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Oral disease in relation to future risk of dementia and cognitive decline: prospective cohort study based on the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation) trial

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Abstract

Objective—Examine the association of oral disease with dementia/cognitive decline in a cohort of people with type 2 diabetes.

Methods—A total of 11,140 men and women aged 55–88 years with type 2 diabetes participated in a baseline medical examination when they reported the number of natural teeth and days of bleeding gums. Dementia and cognitive decline were ascertained periodically during a 5 year follow-up.

Results—Relative to the group with the greatest number of teeth (≥ 22), having no teeth was associated with the highest risk of both dementia (hazard ratio; 95% confidence interval: 1.48; 1.24, 1.78) and cognitive decline (1.39; 1.21, 1.59). Number of days of bleeding gums was unrelated to these outcomes.

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Conclusions—Tooth loss was associated with an increased risk of both dementia and cognitive decline.

Keywords

cognitive decline; cohort study; dementia; oral disease

Introduction

While it is well established that dementia is a predictor of poor oral health,^{1, 2} the converse has been little examined. However, there is a strong *prima facie* case implicating oral disease in the aetiology of dementia. First, fewer teeth – a commonly used proxy for oral disease – impairs masticatory function, thereby influencing food choice and affecting nutritional status.³ Micronutrient deficiencies⁴ and weight loss⁵ are potentially important determinants of dementia. Second, there is a suggestion that indicators of poor oral health predict major vascular disease, such as coronary heart disease.⁶ Given that vascular disease and dementia are thought to have a shared pathophysiology,⁷ a link between oral disease and dementia would be anticipated. Third, it has recently been proposed that oral disease may give rise to systemic inflammation,⁸⁻¹⁰ as illustrated, for instance, by raised levels of C-reactive protein. Inflammation, possibly within the central nervous system, is thought to have a pivotal role in the pathogenesis of dementia.⁸

Studies examining the relation of oral disease with dementia are scarce,¹¹⁻¹⁶ and several have methodological shortcomings which hamper data interpretation. Case-control studies^{11, 12, 17} are subject to the problem of reverse causality. Thus, while it is possible that oral disease may give rise to an increased prevalence of dementia, it is equally likely that, owing to their simultaneous measurement, dementia may, as described, influence oral disease as patients become increasingly incapable of self-care. In the prospective studies,¹³⁻¹⁵ which are best placed to address this shortcoming, are generally small in scale and so offer limited statistical power.

We directly address these issues of paucity of evidence, low study power, and methodological limitations by utilising data from cohort analyses of the ADVANCE trial.¹⁸⁻²⁰ This allows us to examine the predictive value of oral disease for dementia and, additionally, cognitive decline, for which there is also a marked paucity of data.^{21, 22}

Methods

The Action in Diabetes and Vascular disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial, which has been described in detail elsewhere,¹⁸⁻²⁰ was designed to investigate the separate effects of routine blood pressure lowering and intensive glucose control on vascular outcomes in people with type 2 diabetes. In brief, in 2001/3, 11,140 men and women aged 55-88 years with type 2 diabetes and a history of major macro- or microvascular disease, or at least one other cardiovascular risk factor, were recruited from 215 centres (20 countries).¹⁸ For the purposes of the present analyses, data from the trial are utilised using a prospective cohort study design.

At study induction, participants responded to questionnaire enquiries and took part in a medical examination. Glycated haemoglobin (HbA1c), blood cholesterol (and fractions), blood pressure, resting heart rate, and serum creatinine were measured using standard protocols.¹⁸ Height and weight were used to derive body mass index ($\text{weight}[\text{kg}]/\text{height}[\text{m}]^2$). Participants were administered a series of questions regarding ethnicity, educational attainment, physical activity, alcohol intake, cigarette smoking habit, licit drug use, major chronic disease, assistance with activities of daily living, and quality of life ('EuroQol5d').^{23, 24}

Study members also responded to two questions about oral disease. Participants were asked to count the number of natural teeth present in their mouth. Artificial teeth were not included but any tooth or part of a tooth that was visible in the mouth and connected to the gum or jawbone counted as one tooth. Study members also reported the number of days their teeth had bled in the preceding year. This included spontaneous bleeding, bleeding on cleaning the teeth, and bleeding on eating food but not bleeding associated with dental treatment, tooth loss or facial trauma. Lower numbers of natural teeth and higher numbers of days that gums bled indicate poorer oral health. Responses to the enquiries regarding number of natural teeth (0; 1-21; ≥ 22) and days of bleeding gums (0; < 12 days; ≥ 12 days) were divided into three groups based on the distribution of data.

Cognitive function was assessed using the Mini Mental State Examination (MMSE)²⁵. At baseline, individuals with a health professional-administered MMSE score of less than 24, or where the physician or nurse suspected dementia, were referred to a suitably qualified medical specialist, expert in making a diagnosis, for an assessment of dementia status according to Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria²⁶. The clinical assessment included, wherever possible, an interview with both the patient and a close friend or relative. These methods were standardised across study centres. Individuals with either a contemporaneous or prior diagnosis of dementia did not enter the study. During 5 years of follow-up, the MMSE was administered on 3 occasions. The protocol used to identify dementia at baseline and follow-up was the same. Cognitive decline during follow-up was defined as a decrease of at least 3 points in MMSE score between study induction and the third assessment²⁷.

Statistical Analysis

Having first determined that the proportional hazards assumption had not been violated for the two proxies for oral health in relation to dementia and cognitive decline, we computed hazard ratios with accompanying 95% confidence intervals.³⁴ With no evidence of effect modification by gender, statistical models were initially adjusted for sex (and age). We then added a series of covariates to produce a multivariable-adjusted model.

Results

In table 1 we present baseline characteristics according to the two indicators of oral disease. Around one fifth (21%) of study members reported complete tooth loss, while only 6.6% indicated that their gums had bled for 12 days or more in the preceding year. People with fewer natural teeth typically had less favourable biological, social, behavioural and

psychological characteristics. The relation of days of bleeding gums with study characteristics was more complex. On the one hand, people who reported more bleeding days relative to fewer were younger, better educated, were leaner, had lower creatinine values, and smoked less; however, they also had higher systolic blood pressure and alcohol intake.

In table 2, hazards ratios for the two indicators of oral disease in relation to incident dementia and cognitive decline during follow-up are depicted. In the simplest model (age, sex and treatment-adjusted), the group with no teeth experienced almost twice the risk of dementia (hazard ratio; 95% CI: 1.82; 1.54, 2.15) relative to those with 22 teeth or more. This effect was incremental across the teeth loss groups (p for trend: <0.0001). Controlling separately for a series of covariates had very little impact on these effects estimates. Although marked attenuation was apparent for the corresponding hazard ratios in the multiply-adjusted model, men and women with the fewest teeth still experienced an almost 50% higher risk of dementia (1.48; 1.24, 1.78). When cognitive decline was the outcome of interest there was also a positive relation with tooth loss, such that study members reporting the greatest tooth loss had a 25% increase in the risk of cognitive decline (1.25; 1.11, 1.42). Again, a dose-response effects was apparent across the tooth loss categories (p[trend]=0.0003). Although this gradient was shallower than that for dementia, it was more robust to statistical adjustment. There was essentially no relationship between days of gums bleeding and either cognitive decline or dementia in any of our analyses.

Discussion

The main finding of this study – the largest and best characterised to date to explore the relation of oral disease with dementia and cognitive decline – was that men and women with fewer teeth experienced a markedly increased risk of developing dementia and cognitive decline. Our other marker of oral disease – days of bleeding gums – was unrelated to either of these outcomes. This may be because very few people reported any gum bleeding, that attempting to recall the number of days of bleeding gums over 12 months is problematic, or that, in comparison to tooth loss, gum bleeding does not capture oral disease severe enough to yield an association with dementia or cognitive impairment.

After controlling for a range of covariates, the effect estimate for the relation of tooth loss with dementia was attenuated by around 40% (table 2). This raises the possibility that the excess risk could be explained by more accurate or repeated measurement of existing confounders (residual confounding), or the assessment of new, unmeasured characteristics, or both. By contrast, the tooth loss-cognitive decline gradient was robust to all statistical adjustments we made; indeed, in the fully adjusted model this association was strengthened.

Our results signal the possibility that tooth loss may be mechanistically linked to dementia and cognitive decline. As described, reduced masticatory capacity may impair nutritional intake and this may be a risk factor for dementia and/or cognitive function. Although we did not collect data on dietary intake, study members who had a higher number of natural teeth had a *lower* body mass index than those with greater tooth loss, suggesting that nutritional intake, and certainly weight loss, is an unlikely explanation. Inflammation resulting, for

instance, from poor oral health has also been implicated in the aetiology dementia,⁹ however, we did not have data on markers of systemic inflammation to test such a hypothesis. While people with greater tooth loss have higher levels of circulating C-reactive protein,²⁸ we are unaware of any study relating self-reported gum bleeding to markers of systemic inflammation.

The strengths of this study lie in its large size and the fact that it is well characterised. It is not without its weaknesses, however. A clear shortcoming of our study is that data on type of dementia were not available. We also had no information on the APOE4 allele nor chronic low-level exposure to mercury from dental amalgam, both of which have been associated with dementia and/or cognitive decline.

In conclusion, our observation that poor oral health, as indexed by tooth loss only, is an apparent risk factor for dementia and cognitive decline requires further investigation, particularly in studies with markers of inflammatory response and in those with information on dementia sub-type.

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Table 1
Oral health and baseline characteristics in ADVANCE (N=11,140 men and women)

	Number of natural teeth			P-value for trend	Days of bleeding gums			P-value for trend
	0 teeth (n=2352)	1-21 teeth (n=4239)	>=22 teeth* (n=4549)		0 days* (n=9704)	<12 days (n=698)	>=12 days (n=738)	
		<i>Mean (SD)</i>				<i>Mean (SD)</i>		
Age at baseline examination (yr)	68.6 (6.41)	66.22 (6.24)	63.90 (5.90)	0.001	66.05 (6.41)	64.15 (5.98)	63.63 (5.93)	0.001
Age at completion of education (yr)	17.03 (6.48)	18.27 (7.24)	19.34 (7.59)	0.001	18.29 (7.20)	19.46 (8.01)	19.43 (7.57)	0.001
Haemoglobin A1c (%)	7.46 (1.45)	7.53 (1.60)	7.53 (1.57)	0.19	7.50 (1.55)	7.57 (1.54)	7.63 (1.61)	0.017
Height (cm)	165.6 (9.93)	166.0 (9.44)	165.6 (9.07)	0.70	165.7 (9.43)	166.0 (9.13)	166.6 (9.25)	0.01
Body mass index (kg/m ²)	29.24 (5.42)	28.90 (5.26)	27.35 (4.82)	0.001	28.25 (5.17)	28.43 (5.09)	29.47 (5.37)	0.001
Total cholesterol (mmol/L)	5.13 (1.13)	5.22 (1.17)	5.21 (1.24)	0.04	5.20 (1.19)	5.13 (1.21)	5.27 (1.25)	0.40
High-density lipoprotein cholesterol (mmol/L)	1.24 (0.34)	1.25 (0.34)	1.27 (0.36)	0.001	1.26 (0.35)	1.24 (0.36)	1.25 (0.35)	0.36
Systolic blood pressure (mmHg)	148.4 (22.47)	146.3 (21.63)	142.0 (20.55)	0.001	145.2 (21.56)	142.8 (20.65)	144.8 (22.02)	0.14
Diastolic blood pressure (mmHg)	80.26 (11.05)	81.09 (11.19)	80.43 (10.61)	0.95	80.51 (10.90)	80.92 (10.59)	82.15 (11.53)	0.001
Resting heart rate (BPM)	73.19 (12.52)	74.12 (12.06)	74.60 (11.84)	0.001	74.14 (12.10)	74.56 (12.21)	73.44 (11.74)	0.32
Serum creatinine (umol/L)	88.97 (23.58)	87.50 (26.14)	84.38 (25.38)	0.001	86.84 (25.96)	84.93 (21.19)	84.05 (20.53)	0.001
Cognitive function (MMSE)	28.21 (2.08)	28.38 (1.91)	28.79 (1.75)	0.001	28.50 (1.92)	28.57 (1.77)	28.62 (1.72)	0.07
Quality of life (EQ-5d)	0.80 (0.21)	0.81 (0.19)	0.84 (0.18)	0.001	0.82 (0.19)	0.81 (0.20)	0.79 (0.21)	0.001
Diabetes duration (years)	7.86 (6.50)	8.03 (6.51)	7.89 (6.13)	0.96	7.97 (6.39)	7.95 (5.92)	7.52 (6.22)	0.09
No. occasions exercise 15 mins/week	3.00 (5.00)	3.18 (5.56)	3.78 (6.45)	0.001	3.39 (5.71)	3.20 (5.94)	3.56 (7.27)	0.73
Current number of drinks/ week	3.02 (7.40)	3.06 (7.79)	2.93 (8.13)	0.57	2.93 (7.75)	3.60 (8.16)	3.37 (8.83)	0.03
		<i>N (Percentage)</i>				<i>N (Percentage)</i>		
Female	1118(47.5)	1788(42.2)	1827(40.2)	0.001	4137(42.6)	279(40.0)	317(43.0)	0.38
Caucasian/European ethnicity	1962 (83.4)	2967 (70.0)	1756 (38.6)	0.001	5786 (59.6)	409 (58.6)	490 (66.4)	0.001
Current cigarettes smoker	359 (15.3)	628 (14.8)	563 (12.4)	0.004	1392 (14.3)	96 (13.8)	62 (8.4)	0.001

	Number of natural teeth			P-value for trend	Days of bleeding gums			P-value for trend
	0 teeth (n=2352)	1-21 teeth (n=4239)	>=22 teeth* (n=4549)		0 days* (n=9704)	<12 days (n=698)	>=12 days (n=738)	
Use of metformin or beta-blocker	1675 (71.2)	3021 (71.3)	3174 (69.8)	0.24	6876 (70.9)	490 (70.2)	504 (68.3)	Batty et al. 0.33
Require assistance with daily activities	136 (5.8)	143 (3.4)	98 (2.2)	0.001	332 (3.4)	17 (2.4)	28 (3.8)	0.31
History of major macrovascular disease	818 (34.8)	1411 (33.3)	1361 (29.9)	0.001	3120 (32.2)	218 (31.2)	252 (34.1)	0.45
History of major microvascular disease	274 (11.6)	452 (10.7)	429 (9.4)	0.01	1007 (10.4)	80 (11.5)	68 (9.2)	0.38
History of major diabetic disease	183 (7.8)	302 (7.1)	310 (6.8)	0.34	695 (7.2)	51 (7.3)	49 (6.6)	0.85

* Indicates superior oral health

Table 2
Hazard ratio (95% CI) for the relation of baseline oral disease with future dementia and cognitive decline in ADVANCE (N=11140)

Adjustment	Number of natural teeth			P-trend	Days of bleeding gums/year			P-trend
	>=22* (n=4549)	1-21 (n=4239)	0 (n=2352)		0 days* (n=9704)	<12 days (n=698)	>=12 days (n=738)	
Dementia (n=109)	22	47	40		101	2	6	
Age + sex	1 (ref)	1.44 (1.23, 1.68)	1.82 (1.54, 2.15)	0.001	1 (ref)	0.35 (0.09, 1.40)	1.03 (0.45, 2.36)	0.58
Age, sex + quality of life	1	1.39 (1.19, 1.62)	1.74 (1.47, 2.06)	0.001	1	0.34 (0.08, 1.40)	1.00 (0.44, 2.29)	0.54
Age, sex + existing illness	1	1.39 (1.19, 1.62)	1.74 (1.47, 2.06)	0.001	1	0.35 (0.09, 1.42)	1.05 (0.46, 2.41)	0.61
Age, sex + behavioural CVD risk factors	1	1.41 (1.21, 1.65)	1.77 (1.49, 2.09)	0.001	1	0.36 (0.09, 1.46)	1.09 (0.47, 2.50)	0.67
Age, sex + physiological CVD risk factors	1	1.37 (1.17, 1.60)	1.71 (1.44, 2.03)	0.001	1	0.35 (0.09, 1.43)	1.05 (0.46, 2.41)	0.61
Age, sex + psychological CVD risk factors	1	1.36 (1.16, 1.59)	1.70 (1.44, 2.01)	0.001	1	0.38 (0.09, 1.56)	1.07 (0.46, 2.46)	0.69
Age, sex + socio-economic CVD risk factors	1	1.43 (1.22, 1.67)	1.80 (1.52, 2.13)	0.001	1	0.37 (0.09, 1.51)	1.09 (0.48, 2.51)	0.71
Multiple adjustment	1	1.24 (1.05, 1.46)	1.48 (1.24, 1.78)	0.001	1	0.42 (0.10, 1.71)	1.19 (0.51, 2.75)	0.90
Cognitive decline (n=1806)	620	719	467		1605	100	101	
Age + sex	1 (ref)	1.14 (1.02, 1.27)	1.25 (1.11, 1.42)	0.001	1 (ref)	0.89 (0.73, 1.09)	0.87 (0.71, 1.07)	0.11
Age, sex + quality of life	1	1.13 (1.02, 1.26)	1.23 (1.08, 1.40)	0.001	1	0.88 (0.72, 1.08)	0.86 (0.70, 1.06)	0.08
Age, sex + existing illness	1	1.14 (1.02, 1.27)	1.25 (1.10, 1.42)	0.001	1	0.89 (0.73, 1.09)	0.88 (0.72, 1.08)	0.12
Age, sex + behavioural CVD risk factors	1	1.14 (1.02, 1.27)	1.25 (1.10, 1.42)	0.001	1	0.90 (0.73, 1.10)	0.88 (0.72, 1.08)	0.14
Age, sex + physiological CVD risk factors	1	1.15 (1.03, 1.28)	1.27 (1.11, 1.44)	0.001	1	0.91 (0.74, 1.12)	0.90 (0.73, 1.10)	0.20
Age, sex + psychological CVD risk factors	1	1.12 (1.01, 1.25)	1.22 (1.08, 1.39)	0.001	1	0.89 (0.72, 1.09)	0.87 (0.71, 1.06)	0.09
Age, sex + socio-economic CVD risk factors	1	1.14 (1.02, 1.27)	1.24 (1.10, 1.41)	0.001	1	0.91 (0.74, 1.11)	0.91 (0.74, 1.11)	0.23
Multiple adjustment	1	1.23 (1.10, 1.38)	1.39 (1.21, 1.59)	0.001	1	0.92 (0.75, 1.13)	0.94 (0.77, 1.15)	0.39

All analyses are treatment-adjusted. Existing illness: comprises one or more of the following: use of Metformin/beta-blockers, history of macrovascular or microvascular disease, or those requiring assistance with daily activities, plus diabetes duration; Behavioural CVD risk factors: Cigarette smoking, alcohol intake, vigorous physical activity in previous week; Physiological CVD risk factors: Haemoglobin A1c, Creatinine, BMI, total cholesterol, HDL cholesterol, resting heart rate, SBP, DBP; Psychological CVD risk factors: Quality of life (EQ-5d score), and Mini Mental State Exam Score; Socio-economic CVD risk factors: Age at completion of highest level of education, height; Multiple adjusted: All above covariates plus treatment allocation and ethnicity.

* Indicates superior oral health. Hazard ratios were computed using Cox proportional hazard regression models.