factors were less prevalent in the AATD group, but despite this, the prevalence of periodontitis was still higher than that reported in an unselected community-dwelling adult population (Eke et al., 2015), potentially supporting a mechanistic link between COPD, AATD and periodontitis. To explore this, periodontal severity scores were compared to lung function.

3.4 | Periodontitis is associated with worse lung function in AATD but not NON-AATD COPD

Participants were divided into those with and without periodontitis using the CDC-AAP definition. For the WWP definition, there were too few people without periodontitis to analyse further, and so the groups were divided into those with no or mild (none or stage

I) periodontitis and those with moderate (stage II)-to-severe (stage III/IV) periodontitis. Relationships were seen with lung function in the AATD group, with no or mild periodontitis being associated with more preserved lung function, as shown in Table 4.

3.5 | Inflammation

Salivary levels of CXCL8 and CRP, and plasma CRP were assessed. In COPD, saliva CRP correlated with saliva CXCL8 (Spearman's rho = 0.476, $p = .0002$) but there were no other relationships between inflammatory markers. In AATD, there was a correlation between plasma CRP and salivary CRP (Spearman's Rho = 0.41, $p = .01$) and salivary CRP and CXCL8 (Spearman's Rho = 0.368, $p = .003$).

When patients were divided into those with or without periodontitis (CDC-AAP definition) and those with no/mild (WWP none or stage I) periodontitis and those with moderate/severe periodontitis (WWP stage II or III/IV) (WWP definition), only salivary CXCL8 was higher in patients with COPD and periodontitis compared to those with COPD and no periodontitis (see Table 5).

3.6 | Neutrophil function in periodontitis

Peripheral blood neutrophil chemotaxis was performed in 33 non-AATD COPD and 34 patients with AATD. See Table 6 for demographics. As described previously (Sapey et al., 2011), COPD-isolated, peripheral blood neutrophils were faster and less accurate than cells isolated from patients with AATD (median (IQR) speed: COPD 5.71 μm/min (4.85–6.00) versus AATD 3.96 μm/min (3.21–4.30) Mann–Whitney U, $p < .0001$); velocity: COPD 0.87 μm/min (0.42–1.50) versus AATD 1.99 μm/min (1.67–2.34) Mann–Whitney U, $p < .0001$).

Neutrophils from patients with non-AATD COPD and moderate/severe periodontitis (WWP: stage II–IV) were slower and less accurate in their migratory pathways than cells from patients with no/mild periodontitis (WWP: none or stage I). Neutrophils isolated from patients with AATD and moderate/severe (WWP Stage II–IV) periodontitis were less accurate in their migratory pathways than cells from patients with no/mild (WWP: none or stage I) periodontitis, but there were no differences in speed between these groups (See Figure 1).

3.7 | Exacerbations at 12-month assessment

All patients were provided with brief advice on future preventive oral care strategies. Primary care documentation of exacerbations was collected from all AATD patients and 86/88 COPD patients (2 declined to provide data). There was a reduction in exacerbations in the non-AATD COPD but not in the AATD group in the following year; see Table 2 for dental habits and Table 4 for the relationship between lung function and exacerbations.

4 | DISCUSSION

The reported studies were undertaken to assess whether there were relationships between extensively characterized patients with non-AATD COPD, AATD and periodontitis; potential pathophysiology; and the potential effect of oral hygiene advice on exacerbation frequency.

TABLE 4 Relationship between periodontal indices, lung function parameters and exacerbation frequency

	COPD			AATD		
Variable	**Perio**	**No perio**	***p* value**	**Perio**	**No Perio**	***p* value**
CDC-AAP criteria						
n	79	9		49	19	
FEV_1% predicted	50.0 (38.0–72.0)	41.0 (36.5–51.50)	.153	**56.0 (40.0–76.0)**	**99.0 (87.0–113.2)**	**<.0001**
TLco % predicted	49.5 (38.6–63.3)	62.0 (47.5–71.5)	.269	**59.0 (45.0–71.0)**	**81.0 (69.0–89.0)**	**<.0001**
Kco % predicted	60 (49.3–75.3)	80 (59.0–91.5)	.032	**63.0 (52.5–71.0)**	**77.0 (68.0–94.0)**	**.0014**
Exacerbation frequency	2.8 (1.9–4.0)	3.0 (1.5–6.3)	.154	1 (0–2.2)	1 (0–1)	.0967
WWP	**Moderate/severe Perio (Stages II–IV)**	**No or mild Perio (Stages 0–I)**	***p* value**	**Moderate/severe Perio (Stages II–IV)**	**No or mild Perio (Stages 0–I)**	***p* value**
n	44	44		20	48	
FEV_1% predicted	53.6 (37.8–75.3)	44.0 (38.0–65.0)	.235	**45.0 (38.0–78.5)**	**81.0 (61.9–100.0)**	**<.0001**
TLco % predicted	50.0 (35.0–62.0)	48.0 (39.5–64.5)	.801	**52.0 (37.0–66.8)**	**69.0 (52.0–83.0)**	**.0078**
Kco % predicted	65.0 (51.5–80.0)	71.0 (56.0–83.0)	.367	57.5 (52.5–70.5)	69.3 (57.3–86.5)	.0147
Exacerbation frequency	3 (0–4)	2 (1–6)	.012	1 (0–3)	1 (0–2)	.105

Note: Numbers of patients in each group and median and inter-quartile ranges are given. All comparisons compare the presence or absence of periodontitis (apart from for WWP definition, where no or mild periodontitis was compared to moderate-to-severe periodontitis). Comparisons are made using Mann–Whitney U tests. Exact p values are given, but only those in bold typeface remained significant after Holm–Bonferroni correction.

TABLE 5 Relationship between periodontal indices and inflammation

	COPD	AATD	P value
Plasma CRP (ug/ml)	**5.81 (2.19 – 9.18)**	**0.88 (0.44 – 1.89)**	**<.0001**
Saliva CRP (pg/ml)	407.01 (241.3 – 960.4)	284.1 (179.1 – 519.7)	.020
Saliva CXCL8 (pg/ml)	923.1 (387.3 – 1656.0)	723.9 (433.7 – 1,389.0)	.652

Variable	Perio	No perio	*p* value	Perio	No Perio	*p* value
CDC-AAP criteria						
n	79	9		49	19	
Plasma CRP (ug/ml)	5.84 (2.19–9.39)	4.89 (2.70–8.44)	.703	0.86 (0.37–2.31)	1.05 (0.62–1.65)	.700
Saliva CRP (pg/ml)	410.2 (222.1–967.1)	379.5 (267.3–761.7)	.984	346.5 (189.4–752.6)	214.5 (169.8–266.1)	.032[a]
Saliva CXCL8 (pg/ml)	**1,000 (439.2–1,661)**	**214.6 (124.7–514.2)**	**.0027**[a]	729.6 (450.0–1,665)	703.6 (317.8–1,094)	.539

WWP	Moderate/severe Perio (Stages II–IV)	No or mild Perio (Stages 0–I)	*p* value	Moderate/severe Perio (Stages II–IV)	No or mild Perio (Stages 0–I)	*p* value
n	44	44		20	48	
Plasma CRP (ug/ml)	4.18 (2.01–7.80)	7.36 (2.25–9.55)	.114	0.52 (0.18–2.22)	0.98 (0.6–1.84)	.206
Saliva CRP (pg/ml)	435.4 (237.3–938.4)	379.5 (220.5–1,066)	.761	339.9 (230.3–828.6)	237.3 (167.9–505.6)	.157
Saliva CXCL8 (pg/ml)	923.1 (387.9–1,439)	905.3 (319.1–2089)	.647	**972.9 (723.9–1577)**	**597.5 (320.8–1,304)**	**.011**[a]

Note: Numbers of patients in each group and median and inter-quartile ranges are given. Initial comparisons were between patients with non-AATD COPD and AATD, irrespective of periodontitis. Then, all comparisons compare the presence or absence of periodontitis (apart from for WWP definition, where no or mild periodontitis was compared to moderate-to-severe periodontitis). Comparisons were made using Mann–Whitney U tests. Exact p values are given.

[a]Reached conventional significance levels, but only those in bold typeface remained significant after Holm–Bonferroni correction.

TABLE 6 Characteristics of patients for neutrophil studies

Demographics	COPD		AATD	
WWP periodontal disease status	No/Mild (Stages 0–I)	Mod/Severe (Stages II–IV)	No/Mild (Stages 0–I)	Mod/Severe (Stages II–IV)
n	16	17	16	18
Age (years)	66 (62–74)	72 (65–75)	51 (45–55)	55 (44–65)
Pack-year history	40 (18–45.5)	43.5 (21.5–67.5)	14 (0.0–27.3)	14.4 (0.0–35.7)
GOLD stage	2 (2–3)	2 (2–3)	1 (0–2)	2 (1–3)

Note: Demographic details of patients with and without periodontitis. Data are number (*n*) or median and IQR. Comparisons are made using Mann–Whitney *U* tests between groups. There were no differences between COPD patients with and without moderate-to-severe periodontitis for age ($p = .385$), pack-year history of smoking ($p = .493$) or GOLD stage ($p = .085$). There were no differences between AATD patients with or without moderate-to-severe periodontitis for age ($p = .254$) or pack-year history ($p = .802$). Although those AATD patients with moderate-to-severe periodontitis had a higher GOLD stage severity of COPD ($p = .038$), this was not significant after Bonferroni correction.

Our data highlight several potentially important points. First, the prevalence of periodontitis in both groups appears higher than that reported in unselected patients in the US NHANES (Eke et al., 2015) and the UK ADHS (Adult Dental health Survey, 2009) studies. There is only one previous report of a pilot study of periodontitis in 10 AATD with COPD (Wallin-Bengtsson, Piitulainen, Hamberg, Lindh, & Bratthall, 2011), but the percentage of affected COPD patients in the current study was similar to that described in other COPD cohorts (e.g. Zeng et al. (2012)).

Second, the prevalence of periodontitis was high in AATD (72%), even though recognized risk factors for periodontitis were low and dental habits were as good as, and in some cases better than, those described in an unselected UK community-dwelling adult population where the age-matched prevalence of periodontitis was 55% (Adult Dental health Survey, 2009). Therefore, in AATD, periodontitis could not be explained by poor dental habits, current smoking or low education or socio-economic status. In this group, there were relationships between the severity of periodontitis and lung function. Furthermore, moderate-to-severe periodontitis was associated with elevated salivary inflammatory markers and reduced accuracy of systemic neutrophil chemotaxis towards CXCL8. When considered together, this is highly suggestive of a shared mechanistic link between periodontitis and AATD.

Neutrophils, neutrophil proteinases and neutrophil dysfunction have been heavily implicated in disease pathogenesis in both

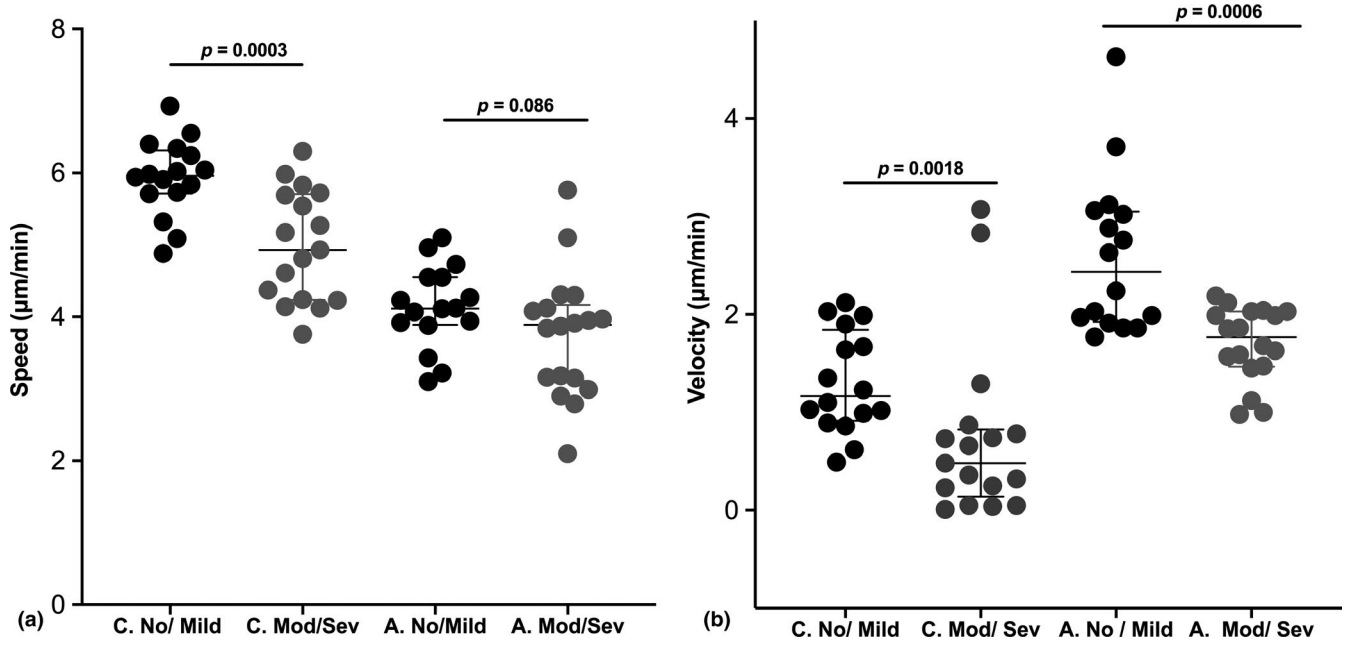

FIGURE 1 The speed and accuracy of neutrophil migration in patients with no or mild and moderate-to-severe periodontitis. Data include patients with non-AATD COPD ($n = 33$) and AATD ($n = 34$) when divided into those with no or mild or moderate-to-severe periodontitis by WWP. Patients were matched by age, smoking status and lung function by GOLD grouping. Each dot represents one patient. Groups are compared by Mann–Whitney *U* tests, and *p* values are given in the figure. (a) is the speed of migration in response to CXCL8. (b) is the velocity (or accuracy) of unidirectional migration, both measured in um/minute. Patients with non-AATD COPD demonstrated neutrophil migration which was faster and less accurate than patients with AATD. Patients in this group had less accurate and slower migration if they had worse periodontitis. In AATD, patients with moderate-to-severe periodontitis were less accurate than neutrophils isolated from patients with no or mild periodontitis

periodontitis (Nauseef, 2014) and AATD (McCarthy, Reeves, & McElvaney, 2016). In the current study, systemic neutrophils displayed less accurate migratory pathways in AATD patients with moderate-to-severe periodontitis compared with no or mild periodontitis. Reduced accuracy may equate to an increased burden of neutrophil proteinases released when migrating through the lung extracellular matrix or the periodontium. AATD is associated with a larger area of proteinase-associated tissue destruction compared to when wild-type levels of alpha-1 antitrypsin are present; therefore, targeting neutrophils with an aim to normalize migratory function could form a therapeutic strategy to improve patient outcomes (Walton et al., 2016). Studies have suggested partial restoration of neutrophil migratory accuracy follows treatment of periodontitis (Roberts et al., 2015). Treating AATD with augmentation therapy (plasma-derived alpha-1 antitrypsin) has also been associated with improvements in systemic neutrophil function (Hurley et al., 2014). Whether the treatment of periodontitis may improve inflammation or clinical outcomes in AATD or whether augmentation therapy with alpha-1 antitrypsin could improve periodontitis is unknown, but these strategies are worthy of exploring. A study determining the prevalence of periodontitis in patients who have received augmentation therapy would provide further insight into this association.

Third, regression analysis suggested that age, smoking status and socio-economic status contributed to the association between periodontitis in non-AATD COPD. Poor oral hygiene increases the risk of periodontitis fivefold (Lertpimonchai, Rattanasiri, Arj-Ong Vallibhakara, Attia, & Thakkinstian, 2017), and in our study, non-deficient COPD patients had poorer dental habits compared to our AATD group. Several other studies have shown COPD patients have significantly reduced brushing frequency compared to the general population (Wang et al., 2009), and this is likely to confound associations with oral disease. The increased presence of these confounding factors makes identifying shared mechanisms more complex, and in keeping with this, there were no clear associations with lung disease severity or systemic inflammation and the presence or severity of periodontitis in our COPD cohort, although analysis was hampered by the small numbers of patients who did not have periodontitis making some assessments underpowered. However, other studies have also failed to find this association including a small study of carefully matched smokers with and without COPD (Bergström et al., 2013) and one analysis of the NHANES III survey although an association with smoking and periodontitis was described (Hyman Jeffrey & Reid, 2004).

Salivary CXCL8 was higher in COPD patients with periodontitis, and more severe periodontitis was associated with a reduced neutrophil speed and accuracy when migrating towards CXCL8 in neutrophils from patients with COPD. Previous studies have described neutrophils becoming less accurate with age and, during acute inflammatory insults in older adults (Sapey et al., 2017, 2019), being faster in migratory dynamics but less accurate in the presence of COPD (Sapey et al., 2011) and being slower in migratory dynamics and less accurate with periodontitis (Roberts et al., 2015). The results here suggest the

combination of COPD and periodontitis is associated with worse migratory accuracy than COPD alone. This might increase susceptibility to infection and enhance tissue damage, and a systematic review has described the association between periodontitis and respiratory infections such as pneumonia (Scannapieco, Bush, & Paju, 2003). The potential association between neutrophilic inflammation and COPD is not new (e.g. Travis, Pike, Imamura, and Potempa (1994)), but this is the first study to describe a neutrophil function in both conditions and provides more support for immunotherapeutics or proteinase inhibitors, aimed at normalizing neutrophil function or reducing the damaging capacity of their proteinases, in both periodontitis and COPD, especially in COPD associated with AATD.

Fourth, there was a reduction in exacerbation frequency in COPD in the year after the baseline dental examination. This was associated with an improvement in self-reported dental habits (patients who registered with a dentist and increased toothbrushing frequency). These changes might be coincidental, and this study was not designed to specifically assess the impact of periodontal treatment on COPD exacerbations, and so, this finding must be interpreted with caution. Exacerbations of COPD are most frequently associated with bacteria or viruses (Sethi & Murphy, 2008; Wedzicha, Singh, & Mackay, 2014), and any impact of periodontal treatment on frequency and nature of exacerbations would need to be explored in detail considering these putative causative pathogens. However, there is evidence that improved dental habits impact positively on periodontal health(Worthington et al., 2019), and in one COPD study, receiving treatment for periodontitis was also associated with a reduction in exacerbation frequency (Zhou et al., 2014), although the nature of exacerbations in the study was not explored. Given the enormous burden of COPD exacerbations on patients, healthcare resources and the economy (Erdal et al., 2018); the negative health impacts of periodontitis (Ferreira, Dias-Pereira, Branco-de-Almeida, Martins, & Paiva, 2017); the high prevalence of periodontitis in COPD; and the positive signal from the previous study (Zhou et al., 2014) and our current one, a more definitive study is warranted to determine whether treating periodontitis and improving oral hygiene habits can reduce exacerbation severity, nature or frequency.

There are limitations with the current study. There are errors that may arise from periodontal probing (Chapple et al., 2018). However, the UB-WHO-CF15 probe is a constant force probe, which should reduce such errors arising due to probing pressures. It was not possible to obtain dental radiographs for volunteers, and therefore, clinical attachment loss alone was employed for the WWP classification. Due to the high prevalence of periodontitis, insufficient numbers without periodontitis meant that comparisons of lung function and inflammation became underpowered. Ideally, non-COPD participants could have been studied. A contemporary healthy control group would have added to the findings of this study, and the lack of such a group should be considered as a limitation; however, we have compared our prevalence data to the results of large population-based studies to provide comparator confidence. Other aspects of neutrophil function could have been studied, but the complexity of experimental procedures precluded such other investigations being performed simultaneously. The use of patients from well-characterized cohorts can introduce population bias. Repeating a dental examination at 12 months to explore whether changes in oral habits impacted on periodontal health would (in retrospect) have provided further data supporting cause and effect.

Despite these limitations, this remains the most in-depth study of oral health in COPD and AATD and has highlighted some intriguing relationships. Our results suggest AATD may enhance not only lung destruction but also increased periodontal damage irrespective of other demographic confounders. The presence of stage II to stage III-IV periodontitis altered neutrophil migration in both COPD and AATD, which might impact on local tissue degradation and the ability to respond to infection. Although these relationships are complex, studies assessing the impact of treatments to lessen neutrophilic inflammation for periodontitis and both usual COPD and that due to AATD may confirm health benefits, and there remains the possibility that periodontal treatment could preserve stability of lung health.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data can be accessed for ethically approved research by application to the corresponding author.

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REFERENCES

Adult Dental health Survey.(2009). *Oral health and function – a report from the adult dental health survey 2009*. Retrieved from: https://filesdigitalnhsuk/publicationimport/pub01xxx/pub01086/adul-dent-heal-surv-summ-them-the1-2009-rep3pdf

ARTP Handbook. (2003). *The ARTP practical handbook of respiratory function testing*. 2nd ed. Retrieved from http://wwwartporguk/en/publications/artp-part-1-handbookcfm

Barros, S. P., Suruki, R., Loewy, Z. G., Beck, J. D., & Offenbacher, S. (2013). A cohort study of the impact of tooth loss and periodontal disease on respiratory events among copd subjects: Modulatory role of systemic biomarkers of inflammation. *PLoS One*, *8*(8), e68592. https://doi.org/10.1371/journal.pone.0068592

Bergström, J., Cederlund, K., Dahlén, B., Lantz, A.-S., Skedinger, M., Palmberg, L., … Larsson, K. (2013). Dental health in smokers with and without copd. *PLoS One*, *8*(3), e59492. https://doi.org/10.1371/journal.pone.0059492

Blanco, I., Bueno, P., Diego, I., Pérez-Holanda, S., Casas-Maldonado, F., Esquinas, C., & Miravitlles, M. (2017). Alpha-1 antitrypsin pi*z gene frequency and pi*zz genotype numbers worldwide: An update. *International Journal of Chronic Obstructive Pulmonary Disease*, *12*, 561–569.

Buist, A. S., McBurnie, M. A., Vollmer, W. M., Gillespie, S., Burney, P., Mannino, D. M., … Nizankowska-Mogilnicka, E. (2007). International variation in the prevalence of copd (the bold study): A population-based prevalence study. *Lancet*, *370*(9589), 741–750. https://doi.org/10.1016/S0140-6736(07)61377-4

Burge, S., & Wedzicha, J. A. (2003). Copd exacerbations: Definitions and classifications. *European Respiratory Journal*, *21*(41 suppl), 46s–53s. https://doi.org/10.1183/09031936.03.00078002

Cavailles, A., Brinchault-Rabin, G., Dixmier, A., Goupil, F., Gut-Gobert, C., Marchand-Adam, S., … Diot, P. (2013). Comorbidities of COPD. *European Respiratory Review*, *22*(130), 454. https://doi.org/10.1183/09059180.00008612

Chapple, I. L. C., Mason, G. I., Garner, I., Matthews, J. B., Thorpe, G. H., Maxwell, S. R. J., & Whitehead, T. P. (1997). Enhanced chemiluminescent assay for measuring the total antioxidant capacity of serum, saliva and crevicular fluid. *Annals of Clinical Biochemistry*, *34*(4), 412–421. https://doi.org/10.1177/000456329703400413

Chapple, I. L. C., Mealey, B. L., Van Dyke, T. E., Bartold, P. M., Dommisch, H., Eickholz, P., … Yoshie, H. (2018). Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. *Journal of Clinical Periodontology*, *45*(S20), S68–S77. https://doi.org/10.1002/JPER.17-0719

Cooper, B. G., Stocks, J., Hall, G. L., Culver, B., Steenbruggen, I., Carter, K. W., … Stanojevic, S. (2017). The global lung function initiative (gli) network: Bringing the world's respiratory reference values together. *Breathe*, *13*(3), e56–e64. https://doi.org/10.1183/20734735.012717

Deo, V., Bhongade, M. L., Ansari, S., Ramesh, S., & Chavan, R. S. (2009). Periodontitis as a potential risk factor for chronic obstructive pulmonary disease: A retrospective study. *Indian Journal of Dental Research*, *20*(4), 466–470. https://doi.org/10.4103/0970-9290.59456

Di Stefano, A., Capelli, A., Lusuardi, M., Balbo, P., Vecchio, C., Maestrelli, P., … Saetta, M. (1998). Severity of airflow limitation is associated with severity of airway inflammation in smokers. *American Journal of Respiratory and Critical Care Medicine*, *158*(4), 1277–1285.

Divo, M. J., Casanova, C., Marin, J. M., Pinto-Plata, V. M., de-Torres, J. P., Zulueta, J. J., … Celli, B. R. (2015). COPD comorbidities network. *European Respiratory Journal*, *46*(3), 640–650. https://doi.org/10.1183/09031936.00171614

Eke, P. I., Dye, B. A., Wei, L., Slade, G. D., Thornton-Evans, G. O., Borgnakke, W. S., … Genco, R. J. (2015). Update on prevalence of periodontitis in adults in the United States: Nhanes 2009 to 2012. *Journal of Periodontology*, *86*(5), 611–622. https://doi.org/10.1902/jop.2015.140520

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. *Journal of Periodontology*, *83*(12), 1449–1454. https://doi.org/10.1902/jop.2012.110664

Erdal, M., Johannessen, A., Eagan, T. M., Bakke, P., Gulsvik, A., Askildsen, J. E., & Grønseth, R. (2018). Costs of copd exacerbations in a general population. *European Respiratory Journal*, *52*, PA3157.

Ferreira, M. C., Dias-Pereira, A. C., Branco-de-Almeida, L. S., Martins, C. C., & Paiva, S. M. (2017). Impact of periodontal disease on quality of life: a systematic review. *Journal of Periodontal Research*, *52*(4), 651–665. https://doi.org/10.1111/jre.12436

Figueredo, C. M. S., Gustafsson, A., Åsman, B., & Bergström, K. (2000). Expression of intracellular elastase activity in peripheral neutrophils from patients with adult periodontitis. *Journal of Clinical Periodontology*, *27*(8), 572–577. https://doi.org/10.1034/j.1600-051x.2000.027008572.x

Gaeckle, N. T., Heyman, B., Criner, A. J., & Criner, G. J. (2018). Markers of dental health correlate with daily respiratory symptoms in COPD. *Chronic Obstructive Pulmonary Diseases*, *5*(2), 97–105. https://doi.org/10.15326/jcopdf.5.2.2017.0159

Garcia, R. I., Krall, E. A., & Vokonas, P. S. (1998). Periodontal disease and mortality from all causes in the va dental longitudinal study. *Annals of Periodontology*, *3*(1), 339–349. https://doi.org/10.1902/annals.1998.3.1.339

Garcia, R. I., Nunn, M. E., & Vokonas, P. S. (2001). Epidemiologic associations between periodontal disease and chronic obstructive pulmonary disease. *Annals of Periodontology*, *6*(1), 71–77.

Gershon, A. S., Dolmage, T. E., Stephenson, A., & Jackson, B. (2012). Chronic obstructive pulmonary disease and socioeconomic status: A systematic review. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *9*(3), 216–226. https://doi.org/10.3109/15412555.2011.648030

Global Initiative for Chronic Obstructive Lung Disease. (2019). *2019 global strategy for prevention, diagnosis and management of copd*. Retrieved from https://goldcopdorg/gold-reports/

Gomez-Cabrero, D., Menche, J., Vargas, C., Cano, I., Maier, D., Barabási, A.-L., …,Roca, J. (2016). From comorbidities of chronic obstructive pulmonary disease to identification of shared molecular mechanisms by data integration. *BMC Bioinformatics*, *17*(Suppl 15), 23–35. https://doi.org/10.1186/s12859-016-1291-3

Hajiro, T., Nishimura, K., Tsukino, M., Ikeda, A., Koyama, H., & Izumi, T. (1998). Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *158*(4), 1185–1189.

Hobbins, S., Chapple, I. L., Sapey, E., & Stockley, R. A. (2017). Is periodontitis a comorbidity of copd or can associations be explained by shared risk factors/behaviors? *International Journal of Chronic Obstructive Pulmonary Disease*, *12*, 1339–1349.

Hurley, K., Lacey, N., O'Dwyer, C. A., Bergin, D. A., McElvaney, O. J., O'Brien, M. E., … McElvaney, N. G. (2014). Alpha-1 antitrypsin augmentation therapy corrects accelerated neutrophil apoptosis in deficient individuals. *The Journal of Immunology*, *193*(8), 3978.

Hyman Jeffrey, J., & Reid, B. C. (2004). Cigarette smoking, periodontal disease, and chronic obstructive pulmonary disease. *Journal of Periodontology*, *75*(1), 9–15. https://doi.org/10.1902/jop.2004.75.1.9

Kassebaum, N. J., Bernabé, E., Dahiya, M., Bhandari, B., Murray, C. J. L., & Marcenes, W. (2014). Global burden of severe periodontitis in 1990–2010: A systematic review and meta-regression. *Journal of Dental Research*, *93*(11), 1045–1053. https://doi.org/10.1177/0022034514552491

Lertpimonchai, A., Rattanasiri, S., Arj-Ong Vallibhakara, S., Attia, J., & Thakkinstian, A. (2017). The association between oral hygiene and periodontitis: A systematic review and meta-analysis. *International Dental Journal*, *67*(6), 332–343. https://doi.org/10.1111/idj.12317

Linden, G. J., Lyons, A., & Scannapieco, F. A. (2013). Periodontal systemic associations: Review of the evidence. *Journal of Clinical Periodontology*, *40*(s14), S8–S19. https://doi.org/10.1111/jcpe.12064

Ling, M. R., Chapple, I. L. C., & Matthews, J. B. (2015). Peripheral blood neutrophil cytokine hyper-reactivity in chronic periodontitis. *Innate Immunity*, *21*(7), 714–725. https://doi.org/10.1177/1753425915589387

Listl, S., Galloway, J., Mossey, P. A., & Marcenes, W. (2015). Global economic impact of dental diseases. *Journal of Dental Research*, *94*(10), 1355–1361. https://doi.org/10.1177/0022034515602879

Mannino, D. M., Thorn, D., Swensen, A., & Holguin, F. (2008). Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in copd. *The European Respiratory Journal*, *32*(4), 962–969. https://doi.org/10.1183/09031936.00012408

Matthews, J. B., Wright, H. J., Roberts, A., Ling-Mountford, N., Cooper, P. R., & Chapple, I. L. C. (2007). Neutrophil hyper-responsiveness in periodontitis. *Journal of Dental Research*, *86*(8), 718–722. https://doi.org/10.1177/154405910708600806

McCarthy, C., Reeves, E. P., & McElvaney, N. G. (2016). The role of neutrophils in alpha-1 antitrypsin deficiency. *Annals of the American Thoracic Society*, *13*(Supplement_4), S297–S304. https://doi.org/10.1513/AnnalsATS.201509-634KV

Meyle, J., & Chapple, I. (2015). Molecular aspects of the pathogenesis of periodontitis. *Periodontology 2000*, *69*(1), 7–17.

National statistics socio-economic classification (2010). Retrieved from http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec–rebased-on-soc2010–user-manual/index.html

Nauseef, W. M. (2014). Proteases, neutrophils, and periodontitis: The net effect. *The Journal of Clinical Investigation*, *124*(10), 4237–4239.

Offenbacher, S., Beck, J. D., Barros, S. P., Suruki, R. Y., & Loewy, Z. G. (2012). Obstructive airway disease and edentulism in the atherosclerosis risk in communities (aric) study. *British Medical Journal Open*, *2*(6), e001615. https://doi.org/10.1136/bmjopen-2012-001615

Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., … Tonetti, M. S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. *Journal of Periodontology*, *89*(S1), S173–S182. https://doi.org/10.1002/JPER.17-0721

Prasanna, S. J. (2011). Causal relationship between periodontitis and chronic obstructive pulmonary disease. *Journal of Indian Society of Periodontology*, *15*(4), 359–365. https://doi.org/10.4103/0972-124X.92570

Rizzuto, D., Melis, R. J. F., Angleman, S., Qiu, C., & Marengoni, A. (2017). Effect of chronic diseases and multimorbidity on survival and functioning in elderly adults. *Journal of the American Geriatrics Society*, *65*(5), 1056–1060. https://doi.org/10.1111/jgs.14868

Roberts, H. M., Ling, M. R., Insall, R., Kalna, G., Spengler, J., Grant, M. M., & Chapple, I. L. C. (2015). Impaired neutrophil directional chemotactic accuracy in chronic periodontitis patients. *Journal of Clinical Periodontology*, *42*(1), 1–11. https://doi.org/10.1111/jcpe.12326

Sanz, M., Ceriello, A., Buysschaert, M., Chapple, I., Demmer, R. T., Graziani, F., … Vegh, D. (2018). Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the international diabetes federation and the European federation of periodontology. *Journal of Clinical Periodontology*, *45*(2), 138–149. https://doi.org/10.1111/jcpe.12808

Sapey, E., Patel, J. M., Greenwood, H., Walton, G. M., Grudzinska, F., Parekh, D., … Howells, P. A. et al (2019). Simvastatin improves neutrophil function and clinical outcomes in pneumonia: A pilot randomised controlled trial. *American Journal of Respiratory and Critical Care Medicine*, *200*, 1282–1293.

Sapey, E., Patel, J. M., Greenwood, H. L., Walton, G. M., Hazeldine, J., Sadhra, C., … Lord, J. M. (2017). Pulmonary infections in the elderly lead to impaired neutrophil targeting, which is improved by simvastatin. *American Journal of Respiratory and Critical Care Medicine*, *196*(10), 1325–1336.

Sapey, E., Stockley, J. A., Greenwood, H., Ahmad, A., Bayley, D., Lord, J. M., … Stockley, R. A. (2011). Behavioral and structural differences in migrating peripheral neutrophils from patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *183*(9), 1176–1186.

Scannapieco, F. A., Bush, R. B., & Paju, S. (2003). Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. *Annals of Periodontology*, *8*(1), 54–69. https://doi.org/10.1902/annals.2003.8.1.54

Scannapieco, F. A., & Ho, A. W. (2001). Potential associations between chronic respiratory disease and periodontal disease: Analysis of national health and nutrition examination survey iii. *Journal of Periodontology*, *72*(1), 50–56. https://doi.org/10.1902/jop.2001.72.1.50

Sethi, S., & Murphy, T. F. (2008). Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *New England Journal of Medicine*, *359*(22), 2355–2365.

Stockley, R. A., & Turner, A. M. (2014). A-1-antitrypsin deficiency: Clinical variability, assessment, and treatment. *Trends in Molecular Medicine*, *20*(2), 105–115. https://doi.org/10.1016/j.molmed.2013.11.006

Stone, H., McNab, G., Wood, A. M., Stockley, R. A., & Sapey, E. (2012). Variability of sputum inflammatory mediators in copd and alpha1-antitrypsin deficiency. *European Respiratory Journal*, *40*(3), 561–569.

The English index of multiple deprivation (imd) 2015. (2015). Retrieved from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/464430/English_Index_of_Multiple_Deprivation_2015_-_Guidance.pdf

Tonetti, M. S., & Sanz, M. (2019). Implementation of the new classification of periodontal diseases: Decision-making algorithms for clinical practice and education. *Journal of Clinical Periodontology*, *46*(4), 398–405. https://doi.org/10.1111/jcpe.13104

Travis, J., Pike, R., Imamura, T., & Potempa, J. (1994). The role of proteolytic enzymes in the development of pulmonary emphysema and periodontal disease. *American Journal of Respiratory and Critical Care Medicine*, 150(6_pt_2):S143–S146. https://doi.org/10.1164/ajrccm/150.6_Pt_2.S143

Wallin-Bengtsson, V., Piitulainen, E., Hamberg, K., Lindh, C., & Bratthall, G. (2011). Alpha-1-antitrypsin deficiency and periodontitis, a pilot study. *Swedish Dental Journal*, *35*, 33–40.

Walton, G. M., Stockley, J. A., Griffiths, D., Sadhra, C. S., Purvis, T., & Sapey, E. (2016). Repurposing Treatments to Enhance Innate Immunity. Can Statins Improve Neutrophil Functions and Clinical Outcomes in COPD? *Journal of Clinical Medicine*, *5*(10), 89.

Wang, Z., Zhou, X., Zhang, J., Zhang, L., Song, Y., Hu, F. B., & Wang, C. (2009a). Periodontal health, oral health behaviours, and chronic obstructive pulmonary disease. *Journal of Clinical Periodontology*, *36*(9), 750–755.

Wedzicha, J. A., Singh, R., & Mackay, A. J. (2014). Acute copd exacerbations. *Clinics in Chest Medicine*, *35*(1), 157–163. https://doi.org/10.1016/j.ccm.2013.11.001

Winning, L., Patterson, C. C., Cullen, K. M., Kee, F., & Linden, G. J. (2019). Chronic periodontitis and reduced respiratory function. *Journal of Clinical Periodontology*, *46*(3), 266–275. https://doi.org/10.1111/jcpe.13076

Worthington, H. V., MacDonald, L., Poklepovic Pericic, T., Sambunjak, D., Johnson, T. M., Imai, P., & Clarkson, J. E. (2019). Home use of interdental cleaning devices, in addition to toothbrushing, for preventing and controlling periodontal diseases and dental caries. *Cochrane Database of Systematic Reviews*, (4). https://doi.org/10.1002/14651858.CD012018.pub2

Zeng, X.-T., Tu, M.-L., Liu, D.-Y., Zheng, D., Zhang, J., & Leng, W. (2012). Periodontal disease and risk of chronic obstructive pulmonary disease: A meta-analysis of observational studies. *PLoS One*, *7*(10), e46508. https://doi.org/10.1371/journal.pone.0046508

Zhao, D., Zhen, Z., Pelekos, G., Yiu, K. H., & Jin, L. (2019). Periodontal disease increases the risk for onset of systemic comorbidities in dental hospital attendees: An 18-year retrospective cohort study. *Journal of Periodontology*, *90*(3), 225–233. https://doi.org/10.1002/JPER.18-0224

Zhou, X., Han, J., Liu, Z., Song, Y., Wang, Z., & Sun, Z. (2014). Effects of periodontal treatment on lung function and exacerbation frequency in patients with chronic obstructive pulmonary disease and chronic periodontitis: A 2-year pilot randomized controlled trial. *Journal of Clinical Periodontology*, *41*(6), 564–572. https://doi.org/10.1111/jcpe.12247

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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