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The association between self-reported poor oral health and gastrointestinal cancer risk in the UK Biobank: A large prospective cohort study

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Abstract

Background: Controversy remains as to whether poor oral health is independently associated with gastrointestinal cancers, due to potential confounding by smoking, alcohol and poor nutrition. The aim of this study was to investigate the association between oral health conditions and gastrointestinal cancer risk.

Methods: Data from the large, prospective UK Biobank cohort, which includes $n = 475{,}766$ participants, were analysed. Cox proportional hazard models were applied to estimate the relationship between gastrointestinal cancer risk and self-reported poor oral health (defined as painful gums, bleeding gums and/or having loose teeth), adjusting for confounders.

Results: During an average six years of follow-up, $n = 4069$ gastrointestinal cancer cases were detected, of which 13% self-reported poor oral health. Overall, there was no association between self-reported poor oral health and risk of gastrointestinal cancer detected (hazard ratio 0.97, 95% confidence interval 0.88–1.07). In site-specific analysis, an increased risk of hepatobiliary cancers was observed in those with self-reported poor oral health (hazard ratio 1.32, 95% confidence interval 0.95–1.80), which was stronger for hepatocellular carcinoma (hazard ratio 1.75, 95% confidence interval 1.04–2.92).

Conclusion: Overall there was no association between self-reported poor oral health and gastrointestinal cancer risk. However, there was a suggestion of an increased risk of hepatobiliary cancer, specifically hepatocellular carcinoma.

Keywords

Gastrointestinal cancer, liver cancer, poor oral health, epidemiology

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Key summary

Summarise the established knowledge on this subject

- Previous studies have judged that poor oral health (including gingivitis, periodontitis and tooth loss) is associated with an increased risk of developing some gastrointestinal cancers.
- There is inconsistent evidence for the association between poor oral health and specific types of gastrointestinal cancers.
- There is significant variation in the association between poor oral health and gastrointestinal cancer risk between different geographic settings and the development index of countries.

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What are the new findings?

- No association between self-reported poor oral health and risk of oesophageal, stomach, pancreatic, small intestine and colorectal cancers were observed in this UK Biobank cohort.
- An association between self-reported poor oral health and an increased risk of hepatobiliary tract cancers was observed, which was strongest for hepatocellular carcinoma.

Introduction

Gastrointestinal cancer is a major global health burden and was attributable to approximately 28% of new cancer cases and 37% of cancer deaths in 2018.[1] The rising burden of some types of gastrointestinal cancers can be partially attributed to population increases, ageing populations and a greater prevalence of certain environmental and behavioural risk factors.[1]

Poor oral health is an established risk factor for several chronic systemic diseases such as heart disease, stroke, diabetes and cancers.[2–5] Specifically, with regards to gastrointestinal cancers, associations between poor oral health and oesophageal, gastric, liver and pancreatic cancer risk or mortality have been reported.[5–7] For example, in a Chinese population, above-median tooth loss was associated with a 35% increased risk of death from upper gastrointestinal cancers, with a relative risk (RR) of 1.35 (95% confidence interval (CI) 1.14–1.59).[5] A systematic review with eight studies also identified direct associations between periodontitis (RR 1.74, 95% CI 1.41–2.15), edentulism (RR 1.54, 95% CI 1.16–2.05) and pancreatic cancer risk.[7] Similarly, a Finnish cohort study reported greater tooth loss to be associated with an increased primary liver cancer risk.[6] Interestingly, a large cohort of Taiwanese patients undergoing treatment for periodontitis had reduced risks of gastrointestinal cancer compared with patients not undergoing treatment, adding further evidence for a relationship between oral health and gastrointestinal carcinogenesis.[8] Nonetheless, the evidence is not consistent, as recent findings revealed no association between tooth loss or periodontitis and colorectal cancer risk within a meta-analysis of six studies originating from the USA and China (pooled odds ratio (OR) 1.00, 95% CI 0.99–1.01 and 1.05, 95% CI 0.86–1.29, respectively).[9]

Periodontitis, gingivitis, dental caries and tooth loss can all be considered as oral diseases or clinical indicators of poor oral health.[10,11] Periodontitis is an irreversible inflammatory disease that can lead to a destruction of connective tissue, alveolar bone, bleeding gums and negatively impacts the chewing process.[5,12] Periodontitis is also an important cause of natural tooth loss in adults.[13] Whilst tooth loss is often assessed in large epidemiological studies, it is a relatively crude assessment of oral health status as teeth may be lost due to a variety of factors. Additionally, potential common risk factors such as smoking, alcohol consumption and poor nutrition may provide explanations for the reported associations between poor oral health and gastrointestinal cancer development.[14,15]

Overall, it remains unclear if previously reported inconsistent associations between poor oral health and gastrointestinal cancer risk are real, due to potential confounding or measurement errors and differences between study designs. It is also unclear if this association is relevant to a UK population, as a very high-income country where access to dental care is provided as part of the state-funded National Health Service.

The aim of this study was to investigate the association between self-reported poor oral health and risk of different types of gastrointestinal cancer within the large UK Biobank prospective cohort study.

Methods

Study population

The UK Biobank cohort study includes adults from England, Wales and Scotland aged 40–69 years.[16] Between 2006–2010, approximately 500,000 individuals provided written consent to participate in this study. For the purposes of this analysis, participants were excluded if they provided incomplete information or data on oral health conditions, and if participants presented a history of cancer at baseline (except for non-melanoma skin cancer). Therefore, the final analytical cohort consisted of 469,628 participants. The UK Biobank cohort study obtained full ethical approval that reflects the ethical guidelines of the 1975 Declaration of Helsinki from the North West Multicentre Research Ethics Committee (10 May 2016).[16]

Demographic information and assessment of confounders

Participants self-completed a touchscreen questionnaire including information on month and year of birth, geographic location, socioeconomic status (Townsend deprivation index), education level (university degree or not). Smoking status, alcohol consumption, fruit and vegetable consumption, and waist circumference based on International Diabetes Federation criteria (>94 cm in men; > 80 cm in women) were recorded. Body mass index (BMI) was derived by dividing weight (kg) by height (m) squared.

Assessment of oral health conditions

At baseline, participants were asked to indicate if they had suffered from any of the oral health conditions listed: mouth ulcers, painful gums, bleeding gums, loose teeth and toothache. For the purpose of this study, participants were categorised as having poor oral health if they self-reported painful gums, bleeding gums and/or loose teeth. Whilst crude measures, these three conditions are regarded as clinical markers of periodontitis and therefore considered as indicative of poor oral health for the purpose of this study.

Follow-up and outcomes

Participants were followed from their baseline visit until primary gastrointestinal tumour diagnosis (through linkage with national cancer registries), death (through linkage with national death records), withdrawal from the study, or the end of follow-up which was 30 September 2014.

Gastrointestinal cancer was classified according to the International Classification of Diseases 2010 (ICD-10) codes C15–C26. Separate analyses were conducted for oesophageal (C15), stomach (C16), small intestine (C17), colon (C18 and C19), rectum (C20), liver (C22), biliary tract (C23 and 24) and pancreatic (C25) cancers. These topography codes were combined with ICD-3 for oncology morphological codes[17] to further categorise oesophageal cancer into adenocarcinoma (8140, 8144–8145, 8260, 8480–8481, 8490, 8574) and squamous cell carcinoma (8070–8071), and gastric cancer into adenocarcinoma (8140, 8142, 8144–8145, 8210, 8260, 8480–8481, 8490, 8574) and non-adenocarcinoma (8000, 8010, 8020, 8070, 8240–8041, 8246, 8800, 8936, 8990). Further analysis combined oesophageal and gastric cardia (C15 and C16.1) adenocarcinoma codes. Similarly, liver cancers were further divided into hepatocellular carcinoma (8170–8175) and intrahepatic cholangiocarcinoma (8032–8033, 8041, 8050, 8070–8071, 8140–8141, 8160, 8260, 8480, 8481, 8490, and 8560). Nineteen participants had synchronous cancer, i.e. more than one digestive cancer type diagnosed in the same individual at the same time and were excluded from this analysis.

Statistical analysis

The proportion of participants with self-reported poor oral health and those with self-reported good oral health were compared for baseline characteristics using chi-squared tests. Cox proportional hazards model were applied to generate hazard ratios (HRs) and 95% CIs to examine the association between self-reported poor oral health and total gastrointestinal cancer risk and individual gastrointestinal cancer site risk. Adjusted analyses included the potential confounders: age, sex, socioeconomic status, education, smoking status, alcohol intake, BMI, waist circumference and daily consumption of fruits and vegetables. Additional subgroup analyses were conducted for total gastrointestinal and hepatobiliary tract cancers, stratified by potential effect modifiers. Likelihood ratio tests were applied to formally test for interactions. Sensitivity analyses excluding the first year and first three years of follow-up was conducted to assess the potential for reverse causation. All statistical analyses were performed using Stata version 13 (Stata Corp, College Station, Texas, USA).

Results

Our analysis included 469,628 participants, of whom 4069 developed incident gastrointestinal cancer during an average of six years follow-up. Of the 4069 gastrointestinal cancer cases, 531(13%) reported poor oral health.

Table 1 demonstrates the baseline characteristics of the cohort study according to oral health. Participants with self-reported poor oral health were more likely to be younger, female, living in deprived socioeconomic areas, current or former smokers, current alcohol drinkers, obese and consume less than two pieces of fruits/vegetables daily, in comparison with participants with good oral health.

Table 2 illustrates the association between self-reported poor oral health and each type of gastrointestinal cancer adjusted by defined confounders. Overall, there were no significant associations between self-reported poor oral health and risk of individual types of gastrointestinal cancers. However, self-reported poor oral health was associated with an increased risk of hepatobiliary cancer in unadjusted analyses (HR 1.42, 95% CI 1.05–1.92), although this became attenuated in fully adjusted models (HR 1.32, 95% CI 0.95–1.80) when compared with participants reporting good oral health.

The relationship between self-reported poor oral health and total gastrointestinal or hepatobiliary cancers was further investigated in analyses stratified by potential confounders (Table 3). As per the main analyses, no significant associations between total gastrointestinal cancer risk and self-reported poor oral health were observed in these stratified analyses. However, the association between self-reported poor oral health and hepatobiliary cancer was stronger in subgroups of participants who consumed less than five pieces of fruits and vegetables daily (HR 1.51, 95% CI 1.03–2.22), were smokers (HR 1.51, 95% CI 1.02–2.23), were overweight or obese (HR 1.53, 95% CI 1.08–2.16) or living in more

Table 1. Characteristics of participants by self-reported oral health conditions in the UK Biobank cohort study.

Characteristic	Good oral health[a] $n = 399,548$ (%)	Poor oral health[b] $n = 70,080$ (%)
Age at baseline, years		
<50	93,929 (23.5)	19,510 (27.8)
50–55	59,783 (14.9)	12,628 (18.0)
55–60	71,607 (17.9)	13,582 (19.4)
60–65	97,252 (24.3)	14,868 (21.2)
≥65	76,977 (19.3)	9492 (13.5)
Sex		
Female	212,002 (53.1)	41,124 (58.7)
Male	187,546 (46.9)	28,956 (41.3)
Socioeconomic status		
Affluent (least deprived)	82,279 (20.6)	12,035 (17.2)
Semi-affluent	81,220 (20.3)	12,455 (17.8)
Middle	80,493 (20.2)	13,255 (18.9)
Semi-deprived	79,173 (19.8)	14,828 (21.2)
Most deprived	75,903 (19.0)	17,394 (24.8)
Missing	480 (0.1)	113 (0.2)
Education (third level degree)		
No	264,311 (66.2)	47,434 (67.7)
Yes	131,149 (32.8)	21,876 (31.2)
Missing	4088 (1.0)	770 (1.1)
Smoking status		
Never	221,188 (55.4)	35,960 (51.3)
Former light smoker (<20 pack-years)	100,453 (25.1)	17,356 (24.8)
Former heavy smoker (≥20 pack-years)	34,946 (8.8)	8233 (11.8)
Current light smoker (<20 pack-years)	21,524 (5.4)	4058 (5.8)
Current heavy smoker (≥20 pack-years)	19,967 (5.0)	4241 (6.1)
Missing	1470 (0.4)	232 (0.3)
Alcohol intake		
Never	17,398 (4.4)	3457 (4.9)
Occasional (drink only 1–3 times per month)	224,424 (56.2)	38,452 (54.9)
Current (>0–14 units to 21 units//week)	141,918 (35.5)	25,118 (35.8)
Former	14,039 (3.5)	2692 (3.8)
Missing	1769 (0.4)	361 (0.5)
BMI status (kg/m^2)		
Underweight (<18.5)	2059 (0.52)	328 (0.5)
Normal ($18.5 \leq 25$)	131,065 (32.8)	20,870 (29.8)
Overweight ($25 \leq 30$)	169,968 (42.5)	28,826 (41.1)
Obese (30+)	94,444 (23.6)	19,616 (28,0)
Missing	2012 (0.5)	440 (0.6)
Waist circumference[31]		
≤94 cm in men; ≤ 80 cm in women	193,068 (48.3)	30,074 (42.9)
>94 cm in men; > 80 cm in women[c]	205,111 (51.3)	39,715 (56.7)
Missing	1369 (0.3)	291 (0.4)
Fruit and vegetable intake (servings/day)		
<2	75,552 (18.9)	15,725 (22.4)
2–5	160,719 (40.2)	28,170 (40.2)
>5	152,392 (38.1)	23,944 (34.2)
Missing	10,885 (2.7)	2241 (3.2)

[a]Good oral health: mouth ulcers, toothache /dentures.
[b]Poor oral health: painful gums, bleeding gums and loose teeth.
[c]Abdominal obesity according to International Diabetes Federation guidelines.

Table 2. The association between oral health conditions and gastrointestinal cancers risk in the UK Biobank cohort study.

Oral health	Non-cases/ cancer cases	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
Total gastrointestinal cancer				
Good oral health[d]	396,088/3460	1	1	1
Poor oral health[e]	69,549/531	0.99 (0.91–1.09)	1.03 (0.94–1.12)	0.97 (0.89–1.07)
Oesophageal cancer				
Good oral health	396,088/354	1	1	1
Poor oral health	69,549/50	0.92 (0.68–1.24)	0.99 (0.73–1.33)	0.87 (0.63–1.18)
Gastric cancer				
Good oral health	396,088/245	1	1	1
Poor oral health	69,549/39	1.04 (0.75–1.47)	1.12 (0.79–1.57)	0.94 (0.65–1.35)
Pancreatic cancer				
Good oral health	396,088/374	1	1	1
Poor oral health	69,549/62	1.09 (0.83–1.43)	1.10 (0.84–1.45)	1.05 (0.80–1.39)
Hepatobiliary cancer				
Good oral health	396,323/235	1	1	1
Poor oral health	69,587/51	1.42 (1.05–1.92)	1.45 (1.07–1.96)	1.32 (0.95–1.80)
Small intestine cancer				
Good oral health	396,088/78	1	1	1
Poor oral health	69,549/11	0.91 (0.48–1.71)	0.92 (0.49–1.74)	0.93 (0.49–1.76)
Colon cancer				
Good oral health	397,941/1607	1	1	1
Poor oral health	69,852/228	0.91 (0.80–1.05)	0.93 (0.81–1.07)	0.92 (0.80–1.06)
Rectal cancer				
Good oral health	398,957/591	1	1	1
Poor oral health	69,986/94	1.00 (0.80–1.24)	1.04 (0.84–1.30)	1.02 (0.81–1.30)
Colorectal cancer				
Good oral health	396,088/2189	1	1	1
Poor oral health	69,549/319	0.93 (0.83–1.05)	0.96 (0.85–1.08)	0.93 (0.83–1.06)

BMI: body mass index; CI: confidence interval; HR: hazard ratio.
[a]Model 1: unadjusted model.
[b]Model 2: age and sex adjusted.
[c]Model 3: adjusted for age, sex, socioeconomic status, tertiary education degree, smoking status by pack years, alcohol status, BMI, waist circumference, daily consumption of fruit and vegetables.
[d]Good oral health: includes mouth ulcers, toothache/dentures.
[e]Poor oral health: includes painful gums, bleeding gums and loose teeth.

affluent socioeconomic areas (HR 1.54, 95% CI 1.03–2.31). When the likelihood test was performed, none of the tests for interaction were statistically significant (all p-values > 0.05).

As shown in Table 4, in the adjusted analysis, self-reported poor oral health was associated with a 75% increased risk of hepatocellular carcinoma (HR 1.75, 95% CI 1.04–2.92). There was no significant association observed between self-reported poor oral health and Intrahepatic cholangiocarcinoma (HR 0.81, 95% CI 0.43–1.53) or biliary tract cancer (HR 1.29, 95% 0.77–2.19) risk. Analyses by histological subtypes of oesophago-gastric cancer did not reveal any significant associations with self-reported poor oral health (Supplementary Material Table 1).

Supplementary Material Table 2 presents the association between self-reported poor oral health and hepatocellular carcinoma and intrahepatic cholangiocarcinoma, further stratified by potential effect modifiers. These results showed largely similar associations to those observed in Table 4, although statistical power was more limited. There were a few exceptions, such as increased the association between hepatocellular carcinoma risk and poor oral health being stronger in those consuming more than five portions of fruit and vegetables per day. However,

Table 3. The association between oral health conditions and gastrointestinal cancer and hepatobiliary cancer risk, stratified by potential effect modifiers and its interaction with poor oral health, in the UK Biobank cohort study.

Potential effect modifiers	Oral health[a]	Non-cases/ cancer cases	Total GI cancer risk[b], adjusted HR (95% CI)[c]	*p*-Value for interaction	Non-cases/ cancer cases	Hepatobiliary cancer risk, adjusted HR (95% CI)[c]	*p*-Value for interaction
Socioeconomic status[d]							
Affluent	Good oral health	241,911/2081	1	0.69	242,040/137	1	0.68
	Poor oral health	37,465/280	0.96 (0.85–1.09)		37,476 /29	1.54 (1.03–2.31)	
Deprived	Good oral health	153,701/1375	1		153,806/98	1	
	Poor oral health	31,971/251	1.00 (0.87–1.16)		31,998/22	1.22 (0.75–1.99)	
Smoking[e]							
Never	Good oral health	219,673/1515	1	0.66	219,772/102	1	0.47
	Poor oral health	35,750/210	0.95 (0.82–1.10)		35,760/18	1.24 (0.73–2.08)	
Ever	Good oral health	133,909/1490	1		134,009/105	1	
	Poor oral health	25,337/252	1.00 (0.88–1.13)		25,356/26	1.51 (1.02–2.23)	
Alcohol intake[f]							
Never or light	Good oral health	239,997/1825	1	0.94	240,114/144	1	0.92
	Poor oral health	41,631/278	0.97 (0.85–1.11)		41,656/30	1.39 (0.93–2.09)	
Current/former	Good oral health	154,333/1624	1		154,449/91	1	
	Poor oral health	27,561/249	0.99 (0.86–1.13)		27,574/21	1.41 (0.86–2.31)	
Body mass index[g]							
Normal weight	Good oral health	132,213/911	1	0.25	132,272/61	1	0.35
	Poor oral health	21,078/120	0.88 (0.72–1.07)		21,085/10	1.03 (0.51–2.10)	
Overweight	Good oral health	261,882/2530	1		262,058/173	1	
	Poor oral health	48,036/406	1.01 (0.91–1.13)		48,067/41	1.53 (1.08–2.16)	
Daily fruit and vegetable portions							
<5	Good oral health	234,189/2082	1	0.67	234,329/139	1	0.65
	Poor oral health	43,557/338	1.00 (0.89–1.12)		43,582/33	1.51 (1.03–2.22)	
≥5	Good oral health	151,125/1267	1		151,214/89	1	
	Poor oral health	23,769/175	0.94 (0.80–1.11)		23,780/16	1.22 (0.71–2.09)	

BMI: body mass index; CI: confidence interval; GI: gastrointestinal; HR: hazard ratio.
[a]Good oral health: includes mouth ulcers, toothache/dentures; poor oral health: includes painful gums, bleeding gums and loose teeth.
[b]GI cancers (oesophageal, stomach, small intestine, pancreatic, liver and colon).
[c]Adjusted for age, sex, socioeconomic status, tertiary education degree, smoking status, alcohol status, BMI, waist circumference, daily consumption of fruit and vegetables (confounder excluded when it is the exposure of interest).
[d]Socioeconomic status: based on Townsend deprivation index and dichotomised as affluent (including affluent, semi-affluent, middle) or deprived (semi-deprived, most deprived).
[e]Smoking: categorised as never or ever Smoker (including smokers categorised as former low, former high, current low and current high pack-years of smoking).
[f]Alcohol intake: categorised as never/light (when participants drink occasionally or drink only 1–3 times per month) or current/former (when participants drink > 0– > 21 unit of wine, beer, spirits, fortified wine and alcopops weekly).
[g]Body mass index: categorised as normal weight (<25 kg/m^2) and overweight (≥25 kg/m^2).

formal statistical tests for interaction were not significant.

Supplementary Material Tables 3 and 4 display the association between self-reported poor oral health and each type of gastrointestinal cancer after excluding cases that developed within the first year and three years of follow-up, adjusted by confounders. The results remain largely similar, with no association between self-reported poor oral health and overall gastrointestinal cancer risk. However, for hepatobiliary cancer, the associations became weaker compared with main analyses shown in Table 2.

Discussion

Overall, in this large cohort study, there was no association between self-reported poor oral health and risk of all gastrointestinal cancers detected. However,

Table 4. The association between oral health conditions and hepatocellular carcinoma, intrahepatic cholangiocarcinoma and biliary tract cancer risk in the UK Biobank cohort study.

Oral health	Non-cases/ cancer cases	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
Hepatocellular carcinoma				
Good oral health[d]	399,478 /70	1	1	1
Poor oral health[e]	70,061/19	1.91 (1.17–3.12)	2.07 (1.27–3.38)	1.75 (1.04–2.92)
Intrahepatic cholangiocarcinoma				
Good oral health	399,474/74	1	1	1
Poor oral health	70,068/12	0.91 (0.49–1.67)	0.89 (0.49–1.65)	0.81 (0.43–1.53)
Biliary tract cancer				
Good oral health	399,459/89	1	1	1
Poor oral health	70,062/18	1.35 (0.81–2.24)	1.34 (0.80–2.22)	1.29 (0.77–2.19)

BMI: body mass index; CI: confidence interval; HR: hazard ratio.
[a]Model 1: unadjusted model.
[b]Model 2: age and sex adjusted.
[c]Model 3: adjusted for age, sex, socioeconomic status, tertiary education degree, smoking status, alcohol status, BMI, waist circumference, daily consumption of fruit and vegetables.
[d]Good oral health: includes mouth ulcers, toothache/dentures.
[e]Poor oral health: includes painful gums, bleeding gums and loose teeth.

in site-specific analysis, an increased risk of hepatobiliary cancer in those with self-reported poor oral health was observed, particularly for hepatocellular carcinoma.

Our findings, which are the first within a UK population, corroborate those of previous reports from other populations. For example, a US prospective cohort study observed a strong association between self-reported periodontitis and liver cancer risk (HR 1.33, 95% CI 1.07–1.65) in male health professionals, although they had a small sample size of only 24 liver cancer cases.[18] Similarly, in a large Finnish prospective cohort study with 29,133 participants who completed questionnaires about dental issues, male smokers with fewer teeth had an increased risk of liver cancer.[6] The risk was 42% and 45% greater for 11–31 and ≥32 permanent teeth lost, compared with participants with 0–10 teeth lost.[6] Lastly, a prospective cohort analysis within a vitamin and mineral supplement trial in Linxian, China, found a similar result. All participants completed a questionnaire and dental examination, and those within the highest quartile of age-specific tooth loss were observed to have an increased risk of liver cancer HR 1.27 (95%, CI 0.96–1.67).[19]

In stratified analysis, we did observe stronger increased associations between self-reported poor oral health and hepatocellular carcinoma in smokers, which suggests this may be explaining the associations shown. However, there could also be a multiplicative effect of poor oral health and smoking that increases liver cancer risk over-and-above smoking. However, formal tests for interaction by effect modifiers were not statistically significant, possibly due to limited statistical power for such analyses. We also observed inconsistent findings in stratified analyses by socioeconomic status, alcohol intake, body mass index or fruits and vegetables intake, which we speculate might be due to the smaller sample size in these analyses.

Our result of a lack of association between self-reported poor oral health and risk of other digestive cancers is consistent with some previous publications. A meta-analysis revealed no significant association between tooth loss (uppermost versus no tooth loss) and colorectal cancer with an OR of 1.00 (95% CI 0.99–1.01).[9] Likewise, the large US Health Professionals Follow-Up study did not identify an association between the number of remaining teeth and oesophageal, stomach or colorectal cancer risk once smoking history had been included in multivariate adjusted models.[20] However, this study did report an increased risk of pancreatic cancer for men with periodontitis even after adjustment for smoking (HR 1.54, 95% CI 1.16–2.04), which we did not observe in the current study.[20] Unfortunately, the Health Professionals Follow-Up study did not report the association between tooth loss, periodontitis and hepatobiliary tract cancer risk due to small sample size, preventing comparisons with our current findings.[20] A similar conclusion was reached by Hujoel et al. in a study investigating cancer-associated mortality by finding no significant association between periodontitis and pancreatic cancer (OR 1.77, 95% CI 0.85–3.67) and also no association between periodontitis and gastric and colon cancers.[21]

The biological mechanisms by which poor oral health may be more strongly associated with liver, rather than other digestive, cancer risk is unclear.

Several general mechanisms linking periodontitis and carcinogenesis have been proposed, particularly highlighting the role of periodontitis in exposing the body to chronic inflammation.[22] Tamaki et al. propose that reactive oxygen metabolites may be a possible physiopathology linkage between periodontitis and liver cancer.[23] In their study, they investigated hepatocellular carcinoma patients in Japan, comparing 31 chronic periodontitis patients with 33 periodontally healthy patients. Patients with chronic periodontitis presented a higher tumour stage, reflected by the Japan Integrated Stage score, and had 25.3% higher circulating levels of reactive oxygen metabolites than patients without periodontitis.[23] Since this was a cross-sectional study, it is difficult to imply causal associations, but it is evidence for a liver-specific effect of periodontitis, mediated by serum reactive oxygen species.

An alternative explanation is the potential role of the oral and gut microbiome in disease development. The liver contributes to the elimination of bacteria from the human body.[24] However, when the liver is affected by diseases such as hepatitis, cirrhosis or cancer, its function can decline and bacteria can survive for longer or have the potential to cause more harm.[24] One such bacterium is *Fusobacterium nucleatum*, which originates in the oral cavity and has been implicated in colorectal carcinogenesis.[25] The role of *Fusobacterium nucleatum* in liver cancer development is unclear and, of the limited studies conducted, there has been no evidence for its detection in liver tumour tissue.[26] Future studies investigating the microbiome and liver cancer aetiology are warranted.

Finally, Abnet et al. have proposed an alternative theory about the possible connection between poor oral health and cancer.[27] Having a higher number of missing teeth may influence participants to choose softer foods which are easier to masticate.[27] These foods are often less nutritious and result in a diet that is lower in essential vitamins and minerals, potentially contributing to cancer risk.[15] A number of studies have demonstrated that reduced dentition has negative impacts on dietary intake, particularly in older adults.[28] Although we adjusted for fruit and vegetable consumption in our analyses, there may be residual confounding from other aspects of dietary quality that we have not accounted for in our analysis. Abnet and colleagues also hypothesised that edentulous people may swallow large pieces of food that could lead to mucosal lesions and result in a chronic inflammatory condition favourable for cancer development.[27] However, these hypothesised mechanisms are not specific for liver cancer aetiology. We must also acknowledge the potential for some reverse causation to explain the associations observed, given that our results became attenuated in a sensitivity analysis excluding the first year of follow-up.

The strengths of this study include the large size, the recent timeframe in which data was collected, and information about potential confounders. This is also the first study investigating self-reported poor oral health in relation to the spectrum of digestive cancers within the UK population, for whom dental healthcare is readily accessible. Furthermore, the prevalence of periodontitis in our study (13%) is similar to other reports, suggesting our findings are generalisable.[20]

This study has a number of limitations. The self-reported measures for oral health are very crude. This study considered painful gums, bleeding gums and loose teeth as a proxy for poor oral health. However, these may reflect a number of physiological and pathological conditions including ageing, trauma and previous orthodontic treatment, and may not necessarily reflect simply periodontitis.[4] The UK Biobank cohort study does not offer a clinically accurate questionnaire to measure periodontitis or oral health status despite a number of validated self-report tools being available.[29] A more comprehensive assessment for oral health in subsequent data collection rounds could be beneficial to other research and researchers. Alternative methods could include evaluation of existing dental records or, ideally, a clinical dental examination supplemented with radiographs to more accurately define oral health.[29] Lastly, the characteristics of the UK Biobank population are recognised to be healthier than those of the general population, which is typical of many epidemiological studies relying on volunteers.[30] However, it is recognised that this limitation does not negate studying aetiological associations such as those reported in this study.[30]

In summary, this study found an association between self-reported poor oral health and increased risk of hepatobiliary cancer, particularly hepatocellular carcinoma however, no association was observed for risk of other gastrointestinal cancers.

Declaration of conflicting interests

This study has no conflicts of interest.

Ethics approval

The UK Biobank conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the North West Multi-Centre Research Ethics Committee (10 May 2016). This research was conducted using the UK Biobank Resource under application number 34374. Investigators may apply to access the UK Biobank study data through the processes described at http://www.ukbiobank.ac.uk/register-apply/.

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Informed consent

All participants provided written informed consent.

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References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Chen Y, Yu C, Li Y, et al. Association between oral health and gastric precancerous lesions. *J Carcinogenesis* 2012; 33: 399–403.
3. Mai X, LaMonte MJ, Hovey KM, et al. Periodontal disease severity and cancer risk in postmenopausal women: The Buffalo OsteoPerio Study. *Cancer Causes Control* 2016; 27: 217–228.
4. Huang J, Roosaar A, Ax Ell T, et al. A prospective cohort study on poor oral hygiene and pancreatic cancer risk. *Int J Cancer* 2016; 138: 340–347.
5. Abnet CC, Qiao Y-L, Dawsey SM, et al. Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort. *Int J Epidemiol* 2005; 34: 467–474.
6. Yang B, Petrick JL, Abnet CC, et al. Tooth loss and liver cancer incidence in a Finnish cohort. *Cancer Causes Control* 2017; 28: 899–904.
7. Maisonneuve P, Amar S and Lowenfels AB. Periodontal disease, edentulism and pancreatic cancer: A meta-analysis. *Ann Oncol* 2017; 28: 985–995.
8. Hwang IM, Sun LM, Lin CL, et al. Periodontal disease with treatment reduces subsequent cancer risks. *QJM* 2014; 107: 805–812.
9. Ren HG, Luu HN, Cai H, et al. Oral health and risk of colorectal cancer: Results from three cohort studies and a meta-analysis. *Ann Oncol* 2016; 27: 1329–1336.
10. Stolzenberg-Solomon RZ, Dodd KW, Blaser MJ, et al. Tooth loss, pancreatic cancer, and Helicobacter pylori. *Am J Clin Nutr* 2003; 78: 176–181.
11. Shakeri R, Malekzadeh R, Etemadi A, et al. Association of tooth loss and oral hygiene with risk of gastric adenocarcinoma. *Cancer Prev Res* 2013; 6: 477–482.
12. Pihlstrom BL, Michalowicz BS and Johnson NW. Periodontal diseases. *Lancet* 2005; 366: 1809–1820.
13. Meyer MS, Joshipura K, Giovannucci E, et al. A review of the relationship between tooth loss, periodontal disease, and cancer. *Cancer Causes Control* 2008; 19: 895–907.
14. Nair J, Ohshima H, Nair UJ, et al. Endogenous formation of nitrosamines and oxidative DNA-damaging agents in tobacco users. *Crit Rev Toxicol* 1996; 26: 149–161.
15. World Cancer Research Fund/American Institute for Cancer Research. Diet, nutrition, physical activity, and cancer: A global perspective. Continuous Update Project Expert Report 2018, www.wcrf.org/sites/default/files/Summary-third-expert-report.pdf (2018, accessed 5 February 2019).
16. UK Biobank. About UK Biobank, www.ukbiobank.ac.uk/about-biobank-uk/ (accessed 29 November 2017).
17. World Health Organization. International classification of diseases for oncology ICD-O-3 online, https://codes.iarc.fr/codegroup/2 (2011, accessed 20 May 2019).
18. Michaud DS, Kelsey KT, Papathanasiou E, et al. Periodontal disease and risk of all cancers among male never smokers: An updated analysis of the Health Professionals Follow-up Study. *Ann Oncol* 2016; 27: 941–947.
19. Thistle JE, Yang B, Petrick JL, et al. Association of tooth loss with liver cancer incidence and chronic liver disease mortality in a rural Chinese population. *PLoS One* 2018; 13: 1–12.
20. Michaud DS, Liu Y, Meyer M, et al. Periodontal disease, tooth loss, and cancer risk in male health professionals: A prospective cohort study. *Lancet Oncol* 2008; 9: 550–558.
21. Hujoel PP, Drangsholt M, Spiekerman C, et al. An exploration of the periodontitis-cancer association. *Ann Epidemiol* 2003; 13: 312–316.
22. Van Dyke TE and Sheilesh D. Risk factors for periodontitis. *J Int Acad Periodontol* 2005; 7: 3–7.
23. Tamaki N, Takaki A, Tomofuji T, et al. Stage of hepatocellular carcinoma is associated with periodontitis. *J Clin Periodontol* 2011; 38: 1015–1020.
24. Elhassan AT and Peeran SW. The linking mechanisms between liver and periodontal diseases. *EC Dental Science* 2016; 2: 758–766.
25. Mima K, Nishihara R, Qian ZR, et al. *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. *Gut* 2016; 65: 1973–1980.
26. Yamamura K, Baba Y, Miyake K, et al. *Fusobacterium nucleatum* in gastroenterological cancer: Evaluation of measurement methods using quantitative polymerase chain reaction and a literature review. *Oncol Lett* 2017; 14: 637–638.
27. Abnet CC, Qiao YL, Mark SD, et al. Prospective study of tooth loss and incident esophageal and gastric cancers in China. *Cancer Causes Control* 2001; 12: 847–854.
28. Wallace S, Samietz S, Abbas M, et al. Impact of prosthodontic rehabilitation on the masticatory performance of partially dentate older patients: Can it predict nutritional state? Results from a RCT. *J Dent* 2018; 68: 66–71.
29. Burgess A, Shah K, Hough O, et al. Validity of a self-reported periodontal disease measure. *J Public Health Dent* 2016; 15: 477–491.
30. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *Am J Epidemiol* 2017; 186: 1026–1034.
31. Ford E. Prevalence of the metabolic syndrome defined by the International Diabetes. Federation among adults in the U.S. *Diabetes Care* 2005; 28: 2745–9.