

# Increased cardiovascular risk in people with type 2 diabetes and periodontitis: an analysis from a global real-world federated database

Hani Essa,<sup>\*1,2,3</sup> Ingeborg Welters,<sup>1,2,3</sup> Iram Yasin,<sup>4</sup> Alexander E. Henney,<sup>3</sup> Gema Hernandez,<sup>3,5</sup> Sondos Albadri,<sup>6</sup> Sizheng Steven Zhao,<sup>7,8</sup> Gregory Y. H. Lip,<sup>1,3,9,10</sup> Daniel J. Cuthbertson<sup>1,11</sup> and Uazman Alam<sup>1,11,12</sup>

## Key points

Periodontitis is associated with long-term cardiovascular consequences in people with type 2 diabetes.

Public health interventions in people with diabetes could reduce long-term cardiovascular consequences.

Periodontitis in people with type 2 diabetes is associated with a significantly increased risk of cardiovascular complications, including but not limited to, stroke, myocardial infarction, atrial arrhythmias, diabetic retinopathy, and nephropathy.

These findings underscore the potential value of integrating periodontal screening and management into routine diabetes care to help mitigate long-term cardiovascular and microvascular risks in this high-risk population.

## Abstract

**Introduction** Type 2 diabetes (T2D) is a global health challenge conferring significant morbidity and mortality with accelerated cardiovascular, renovascular and cerebrovascular disease. Periodontitis has a higher prevalence in people with diabetes. We aimed to evaluate the risk of incident cardiovascular-related diseases in people with type 2 diabetes with and without periodontitis.

**Methods** We conducted a retrospective cohort study using TriNetX, a global federated health research network of patients  $\geq 18$  years with a diagnosis of T2D after the initiation of insulin. Cohorts were divided based on the absence or presence of periodontitis identified using ICD-10 (International Classification of Diseases) codes. Outcomes were recorded at three years from initiation of insulin. The primary outcomes of interest were: 1) mortality; 2) myocardial infarction; 3) stroke; 4) dementia; 5) atrial fibrillation; 6) atrial flutter; 7) diabetic nephropathy; 8) diabetic retinopathy; and 9) infective endocarditis.

**Results** After propensity score matching (1:1), a total of 56,525 patients were identified in each cohort. At three years, patients with periodontitis had similar mortality risk as the control group (risk ratio [RR] plus 95% confidence interval [CI]) (RR: 1.014, 0.979–1.049;  $p=0.44$ ). However, the periodontitis cohort demonstrated higher risk of stroke (RR: 1.264, 1.189–1.344;  $p<0.0001$ ), myocardial infarction (RR: 1.151, 1.084–1.222;  $p<0.0001$ ), atrial fibrillation (RR: 1.141, 1.08–1.205;  $p<0.0001$ ), atrial flutter (RR: 1.21, 1.1–1.331;  $p<0.0001$ ), diabetic retinopathy (RR: 1.735, 1.648–1.826;  $p<0.0001$ ), diabetic nephropathy (RR: 1.433, 1.35–1.521;  $p<0.0001$ ), infective endocarditis (RR: 1.83, 1.627–2.059;  $p<0.0001$ ) and dementia (RR: 1.364, 1.254–1.483;  $p<0.0001$ ).

**Conclusion** Our findings add to the growing body of evidence that periodontitis is associated with long-term cardiovascular consequences in people with T2D. However, due to the study's retrospective nature, there is a need for well-designed, prospective research, including mechanistic and interventional studies to further explore this relationship.

## Introduction

Diabetes mellitus is a significant global health challenge affecting an estimated 529 million individuals in 2021 and is expected to rise to 1.31 billion individuals by 2050.<sup>1</sup> Type 2 diabetes (T2D) accounts for 90% of all cases. The rise in T2D is fuelled by increasing rates of obesity, dietary risks in combination with low physical activity, and environmental risks.<sup>2</sup> T2D also confers significant morbidity and mortality in the form of accelerated cardiovascular, renovascular and cerebrovascular disease.<sup>3</sup>

Periodontitis is a disease of the tissue surrounding the tooth structure and is one of the most common diseases associated with the

<sup>1</sup>Department of Cardiovascular and Metabolic Medicine, University of Liverpool, Liverpool, UK; <sup>2</sup>Royal Liverpool University Hospital, Liverpool University Hospitals, NHS Foundation Trust, Liverpool, UK; <sup>3</sup>Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital; Liverpool, UK; <sup>4</sup>Arrows Park Dental Practice, Upton, Wirral, UK; <sup>5</sup>TriNetX, Cambridge, Massachusetts, USA; <sup>6</sup>School of Dentistry, University of Liverpool, Liverpool, UK; <sup>7</sup>Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Science, School of Biological Sciences, Faculty of Biological Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; <sup>8</sup>NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester, UK; <sup>9</sup>Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; <sup>10</sup>Department of Cardiology, Lipidology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; <sup>11</sup>Department of Diabetes, Obesity and Endocrinology, University Hospital Aintree, Liverpool University NHS Foundation Trust, Liverpool, UK; <sup>12</sup>Centre for Biomechanics and Rehabilitation Technologies, Staffordshire University, Stoke-on-Trent, UK.

\*Correspondence to: Hani Essa  
Email address: hani.essa@liverpool.ac.uk

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oral cavity. It is estimated that approximately 10% of the global population is affected by severe periodontitis which rises to ~15% in people with diabetes.<sup>4</sup> Periodontitis has a multifactorial origin and is related to bacterial biofilm growing on the dental surface<sup>5</sup> and leads to chronic soft tissue inflammation and destruction of the supporting tooth structure.<sup>6</sup> This subsequently acts as a reservoir of infection and leads to loss of the periodontal attachment and, ultimately, tooth loss.<sup>6</sup>

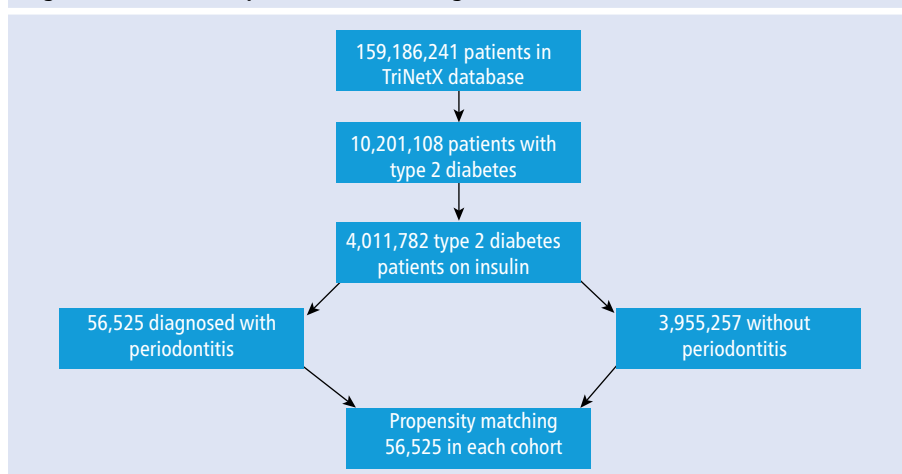
There is an interconnected complex but well-established bidirectional relationship.<sup>7,8</sup> In individuals without diabetes, periodontitis results in an increased risk of developing diabetes.<sup>4,7,8</sup> Additionally, in people with T2D, periodontitis is associated with deteriorating glycaemic control.<sup>7,8,9</sup> Periodontitis is associated in a variety of systemic conditions, including several cardiovascular diseases, such as infective endocarditis, myocardial infarction, peripheral arterial disease, and cerebrovascular disease.<sup>10</sup> However, there are limited data on the long-term cardiovascular outcomes for those with T2D who suffer from periodontitis. A large systematic review by Nguyen *et al.*<sup>8</sup> in 2020 demonstrated that in T2D patients with periodontitis, there is a significantly higher risk of mortality, diabetic and cardiovascular complications. However, these findings were not replicated in a large, retrospective, Swedish registry-based study conducted by Trullenque-Eriksson *et al.*,<sup>11</sup> who noted a significantly increased risk of microvascular complications but not macrovascular complications or mortality. As such, there is need for further research to further establish the association between periodontitis and cardiovascular complications in T2D.

In this study, we use a large global federated database of real-world data to evaluate the outcomes for people with T2D with and without periodontitis.

## Methods

We used data from the TriNetX Global Collaborative Network, a global health research network offering real-world patient data from healthcare organisations (HCOs) covering around 163 million individuals. The TriNetX database includes data from 144 HCOs across 14 countries. Both dental practices and hospitals are well-represented within this database. The platform features anonymised electronic health record data, including diagnoses, treatments, medications, procedures, and outcomes.

**Fig. 1 A breakdown of patient selection using the TriNetX network**



It enables users to build targeted patient cohorts based on conditions, treatments, and demographic information, supporting group comparisons and offering a strong tool for generating and validating hypotheses.<sup>12</sup>

All data collection, processing and transmission is done in compliance with all Data Protection laws applicable to the contributing HCOs, including the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation on the protection of natural persons with regards to the processing of personal data, and the Health Insurance Portability and Accountability Act, the US federal law which protects the privacy and security of healthcare data. The TriNetX Collaborative Networks operate as distributed networks, with analytics conducted at the HCO level, and only aggregate results are shared and returned to the platform.

## Ethics

The TriNetX platform is a federated network and analyses performed on the platform do not require ethical approval. All data collection, processing and transmission are performed in compliance with all data protection laws applicable to the underlying HCOs. This includes the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation on the protection of natural persons regarding the processing of personal data, and Health Insurance Portability and Accountability Act, the USA federal law which protects the privacy and security of healthcare data. Network analytics are performed at the underlying HCO with only aggregate counts and statistical summary results being returned to the platform. The platform does not provide any personal data or health information data. All participating

HCOs affirm that they have the necessary rights, consents, approvals, and authority to share the data with TriNetX under a business associate agreement for research purposes with agreements in place for publication.

## Study design

The data analysis was conducted on 8 January 2024, with pre-defined inclusion and exclusion criteria based on the relevant ICD-10 (International Classification of Diseases) codes to create our cohorts. All participants had to be diagnosed with T2D (ICD-10 E11) treated with insulin (VA HS501). Eligible patients were identified and then two cohorts were created based on the presence of periodontitis (ICD K05 [gingivitis and periodontal diseases], K05.6 [periodontal disease, unspecified], K05.21 [aggressive periodontitis, localised], K05.5 [other periodontal diseases]) recorded in the patients' medical record at any time point.

## Statistical analysis

We used the TriNetX database to create an analysis based on an index event (initiation of insulin), a time window before the index event, and a list of outcomes in a timepoint after the index event. The index event is the point in the study that a patient enters the analysis – this is determined based on the inclusion criteria. The index event refers to the day a patient was first recorded as meeting these criteria. Figure 1 represents our patient recruitment flowchart. The time window analysed was three years after the index event. Normally distributed data were presented as mean (standard deviation [SD]). Data are reported as a risk ratio (RR) plus 95% confidence interval (CI). *P* values of <0.05 were considered statistically significant. Patients are censored after the last observation in TriNetX or

**Table 1 Cohort 1 and Cohort 2 patient count before and after propensity score matching**

	Before PSM			After PSM		
	Periodontitis	Control group	p value, SSMD	Periodontitis	Control group	p value, SSMD
Age at index	58.8 ± 15.5	61.5 ± 16	<0.0001, 0.17	58.8 ± 15.5	58.7 ± 15.4	0.095, 0.001
Female	26,653 (47.15%)	1,846,895 (46.70%)	<0.0001, 0.03	10,668 (48.08%)	10,725 (48.34%)	0.59, 0.005
White	23,335 (41.28%)	2,284,824 (57.767%)	<0.0001, 0.3343	23,335 (41.283%)	23,453 (41.491%)	0.4761, 0.0042
Black or African American	12,901 (22.822%)	716,354 (18.111%)	<0.0001, 0.1170	12,901 (22.824%)	12,998 (22.995%)	0.4924, 0.0041
Asian	8,912 (15.766%)	216,977 (5.486%)	<0.0001, 0.3383	8,909 (15.761%)	8,935 (15.807%)	0.8320, 0.0013
Obesity	13,479 (23.845%)	700,242 (17.704%)	<0.0001, 0.1518	13,476 (23.841%)	13,993 (24.755%)	0.0003, 0.0213
Hypertension	32,512 (57.515%)	1,723,916 (43.585%)	<0.0001, 0.2813	32,509 (57.513%)	32,785 (58.001%)	0.0965, 0.0099
Ischemic heart disease	13,515 (23.909%)	710,282 (17.958%)	<0.0001, 0.1467	13,513 (23.906%)	13,248 (23.437%)	0.0637, 0.0110
Heart failure	8,450 (14.948%)	399,960 (10.112%)	<0.0001, 0.1465	8,449 (14.947%)	8,324 (14.726%)	0.2956, 0.0062
Chronic kidney disease	10,121 (17.904%)	495,609 (12.53%)	<0.0001, 0.1500	10,119 (17.902%)	10,132 (17.925%)	0.9197, 0.0006
Cerebrovascular disease	7,835 (13.86%)	346,717 (8.766%)	<0.0001, 0.1614	7,834 (13.859%)	7,487 (13.245%)	0.0026, 0.0179
Chronic obstructive pulmonary disease	6,241 (11.041%)	283,294 (7.162%)	<0.0001, 0.1351	6,240 (11.039%)	5,991 (10.599%)	0.0171, 0.0142
Peripheral vascular disease	3,086 (5.459%)	159,989 (4.045%)	<0.0001, 0.0665	3,086 (5.46%)	2,902 (5.134%)	0.0145, 0.0145
Ophthalmic complication of type 2 diabetes	4,010 (7.094%)	131,218 (3.318%)	<0.0001, 0.1706	4,008 (7.091%)	3,974 (7.031%)	0.6930, 0.0023
Problems relating to housing and economic circumstances	803 (1.5%)	28,983 (0.7%)	<0.0001, 0.0715	803 (1.5%)	751 (1.4%)	0.1839, 0.0081
Tobacco use	2,072 (3.9%)	87,265 (2.2%)	<0.0001, 0.0943	2,072 (3.9%)	1,938 (3.6%)	0.0310, 0.0132
Aspirin	16,251 (28.749%)	694,186 (17.551%)	<0.0001, 0.2678	16,248 (28.745%)	16,261 (28.768%)	0.9319, 0.0005
Clopidogrel	4,158 (7.356%)	182,269 (4.608%)	<0.0001, 0.1160	4,155 (7.351%)	4,002 (7.08%)	0.0786, 0.0105
Anticoagulants	13,701 (24.238%)	792,920 (20.047%)	<0.0001, 0.1010	13,699 (24.235%)	13,794 (24.403%)	0.5102, 0.0039
Beta blockers	18,290 (32.356%)	918,621 (23.225%)	<0.0001, 0.2049	18,287 (32.352%)	18,383 (32.522%)	0.5419, 0.0036
Angiotensin II receptor blockers	10,001 (17.692%)	435,400 (11.008%)	<0.0001, 0.1915	9,998 (17.688%)	9,856 (17.437%)	0.2670, 0.0066
Spironolactone	3,273 (5.79%)	116,650 (2.949%)	<0.0001, 0.1393	3,271 (5.787%)	3,101 (5.486%)	0.0284, 0.0130
Eplerenone	135 (0.239%)	5,070 (0.128%)	<0.0001, 0.0259	135 (0.239%)	113 (0.2%)	0.1620, 0.0083
Sodium-glucose co-transporter 2 inhibitors	2,297 (4.063%)	135,456 (3.425%)	<0.0001, 0.0337	2,297 (4.064%)	2,143 (3.791%)	0.0184, 0.0140
Haemoglobin A1c	7.69 ± 2.18	7.58 ± 2.15	<0.0001, 0.0527	7.69 ± 2.18	7.59 ± 2.17	<0.0001, 0.0473

PSM = propensity score matching  
SSMD = strictly standardised mean differences

the end of the analysis time-window, whatever happens first. To mitigate differences in baseline characteristics, we conducted a one-to-one propensity score matching (PSM) analysis through the TriNetX platform, employing logistic regression modelling. This system implements a greedy nearest-neighbour algorithm, constrained by a calliper width of 0.1 standard deviations and a maximum allowable propensity score deviation of 0.1. We evaluated the equivalence of covariates between the matched cohorts using strictly standardised mean differences (SSMDs), with a threshold of less than 0.1 indicating satisfactory balance across variables. The covariates included

in PSM were age at index event, ethnicity (Black, white and Asian), smoking status, socioeconomic status, female sex, hypertension, obesity, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, and diabetic retinopathy. We also matched for common cardiac medications, including aspirin, anticoagulants, angiotensin receptor inhibitors, clopidogrel, spironolactone, sodium-glucose cotransport 2 inhibitors and eplerenone. We also matched for HbA1c. Statistical analyses were completed using the TriNetX online platform using R for statistical computing.

## Results

At baseline, there was 56,525 individuals in the periodontitis group and 3,955,257 individuals in the comparator/control group. At baseline, the periodontitis cohort were younger and had higher prevalence of hypertension, ischemic heart disease, heart failure, chronic kidney disease, cerebrovascular disease, chronic kidney disease and peripheral vascular disease. After PSM matching, our cohorts were deemed well-matched. Table 1 demonstrates baseline differences between both cohorts before and after PSM matching.

Figure 2 represents our PSM matching graph. After PSM, there was a total of 56,525 patients in both cohorts. Median follow-up in the periodontitis cohort was 1,095 (SD: 366 days), and 1,007 days (SD: 437 days) in the control group.

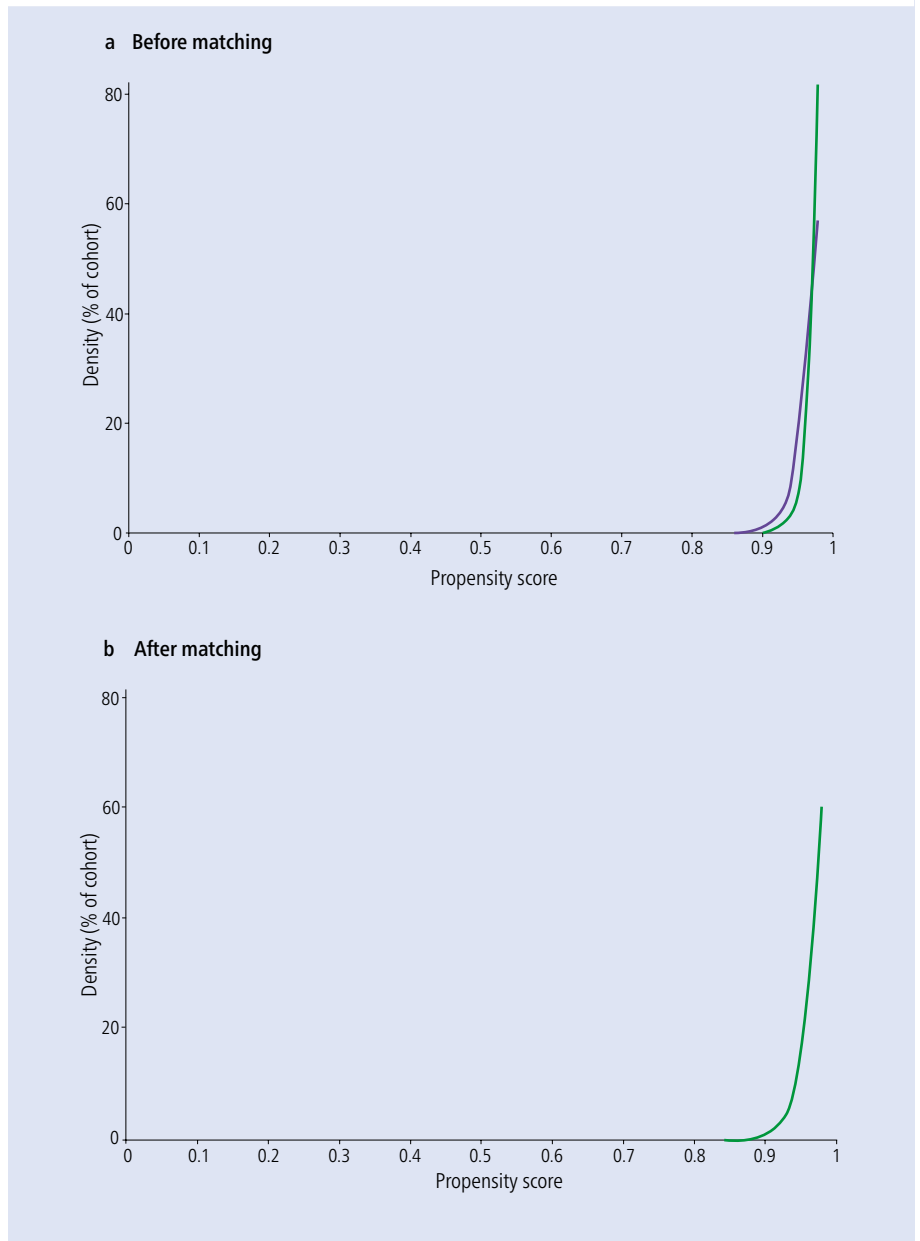
Three years of the initiation of insulin (index event), patients with periodontitis had similar mortality risk compared to the PSM control group (RR plus 95% CI) ( $p = 0.46$ ). However, the periodontitis cohort demonstrated higher rates of stroke ( $p < 0.0001$ ), myocardial infarction ( $p < 0.0001$ ), atrial fibrillation ( $p < 0.0001$ ), atrial flutter ( $p < 0.0001$ ), diabetic retinopathy ( $p < 0.0001$ ), diabetic nephropathy ( $p < 0.0001$ ), infective endocarditis ( $p < 0.0001$ ) and dementia ( $p < 0.0001$ ). Table 2 demonstrates RRs for these events. Figure 3 represents a forest plot of the results.

E-values were calculated to establish the minimum strength of association required for an unmeasured confounder to have an interaction with both the exposure and the outcome to fully explain away a specific exposure-outcome association (conditional on the measured covariates)<sup>13</sup> (Table 2). A higher E-value suggests that substantial unmeasured confounding is required to dismiss an effect estimate, whereas a low E-value intimates minimal unmeasured confounding is needed for a similar purpose. E-values for diabetic retinopathy, diabetic nephropathy, infective endocarditis and dementia were  $>2$ .

### Discussion

In this real-world data study, we looked at the outcomes of over 55,000 propensity-matched patients with T2D based on the presence or absence of periodontitis. Our results demonstrate that in people with T2D, periodontitis is associated with worse outcomes and higher risk of myocardial infarction, stroke, atrial fibrillation, atrial flutter, dementia, infective endocarditis, diabetic nephropathy, and diabetic retinopathy. However, there was no statistically significant increased risk in mortality. Our analysis stands as one of the most extensive retrospective investigations into the impact of periodontitis on the long-term health outcomes of patients with T2D. The findings from the present study reinforce the increasingly recognised link between periodontitis and systemic complications in diabetes.

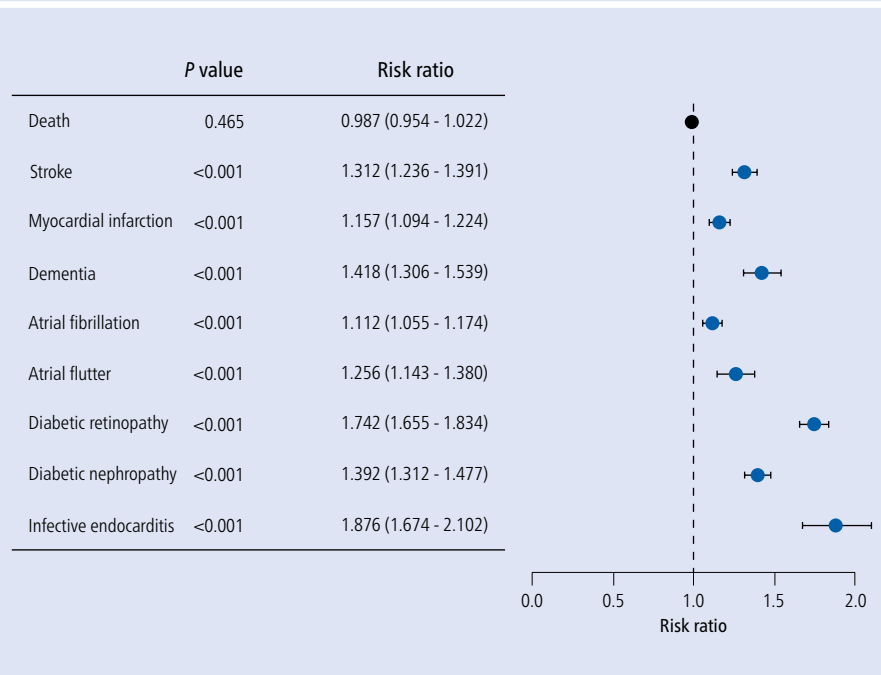
**Fig. 2 Propensity score density function. Purple represents patients with periodontitis, green represents controls. Both cohorts are deemed well matched post-matching (a = before; b = after)**



**Table 2 Individual outcome measures with respective risk ratios and E-values**

Event	Risk ratio	95% confidence interval	p value	E value
Death	1.014	0.979–1.049	0.4450	1.13
Stroke	1.264	1.189–1.344	<0.0001	1.84
Myocardial infarction	1.151	1.084–1.222	<0.0001	1.56
Dementia	1.364	1.254–1.473	<0.0001	2.06
Atrial fibrillation	1.141	1.08–1.205	<0.0001	1.54
Atrial flutter	1.21	1.1–1.331	<0.0001	1.71
Diabetic retinopathy	1.735	1.648–1.826	<0.0001	2.86
Diabetic nephropathy	1.433	1.35–1.521	<0.0001	2.22
Infective endocarditis	1.83	1.627–2.059	<0.0001	3.06

**Fig. 3 Forest plot and table of risk ratios comparing the periodontitis cohort with the control cohort. Created using SRplot<sup>26</sup>**



The existing evidence base suggests a strong bidirectional relationship between T2D and periodontitis with both conditions exacerbating each other.<sup>4,7,14</sup> Periodontitis has previously been referred to as the 'sixth complication' of diabetes (after cardiovascular, eye, neuropathic, nephropathic, and peripheral vascular disease).<sup>15</sup> Periodontitis prevalence is directly linked to glycaemic control, with worsening control conferring higher risk. Conversely, periodontal inflammation can worsen glycaemic control and is associated with an increased risk of diabetes onset in non-diabetic individuals.<sup>16</sup> Prior work from Dietrich *et al.* has demonstrated an increased risk of cerebrovascular and coronary events in patients with periodontitis.<sup>17</sup> Additionally, analysis of data from the ARIC (Atherosclerosis Risk in Communities) study demonstrated an association between periodontal profile class and incident ischaemic stroke with a greater than twofold risk of cardioembolic and thrombotic stroke.<sup>18</sup> It is well-recognised that simple population-based dental hygiene interventions, such as promoting frequent toothbrushing and regular dental visits for professional cleaning, can reduce the risk of cardiovascular events in healthy adults.<sup>19</sup> The NHANES (National Health and Nutrition Examination Survey) (1999–2002) and KoGES-CAVAS (Korean Genome and Epidemiology Study – Cardiovascular Disease Association Study) studies demonstrated

positive association between the extent of clinical attachment loss (odds ratio: 2.2; 95% CI: 1.2–4.2) and severity of radiographic bone loss (odds ratio: 2.0; 95% CI: 1.1–3.9) with peripheral arterial disease.<sup>20,21</sup> In analysis of NHANES data (2009–12 survey data linked to outcome/mortality data until 2019), low oral microbiome alpha diversity was associated with higher risk for all-cause mortality and cardiovascular disease.<sup>22</sup>

Notably, our study also identified associations demonstrating an increased risk of atrial fibrillation, atrial flutter, and dementia, outcomes less commonly examined in this context. This is supported by emerging data, for example, a large Korean cohort observed an association between improved oral hygiene and a lower incidence of atrial fibrillation,<sup>23</sup> and a recent meta-analysis found that moderate-to-severe periodontitis is significantly associated with about twofold higher odds of dementia.<sup>24</sup> This builds on the existing evidence base demonstrating the association between oral health and systemic disease extends beyond classical atherosclerotic events to other conditions linked by inflammation and vascular health. Additionally, the strong association we observed between periodontitis and diabetic microvascular complications (nephropathy and retinopathy) echoes prior findings. Nguyen *et al.*<sup>8</sup> conducted a large systematic review in 2020 which demonstrated that patients with diabetes with periodontitis

have significantly higher risks of both diabetic complications and increased mortality compared to otherwise well-matched patients without periodontitis.<sup>8</sup> This aligns with our results, demonstrating that both diabetic nephropathy and retinopathy were more common in the periodontitis cohort.

Interestingly, not all studies have reported such broad associations, and the literature contains some contrasting findings. A recent large, Swedish, registry-based cohort study provides an instructive counterpoint.<sup>11</sup> In that study, people with T2D with periodontitis showed a significantly increased incidence of microvascular complications, specifically, diabetic retinopathy and albuminuria (early nephropathy), but no significant increase in the risk of stroke, ischemic heart disease, or mortality was observed. These discrepancies likely stem from inherent differences in study design and populations studied. We identified patients who had been started on insulin therapy (indicating more advanced T2D) as compared to the Swedish registry data which identified all patients with periodontitis on their medical record. Furthermore, we used PSM to create well-balanced cohorts. It is biologically plausible that systemic inflammation from periodontitis may exert more macrovascular harm in patients with more advanced diabetes.

Our analysis, which is one of the largest to date, extends the literature by confirming these associations using real-world data and highlighting less well-studied outcomes (such as atrial arrhythmias, dementia, and infective endocarditis). Overall, the evidence base supports the idea that periodontal disease in T2D is a marker of and likely contributes to an increased risk of systemic complications, possibly mediated by chronic inflammation.

Our study highlights the importance of recognising periodontitis as an additional risk factor in patients with T2D. Clinicians should view periodontitis as an additional risk factor in T2D, similar to hypertension or dyslipidaemia. The presence of periodontitis warrants closer monitoring and more intensive management of diabetes and cardiovascular risk factors. Clinicians should routinely screen people with diabetes for signs of gum disease. Early identification might be key in attenuating cardiovascular disease risk. Patients should be educated on the bidirectional link and the importance of good oral hygiene for preventing cardiovascular risk.

Our results should be viewed within the context of their limitations. First, as an observational study, while we can demonstrate an association, we are unable to comment on causality. Second, this is a retrospective study and therefore data are not randomised, nor is it controlled. While we used PSM to try to control potential confounders, residual confounding due to electronic health record data incompleteness may be present. Third, data are extracted from a database based on medical coding, and these are usually designed for billing purposes. Furthermore, we are unable to review individual medical chart data to ensure conditions have been coded appropriately; data can also be incomplete or unsuitable for extraction. Therefore, we must rely on accurate coding at the HCO source. Most importantly, we did not have granular data on the severity of periodontitis based on current staging and grading criteria.<sup>25</sup> This limits overall interpretability. Further analyses based on the classification of periodontitis would provide a more detailed analysis. Furthermore, data can be missing if the event/diagnosis occurred outside a participating HCO. Finally, TriNetX only records patient data within its networks, and patients who are treated outside the network are lost to follow-up. Our results should serve as a hypothesis-generating exercise to help guide robust prospective studies and public health interventions looking at the effect of periodontitis in T2D patients' long-term outcomes.

## Conclusion

Our findings add to the growing body of evidence that links periodontitis to long-term cardiovascular consequences in T2D. However, the study's observational retrospective nature limits our findings. There is a need for well-designed, prospective research, including mechanistic and interventional studies to further explore this relationship.

### Ethics declaration

HE, IW, SSZ, SA, AH, GH and IY report no conflicts of interest. UA has received honoraria from Viatrix, Grünenthal, Eli Lilly, Procter & Gamble for educational meetings and has received investigator-led funding from Procter & Gamble. UA has received sponsorship to attend educational meetings from Daiichi Sankyo and Sanofi. GYHL is a National Institute for Health and Care Research (NIHR) Senior Investigator. He is Consultant and speaker for

BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos (no fees are received personally). He is co-PI/lead of the AFFIRMO project on multimorbidity in AF (grant agreement no. 899871), TARGET project on digital twins for personalised management of atrial fibrillation and stroke (grant agreement no. 101136244) and ARISTOTELES project on artificial intelligence for management of chronic long term conditions (grant agreement no. 101080189), which are all funded by the EU's Horizon Europe Research & Innovation programme. GH is a full-time employee of TriNetX LLC. The TriNetX platform is a federated network that provides access only to de-identified data, and analyses performed on the platform do not require ethical approval or informed consent. This is accordance with all data protection laws applicable to the underlying healthcare organisations (HCOs), including the EU General Data Protection Regulation (Regulation 2016/679, GDPR) and the US Health Insurance Portability and Accountability Act. Written informed consent to participate in this study is not required in accordance with the relevant legislation. Network analytics are performed locally at each participating HCO, with only aggregate counts and statistical summary results being returned to the TriNetX platform. The platform does not provide access to any personal data or protected health information, ensuring that individual patients cannot be identified. All participating HCOs affirm that they have the necessary rights, consents, approvals, and authority to share de-identified data with TriNetX under a business associate agreement for research purposes. Because our research involves only secondary analysis of de-identified, aggregate data with no direct patient interaction or identifiable private information, it is considered exempt from institutional review board or ethics committee review under applicable regulations.

### Data availability

The TriNetX database is a real-world, real-time data ecosystem and access to the underlying raw data are not provided. The data that support the findings of this study are available from TriNetX LLC, <https://trinetx.com/>, but third-party restrictions apply to the availability of these data. Data access may require a data sharing agreement and may incur data access fees. Data used in the generation of this paper was collected from the global TriNetX network, and local data at LUHFT were not used. TriNetX is a custom-built technology platform, the underlying technology is proprietary.

### Author contributions

HE, IY, UA conceived the idea and supervised the overall project and contributed to the draft. HE ran the analyses on the TriNetX platform and wrote the draft. GH reviewed the data query and advised on

how best to run the query and helped contribute to the draft. IY, AH, IW, SA, STZ, GYHL, DJC all helped supervise the project and contributed to the draft and final manuscript

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