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Short communication

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

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ABSTRACT

Objective: Examine the association of oral disease with future 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 at study induction 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 (more than or equal to 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.
Conclusions: Tooth loss was associated with an increased risk of both dementia and cognitive decline.

1. Introduction

While it is well established that dementia is a predictor of poor oral health [8,23], 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 [5]. Micronutrient deficiencies [16] and weight loss [26] 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 [15]. Given that vascular disease and dementia are thought to have a shared pathophysiology, [21] 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, [9,3,29] as indicated, 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 [9].

Studies examining the relation of oral disease with dementia are scarce, [13,7,11,24,22,17] and several have methodological shortcomings which hamper data interpretation. Case-control studies [13,7,10] 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. The prospective studies, [11,24,22] which are best placed to address this shortcoming, are generally small in scale, so offering limited statistical power.

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We directly address these issues of paucity of evidence, low study power, and methodological limitations by utilising data from cohort analyses of the Action in Diabetes and Vascular disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial [2,20,19]. This allows us to examine the predictive value of oral disease for dementia and, additionally, cognitive decline, which, with very few exceptions [25,18], no studies exist.

2. Methods

The ADVANCE trial, which has been described in detail elsewhere, [2,20,19] 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) [2]. 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 (HbA^{1c}), blood cholesterol (and fractions), blood pressure, resting heart rate, and serum creatinine were measured using standard protocols [2]. Height and weight were used to derive body mass index (weight[kg]/height[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) [28,12].

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; more or equal to 22) and days of bleeding gums (0; less than 12 days; more or equal to 12 days) were divided into three groups based on the distribution of data.

Cognitive function was assessed using the Mini Mental State Examination (MMSE) [6]. 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) criteria [1]. 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 three 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 assessment [4].

3. Statistical analysis

Having first determined that the proportional hazards assumption had not been violated for the two proxies of oral health in relation to dementia and cognitive decline, we computed hazard ratios with accompanying 95% confidence intervals. With no evidence of effect modification by gender, statistical models were

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) Mean (SD)	1–21 teeth (n = 4239) Mean (SD)	≥22 teeth[a] (n = 4549) Mean (SD)		0 days[a] (n = 9704) Mean (SD)	<12 days (n = 698) Mean (SD)	≥12 days (n = 738) Mean (SD)	
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
N° 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
	N (percentage)	N (percentage)	N (percentage)		N (percentage)	N (percentage)	N (percentage)	
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
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)	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

[a] Indicates superior oral health.