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The burden of chronic diseases associated with periodontal diseases: A retrospective cohort study using UK primary care data

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The burden of chronic diseases associated with periodontal diseases: A retrospective cohort study using UK primary care data

Running Title: The association between chronic disease and periodontal diseases

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Data sharing: The full data-set and statistical analysis code are available from author JSC (joht.chandan@nhs.net).

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Transparency statement: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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ABSTRACT

Objectives: To identify the association between periodontal diseases (gingivitis and periodontitis) and chronic diseases including cardiovascular disease, cardiometabolic disease, autoimmune disease and mental ill health.

Design: Retrospective cohort study.

Setting: UK primary care database (IQVIA Medical Research Data-UK) between 1st January 1995 and 1st January 2019.

Participants: 64,379 adult patients with a general practitioner recorded diagnosis of periodontal disease (exposed patients) were matched to 251,161 unexposed patients by age, sex, deprivation, and registration date.

Main outcome measures: Effect sizes for various chronic diseases are presented as adjusted odds ratios (aOR) and adjusted hazard ratios (aHR) with confidence intervals (CI).

Results: The average age at cohort entry was 45 years and the median follow-up was 3.4 years. At study entry, the exposed cohort had an increased likelihood of having a diagnosis of cardiovascular disease (aOR 1.43; 95% CI 1.38-1.48), cardiometabolic disease (aOR 1.16; 95% CI 1.13-1.19), autoimmune disease (aOR 1.33; 95% CI 1.28-1.37), and mental ill health (aOR 1.79; 95% CI 1.75-1.83) compared to the unexposed group. During follow-up of individuals without pre-existing outcomes of interest, the exposed group had an increased risk of developing cardiovascular disease (HR 1.18; 95% CI 1.13-1.23), cardiometabolic disease (HR 1.07; 95% CI 1.03-1.10), autoimmune disease (HR 1.33; 95% CI 1.26-1.40), and mental ill health (HR 1.37; 95% CI 1.33-1.42) compared to the unexposed group.

Conclusions: Periodontal diseases are very common; therefore, an increased risk of other chronic diseases represents a substantial public health burden. It is imperative that preventative approaches, including those aimed at preventing and detecting gingival

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inflammation and its associated consequences, and improved communication between medical and dental teams, are implemented to reduce the risk of ill health.

Keywords: oral health; gingivitis; periodontitis; epidemiology; chronic disease

Strengths and limitations:

- Periodontal diseases including gingivitis and periodontitis are highly prevalent inflammatory conditions and lead to substantiative morbidity, however studying their epidemiology in a general practice dataset had yet to be conducted prior to this study
- We found that those with a diagnosis of periodontal diseases had an increased risk of developing cardiovascular disease, cardiometabolic disease, autoimmune disease with similar effect sizes seen in validated smaller cohorts
- This was the first study to explore and quantify the association between mental ill health and periodontal diseases
- Despite the vast cohort size and medical implications of periodontal diseases, this study also highlights an important need for improved communication between dentists and general practitioners as to the health and wellbeing of their shared patients

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INTRODUCTION

Poor oral health is extremely common and is frequently characterised by chronic inflammation.[1] Advanced stages manifest as periodontitis where there is irreversible damage to local bone and tissue.[2] Earlier stages include gingivitis, a reversible inflammation of the gingiva initiated by dental plaque.[2] This spectrum from gingivitis to periodontitis, is widely termed 'periodontal diseases.[2,3] Although, the exact aetiological mechanisms have yet to be fully elucidated, the development of a dysbiotic microbial biofilm, overactivation of inflammatory pathways and genetic susceptibility are all implicated.[2,4–6]

Progressive periodontal disease leads to a reduction in quality of life (QoL) due to problems relating with mastication (due to tooth loss), aesthetics (due to gum recession) and verbal communication.[2,7,8] Periodontal disease also results in a systemic pro-inflammatory state which in itself is implicated in the aetiology of chronic diseases including cardiovascular disease (CVD), cardiometabolic disease (CMD), mental ill health (MIH) and autoimmune disease (AID), each of which are highly prevalent and potentially preventable causes of global morbidity and mortality.[1,9–17] Therefore, a high prevalence of periodontal disease could translate to a substantial burden of morbidity and associated mortality. Epidemiological data have demonstrated associations between periodontitis and all-cause mortality in Western European males (aHR 1.57; 95% CI 1.04-2.36).[18] Although, this relationship could be explained through activation of a pro-inflammatory state, there is a lack of robust epidemiological evidence as many of these chronic diseases share similar pathogenic pathways, often mediated by lifestyle factors including smoking and socioeconomic status.[2,19–22]

The association between periodontal disease and CVD is one of the more commonly researched. In 2012, the American Heart Association highlighted that, despite the literature supporting an association between periodontitis and atherosclerotic disease independent of known confounders, due to methodological limitations of available observational studies they were not able to confirm a causal relationship.[23] Existing studies are limited by an inability to distinguish reverse causality or account for recall bias (case-control or cross sectional designs), absence of adequate confounder control, lack of generalisability to other

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populations and heterogeneity in definitions of exposure and outcomes.[23–25] A 2019 joint workshop held between the European Federation of Periodontology (EFP) and World Heart Federation (WHF) confirmed robust evidence for positive associations between periodontitis and cardiovascular/cerebrovascular disease including an increased risk of first cardiac or cerebrovascular event in patients with severe periodontitis.[26]

A recent review from the US Centre for Disease Control (CDC) assessed the relationships between periodontal disease and other chronic diseases suggested that after CVD, the next most frequent association with periodontal disease was with levels of type 2 diabetes mellitus (T2DM) control. Emerging randomised trials suggest that treatment of periodontal disease reduces Hba1c levels in patients with diabetes[27–29].[28] However, there is limited evidence exploring the risk of T2DM subsequent to periodontal disease and further investigation is needed.[30] Existing evidence suggests an association with autoimmune diseases such as rheumatoid arthritis (RA) and Sjogren's syndrome (SS), however, this is yet to be validated in longitudinal cohort datasets accounting for important covariates.[31–33] Few studies have explored the association between periodontal disease and subsequent mental ill health though a bi-directional mechanism relating to inflammation, psychosocial effects and the impact of psychopharmacological therapies has been proposed.[34,35]

It is important to strengthen understanding of the link between oral health and chronic diseases as cost-effective dental interventions are available that could be preventive, reducing the subsequent public health burden of disease.[2] Therefore, we have conducted the first retrospective cohort study using a large medical dataset to explore the association between poor oral health and a range of chronic diseases including CVD, CMD, MIH and AID.

METHODS

Study design and data source

This study is a population based, retrospective open cohort study utilising IQVIA Medical Research Data (IMRD-UK), previously known as The Health Improvement Network (THIN)

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database. The study period was set between 1st January 1995 and 1st January 2019. An open cohort study allows patients to enter and exit the study at different time points, with each patient only contributing person years of follow-up from the time of cohort entry (index date) to the time they leave the cohort (exit date).

During this study period, the database consisted of pseudo-anonymised electronic medical records of more than 15 million patients derived from 787 general practices using the Vision software system. The database is representative of the UK population in terms of demographic structure and prevalence of key comorbidities.[36] Symptoms, examinations, and diagnoses in THIN are recorded using a hierarchical clinical coding system called Read codes.[37] To improve data quality and reduce under-recording of events, general practices were included 12 months following instalment of electronic practice records or from the practice's acceptable mortality recording date.[38,39] A total of 8,618,829 patients were eligible to contribute during the study period. The data extraction and cohort selection was facilitated using the data extraction for epidemiological research (DExtER) tool.[40]

Exposure and outcome definition

The purpose of this study was to compare exposed patients (those with a GP recorded code of a periodontal disease, defined as either gingivitis or periodontitis) to unexposed patients (those without such codes) and then calculate their risk of developing chronic diseases defined through Read codes. The chronic disease outcomes were categorised as: CVD (CVD composite measure; heart failure (HF), ischaemic heart disease (HF), stroke/transient-ischaemic attack (TIA), peripheral vascular disease (PVD)), and vascular dementia (VD)), CMD (CMD composite measure; type 2 diabetes mellitus (T2DM), and hypertension (HTN)), AID (AID composite measure; type 1 diabetes mellitus (T1DM), rheumatoid arthritis (RA), systemic lupus erythematous (SLE), Sjogren's syndrome (SS), vitiligo, psoriasis, pernicious anaemia (PA), inflammatory bowel disease (IBD), coeliac disease (CD), autoimmune thyroiditis (AT), and scleroderma), and MIH (MIH composite; depression, anxiety and serious mental illness (SMI). In addition, this study examined the odds ratio of having any chronic disease at the point of cohort entry (baseline) between the exposed and unexposed groups.

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Codes relating to exposure and outcomes were selected with the assistance of general practitioners, public health doctors and a periodontal specialist. Although, the IMRD-UK (previously named the THIN database) has been previously used to examine oral disorders such as temporomandibular joint disorders,[41,42] exposure code lists relating to gingivitis and periodontitis have never been previously validated. Outcome code lists included in this study have been used extensively in previously published work using the same database and many of the conditions included feature in the Quality Outcomes Framework.[43–51] Read code lists relating to exposure terms are provided in appendix (**eTable 1**).

Selection of unexposed group

Each exposed patient was matched with up to four unexposed control patients from the remaining sample of patients in the dataset, who had no previously documented code relating to exposure. Controls were taken from a pool from eligible patients registered at a general practice within the same country of the UK and were matched by age at index date (+/- one year), sex, Townsend deprivation index[52] and registration date (+/- 12 months).

Follow-up period

The index date for those in the exposed group was the date of the first Read code relating to exposure or when they became eligible to enter the study for those with a previous history of exposure (prevalent cases). Patients aged 18 years or older were eligible for entry into the cohort, therefore those who had the exposure of interest at an earlier age would enter the study as a prevalent case. To mitigate immortality time bias,[53] the same index date was assigned to the corresponding unexposed patient. The follow-up period for each patient was from the index date until the exit date. Exit date was defined as the earliest of the following end dates: study end date, last date of data collection from a given general practice, date patient transferred from general practice, date of death or date the outcome of interest occurred.

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Statistical analysis

Categorical baseline data were described using proportions and continuous data described using means with standard deviations (sd). Missing data are highlighted in relevant baseline characteristic tables. Missing covariate data were treated as a separate missing category and included in the final analysis. Co-variates considered in our modelling were selected due to their independent relationship with the outcome of interest or to remove any residual confounding. These included: age, sex, body mass index (BMI), Townsend deprivation index (measured in quintiles), smoking status and ethnicity.

To describe the prevalence of chronic disease at baseline, we used logistic regression to estimate unadjusted odds ratio (OR) and adjusted OR (aOR), following adjustment for key covariates. To calculate an incidence rate ((IR) per 1000 person-years) for each of the outcomes of interest, patients with pre-existing chronic disease were excluded to ensure the IR reflected outcomes which occurred following cohort entry. Cox regression accounting for person years of follow-up was then used to calculate a hazard ratio (HR) for each outcome of interest during the study period. Following adjustment for the co-variates, we calculated and presented an adjusted HR (aHR). ORs and HRs are presented with 95% confidence intervals with statistical significance set at p<0·05.

An initial sensitivity analysis was conducted, isolating incident only cases (where the exposure occurred during the study period) compared to their respective controls. Throughout this paper we use the term periodontal disease to reflect the continuum from gingivitis to periodontitis though we conducted a second sensitivity analysis to examine if the outcomes differed when only examining cases with recorded periodontitis and their respective controls (exclusion of patients with a record of gingivitis and their respective controls). Stata version 15.1 SE software (StataCorp 2017) was used to conduct all analyses.

Patient and public involvement

No patients were actively involved in setting the research question, outcome measures nor involved in the design of the study. Patients were not involved in interpretation or write up

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of the results, nor are there plans for the results to be disseminated to the patient community affected by this research.

RESULTS

Study characteristics

Of the eligible patients during the study period, we identified 64,379 patients with a recorded history of a periodontal disease, of whom 60,995 had gingivitis and 3,384 had periodontitis, who were matched to 251,161 unexposed patients. The median follow-up was similar in the two groups (exposed: 3.3 years, and unexposed: 3.5 years). The mean age at cohort entry was 44 years and 43% of the cohort were male. Due to matching, smoking status (30% current smokers) and deprivation levels were similar between the groups. Additionally, BMI and ethnicity (despite 56% missing data) profiles were similar between the groups. Further details can be seen in **Table 1**.

Table 1: Baseline characteristics of the study population

	Primary cohort	
	Exposed n (%)	Unexposed n (%)
All	(n=64,379)	(n=251,161)
Sex (Male)	27699 (43.02)	107977 (42.99)
Age at index date	45.66 (19.12)	45.40 (18.97)
Age categories		
18 - 24 years	10680 (16.59)	42204 (16.80)
25 - 34 years	11266 (17.50)	44556 (17.74)
35 - 44 years	10895 (16.92)	42641 (16.98)
45 - 54 years	10186 (15.82)	39795 (15.84)
55 - 64 years	8917 (13.85)	34621 (13.78)
65 - 74 years	6900 (10.72)	26649 (10.61)
75 & overs	5535 (8.60)	20695 (8.24)
BMI	26.29 (5.64)	26.27 (5.51)
BMI Categories		
Under/Normal weight (18.5-25)	23743 (36.88)	91020 (36.24)

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Overweight (25-30)	16044 (24.92)	63782 (25.39)
Obese (>30)	10857 (16.86)	40589 (16.16)
Missing	13735 (21.33)	55770 (22.20)
Townsend quintiles		
1 (Least deprived)	11548 (17.94)	42631 (16.97)
2	10868 (16.88)	38909 (15.49)
3	12216 (18.98)	43494 (17.32)
4	12005 (18.65)	41440 (16.50)
5 (Most deprived)	9610 (14.93)	30831 (12.28)
Missing	8132 (12.63)	53856 (21.44)
Smoking categories		
Non-smoker	29100 (45.20)	114513 (45.59)
Smoker	19279 (29.95)	75155 (29.92)
Ex-smoker	11107 (17.25)	42647 (16.98)
Missing	4893 (7.60)	18846 (7.50)
Ethnicity		
Caucasian	24327 (37.79)	96169 (38.29)
Mixed race	477 (0.74)	1860 (0.74)
Other	215 (0.33)	925 (0.37)
Black	937 (1.46)	2951 (1.17)
South Asian	2512 (3.90)	4340 (1.73)
Missing	35911 (55.78)	144916 (57.70)

Chronic disease at cohort entry

At cohort entry there were 6,355 patients (9.9%) in the exposed group who had a diagnosis of CVD compared to 18,594 (7.4%) in the unexposed group. Following adjustment for co-variates this translated to an aOR of 1.43 (95% CI 1.38-1.48). When examining CMD, 12,321 patients (19.1%) in the exposed group had a diagnosis of CMD at cohort entry compared to 42,828 (17.1%) in the unexposed group. This translated into an aOR of 1.16 (95% CI 1.13-1.19), and the association with the presence of T2DM (aOR 1.23; 95% CI 1.18-1.28) was notable. With AID, 5,265 patients (8.2%) in the exposed group had a diagnosis of AID at cohort entry compared to 15,690 (6.3%) in the unexposed group equating to an aOR of 1.33 (95% CI 1.28-1.37). Lastly, MIH was seen to have the greatest odds ratio (aOR 1.79; 95% CI 1.75-1.83) with periodontal disease at cohort entry with 19,142 patients (29.7%) in the exposed group who had a diagnosis of AID at cohort entry compared to 48,998 (19.5%) in the unexposed group. Further results can be seen in **Table 2** and **Figure 1.**

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Table 2: Risk of chronic diseases at baseline in patients exposed and unexposed to periodontal diseases

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	6,355 (9.87)	18,594 (7.40)	977 (1.52)	2,608 (1.04)	3,963 (6.16)	11,759 (4.68)	2,161 (3.36)	6,154 (2.45)	860 (1.34)	2,345 (0.93)
OR (95% CI)*	1.37 (1.33-1.41)		1.47 (1.36-1.58)		1.34 (1.29-1.39)		1.38 (1.32-1.45)		1.44 (1.33-1.55)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.43 (1.38-1.48)		1.43 (1.32-1.54)		1.34 (1.28-1.39)		1.36 (1.29-1.44)		1.37 (1.26-1.49)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	146 (0.23)	363 (0.14)	12,321 (19.14)	42,828 (17.05)	3,432 (5.33)	10,342 (4.12)	10,841 (16.84)	38,649 (15.39)	5,265 (8.18)	15,690 (6.25)
OR (95% CI)*	1.57 (1.30-1.90)		1.15 (1.13-1.18)		1.31 (1.26-1.36)		1.11 (1.09-1.14)		1.34 (1.29-1.38)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.47 (1.20-1.79)		1.16 (1.13-1.19)		1.23 (1.18-1.28)		1.11 (1.08-1.15)		1.33 (1.28-1.37)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	

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	Type 1 diabetes mellitus		Rheumatoid arthritis		Systemic lupus erythematosus		Sjogren		Vitiligo	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	591 (0.92)	1,473 (0.59)	656 (1.02)	1,786 (0.71)	164 (0.25)	346 (0.14)	103 (0.16)	189 (0.08)	239 (0.37)	629 (0.25)
OR (95% CI)*	1.57 (1.43-1.73)		1.44 (1.31-1.57)		1.85 (1.54-2.23)		2.13 (1.67-2.71)		1.48 (1.28-1.72)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.55 (1.41-1.71)		1.39 (1.27-1.53)		1.79 (1.48-2.16)		1.99 (1.56-2.54)		1.40 (1.20-1.62)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	2,615 (4.06)	8,105 (3.23)	231 (0.36)	738 (0.29)	560 (0.87)	1,767 (0.70)	206 (0.32)	576 (0.23)	209 (0.32)	721 (0.29)
OR (95% CI)*	1.27 (1.21-1.33)		1.22 (1.05-1.42)		1.24 (1.13-1.36)		1.40 (1.19-1.64)		1.13 (0.97-1.32)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p=0.12	
aOR (95% CI)**	1.27 (1.21-1.33)		1.16 (1.00-1.35)		1.24 (1.12-1.36)		1.40 (1.19-1.65)		1.12 (0.96-1.31)	
P value	p<0.01		p=0.05		p<0.01		p<0.01		p=0.16	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed

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Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	42 (0.07)	94 (0.04)	19,142 (29.73)	48,998 (19.51)	13,496 (20.96)	34,415 (13.70)	9,623 (14.95)	22,093 (8.80)	1,242 (1.93)	2,905 (1.16)
OR (95% CI)*	1.74 (1.21-2.51)		1.75 (1.71-1.78)		1.67 (1.63-1.71)		1.82 (1.78-1.87)		1.68 (1.57-1.80)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.69 (1.17-2.44)		1.79 (1.75-1.83)		1.69 (1.65-1.73)		1.83 (1.79-1.88)		1.66 (1.55-1.77)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	

* Unadjusted odds ratio, OR: odds ratio, aOR: adjusted odds ratio

** Adjusted odds ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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The risk of developing subsequent chronic disease

During the study period there were 3,104 (5.4%) new diagnoses of CVD in the exposed cohort equating to an IR of 8.2 per 1000 person-years compared to 7.3 per 1000 person-years (10,439 (4.5%) new recorded diagnoses) in the unexposed cohort. This translated to an aHR of 1.18 (95% CI 1.13-1.23). When examining CMD, there were 5,005 (9.6%) new diagnoses of CMD in the exposed cohort equating to an IR of 15.5 per 1000 person-years compared to 14.6 per 1000 person-years (17,822 (8.6%) new recorded diagnoses) in the unexposed cohort. Ultimately this translated into an aHR of 1.07 (95% CI 1.03-1.10) where the risk was highest for the development of T2DM (aHR 1.26; 95% CI 1.21-1.32). When examining AID, there were 1,945 (3.3%) new diagnoses of AID in the exposed cohort equating to an IR of 5.8 per 1000 person-years compared to 4.3 per 1000 person-years (5,674 (2.4%) new recorded diagnoses) in the unexposed cohort. This translated into an aHR of 1.33 (95% CI 1.26-1.40). Finally, with MIH, there were 5,296 (11.7%) new diagnoses of MIH in the exposed cohort relating to an IR of 19.2 per 1000 person-years compared to 14.2 per 1000 person-years (16,758 (8.3%) new recorded diagnoses) in the unexposed cohort. This translated into an aHR of 1.37 (95% CI 1.33-1.42). Further details can be seen on **Table 3 and Figure 2.**

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Table 3: Risk of subsequent development of chronic diseases in patients exposed and unexposed to periodontal diseases

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	58,024	232,567	63,402	248,553	60,416	239,402	62,218	245,007	63,519	248,816
Number of outcomes, n(%)	3,104 (5.35)	10,439 (4.49)	906 (1.43)	2,913 (1.17)	1,535 (2.54)	4,821 (2.01)	1,524 (2.45)	4,956 (2.02)	615 (0.97)	1,716 (0.69)
Person-years	379,982	1,433,611	423,176	1,560,448	398,431	1,489,663	413,659	1,531,088	422,593	1,560,781
IR (per 1000 person-years)	8.17	7.28	2.14	1.87	3.85	3.24	3.68	3.24	1.46	1.1
Follow-up, Median(IQR)	5.49 (2.36-9.85)	5.00 (2.07-9.33)	5.62 (2.45-10.10)	5.15 (2.14-9.51)	5.52 (2.39-9.95)	5.08 (2.11-9.42)	5.59 (2.44-10.04)	5.11 (2.12-9.46)	5.59 (2.43-10.05)	5.14 (2.14-9.50)
HR (95% CI)*	1.12 (1.07-1.16)		1.14 (1.06-1.23)		1.19 (1.12-1.26)		1.13 (1.07-1.20)		1.32 (1.20-1.45)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.18 (1.13-1.23)		1.15 (1.07-1.24)		1.22 (1.16-1.30)		1.16 (1.10-1.23)		1.32 (1.20-1.45)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	64,233	250,798	52,058	208,333	60,947	240,819	53,538	212,512	59,114	235,471
Number of outcomes, n(%)	262 (0.41)	849 (0.34)	5,005 (9.61)	17,822 (8.55)	2,654 (4.35)	7,762 (3.22)	4,146 (7.74)	15,340 (7.22)	1,945 (3.29)	5,674 (2.41)
Person-years	429,726	1,578,418	323,472	1,218,325	397,557	1,486,326	335,761	1,252,770	334,525	1,325,645
IR (per 1000 person-years)	0.61	0.54	15.47	14.63	6.68	5.22	12.35	12.24	5.81	4.28
Follow-up, Median(IQR)	5.63 (2.46-10.12)	5.17 (2.15-9.51)	5.10 (2.16-9.38)	4.61 (1.90-8.82)	5.44 (2.34-9.83)	5.01 (2.08-9.34)	5.16 (2.19-9.48)	4.67 (1.92-8.89)	4.34 (1.73-8.60)	4.34 (1.73-8.54)

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HR (95% CI)*	1.12 (0.97-1.29)		1.05 (1.02-1.09)		1.27 (1.22-1.33)		1.01 (0.97-1.04)		1.34 (1.28-1.41)	
P value	p=0.11		p<0.01		p<0.01		p=0.73		p<0.01	
aHR (95% CI)**	1.12 (0.97-1.29)		1.07 (1.03-1.10)		1.26 (1.21-1.32)		1.02 (0.98-1.05)		1.33 (1.26-1.40)	
P value	p=0.12		p<0.01		p<0.01		p=0.33		p<0.01	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	63,788	249,688	63,723	249,375	64,215	250,815	64,276	250,972	64,140	250,532
Number of outcomes, n(%)	144 (0.23)	283 (0.11)	298 (0.47)	819 (0.33)	75 (0.12)	143 (0.06)	77 (0.12)	109 (0.04)	115 (0.18)	293 (0.12)
Person-years	425,877	1,570,752	425,066	1,565,997	429,121	1,578,247	429,555	1,579,238	428,400	1,575,663
IR (per 1000 person-years)	0.34	0.18	0.7	0.52	0.17	0.09	0.18	0.07	0.27	0.19
Follow-up, Median(IQR)	5.62 (2.45-10.10)	5.16 (2.15-9.51)	5.61 (2.45-10.08)	5.15 (2.14-9.51)	5.62 (2.45-10.11)	5.17 (2.15-9.51)	5.63 (2.46-10.10)	5.17 (2.15-9.51)	5.62 (2.45-10.10)	5.16 (2.15-9.51)
HR (95% CI)*	1.89 (1.55-2.32)		1.33 (1.17-1.52)		1.93 (1.46-2.56)		2.58 (1.92-3.45)		1.45 (1.17-1.80)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.80 (1.47-2.20)		1.33 (1.16-1.52)		1.93 (1.46-2.56)		2.51 (1.87-3.38)		1.37 (1.10-1.71)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	61,764	243,056	64,148	250,423	63,819	249,394	64,173	250,585	64,170	250,440
Number of outcomes, n(%)	892 (1.44)	2,799 (1.15)	156 (0.24)	463 (0.18)	228 (0.36)	667 (0.27)	121 (0.19)	334 (0.13)	99 (0.15)	298 (0.12)
Person-years	408,643	1,514,347	428,404	1,574,721	425,814	1,566,813	428,547	1,575,926	428,443	1,574,813
IR (per 1000 person-years)	2.18	1.85	0.36	0.29	0.54	0.43	0.28	0.21	0.23	0.19

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Follow-up, Median(IQR)	5.55 (2.42-9.98)	5.09 (2.11-9.44)	5.62 (2.46-10.10)	5.16 (2.15-9.51)	5.61 (2.45-10.09)	5.15 (2.14-9.51)	5.62 (2.45-10.10)	5.16 (2.15-9.51)	5.62 (2.45-10.09)	5.16 (2.15-9.51)
HR (95% CI)*	1.18 (1.10-1.27)		1.24 (1.03-1.48)		1.26 (1.08-1.46)		1.33 (1.08-1.64)		1.22 (0.97-1.53)	
P value	p<0.01		p=0.02		p<0.01		p<0.01		p=0.08	
aHR (95% CI)**	1.17 (1.09-1.27)		1.23 (1.02-1.47)		1.25 (1.08-1.46)		1.33 (1.08-1.64)		1.19 (0.95-1.50)	
P value	p<0.01		p=0.03		p<0.01		p<0.01		p=0.13	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	64,337	251,067	45,237	202,163	50,883	216,746	54,756	229,068	63,137	248,256
Number of outcomes, n(%)	16 (0.02)	45 (0.02)	5,296 (11.71)	16,758 (8.29)	4,197 (8.25)	12,706 (5.86)	3,331 (6.08)	9,230 (4.03)	400 (0.63)	925 (0.37)
Person-years	430,156	1,580,157	275,375	1,184,298	318,974	1,299,096	345,927	1,386,791	421,760	1,561,193
IR (per 1000 person-years)	0.04	0.03	19.23	14.15	13.16	9.78	9.63	6.66	0.95	0.59
Follow-up, Median(IQR)	5.63 (2.46-10.11)	5.17 (2.15-9.51)	4.93 (2.08-9.21)	4.61 (1.89-8.87)	5.14 (2.19-9.48)	4.77 (1.96-9.10)	5.23 (2.23-9.53)	4.88 (2.02-9.17)	5.62 (2.46-10.10)	5.16 (2.14-9.51)
HR (95% CI)*	1.30 (0.74-2.31)		1.36 (1.32-1.41)		1.35 (1.31-1.40)		1.45 (1.39-1.51)		1.61 (1.43-1.81)	
P value	p=0.36		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.32 (0.75-2.35)		1.37 (1.33-1.42)		1.36 (1.31-1.41)		1.44 (1.38-1.50)		1.59 (1.41-1.79)	
P value	p=0.34		p<0.01		p<0.01		p<0.01		p<0.01	

* Unadjusted hazard ratio, IR: incidence rate, HR: hazard ratio, aHR: adjusted hazard ratio

** Adjusted hazard ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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Sensitivity analysis: Incident only cohort

Of the total exposed cohort, 31,968 (49.7% of total exposed cohort) patients had an exposure code entered during the study period (incident cohort) and were matched to 126,278 (50.3% of total unexposed cohort) unexposed cohort (baseline characteristics in **eTable 2**). The median follow-up in this cohort was 3.4 years. The average age was 49 years, 43% of cohort were male and the proportion of obese patients, current smokers and deprivation quintiles were similar with the primary analysis.

In the incident only sensitivity analysis, the odds ratio of having chronic disease were similar to the primary cohort. There was an increased aOR of having CVD (1.42; 95% CI 1.36-1.49), CMD (1.14; 95% CI 1.10-1.19), AID (1.26; 95% CI 1.21-1.32) and MIH (1.71; 95% CI 1.66-1.76). Further details in appendix **(eTable 3).** When examining subsequent disease outcomes, there also remained an increased risk (described as an aHR) of developing CVD (1.17; 95% CI 1.10-1.24), CMD (1.07; 95% CI 1.02-1.12), AID (1.48; 95% CI 1.37-1.59) and MIH (1.47; 95% CI 1.40-1.53). Further details in appendix **(eTable 4)**.

Sensitivity analysis: Periodontitis only cohort

When restricting the analysis to only those with periodontitis, the exposed cohort of 3,384 patients (5.3% of the total exposed group) were matched to 12,893 patients (5.1% of the unexposed group). The median follow-up in this cohort was 3.6 years. The average age was 48 years, 46% of cohort were male and the proportion of other baseline characteristics were also similar to the primary analysis. Further details in appendix **(eTable 5)**.

In this analysis, the odds ratio of having chronic disease were similar to the primary cohort. There was an increased aOR of having CVD (1.50; 95% CI 1.30-1.74), CMD (1.19; 95% CI 1.06-1.34), AID (1.32; 95% CI 1.15-1.52) and MIH (1.63; 95% CI 1.49-1.78). Further details can be seen in appendix **(eTable 6)**. When examining subsequent disease outcomes, an increased risk (aHR) remained for developing CVD (1.31; 95% CI 1.12-1.52) and MIH (1.33; 95% CI 1.16-1.52) but not for CMD (0.96; 95% CI 0.85-1.10) and AID (1.21; 95% CI 0.96-1.51). Further details demonstrated in appendix **(eTable 7)**.

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DISCUSSION

Summary of key results

To our knowledge, this is the first attempt to synthesise data exploring the relationship between periodontal diseases and the development of chronic disease in a UK retrospective cohort derived from medical records. Our study demonstrates that the presence of a GP recorded diagnosis of a periodontal disease is associated with an 18%, 7% (Although 26% risk of T2DM), 33% and 37% increased risk of CVD, CMD, AID and MIH respectively. This risk persisted when analysing patients who were diagnosed with a periodontal disease during the study period. However, in patients specifically with periodontitis, this risk was not evident for CMD or AID.

Results in context of current literature

To date, research evaluating the association between periodontal diseases and systemic health has focussed on periodontitis, rather than gingivitis, due to the more extensive inflammatory process and thus the potential for greater systemic effects.

This study concurs with the extensive literature highlighting the association of atherosclerotic diseases with periodontal disease. Humphrey et al, demonstrated a risk ratio of 1.24 (95 % CI 1.01 – 1.51) of a CVD/CHD event in the presence of periodontitis.[54] More recently a systematic review by Dietrich et al, demonstrated there was an increased risk of CVD when considering various periodontal disease measures ranging from probing pocket depth measurements to radiographic assessments of bone levels.[55] For those studies where severe periodontitis was the exposure, the associations with ACVD were stronger than in our study. This may be due to limitations in our coding, whereby we were unable to classify the severity of periodontitis.

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There are several potential mechanisms explaining the increase in atherosclerosis in patients with periodontitis. Firstly, transient bacteraemia in patients with periodontitis may be pathogenic.[56] Furthermore, periodontitis patients have elevated circulating levels of pro-inflammatory mediators implicated in atherosclerosis.[57] There is robust evidence that treatment of periodontitis improves markers of systemic inflammation and surrogate markers of CVD risk such as flow-mediated dilatation.[58,59]

T2DM demonstrates a bi-directional relationship with periodontitis i.e. poorly controlled diabetes is a risk factor for periodontitis and periodontitis itself impacts the diabetes disease process. A systematic review commissioned by the International Diabetes Federation and EFP [60] concluded that individuals with periodontitis have a greater risk of developing T2DM with a HR 1.19 –1.33 which is in agreement with the increased aHR demonstrated in this study. Literature also exists investigating the impact of periodontal therapy on diabetic outcomes. A recent review demonstrates reductions in HbA1c (-0.40% at 3 months) following periodontal therapy.[61] Evidence suggests appropriate targeted screening in dental settings may successfully identify cases of undiagnosed diabetes.[62,63] Within the UK there is a drive to utilise the dental team in identifying and managing T2DM, evident by the recent publication of the NHS England Commissioning Standard '*Dental Care for People with Diabetes.*'[64] This document proposes a formalised pathway between general medical practitioner and dentist upon diagnosis of T2DM.

Whilst the evidence base for T2DM is long established, there is limited evidence that Type 1 Diabetes (T1DM) demonstrates a similar relationship. Systematic reviews conducted in 2013 and 2018 were unable to find any studies that met eligibility criteria investigating the association between periodontal health and T1DM.[60,65] The reason for this may be that the age of periodontal disease diagnosis is typically much older than the age of T1DM diagnosis which limits the available data to answer such a question. Our study suggests an increased risk for incident Type 1 Diabetes in patients with a periodontal disease (aHR 1.80; CI 1.47-2.20) but was not clearly evident when considering only those patients with periodontitis (aHR 1.62; CI 0.70-3.76).

The mechanisms connecting mental health with periodontal inflammation include both behavioural and immunological. Existing literature focuses on depression and anxiety as risk

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factors for periodontitis. Individuals under increased stress may reduce health promoting behaviours (e.g. optimal oral hygiene practices) and instead be driven towards detrimental health behaviours (e.g. smoking). The research linking depression as a risk factor for periodontitis has been contradictory.[66]

Conversely, studies assessing mental health outcomes consequent upon periodontal diseases are sparse. Potential mechanisms underlying such a relation include psychological mechanisms with outcomes of periodontal diseases (e.g. halitosis, loss of teeth, drifting of teeth) impacting negatively on social and functional aspects of life, thus impacting on mood. One study utilised the well-established EuroQoL questionnaire to review oral health in relation to anxiety/depression. In 10% of individuals with increased probing pocket depth (≥6mm) anxiety/depression was experienced 25% of the time.[67] Our study demonstrates a significantly increased risk of all mental health illnesses in patients with a periodontal disease (aOR 1.79; CI 1.75-1.83) and an increased risk of developing a mental health condition (aHR 1.37; CI 1.33-1.42). Whilst severe mental illness in particular did not demonstrate a significant increase in the incident only analysis of the periodontitis cohort, we found that individuals with periodontitis have a 37% increased risk of developing anxiety. Furthermore, within the same periodontitis cohort there was a significantly higher risk of developing depression (aHR 1.29; CI 1.11-1.50). This provides further evidence for the potential psychosocial impact of periodontal diseases and an issue that is under-reported in the literature.

Of the autoimmune conditions included within our analysis, the one most frequently reported in the context of periodontitis is RA. A number of mechanisms have been proposed linking the periodontium with the progression of RA. For example *P. gingivalis*, expresses peptidyl arginine deiminases (PADs), which drive protein citrullination. Exposure to citrullinated proteins in periodontitis patients may then lead to the generation of anti-citrullinated protein antibodies (ACPA), stimulating a systemic autoimmune response characteristic of RA.[33] A study analysing the third US National Health and Nutrition Examination Survey (NHANES III) identified that individuals with RA were more likely to present with both periodontitis (OR 1.82; CI 1.04 – 3.20) and edentulism (OR 2.27; CI 1.56 – 3.31).[68] Our data support an association between periodontal diseases and development of

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RA. For periodontitis alone, the increased risk of RA at baseline approached significance, although no significant risk was identified for subsequent development of RA. This may be attributed to the low number of outcomes during this subset analysis and is in agreement with a previous study based on the Taiwanese National Health Insurance Research Database (NHIRD).[69] The Taiwanese study also demonstrated an increased risk of developing Sjogren's syndrome in patients with chronic periodontitis (CP) (HR 1.87; CI 1.64 – 2.13.)[70] Our study also demonstrates an increased risk of developing Sjogren's syndrome with periodontal diseases in general (HR 2.51; CI 1.87-3.38), with the periodontitis only cohort showing a substantial increased hazard ratio; however, the low number of outcomes means that the results must be interpreted with caution (aHR 6.67; CI 1.66-26.86).

Limitations

The primary limitation is that the validity of the results rely upon the accuracy of documentation by the healthcare professionals contributing to the dataset. To date, the accuracy of oral health read codes in primary care datasets have not been validated[71]. However, it is important to highlight that in the UK GPs are not usually the professionals responsible for diagnosing periodontal disease and this is typically identified by dental practitioners based on a clinical examination. Periodontal Read codes are thus likely to be inputted following receipt of clinical letters from dental healthcare professional, though GP diagnosis and self-report are also possibilities. Overall, it is likely that there is under recording of periodontal diseases in this data set i.e. it is likely that patients with a periodontal disease are not recorded as having it. Therefore, it is possible our findings may not reflect the true effect size and are likely to be an underestimate. On the other hand, selective recording of severe periodontal disease might have led to an overestimation of the true effect size.

Conclusion

In conclusion, this study demonstrates that periodontal diseases (including gingivitis and periodontitis) are associated with an increased risk of developing cardiovascular, cardiometabolic, autoimmune diseases and mental ill health. With this in mind, it is

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important to highlight patients with periodontal diseases and to tackle risk factors to prevent the development and progression of such conditions. An important implication of our findings is the need for effective communication between dental and other health care professionals to ensure patients obtain an effective treatment plan targeting both oral and extra-oral health to improve current health and reduce the risk of future ill health.

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Figure legends

Figure 1: Forest plots showing odds ratios at baseline for chronic diseases in patients exposed to periodontal diseases compared to unexposed patients

Figure 2: Forest plots showing hazard ratios for subsequent development of chronic diseases in patients exposed to periodontal diseases compared with unexposed patients.

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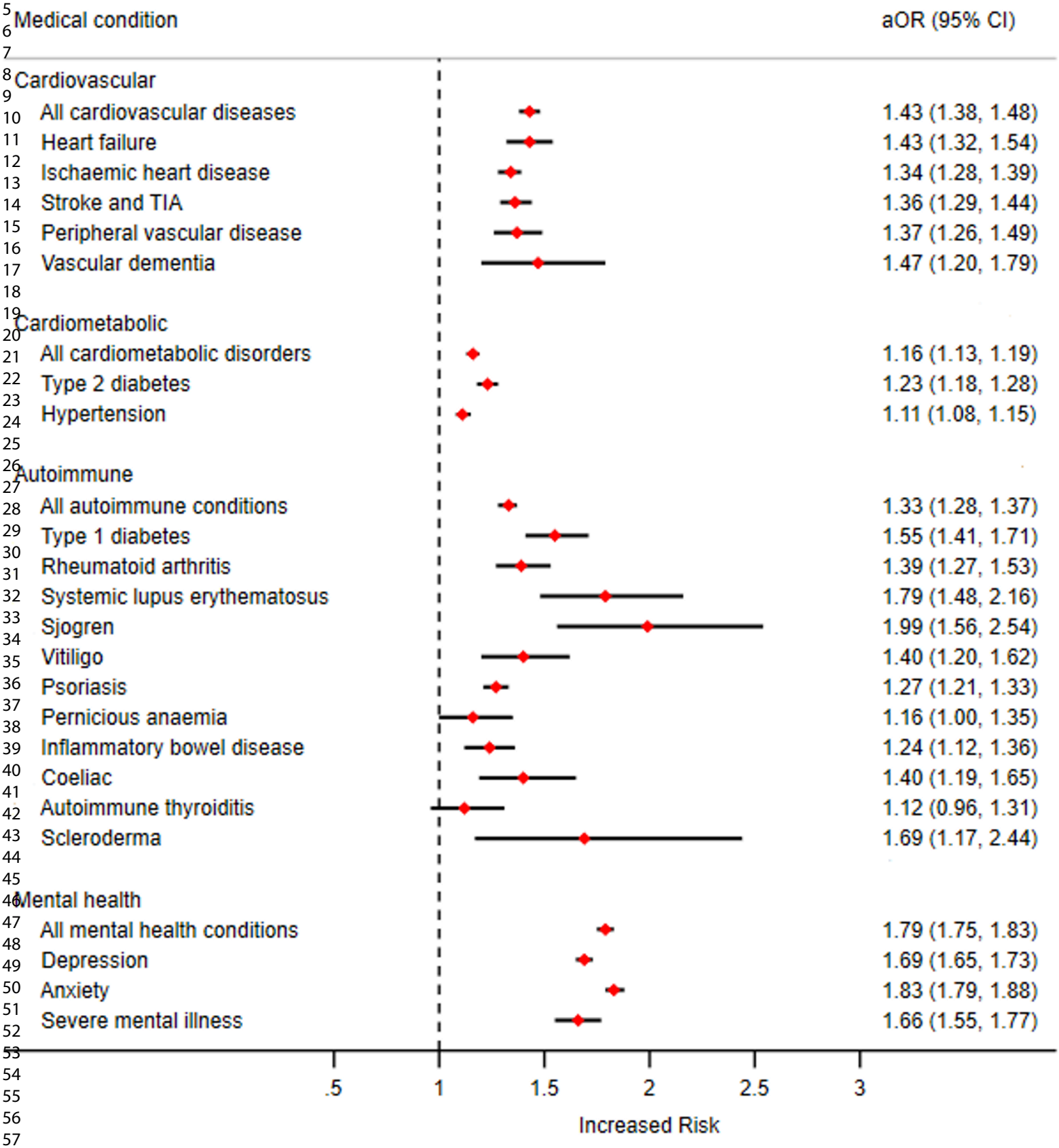
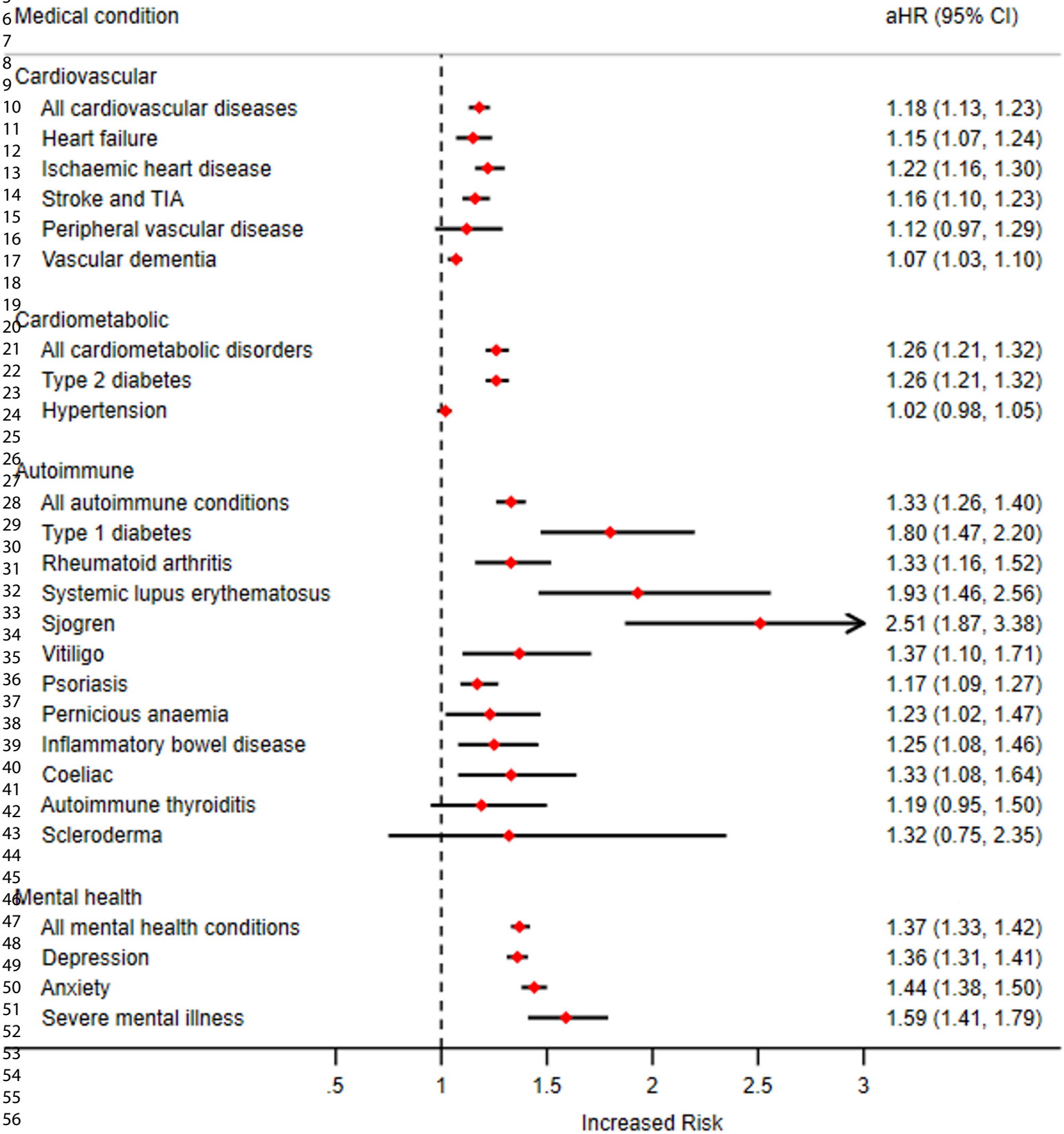


TIA: transient ischemic attack, aOR: adjusted odds ratio, CI: confidence interval



TIA: transient ischemic attack, aHR: adjusted hazard ratio, CI: confidence interval

Supplementary materials

eTable 1. Read codes for periodontal disease exposure.

Gingivitis

Code	Description
2552	O/E - gingivitis
2556	O/E - bleeding gums
J031z00	Chronic gingivitis NOS
1928	Bleeding gums
J030.00	Acute gingivitis
J031.11	Gingivitis
J031.00	Chronic gingivitis
J031300	Hyperplastic gingivitis
J031200	Desquamative gingivitis
J031100	Ulcerative gingivitis
J03..11	Gingivitis/gingival disease
J031000	Simple marginal gingivitis
J03z.00	Gingival and periodontal disease NOS

Periodontitis

Code	Description
J033200	Paradontal abscess
J034400	Alveolar pyorrhoea
J033300	Periodontal abscess
J03..12	Periodontal disease
J033.00	Acute periodontitis
2553	O/E - pyorrhoea
J051200	Loss of teeth due to local periodontal disease
J034200	Chronic periodontitis simplex
J033z00	Acute periodontitis NOS
J034.00	Chronic periodontitis
J035.00	Periodontosis
J034z00	Chronic periodontitis NOS

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eTable 2. Baseline characteristics of the incident OA cohort

	Incident cohort	
	Exposed n (%)	Unexposed n (%)
All	(n=31,968)	(n=126,278)
Sex (Male)	13715 (42.90)	54062 (42.81)
Age at index date	48.77 (18.77)	48.59 (18.67)
Age categories		
18 - 24 years	3788 (11.85)	15081 (11.94)
25 - 34 years	4921 (15.39)	19604 (15.52)
35 - 44 years	5381 (16.83)	21272 (16.85)
45 - 54 years	5411 (16.93)	21518 (17.04)
55 - 64 years	5124 (16.03)	20212 (16.01)
65 - 74 years	4028 (12.60)	15908 (12.60)
75 & overs	3315 (10.37)	12683 (10.04)
BMI	26.60 (5.73)	26.62 (5.62)
BMI Categories		
Under/Normal weight (18.5-25)	11755 (36.77)	45183 (35.78)
Overweight (25-30)	8573 (26.82)	34623 (27.42)
Obese (>30)	6192 (19.37)	23359 (18.50)
Missing	5448 (17.04)	23113 (18.30)
Townsend quintiles		
1 (Least deprived)	5813 (18.18)	21910 (17.35)
2	5346 (16.72)	19600 (15.52)
3	6118 (19.14)	22190 (17.57)
4	6079 (19.02)	21452 (16.99)
5 (Most deprived)	4810 (15.05)	15776 (12.49)
Missing	3802 (11.89)	25350 (20.07)
Smoking categories		
Non-smoker	14514 (45.40)	57617 (45.63)
Smoker	9452 (29.57)	37338 (29.57)
Ex-smoker	6494 (20.31)	25445 (20.15)
Missing	1508 (4.72)	5878 (4.65)
Ethnicity		
Caucasian	11976 (37.46)	49505 (39.20)
Mixed race	229 (0.72)	764 (0.61)
Other	101 (0.32)	358 (0.28)
Black	509 (1.59)	1415 (1.12)
South Asian	1510 (4.72)	2154 (1.71)
Missing	17643 (55.19)	72082 (57.08)

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eTable 3. Risk of chronic diseases at baseline in the incident only sensitivity analysis cohort

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278
Number of patients with condition at baseline, n(%)	3,700 (11.57)	11,032 (8.74)	524 (1.64)	1,541 (1.22)	2,352 (7.36)	7,022 (5.56)	1,260 (3.94)	3,660 (2.90)	478 (1.50)	1,388 (1.10)
OR (95% CI)*	1.37 (1.31-1.42)		1.35 (1.22-1.49)		1.35 (1.29-1.42)		1.37 (1.29-1.47)		1.37 (1.23-1.52)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.42 (1.36-1.49)		1.30 (1.18-1.45)		1.35 (1.28-1.42)		1.36 (1.27-1.46)		1.31 (1.18-1.46)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278
Number of patients with condition at baseline, n(%)	89 (0.28)	204 (0.16)	7,488 (23.42)	26,602 (21.07)	2,126 (6.65)	6,773 (5.36)	6,597 (20.64)	23,995 (19.00)	2,833 (8.86)	8,948 (7.09)
OR (95% CI)*	1.73 (1.34-2.21)		1.15 (1.11-1.18)		1.26 (1.20-1.32)		1.11 (1.08-1.14)		1.28 (1.22-1.33)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.64 (1.27-2.12)		1.14 (1.10-1.19)		1.15 (1.09-1.22)		1.10 (1.06-1.15)		1.26 (1.21-1.32)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278

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Number of patients with condition at baseline, n(%)	304 (0.95)	836 (0.66)	403 (1.26)	1,044 (0.83)	104 (0.33)	189 (0.15)	58 (0.18)	119 (0.09)	130 (0.41)	355 (0.28)
OR (95% CI)*	1.44 (1.26-1.64)		1.53 (1.36-1.72)		2.18 (1.71-2.77)		1.93 (1.41-2.64)		1.45 (1.18-1.77)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.40 (1.23-1.61)		1.48 (1.32-1.67)		2.14 (1.68-2.73)		1.79 (1.30-2.47)		1.31 (1.07-1.61)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p=0.01	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278
Number of patients with condition at baseline, n(%)	1,362 (4.26)	4,558 (3.61)	134 (0.42)	457 (0.36)	317 (0.99)	1,031 (0.82)	119 (0.37)	336 (0.27)	104 (0.33)	408 (0.32)
OR (95% CI)*	1.19 (1.12-1.26)		1.16 (0.96-1.41)		1.22 (1.07-1.38)		1.40 (1.14-1.73)		1.01 (0.81-1.25)	
P value	p<0.01		p=0.13		p<0.01		p<0.01		p=0.95	
aOR (95% CI)**	1.19 (1.12-1.27)		1.10 (0.90-1.34)		1.21 (1.07-1.38)		1.41 (1.14-1.74)		0.98 (0.79-1.22)	
P value	p<0.01		p=0.35		p<0.01		p<0.01		p=0.84	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278
Number of patients with condition at baseline, n(%)	23 (0.07)	59 (0.05)	10,036 (31.39)	27,197 (21.54)	7,187 (22.48)	19,341 (15.32)	4,894 (15.31)	12,153 (9.62)	703 (2.20)	1,651 (1.31)
OR (95% CI)*	1.54 (0.95-2.49)		1.67 (1.62-1.71)		1.60 (1.56-1.65)		1.70 (1.64-1.76)		1.70 (1.55-1.86)	
P value	p=0.08		p<0.01		p<0.01		p<0.01		p<0.01	

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aOR (95% CI)**	1.45 (0.89-2.37)	1.71 (1.66-1.76)	1.63 (1.58-1.68)	1.71 (1.65-1.78)	1.68 (1.53-1.84)
P value	p=0.14	p<0.01	p<0.01	p<0.01	p<0.01

* Unadjusted odds ratio, OR: odds ratio, aOR: adjusted odds ratio
** Adjusted odds ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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eTable 4. Risk of subsequent development of chronic diseases in the incident only sensitivity analysis

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	28,268	115,246	31,444	124,737	29,616	119,256	30,708	122,618	31,490	124,890
Number of outcomes, n(%)	1,473 (5.21)	5,196 (4.51)	409 (1.30)	1,455 (1.17)	715 (2.41)	2,303 (1.93)	745 (2.43)	2,604 (2.12)	272 (0.86)	784 (0.63)
Person-years	171,643	668,935	193,503	734,319	180,791	698,131	188,372	718,635	193,366	734,953
IR (per 1000 person-years)	8.58	7.77	2.11	1.98	3.95	3.3	3.95	3.62	1.41	1.07
Follow-up, Median(IQR)	5.37 (2.41-8.99)	4.99 (2.19-8.68)	5.46 (2.47-9.12)	5.09 (2.24-8.80)	5.41 (2.43-9.04)	5.05 (2.22-8.75)	5.44 (2.47-9.08)	5.06 (2.23-8.76)	5.45 (2.46-9.11)	5.08 (2.24-8.80)
HR (95% CI)*	1.10 (1.04-1.17)		1.06 (0.95-1.19)		1.20 (1.10-1.30)		1.09 (1.00-1.18)		1.32 (1.15-1.51)	
P value	p<0.01		p=0.27		p<0.01		p=0.04		p<0.01	
aHR (95% CI)**	1.17 (1.10-1.24)		1.07 (0.96-1.20)		1.23 (1.13-1.34)		1.12 (1.03-1.22)		1.32 (1.15-1.52)	
P value	p<0.01		p=0.23		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	31,879	126,074	24,480	99,676	29,842	119,505	25,371	102,283	29,135	117,330
Number of outcomes, n(%)	148 (0.46)	474 (0.38)	2,310 (9.44)	8,363 (8.39)	1,355 (4.54)	3,913 (3.27)	1,881 (7.41)	7,192 (7.03)	964 (3.31)	2,700 (2.30)
Person-years	196,449	743,531	142,524	554,252	179,645	693,204	148,885	572,392	152,881	627,091
IR (per 1000 person-years)	0.75	0.64	16.21	15.09	7.54	5.64	12.63	12.56	6.31	4.31
Follow-up, Median(IQR)	5.47 (2.48-9.13)	5.10 (2.25-8.81)	5.02 (2.21-8.68)	4.68 (2.02-8.32)	5.27 (2.35-8.96)	4.98 (2.18-8.68)	5.09 (2.25-8.72)	4.73 (2.04-8.38)	4.24 (1.75-7.95)	4.41 (1.85-8.05)
HR (95% CI)*	1.17 (0.98-1.41)		1.07 (1.03-1.12)		1.34 (1.26-1.42)		1.01 (0.96-1.06)		1.47 (1.37-1.59)	

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P value	p=0.09		p<0.01		p<0.01		p=0.83		p<0.01	
aHR (95% CI)**	1.20 (1.00-1.45)		1.07 (1.02-1.12)		1.30 (1.22-1.38)		1.01 (0.96-1.06)		1.48 (1.37-1.59)	
P value	p=0.06		p<0.01		p<0.01		p=0.77		p<0.01	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	31,664	125,442	31,565	125,234	31,864	126,089	31,910	126,159	31,838	125,923
Number of outcomes, n(%)	63 (0.20)	120 (0.10)	146 (0.46)	409 (0.33)	45 (0.14)	72 (0.06)	44 (0.14)	63 (0.05)	63 (0.20)	138 (0.11)
Person-years	194,829	739,746	193,993	737,315	196,108	743,639	196,422	744,022	195,815	742,249
IR (per 1000 person-years)	0.32	0.16	0.75	0.55	0.23	0.1	0.22	0.08	0.32	0.19
Follow-up, Median(IQR)	5.46 (2.47-9.13)	5.10 (2.25-8.82)	5.45 (2.47-9.11)	5.09 (2.25-8.80)	5.46 (2.47-9.13)	5.10 (2.25-8.81)	5.47 (2.47-9.13)	5.10 (2.25-8.81)	5.46 (2.47-9.12)	5.10 (2.25-8.81)
HR (95% CI)*	2.01 (1.48-2.72)		1.35 (1.12-1.64)		2.37 (1.64-3.45)		2.64 (1.79-3.87)		1.74 (1.29-2.34)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.84 (1.35-2.51)		1.37 (1.13-1.66)		2.45 (1.68-3.57)		2.57 (1.74-3.80)		1.59 (1.18-2.16)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	30,606	121,720	31,834	125,821	31,651	125,247	31,849	125,942	31,864	125,870
Number of outcomes, n(%)	443 (1.45)	1,294 (1.06)	89 (0.28)	243 (0.19)	105 (0.33)	321 (0.26)	56 (0.18)	173 (0.14)	50 (0.16)	144 (0.11)
Person-years	186,612	712,529	195,847	741,633	194,586	737,712	195,911	742,372	196,034	741,787
IR (per 1000 person-years)	2.37	1.82	0.45	0.33	0.54	0.44	0.29	0.23	0.26	0.19
Follow-up, Median(IQR)	5.40 (2.43-9.03)	5.04 (2.22-8.75)	5.46 (2.48-9.12)	5.10 (2.25-8.81)	5.45 (2.47-9.12)	5.10 (2.25-8.81)	5.46 (2.47-9.12)	5.10 (2.25-8.81)	5.46 (2.47-9.12)	5.10 (2.25-8.81)

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HR (95% CI)*	1.31 (1.17-1.46)		1.39 (1.09-1.77)		1.24 (1.00-1.55)		1.23 (0.91-1.66)		1.32 (0.95-1.82)	
P value	p<0.01		p<0.01		p=0.05		p=0.18		p=0.09	
aHR (95% CI)**	1.31 (1.18-1.46)		1.41 (1.10-1.80)		1.23 (0.98-1.53)		1.26 (0.93-1.70)		1.29 (0.93-1.78)	
P value	p<0.01		p<0.01		p=0.07		p=0.14		p=0.12	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	31,945	126,219	21,932	99,081	24,781	106,937	27,074	114,125	31,265	124,627
Number of outcomes, n(%)	5 (0.02)	16 (0.01)	2,450 (11.17)	7,513 (7.58)	1,955 (7.89)	5,746 (5.37)	1,586 (5.86)	4,127 (3.62)	202 (0.65)	418 (0.34)
Person-years	196,725	744,579	124,610	551,747	144,563	605,666	158,613	653,590	192,266	734,597
IR (per 1000 person-years)	0.03	0.02	19.66	13.62	13.52	9.49	10	6.31	1.05	0.57
Follow-up, Median(IQR)	5.47 (2.48-9.13)	5.10 (2.25-8.82)	4.83 (2.13-8.47)	4.69 (2.03-8.35)	5.00 (2.22-8.70)	4.80 (2.09-8.49)	5.08 (2.27-8.73)	4.90 (2.14-8.57)	5.45 (2.47-9.12)	5.10 (2.25-8.81)
HR (95% CI)*	1.19 (0.43-3.24)		1.45 (1.38-1.51)		1.43 (1.36-1.51)		1.58 (1.50-1.68)		1.85 (1.57-2.19)	
P value	p=0.74		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.20 (0.43-3.32)		1.47 (1.40-1.53)		1.45 (1.37-1.52)		1.58 (1.49-1.68)		1.86 (1.57-2.20)	
P value	p=0.72		p<0.01		p<0.01		p<0.01		p<0.01	

* Unadjusted hazard ratio, IR: incidence rate, HR: hazard ratio, aHR: adjusted hazard ratio

** Adjusted hazard ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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eTable 5. Baseline characteristics of the periodontitis cohort

	Periodontitis only cohort	
	Exposed n (%)	Unexposed n (%)
All	(n=3,384)	(n=12,893)
Sex (Male)	1560 (46.10)	5927 (45.97)
Age at index date	48.10 (17.43)	47.81 (17.25)
Age categories		
18 - 24 years	330 (9.75)	1269 (9.84)
25 - 34 years	502 (14.83)	1952 (15.14)
35 - 44 years	650 (19.21)	2515 (19.51)
45 - 54 years	701 (20.72)	2646 (20.52)
55 - 64 years	560 (16.55)	2148 (16.66)
65 - 74 years	369 (10.90)	1368 (10.61)
75 & overs	272 (8.04)	995 (7.72)
BMI	26.49 (5.62)	26.43 (5.43)
BMI Categories		
Under/Normal weight (18.5-25)	1203 (35.55)	4539 (35.21)
Overweight (25-30)	905 (26.74)	3475 (26.95)
Obese (>30)	571 (16.87)	2122 (16.46)
Missing	705 (20.83)	2757 (21.38)
Townsend quintiles		
1 (Least deprived)	584 (17.26)	2128 (16.51)
2	580 (17.14)	2051 (15.91)
3	614 (18.14)	2187 (16.96)
4	644 (19.03)	2135 (16.56)
5 (Most deprived)	520 (15.37)	1616 (12.53)
Missing	442 (13.06)	2776 (21.53)
Smoking categories		
Non-smoker	1359 (40.16)	5221 (40.49)
Smoker	1124 (33.22)	4274 (33.15)
Ex-smoker	585 (17.29)	2224 (17.25)
Missing	316 (9.34)	1174 (9.11)
Ethnicity		
Caucasian	1271 (37.56)	4906 (38.05)
Mixed race	21 (0.62)	67 (0.52)
Other	5 (0.15)	40 (0.31)
Black	45 (1.33)	132 (1.02)
South Asian	82 (2.42)	170 (1.32)
Missing	1960 (57.92)	7578 (58.78)

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eTable 6. Risk of chronic diseases at baseline in the periodontitis only sensitivity analysis cohort

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893
Number of patients with condition at baseline, n(%)	355 (10.49)	971 (7.53)	53 (1.57)	120 (0.93)	244 (7.21)	607 (4.71)	112 (3.31)	297 (2.30)	59 (1.74)	141 (1.09)
OR (95% CI)*	1.44 (1.27-1.64)		1.69 (1.22-2.35)		1.57 (1.35-1.83)		1.45 (1.16-1.81)		1.60 (1.18-2.18)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.50 (1.30-1.74)		1.71 (1.22-2.41)		1.64 (1.38-1.94)		1.43 (1.14-1.81)		1.57 (1.15-2.15)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893
Number of patients with condition at baseline, n(%)	4 (0.12)	18 (0.14)	659 (19.47)	2,221 (17.23)	172 (5.08)	529 (4.10)	590 (17.43)	2,006 (15.56)	286 (8.45)	836 (6.48)
OR (95% CI)*	0.85 (0.29-2.50)		1.16 (1.06-1.28)		1.25 (1.05-1.49)		1.15 (1.04-1.27)		1.33 (1.16-1.53)	
P value	p=0.76		p<0.01		p=0.01		p<0.01		p<0.01	
aOR (95% CI)**	0.71 (0.23-2.19)		1.19 (1.06-1.34)		1.25 (1.03-1.51)		1.17 (1.04-1.32)		1.32 (1.15-1.52)	
P value	p=0.55		p<0.01		p=0.02		p<0.01		p<0.01	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893

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Number of patients with condition at baseline, n(%)	43 (1.27)	79 (0.61)	37 (1.09)	96 (0.74)	10 (0.30)	20 (0.16)	4 (0.12)	9 (0.07)	13 (0.38)	25 (0.19)
OR (95% CI)*	2.09 (1.44-3.03)		1.47 (1.01-2.16)		1.91 (0.89-4.08)		1.69 (0.52-5.50)		1.98 (1.01-3.88)	
P value	p<0.01		p=0.05		p=0.10		p=0.38		p=0.05	
aOR (95% CI)**	2.07 (1.42-3.02)		1.44 (0.98-2.13)		1.82 (0.84-3.93)		1.45 (0.44-4.79)		1.99 (1.01-3.92)	
P value	p<0.01		p=0.06		p=0.13		p=0.54		p=0.05	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893
Number of patients with condition at baseline, n(%)	125 (3.69)	437 (3.39)	14 (0.41)	31 (0.24)	36 (1.06)	94 (0.73)	8 (0.24)	32 (0.25)	9 (0.27)	42 (0.33)
OR (95% CI)*	1.09 (0.89-1.34)		1.72 (0.92-3.24)		1.46 (1.00-2.15)		0.95 (0.44-2.07)		0.82 (0.40-1.68)	
P value	p=0.39		p=0.09		p=0.05		p=0.90		p=0.58	
aOR (95% CI)**	1.09 (0.89-1.34)		1.54 (0.81-2.92)		1.45 (0.98-2.14)		0.98 (0.45-2.15)		0.81 (0.39-1.67)	
P value	p=0.40		p=0.19		p=0.06		p=0.97		p=0.57	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893
Number of patients with condition at baseline, n(%)	7 (0.21)	7 (0.05)	1,021 (30.17)	2,745 (21.29)	704 (20.80)	1,942 (15.06)	531 (15.69)	1,252 (9.71)	70 (2.07)	149 (1.16)
OR (95% CI)*	3.82 (1.34-10.89)		1.60 (1.47-1.74)		1.48 (1.35-1.63)		1.73 (1.55-1.93)		1.81 (1.36-2.41)	
P value	p=0.01		p<0.01		p<0.01		p<0.01		p<0.01	

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aOR (95% CI)**	4.18 (1.45-12.10)	1.63 (1.49-1.78)	1.50 (1.36-1.66)	1.74 (1.55-1.94)	1.83 (1.37-2.44)
P value	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01

* Unadjusted odds ratio, OR: odds ratio, aOR: adjusted odds ratio

** Adjusted odds ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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eTable 7. Risk of subsequent development of chronic diseases in the periodontitis only sensitivity analysis

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,029	11,922	3,331	12,773	3,140	12,286	3,272	12,596	3,325	12,752
Number of outcomes, n(%)	221 (7.30)	646 (5.42)	57 (1.71)	156 (1.22)	106 (3.38)	301 (2.45)	97 (2.96)	311 (2.47)	47 (1.41)	101 (0.79)
Person-years	21,705	80,954	24,737	88,720	22,881	84,397	24,127	86,844	24,625	88,567
IR (per 1000 person-years)	10.18	7.98	2.3	1.76	4.63	3.57	4.02	3.58	1.91	1.14
Follow-up, Median(IQR)	5.92 (2.63-10.83)	5.60 (2.30-10.26)	6.31 (2.81-11.32)	5.83 (2.42-10.46)	6.19 (2.75-11.03)	5.70 (2.36-10.36)	6.23 (2.81-11.15)	5.73 (2.39-10.37)	6.29 (2.77-11.23)	5.83 (2.42-10.48)
HR (95% CI)*	1.27 (1.09-1.48)		1.30 (0.96-1.77)		1.30 (1.04-1.62)		1.12 (0.89-1.41)		1.67 (1.18-2.36)	
P value	p<0.01		p=0.09		p=0.02		p=0.33		p<0.01	
aHR (95% CI)**	1.31 (1.12-1.52)		1.27 (0.94-1.73)		1.35 (1.08-1.69)		1.12 (0.89-1.41)		1.67 (1.18-2.38)	
P value	p<0.01		p=0.12		p<0.01		p=0.34		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,380	12,875	2,725	10,672	3,212	12,364	2,794	10,887	3,098	12,057
Number of outcomes, n(%)	20 (0.59)	55 (0.43)	303 (11.12)	1,133 (10.62)	173 (5.39)	449 (3.63)	247 (8.84)	982 (9.02)	104 (3.36)	308 (2.55)
Person-years	25,137	89,654	18,750	68,456	23,111	84,508	19,504	70,497	19,592	74,615
IR (per 1000 person-years)	0.8	0.61	16.16	16.55	7.49	5.31	12.66	13.93	5.31	4.13
Follow-up, Median(IQR)	6.31 (2.84-11.32)	5.86 (2.44-10.51)	5.54 (2.38-10.38)	5.16 (2.12-9.61)	6.00 (2.65-10.90)	5.66 (2.34-10.32)	5.67 (2.45-10.54)	5.23 (2.14-9.72)	4.86 (1.93-9.57)	4.89 (1.89-9.45)
HR (95% CI)*	1.27 (0.76-2.12)		0.97 (0.86-1.10)		1.40 (1.18-1.67)		0.90 (0.79-1.04)		1.25 (1.00-1.56)	

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P value	p=0.36		p=0.65		p<0.01		p=0.16		p=0.05	
aHR (95% CI)**	1.23 (0.73-2.07)		0.96 (0.85-1.10)		1.43 (1.20-1.71)		0.91 (0.79-1.05)		1.21 (0.96-1.51)	
P value	p=0.44		p=0.57		p<0.01		p=0.20		p=0.10	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,341	12,814	3,347	12,797	3,374	12,873	3,380	12,884	3,371	12,868
Number of outcomes, n(%)	8 (0.24)	17 (0.13)	13 (0.39)	51 (0.40)	6 (0.18)	10 (0.08)	6 (0.18)	3 (0.02)	8 (0.24)	9 (0.07)
Person-years	24,868	89,212	24,897	88,889	25,097	89,628	25,152	89,766	25,066	89,569
IR (per 1000 person-years)	0.32	0.19	0.52	0.57	0.24	0.11	0.24	0.03	0.32	0.1
Follow-up, Median(IQR)	6.31 (2.81-11.32)	5.86 (2.44-10.51)	6.31 (2.81-11.32)	5.83 (2.42-10.48)	6.31 (2.84-11.32)	5.86 (2.44-10.51)	6.31 (2.84-11.32)	5.86 (2.44-10.51)	6.31 (2.84-11.32)	5.85 (2.44-10.51)
HR (95% CI)*	1.71 (0.74-3.97)		0.90 (0.49-1.66)		2.13 (0.77-5.86)		7.02 (1.76-28.09)		3.13 (1.21-8.13)	
P value	p=0.21		p=0.74		p=0.14		p<0.01		p=0.02	
aHR (95% CI)**	1.62 (0.70-3.76)		0.96 (0.52-1.77)		2.15 (0.77-6.00)		6.67 (1.66-26.86)		2.90 (1.11-7.61)	
P value	p=0.26		p=0.90		p=0.14		p<0.01		p=0.03	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,259	12,456	3,370	12,862	3,348	12,799	3,376	12,861	3,375	12,851
Number of outcomes, n(%)	49 (1.50)	165 (1.32)	13 (0.39)	25 (0.19)	13 (0.39)	34 (0.27)	5 (0.15)	20 (0.16)	1 (0.03)	12 (0.09)
Person-years	23,982	85,868	25,033	89,510	24,901	89,000	25,106	89,487	25,127	89,498
IR (per 1000 person-years)	2.04	1.92	0.52	0.28	0.52	0.38	0.2	0.22	0.04	0.13
Follow-up, Median(IQR)	6.25 (2.77-11.10)	5.76 (2.39-10.37)	6.31 (2.84-11.25)	5.84 (2.44-10.50)	6.31 (2.81-11.32)	5.85 (2.43-10.50)	6.31 (2.82-11.32)	5.85 (2.44-10.50)	6.31 (2.84-11.32)	5.86 (2.44-10.51)
HR (95% CI)*	1.06 (0.77-1.46)		1.85 (0.95-3.62)		1.35 (0.71-2.57)		0.90 (0.34-2.39)		0.30 (0.04-2.29)	

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P value	p=0.71		p=0.07		p=0.35		p=0.83		p=0.24	
aHR (95% CI)**	1.05 (0.76-1.44)		1.89 (0.96-3.74)		1.35 (0.71-2.57)		0.85 (0.32-2.28)		0.29 (0.04-2.23)	
P value	p=0.78		p=0.07		p=0.36		p=0.75		p=0.23	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,377	12,886	2,363	10,148	2,680	10,951	2,853	11,641	3,314	12,744
Number of outcomes, n(%)	2 (0.06)	3 (0.02)	287 (12.15)	875 (8.62)	224 (8.36)	671 (6.13)	189 (6.62)	521 (4.48)	15 (0.45)	46 (0.36)
Person-years	25,152	89,739	16,121	65,906	18,839	72,978	19,995	77,498	24,744	88,828
IR (per 1000 person-years)	0.08	0.03	17.8	13.28	11.89	9.19	9.45	6.72	0.61	0.52
Follow-up, Median(IQR)	6.31 (2.84-11.32)	5.86 (2.44-10.51)	5.59 (2.33-10.37)	5.24 (2.09-9.85)	5.76 (2.54-10.52)	5.47 (2.21-10.09)	5.77 (2.54-10.63)	5.50 (2.24-10.04)	6.34 (2.86-11.32)	5.86 (2.44-10.51)
HR (95% CI)*	2.40 (0.40-14.36)		1.35 (1.18-1.54)		1.30 (1.12-1.52)		1.41 (1.19-1.66)		1.18 (0.66-2.12)	
P value	p=0.34		p<0.01		p<0.01		p<0.01		p=0.57	
aHR (95% CI)**	2.26 (0.37-13.70)		1.33 (1.16-1.52)		1.29 (1.11-1.50)		1.37 (1.16-1.62)		1.24 (0.69-2.23)	
P value	p=0.37		p<0.01		p<0.01		p<0.01		p=0.47	

* Unadjusted hazard ratio, IR: incidence rate, HR: hazard ratio, aHR: adjusted hazard ratio

** Adjusted hazard ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Reporting Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods

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Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Methods Results: Table 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Methods/discussion
Study size	10	Explain how the study size was arrived at	Methods

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Methods
		(*c*) Explain how missing data were addressed	Methods
		(*d*) If applicable, explain how loss to follow-up was addressed	Methods
		(*e*) Describe any sensitivity analyses	Methods
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods and results

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		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results and Table 2/3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results and Table 2/3
		(*b*) Report category boundaries when continuous variables were categorized	Results and Table 2/3

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		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Mentioned in results and throughout etables
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			

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Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Highlighted in funding and acknowledgements section

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The burden of chronic diseases associated with periodontal diseases: A retrospective cohort study using UK primary care data

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The burden of chronic diseases associated with periodontal diseases: A retrospective cohort study using UK primary care data

Running Title: The association between chronic disease and periodontal diseases

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Ethics approval: Anonymised data were used throughout the study provided by the data provider to the University of Birmingham. Studies using IMRD-UK database have had initial ethical approval from the NHS South-East Multicentre Research Ethics Committee, subject to prior independent scientific review. The Scientific Review Committee (IQVIA) approved the study protocol (SRC Reference Number: SRC20THIN036).

Transparency statement: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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ABSTRACT

Objectives: To identify the association between periodontal diseases (gingivitis and periodontitis) and chronic diseases including cardiovascular disease, cardiometabolic disease, autoimmune disease, and mental ill health.

Design: Retrospective cohort.

Setting: IQVIA Medical Research Data-UK between 1st January 1995 and 1st January 2019.

Participants: 64,379 adult patients with a general practitioner recorded diagnosis of periodontal disease (exposed patients) were matched to 251,161 unexposed patients by age, sex, deprivation, and registration date.

Main outcome measures: Logistic regression models accounting for covariates of clinical importance were undertaken to estimate the adjusted odds ratio (aOR) of having chronic diseases at baseline in the exposed compared to the unexposed group. Incidence rates for each outcome of interest were then provided followed by the calculation of adjusted hazard ratios (aHR) using cox regression modelling to describe the risk of outcome development in each group.

Results: The average age at cohort entry was 45 years and the median follow-up was 3.4 years. At study entry, the exposed cohort had an increased likelihood of having a diagnosis of cardiovascular disease (aOR 1.43; 95% CI 1.38-1.48), cardiometabolic disease (aOR 1.16; 95% CI 1.13-1.19), autoimmune disease (aOR 1.33; 95% CI 1.28-1.37), and mental ill health (aOR 1.79; 95% CI 1.75-1.83) compared to the unexposed group. During follow-up of individuals without pre-existing outcomes of interest, the exposed group had an increased risk of developing cardiovascular disease (HR 1.18; 95% CI 1.13-1.23), cardiometabolic disease (HR 1.07; 95% CI 1.03-1.10), autoimmune disease (HR 1.33; 95% CI 1.26-1.40), and mental ill health (HR 1.37; 95% CI 1.33-1.42) compared to the unexposed group.

Conclusions: In this cohort, periodontal diseases appeared to be associated with an increased risk of developing cardiovascular, cardiometabolic, autoimmune diseases and mental ill health. Periodontal diseases are very common; therefore, an increased risk of other chronic diseases represent a substantial public health burden.

Keywords: chronic disease; epidemiology; gingivitis; oral health; periodontitis

Strengths and limitations:

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- This is the largest epidemiological study exploring the health outcomes of periodontal disease using primary care records
- This was the first study to explore and quantify the association between mental ill health and periodontal diseases
- Periodontal coding was not validated prior to this study so there may be misclassification bias
- Outcomes of interest were adjusted for known covariates recorded in primary care

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INTRODUCTION

Poor oral health is extremely common and is frequently characterised by chronic inflammation.[1] Advanced stages manifest as periodontitis where there is irreversible damage to local bone and tissue.[2] Earlier stages include gingivitis, a reversible inflammation of the gingiva initiated by dental plaque.[2] This spectrum from gingivitis to periodontitis, is widely termed 'periodontal diseases.[2,3] Although, the exact aetiological mechanisms have yet to be fully elucidated, the development of a dysbiotic microbial biofilm, overactivation of inflammatory pathways and genetic susceptibility are all implicated.[2,4–6]

Progressive periodontal disease leads to a reduction in quality of life (QoL) due to problems relating with mastication (due to tooth loss), aesthetics (due to gum recession) and verbal communication.[2,7,8] Periodontal disease also results in a systemic pro-inflammatory state which in itself is implicated in the aetiology of chronic diseases including cardiovascular disease (CVD), cardiometabolic disease (CMD), mental ill health (MIH) and autoimmune disease (AID), each of which are highly prevalent and potentially preventable causes of global morbidity and mortality.[1,9–17] Therefore, a high prevalence of periodontal disease could translate to a substantial burden of morbidity and associated mortality. Epidemiological data have demonstrated associations between periodontitis and all-cause mortality in Western European males (aHR 1.57; 95% CI 1.04-2.36).[18] Although, this relationship could be explained through activation of a pro-inflammatory state, there is a lack of robust epidemiological evidence as many of these chronic diseases share similar pathogenic pathways, often mediated by lifestyle factors including smoking and socioeconomic status.[2,19–22]

The association between periodontal disease and CVD is one of the more commonly researched. In 2012, the American Heart Association highlighted that, despite the literature supporting an association between periodontitis and atherosclerotic disease independent of known confounders, due to methodological limitations of available observational studies they were not able to confirm a causal relationship.[23] Existing studies are limited by an inability to distinguish reverse causality or account for recall bias (case-control or cross sectional designs), absence of adequate confounder control, lack of generalisability to other

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populations and heterogeneity in definitions of exposure and outcomes.[23–25] A 2019 joint workshop held between the European Federation of Periodontology (EFP) and World Heart Federation (WHF) confirmed robust evidence for positive associations between periodontitis and cardiovascular/cerebrovascular disease including an increased risk of first cardiac or cerebrovascular event in patients with severe periodontitis.[26]

A recent review from the US Centre for Disease Control (CDC) assessed the relationships between periodontal disease and other chronic diseases suggested that after CVD, the next most frequent association with periodontal disease was with levels of type 2 diabetes mellitus (T2DM) control. Emerging randomised trials suggest that treatment of periodontal disease reduces Hba1c levels in patients with diabetes[27–29].[28] However, there is limited evidence exploring the risk of T2DM subsequent to periodontal disease and further investigation is needed.[30] Existing evidence suggests an association with autoimmune diseases such as rheumatoid arthritis (RA) and Sjogren's syndrome (SS), however, this is yet to be validated in longitudinal cohort datasets accounting for important covariates.[31–33] Few studies have explored the association between periodontal disease and subsequent mental ill health though a bi-directional mechanism relating to inflammation, psychosocial effects and the impact of psychopharmacological therapies has been proposed.[34,35]

It is important to strengthen understanding of the link between oral health and chronic diseases as cost-effective dental interventions are available that could be preventive, reducing the subsequent public health burden of disease.[2] Therefore, we have conducted the first retrospective cohort study using a large medical dataset to explore the association between poor oral health and a range of chronic diseases including CVD, CMD, MIH and AID.

METHODS

Study design and data source

This study is a population based, retrospective open cohort study utilising IQVIA Medical Research Data (IMRD-UK), previously known as The Health Improvement Network (THIN)

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database. The study period was set between 1st January 1995 and 1st January 2019. An open cohort study allows patients to enter and exit the study at different time points, with each patient only contributing person years of follow-up from the time of cohort entry (index date) to the time they leave the cohort (exit date).

During this study period, the database consisted of pseudo-anonymised electronic medical records of more than 15 million patients derived from 787 general practices using the Vision software system. The database is representative of the UK population in terms of demographic structure and prevalence of key comorbidities.[36] Symptoms, examinations, and diagnoses in THIN are recorded using a hierarchical clinical coding system called Read codes.[37] To improve data quality and reduce under-recording of events, general practices were included 12 months following instalment of electronic practice records or from the practice's acceptable mortality recording date.[38,39] The acceptable mortality reporting date for each practice is when the practice publishes mortality rates similar to the expected rate for their population outlined by the Office for National Statistics (ONS).[38] A total of 8,618,829 patients were eligible to contribute during the study period. The data extraction and cohort selection was facilitated using the data extraction for epidemiological research (DExtER) tool.[40] DExtER utilises an extract, transform and load mechanism to extract study specific data with demonstrated reliability and validity.[40]

Exposure and outcome definition

The purpose of this study was to compare exposed patients (those with a GP recorded code of a periodontal disease, defined as either gingivitis or periodontitis) to unexposed patients (those without such codes) and then calculate their risk of developing chronic diseases defined through Read codes. The chronic disease outcomes were categorised as: CVD (CVD composite measure; heart failure (HF), ischaemic heart disease (HF), stroke/transient-ischaemic attack (TIA), peripheral vascular disease (PVD)), and vascular dementia (VD)), CMD (CMD composite measure; type 2 diabetes mellitus (T2DM), and hypertension (HTN)), AID (AID composite measure; type 1 diabetes mellitus (T1DM), rheumatoid arthritis (RA), systemic lupus erythematous (SLE), Sjogren's syndrome (SS), vitiligo, psoriasis, pernicious anaemia (PA), inflammatory bowel disease (IBD), coeliac disease (CD), autoimmune

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thyroiditis (AT), and scleroderma), and MIH (MIH composite; depression, anxiety and serious mental illness (SMI). In addition, this study examined the odds ratio of having any chronic disease at the point of cohort entry (baseline) between the exposed and unexposed groups.

Codes relating to exposure and outcomes were selected with the assistance of general practitioners, public health doctors and a periodontal specialist. Although, the IMRD-UK (previously named the THIN database) has been previously used to examine oral disorders such as temporomandibular joint disorders,[41,42] exposure code lists relating to gingivitis and periodontitis have never been previously validated. Outcome code lists included in this study have been used extensively in previously published work using the same database and many of the conditions included feature in the Quality Outcomes Framework.[43–52] Read code lists relating to exposure terms and outcomes are provided in appendix (eTable 1).

Selection of unexposed group

Each exposed patient was matched with up to four unexposed control patients from the remaining sample of patients in the dataset, who had no previously documented code relating to exposure. Controls were taken from a pool from eligible patients registered at a general practice within the same country of the UK and were matched by age at index date (+/- one year), sex, Townsend deprivation index[53] and registration date (+/- 12 months). The Townsend score is a measure of material deprivation within a locality, incorporating information on unemployment, household overcrowding and car/home ownership;[53] a higher score indicates a greater level of socioeconomic deprivation.

Follow-up period

The index date for those in the exposed group was the date of the first Read code relating to exposure or when they became eligible to enter the study for those with a previous history of exposure (prevalent cases). Patients aged 18 years or older were eligible for entry into the cohort, therefore those who had the exposure of interest at an earlier age would enter the study as a prevalent case. To mitigate immortality time bias,[54] the same index date was

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assigned to the corresponding unexposed patient. Immortality time bias refers to a period of follow up where death or the study outcome cannot occur. The follow-up period for each patient was from the index date until the exit date. Exit date was defined as the earliest of the following end dates: study end date, last date of data collection from a given general practice, date patient transferred from general practice, date of death or date the outcome of interest occurred.

Statistical analysis

Categorical baseline data were described using proportions and continuous data described using means with standard deviations (sd). Missing data are highlighted in relevant baseline characteristic tables. Missing covariate data were treated as a separate missing category and included in the final analysis. Co-variates considered in our modelling were selected due to their independent relationship with the outcome of interest or to remove any residual confounding. These included: age, sex, body mass index (BMI), Townsend deprivation index (measured in quintiles), smoking status and ethnicity.

To describe the prevalence of chronic disease at baseline, we used logistic regression to estimate unadjusted odds ratio (OR) and adjusted OR (aOR), following adjustment for key covariates (age categories, sex, body mass index categories, Townsend deprivation index, smoking status categories and ethnicity categories). To calculate an incidence rate ((IR) per 1000 person-years) for each of the outcomes of interest, patients with pre-existing chronic disease were excluded to ensure the IR reflected outcomes which occurred following cohort entry. Cox regression accounting for person years of follow-up was then used to calculate a hazard ratio (HR) for each outcome of interest during the study period. Following adjustment for the co-variates, we calculated and presented an adjusted HR (aHR). ORs and HRs are presented with 95% confidence intervals with statistical significance set at $p<0{\cdot}05$.

An initial sensitivity analysis was conducted, isolating incident only cases (where the exposure occurred during the study period) compared to their respective controls. The purpose of this analysis was to exclude patients who may have had the exposure recorded prior to their study eligibility or study start date, leading to an unaccounted period where

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time dependent confounding factors may not have been sufficiently recorded in the patient's medical records. Throughout this paper we use the term periodontal disease to reflect the continuum from gingivitis to periodontitis though we conducted a second sensitivity analysis to examine if the outcomes differed when only examining cases with recorded periodontitis and their respective controls (exclusion of patients with a record of gingivitis and their respective controls). Stata version 15.1 SE software (StataCorp 2017) was used to conduct all analyses.

Patient and public involvement

No patients were actively involved in setting the research question, outcome measures nor involved in the design of the study. Patients were not involved in interpretation or write up of the results, nor are there plans for the results to be disseminated to the patient community affected by this research.

RESULTS

Study characteristics

Of the eligible patients during the study period, we identified 64,379 patients with a recorded history of a periodontal disease, of whom 60,995 had gingivitis and 3,384 had periodontitis, who were matched to 251,161 unexposed patients. The median follow-up was similar in the two groups (exposed: 3.3 years, and unexposed: 3.5 years). The mean age at cohort entry was 44 years and 43% of the cohort were male. Due to matching, smoking status (30% current smokers) and deprivation levels were similar between the groups. Additionally, BMI and ethnicity (despite 56% missing data) profiles were similar between the groups. Further details can be seen in **Table 1**.

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Table 1: Baseline characteristics of the study population

	Primary cohort	
	Exposed n (%)	Unexposed n (%)
All	(n=64,379)	(n=251,161)
Sex (Male)	27699 (43.02)	107977 (42.99)
Age at index date	45.66 (19.12)	45.40 (18.97)
Age categories		
18 - 24 years	10680 (16.59)	42204 (16.80)
25 - 34 years	11266 (17.50)	44556 (17.74)
35 - 44 years	10895 (16.92)	42641 (16.98)
45 - 54 years	10186 (15.82)	39795 (15.84)
55 - 64 years	8917 (13.85)	34621 (13.78)
65 - 74 years	6900 (10.72)	26649 (10.61)

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75 & overs	5535 (8.60)	20695 (8.24)
BMI	26.29 (5.64)	26.27 (5.51)
BMI Categories		
Under/Normal weight (18.5-25)	23743 (36.88)	91020 (36.24)
Overweight (25-30)	16044 (24.92)	63782 (25.39)
Obese (>30)	10857 (16.86)	40589 (16.16)
Missing	13735 (21.33)	55770 (22.20)
Townsend quintiles		
1 (Least deprived)	11548 (17.94)	42631 (16.97)
2	10868 (16.88)	38909 (15.49)
3	12216 (18.98)	43494 (17.32)
4	12005 (18.65)	41440 (16.50)
5 (Most deprived)	9610 (14.93)	30831 (12.28)
Missing	8132 (12.63)	53856 (21.44)
Smoking categories		
Non-smoker	29100 (45.20)	114513 (45.59)
Smoker	19279 (29.95)	75155 (29.92)
Ex-smoker	11107 (17.25)	42647 (16.98)
Missing	4893 (7.60)	18846 (7.50)
Ethnicity		
Caucasian	24327 (37.79)	96169 (38.29)
Mixed race	477 (0.74)	1860 (0.74)
Other	215 (0.33)	925 (0.37)
Black	937 (1.46)	2951 (1.17)
South Asian	2512 (3.90)	4340 (1.73)
Missing	35911 (55.78)	144916 (57.70)

Chronic disease at cohort entry

At cohort entry there were 6,355 patients (9.9%) in the exposed group who had a diagnosis of CVD compared to 18,594 (7.4%) in the unexposed group. Following adjustment for co-variates this translated to an aOR of 1.43 (95% CI 1.38-1.48). When examining CMD, 12,321 patients (19.1%) in the exposed group had a diagnosis of CMD at cohort entry compared to 42,828 (17.1%) in the unexposed group. This translated into an aOR of 1.16 (95% CI 1.13-1.19), and the association with the presence of T2DM (aOR 1.23; 95% CI 1.18-1.28) was notable. With AID, 5,265 patients (8.2%) in the exposed group had a diagnosis of AID at cohort entry compared to 15,690 (6.3%) in the unexposed group equating to an aOR of 1.33 (95% CI 1.28-1.37). Lastly, MIH was seen to have the greatest odds ratio (aOR 1.79; 95% CI

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1.75-1.83) with periodontal disease at cohort entry with 19,142 patients (29.7%) in the exposed group who had a diagnosis of AID at cohort entry compared to 48,998 (19.5%) in the unexposed group. Further results can be seen in **Table 2** and **Figure 1.**

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Table 2: Risk of chronic diseases at baseline in patients exposed and unexposed to periodontal diseases

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	6,355 (9.87)	18,594 (7.40)	977 (1.52)	2,608 (1.04)	3,963 (6.16)	11,759 (4.68)	2,161 (3.36)	6,154 (2.45)	860 (1.34)	2,345 (0.93)
OR (95% CI)*	1.37 (1.33-1.41)		1.47 (1.36-1.58)		1.34 (1.29-1.39)		1.38 (1.32-1.45)		1.44 (1.33-1.55)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.43 (1.38-1.48)		1.43 (1.32-1.54)		1.34 (1.28-1.39)		1.36 (1.29-1.44)		1.37 (1.26-1.49)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	146 (0.23)	363 (0.14)	12,321 (19.14)	42,828 (17.05)	3,432 (5.33)	10,342 (4.12)	10,841 (16.84)	38,649 (15.39)	5,265 (8.18)	15,690 (6.25)
OR (95% CI)*	1.57 (1.30-1.90)		1.15 (1.13-1.18)		1.31 (1.26-1.36)		1.11 (1.09-1.14)		1.34 (1.29-1.38)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.47 (1.20-1.79)		1.16 (1.13-1.19)		1.23 (1.18-1.28)		1.11 (1.08-1.15)		1.33 (1.28-1.37)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	

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	Type 1 diabetes mellitus		Rheumatoid arthritis		Systemic lupus erythematosus		Sjogren		Vitiligo	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	591 (0.92)	1,473 (0.59)	656 (1.02)	1,786 (0.71)	164 (0.25)	346 (0.14)	103 (0.16)	189 (0.08)	239 (0.37)	629 (0.25)
OR (95% CI)*	1.57 (1.43-1.73)		1.44 (1.31-1.57)		1.85 (1.54-2.23)		2.13 (1.67-2.71)		1.48 (1.28-1.72)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.55 (1.41-1.71)		1.39 (1.27-1.53)		1.79 (1.48-2.16)		1.99 (1.56-2.54)		1.40 (1.20-1.62)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	2,615 (4.06)	8,105 (3.23)	231 (0.36)	738 (0.29)	560 (0.87)	1,767 (0.70)	206 (0.32)	576 (0.23)	209 (0.32)	721 (0.29)
OR (95% CI)*	1.27 (1.21-1.33)		1.22 (1.05-1.42)		1.24 (1.13-1.36)		1.40 (1.19-1.64)		1.13 (0.97-1.32)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p=0.12	
aOR (95% CI)**	1.27 (1.21-1.33)		1.16 (1.00-1.35)		1.24 (1.12-1.36)		1.40 (1.19-1.65)		1.12 (0.96-1.31)	
P value	p<0.01		p=0.05		p<0.01		p<0.01		p=0.16	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed

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Total number of patients	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161	64,379	251,161
Number of patients with condition at baseline, n(%)	42 (0.07)	94 (0.04)	19,142 (29.73)	48,998 (19.51)	13,496 (20.96)	34,415 (13.70)	9,623 (14.95)	22,093 (8.80)	1,242 (1.93)	2,905 (1.16)
OR (95% CI)*	1.74 (1.21-2.51)		1.75 (1.71-1.78)		1.67 (1.63-1.71)		1.82 (1.78-1.87)		1.68 (1.57-1.80)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.69 (1.17-2.44)		1.79 (1.75-1.83)		1.69 (1.65-1.73)		1.83 (1.79-1.88)		1.66 (1.55-1.77)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	

* Unadjusted odds ratio, OR: odds ratio, aOR: adjusted odds ratio

** Adjusted odds ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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The risk of developing subsequent chronic disease

During the study period there were 3,104 (5.4%) new diagnoses of CVD in the exposed cohort equating to an IR of 8.2 per 1000 person-years compared to 7.3 per 1000 person-years (10,439 (4.5%) new recorded diagnoses) in the unexposed cohort. This translated to an aHR of 1.18 (95% CI 1.13-1.23). When examining CMD, there were 5,005 (9.6%) new diagnoses of CMD in the exposed cohort equating to an IR of 15.5 per 1000 person-years compared to 14.6 per 1000 person-years (17,822 (8.6%) new recorded diagnoses) in the unexposed cohort. Ultimately this translated into an aHR of 1.07 (95% CI 1.03-1.10) where the risk was highest for the development of T2DM (aHR 1.26; 95% CI 1.21-1.32). When examining AID, there were 1,945 (3.3%) new diagnoses of AID in the exposed cohort equating to an IR of 5.8 per 1000 person-years compared to 4.3 per 1000 person-years (5,674 (2.4%) new recorded diagnoses) in the unexposed cohort. This translated into an aHR of 1.33 (95% CI 1.26-1.40). Finally, with MIH, there were 5,296 (11.7%) new diagnoses of MIH in the exposed cohort relating to an IR of 19.2 per 1000 person-years compared to 14.2 per 1000 person-years (16,758 (8.3%) new recorded diagnoses) in the unexposed cohort. This translated into an aHR of 1.37 (95% CI 1.33-1.42). Further details can be seen on **Table 3 and Figure 2.**

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Table 3: Risk of subsequent development of chronic diseases in patients exposed and unexposed to periodontal diseases

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	58,024	232,567	63,402	248,553	60,416	239,402	62,218	245,007	63,519	248,816
Number of outcomes, n(%)	3,104 (5.35)	10,439 (4.49)	906 (1.43)	2,913 (1.17)	1,535 (2.54)	4,821 (2.01)	1,524 (2.45)	4,956 (2.02)	615 (0.97)	1,716 (0.69)
Person-years	379,982	1,433,611	423,176	1,560,448	398,431	1,489,663	413,659	1,531,088	422,593	1,560,781
IR (per 1000 person-years)	8.17	7.28	2.14	1.87	3.85	3.24	3.68	3.24	1.46	1.1
Follow-up, Median(IQR)	5.49 (2.36-9.85)	5.00 (2.07-9.33)	5.62 (2.45-10.10)	5.15 (2.14-9.51)	5.52 (2.39-9.95)	5.08 (2.11-9.42)	5.59 (2.44-10.04)	5.11 (2.12-9.46)	5.59 (2.43-10.05)	5.14 (2.14-9.50)
HR (95% CI)*	1.12 (1.07-1.16)		1.14 (1.06-1.23)		1.19 (1.12-1.26)		1.13 (1.07-1.20)		1.32 (1.20-1.45)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.18 (1.13-1.23)		1.15 (1.07-1.24)		1.22 (1.16-1.30)		1.16 (1.10-1.23)		1.32 (1.20-1.45)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	64,233	250,798	52,058	208,333	60,947	240,819	53,538	212,512	59,114	235,471
Number of outcomes, n(%)	262 (0.41)	849 (0.34)	5,005 (9.61)	17,822 (8.55)	2,654 (4.35)	7,762 (3.22)	4,146 (7.74)	15,340 (7.22)	1,945 (3.29)	5,674 (2.41)
Person-years	429,726	1,578,418	323,472	1,218,325	397,557	1,486,326	335,761	1,252,770	334,525	1,325,645
IR (per 1000 person-years)	0.61	0.54	15.47	14.63	6.68	5.22	12.35	12.24	5.81	4.28
Follow-up, Median(IQR)	5.63 (2.46-10.12)	5.17 (2.15-9.51)	5.10 (2.16-9.38)	4.61 (1.90-8.82)	5.44 (2.34-9.83)	5.01 (2.08-9.34)	5.16 (2.19-9.48)	4.67 (1.92-8.89)	4.34 (1.73-8.60)	4.34 (1.73-8.54)

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HR (95% CI)*	1.12 (0.97-1.29)		1.05 (1.02-1.09)		1.27 (1.22-1.33)		1.01 (0.97-1.04)		1.34 (1.28-1.41)	
P value	p=0.11		p<0.01		p<0.01		p=0.73		p<0.01	
aHR (95% CI)**	1.12 (0.97-1.29)		1.07 (1.03-1.10)		1.26 (1.21-1.32)		1.02 (0.98-1.05)		1.33 (1.26-1.40)	
P value	p=0.12		p<0.01		p<0.01		p=0.33		p<0.01	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	63,788	249,688	63,723	249,375	64,215	250,815	64,276	250,972	64,140	250,532
Number of outcomes, n(%)	144 (0.23)	283 (0.11)	298 (0.47)	819 (0.33)	75 (0.12)	143 (0.06)	77 (0.12)	109 (0.04)	115 (0.18)	293 (0.12)
Person-years	425,877	1,570,752	425,066	1,565,997	429,121	1,578,247	429,555	1,579,238	428,400	1,575,663
IR (per 1000 person-years)	0.34	0.18	0.7	0.52	0.17	0.09	0.18	0.07	0.27	0.19
Follow-up, Median(IQR)	5.62 (2.45-10.10)	5.16 (2.15-9.51)	5.61 (2.45-10.08)	5.15 (2.14-9.51)	5.62 (2.45-10.11)	5.17 (2.15-9.51)	5.63 (2.46-10.10)	5.17 (2.15-9.51)	5.62 (2.45-10.10)	5.16 (2.15-9.51)
HR (95% CI)*	1.89 (1.55-2.32)		1.33 (1.17-1.52)		1.93 (1.46-2.56)		2.58 (1.92-3.45)		1.45 (1.17-1.80)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.80 (1.47-2.20)		1.33 (1.16-1.52)		1.93 (1.46-2.56)		2.51 (1.87-3.38)		1.37 (1.10-1.71)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	61,764	243,056	64,148	250,423	63,819	249,394	64,173	250,585	64,170	250,440
Number of outcomes, n(%)	892 (1.44)	2,799 (1.15)	156 (0.24)	463 (0.18)	228 (0.36)	667 (0.27)	121 (0.19)	334 (0.13)	99 (0.15)	298 (0.12)
Person-years	408,643	1,514,347	428,404	1,574,721	425,814	1,566,813	428,547	1,575,926	428,443	1,574,813
IR (per 1000 person-years)	2.18	1.85	0.36	0.29	0.54	0.43	0.28	0.21	0.23	0.19

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Follow-up, Median(IQR)	5.55 (2.42-9.98)	5.09 (2.11-9.44)	5.62 (2.46-10.10)	5.16 (2.15-9.51)	5.61 (2.45-10.09)	5.15 (2.14-9.51)	5.62 (2.45-10.10)	5.16 (2.15-9.51)	5.62 (2.45-10.09)	5.16 (2.15-9.51)
HR (95% CI)*	1.18 (1.10-1.27)		1.24 (1.03-1.48)		1.26 (1.08-1.46)		1.33 (1.08-1.64)		1.22 (0.97-1.53)	
P value	p<0.01		p=0.02		p<0.01		p<0.01		p=0.08	
aHR (95% CI)**	1.17 (1.09-1.27)		1.23 (1.02-1.47)		1.25 (1.08-1.46)		1.33 (1.08-1.64)		1.19 (0.95-1.50)	
P value	p<0.01		p=0.03		p<0.01		p<0.01		p=0.13	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	64,337	251,067	45,237	202,163	50,883	216,746	54,756	229,068	63,137	248,256
Number of outcomes, n(%)	16 (0.02)	45 (0.02)	5,296 (11.71)	16,758 (8.29)	4,197 (8.25)	12,706 (5.86)	3,331 (6.08)	9,230 (4.03)	400 (0.63)	925 (0.37)
Person-years	430,156	1,580,157	275,375	1,184,298	318,974	1,299,096	345,927	1,386,791	421,760	1,561,193
IR (per 1000 person-years)	0.04	0.03	19.23	14.15	13.16	9.78	9.63	6.66	0.95	0.59
Follow-up, Median(IQR)	5.63 (2.46-10.11)	5.17 (2.15-9.51)	4.93 (2.08-9.21)	4.61 (1.89-8.87)	5.14 (2.19-9.48)	4.77 (1.96-9.10)	5.23 (2.23-9.53)	4.88 (2.02-9.17)	5.62 (2.46-10.10)	5.16 (2.14-9.51)
HR (95% CI)*	1.30 (0.74-2.31)		1.36 (1.32-1.41)		1.35 (1.31-1.40)		1.45 (1.39-1.51)		1.61 (1.43-1.81)	
P value	p=0.36		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.32 (0.75-2.35)		1.37 (1.33-1.42)		1.36 (1.31-1.41)		1.44 (1.38-1.50)		1.59 (1.41-1.79)	
P value	p=0.34		p<0.01		p<0.01		p<0.01		p<0.01	

* Unadjusted hazard ratio, IR: incidence rate, HR: hazard ratio, aHR: adjusted hazard ratio

** Adjusted hazard ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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Sensitivity analysis: Incident only cohort

Of the total exposed cohort, 31,968 (49.7% of total exposed cohort) patients had an exposure code entered during the study period (incident cohort) and were matched to 126,278 (50.3% of total unexposed cohort) unexposed cohort (baseline characteristics are described in **eTable 2**). The median follow-up in this cohort was 3.4 years. The average age was 49 years, 43% of cohort were male and the proportion of obese patients, current smokers and deprivation quintiles were similar with the primary analysis.

In the incident only sensitivity analysis, the odds ratio of having chronic disease were similar to the primary cohort. There was an increased aOR of having CVD (1.42; 95% CI 1.36-1.49), CMD (1.14; 95% CI 1.10-1.19), AID (1.26; 95% CI 1.21-1.32) and MIH (1.71; 95% CI 1.66-1.76). Further details in appendix **(eTable 3).** When examining subsequent disease outcomes, there also remained an increased risk (described as an aHR) of developing CVD (1.17; 95% CI 1.10-1.24), CMD (1.07; 95% CI 1.02-1.12), AID (1.48; 95% CI 1.37-1.59) and MIH (1.47; 95% CI 1.40-1.53). Further details in appendix **(eTable 4)**.

Sensitivity analysis: Periodontitis only cohort

When restricting the analysis to only those with periodontitis, the exposed cohort of 3,384 patients (5.3% of the total exposed group) were matched to 12,893 patients (5.1% of the unexposed group). The median follow-up in this cohort was 3.6 years. The average age was 48 years, 46% of cohort were male and the proportion of other baseline characteristics were also similar to the primary analysis. Further details in appendix **(eTable 5)**.

In this analysis, the odds ratio of having chronic disease were similar to the primary cohort. There was an increased aOR of having CVD (1.50; 95% CI 1.30-1.74), CMD (1.19; 95% CI 1.06-1.34), AID (1.32; 95% CI 1.15-1.52) and MIH (1.63; 95% CI 1.49-1.78). Further details can be seen in appendix **(eTable 6)**. When examining subsequent disease outcomes, an increased risk (aHR) remained for developing CVD (1.31; 95% CI 1.12-1.52) and MIH (1.33;

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95% CI 1.16-1.52) but not for CMD (0.96; 95% CI 0.85-1.10) and AID (1.21; 95% CI 0.96-1.51). Further details demonstrated in appendix **(eTable 7)**.

DISCUSSION

Summary of key results

To our knowledge, this is the first attempt to synthesise data exploring the relationship between periodontal diseases and the development of chronic disease in a UK retrospective cohort derived from medical records. Our study demonstrates that the presence of a GP recorded diagnosis of a periodontal disease is moderately associated with an 18%, 7% (Although 26% risk of T2DM), 33% and 37% increased risk of CVD, CMD, AID and MIH respectively. This risk persisted when analysing patients who were diagnosed with a periodontal disease during the study period. However, in patients specifically with periodontitis, this risk was not evident for CMD or AID.

Results in context of current literature

To date, research evaluating the association between periodontal diseases and systemic health has focussed on periodontitis, rather than gingivitis, due to the more extensive inflammatory process and thus the potential for greater systemic effects.

This study concurs with the extensive literature highlighting the association of atherosclerotic diseases with periodontal disease. Humphrey et al, demonstrated a risk ratio of 1.24 (95 % CI 1.01 – 1.51) of a CVD/CHD event in the presence of periodontitis.[55] More recently a systematic review by Dietrich et al, demonstrated there was an increased risk of CVD when considering various periodontal disease measures ranging from probing pocket depth measurements to radiographic assessments of bone levels.[56] For those studies where severe periodontitis was the exposure, the associations with ACVD were stronger than in

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our study. This may be due to limitations in our coding, whereby we were unable to classify the severity of periodontitis.

There are several potential mechanisms explaining the increase in atherosclerosis in patients with periodontitis. Firstly, transient bacteraemia in patients with periodontitis may be pathogenic.[57] Furthermore, periodontitis patients have elevated circulating levels of pro-inflammatory mediators implicated in atherosclerosis.[58] There is robust evidence that treatment of periodontitis improves markers of systemic inflammation and surrogate markers of CVD risk such as flow-mediated dilatation.[59,60]

T2DM demonstrates a bi-directional relationship with periodontitis i.e. poorly controlled diabetes is a risk factor for periodontitis and periodontitis itself impacts the diabetes disease process. A systematic review commissioned by the International Diabetes Federation and EFP [61] concluded that individuals with periodontitis have a greater risk of developing T2DM with a HR 1.19 –1.33 which is in agreement with the increased aHR demonstrated in this study. Literature also exists investigating the impact of periodontal therapy on diabetic outcomes. A recent review demonstrates reductions in HbA1c (-0.40% at 3 months) following periodontal therapy.[62] Evidence suggests appropriate targeted screening in dental settings may successfully identify cases of undiagnosed diabetes.[63,64] Within the UK there is a drive to utilise the dental team in identifying and managing T2DM, evident by the recent publication of the NHS England Commissioning Standard '*Dental Care for People with Diabetes.*'[65] This document proposes a formalised pathway between general medical practitioner and dentist upon diagnosis of T2DM.

Whilst the evidence base for T2DM is long established, there is limited evidence that Type 1 Diabetes (T1DM) demonstrates a similar relationship. Systematic reviews conducted in 2013 and 2018 were unable to find any studies that met eligibility criteria investigating the association between periodontal health and T1DM.[61,66] The reason for this may be that the age of periodontal disease diagnosis is typically much older than the age of T1DM diagnosis which limits the available data to answer such a question. Our study suggests an increased risk for incident Type 1 Diabetes in patients with a periodontal disease (aHR 1.80; CI 1.47-2.20) but was not clearly evident when considering only those patients with periodontitis (aHR 1.62; CI 0.70-3.76).

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The mechanisms connecting mental health with periodontal inflammation include both behavioural and immunological. Existing literature focuses on depression and anxiety as risk factors for periodontitis. Individuals under increased stress may reduce health promoting behaviours (e.g. optimal oral hygiene practices) and instead be driven towards detrimental health behaviours (e.g. smoking). The research linking depression as a risk factor for periodontitis has been contradictory.[67]

Conversely, studies assessing mental health outcomes consequent upon periodontal diseases are sparse. Potential mechanisms underlying such a relation include psychological mechanisms with outcomes of periodontal diseases (e.g. halitosis, loss of teeth, drifting of teeth) impacting negatively on social and functional aspects of life, thus impacting on mood. One study utilised the well-established EuroQoI questionnaire to review oral health in relation to anxiety/depression. In 10% of individuals with increased probing pocket depth (≥6mm) anxiety/depression was experienced 25% of the time.[68] Our study demonstrates a significantly increased risk of all mental health illnesses in patients with a periodontal disease (aOR 1.79; CI 1.75-1.83) and an increased risk of developing a mental health condition (aHR 1.37; CI 1.33-1.42). Whilst severe mental illness in particular did not demonstrate a significant increase in the incident only analysis of the periodontitis cohort, we found that individuals with periodontitis have a 37% increased risk of developing anxiety. Furthermore, within the same periodontitis cohort there was a significantly higher risk of developing depression (aHR 1.29; CI 1.11-1.50). This provides further evidence for the potential psychosocial impact of periodontal diseases and an issue that is under-reported in the literature.

Of the autoimmune conditions included within our analysis, the one most frequently reported in the context of periodontitis is RA. A number of mechanisms have been proposed linking the periodontium with the progression of RA. For example *P. gingivalis*, expresses peptidyl arginine deiminases (PADs), which drive protein citrullination. Exposure to citrullinated proteins in periodontitis patients may then lead to the generation of anti-citrullinated protein antibodies (ACPA), stimulating a systemic autoimmune response characteristic of RA.[33] A study analysing the third US National Health and Nutrition Examination Survey (NHANES III) identified that individuals with RA were more likely to

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present with both periodontitis (OR 1.82; CI 1.04 – 3.20) and edentulism (OR 2.27; CI 1.56 – 3.31).[69] Our data support an association between periodontal diseases and development of RA. For periodontitis alone, the increased risk of RA at baseline approached significance, although no significant risk was identified for subsequent development of RA. This may be attributed to the low number of outcomes during this subset analysis and is in agreement with a previous study based on the Taiwanese National Health Insurance Research Database (NHIRD).[70] The Taiwanese study also demonstrated an increased risk of developing Sjogren's syndrome in patients with chronic periodontitis (CP) (HR 1.87; CI 1.64 – 2.13.)[71] Our study also demonstrates the most substantial increased risk ratio was seen in the development of Sjogren's syndrome in those with periodontal diseases (HR 2.51; CI 1.87-3.38), with the periodontitis only cohort showing a substantial increased hazard ratio; however, the low number of outcomes means that the results must be interpreted with caution (aHR 6.67; CI 1.66-26.86). Despite these significant findings, the pathophysiology explaining this relationship is well understood. It is apparent that both conditions may present with xerostomia leading to bacterial overgrowth in the oral cavity and over expression of pro-inflammatory cytokines which may in turn act as risk factors for either periodontal disease or Sjogren's syndrome progression.[32] In addition to the known relationship between successful periodontal treatment and glycaemic management, there is an emerging field of literature identifying that periodontal treatment can lower levels of oral bacteria and circulating inflammatory markers.[72] Although, the relevance on how this relationship may translate into clinical endpoints such as the reduced incidence of chronic conditions is still unclear and requires further research.

Limitations

The primary limitation is that the validity of the results rely upon the accuracy of documentation by the healthcare professionals contributing to the dataset. To date, the accuracy of oral health read codes in primary care datasets have not been validated[73]. However, it is important to highlight that in the UK GPs are not usually the professionals responsible for diagnosing periodontal disease and this is typically identified by dental

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practitioners based on a clinical examination. Periodontal Read codes are thus likely to be inputted following receipt of clinical letters from dental healthcare professional, though GP diagnosis (more likely for gingivitis) and self-report are also possibilities. Overall, it is likely that there is under recording of periodontal diseases in this data set i.e. it is likely that patients with a periodontal disease are not recorded as having it. Therefore, it is possible our findings may not reflect the true effect size and are likely to be an underestimate. On the other hand, selective recording of severe periodontal disease might have led to an overestimation of the true effect size.

Conclusion

In conclusion, this study demonstrates that periodontal diseases (including gingivitis and periodontitis) are moderately associated with an increased risk of developing cardiovascular, cardiometabolic, autoimmune diseases and mental ill health; and these were statistically significant. With this in mind, it is important to highlight patients with periodontal diseases and to tackle risk factors to prevent the development and progression of such conditions. It is imperative that preventative approaches, including those aimed at preventing and detecting gingival inflammation and its associated consequences, and improved communication between medical and dental teams, are implemented to reduce the risk of ill health. We also stress the importance of improving dental coding as per the 2017 periodontal classification system in general practice settings to support holistic patient care and oral epidemiological research.[74] An important implication of our findings is the need for effective communication between dental and other health care professionals to ensure patients obtain an effective treatment plan targeting both oral and extra-oral health to improve current health and reduce the risk of future ill health.

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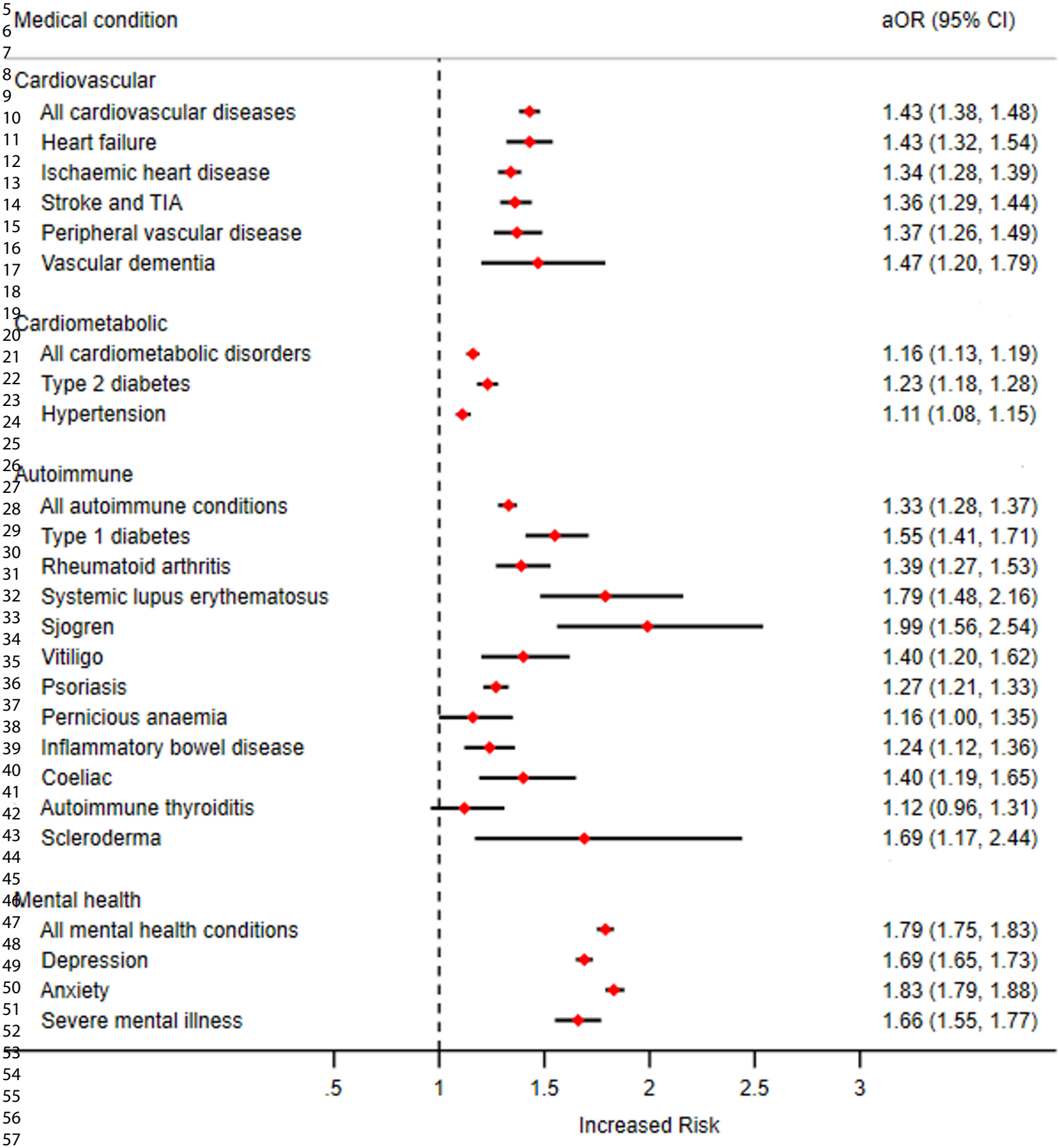
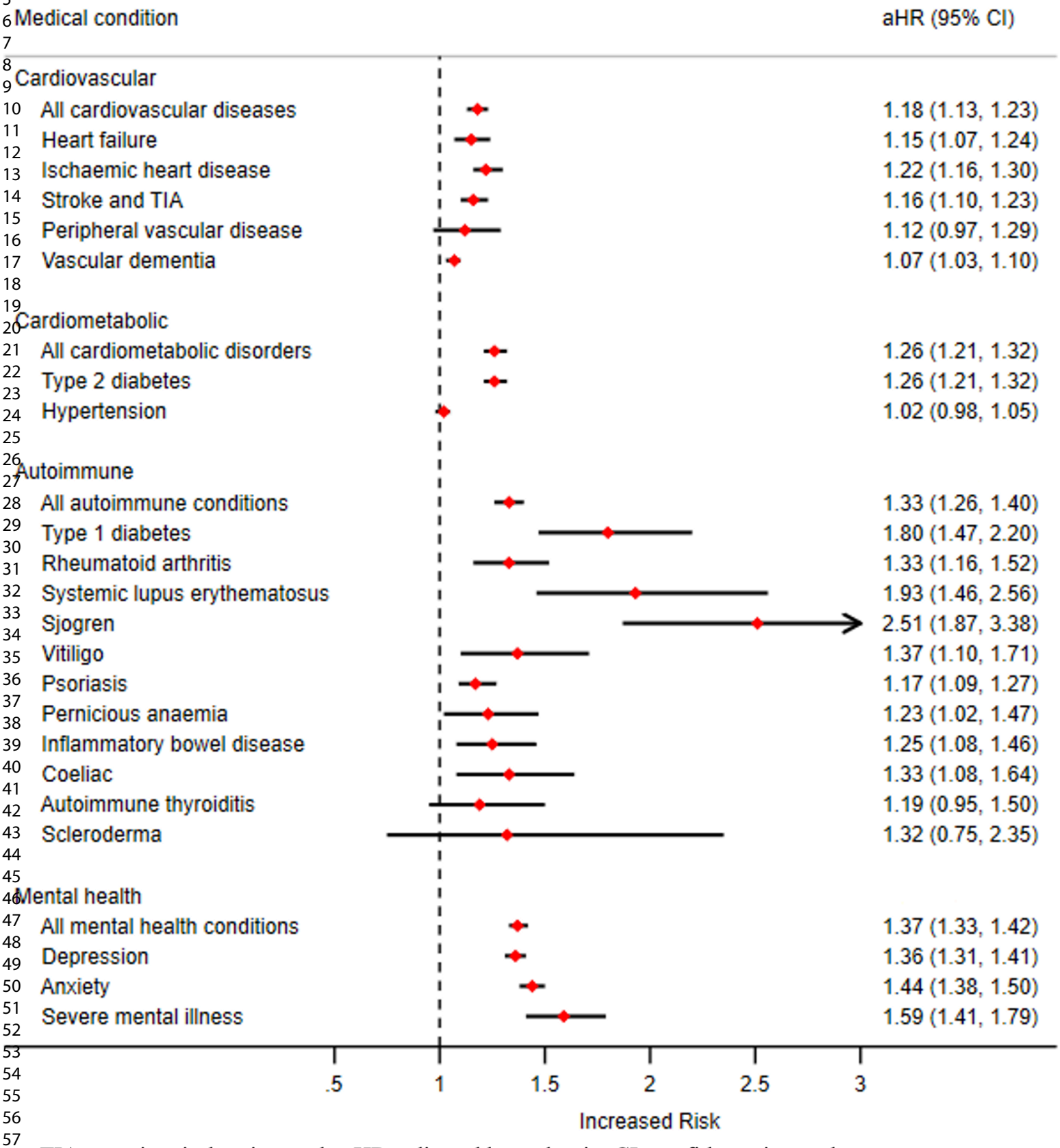


TIA: transient ischemic attack, aOR: adjusted odds ratio, CI: confidence interval



TIA: transient ischemic attack, aHR: adjusted hazard ratio, CI: confidence interval

Supplementary materials

eTable 1. Read codes for periodontal disease exposure.

Gingivitis

Code	Description
2552	O/E - gingivitis
2556	O/E - bleeding gums
J031z00	Chronic gingivitis NOS
1928	Bleeding gums
J030.00	Acute gingivitis
J031.11	Gingivitis
J031.00	Chronic gingivitis
J031300	Hyperplastic gingivitis
J031200	Desquamative gingivitis
J031100	Ulcerative gingivitis
J03..11	Gingivitis/gingival disease
J031000	Simple marginal gingivitis
J03z.00	Gingival and periodontal disease NOS

Periodontitis

Code	Description
J033200	Paradontal abscess
J034400	Alveolar pyorrhoea
J033300	Periodontal abscess
J03..12	Periodontal disease
J033.00	Acute periodontitis
2553	O/E - pyorrhoea
J051200	Loss of teeth due to local periodontal disease
J034200	Chronic periodontitis simplex
J033z00	Acute periodontitis NOS
J034.00	Chronic periodontitis
J035.00	Periodontosis
J034z00	Chronic periodontitis NOS

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eTable 2. Baseline characteristics of the incident cohort

	Incident cohort	
	Exposed n (%)	Unexposed n (%)
All	(n=31,968)	(n=126,278)
Sex (Male)	13715 (42.90)	54062 (42.81)
Age at index date	48.77 (18.77)	48.59 (18.67)
Age categories		
18 - 24 years	3788 (11.85)	15081 (11.94)
25 - 34 years	4921 (15.39)	19604 (15.52)
35 - 44 years	5381 (16.83)	21272 (16.85)
45 - 54 years	5411 (16.93)	21518 (17.04)
55 - 64 years	5124 (16.03)	20212 (16.01)
65 - 74 years	4028 (12.60)	15908 (12.60)
75 & overs	3315 (10.37)	12683 (10.04)
BMI	26.60 (5.73)	26.62 (5.62)
BMI Categories		
Under/Normal weight (18.5-25)	11755 (36.77)	45183 (35.78)
Overweight (25-30)	8573 (26.82)	34623 (27.42)
Obese (>30)	6192 (19.37)	23359 (18.50)
Missing	5448 (17.04)	23113 (18.30)
Townsend quintiles		
1 (Least deprived)	5813 (18.18)	21910 (17.35)
2	5346 (16.72)	19600 (15.52)
3	6118 (19.14)	22190 (17.57)
4	6079 (19.02)	21452 (16.99)
5 (Most deprived)	4810 (15.05)	15776 (12.49)
Missing	3802 (11.89)	25350 (20.07)
Smoking categories		
Non-smoker	14514 (45.40)	57617 (45.63)
Smoker	9452 (29.57)	37338 (29.57)
Ex-smoker	6494 (20.31)	25445 (20.15)
Missing	1508 (4.72)	5878 (4.65)
Ethnicity		
Caucasian	11976 (37.46)	49505 (39.20)
Mixed race	229 (0.72)	764 (0.61)
Other	101 (0.32)	358 (0.28)
Black	509 (1.59)	1415 (1.12)
South Asian	1510 (4.72)	2154 (1.71)
Missing	17643 (55.19)	72082 (57.08)

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eTable 3. Risk of chronic diseases at baseline in the incident only sensitivity analysis cohort

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278
Number of patients with condition at baseline, n(%)	3,700 (11.57)	11,032 (8.74)	524 (1.64)	1,541 (1.22)	2,352 (7.36)	7,022 (5.56)	1,260 (3.94)	3,660 (2.90)	478 (1.50)	1,388 (1.10)
OR (95% CI)*	1.37 (1.31-1.42)		1.35 (1.22-1.49)		1.35 (1.29-1.42)		1.37 (1.29-1.47)		1.37 (1.23-1.52)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.42 (1.36-1.49)		1.30 (1.18-1.45)		1.35 (1.28-1.42)		1.36 (1.27-1.46)		1.31 (1.18-1.46)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278
Number of patients with condition at baseline, n(%)	89 (0.28)	204 (0.16)	7,488 (23.42)	26,602 (21.07)	2,126 (6.65)	6,773 (5.36)	6,597 (20.64)	23,995 (19.00)	2,833 (8.86)	8,948 (7.09)
OR (95% CI)*	1.73 (1.34-2.21)		1.15 (1.11-1.18)		1.26 (1.20-1.32)		1.11 (1.08-1.14)		1.28 (1.22-1.33)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.64 (1.27-2.12)		1.14 (1.10-1.19)		1.15 (1.09-1.22)		1.10 (1.06-1.15)		1.26 (1.21-1.32)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278

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Number of patients with condition at baseline, n(%)	304 (0.95)	836 (0.66)	403 (1.26)	1,044 (0.83)	104 (0.33)	189 (0.15)	58 (0.18)	119 (0.09)	130 (0.41)	355 (0.28)
OR (95% CI)*	1.44 (1.26-1.64)		1.53 (1.36-1.72)		2.18 (1.71-2.77)		1.93 (1.41-2.64)		1.45 (1.18-1.77)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.40 (1.23-1.61)		1.48 (1.32-1.67)		2.14 (1.68-2.73)		1.79 (1.30-2.47)		1.31 (1.07-1.61)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p=0.01	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278
Number of patients with condition at baseline, n(%)	1,362 (4.26)	4,558 (3.61)	134 (0.42)	457 (0.36)	317 (0.99)	1,031 (0.82)	119 (0.37)	336 (0.27)	104 (0.33)	408 (0.32)
OR (95% CI)*	1.19 (1.12-1.26)		1.16 (0.96-1.41)		1.22 (1.07-1.38)		1.40 (1.14-1.73)		1.01 (0.81-1.25)	
P value	p<0.01		p=0.13		p<0.01		p<0.01		p=0.95	
aOR (95% CI)**	1.19 (1.12-1.27)		1.10 (0.90-1.34)		1.21 (1.07-1.38)		1.41 (1.14-1.74)		0.98 (0.79-1.22)	
P value	p<0.01		p=0.35		p<0.01		p<0.01		p=0.84	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278	31,968	126,278
Number of patients with condition at baseline, n(%)	23 (0.07)	59 (0.05)	10,036 (31.39)	27,197 (21.54)	7,187 (22.48)	19,341 (15.32)	4,894 (15.31)	12,153 (9.62)	703 (2.20)	1,651 (1.31)
OR (95% CI)*	1.54 (0.95-2.49)		1.67 (1.62-1.71)		1.60 (1.56-1.65)		1.70 (1.64-1.76)		1.70 (1.55-1.86)	
P value	p=0.08		p<0.01		p<0.01		p<0.01		p<0.01	

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aOR (95% CI)**	1.45 (0.89-2.37)	1.71 (1.66-1.76)	1.63 (1.58-1.68)	1.71 (1.65-1.78)	1.68 (1.53-1.84)
P value	p=0.14	p<0.01	p<0.01	p<0.01	p<0.01

* Unadjusted odds ratio, OR: odds ratio, aOR: adjusted odds ratio

** Adjusted odds ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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eTable 4. Risk of subsequent development of chronic diseases in the incident only sensitivity analysis

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	28,268	115,246	31,444	124,737	29,616	119,256	30,708	122,618	31,490	124,890
Number of outcomes, n(%)	1,473 (5.21)	5,196 (4.51)	409 (1.30)	1,455 (1.17)	715 (2.41)	2,303 (1.93)	745 (2.43)	2,604 (2.12)	272 (0.86)	784 (0.63)
Person-years	171,643	668,935	193,503	734,319	180,791	698,131	188,372	718,635	193,366	734,953
IR (per 1000 person-years)	8.58	7.77	2.11	1.98	3.95	3.3	3.95	3.62	1.41	1.07
Follow-up, Median(IQR)	5.37 (2.41-8.99)	4.99 (2.19-8.68)	5.46 (2.47-9.12)	5.09 (2.24-8.80)	5.41 (2.43-9.04)	5.05 (2.22-8.75)	5.44 (2.47-9.08)	5.06 (2.23-8.76)	5.45 (2.46-9.11)	5.08 (2.24-8.80)
HR (95% CI)*	1.10 (1.04-1.17)		1.06 (0.95-1.19)		1.20 (1.10-1.30)		1.09 (1.00-1.18)		1.32 (1.15-1.51)	
P value	p<0.01		p=0.27		p<0.01		p=0.04		p<0.01	
aHR (95% CI)**	1.17 (1.10-1.24)		1.07 (0.96-1.20)		1.23 (1.13-1.34)		1.12 (1.03-1.22)		1.32 (1.15-1.52)	
P value	p<0.01		p=0.23		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	31,879	126,074	24,480	99,676	29,842	119,505	25,371	102,283	29,135	117,330
Number of outcomes, n(%)	148 (0.46)	474 (0.38)	2,310 (9.44)	8,363 (8.39)	1,355 (4.54)	3,913 (3.27)	1,881 (7.41)	7,192 (7.03)	964 (3.31)	2,700 (2.30)
Person-years	196,449	743,531	142,524	554,252	179,645	693,204	148,885	572,392	152,881	627,091
IR (per 1000 person-years)	0.75	0.64	16.21	15.09	7.54	5.64	12.63	12.56	6.31	4.31
Follow-up, Median(IQR)	5.47 (2.48-9.13)	5.10 (2.25-8.81)	5.02 (2.21-8.68)	4.68 (2.02-8.32)	5.27 (2.35-8.96)	4.98 (2.18-8.68)	5.09 (2.25-8.72)	4.73 (2.04-8.38)	4.24 (1.75-7.95)	4.41 (1.85-8.05)
HR (95% CI)*	1.17 (0.98-1.41)		1.07 (1.03-1.12)		1.34 (1.26-1.42)		1.01 (0.96-1.06)		1.47 (1.37-1.59)	

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P value	p=0.09		p<0.01		p<0.01		p=0.83		p<0.01	
aHR (95% CI)**	1.20 (1.00-1.45)		1.07 (1.02-1.12)		1.30 (1.22-1.38)		1.01 (0.96-1.06)		1.48 (1.37-1.59)	
P value	p=0.06		p<0.01		p<0.01		p=0.77		p<0.01	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	31,664	125,442	31,565	125,234	31,864	126,089	31,910	126,159	31,838	125,923
Number of outcomes, n(%)	63 (0.20)	120 (0.10)	146 (0.46)	409 (0.33)	45 (0.14)	72 (0.06)	44 (0.14)	63 (0.05)	63 (0.20)	138 (0.11)
Person-years	194,829	739,746	193,993	737,315	196,108	743,639	196,422	744,022	195,815	742,249
IR (per 1000 person-years)	0.32	0.16	0.75	0.55	0.23	0.1	0.22	0.08	0.32	0.19
Follow-up, Median(IQR)	5.46 (2.47-9.13)	5.10 (2.25-8.82)	5.45 (2.47-9.11)	5.09 (2.25-8.80)	5.46 (2.47-9.13)	5.10 (2.25-8.81)	5.47 (2.47-9.13)	5.10 (2.25-8.81)	5.46 (2.47-9.12)	5.10 (2.25-8.81)
HR (95% CI)*	2.01 (1.48-2.72)		1.35 (1.12-1.64)		2.37 (1.64-3.45)		2.64 (1.79-3.87)		1.74 (1.29-2.34)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.84 (1.35-2.51)		1.37 (1.13-1.66)		2.45 (1.68-3.57)		2.57 (1.74-3.80)		1.59 (1.18-2.16)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	30,606	121,720	31,834	125,821	31,651	125,247	31,849	125,942	31,864	125,870
Number of outcomes, n(%)	443 (1.45)	1,294 (1.06)	89 (0.28)	243 (0.19)	105 (0.33)	321 (0.26)	56 (0.18)	173 (0.14)	50 (0.16)	144 (0.11)
Person-years	186,612	712,529	195,847	741,633	194,586	737,712	195,911	742,372	196,034	741,787
IR (per 1000 person-years)	2.37	1.82	0.45	0.33	0.54	0.44	0.29	0.23	0.26	0.19
Follow-up, Median(IQR)	5.40 (2.43-9.03)	5.04 (2.22-8.75)	5.46 (2.48-9.12)	5.10 (2.25-8.81)	5.45 (2.47-9.12)	5.10 (2.25-8.81)	5.46 (2.47-9.12)	5.10 (2.25-8.81)	5.46 (2.47-9.12)	5.10 (2.25-8.81)

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HR (95% CI)*	1.31 (1.17-1.46)		1.39 (1.09-1.77)		1.24 (1.00-1.55)		1.23 (0.91-1.66)		1.32 (0.95-1.82)	
P value	p<0.01		p<0.01		p=0.05		p=0.18		p=0.09	
aHR (95% CI)**	1.31 (1.18-1.46)		1.41 (1.10-1.80)		1.23 (0.98-1.53)		1.26 (0.93-1.70)		1.29 (0.93-1.78)	
P value	p<0.01		p<0.01		p=0.07		p=0.14		p=0.12	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	31,945	126,219	21,932	99,081	24,781	106,937	27,074	114,125	31,265	124,627
Number of outcomes, n(%)	5 (0.02)	16 (0.01)	2,450 (11.17)	7,513 (7.58)	1,955 (7.89)	5,746 (5.37)	1,586 (5.86)	4,127 (3.62)	202 (0.65)	418 (0.34)
Person-years	196,725	744,579	124,610	551,747	144,563	605,666	158,613	653,590	192,266	734,597
IR (per 1000 person-years)	0.03	0.02	19.66	13.62	13.52	9.49	10	6.31	1.05	0.57
Follow-up, Median(IQR)	5.47 (2.48-9.13)	5.10 (2.25-8.82)	4.83 (2.13-8.47)	4.69 (2.03-8.35)	5.00 (2.22-8.70)	4.80 (2.09-8.49)	5.08 (2.27-8.73)	4.90 (2.14-8.57)	5.45 (2.47-9.12)	5.10 (2.25-8.81)
HR (95% CI)*	1.19 (0.43-3.24)		1.45 (1.38-1.51)		1.43 (1.36-1.51)		1.58 (1.50-1.68)		1.85 (1.57-2.19)	
P value	p=0.74		p<0.01		p<0.01		p<0.01		p<0.01	
aHR (95% CI)**	1.20 (0.43-3.32)		1.47 (1.40-1.53)		1.45 (1.37-1.52)		1.58 (1.49-1.68)		1.86 (1.57-2.20)	
P value	p=0.72		p<0.01		p<0.01		p<0.01		p<0.01	

* Unadjusted hazard ratio, IR: incidence rate, HR: hazard ratio, aHR: adjusted hazard ratio

** Adjusted hazard ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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eTable 5. Baseline characteristics of the periodontitis cohort

	Periodontitis only cohort	
	Exposed n (%)	Unexposed n (%)
All	(n=3,384)	(n=12,893)
Sex (Male)	1560 (46.10)	5927 (45.97)
Age at index date	48.10 (17.43)	47.81 (17.25)
Age categories		
18 - 24 years	330 (9.75)	1269 (9.84)
25 - 34 years	502 (14.83)	1952 (15.14)
35 - 44 years	650 (19.21)	2515 (19.51)
45 - 54 years	701 (20.72)	2646 (20.52)
55 - 64 years	560 (16.55)	2148 (16.66)
65 - 74 years	369 (10.90)	1368 (10.61)
75 & overs	272 (8.04)	995 (7.72)
BMI	26.49 (5.62)	26.43 (5.43)
BMI Categories		
Under/Normal weight (18.5-25)	1203 (35.55)	4539 (35.21)
Overweight (25-30)	905 (26.74)	3475 (26.95)
Obese (>30)	571 (16.87)	2122 (16.46)
Missing	705 (20.83)	2757 (21.38)
Townsend quintiles		
1 (Least deprived)	584 (17.26)	2128 (16.51)
2	580 (17.14)	2051 (15.91)
3	614 (18.14)	2187 (16.96)
4	644 (19.03)	2135 (16.56)
5 (Most deprived)	520 (15.37)	1616 (12.53)
Missing	442 (13.06)	2776 (21.53)
Smoking categories		
Non-smoker	1359 (40.16)	5221 (40.49)
Smoker	1124 (33.22)	4274 (33.15)
Ex-smoker	585 (17.29)	2224 (17.25)
Missing	316 (9.34)	1174 (9.11)
Ethnicity		
Caucasian	1271 (37.56)	4906 (38.05)
Mixed race	21 (0.62)	67 (0.52)
Other	5 (0.15)	40 (0.31)
Black	45 (1.33)	132 (1.02)
South Asian	82 (2.42)	170 (1.32)
Missing	1960 (57.92)	7578 (58.78)

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eTable 6. Risk of chronic diseases at baseline in the periodontitis only sensitivity analysis cohort

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893
Number of patients with condition at baseline, n(%)	355 (10.49)	971 (7.53)	53 (1.57)	120 (0.93)	244 (7.21)	607 (4.71)	112 (3.31)	297 (2.30)	59 (1.74)	141 (1.09)
OR (95% CI)*	1.44 (1.27-1.64)		1.69 (1.22-2.35)		1.57 (1.35-1.83)		1.45 (1.16-1.81)		1.60 (1.18-2.18)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
aOR (95% CI)**	1.50 (1.30-1.74)		1.71 (1.22-2.41)		1.64 (1.38-1.94)		1.43 (1.14-1.81)		1.57 (1.15-2.15)	
P value	p<0.01		p<0.01		p<0.01		p<0.01		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893
Number of patients with condition at baseline, n(%)	4 (0.12)	18 (0.14)	659 (19.47)	2,221 (17.23)	172 (5.08)	529 (4.10)	590 (17.43)	2,006 (15.56)	286 (8.45)	836 (6.48)
OR (95% CI)*	0.85 (0.29-2.50)		1.16 (1.06-1.28)		1.25 (1.05-1.49)		1.15 (1.04-1.27)		1.33 (1.16-1.53)	
P value	p=0.76		p<0.01		p=0.01		p<0.01		p<0.01	
aOR (95% CI)**	0.71 (0.23-2.19)		1.19 (1.06-1.34)		1.25 (1.03-1.51)		1.17 (1.04-1.32)		1.32 (1.15-1.52)	
P value	p=0.55		p<0.01		p=0.02		p<0.01		p<0.01	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893

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Number of patients with condition at baseline, n(%)	43 (1.27)	79 (0.61)	37 (1.09)	96 (0.74)	10 (0.30)	20 (0.16)	4 (0.12)	9 (0.07)	13 (0.38)	25 (0.19)
OR (95% CI)*	2.09 (1.44-3.03)		1.47 (1.01-2.16)		1.91 (0.89-4.08)		1.69 (0.52-5.50)		1.98 (1.01-3.88)	
P value	p<0.01		p=0.05		p=0.10		p=0.38		p=0.05	
aOR (95% CI)**	2.07 (1.42-3.02)		1.44 (0.98-2.13)		1.82 (0.84-3.93)		1.45 (0.44-4.79)		1.99 (1.01-3.92)	
P value	p<0.01		p=0.06		p=0.13		p=0.54		p=0.05	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893
Number of patients with condition at baseline, n(%)	125 (3.69)	437 (3.39)	14 (0.41)	31 (0.24)	36 (1.06)	94 (0.73)	8 (0.24)	32 (0.25)	9 (0.27)	42 (0.33)
OR (95% CI)*	1.09 (0.89-1.34)		1.72 (0.92-3.24)		1.46 (1.00-2.15)		0.95 (0.44-2.07)		0.82 (0.40-1.68)	
P value	p=0.39		p=0.09		p=0.05		p=0.90		p=0.58	
aOR (95% CI)**	1.09 (0.89-1.34)		1.54 (0.81-2.92)		1.45 (0.98-2.14)		0.98 (0.45-2.15)		0.81 (0.39-1.67)	
P value	p=0.40		p=0.19		p=0.06		p=0.97		p=0.57	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Total number of patients, n	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893	3,384	12,893
Number of patients with condition at baseline, n(%)	7 (0.21)	7 (0.05)	1,021 (30.17)	2,745 (21.29)	704 (20.80)	1,942 (15.06)	531 (15.69)	1,252 (9.71)	70 (2.07)	149 (1.16)
OR (95% CI)*	3.82 (1.34-10.89)		1.60 (1.47-1.74)		1.48 (1.35-1.63)		1.73 (1.55-1.93)		1.81 (1.36-2.41)	
P value	p=0.01		p<0.01		p<0.01		p<0.01		p<0.01	

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aOR (95% CI)**	4.18 (1.45-12.10)	1.63 (1.49-1.78)	1.50 (1.36-1.66)	1.74 (1.55-1.94)	1.83 (1.37-2.44)
P value	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01

* Unadjusted odds ratio, OR: odds ratio, aOR: adjusted odds ratio
** Adjusted odds ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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eTable 7. Risk of subsequent development of chronic diseases in the periodontitis only sensitivity analysis

	All cardiovascular disease		Heart failure		Ischaemic heart disease		Stroke/transient-ischaemic attack		Peripheral vascular disease	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,029	11,922	3,331	12,773	3,140	12,286	3,272	12,596	3,325	12,752
Number of outcomes, n(%)	221 (7.30)	646 (5.42)	57 (1.71)	156 (1.22)	106 (3.38)	301 (2.45)	97 (2.96)	311 (2.47)	47 (1.41)	101 (0.79)
Person-years	21,705	80,954	24,737	88,720	22,881	84,397	24,127	86,844	24,625	88,567
IR (per 1000 person-years)	10.18	7.98	2.3	1.76	4.63	3.57	4.02	3.58	1.91	1.14
Follow-up, Median(IQR)	5.92 (2.63-10.83)	5.60 (2.30-10.26)	6.31 (2.81-11.32)	5.83 (2.42-10.46)	6.19 (2.75-11.03)	5.70 (2.36-10.36)	6.23 (2.81-11.15)	5.73 (2.39-10.37)	6.29 (2.77-11.23)	5.83 (2.42-10.48)
HR (95% CI)*	1.27 (1.09-1.48)		1.30 (0.96-1.77)		1.30 (1.04-1.62)		1.12 (0.89-1.41)		1.67 (1.18-2.36)	
P value	p<0.01		p=0.09		p=0.02		p=0.33		p<0.01	
aHR (95% CI)**	1.31 (1.12-1.52)		1.27 (0.94-1.73)		1.35 (1.08-1.69)		1.12 (0.89-1.41)		1.67 (1.18-2.38)	
P value	p<0.01		p=0.12		p<0.01		p=0.34		p<0.01	
	Vascular dementia		**All cardiometabolic disease**		**Type 2 diabetes mellitus**		**Hypertension**		**All autoimmune conditions**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,380	12,875	2,725	10,672	3,212	12,364	2,794	10,887	3,098	12,057
Number of outcomes, n(%)	20 (0.59)	55 (0.43)	303 (11.12)	1,133 (10.62)	173 (5.39)	449 (3.63)	247 (8.84)	982 (9.02)	104 (3.36)	308 (2.55)
Person-years	25,137	89,654	18,750	68,456	23,111	84,508	19,504	70,497	19,592	74,615
IR (per 1000 person-years)	0.8	0.61	16.16	16.55	7.49	5.31	12.66	13.93	5.31	4.13
Follow-up, Median(IQR)	6.31 (2.84-11.32)	5.86 (2.44-10.51)	5.54 (2.38-10.38)	5.16 (2.12-9.61)	6.00 (2.65-10.90)	5.66 (2.34-10.32)	5.67 (2.45-10.54)	5.23 (2.14-9.72)	4.86 (1.93-9.57)	4.89 (1.89-9.45)
HR (95% CI)*	1.27 (0.76-2.12)		0.97 (0.86-1.10)		1.40 (1.18-1.67)		0.90 (0.79-1.04)		1.25 (1.00-1.56)	

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P value	p=0.36		p=0.65		p<0.01		p=0.16		p=0.05	
aHR (95% CI)**	1.23 (0.73-2.07)		0.96 (0.85-1.10)		1.43 (1.20-1.71)		0.91 (0.79-1.05)		1.21 (0.96-1.51)	
P value	p=0.44		p=0.57		p<0.01		p=0.20		p=0.10	
	Type 1 diabetes mellitus		**Rheumatoid arthritis**		**Systemic lupus erythematosus**		**Sjogren**		**Vitiligo**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,341	12,814	3,347	12,797	3,374	12,873	3,380	12,884	3,371	12,868
Number of outcomes, n(%)	8 (0.24)	17 (0.13)	13 (0.39)	51 (0.40)	6 (0.18)	10 (0.08)	6 (0.18)	3 (0.02)	8 (0.24)	9 (0.07)
Person-years	24,868	89,212	24,897	88,889	25,097	89,628	25,152	89,766	25,066	89,569
IR (per 1000 person-years)	0.32	0.19	0.52	0.57	0.24	0.11	0.24	0.03	0.32	0.1
Follow-up, Median(IQR)	6.31 (2.81-11.32)	5.86 (2.44-10.51)	6.31 (2.81-11.32)	5.83 (2.42-10.48)	6.31 (2.84-11.32)	5.86 (2.44-10.51)	6.31 (2.84-11.32)	5.86 (2.44-10.51)	6.31 (2.84-11.32)	5.85 (2.44-10.51)
HR (95% CI)*	1.71 (0.74-3.97)		0.90 (0.49-1.66)		2.13 (0.77-5.86)		7.02 (1.76-28.09)		3.13 (1.21-8.13)	
P value	p=0.21		p=0.74		p=0.14		p<0.01		p=0.02	
aHR (95% CI)**	1.62 (0.70-3.76)		0.96 (0.52-1.77)		2.15 (0.77-6.00)		6.67 (1.66-26.86)		2.90 (1.11-7.61)	
P value	p=0.26		p=0.90		p=0.14		p<0.01		p=0.03	
	Psoriasis		**Pernicious anaemia**		**Inflammatory bowel disease**		**Coeliac**		**Autoimmune thyroiditis**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,259	12,456	3,370	12,862	3,348	12,799	3,376	12,861	3,375	12,851
Number of outcomes, n(%)	49 (1.50)	165 (1.32)	13 (0.39)	25 (0.19)	13 (0.39)	34 (0.27)	5 (0.15)	20 (0.16)	1 (0.03)	12 (0.09)
Person-years	23,982	85,868	25,033	89,510	24,901	89,000	25,106	89,487	25,127	89,498
IR (per 1000 person-years)	2.04	1.92	0.52	0.28	0.52	0.38	0.2	0.22	0.04	0.13
Follow-up, Median(IQR)	6.25 (2.77-11.10)	5.76 (2.39-10.37)	6.31 (2.84-11.25)	5.84 (2.44-10.50)	6.31 (2.81-11.32)	5.85 (2.43-10.50)	6.31 (2.82-11.32)	5.85 (2.44-10.50)	6.31 (2.84-11.32)	5.86 (2.44-10.51)
HR (95% CI)*	1.06 (0.77-1.46)		1.85 (0.95-3.62)		1.35 (0.71-2.57)		0.90 (0.34-2.39)		0.30 (0.04-2.29)	

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P value	p=0.71		p=0.07		p=0.35		p=0.83		p=0.24	
aHR (95% CI)**	1.05 (0.76-1.44)		1.89 (0.96-3.74)		1.35 (0.71-2.57)		0.85 (0.32-2.28)		0.29 (0.04-2.23)	
P value	p=0.78		p=0.07		p=0.36		p=0.75		p=0.23	
	Scleroderma		**All mental health conditions**		**Depression**		**Anxiety**		**Severe mental illness**	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of patients	3,377	12,886	2,363	10,148	2,680	10,951	2,853	11,641	3,314	12,744
Number of outcomes, n(%)	2 (0.06)	3 (0.02)	287 (12.15)	875 (8.62)	224 (8.36)	671 (6.13)	189 (6.62)	521 (4.48)	15 (0.45)	46 (0.36)
Person-years	25,152	89,739	16,121	65,906	18,839	72,978	19,995	77,498	24,744	88,828
IR (per 1000 person-years)	0.08	0.03	17.8	13.28	11.89	9.19	9.45	6.72	0.61	0.52
Follow-up, Median(IQR)	6.31 (2.84-11.32)	5.86 (2.44-10.51)	5.59 (2.33-10.37)	5.24 (2.09-9.85)	5.76 (2.54-10.52)	5.47 (2.21-10.09)	5.77 (2.54-10.63)	5.50 (2.24-10.04)	6.34 (2.86-11.32)	5.86 (2.44-10.51)
HR (95% CI)*	2.40 (0.40-14.36)		1.35 (1.18-1.54)		1.30 (1.12-1.52)		1.41 (1.19-1.66)		1.18 (0.66-2.12)	
P value	p=0.34		p<0.01		p<0.01		p<0.01		p=0.57	
aHR (95% CI)**	2.26 (0.37-13.70)		1.33 (1.16-1.52)		1.29 (1.11-1.50)		1.37 (1.16-1.62)		1.24 (0.69-2.23)	
P value	p=0.37		p<0.01		p<0.01		p<0.01		p=0.47	

* Unadjusted hazard ratio, IR: incidence rate, HR: hazard ratio, aHR: adjusted hazard ratio

** Adjusted hazard ratio: adjusted for age, sex, body mass index, Townsend deprivation index, smoking status and ethnicity at baseline

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Reporting Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods

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Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Methods Results: Table 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Methods/discussion
Study size	10	Explain how the study size was arrived at	Methods

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Methods
		(*c*) Explain how missing data were addressed	Methods
		(*d*) If applicable, explain how loss to follow-up was addressed	Methods
		(*e*) Describe any sensitivity analyses	Methods
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods and results

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		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results and Table 2/3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results and Table 2/3
		(*b*) Report category boundaries when continuous variables were categorized	Results and Table 2/3

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		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Mentioned in results and throughout etables
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			

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Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Highlighted in funding and acknowledgements section

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