Association Between Oral Health and Cognitive Status: A Systematic Review

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Abstract

OBJECTIVES—We have carried out a systematic review of longitudinal studies examining the association between oral health and cognitive decline.

DESIGN—Studies, published 01/1993-03/2013, were identified by search of English language publications in PubMed/Medline using relevant MeSH terms and title/abstract keywords, and from CINAHL using relevant subject headings. After applying eligibility criteria, and adding four studies identified from article references, 56 of the 1412 articles identified remained: 40 were cross-sectional, and 16 longitudinal; 11 of the latter examined the impact of oral health on change in cognitive health or dementia incidence, five examined the reverse.

SETTING—Sources of information included administrative data, subject evaluations in parent studies, medical and dental records, self-reports, and in-person evaluations.

MEASUREMENTS—Most studies used subjects whose oral or cognitive status was known, adding the missing piece using standard measures. The oral health information most frequently studied included number of teeth, periodontal and caries problems, and denture use. Cognition was most frequently evaluated using the MMSE, or by determination of dementia.

RESULTS—Some studies found that oral health measures such as number of teeth and periodontal disease were associated with increased risk of cognitive decline or incident dementia, while others did not find the association. Similarly, cognitive decline was not consistently associated with greater loss of teeth or number of caries. Methodological limitations likely play a major role in explaining the inconsistent findings.

CONCLUSION—It is unclear how or whether oral health and cognitive status are related. Additional research is needed in which there is greater agreement on how oral health and cognitive states are assessed, in order to better examine the linkages between these two health outcomes.

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Keywords

Oral health; dementia; cognitive decline

INTRODUCTION

In the past two decades, an increasing number of studies has examined the relationship between cognitive impairment and oral health in older adults, since question has arisen as to whether, in the elderly, there is an association between oral health status and cognitive status, possibly through a common inflammatory pathway.[1,2] This issue is of considerable relevance given the rapid increase in the proportion and number of older persons in the population, an increasing number of whom are retaining their natural teeth.[3] Further, approximately 36% of those over age 70 are cognitively impaired,[4] and the prevalence of cognitive impairment and dementia increases with age.[5] Up to 5.1 million Americans currently have a dementing disorder,[6] with an expected doubling by 2050.[7]

Concomitantly, evidence from clinical samples suggests that the elderly have an increased incidence of oral disease, the frequency of oral health problems increasing significantly in cognitively impaired elderly, particularly those with dementia. Any intervention that might help delay the onset or progression of dementia, including improvement of oral hygiene and dental services, could have a significant impact on personal and family well-being, and health care costs.

In order to examine the association between oral health and cognition in the elderly, and provide direction for future studies, we conducted a systematic review of the existing literature. Our focus is on longitudinal studies, since they may be informative with respect to causation.

METHODS

Search Strategy

The time frame considered was from the first relevant publication found in 1993,[8] to 03/01/2013. We searched for human study publications in English in the *PubMed/Medline* database, using the MeSH terms (Memory Disorders or Cognition or Cognition Disorders or Dementia) AND (Oral Health or Mouth Diseases or Tooth Diseases), which identified 515 articles; a title/abstract keyword search using (mouth or tooth or oral AND cogni* or Alzheimer or dement*), which identified 790 articles; and the CINAHL database using the subject headings (dementia+ or Alzheimer's diseases or cognition+ or cognition disorders+ or memory disorders+) AND (mouth diseases or tooth loss or dental caries), identifying 107 articles. After removing 41 duplicates from the 1412 articles identified, 1371 unique articles remained (Figure 1).

We applied two exclusionary criteria to identify non-qualifying articles. The first criterion excluded 1,273 articles that, by title/abstract, did not examine the association between cognition and oral health diseases and conditions in adults; this left 98 articles. The second criterion excluded articles that, based on review of the abstract by two readers, had

inadequate information on oral health or cognitive status. Any disagreement was resolved by a third reviewer. In consequence, an additional 46 articles were excluded and 52 retained. To these were added four articles culled from article reference lists, resulting in a total of 56 articles, based on 55 studies. Of these, 40 articles represented cross-sectional studies, and 16 represented longitudinal studies.

Data Extraction

Two reviewers independently extracted information from each longitudinal article on: first author and date of publication, study name, location; study date(s), sample demographics; cognitive and oral health measures; covariates; and key findings. Disagreements on data extraction were resolved by consensus with the assistance of a third person.

RESULTS

The characteristics of the 16 longitudinal studies are summarized in Table 1. The first section summarizes the 11 studies of oral health predicting cognitive decline, the second section summarizes the five studies of cognitive status/dementia predicting oral health.

Several developed countries are represented: U.S. (n=8), Japan (n=3), Australia (n=1), France (n=1), Denmark (n=1), Sweden (n=1), and a European consortium (n=1). Two studies used the same sample, but different outcomes and statistical analyses.[9,10] All but four studies[9–12] were conducted among community residents, but some community-based studies may have included nursing home residents. Sample sizes ranged from small (N=42)[13] to large (N=11,140, from 215 centers in 20 European countries).[14]

Subject selection and source of data reflected several creative, overlapping approaches. These included use solely of administrative data, [15] use of data already gathered in longitudinal studies (often designed for other purposes), [9,10,16–20] selecting subjects for whom cognitive status or oral health status had been established and adding an oral or cognitive evaluation, [8,11,13,21,22] and linking subject data to administrative records.[23]

Study design varied: intervention studies of good oral care;[12,24] samples matched on demographics, by randomization,[8,12,13,21] or through use of propensity scores;[24] and natural history studies.[9–11,14–17,19,20,22,23]

Measures of Oral Health Status (information is summarized in on-line Table S1.)

Of the 16 studies, nine used oral health evaluation, and seven used dental records. In studies gathering oral health data, examiners were trained, calibrated if more than one participated, and reliability determined for assessing a variety of oral health measures. The amount of oral health information gathered in person or from records, and used in analysis, varied from extensive and highly detailed, particularly in studies of oral health predicting cognitive impairment (number of decayed, missing, filled teeth; plaque; periodontal disease), [8,13,20,22] to minimal (self-reported approximate number of teeth currently or when younger). [14,15,19,23] Subject-provided information included pain or discomfort, [17] bleeding gums, [14] and denture use.[11,19,23] Information from dental records was used in three studies, [9,10,24] two of which relied on up to 40 years of records.[9, 10, 25]

Tooth loss was the most common measure of oral health, recorded in 14 of the 16 studies, with a significant relationship to cognition reported in 11.[9–11,13,15–17,19,20,22,23] When used in analysis, the number of teeth present was typically categorized, with categorization varying from study to study, and sometimes linked to denture use. [9,11,15,17]

Eleven studies used clinical evaluation to assess oral health status.[8–13,16,17,20,21,24] In some studies, standard oral health indices were used: Debris Index for plaque score, [12] Community Periodontal Index, [17] Gingival Index, [20] Plaque Index, [20] Katz criteria for roots, and adjusted caries increment, [21] and National Institute for Dental Research (NIDR) criteria.[8,13,21,22]

In examining periodontal disease, attention was paid to [1)] extent of gingival bleeding on probing (ratio of examined sites), [2)] proportion of examined sites with loss of attachment >3 mm, and 3) mean pocket depth. Periodontal diseases were assessed in five studies, four on the impact of oral health on cognitive impairment (three studies used clinical assessment, [16,17,20] one used self-report[14]) and in one study of the effect of cognitive impairment on oral health.[13] In addition, two studies assessed periodontal damage based on decades of dental records.[9,10]

Measures of Cognitive Assessment (information is summarized in on-line Table S2.)

Assessment of the presence of dementia included self-reported diagnosis, use of standard clinical diagnostic criteria, neuropathological diagnostic criteria, and information from medical, dental, and administrative records. Cognitive status was based on a variety of neuropsychology measures, ranging from use of a substantial battery to reliance on a single brief measure.

The standard diagnostic criteria for dementia included DSM-III-R, DSM-IV, ICD-9CM-R, ICD-10, reflecting the date of evaluation.[13–15,17,22] At times these criteria were supplemented by NINCDS-ADRDA (Alzheimer's disease [AD]), [13,15,17] NINDS-AIREN (vascular dementia), [15] Hachinski scale (vascular dementia),[17] Lund & Manchester (frontal lobe dementia),[15] Geriatric Mental State examination,[17] and the Global Deterioration Scale,[26] which assesses both presence and severity of dementia.[21,22] Neuropathological criteria[27] were also used, but available for only one dataset.[9]

Non-AD dementias[15,17,22] were rarely analyzed separately because of limited numbers. The validity of administrative records, which were frequently used, was evaluated for only one study.[15] Both cognitive batteries and individual measures were used to assess cognitive change and ascertain the presence of dementia. The most popular single measure was the

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Mini-Mental State Exam (MMSE), [28] used in 10 studies – in eight as a single measure, four of which examined the effect of oral condition on cognitive state, [12,14,16,19] and four the reverse, [8,13,21,22] and in two studies as part of a larger neuropsychology battery.[9,17] All neuropsychology measures had established validity and reliability. Criteria used to assess cognitive change included self-perceived deterioration, change in score on neuropsychology measures, a specific decline (which differed across studies), crossing a cut-point (with cut-points differing across studies), or reaching an administrative criterion indicating need for assistance.

Covariates Used in Analysis (summarized in online Table S3.)

The covariates used varied widely across studies. They included demographic characteristics (sex, race, education, income, -- none uniformly reported); and specific health conditions and associated risk factors or the number of health conditions present (12 studies), and the Charlson Index.[31] Also considered were biomarker and genetic information (interleukin (IL)-6, C-reactive protein, APOE ε4, 1st degree kin with dementia); [9,10,19,20] prescription and over-the-counter medications, particularly anticholinergics;[16,20,21,24] scales of depression and caregiver burden;[14,17,21] and measures of life style and health behaviors (included by 10 studies). No study included all these areas.

Findings

The impact of oral health on cognitive status (11 articles)—Two studies indicated that having fewer teeth at baseline or decline in number of teeth, was not associated significantly with cognitive decline.[11,20] This was contradicted by other studies which found an association with cognitive decline, [10,16] and with dementia.[14,15,23] Findings are further complicated: one reported an association only in women; [19] another reported that with higher education the number of missing teeth was not associated with dementia, but among those with lower education, individuals with a greater number of missing teeth were less likely to have dementia;[17] and a third reported that having fewer teeth increased the hazard of dementia, but not when periodontal damage was present.[9] Development of caries or the presence of new restoration was associated with lower performance on the MMSE and a spatial copying task.[16] Mastication difficulty was not associated with incident dementia.[23]

Five studies examined the effect of periodontal disease on incident dementia, cognitive decline, or low level of cognitive functioning.[9,14,16,17,20] Two of them found some indication of a relationship: alveolar bone loss and pocket depth was associated with poor cognitive functioning,[16] the other found a significant decline on the Modified Mini-Mental State (3MS) Examination (which assesses several areas of cognition), but only when the continuous form of the gingival index was categorized, and the bottom quartile compared with the rest; no significant decline was found on the Digit Symbol Substitution Test.[20]

Three studies asked about or provided personal dental care. An intervention in nursing homes to make sure that teeth, dentures, and the oral cavity were cleaned, and plaque and calculus controlled, found a significantly smaller decline in MMSE score in the group receiving this oral care, however, variation was large and the numbers present at study end were unclear.[12] In one study, poor oral hygiene and no regular visits to the dentist predicted

incident dementia.[23] Similar findings were reported in another study but were sex-specific -- no daily tooth brushing (women only), and no dental visits in the previous 12 months (men only) predicted incident dementia.[19]

The impact of cognitive status on oral health (5 articles)—Sample sizes tended to be small when examining the impact of cognitive status on longitudinal oral status, while the number of oral outcomes of interest was large. One study, which provided routine dental care and treatment, focused specifically on tooth loss; neither number of teeth lost, nor rate of loss differed significantly between the dementia and no dementia groups.[24] Other studies also found no statistically significant differences in number of teeth or restored surfaces.[13,22]

Considerable attention was paid to increase in the number of caries, which, variously, was higher in patients with dementia,[21] higher but not significant because of small sample size,[8] or not significantly different.[22] Poorer MMSE scores were associated with increased gingival bleeding and plaque and diminished mucosal health, but with small sample size these findings were only suggestive.[12,14,16]

Assessment of strength of the eligible studies

We used a set of criteria to assess each of the studies, including sample selection, adequate sample size, description of the sample, validated assessment of the exposure (e.g., cognitive status or oral health measure) and outcome (e.g., cognitive status or oral health measure), length of follow-up period, attrition, controls for confounding, and appropriate analytic approach.[40] The evidence suggests that there are methodological deficiencies in this area, most notably due to small sample size or lack of representativeness of the population, inadequate assessment of cognitive function and lack of clinical evaluation of oral health. Thus, there was insufficient evidence to date for a causal association between cognitive function and oral health.

DISCUSSION

Our systematic review of the first two decades of longitudinal studies designed to examine the association between oral health and cognitive status identified 16 studies, 11 examined the effect of oral status on change in cognitive status, and five the reverse. The uneven distribution likely reflects the costs and difficulties of carrying out oral health assessments. It is easier and cheaper to add cognitive assessments to a study for which oral health has already been measured, than to do the reverse.

It is currently unclear how or whether oral health conditions and cognitive status are related. Findings based on number or change in number of teeth or caries, are conflicting, or, because of inadequate sample size, do not reach statistical significance. Limited studies (two out of five) found periodontal conditions, such as gingival health or pocket depth, was associated with poorer cognitive status or cognitive decline, with findings possibly sensitive to the neuropsychology assessments used. There are indications, albeit weak, that better oral hygiene and regular dental visits may reduce the rate of cognitive decline, and the hazard of incident dementia.[12,19,23] Certainly, with good dental care, the dental status of patients with dementia remained comparable to that of patients without a dementing disorder.[24] These

findings may reflect that incipient cognitive decline or dementia leads to decline in hygiene, but that oral health can be maintained with self or assisted oral hygiene, and dental appointments.

While the argument of a common underlying cause associated with inflammation may be enticing,[1,2] it was examined directly in only one study, and there found to be only marginally relevant.[20] Current studies are not adequate to indicate whether poor oral health and cognitive decline have a common underlying cause in inflammation, but with the increase in major surveys with biomarker data, test of this hypothesis is becoming more feasible.

Because of the costs of detailed dental examination, there may be a temptation to carry out small sample studies. As seen in the current review, this results in a lack of power. There is also a temptation to match cases and controls, but matching must be considered carefully. Doing so eliminates the possibility of examining the "matching" conditions (e.g., demographic characteristics), which may be associated with both oral health and cognitive status. With an older population, the duration of a study becomes an issue because of incidence of additional chronic conditions which may affect oral health and cognition, attrition due to sickness, and death.

To better compare findings across studies, agreement is needed regarding the oral health issues to be explored, oral health and neuropsychological measures to use, and covariates for which to adjust. In particular, to reduce the costs of dental studies, additional information is needed on the extent to which self-report accurately determines oral health condition, oral hygiene behavior, and dental visits. While it appears that self-assessment of obvious conditions (e.g., number of teeth), and those that are salient (e.g., root canal, dentures) can be reported reliably (with accuracy varying by demographic status), report is less reliable for conditions requiring oral health expertise (e.g., caries, periodontal disease).[32,33] However, since no studies have been conducted to examine the reliability of self-reported data among individuals with cognitive impairment, we are less certain how reliable the self-reported oral health data is in such individuals.

There is a considerable literature on assessment of cognitive state, with agreement on preferred measures to use in Memory Disorders clinics to assess dementing disorders,[34] and procedures to follow in epidemiological studies, such as diagnostic adjudication. With increasing information on dementia, diagnostic criteria are changing, and diagnosis at an earlier stage of disease is becoming possible. Consequently, the characteristics of diagnosed subjects may change, with findings on an oral health/dementia association changing also.

Standardization of assessment of cognitive status should be considered. The most frequently used measure has been the MMSE,[28] indicating preference for a brief, easy to administer assessment. The MMSE has several drawbacks: multiple versions with unknown equivalence; performance, as with many brief cognitive screens, that is age-, race-, and education-biased; a ceiling effect, and payment required for use. Improved screens, such as the Montreal Cognitive Assessment[35] have become available since data were gathered for many of the current studies, and these screens should be considered. Agreement on use of a brief screen would facilitate comparison of findings, and aggregation of data.

Covariates varied from study to study, with a large variety reported: demographic, health conditions (in particular cardiovascular conditions and risk factors), medications (anticholinergics), health behaviors, and an assortment of other characteristics (e.g., scales of depression, caregiver burden). Certain relevant information was rarely included: e.g., nutrition, which affects oral health and general health, and environmental characteristics (dental insurance, access to dentists, cultural expectations regarding dentition). Although many studies have found self-report of medical conditions to be valid,[36] caution is needed regarding medical and dental records and administrative data. Diagnosis of dementia based on administrative records which determine level of care to be provided may yield over-diagnosis, while dementing disorders may be under-reported in administrative medical records and death certificates.[37,38] Agreement is needed on which covariates to include in analysis, and the manner in which they should be handled, in particular, regarding categorization of age, and education.

Current studies that capitalize on already available information on oral health, cognition, or biomarkers, illustrate how sample size and possibly representativeness can be increased, and costs reduced. In addition to secondary analysis of data,[14,16,20] some studies have used administrative records with known sensitivity and specificity for diagnosis of dementia,[15] while others have linked the main study data to dental records.[9,10] Although there is no report as to whether those dental records were evaluated, studies that have examined pre-existing radiographs have found them to be usable for assessment of periodontal disease.[39]

This is the first systematic review to examine longitudinal studies focused on oral health and cognition. As such, it shows substantial diversity across studies with regard to data and sample sources, sample size, and variety of oral health data and cognitive data obtained. In summary, the strength of the evidence is weak, and findings were often inconsistent. For example, some studies found a significant association, albeit relatively weak, between periodontal disease and cognitive decline; but other studies found no association. Similarly the association between dental caries and cognition was inconsistent across studies. Findings are even more complex for the association between tooth loss and cognitive decline, ranging from a positive association, to no association, to a negative association (only in the group with a lower level of education) across different studies. However, these studies lay the groundwork for future longitudinal work.

While research in the field appears to be moving in the right direction, we would like to make some specific suggestions, operationalization of which may permit more accurate determination of the grounds for an association, if one is present, between oral health and cognitive status. In the current studies, cognitive function has been evaluated using a great variety of cognitive measures. Information could be better evaluated if there was agreement on a uniform set of cognitive assessments. When change in cognition is assessed, it may be preferable to examine decline in cognitive function (which is more straightforward to assess), instead of development of dementing disorders, with attendant complexities in diagnosis. Regarding the assessment of oral health status, several studies used standardized oral health examination protocols, such as the U.S. National Institute of Dental Research protocol,[21,22], a procedure which should be emphasized. Future research should pay more attention to calibration of dental assessment, both between and within dental evaluators. The

oral health outcomes used should reflect oral health status which can change during the study period. With respect to other aspects of study design, use of standard covariates, samples sized adequately for the number and type of outcomes to be measured and better representative of the study population, a study duration appropriate to the planned outcome, and sophisticated statistical approaches already in use should be encouraged.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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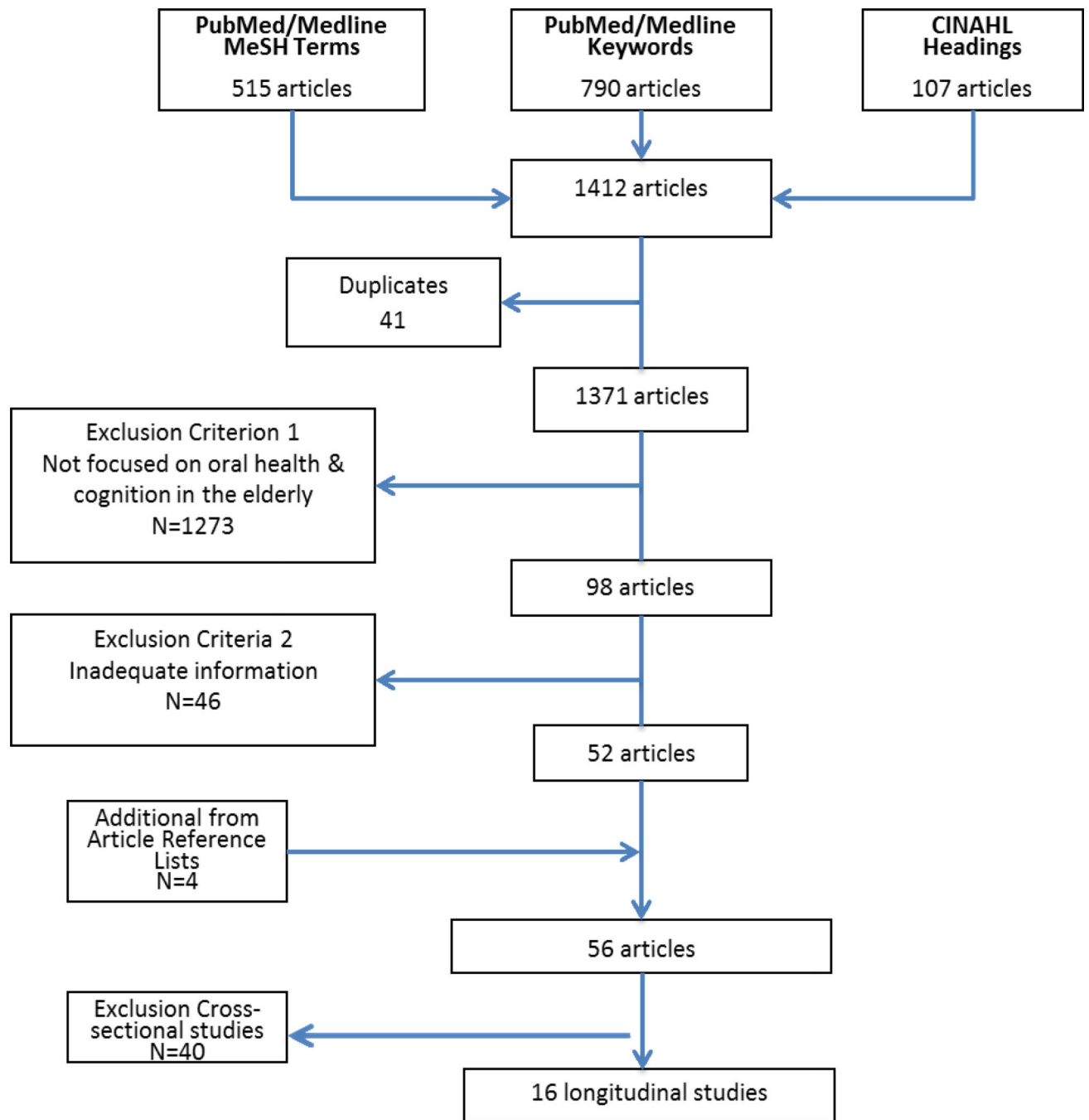
Figure 1.
Identification of relevant articles

Table 1

Characteristics of longitudinal studies of oral health and cognitive status[a]

Author/Location/ Study Title	Sample/ Study Design	Cognitive Measures	Oral Health Measures	Primary Covariates	Key findings and analytic procedures[b]
ORAL DISEASE PREDICTS COGNITIVE IMPAIRMENT					
Shimazaki et al., 2001[11] Kitakyushu City, Japan 29 institutions for elderly	Baseline: 10/1988–02/1989 N=1929 (87% of residents) Followup:10/1994–03/1995 N=719 (856 died, 167 status unknown, 187 hospitalized) M=169; F=550 Age range: 59–107; mean age 79.7±7.5y	From medical records Mental health status: Good/ Fair/ Poor re: symptoms of dementia or cognitive disability Followup: Deterioration = symptoms of dementia, or cognitive disability status at lower level	Baseline: 2 dentists trained in use of epidemiological indices for oral health No. teeth (excluding retained roots) categorized, denture use for eating	From medical records Age, sex, mobility, type of institution, chronic diseases	Logistic regression adjusted for age, physical health status, type of institution, cerebrovascular disorder: *No. teeth, denture use, not associated with decline in mental health status* Reference = 20+ teeth (OR, 95% CI) 1–19 teeth+dentures 1.9 (0.8–4.6) 1–19 teeth-dentures 2.3 (0.9–5.8) 0 teeth+dentures 1.0 (0.7–4.0) 0 teeth-dentures 2.4 (0.9–6.5)
Yoneyama et al., 2002[12] Japan 11 nursing homes	Baseline: 09/1996, followed at 6, 12, 18, 24 months N=366, randomized: 184 oral care (M=36, F=148; mean age 82.0±7.8y) 182 no oral care (M=37, F=145; mean age 82.1±7.5y) Oral intervention – brush teeth for 5″ after each meal, or clean oral cavity. Clean dentures daily. Plaque and calculus control as necessary.	MMSE score at baseline, 24 months	Debris index for plaque score		Survivors only. *24 month change in MMSE score:* Oral care: –1.5 +/– 4.9 No oral care: –3.0 +/– 5.9 P <.05
Gatz M et al., 2006[15] Sweden, Swedish Twin Registry HARMONY study	Questionnaires mailed 1961, 1963, 1967 (1970 if no response in 1967) 1998 survivors age 65+ of same sex twins born before 1926, and contacted for HARMONY study N=310 dementia (M=85, F=225), average onset age: 78.95±7.00y N=3,063 nondemented (M=1,200, F=1,863), mean age 79.23 ± 4.73y	Dementia determined from Swedish Inpatient Discharge Registry and Swedish Cause of Death Registry (sensitivity 63%, specificity 98% for dementia)	Self-report of own teeth at age 35 (all or most/ half/ few or none)	Age, sex, education CVD Lifestyle before age 40: Mental activity (reading, cultural activities, studies) Physical exercise Adult height (>1sd shorter vs. rest) Parents' social class (upper, middle, lower)	Analyses adjusted for all covariates. *Loss of all teeth* *Case control analysis predicting* (1) all dementias, (2) Alzheimer's disease: (1) OR 1.49 (1.14–1.95) (2) OR 1.68 (1.21–2.32) *Monozygotic co-twin control analyses:* (1) OR 3.60 (1.34–9.70) OR 5.50 (1.22–24.80)
Stein et al., 2007[9] Milwaukee, WI Nun Study[25] (Snowdon, 1997)	Baseline: 1991–1992 N=144 nuns with cognitive assessment and known APOE e4 status Age range 75–98y N=32 with dementia	CERAD neuro- psychology battery, administered annually for 12 years Dementia criteria: NINCDS-ADRDA	40 years of dental records No. teeth excluding non- third molars present at first cognitive evaluation.	Age, education APOE e4 status Medical history in dental records (N=133) Medical conditions	*Incident dementia over 12 years:* Adjusted for age, education, APOE e4: 0–9 teeth vs 10–28 teeth: HR 2.20 (1.1–4.5)

Author/Location/ Study Title	Sample/ Study Design	Cognitive Measures	Oral Health Measures	Primary Covariates	Key findings and analytic procedures[b]
	N=112 without dementia. N=101 with adequate followup data. Neuropathology data on 118/129 decedents. Followup: annual, 12 years	Braak staging for AD neuropathology	Presence of periodontal damage	associated with inflammatory process	Further adjusted for periodontal damage, no association HR 2.4 (0.86–6.6) For 118 deceased, adjusted for age, education, APOE e4: No association between no. of teeth and severity of AD neuropathology (Braak stage): 1.1 (0.49–2.7); or brain infarcts: 1.14 (0.49–2.66)
Kaye et al., 2010[16] US Dept. of Veterans Affairs Dental Longitudinal Study Boston, Mass metropolitan area	Baseline: 1968 Original N = 1,231 Race: 97% White, 3% Black Current study: N=597 men with necessary dental and cognitive data Age 24–84 Convenience sample, community dwellers Followup: up to 32 years (until 2002)	Given at each dental exam. (~every 3 years) MMSE (low score = <25, or <90% of age/education specific median) Spatial copying task (SCT)	Dental exam ~every 3 years by calibrated periodontist, reliability of measurements determined Number of teeth, maximum probing pocket depth for each tooth, alveolar bone loss Caries or restoration (5 tooth surfaces examined)	Age, education smoking aspirin use, NSAIDs BMI, CHD, stroke, hypertension, CVD, cancer, diabetes alcohol, coffee, tea, folate, B6, B12	Adjusted analyses *Additional tooth loss/decade associated with low:* MMSE: HR 1.09 (1.01–1.18) SCT: HR 1.12 (1.05–1.18) *Increased alveolar bone loss associated with low:* MMSE: HR 1.03 (1.00–1.07) SCT: HR 1.03 (1.01–1.06) *Increased pocket depth associated with low:* MMSE: HR1.04 (1.01–1.09) SCT: HR 1.04 (1.01–1.06) *New caries, restoration: associated with low:* MMSE: HR 1.02 (0.97–1.08) SCT: HR 1.05 (1.01–1.08)
Stein et al., 2010[10] Milwaukee, WI	Same sample as Stein et al., 2007	Delayed word recall (from CERAD Neuropsychology battery)	Same as Stein et al., 2007.	Education (high school vs >high school) APOE e4	Persons with *APOE e4 allele,* 9 *teeth, or both,* had poorer delayed recall scores at baseline and declined faster than those with either one or neither of these risk factors.
Arrivé, et al., 2012[17] PAQUIDENT (PAQUID Dental study), substudy of Personnes Agées QUID (PAQUID) study (Dartigues et al., 1992) Gironde, southwest France	PAQUIDENT baseline: 1989–1990 N=405 Age 66–80 Median age=70 M=184, F=221 No dementia Median followup=10y PAQUID baseline: 1988 Followup: 1,3,5,8,10,13,15y (through 2003) Community dwellers	MMSE, Benton Visual Retention Test, Wechsler Paired Associates, verbal fluency, visuospatial attention, digit symbol Dementia criteria: DSM-III-R NINCDS-ADRDA (for AD) Hachinski score (vascular dementia) Dementia status ascertained after in-person assessment by neurologist (demented vs normal).	In-home oral exam by 10 trained, calibrated dentists. No. decayed, missing, filled teeth (DFMT) (for 28 teeth) No. missing teeth (denture substitution counts as own teeth) Plaque/calculus Periodontal exam for Community Periodontal Index (CPI)	Sex, education (lower vs higher, years not specified), living condition, Tobacco, alcohol use Health status: CES-D depression, BMI, vascular risk factors	Adjusted for sex, BMI, vascular risk factors Predicting incident dementia *Higher education* 11 missing teeth vs <11: HR 1.07 (0.57–2.02) Bleed/calculus: HR 0.71 (0.31–1.63) Pockets: HR 0.42 (0.15–1.15) No eligible sextant: HR 1.51 (0.63–3.57) *Lower education* 11 missing teeth vs <11: HR 0.30 (0.11–0.79) Bleed/calculus: HR 1.24 (0.39–3.88) HR Pockets: 0.97 (0.29–3.19) No eligible sextant: HR 0.02 (0.28–3.66)

Author/Location/ Study Title	Sample/ Study Design	Cognitive Measures	Oral Health Measures	Primary Covariates	Key findings and analytic procedures[b]
Paganini-Hill et al., 2012[19] Leisure World Laguna Hills, CA, USA	Study dates: 1992–2010 N=5,468 Median age: 81y, range 52–105 M=1,733; F=3,735 No. with incident dementia: 1,145 (followed up to 18 years) Retirement community	Dementia determined by: In-person evaluation for age 90+ with dementia, identified by different study). Self-report (n=90), hospital records (n= 46), death certificates (n=490) Date of diagnosis = date dementia first mentioned	Self-report: # natural teeth: <16/ 16–25/ 26+ Adequate natural dentition (10 in upper jaw, 6 in lower jaw) Inadequate natural dentition: wears dentures/ does not Oral health habits	1992 -- Self-reported education, head injury, first degree relative with Alzheimer's disease, senility or dementia 1983/1985 – smoke, alcohol, caffeine BMI, hypertension, angina pectoris, heart attack, rheumatoid arthritis, cancer, HBP, stroke, diabetes Active/sedentary	Fully adjusted, predicting incident dementia. Separate analyses for men and women No. natural teeth – NS (men and women) Inadequate natural dentition, no dentures, men: HR 1.91 (1.13–3.21), women: HR 1.22 (0.86–1.73) Inadequate dentition, alone or with dentures: – NS (men + women) Oral health habits (40 comparisons) No daily tooth brushing: HR 1.65 (1.05–2.62), women only. No dental visits last 12 months: HR 1.89 (1.21–2.95), men only
Yamamoto et al., 2012[23] Aichi Gerontological Evaluation Study (AGES) Six municipalities in Aichi province, Japan	Baseline: 2003 N=4,425 (from mail survey of random sample of 9,783 community residents) Age: 65+ Sex: M=2,158; F=2,267 Race/ethnicity: Asian Follow up: 4-year cohort study Community residents	Dementia onset: from administrative data -- Certified to receive insurance benefits, based on Ministry questionnaire on functional, cognitive, behavioral, communication problems in dementia. Graded I-IV, M (I=can still live independently, IV=consistent care needed, M=severe psychiatric symptoms, specialized medical service needed)	Self-report 20 teeth / 19 teeth Few teeth + denture use Few teeth no dentures Data missing Mastication: Chew anything/ cannot chew at all Have regular dentist (yes/no) Personal dental care good (yes/no)	Age, gender, adjusted household income BMI, current illnesses (up to 18 conditions) Smoking history, alcohol use Exercise Forgetfulness	Adjusted for all characteristics excluding "forgetfulness". Predicting incident dementia. Only significant findings reported. *Oral health status. Reference: 20 teeth* Few teeth no dentures: HR 1.85 (1.04–3.29) *Mastication* Can't chew very well: HR 1.47 (0.95–2.25) *No regular dentist* HR 1.44 (1.04–2.01) *Poor personal dental care* HR 2.01 (1.11–3.63)
Batty et al., 2013[14] ADVANCE trial Impact of reducing blood pressure, intensive glucose control, on Type II diabetes. 215 centers, 20 countries	Baseline: 2001–2003 N=11,140 M=6,407; F=4,733 Age: 55–88 (all with type II diabetes and history of major macro- or microvascular disease, or at least 1 other cardiovascular risk factor) White (67%) (other ethnicities not reported) Followup: for 5 years	MMSE (3 assessments over 5 years) If MMSE <24, or MD or nurse suspected dementia, referred to specialist for dementia evaluation, DSM IV criteria Cognitive decline = drop ≥3 MMSE points by 3rd assessment	Baseline: Self-reported no. of natural teeth connected to gum or jawbone. No. days bleeding gums in past 12 mos.	Age, sex, EQ-5D, socioeconomic, CVD risk factors: -behavioral -physiological -psychological	Fully adjusted *Incident dementia (N=109)* No. of teeth Reference 22 teeth 0 teeth HR 1.48 (1.24–1.78) 1–21 teeth HR 1.24 (1.05–1.46) Bleeding gums 12 days HR 1.19 (0.51–2.75) <12 days HR 0.42 (0.10–1.71) *Cognitive decline (N=1,806)* No. of teeth 0 teeth HR 1.39 (1.21–1.59) 1–21 teeth HR 1.23 (1.10–1.38) Bleeding gums 12 days HR 0.94 (0.77–1.15) <12 days HR 0.92 (0.75–1.13)
Stewart et al., 2013[20] Memphis and Pittsburgh, US	Baseline: 1997/1998 N=947 (with cognitive data, y5) Age 70–79	Cognitive assessment: 1997/1998 (y1), 1999/2000 (y3), 2000/2001 (y5)	Dental examination 1998/99 (year 2) No. of teeth No. occluding tooth	Age, sex, education, race Self-reported cardiovascular disease	*Change in year1-year3 3MS* 3MS cognitive impairment and decline; stratified by APOE e4 genotype to ascertain effect

Author/Location/ Study Title	Sample/ Study Design	Cognitive Measures	Oral Health Measures	Primary Covariates	Key findings and analytic procedures[b]
Health Aging & Body Composition (Health ABC) study	M=~50%; F=~50% Race/ethnicity: Black 34%, White 66% Healthy Medicare community residents in local area, unimpaired basic ADL or mobility. Included all Blacks, and random sample of Whites Sample based on year 2 oral health participants Followup: year 5	Cognitive impairment: 3MS score <80 (bottom 10%) Cognitive decline: Decline 5 points (~20%) Year 3 – Digit Symbol Substitution test (DSST), clock drawing Cognitive impairment = bottom 10%	pairs Probing depth Attachment loss (no. & proportion of sites) Mean gingival index Mean plaque score No. sites bleeding on probing All measures categorized into quartiles	and risk factors CES-D score C-reactive protein, IL-6 at y1; weight loss y1-y3 Anticholinergic medication APOE e4	modification. No significant association of any dental measure with cognitive decline on 3MS Closest: no. of teeth, OR 0.88 (0.77–1.00), gingival index OR 1.17 (0.99–1.38) DSST decline: no association Dichotomized gingival index (Q4/rest): associated with decline in 3MS, fully adjusted: OR 2.28 (1.60–3.25) No association with DSST
COGNITIVE IMPAIRMENT PREDICTS ORAL DISEASE					
Study	Sample	Cognitive Assessment	Oral Health Measures	Primary covariates	Key findings
Jones et al., 1993[8] Dept. of Veterans Affairs (VA) Longitudinal Study of Dementia. VAMC, Bedford, MA Dept. of Veterans Affairs Dental Longitudinal Study – VA-DLS (subset of VA Normative Aging Study). Boston VA	Baseline: 1986–1989 Dementia (AD) N=23 male veterans (from Dept. of Veterans Affairs Longitudinal Study of Dementia) Age: 67.4±7.5 Controls (matched on age, number of teeth, education) N=46 male veterans (VA-DLS) Age: 65±12 Followup: 23, 50 months Retrospective data	AD cases drawn from VA Longitudinal Study of Dementia, with previously determined diagnosis. MMSE	Initial caries examination: after teeth scaled and polished 50 month followup: caries examination (teeth not scaled or polished) NIDR criteria Katz criteria for root caries evaluation Annualized net caries increment (% per 100 available surfaces)	Demographic (from medical records)	Annualized followup: *Veterans with AD* had increased coronal caries increment 2.29±4.29 vs 0.88±1.14; root caries 2.38±5.57 vs. 0.31±0.69 per 100 available surfaces compared with control group. All findings NS.
Ship & Puckett, 1994[13] National Institute on Aging Normative Aging Program Also, Clinical Center, National Institutes of Health, Bethesda, MD	Baseline: AD: N = 21 M=13; F=8 Age: 64±9 Controls (age, gender matched) N=21; M=13; F=8 (from National Institute on Aging Normative Aging Program Age: 65±12 Community residents, unmedicated Persons with other medical, neurological, psychiatric conditions excluded. Followup interval: AD 23±11 months Controls: 36±1.5 months	NINCDS-ADRDA criteria for AD (vigorous screening) MMSE Change in MMSE score	Unstimulated & stimulated major salivary gland flow rates Extensive assessment of gingival, periodontal (NIDR criteria), dental and oral mucosal tissues. Standard criteria and scales used in assessment. Test-retest reliability of assessment determined. Annualized change		No association between *change in salivary flow rate and change in MMSE* *Gingival health*: Poorer MMSE scores associated with increased gingival bleeding and plaque. *Periodontal health*: no difference between groups *Number of teeth, restored surfaces* no difference *Loss of tooth attachment*: findings unclear *Intraoral mucosal tissue*: no difference between groups, but lower MMSE scores related to diminished mucosal health
Chalmers et al., 2002[21]	Baseline: 1998/99 116 dementia	Physician confirmed diagnosis	Two calibrated dentists NIDR protocol	ADL (Katz) IADL (Lawton Brody)	*Caries increments* (dementia vs nondementia):

Author/Location/ Study Title	Sample/ Study Design	Cognitive Measures	Oral Health Measures	Primary Covariates	Key findings and analytic procedures[b]
"Oral health of community dwelling older adults with dementia" South Australian Dental Longitudinal Study (SADLS) Adelaide, Australia	116 no dementia Gender, age matched (M=66, F=50), age (79 = 91, 80 = 25) Followup: 1999/2000 103 dementia 113 no dementia. Exclusionary factors: Edentulous, too ill, refused Dementia cases -- in-home assessment only No dementia – in-home or clinic assessment Community residents	Dementia: 76% AD, 24% other MMSE 26 no dementia 21–25 mild 11–20 moderate 10 severe dementia GDS	Tooth status (present, absent, replaced, root status) Caries (initial, incident): coronal, root surface; sound, decayed, treated; gingival recession Assessed as crude caries increment (CCI), net caries increment (NCI), adjusted caries increment (ADJCI) Reliability of assessing caries incidence determined	No. medical conditions Anticholinergics: (severity: none, low, high) Dental care issues Zarit Burden Scale Medical status, medication status, cognitive status	Coronal: CCI=3.7 vs 1.5 NCI=3.5 vs 1.4 ADJCI=3.6 vs 1.4, all P<0.01. Incidence: 71.8% vs 48.7%, P<0.01. Root surfaces: CCI=1.9 vs 0.9 NCI=1.7 vs 0.8 ADJCI=1.8 vs 0.9, all P<0.01. Incidence: 62.1% vs 44.2%, P<0.01. Greater root caries incidence in high maintenance patients. Dementia group – coronal caries increment: 3.5 (for 1 increment in nondemented) (p=0.001) GDS moderate-severe dementia – additional 1.78 coronal increments (p=0.01); 0.95 root caries increment (p = 0.001)
Ellefsen et al., 2009[22] Copenhagen, Denmark Two hospital memory clinics	Baseline: 2002–2004 N=106 (AD=61, other dementia (OD)=26, no dementia=19) M=37, F=69 Followup: ~1 year later N = 77 (AD=49, other dementia=15, no dementia=13) M=28, F=49 Mean age: 81.9 (no information on age range)	MMSE Dementia criteria: ICD-10 AD vs. other dementia vs. no dementia	Oral evaluation in home NIDR criteria for coronal and root decayed surfaces and filled surfaces, gingival recession. Calculated Adjusted Caries and filling Increments (ADJCIs) Number of teeth present, dental prostheses	Demographic, functional, social variables from structured questionnaire	No statistically significant differences for decayed and filled coronal and root surfaces, although rates higher for AD, OD, than for nondemented. ADJCIs higher for age 80+, but not always significant. No difference for MMSE <24 vs ≥24. Predicting coronal caries AD: OR 0.64 (0.09–4.50) OD: OR 4.13 (0.44–39.05) Predicting root caries AD: OR 0.08 (0.01–0.79) OD: OR 1.01 (0.11–9.56)
Chen et al., 2010[24] St. Paul, Minnesota USA Geriatric dental clinic affiliated with U Minnesota School of Dentistry, for age 55+, persons with disabilities, community and nursing home residents.	Study years: 10/1999-12/2006, followup 1–90 months, mean 38.8 months N = 491 Dementia N=119 M=30, F=89 Mean age: 81.5±9.2 Range: 49–102 No dementia (propensity score matched) N=372 M=110, F=262 Mean age: 73.8±10.7 Range: 44–103 New patients, dentate after initial treatment, returned for routine care at least once.	Medical history from dental records; diagnosis of AD, other dementia, CBS, or ICD-9CM-R codes 290.x, 294.1, 331.2 Medical, cognitive, functional assessment from dental records	From dental records Followup treatment focused on continued treatment as needed	Charlson comorbidity index Anticholinergic drug scale (ADS), to measure medication-related anticholinergic burden	Fully adjusted models *No. teeth lost:* HR 0.92 (0.59–1.63) P=0.99 *Rate of tooth loss:* P=0.52, slightly higher in dementia patients, but difference NS

[a] If there was no indication of race, or of number of men or women, the information was not mentioned in the paper.

Psychological measures for which results are not reported have been excluded to reduce space.

All abbreviations in the table have been spelled out below, together with references where appropriate.

[b] Values in parentheses in this column indicate 95% confidence interval

3MS = Modified Mini-Mental State Examination: Teng EL, Chui HC. The Modified Mini-Mental State (3MS) Examination. J Clin Psychiatry 1987;48:314–318.

AD = Alzheimer's disease

ADjCI = Adjusted Caries Increment, determined as CCI (crude caries increment [number of surfaces] (1-examiner reversals/examiner reversals + x [decayed/recurrent/filled/filled unsatisfactory/root sound])

ADL = activities of daily living: Katz S, Ford AB, Moskowitz RW et al. Studies of illness in the aged. The index of ADL.: a standardized measure of biological and psychosocial functioning. J Am Med Assoc 1963;185:914–919.

ADS = Anticholinergic drug scale: Carnahan RM, Lund BC, Perry PJ et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: association with serum anticholinergic activity. J Clin Pharmacol 2006;46:1481–1486.

Anticholinergic drug scale: Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The anticholinergic drug scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol 2006;46:1481–1486.

APOE = Apolipoprotein E

BentonVisual Retention Test: Benton AL. Manuel pour l'application du test de retention visuelle. Applications cliniques et expérimentales. 2e edition franaise. Paris, Centre de Psycholgie Appliquée, 1965.

BMI = body mass index (weight[kg]/height[m^2])

Braak staging: Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–59.

CBS = chronic brain syndrome

CCI = crude caries increment

CERAD: Morris JC, Heyman A, Mohs RC et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part 1. Clinical and Neuropsychological Assessment of Alzheimer's Disease. Neurology 1989;39:1159–1165.

CES-D = Center for Epidemiologic Studies-Depression Scale: Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. J Appl Psychol Meas 1977;1:385–401.

Charlson comorbidity index: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–383.

CHD = coronary heart disease

CPI = Community Periodontal Index: World Health Organization, Community Periodontal Index (CPI) in Oral Health Surveys – Basic methods, World Health Organization, Editor. 1997: Geneva. Pp.36–38.

CVD = cerebrovascular disease

Debris Index: Green JC, Vermillion JR. The oral hygiene index: a method for classifying oral hygiene status. J Am Dent Assoc 1957;61:171–179.

DSST = Digital Symbol Substitution Test

Digit symbol test: Wechsler D. WAIS-R Manual. New York, Psychological Corporation, 1981.

EQ-5D = Quality of life: The EuroQol Group. EuroQol-a new facility for the measurement of healthrelated quality of life. Health Policy 1990;16:199–208. See http://www.euroqol.org/ for most recent information. Accessed October 21, 2014

GDS = Global Deterioration Scale: Reisberg B, Ferris SH, DeLeon MJ, et al. The Global Deterioration Scale (GDS): an instrument for the assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136–1139.

Gingival Index: Loe H. The Gingival Index, the Plaque Index and the Retention Index systems. J Periodontol 1967;38:610–616.

HBP = High blood pressure

HR = Hazard ratio, analysis in which time to an event is taken into account

IADL = instrumental activities of daily living

IL–6 = interleukin-6, an inflammatory marker

Katz criteria for root caries: Katz RV. Assessing root caries in populations: the evolution of the root caries index. J Pub Hlth Dent 1980; 40:7–16.

L–B = Lawton MP, Brody E. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontotgist 1969;9:179–186.

MMSE: Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

NCI = net caries increment

NIDR = National Institute of Dental Research

NINCDS-ADRDA = National Institute of Neurological, Communicative Disorders, and Stroke-Alzheimer's Disease and Related Disorders Association

NSAID = Non-steroidal anti-inflammatory drug

OR = Odds ratio, analysis concerned with whether an event has taken place

VA = Veterans Administration

VA-DLS = Veterans Administration Dental Longitudinal Study

VAMC = Veterans Administration Medical Center

Verbal Fluency: Isaacs B, Kennie AT. The Set Test as an aid to detecting dementia in old people. J Psychiatry 1973;123:467–470.

Visuo-spatial attention: Zazzo R. Test des deux barrages. Actualités pédagogique et psychologiques, vol 7. Neuchâtel, Delachaux et Nestlé, 1974.

Wechsler Paired Associates: Wechsler D. A standardized scale for clinical use. J Psychol 1945;19:87–95.

Zarit Burden Scale: Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist 1980;20:649–655.