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Miscellaneous

Oral health and mortality in the Golestan Cohort Study

Emily Vogtmann,[1] Arash Etemadi,[1,2] Farin Kamangar,[2,3] Farhad Islami,[2,4] Gholamreza Roshandel,[5] Hossein Poustchi,[2] Akram Pourshams,[2] Masoud Khoshnia,[5] Abdulsamad Gharravi,[2,5] Paul J Brennan,[6] Paolo Boffetta,[7] Sanford M Dawsey,[1] Reza Malekzadeh[2]* and Christian C Abnet[1]

[1]Division of Cancer Epidemiology & Genetics, National Cancer Institute, Bethesda, MD, USA, [2]Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Shariati Hospital, Tehran, Iran, [3]Department of Public Health Analysis, Morgan State University, Baltimore, MD, USA, [4]Surveillance and Health Services Research, American Cancer Society, Atlanta, GA, USA, [5]Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran, [6]International Agency for Research on Cancer, Lyon, France and [7]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

*Corresponding author. Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Shariati Hospital, Tehran, Iran. E-mail: malek@tums.ac.ir

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Abstract

Background: Previous studies have found associations between oral health and mortality, but the majority of previous studies have been conducted in high-income countries.

Methods: We used data from the Golestan Cohort Study, a study of 50 045 people aged 40 to 75 years in north eastern Iran, recruited from January 2004 to June 2008. Tooth loss and decayed, missing and filled teeth (DMFT) were assessed by trained physicians. Frequency of tooth brushing and use of dentures were self-reported. Cause-specific mortality was ascertained through March 2014. We calculated hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the associations between the oral health variables, overall mortality and cause-specific mortality.

Results: Participants with the greatest tooth loss had increased overall mortality (HR 1.43; 95% CI: 1.28, 1.61) compared with those with the least tooth loss; similar estimates were observed for DMFT score. For cause-specific mortality, an increased risk of death was found for tooth loss and mortality from cardiovascular disease (HR 1.33; 95% CI: 1.13, 1.56), cancer (HR 1.30; 95% CI: 1.03, 1.65) and injuries (HR 1.99; 95% CI: 1.28, 3.09). The associations between oral health and injury mortality were strongly attenuated after exclusion of participants with comorbid conditions at baseline. No statistical interaction was found between denture use and tooth loss or DMFT on mortality.

Conclusions: Poor oral health appears to predict overall and cause-specific mortality in populations in economic transition. Investigation of the underlying mechanisms might provide an important contribution to reducing mortality.

Key words: Oral health, tooth loss, mortality, cardiovascular disease, cancer, injury

Key Messages

- Poor oral health, as measured by tooth loss and decayed, missing and filled teeth, was associated with overall mortality in a population of adults in Iran.
- Participants who used dentures had a lower rate of overall mortality.
- Poor oral health was associated with specific causes of death including cardiovascular disease, cancer and injury.
- The nature of the association between oral health and injury is unclear, but it may be related to residual confounding by an unknown factor or some underlying bias, since the association was substantially attenuated among participants who reported no pre-existing conditions at baseline.

Introduction

Poor oral health, including tooth loss and periodontal disease, is common around the world. For example in the USA, the prevalence of periodontal disease among adults was 46% in 2009–12.[1] Poor oral health has been found to be associated with increased risk of a number of health conditions, including cardiovascular disease[2] and cancer.[3] In addition, the association between oral health and overall mortality has been considered in a number of studies; one review found that out of the 15 published studies in the literature, 12 reported a significant positive association between poor oral health and overall mortality.[4] Of the studies in this review, all were conducted in Western or East Asian populations and predominantly in high-income countries.[4] Good oral care practices, such as tooth brushing and denture use, may decrease mortality.[5] Very few studies have investigated the impact of denture use on mortality, but there is some evidence that for people with tooth loss, dentures may decrease mortality risk.[4]

Previous research considering the overall impact of oral health on mortality has primarily focused on high-income countries, but this association may differ in places with less access to dental care or unique dental care practices. The Golestan Cohort Study, a large cohort study conducted in Golestan Province, Iran, provides a unique opportunity to study these associations in a country in economic transition. Two case-control studies in Golestan Province have found associations between oral health and oesophageal squamous cell carcinoma,[6,7] and the findings suggest that better oral health practices may decrease mortality in this population. Therefore, we aimed to test the association between oral health, oral care and denture use with overall and cause-specific mortality using data from the Golestan Cohort Study.

Methods

Study population

The details of the Golestan Cohort Study design have been published previously.[8] In brief, 50 045 people aged 40 to 75 years were recruited in north eastern Iran from January 2004 to June 2008, including a total of 10 032 urban participants from Gonbad City and 40 013 rural participants. In the urban areas, the participation rates were 70% for women and 50% for men, and in rural areas, these were 84% and 70% for women and men, respectively. Potential participants were excluded if they were a temporary resident, had a current or previous diagnosis of upper gastrointestinal cancer or were unwilling to participate. A trained interviewer administered a structured questionnaire and the participants received a physical examination by trained physician and provided samples of blood, urine, hair and nails. This study was approved by the ethical review committees of the Digestive Disease Research Center of Tehran University of Medical Science, the International Agency for Research on Cancer and the United States National Cancer Institute.

Oral health assessment

The structured questionnaire contained questions about the participants' oral health. Specifically, participants were asked if they had lost any permanent teeth, and if so, at what age the first permanent tooth was lost. Participants

were also asked about whether they had removable partial or full dentures and whether they wore these dentures during the day. Frequency of tooth brushing was also reported as once a day, twice a day, three times a day, never or other. The physicians assessed decayed, missing and filled teeth (DMFT) visually and used dental probes to determine open cavitation or pre-cavitation. All of the physicians were trained by a dentist before study initiation. In the pilot study for the Golestan Cohort Study, the agreement between two measurements of teeth counts, at baseline and 2 months after baseline, was found to be 88.3%.[9] When the number of teeth lost or DMFT score exceeded 28, these were coded as 28 to represent total adult teeth excluding third molars.

Mortality ascertainment

The Golestan Cohort Study participants were contacted yearly by telephone for information related to death and incident cancers. When the study participant could not be reached, family members, friends or local health workers were contacted. When a death was reported, a trained physician visited the home of the family or primary caregivers and conducted a verbal autopsy interview which was validated for this population.[10] Death certificates and other medical documents were obtained when available and two physicians independently determined cause of death. In the case of a disagreement, a third physician reviewed all information and determined the final cause of death. The causes of death were coded according to the International Classification of Diseases, Tenth Revision (ICD-10). Follow-up for mortality was available through March 2014. The cohort has a 99.2% success rate for mortality follow-up and 32% of deaths were reported through verbal autopsy.[10,11]

Other covariates of interest

Demographic and behavioral information was obtained from the structured questionnaire. Age, sex, ethnicity (Turkmen or other ethnicity) and residence (urban or rural) were ascertained and educational level was categorized as no education, 5th grade or less, 6th to 8th grade, 9th to 12th grade or more than a high school education. We used the previously developed wealth index as a measure of socioeconomic status (SES), which incorporated information on ownership of a car, motorbike, television, refrigerator, freezer, vacuum, washing machine or home, in addition to house structure, house size, having a personal bath and occupation.[12] Tobacco use, including cigarettes and non-cigarette tobacco [i.e., hookah, nass (a local chewing tobacco product), traditional pipe/calumet and pipe], and opium use history were ascertained. We categorized cigarette smoking as never, former, or current,and calculated the pack-years of cigarette smoking. Body mass index (BMI; kg/m^2) was determined from interviewer-measured height and weight.

Statistical analysis

There were only 22 participants who were missing data on any of the variables of interest, so these were excluded. Due to the strong correlation of oral health variables with age and sex, we calculated the predicted tooth loss and DMFT score by age and sex using a LOESS model. Then we calculated the difference between the predicted tooth loss or DMFT score and the actual values for each participant, and categorized the difference into quintiles ranging from quintile 1 (Q1; fewer teeth missing or lower DMFT score than predicted), Q3 (the expected number of teeth missing or DMFT score was as predicted) to Q5 (more teeth missing or a higher DMFT score than predicted). We calculated descriptive statistics for the whole population and by quintile of tooth loss.

We calculated hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the associations between the oral health variables and overall mortality using the Cox proportional hazards model. The entry time was defined as the age at which the participant was recruited to the Golestan Cohort Study, and the exit time was the age at which the participant died or was censored due to loss to follow-up or end of follow-up in March 2014, whichever occurred first. For the quintiles of tooth loss and DMFT, we included the quintiles both individually and as a continuous variable (i.e. 1–5) to test for trend. We tested the proportional hazards assumption by including a term for the interaction between the main oral health and oral care variables and the log of time. The interaction was not statistically significant, so we assumed that the proportional hazards assumption was not violated. Cause-specific mortality HRs for the most common outcomes including cancer, cardiovascular disease and injury were calculated. We created multivariable adjusted HRs (aHRs) with adjustment for variables selected a priori including age, sex, SES, education, residence, ethnicity, smoking history (cigarettes or non-cigarette tobacco) and opium use. We tested the inclusion of pack-years of cigarette smoking and the inclusion of age squared in the model, but since these did not change the association estimates, we did not include them in the final models. We created models excluding the first 2 years of follow-up and excluding participants who reported having pre-existing conditions at baseline including cardiovascular disease, cerebrovascular accident, hypertension, diabetes mellitus, chronic

Table 1. Demographic characteristics of the Golestan Cohort Study participants overall and by quintile of tooth loss

	Overall cohort	Quintile of tooth loss				
		Q1	Q2	Q3	Q4	Q5
Number	50023	9999	9975	9975	10066	10008
Age in years, mean (SD)	51.9 (8.9)	52.0 (8.6)	49.6 (7.9)	50.8 (8.9)	57.9 (9.9)	49.4 (6.2)
Sex, % female	57.6%	60.4%	51.3%	53.1%	66.3%	56.7%
SES quartile						
% Q1 (low SES)	27.9%	25.6%	24.9%	29.4%	30.8%	28.5%
% Q2	22.3%	21.3%	21.0%	23.7%	22.8%	22.7%
% Q3	25.2%	24.0%	26.1%	25.0%	25.0%	25.6%
% Q4 (high SES)	24.7%	29.1%	28.1%	21.9%	21.4%	23.3%
Education						
% None	70.2%	66.6%	61.5%	68.7%	82.6%	71.4%
% 5th grade or less	16.9%	17.0%	20.4%	18.5%	10.8%	17.9%
% 6th to 8th grade	4.5%	4.7%	6.1%	4.5%	2.7%	4.6%
% 9th to 12th grade	6.3%	8.3%	8.7%	6.4%	3.1%	5.0%
% More than high school	2.1%	3.4%	3.4%	2.0%	0.9%	1.1%
Residence						
% Urban	20.0%	25.2%	19.8%	16.3%	21.5%	17.5%
% Rural	80.0%	74.8%	80.2%	83.7%	78.5%	82.6%
Ethnicity						
% Turkmen	74.4%	60.3%	71.7%	77.9%	79.1%	83.1%
% Other	25.6%	39.7%	28.3%	22.1%	20.9%	16.9%
Cigarette use						
% Current	10.9%	6.6%	10.2%	11.8%	9.3%	16.6%
% Former	6.5%	5.2%	6.3%	6.9%	6.3%	7.5%
% Never	82.7%	88.3%	83.5%	81.3%	84.4%	75.9%
Nass, hookah, calumet, or pipe use, % ever	8.8%	8.9%	8.2%	10.1%	8.6%	8.5%
Opium use, % ever	17.0%	11.8%	14.8%	17.6%	18.6%	22.1%

The quintiles of tooth loss range from Q1, fewer teeth missing than predicted by age/sex, to Q5, more teeth missing than predicted.

obstructive pulmonary disease, tuberculosis or cancer. We also tested for an interaction between having a baseline pre-existing condition and the quintiles of tooth loss or DMFT as continuous variables on the mortality outcomes. Statistical interactions between the quintiles of tooth loss or DMFT and denture use were determined, and stratified models for denture use by the quintiles were created.

Since we observed unexpected associations with injury mortality, we conducted further analyses specifically focused on injury mortality. We created stratified models by sex, ethnicity, residence and baseline age. We also evaluated the effect of residual confounding by occupation by including adjustment for occupation risk categories identified using Iranian insurance classifications. All analyses were conducted using SAS 9.3.

Results

As seen in Table 1, the mean baseline age for participants in the Golestan Cohort Study was 51.9 [standard deviation (SD) 8.9] years and 57.6% were female. On average, males (mean 15.9; SD 8.4) had fewer teeth missing than females (mean 18.7; SD 8.4) and age was positively correlated with the number of missing teeth (Pearson correlation 0.37; $P < 0.0001$). In general, the higher quintiles of tooth loss had greater numbers of participants of low SES, lower education, rural residence, Turkmen ethnicity, cigarette use and opium use.

For overall mortality, participants who were in the highest quintile of tooth loss (i.e. had more teeth missing than expected) had an increased risk of death in unadjusted (HR 1.73; 95% CI: 1.55, 1.93) and adjusted (aHR 1.43; 95% CI: 1.28, 1.61) models compared with those in the lowest quintile (Table 2). Similar estimates were observed for DMFT score. Denture use was also inversely associated with overall mortality (aHR 0.90; 95% CI: 0.84, 0.97). For cause-specific mortality, cardiovascular disease, cancer and injury death had patterns generally similar to overall mortality, although the strongest associations were observed between the quintiles of tooth loss and DMFT with injury mortality. Use of dentures was inversely associated with cardiovascular disease (aHR 0.90; 95% CI: 0.81, 0.99) and cancer (aHR 0.88; 95% CI: 0.75, 1.03)

Table 2. Associations between oral health variables and mortality in the Golestan Cohort Study ($N = 50\,023$)

	Overall mortality				Cardiovascular disease death		Cancer death		Injury death	
	Deaths = 3820				Deaths = 1981		Deaths = 839		Deaths = 217	
	HR	(95% CI)	aHR	(95% CI)	aHR	(95% CI)	aHR	(95% CI)	aHR	(95% CI)
Measured tooth loss										
Q1 (Fewer teeth missing than expected)	Ref		Ref		Ref		Ref		Ref	
Q2	1.13	(1.01, 1.27)	1.07	(0.95, 1.20)	1.11	(0.94, 1.30)	0.90	(0.70, 1.15)	0.98	(0.60, 1.60)
Q3 (Teeth missing as expected)	1.35	(1.21, 1.50)	1.24	(1.11, 1.38)	1.23	(1.06, 1.43)	1.20	(0.96, 1.50)	1.26	(0.80, 2.01)
Q4	1.22	(1.11, 1.35)	1.22	(1.11, 1.35)	1.18	(1.02, 1.35)	0.97	(0.78, 1.20)	1.49	(0.94, 2.35)
Q5 (More teeth missing than expected)	1.73	(1.55, 1.93)	1.43	(1.28, 1.61)	1.33	(1.13, 1.56)	1.30	(1.03, 1.65)	1.99	(1.28, 3.09)
P trend	< 0.0001		< 0.0001		0.0008		0.0566		0.0002	
DMFT										
Q1 (Lower DMFT than expected)	Ref		Ref		Ref		Ref		Ref	
Q2	1.20	(1.06, 1.35)	1.17	(1.04, 1.32)	1.14	(0.97, 1.34)	1.19	(0.93, 1.52)	1.46	(0.89, 2.39)
Q3 (DMFT as expected)	1.13	(1.01, 1.26)	1.19	(1.06, 1.33)	1.10	(0.95, 1.28)	1.04	(0.81, 1.32)	1.94	(1.16, 3.24)
Q4	1.37	(1.22, 1.53)	1.25	(1.11, 1.40)	1.16	(0.99, 1.36)	1.27	(1.00, 1.61)	1.44	(0.86, 2.40)
Q5 (Higher DMFT than expected)	1.81	(1.59, 2.07)	1.43	(1.25, 1.63)	1.21	(0.99, 1.47)	1.50	(1.13, 1.99)	2.38	(1.49, 3.82)
P trend	< 0.0001		< 0.0001		0.0589		0.0114		0.0007	
Uses dentures										
Yes	0.77	(0.72, 0.83)	0.90	(0.84, 0.97)	0.90	(0.81, 0.99)	0.88	(0.75, 1.03)	1.55	(1.14, 2.10)
No	Ref		Ref		Ref		Ref		Ref	
Frequency of tooth brushing										
Never	Ref		Ref		Ref		Ref		Ref	
Once a day	0.65	(0.59, 0.72)	0.80	(0.72, 0.88)	0.79	(0.69, 0.91)	0.83	(0.67, 1.04)	0.84	(0.56, 1.25)
Two or more times a day	0.72	(0.61, 0.85)	0.91	(0.76, 1.09)	1.06	(0.84, 1.32)	0.85	(0.57, 1.27)	0.92	(0.47, 1.80)
Other	0.69	(0.62, 0.76)	0.77	(0.69, 0.85)	0.76	(0.65, 0.88)	0.87	(0.70, 1.09)	0.69	(0.45, 1.06)

Adjusted hazard ratio (aHR) adjusted for age, gender, wealth index, education, residence, ethnicity, smoking history (cigarettes and non-cigarette tobacco) and opium use.

mortality and was positively associated with injury mortality (aHR 1.55; 95% CI: 1.14, 2.10). When we restricted injury death to transport accident mortality, the results were similar (results not shown).

For tooth brushing, any tooth brushing appeared (i.e. once a day, two or more times a day or other frequency) to decrease the risk of overall mortality compared with never brushing (Table 2). For cause-specific mortality, tooth brushing was inversely associated only with cardiovascular disease mortality. Although brushing once a day (aHR 0.79; 95% CI: 0.69, 0.91) and the 'other' category of brushing (aHR 0.76; 95% CI: 0.65, 0.88) had an inverse association, brushing twice a day was not associated with cardiovascular disease mortality (aHR 1.06; 95% CI: 0.84, 1.32) compared with never brushing, although this group was small (total $N = 2746$; deaths = 84).

When we excluded participants who reported any comorbid condition at baseline, the associations for overall, cardiovascular disease and cancer mortality did not change substantially, but the associations for injury death were substantially attenuated (Table 3). In the main analysis, compared with the lowest quintile of DMFT, participants in the highest quintile of DMFT had a 2.38 (95% CI: 1.49, 3.82) times increased risk of injury mortality, and the *P*-value for trend for all of the quintiles was 0.0007 (Table 2). In comparison, when participants with a comorbid condition at baseline were excluded, participants in the highest quintile of DMFT had only 1.70 (95% CI: 1.00, 2.92) times the risk of injury mortality and the *P*-value for trend was 0.0625, although both confidence intervals overlap (Table 3). Although the main effect of having a pre-existing condition at baseline was associated with overall mortality and cause-specific mortality, no interactions between the quintiles of tooth loss or DMFT and a pre-existing condition at baseline were detected (results not shown).

Table 3. Associations between oral health variables and mortality excluding participants with self-reported comorbidities at baseline in the Golestan Cohort Study ($N = 50023$)

	Overall mortality		Cardiovascular disease death		Cancer death		Injury death	
	Deaths = 1737		Deaths = 735		Deaths = 521		Deaths = 141	
	aHR	(95% CI)	aHR	(95% CI)	aHR	(95% CI)	aHR	(95% CI)
Measured tooth loss								
Q1 (Fewer teeth missing than expected)	Ref		Ref		Ref		Ref	
Q2	1.01	(0.85, 1.20)	1.08	(0.83, 1.41)	1.03	(0.76, 1.42)	0.81	(0.45, 1.46)
Q3	1.28	(1.09, 1.50)	1.24	(0.97, 1.60)	1.37	(1.03, 1.82)	1.20	(0.70, 2.06)
Q4	1.27	(1.09, 1.48)	1.27	(1.00, 1.60)	1.11	(0.84, 1.46)	1.22	(0.70, 2.16)
Q5 (More teeth missing than expected)	1.44	(1.22, 1.70)	1.39	(1.08, 1.80)	1.29	(0.96, 1.75)	1.52	(0.90, 2.59)
P trend	< 0.0001		0.0046		0.1175		0.0375	
DMFT								
Q1 (Lower DMFT than expected)	Ref		Ref		Ref		Ref	
Q2	1.21	(1.02, 1.44)	1.16	(0.89, 1.51)	1.22	(0.90, 1.66)	1.22	(0.70, 2.13)
Q3	1.23	(1.04, 1.46)	1.16	(0.90, 1.50)	1.07	(0.79, 1.45)	1.35	(0.73, 2.51)
Q4	1.28	(1.08, 1.52)	1.18	(0.91, 1.52)	1.21	(0.90, 1.63)	1.27	(0.70, 2.30)
Q5 (Higher DMFT than expected)	1.48	(1.23, 1.78)	1.34	(1.00, 1.79)	1.35	(0.96, 1.91)	1.70	(1.00, 2.92)
P trend	< 0.0001		0.0738		0.1606		0.0625	
Uses dentures								
Yes	0.93	(0.83, 1.04)	0.95	(0.80, 1.14)	0.92	(0.75, 1.13)	1.33	(0.90, 1.95)
No	Ref		Ref		Ref		Ref	
Frequency of tooth brushing								
Never	Ref		Ref		Ref		Ref	
Once a day	0.77	(0.66, 0.91)	0.67	(0.52, 0.86)	0.86	(0.64, 1.14)	1.01	(0.63, 1.61)
Two or more times a day	1.01	(0.78, 1.30)	1.14	(0.79, 1.65)	1.12	(0.70, 1.78)	0.72	(0.29, 1.84)
Other	0.84	(0.72, 0.99)	0.74	(0.58, 0.95)	1.04	(0.80, 1.36)	0.85	(0.52, 1.40)

Adjusted hazard ratio (aHR) adjusted for age, gender, wealth index, education, residence, ethnicity, smoking history (cigarettes and non-cigarette tobacco) and opium use.

Self-reported pre-existing conditions included cardiovascular disease, cerebrovascular accident, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, tuberculosis or cancer.

When the first 2 years of follow-up were excluded, the associations for overall cardiovascular disease and cancer mortality did not change substantially, but the associations for injury death were stronger (Supplementary Table 1, available as Supplementary data at *IJE* online). No statistically significant interactions were detected between the quintiles of tooth loss or DMFT and denture use, although the interaction was marginal for tooth loss and cancer death ($P = 0.0786$). In the analysis stratified by quintile of tooth loss or DMFT score, there was little indication of an effect of denture use within the quintiles (Supplementary Table 2, available as Supplementary data at *IJE* online).

In analyses stratified by sex, the associations of tooth loss, DMFT score and denture use with injury mortality were generally similar for both males and females. In analyses stratified by ethnicity, residence or baseline age, these associations appeared to be mainly restricted to the Turkmen ethnicity, participants living in a rural residence and participants who were younger ($\leq$ 50 years) at baseline (Supplementary Table 3, available as Supplementary data at *IJE* online). Adjustment for occupational risk categories did not change the association estimates with injury mortality (results not shown).

Discussion

In this study of 50 023 people from the Golestan Province, Iran, we found an increased risk of overall mortality for participants with poorer oral health as measured by tooth loss or DMFT score. Any tooth brushing appeared to decrease the risk of death, and denture use was also inversely associated with overall mortality. For cause-specific

mortality, participants with poorer oral health had an increased risk of cardiovascular disease, cancer and injury mortality. Denture use was inversely associated with cardiovascular disease and cancer mortality, but positively associated with injury mortality. However, no consistent associations were detected for denture use stratified by quintile of oral health measures. The association between poor oral health and injury mortality did not appear to be due to residual confounding by occupation, but was mainly restricted to participants of Turkmen ethnicity, rural residence and those who were younger at baseline. In addition, when participants with prevalent comorbid conditions at baseline were excluded, the associations between poor oral health and injury mortality were strongly attenuated.

Previous studies have generally found positive associations between poor oral health and mortality.[4] For example in a cohort study in Linxian, China, participants who had greater than the LOESS-smoothed age-specific median number of teeth lost at baseline had 1.13 (95% CI: 1.09, 1.18) times the risk of overall mortality, 1.35 (95% CI: 1.14, 1.59) times the risk of upper gastrointestinal cancer mortality, 1.28 (95% CI: 1.17, 1.40) times the risk of heart disease mortality and 1.11 (95% CI: 1.01, 1.23) times the risk of stroke mortality. Injury-specific mortality was not assessed.[13] In a population of students registered at the University of Glasgow from 1948 to 1968, participants with nine or more missing teeth had 1.35 (95% CI: 1.03, 1.77) times the risk of cardiovascular disease mortality and 1.64 (95% CI: 0.96, 2.80) times the risk of stroke mortality. No significant associations were detected between tooth loss and coronary heart disease or cancer mortality in this study, which is different from our findings. In addition, the association between tooth loss and injury death was assessed, and unlike our findings, no associations were observed.[14] When the data from two independent studies were pooled regarding denture use and mortality, not using dentures was associated with an increased risk of mortality compared with participants who used dentures,[4] which was in agreement with our findings. In this Iranian population, denture use is more common in higher SES groups. Among denture users, 35.6% were in the highest SES quartile compared with 17.8% in the lowest SES quartile. In contrast, among participants without dentures, 20.2% were in the highest SES quartile compared with 32.0% in the lowest SES quartile (results not shown). However, even after adjustment for SES in our models, the association between denture use and overall mortality remained, although the association was attenuated compared with unadjusted models.

It is possible that tooth loss could be associated with mortality, particularly cardiovascular disease and cancer mortality, through changes in the oral microbiome. People with periodontal disease, a condition which can lead to tooth loss, have been found to have increased levels of bacteria in the oral cavity and different bacterial community structure compared with people without periodontal disease.[15] Seroprevalence of periodontal pathogens, such as *Porphyromonas gingivalis*, have been observed to be associated with the risk of pancreatic cancer,[16] coronary heart disease[17] and overall mortality.[18] It is less likely that changes in the oral microbiome were associated with our injury mortality findings, although infection with *Toxoplasma gondii* has been suggested to be associated with traffic accidents[19] and suicide.[20] However, *T. gondii* is not known to colonize the mouth, so it is unlikely that this protozoan is related to the increased injury mortality in this study. Future research should consider whether the oral microbiome, in addition to specific periodontal pathogens, is associated with mortality risk.

The associations between measures of oral health and injury mortality were unexpected and unlikely to be causal. However, associations with injury mortality were also previously observed with other exposures deprived of previous evidence, such as statin use. In early clinical trials, participants randomized to statins or a cholesterol-lowering diet appeared to have increased risks of injury mortality compared with the placebo control group.[21] Much as in the statin literature, we explored in our study the potential for residual confounding in the detected association between oral health and injury mortality, but were unable to identify any variable which could explain the association. However, we did observe a substantial attenuation in the association with injury for both the HR estimates and the *P*-value for trend after removing subjects previously diagnosed with comorbid conditions, which suggests that bias may be inducing an apparent association with injury death. Because we are studying fatal injury (predominantly traffic accidents), not incident injury, this apparent association may be due to poorer outcomes after injury in persons with comorbid conditions. However, future research should consider whether oral health is associated with injury-specific mortality, to evaluate whether this was a true or spurious association.

There are additional limitations to this study. This is an observational cohort study where participants were not randomized to an exposure, so associations may not be causal. In addition, the frequency of tooth brushing was self-reported and the 'other' category (16.8% of the population) was particularly heterogeneous. Similarly, the use of dentures was self-reported and specific information related to the dentures, such as duration of use and type of dentures, was not reported.

There are also a number of important strengths to this study. The Golestan Cohort Study has very complete follow-up, with a follow-up success rate of over 99%.[11] In addition, tooth loss and DMFT were assessed by a

trained physician, which is much more reliable than participant self-report. Since tooth loss and DMFT are highly correlated with age, we created quintiles based on age in order to take this into account, to have a more accurate representation of tooth loss and DMFT by age group.

In conclusion, we found associations between poor oral health and overall, cardiovascular disease, cancer and injury mortality in a large population from Golestan Province, Iran. The associations between poor oral health and injury mortality may be due to residual confounding by an unknown factor or bias. Further research is needed to determine the underlying cause of the increased risk of injury death in participants with poorer oral health or which factors confound or create the bias in this association. Future studies of oral health and mortality should include injury-specific estimates, in addition to other cause-specific outcomes, to determine if this probably aberrant association is population specific. Finally, additional research related to the effect of the oral microbiome on mortality risk is warranted.

Supplementary Data

Supplementary data are available at *IJE* online.

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