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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
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 $54 billion 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 release (Ling, Chapple, & Matthews, 2015), and defects in chemotactic release (Ling, Chapple, & Matthews, 2015), and defects in chemotactic release (Ling, Chapple, & Matthews, 2015), and defects in chemotactic release (Ling, Chapple, & Matthews, 2015), and defects in chemotactic release (Ling, Chapple, & Matthews, 2015), and defects in chemotactic release (Ling, Chapple, & Matthews, 2015), and defects in chemotactic release (Ling, Chapple, & Matthews, 2015), and defects in chemotactic release (Ling, Chapple, & Matthews, 2015). 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 (Gaekle, 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 (Cavallès 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 un-opposed 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 Hereditab, 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 (TLC 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,
|                         | 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) | <.001  |
| 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 exacerbators³ (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 FEV₁ (SD)   | 54.4 (22.2) | 70.8 (28.1) | <.001  |
| FEV₁: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.³Frequent exacerbators were those with two or more exacerbations per year (Global Initiative for Chronic Obstructive Lung Disease, 2019).
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

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**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        | .0001         | 86       | 68        | .0001         |
| Is registered with a dentist (Yes, n, %) | 31 (35%) | 63 (95%)  | .0001         | 48 (56%) | 64 (98%)  | .0001         |
| Visited dentist in last year (Yes, n, %) | 23 (26%) | 50 (76%)  | .0001         | 37 (43%) | 55 (84%)  | .0001         |
| Number of times usually brush teeth per day, median (range) | 1 (0–2) | 2 (0–2)  | .0001         | 2 (1–2)  | 2 (1–2)  | .314          |
| Used floss or mouthwash in past year (n, %) | 9 (10%) | 48 (73%)  | .0001         | 19 (22%) | 54 (83%)  | .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| Adjusted 3.1                               | 0.7–14.1 | .135       |
| WWP adjusted             | 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) to reduce the risk of overfitting the model.
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 \( \mu \)m/min (4.85–6.00) versus AATD 3.96 \( \mu \)m/min (3.21–4.30) Mann–Whitney \( U, p < .0001 \)); velocity: COPD 0.87 \( \mu \)m/min (0.42–1.50) versus AATD 1.99 \( \mu \)m/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.
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, & Brathall, 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.

**TABLE 5** Relationship between periodontal indices and inflammation

| Variable                  | 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 - 1389.0)| .652    |

**TABLE 6** Characteristics of patients for neutrophil studies

| Demographics | COPD | AATD |
|--------------|------|------|
| WWP          | Mod/severe | No/mild |
| periodontal disease status | Stages II–IV | Stages 0–I | Stages II–IV | Stages 0–I |
| 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.
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). 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

![FIGURE 1](image)
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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DATA AVAILABILITY STATEMENT
Data can be accessed for ethically approved research by application to the corresponding author.

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**SUPPORTING INFORMATION**

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

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