

Causal effect of tooth loss on functional capacity in older adults in England: a natural experiment

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35

36 **Impact statement**

- 37 We certify that this work is novel of recent epidemiological research. We identified the
- causal effect of tooth loss on functional capacity among adults aged 50-70 years old in 38
- 39 England, whereby exploiting the exogenous geographical and historical variation in
- 40 childhood exposure to tap water fluoride. Retaining one more tooth reduced the probability of
- 41 having a limitation in the instrumental activity of daily living by 3.1 percentage points. Our
- 42 findings support the causal evidence between tooth loss and functional capacity.

43	Abstract
44	BACKGROUND/OBJECTIVES: Tooth loss is associated with reduced functional capacity, but so
45	far, there is no relevant causal evidence reported. We investigated the causal effect of tooth loss on
46	the instrumental activities of daily living (IADL) among older adults in England.
47	DESIGN: Natural experiment study with instrumental variable analysis.
48	SETTING: The English Longitudinal Study of Aging (ELSA) combined with the participants'
49	childhood exposure to water fluoride due to the community water fluoridation.
50	PARTICIPANTS: 5,631 adults in England born in 1945–1965 participated in the ELSA wave 7
51	survey (conducted in 2014–2015; average age: 61.0 years, 44.6% men).
52	EXPOSURE: The number of natural teeth predicted by the exogenous geographical and historical
53	variation in exposure to water fluoride from age 5 to 20 years old (instrumental variable).
54	MAIN OUTCOME: Having any limitations in IADL (preparing a hot meal, shopping for groceries,
55	making telephone calls, taking medications, doing work around the house or garden, or managing
56	money).
57	RESULTS: Linear probability model with Two-Stage Least Squares estimation was fitted. Being
58	exposed to fluoridated water was associated with having more natural teeth in later life (coefficient:
59	0.726; 95% CI: 0.311, 1.142; F = 11.749). Retaining one more natural tooth reduced the probability
60	of having a limitation in IADL by 3.1 percentage points (coefficient: -0.031; 95% CI: -0.060,

61 -0.002).

- 62 **CONCLUSION:** Preventing tooth loss maintains functional capacity among older adults in England.
- Given the high prevalence of tooth loss, this effect is considerable. Further research on the 63
- 64 mechanism of the observed causal relationship is needed.
- 65
- Keywords: Instrumental Activity of Daily Living; Oral Health; Instrumental variable; Natural 66
- 67 Experiment

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69 INTRODUCTION

70	Instrumental activities of daily living (IADL) represent functional competence for
71	independent living in a community and significantly impact the quality of life in older
72	people.1 A hierarchical model has been proposed for functional competence, and declines in
73	higher-level competence predict future declines in lower-level domains. ² As a decline in
74	IADL is associated with dementia ³ and death, ⁴ maintaining IADL is essential for individuals
75	in early old age and throughout aging society while it also leads to lower medical and long-
76	term care costs. ^{4,5}
77	Studies have reported a longitudinal association between oral conditions and a
78	decline in functional capacity and disability. ^{6–9} More specifically, physical and cognitive
79	decline is more remarkable among edentate (i.e., people with no natural teeth) older people in
80	England compared to their dentate counterparts.9 Having more natural teeth is associated with
81	delaying the onset of disability and death among the Japanese older population. ⁶ Relevant
82	mechanisms include low nutritional status due to tooth loss ¹⁰ and increased risk of
83	cardiovascular disease due to inflammation from past periodontal disease. ¹¹ Social
84	interactions could be another pathway because lack of social interaction increases the risk of
85	disability ¹² and is also associated with having fewer teeth, which in turn is clearly linked to
86	worse oral function and quality of life. ¹³
~-	

In contrast to this accumulating evidence on the association between oral conditions

88	and functional capacity, there is hardly any robust evidence towards a causal relationship
89	(i.e., tooth loss affects functional capacity). Residual confounding is one of the most
90	challenging issues in the interpretation of association results from observational studies, and
91	further studies distilling out the causal effect are needed. ¹⁴ Adverse environment/conditions
92	in early life could be one example of residual confounding; they have been associated with
93	chewing ability, ¹⁵ number of teeth in adulthood, ^{16,17} and functional capacity. ¹⁸ Moreover, it is
94	impossible to measure all potential confounders, including unknown ones.
95	Randomized controlled trial (RCT) is conventionally considered a gold standard to
96	establish causal evidence; however, its generalizability to populations is limited, and it is not
97	well suited to investigate long-term consequences. ¹⁹ Beyond the RCT, causal estimates can
98	also be obtained from certain observational study designs. ²⁰ Natural experiments can be
99	utilized as sources of exogenous variations that were not manipulated by researchers, thereby
100	addressing reverse causation and (unmeasured) confounding.
101	In England, 10% of the population is exposed to artificially/naturally fluoridated
102	water, but the fraction of the population covered by fluoridated water and the year of
103	initiation varies geographically. ²¹ Thus, the likelihood of exposure to tap water fluoride is
104	influenced by year of birth and region lived in childhood. Exploiting quasi-experimental
105	variation in tooth loss due to this regional variation, we aimed to investigate the causal effect
106	of the number of teeth on functional capacity of the late adulthood population in England.

108 **METHODS**

109 Assumptions in the present study

110	We employed the instrumental variable (IV) approach, whereby exploiting the variation in
111	tap water fluoride as an instrument for the number of remaining teeth, thereby estimated the
112	association between the number of teeth and functional capacity without confounding by
113	individual characteristics. Figure 1 summarizes the criteria for a valid IV. In short, IV needs
114	to be 1) associated with the exposure; 2) affecting the outcome only through the exposure; 3)
115	independent of all unobserved variables that affect the outcome. ²² In the present study's
116	setting, the causal effect of the number of teeth can be identified under assumptions of 1)
117	childhood tap water fluoride prevents tooth loss in adulthood, 2) childhood exposure to tap
118	water fluoride affects functional capacity in adulthood only via preventing tooth loss, and 3)
119	factors influenced the decision on community water fluoridation in their childhood do not
120	affect the residents' functional capacity in late adulthood. Assumption 1 is supported by the
121	previous literature reporting the effect of water fluoridation on preventing dental caries. ^{23,24}
122	For example, a 27% reduction in caries experience among 5-years-old and 62% reduction in
123	the incidence of tooth extractions in the hospital among 0–19 year-olds are reported in
124	England. ²⁵ Some studies reported that the preventive effect could also result in retaining more
125	teeth in later adulthood. ^{26,27} As for assumption 2, previous reviews have declined the

126	existence of adverse effects of water fluoridation on other health outcomes related to
127	functional limitation, including bone fracture, cancer, and cognitive ability. ^{23,28–31}
128	Assumption 3 might be challenging because the population supplied with fluoridated tap
129	water in England has increased with time. Also, local characteristics are potential
130	confounders because local public bodies make decisions on community water fluoridation. ³²
131	We addressed the cohort effect confounding by restricting study participants to those born in
132	a specific range of years (between 1945-1965) so that to exclude participants that lived their
133	childhood prior to water fluoridation was introduced in the UK, and also statistically
134	controlled for it in the model. The region effect confounding was addressed by adjusting for
135	regional fixed effects and sensitivity analysis.
136	
137	Study participants
138	We conducted a secondary analysis using the data of the English Longitudinal Study of
139	Ageing (ELSA). ELSA is a sizeable longitudinal panel study targeting a representative
140	sample of the population aged 50 years or older in England. Further details about ELSA are
141	available elsewhere. ³³ We used ELSA wave 7, which was conducted between 2014–2015 and
142	is the only wave that measured the number of remaining teeth. To reduce bias due to the
1 12	
143	cohort effect and effectively utilize the variation in tap water fluoride in childhood, the data

145 analyzed. The present study was approved by the ethical committee at Tokyo Medical and146 Dental University.

147

148 Dependent variable: instrumental activities of daily living

149	IADL, which reduces at an early stage of declining functional capacity, was used to evaluate
150	whether oral health could be one strategy to prevent loss of functional competence. They
151	reflect instrumental self-maintenance by assessing the presence of limitations in the following
152	six activities: preparing a hot meal, shopping for groceries, making telephone calls, taking
153	medications, doing work around the house or garden, and managing money such as paying
154	bills and keeping track of expenses. An aggregate binary variable indicating limitations in
155	any of these six activities was used as the dependent variable to evaluate the impact of tooth
156	loss on daily function, as the daily life of older people is negatively affected when any of the
157	IADL components are compromised. This dichotomized outcome has been used in a previous
158	study. ³

159

160 *Exposure variable: the number of teeth*

161 The number of remaining teeth was assessed through the following question: "Adults usually

162 *have up to 32 natural teeth, but over time people lose some of them. How many natural teeth*

163 *have you got?.* "Respondents were asked to choose the answer from the following options:

164	"None at all," "Between 1 and 9 natural teeth," "Between 10 and 19 natural teeth," and "20
165	or more natural teeth." The variable was used as continuous in analyses with the middle
166	number allocated to each category (i.e., 0, 4.5, 14.5, and 26, respectively). Thereby, the
167	estimated effect size was scaled at the level of retaining one more tooth.
168	
169	Instrumental variable
170	We used the total annual likelihood of being exposed to naturally/artificially fluoridated
171	water between 5 and 20 years of age as the IV for the number of teeth. A similar approach
172	has been used in a previous study, ³⁴ and the age range was selected to cover the period of
173	eruption and post-eruptive maturation of the enamel of permanent teeth, including third
174	molar, that is when they are more prone to the preventive effect of fluoride. ³⁵
175	Figure 2 illustrates the trajectories of population coverage with naturally/artificially
176	fluoridated water in each region. We obtained county-level information on the number of
177	population covered by naturally/artificially fluoridated water and the year of the initiation of
178	artificial water fluoridation from a previous report. ²¹ As residential information of ELSA
179	participants was only available for the region of residence at the time of the survey, we used
180	this variable as a proxy of the region they resided in childhood and aggregated the
181	information on water fluoridation to a regional level. The proportion of people covered by
182	water fluoridation in each region every year was calculated based on the population size in

183	2012. ³⁶ The concentration of fluoride was targeted at 1.0 ppm for artificial water fluoridation,
184	while that of natural water fluoridation varied between 0.5–1.5 ppm. Further detail of the
185	calculation is described in Supplementary Method S1.
186	
187	Covariates
188	To consider differences by year of birth and region of residence, fixed effects of year of birth,
189	sex (men, women), and regional fixed effects were adjusted for. As several examples shown
190	in Supplementary Table S2, there might be differences in general health issues,
191	socioeconomic status, and other unmeasured factors by year of birth and region of residence.
192	Given that the analysis exploited the variation in the number of remaining teeth in adulthood
193	derived by differential exposure to tap water fluoride in childhood, we considered individual
194	general health variables as mediators rather than confounders; and we did not include them in
195	the covariates. The balancing tests showed that the difference in childhood socioeconomic
196	status by the instrument is small (standardized differences were close to or smaller than 0.1,
197	Supplementary Table S3); and we controlled them in the sensitivity analysis.
198	
199	Statistical analyses
200	Linear probability model (LPM) was fitted by Two-Stage-Least-Squares (2SLS) estimation.
201	Formally, let subscripts <i>ig</i> denote individual <i>i</i> living in a region <i>g</i> . <i>Teeth</i> _{<i>ig</i>} , <i>Fluoride</i> _{<i>ig</i>} , <i>Yob</i> _{<i>ig</i>} ,

202 and Sex_{ig} are participants' number of teeth, exposure to fluoridated water when aged 5-20 years, year of birth, and sex, respectively. Region_g indicates dummy variables for each region. 203 v_{ig} is an error term. Accordingly, our first-stage regression can be written as: 204 $Teeth_{ig} = \alpha_0 + \alpha_1 Fluoride_{ig} + \alpha_2 Yob_{ig} + \alpha_3 Sex_{ig} + \alpha_4 Region_g + v_{ig}$ 205 Let $Teeth_{ig}$ be the participant *i*'s number of teeth predicted by the first-stage regression, and 206 $IADL_{ig}$ be a binary variable equals 1 if the participant *i* had any limitation in IADL. e_{ig} is an 207 208 error term. The second-stage regression is then: $IADL_{ig} = \beta_0 + \beta_1 Teeth_{ig} + \beta_2 Yob_{ig} + \beta_3 Sex_{ig} + \beta_4 Region_g + e_{ig}$ 209 The coefficient β_1 indicates the percentage points change in the probability of limitation in 210 IADL per retaining one more tooth.³⁷ Analysis using each IADL item as the dependent 211 variable was also performed to investigate which specific components were affected. 212 213 214 Sensitivity analysis 215 Four sets of sensitivity analyses were performed: 1) assigning mean or median of the 216 clinically examined number of teeth respective to age, sex, and self-reported number of teeth in Adult Dental Health Survey 2009³⁸ to evaluate whether the results are robust to the 217 218 allocation of the midpoint of categorical responses; 2) controlling the cohort effects for linear function and restricted cubic spline function, respectively; 3) adjusting for participants' 219 220 educational qualification and their parents' years of education; 4) stratification analysis by 12

221	age group (50-64 and 65-70 years old). STATA MP version 16.1 (Stata Corp., College
222	Station, TX, USA) was utilized for all analyses.
223	
224	RESULTS
225	Table 1 summarizes the details of naturally/artificially fluoridated water in each region. The
226	fraction of the population covered by fluoridated water in 2012 ranged from 0 (South East
227	and South West) to 0.675 (West Midlands). The average year of initiation of artificial WF
228	ranged from 1968 (North East and Yorkshire and The Humber) to 1980 (West Midlands).
229	Table 2 describes the main characteristics of the respondents by the number of
230	natural teeth. The overall prevalence of the IADL limitation was 11.9% and was higher
231	among people with fewer teeth. Exposure to fluoridated water when aged 5-20 years was
232	greater among people with more natural teeth in later adulthood.
233	Table 3 shows the estimated causal effects of tooth loss on IADL. The first-stage
234	regression showed that exposure to fluoridated water was significantly associated with having
235	more natural teeth (Coefficient = 0.726; 95% confidence interval, CI: 0.311, 1.142). More
236	specifically, one-unit increment in the instrument, which is equivalent to one additional year
237	of exposure to fluoridated water during the age of 5 to 20 years, was associated with having
238	0.726 more teeth on average at an older age. The first-stage F-statistic was 11.749, indicating
239	that the IV was sufficiently strong to predict the number of teeth. ³⁹ The second-stage

240	regression showed that retaining one more tooth reduced probability of limitation in IADL by
241	3.1 (95% CI: 0.2, 6.0) percentage points.
242	The second-stage estimates for each component of IADL are shown in
243	Supplementary Figure S4. With the exception of "taking medications" and "managing
244	money", the point estimates were negative, that is, having more natural teeth was associated
245	with lower probability of each IADL limitation, though only the association with "shopping
246	for groceries" was significant.
247	Similar estimates were obtained when changing the number of teeth assigned to each
248	category (Supplementary Table S5). The results did not change when adjusting for the year of
249	birth with different functions or adjusting for individual educational level (Supplementary
250	Table S6). Further stratification analysis by age showed similar point estimates in aged 50–64
251	year-olds, while the first-stage regression was not significant in those aged 65–70 years old.
252	
253	DISCUSSION
254	The present natural experimental study showed that the number of remaining teeth predicted

- by the differential exposure to tap water fluoride in childhood was associated with a lower
- 256 probability of having limitations in IADL. Under the assumptions supported by previous
- 257 literature, our findings suggest that having one more tooth reduced the probability of having a
- limitation in IADL by 3.1 percentage points among adults aged 50–70 years old in England.

259	Under the monotonicity assumption, IV analyses estimate the local average
260	treatment (LATE) effect among compliers. ³⁷ In the present study, the monotonicity
261	assumption, that is, no one loses their teeth because of being exposed to fluoridated water in
262	childhood, is supported by previous biological and epidemiological studies. ⁴⁰ As our
263	instrument is a continuous scale, the inferential target population consists of all individuals
264	used in the analysis contributing with unknown weights. ³⁷ Given that the preventive effect of
265	water fluoridation is more prominent in high-risk populations (i.e., living in deprivation), ⁴¹
266	our results might primarily reflect the effect of teeth on IADL among people from lower
267	socioeconomic backgrounds. The 2SLS estimate (3.1 percentage points difference) was larger
268	than the OLS estimation (0.7 percentage points difference), which may suggest that the
269	impact of tooth loss is more significant among people from lower socioeconomic
270	backgrounds. It is possible that the lack of resources and limited access to care among the
271	deprived population ⁴² might accelerate the impact of tooth loss on IADL. Our estimates
272	might overestimate the effect of tooth loss on IADL limitation, as the IV estimator can be
273	more biased than the OLS estimator when the IV is only weakly correlated with the exposure
274	variable. ⁴³ The analytical population was younger than the entire ELSA participants. A
275	previous study in the US found that the impact of tooth loss was more considerable among
276	younger people. ⁴⁴ For these reasons, the effect sizes in the present study might be larger than
277	the average treatment effect in the older adult population in England.

278	IADL reflects coordination of higher physical and cognitive functions. ⁴⁵ Thus, the
279	pathway of the association between tooth loss and general physical and cognitive function is
280	also relevant. Low dietary intake due to tooth loss ^{10,46} could result in decline in functional
281	capacity. Lower social interaction, which is a risk factor for the onset of disability, ¹² would
282	also explain the link between tooth loss and IADL, because tooth loss is associated with low
283	social function. ⁴⁷ Further, as a marker of lifetime experience of oral diseases and treatment,
284	tooth loss is related to past dental caries and periodontal diseases, and the latter in particular
285	could partly reflect past oral inflammation. ¹¹ The difference in tooth loss induced by water
286	fluoridation, which we exploited in the analysis, would mainly reflect the differential dental
287	caries experience rather than periodontal diseases. Thus, the pathway through periodontal
288	inflammation might be less likely to explain our findings. The component-specific analysis
289	resulted in "shopping for groceries" and "doing work around the house or garden" having the
290	two largest point estimates, although only the former was significant. These reflect the two
291	most demanding physical tasks from the IADL items included in the study. ⁴⁸ This might
292	suggest that tooth loss affects functional capacity at an early stage of the decline. While the
293	present study provides evidence for a causal relationship between tooth loss and functional
294	capacity, the plausibility and extent of the different pathways would need further
295	investigations in the framework of strong causal inference.

16

Previous studies have shown associations, that is, people with fewer teeth being

297	more likely to have disabilities or limitations in functional capacity, ^{6–9} thereby providing
298	evidence that tooth loss may be useful as an early marker of decline in functional capacity.
299	The present study added the causal evidence to the literature, that is, retaining natural teeth
300	prevents a limitation in IADL. Other observational studies have reported that having
301	recommended levels of physical exercise, ⁴⁹ social participation, ⁵⁰ and living in a walk-up
302	residence, i.e., having to walk upstairs ⁵¹ was associated with 0.53–0.74 times lower odds of
303	having a limitation in IADL. Considering the prevalence of IADL limitation in the present
304	study participants, the estimated causal effect of retaining one more tooth (3.1 percentage
305	points difference) is equivalent to 0.72 in terms of odds ratio scale. The estimated effect size
306	might be larger than the population average because of the reasons described above. Given
307	the high prevalence of tooth loss, this could be a relevant target for interventions to promote
308	functional capacity and avoid or delay limitations in IADLs. The health gain from retaining
309	natural teeth might not be limited to oral health outcomes. We assumed a linear relationship
310	between the number of remaining teeth and IADL, but the marginal effect of losing a tooth
311	might be different for people that have lost many teeth. Further research, such as studies
312	using clinically examined tooth count to consider a potential non-linear effect of tooth loss as
313	well as cost-effectiveness evaluation of interventions incorporating oral and general health
314	outcomes, are needed.

While we addressed and evaluated potential violations of the assumptions, the results

316	need to be interpreted with caution. Assumption 1, the relevance of the instrument, is
317	supported by previous literature ^{23–27} and the results from the first-stage regression.
318	Assumption 2, the exclusion restriction, is at least partly supported by previous
319	literature, ^{23,24,26–31} although it is not possible to prove perfectly. Assumption 3, the exogenous
320	condition, could be violated if the cohort and region effects were not fully controlled in the
321	model. We carefully addressed this issue by restricting participants to the cohorts born during
322	1945–1965 and also controlling the cohort effect with various functions. The results were
323	mostly similar; however, estimates were not significant in further stratification analysis by
324	age group, possibly because of reduced sample size and smaller variation in the instrument
325	among those aged 65–70. As for the region effect confounding, we have adjusted for regional
326	characteristics by including a fixed effect in the models, but it is still possible that the timing
327	of the initiation of water fluoridation is associated with local authorities' characteristics. The
328	political situation in the local community might have influenced the decision; ³² however, it is
329	difficult to be controlled for in the model. We evaluated the regional difference within the
330	data availability; we compared area deprivation between counties with and without water
331	fluoridation and found that the median rank of Index of Multiple Deprivation ⁵² was not
332	significantly different between them ($P = 0.720$). The results did not change when adjusting
333	for participants' educational qualifications and parents' years of education. Nevertheless,
334	unknown but plausible confounders might exist and influence the results.

335	Another assumption is that the participants had lived in the same region in their
336	childhood as in the time of the survey. The assumption may well have been violated as the
337	participants are 50 years old or older because, in England, about 1 to 3% of the population
338	migrated to other regions in 2014.53 We were not able to evaluate this potential
339	misclassification due to lack of data. We believe the misclassification to be non-differential
340	because people would be less likely to decide their region of residence based on whether
341	there is water fluoridation. Therefore, it would have decreased both the reduced-form and the
342	first-stage estimators; and the direction of the bias on the IV estimator (ratio of the reduced-
343	form estimator to the first-stage estimator) might be over or underestimated.
344	Other methodological limitations include that we did not have any information on
345	other sources of fluoride (e.g., toothpaste). Thus, our estimation might be biased if the
346	utilization of fluoride resources differs by regions; however, the frequency of tooth brushing
347	was not different by region in Adult Dental Health Survey 2009. ³⁸ Moreover, data on the
348	number of teeth and IADL was self-reported; however, high accuracy of self-reports for
349	number of teeth has been reported previously.54
350	Few previous studies have applied natural experimental design to investigate the
351	causal relationship between oral and general health outcomes. The present natural
352	experimental study exploited the historical and geographical variation in community water
353	fluoridation and found that retaining one more natural tooth due to exposure to fluoridated

354	water in childhood was associated with a lower probability of limitations in IADL. Preventive
355	oral health strategies can potentially improve independent living in later life.
356	
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	Total population in 2012 ^a	Population covered by fluoridated water in 2012 ^b	Fraction of population covered by fluoridated water in 2012 ^b	Year of initiating artificial water fluoridation ^b
Governmental region				
North East	2,602,300	965,000	0.371	1968
North West	7,084,300	257,000	0.036	1969
Yorkshire and The	5,316,700	136,000	0.026	1968
East Midlands	4,567,700	580,000	0.127	1972
West Midlands	5,642,600	3,810,000	0.675	1980
East of England	5,907,300	198,000	0.034	1977
London	8,308,400	180,000 a	0.022	-
South East	8,724,700	0	0.000	-
South West	5,339,600	0	0.000	-

Table 1. Characteristics of natural/artificial water fluoridation by region

a Source: Office for National Statistics. Population estimates (2012)

b Source: The British Fluoridation Society. The extent of water fluoridation, 3rd ed. One in a Million: the facts about water fluoridation (2012). https://www.bfsweb.org/one-in-a-million c Average year is shown because the year of initiation differed among the parts of the region

5,631)					
	No teeth	1-9 teeth	10-19 teeth	20+ teeth	Number
	n = 234	n = 290	n = 719	n = 4,388	of teeth ^a
	n (%)	n (%)	n (%)	n (%)	Mean
Having IADL					
limitation					
No	175 (74.8%)	217 (74.8%)	584 (81.2%)	3,987 (90.9%)	22.8 (7.0)
Yes	59 (25.2%)	73 (25.2%)	135 (18.8%)	401 (9.1%)	19.1 (9.3)
Year of birth					
1945–1949	120 (51.3%)	128 (44.1%)	286 (39.8%)	1,271 (29.0%)	21.0 (8.5)
1950–1954	76 (32.5%)	88 (30.3%)	243 (33.8%)	1,398 (31.9%)	22.3 (7.4)
1955–1959	30 (12.8%)	61 (21.0%)	128 (17.8%)	1,007 (22.9%)	23.1 (6.6)
1960–1965	8 (3.4%)	13 (4.5%)	62 (8.6%)	712 (16.2%)	24.5 (4.7)
Sex					
Men	92 (39.3%)	161 (55.5%)	337 (46.9%)	1,921 (43.8%)	22.2 (7.5)
Women	142 (60.7%)	129 (44.5%)	382 (53.1%)	2,467 (56.2%)	22.5 (7.3)
Governmental					
region					
North East	26 (11.1%)	18 (6.2%)	57 (7.9%)	237 (5.4%)	20.9 (8.5)
North West	38 (16.2%)	52 (17.9%)	93 (12.9%)	521 (11.9%)	21.5 (8.2)
Yorkshire and					
The Humber	37 (15.8%)	40 (13.8%)	74 (10.3%)	423 (9.6%)	21.4 (8.4)
East Midlands	43 (18.4%)	23 (7.9%)	75 (10.4%)	460 (10.5%)	21.9 (8.1)
West Midlands	43 (18.4%) 20 (8.5%)	23 (7.9%) 38 (13.1%)	83 (11.5%)	400 (10.3%) 490 (11.2%)	21.9 (8.1) 22.4 (7.2)
	· · · · · ·	· · · · · ·	83 (11.3%) 100 (13.9%)	· · · · ·	. ,
East of England	18 (7.7%)	36 (12.4%)		552 (12.6%)	22.6 (6.9)
London	13 (5.6%)	26 (9.0%)	59 (8.2%)	417 (9.5%)	23.0 (6.7)
South East	27 (11.5%)	35 (12.1%)	112 (15.6%)	760 (17.3%)	23.1 (6.6)
South West	12 (5.1%)	22 (7.6%)	66 (9.2%)	528 (12.0%)	23.6 (6.0)
Extent of being					
exposed to	0.328 (0.748)	0.260 (0.652)	0.381 (0.862)	0.401 (0.925)	-
fluoridated water bc					

Table 2. IADL and other characteristics of the respondents, by number of natural teeth (N = 5,631)

Abbreviations: IADL, instrumental activity of daily living, SD, standard deviation a No teeth was coded 0, 1-9 teeth was coded 5, 10-19 teeth was coded 14.5, and 20+ teeth was coded 26

b Total of the annual proportion of people covered by fluoridated water in the region of

residence between 5 and 20 years of age

c Values are expressed as mean (SD)

Table 3. Causal effect of the number of teeth on the instrumental activity of daily living, IADL (N = 5,631)

	Coef. (95% CI)	F-statistic
OLS estimation		
Number of remaining teeth	-0.007 (-0.008, -0.006)	-
2SLS estimation		
Second-stage regression		
Number of remaining teeth	-0.031 (-0.060, -0.002)	-
First-stage regression		
Extent of being exposed to fluoridated water	0.726 (0.311, 1.142)	11.749
Reduced-form estimation		
Extent of being exposed to fluoridated water	-0.023 (-0.041, -0.004)	-
		1 .

Abbreviations: CI, confidence interval; 2SLS, two-stage least square, OLS, ordinary least squares

Adjusted for the fixed effects of year of birth, sex, and governmental region of residence

a No teeth was coded 0, 1–9 teeth was coded 5, 10–19 teeth was coded 14.5, and \geq 20 teeth was coded 26

b Total of the annual proportion of people covered by fluoridated water in the region of residence between 5 and 20 years of age

FIGURE LEGEND

Figure 1. Criteria for a valid instrumental variable (left side) and corresponding assumptions in the present study (right side).

Figure 2. Trajectory of population covered by naturally/artificially fluoridated water

SUPPLEMENTAL INFORMATION LEGENDS

Supplementary Method S1. The detail of the instrumental variable in the present study Supplementary Table S2. Difference in general health issue and educational status by year of birth and region

Supplementary Table S3. Balancing test for participants' socioeconomic status in childhood **Supplementary Figure S4.** Causal effect of the number of teeth on each item of instrumental activity of daily living, IADL (N = 5,631)

Supplementary Table S6. Sensitivity analysis by different adjustment for cohort and regional confounders

Criteria for a valid instrumental variable		Assumptions in the present study	
1.	Instrumental variable is associated with	1.	Childhood exposure to tap water fluoride
	the exposure		prevents tooth loss in adulthood
2.	Instrumental variable affects the outcome	2.	Childhood exposure to tap water fluoride
	only through the exposure but not		affects instrumental activity of daily living
	otherwise		in a dulthood only via preventing tooth \ensuremath{loss}
			but not through other pathways
3.	Independent of all unobserved variables	3.	Factors influenced the decision on
	that affect the outcome		community water fluoridation do not affect $% \left({{{\left({{{{\left({{{\left({{{{}}}} \right)}} \right.}} \right)}_{0,2}}}} \right)$
			the residents' instrumental activity of daily
			living

Figure 1. Criteria for a valid instrumental variable (left side) and corresponding assumptions in the present study (right side).

189x80mm (300 x 300 DPI)

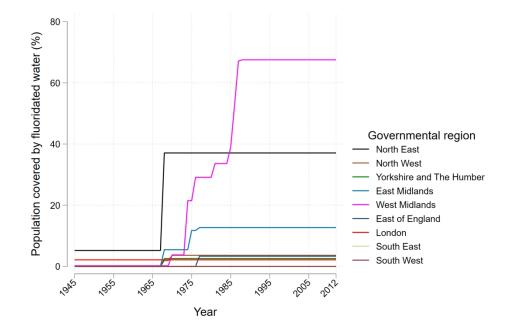


Figure 2. Trajectory of population covered by naturally/artificially fluoridated water

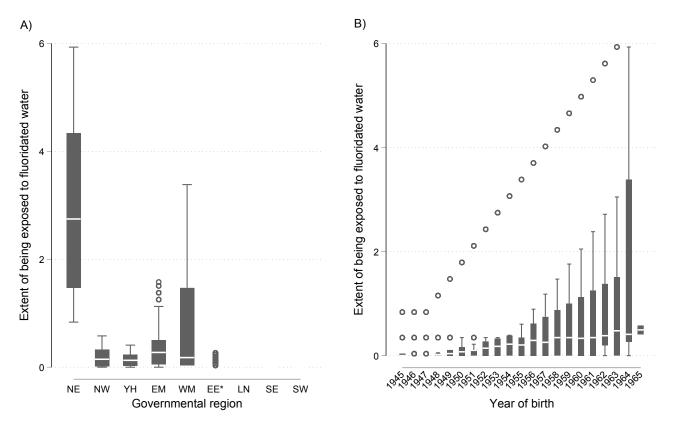
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SUPPLEMENTARY INFORMATION

Supplementary Method S1. The detail of the instrumental variable in the present study

The instrument referred to the likelihood of being exposed to fluoridated tap water during the age of 5-20 years of age. It was determined by the combination of the year of birth and region of residence, assuming that the region of residence is the same as in childhood. The figure below shows the distribution of the instrument according to the region of residence or year of birth.

Supplementary Method S1 Figure. The distribution of the instrument accordding to A) region of residence and B) year of birth; North East, NE, North West, NW, Yorkshire and The Humber, YH, East Midlands, EM, West Midlands, WM, East of England, EE, London, LN, South East, SE, South West, SW



*In East of England, all values were plotted as outliers because 25, 50, and 75 percentiles were zero

For a detailed explanation, suppose the following four individuals: 1) born in West Midlands in 1950; 2) born in West Midlands in 1960; 3) born in London in 1950; 4) born in London in 1960. In West Midlands, 0.2% of the population were supplied naturally fluoridated water in 1955, and artificial water fluoridation was implemented in 1970, resulting in 3.8% of the population supplied naturally/artificially fluoridated water was 0.002 during the age of 5–19 (i.e., during 1955–1969) and 0.038 at the age of 20 (i.e., in 1970). The total is 0.068, which was allocated to the individual 1 as the instrument. On the other hand, in London, artificial water fluoridated water fluoridated to the individual 1 as the population were supplied naturally fluoridated water fluoridated to the individual 1 as the population.

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water. Accordingly, the instruments for individuals 2, 3, and 4 are calculated to 2.047, 0.352, and 0.352, respectively (see Table below). By definition, the instrument values range between 0 (living in a region without naturally/artificially fluoridated water during the age of 5–20) and 16 (living in a region with 100% coverage of fluoridated water 16 years during the age of 5–20). Thus, for the interpretation of effect sizes, a one-unit increment in the instrument reflects exposure to fluoridated water for an additional year.

					• •		
Borr	n in West	Borr	Individual 2 Born in West Midlands Individual 3 Born in London			Individual 4 Born in London	
ge	Fluoride coverage	Age	Fluoride coverage	Age	Fluoride coverage	Age	Fluoride coverage
0				0			
1				1			
2				2			
3				3			
4				4			
5	0.002			5	0.022		
6	0.002			6	0.022		
7	0.002			7	0.022		
8	0.002			8	0.022		
9	0.002			9	0.022		
10	0.002	0		10	0.022	0	
11	0.002	1		- 11	0.022	1	
12	0.002	2		12	0.022	2	
13	0.002	3		13	0.022	3	
14	0.002	4		14	0.022	4	
15	0.002	5	0.002	15	0.022	5	0.022
16	0.002	6	0.002	16	0.022	6	0.022
17	0.002	7	0.002	17	0.022	7	0.022
18	0.002	8	0.002	18	0.022	8	0.022
19	0.002	9	0.002	19	0.022	9	0.022
20	0.038	10	0.038	20	0.022	10	0.022
		11	0.038			- 11	0.022
		12	0.038			12	0.022
		13	0.038			13	0.022
		14	0.215			14	0.022
		15	0.215			15	0.022
		16	0.291			16	0.022
		17	0.291			17	0.022
		18	0.291			18	0.022
		19	0.291			19	0.022
		20	0.291			20	0.022
	0.068		2.047		0.352		0.352
	Borr Mi ge 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	ge coverage 0 1 2 3 4 5 0.002 6 0.002 7 0.002 7 0.002 8 0.002 9 0.002 10 0.002 10 0.002 11 0.002 11 0.002 13 0.002 13 0.002 14 0.002 15 0.002 16 0.002 17 0.002 18 0.002 19 0.002 0.038	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Born in West MidlandsBorn in West MidlandsBorn in West MidlandsInd BorngeFluoride coverageAgeFluoride coverageAge0011222334450.002670.002670.002780.0029100.0020110.00210120.0022130.0023140.0024150.0025160.0026170.0027180.0028190.0029200.03810130.038140.215150.215160.291170.291180.291190.291200.291	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

Supplementary Method S1 Table. Instrumental variable for hypothetical four individuals

a 1	T 11 C	D:00 ·		• •			01 1 1 1
Sunnlementary	7 Table S2	Difference in	general health	i issue and e	educational	status by ve	ear of birth and region
Supprementary		. Difference in	general nearth	i issue and v	cuucationai	status by y	ar or on and region

Supplementary Table S2.	Diabetes ^a	Depression ^b	Self-rated health (fair/poor)	No educational qualification	Having mothers with <14 years of education	Having fathers with <14 years of education
Year of birth: 1945–1949				*		
North East	8.9%	19.1%	32.2%	33.3%	78.9%	85.6%
North West	8.7%	19.0%	24.2%	24.7%	72.3%	74.0%
Yorkshire and The Humber	13.5%	21.1%	24.3%	29.2%	83.2%	80.0%
East Midlands	8.9%	15.5%	24.1%	31.5%	76.8%	75.4%
West Midlands	12.9%	19.6%	28.1%	37.1%	78.7%	76.4%
East of England	9.1%	10.6%	15.6%	24.7%	68.0%	66.2%
London	17.1%	15.4%	23.7%	27.0%	61.2%	61.8%
South East	8.8%	12.8%	15.7%	19.9%	57.7%	54.7%
South West	9.3%	14.2%	17.6%	17.6%	66.2%	68.1%
Year of birth: 1950-1954						
North East	9.5%	21.8%	26.7%	22.9%	81.0%	78.1%
North West	8.4%	13.0%	19.5%	18.1%	68.4%	73.0%
Yorkshire and The Humber	9.6%	16.7%	21.8%	27.1%	72.3%	73.9%
East Midlands	12.5%	19.4%	25.0%	24.6%	70.5%	75.4%
West Midlands	10.6%	20.8%	23.9%	19.1%	64.4%	63.8%
East of England	7.6%	15.7%	16.1%	21.2%	64.0%	62.3%
London	12.0%	20.4%	24.6%	19.8%	58.7%	53.3%
South East	7.4%	14.4%	15.5%	17.0%	50.9%	46.3%
South West	10.6%	12.9%	16.6%	12.1%	55.8%	54.3%
Year of birth: 1955-1959						
North East	9.0%	20.3%	24.4%	19.2%	67.9%	71.8%
North West	6.2%	22.5%	24.1%	16.6%	60.7%	64.8%
Yorkshire and The Humber	4.2%	23.2%	22.5%	22.5%	61.7%	63.3%
East Midlands	6.1%	20.4%	22.6%	17.4%	70.4%	74.8%
West Midlands	5.2%	25.9%	22.6%	16.8%	63.2%	63.9%
East of England	5.6%	24.2%	15.5%	12.7%	51.4%	58.5%
London	7.8%	26.9%	22.7%	13.3%	39.1%	40.6%
South East	3.5%	14.8%	15.3%	13.4%	40.6%	52.5%
South West	2.8%	15.7%	19.9%	7.8%	43.3%	53.9%
Year of birth: 1960-1965						
North East	4.6%	19.4%	23.1%	4.6%	35.4%	46.2%
North West	7.1%	26.0%	24.8%	3.5%	38.1%	46.9%
Yorkshire and The Humber	1.2%	20.8%	17.3%	8.6%	40.7%	45.7%
East Midlands	5.1%	26.0%	16.9%	11.9%	44.1%	55.9%
West Midlands	3.7%	18.8%	17.3%	10.0%	43.6%	44.5%
East of England	1.0%	23.9%	14.4%	2.1%	36.1%	39.2%
London	5.9%	8.6%	11.8%	5.9%	33.8%	33.8%
South East	2.5%	24.5%	16.1%	5.1%	23.7%	36.4%
South West	4.8%	16.0%	16.7%	6.0%	29.8%	36.9%

a Ever being diagnosed diabetes by doctors

b Total score of 8-item Center for Epidemiologic Studies Depression Scale (CES-D) \geq 3

	Un	adjusted mo	del	Ad	ljusted model	a
					of being exposed to oridated water	
Dependent variable	Low ^b	Middle ^c	High ^d	Low ^b	Middle ^c	High ^d
Respondent having educational qualification						
Yes	0.036	0.154	0.104	0.009	0.061	0.103
No	0.094	0.106	0.009	0.025	0.066	0.096
Missing	0.124	0.081	0.196	0.035	0.020	0.006
Mother's years of education						
≤14	0.096	0.232	0.097	0.014	0.033	0.045
>14	0.103	0.230	0.086	0.043	0.028	0.013
Missing	0.012	0.018	0.030	0.070	0.013	0.078
Father's years of education						
≤14	0.120	0.222	0.060	0.041	0.010	0.049
>14	0.141	0.222	0.033	0.031	0.010	0.042
Missing	0.034	0.021	0.057	0.023	0.000	0.018

Supplementary Table S3. Balancing test for participants' socioeconomic status in childhood

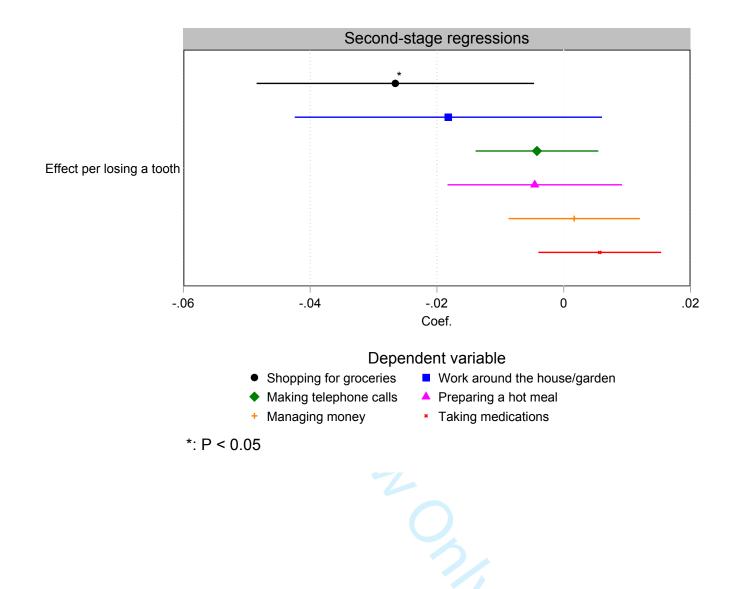
Each dependent variable was regressed on a dummy variable indicating low (= 0), middle (> 0 to 0.29), or high (≥ 0.30) exposure to fluoridated water, respectively. Standardized differences are reported, and values smaller than 0.10 indicates the variable is balanced.

a adjusted for region fixed effect and year of birth fixed effect

b standardized difference between low exposure of fluoridated water and the other two groups combined c standardized difference between middle exposure of fluoridated water and the other two groups combined d standardized difference between high exposure of fluoridated water and the other two groups combined

Supplementary Figure S4. Causal effect of the number of teeth on each item of instrumental activity of daily

living, IADL (N = 5,631); showing coefficients with 95% confidence intervals



Supplementary Table S5. Causal effect of the number of teeth on the instrumental activity of daily living, IADL (N = 5,631); mean or median of the clinically examined number of teeth respective to age, sex, and self-reported number of teeth was linked from Adult Dental Health Survey 2009

1	5	
	Coef. (95% CI)	F-statistic
Mean number of teeth was assigned		
OLS estimation		
Number of remaining teeth	-0.008 (-0.009, -0.006)	-
2SLS estimation		
Second-stage regression		
Number of remaining teeth	-0.036 (-0.069, -0.003)	-
First-stage regression		
Extent of being exposed to fluoridated water ^a	0.627 (0.281, 0.974)	12.572
Reduced-form estimation		
Extent of being exposed to fluoridated water ^a	-0.023 (-0.041, -0.004)	-
Median number of teeth was assigned		
OLS estimation		
Number of remaining teeth	-0.007 (-0.009, -0.006)	-
2SLS estimation		
Second-stage regression		
Number of remaining teeth	-0.033 (-0.063, -0.003)	-
First-stage regression		
Extent of being exposed to fluoridated water ^a	0.682 (0.316, 1.048)	13.325
Reduced-form estimation		
Extent of being exposed to fluoridated water a	-0.023 (-0.041, -0.004)	_
Abbreviations: CI, confidence interval; 2SLS, two-st	age least square, OLS, ordin	ary least squa
Adjusted for the fixed effects of year of birth, sex, an	d governmental region of re	sidence
a Total of the annual proportion of people covered by	y fluoridated water in the reg	tion of resider
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		,

and 20 years of age

	1 1 1 1.00		1 1 1 1 1
Supplementary Lanle S6 Sensitivit	V analveie hv ditterent	adjustment for cohort a	and regional contolinders
Supplementary Table S6. Sensitivit			

	e	
	Coef. (95% CI)	F-statistic
Controlled for year of birth by linear function ($N = 5631$)		
Second-stage regression: number of remaining teeth	-0.036 (-0.070, -0.002)	
First-stage regression: extent of being exposed to fluoridated water ^a	0.630 (0.223, 1.037)	9.212
Controlled for year of birth by restricted cubic spline ($N = 5631$)		
Second-stage regression: number of remaining teeth	-0.031 (-0.060, -0.002)	
First-stage regression: extent of being exposed to fluoridated water ^a	0.715 (0.300, 1.130)	11.421
Age of 50-64, controlled for year of birth by fixed effects (N = 3883)		
Second-stage regression: number of remaining teeth	-0.035 (-0.082, 0.011)	
First-stage regression: extent of being exposed to fluoridated water ^a	0.572 (0.075, 1.070)	5.081
Age of 65-70, controlled for year of birth by fixed effects ($N = 1748$)		
Second-stage regression: number of remaining teeth	0.033 (-0.407, 0.474)	
First-stage regression: extent of being exposed to fluoridated water ^a	0.995 (-7.029, 9.019)	0.059
Adjusted for year of birth fixed effects and participants' and parents' education $b (N = 5631)$		
Second-stage regression: number of remaining teeth	-0.032 (-0.063, -0.001)	
First-stage regression: extent of being exposed to fluoridated water ^a	0.672 (0.267, 1.076)	10.600
Abbreviations: CI, confidence interval;		
All models were estimated with two stage least squares estimation	and adjusted for say and	aaramaaat

All models were estimated with two-stage least squares estimation and adjusted for sex and governmental region of residence

a Total of the annual proportion of people covered by fluoridated water in the region of residence between 5 and 20 years of age

b participants' educational level was assessed by having educational qualification (yes, no); while mother's and father's educational level was assessed by years of education (≤ 14 years, >14 years)

1	Title
2	Causal effect of tooth loss on functional capacity in older adults in England: a natural
3	experiment
4	
5	Short running title
6	Tooth loss and functional capacity
7	
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- 34 Word counts: 248251 (abstract) 3,5172,764 (main text)
- 35 Number of tables/figures: 3 (tables) 2 (figures)
- 36

37 **Impact statement**

- 38 We certify that this work is novel of recent epidemiological research. We identified the
- 39 *causal effect* of tooth loss on functional capacity among adults aged $\geq 50-70$ years old in
- 40 England, whereby exploiting the exogeneous geographical and historical variation in the-
- 41 childhood exposure to tap water fluoride. Retaining Our findings suggest that having one
- 42 more tooth due to exposure to fluoridated water in childhood causally reduced the probability
- rA Linental Le causal evid. 43 of having a limitation in the instrumental activity of daily living IADL by 3.1.9 percentage
- 44 points. Our findings support the causal evidence between tooth loss and functional capacity-in
- 45 later life.

2

46 Abstract

47	BACKGROUND/OBJECTIVES: Tooth loss is associated with reduced functional capacity, but so
48	far, there is no relevant causal evidence reported. We investigated the causal effect of tooth loss on
49	the instrumental activities of daily living (IADL) among <u>older</u> adults aged \geq 50 years in England.
50	DESIGN: Natural experiment study with instrumental variable analysis.
51	SETTING: The English Longitudinal Study of Aging (ELSA) combined with the participants'
52	childhood exposure to water fluoride due to the community water fluoridation.
53	PARTICIPANTS: <u>5,631</u> 9,437 adults in England born in 194523–1965 who-participated in the
54	ELSA wave 7 survey (conducted in 2014–2015; average age: $61.067.7$ years, 44.67% men).
55	EXPOSURE: The number of natural teeth predicted by the exogenous geographical and historical
56	variation in exposure to water fluoride from age 5 to 20 years old (instrumental variable).
57	MAIN OUTCOME: Having any limitations in IADL (preparing a hot meal, shopping for groceries,
58	making telephone calls, taking medications, doing work around the house or garden, or managing
59	money).
60	RESULTS: Linear probability model with Two-Stage Least Squares estimation was fitted. Being
61	exposed to fluoridated water was associated with having more natural teeth in later life (coefficient:
62	<u>0.7261.08</u> ; 95% CI: 0.31170 , 1.14245 ; F = <u>11.74931.49</u>). Retaining one more natural tooth reduced
63	the probability of having a limitation in IADL by $3.1.9$ percentage points (coefficient: -0.0319 ; 95%
64	CI: -0. <u>060</u> 035, -0.00 <u>2</u> 4).

- **CONCLUSION:** Preventing tooth loss maintains functional capacity among <u>older</u> adults $\frac{\text{aged} \geq 50}{2}$ 65 years in England. Given the high prevalence of tooth loss, this effect is considerable. Further 66 67 research on the mechanism of the observed causal relationship is needed.
- 68

71

- 69 Keywords: Instrumental Activity of Daily Living; Oral Health; Instrumental variable; Natural
- 70 Experiment

Jur Daily .

72	INTRODUCTION	_

- 73 Instrumental activities of daily living (IADL) represent Maintaining functional
- 74 <u>competence capacity is essential</u> for independent living in <u>a community and significantly</u>
- 75 <u>impact the quality of later life in older people.¹ A hierarchical model has been proposed for</u>
- 76 <u>functional competence, and declines in higher-level competence predict future declines in</u>
- 77 lower-level domains.² As a decline in IADL is associated with dementia³ and death,⁴
- 78 maintaining IADL is essential for individuals in early old age and throughout aging society
- 79 while it also leads to lower medical and long-term care costs.^{4,5}
- 80 Studies have reported a longitudinal association between oral conditions and a
- 81 decline in functional capacity and disability.⁶⁻⁹ More specifically, physical and cognitive
- 82 decline is more remarkable among edentate (i.e., people with no natural teeth) older people in
- 83 England compared to their dentate counterparts.⁹ Having more natural teeth is associated with
- 84 <u>delaying the onset of disability and death among the Japanese older population.⁶ Relevant</u>
- 85 mechanisms include low nutritional status due to tooth loss¹⁰ and increased risk of
- 86 <u>cardiovascular disease due to inflammation from past periodontal disease.¹¹ Social</u>
- 87 interactions could be another pathway because lack of social interaction increases the risk of
- 88 disability¹² and is also associated with having fewer teeth, which in turn is clearly linked to
- 89 worse oral function and quality of life.¹³
- 90 In contrast to this accumulating evidence on the *association* between oral conditions

91	and functional capacity, there is hardly any robust evidence towards a causal relationship
92	(i.e., tooth loss affects functional capacity). Residual confounding is one of the most
93	challenging issues in the interpretation of association results from observational studies, and
94	further studies distilling out the causal effect are needed. ¹⁴ Adverse environment/conditions
95	in early life could be one example of residual confounding; they have been associated with
96	chewing ability, ¹⁵ number of teeth in adulthood, ^{16,17} and functional capacity. ¹⁸ Moreover, it is
97	impossible to measure all potential confounders, including unknown ones.
98	Randomized controlled trial (RCT) is conventionally considered a gold standard to
99	establish causal evidence; however, its generalizability to populations is limited, and it is not
100	well suited to investigate long-term consequences. ¹⁹ Beyond the RCT, causal estimates can
101	also be obtained from certain observational study designs. ²⁰ Natural experiments can be
102	utilized as sources of exogenous variations that were not manipulated by researchers, thereby
103	addressing reverse causation and (unmeasured) confounding.
104	In England, 10% of the population is exposed to artificially/naturally fluoridated
105	water, but the fraction of the population covered by fluoridated water and the year of
106	initiation varies geographically. ²¹ -Declines in higher-level functional competence predict-
107	future disability and death. ² A billion of the world population are living with disabilities, ³ and
108	the high prevalence of disability strains public healthcare systems and expenditures ⁴
109	Therefore, determining preventive factors of the initial decline in functional capacity is-

110	important in an aging society.
111	
112	in functional capacity and disability. ^{5–8} More specifically, physical and cognitive decline is-
113	greater among edentate (i.e., people with no natural teeth) older people in England compared-
114	to their dentate counterparts. ⁸ Having more natural teeth is associated with delaying the onset-
115	of disability and death among the Japanese older population. ⁵ Tooth loss due to dental caries
116	or periodontal disease leads to poor nutritional status.9 Inflammation related to past
117	periodontal disease may increase the risk of cardiovascular disease. ¹⁰ Social interactions-
118	could be another pathway because lack of social interaction increases the risk of disability ¹¹ -
119	and is also associated with having fewer teeth, which in turn is clearly linked to worse oral
120	function and quality of life. ¹² -
121	In contrast to this accumulating evidence on the association between oral conditions-
122	and functional capacity, there is hardly any robust evidence towards a causal relationship
123	(i.e., tooth loss affects functional capacity). Residual confounding is one of the most-
124	challenging issues in the interpretation of association results from observational studies, and
125	further studies distilling out the causal effect are needed. ¹³ -Adverse environment/conditions-
126	in early life could be one example of residual confounding; they have been associated with
127	chewing ability, ¹⁴ number of teeth in adulthood, ^{15,16} and functional capacity. ¹⁷ Moreover, it is-
128	impossible to measure all potential confounders, including the unknown ones.

129	The randomized controlled trial (RCT) is conventionally considered a gold standard
130	to establish causal evidence; however, its generalizability to populations is limited, and it is
131	not well suited to investigate long-term consequences. ¹⁸ Beyond the RCT, causal estimates-
132	can also be obtained from certain observational study designs. ¹⁹ Natural experiments can be-
133	utilized as sources of exogenous variations that were not manipulated by researchers, thereby-
134	addressing reverse causation and (unmeasured) confounding. Such exogenous variation can-
135	be exploited as an instrumental variable (IV) for the exposure of interest. ²⁰ The IV needs to-
136	be: 1) independent of all confounders that affect the exposure and the outcome; 2) associated
137	with the exposure; 3) affecting the outcome only through the exposure. ²⁰ -
138	In England, 10% of the population is exposed to artificially/naturally fluoridated
139	water, but the fraction of the population covered by fluoridated water and the year of
140	initiation varies geographically. ²¹ Thus, the likelihood of exposure to tap water fluoride is
141	influenced by year of birth and region lived in childhood. Exploiting quasi-experimental
142	variation in tooth loss due to this regional variation, we aimed to investigate the causal effect
143	of the number of teeth on functional capacity of the late adulthood population in England.
144	
145	<u>METHODS</u>

146 Assumptions in the present study

147	We employed the instrumental variable (IV) approach, whereby exploiting the variation in
148	tap water fluoride as an instrument for the number of remaining teeth, thereby estimated the
149	association between the number of teeth and functional capacity without confounding by
150	individual characteristics. Figure 1 summarizes the criteria for a valid IV. In short, IV needs
151	to be 1) associated with the exposure; 2) affecting the outcome only through the exposure; 3)
152	independent of all unobserved variables that affect the outcome. ²² In the present study's
153	setting, the causal effect of the number of teeth can be identified under assumptions of 1)
154	childhood tap water fluoride prevents tooth loss in adulthood, 2) childhood exposure to tap
155	water fluoride affects functional capacity in adulthood only via preventing tooth loss, and 3)
156	factors influenced the decision on community water fluoridation in their childhood do not
157	affect the residents' functional capacity in late adulthood. Assumption 1 is supported by the
158	previous literature reporting the effect of water fluoridation on preventing dental caries. ^{23,24}
159	For example, The effect of water fluoridation (WF) on preventing dental caries has been
160	established ²²⁻²⁴ -and estimated at a 27% reduction in caries experience among 5-years-old and
161	62% reduction in the incidence of tooth extractions in the hospital among 0–19 year-olds are
162	reported in England. ²⁵ Some studies reported that the Its preventive effect could also result in
163	retaining more teeth in later adulthood. ^{26,27} As for assumption 2, previous Previous reviews
164	have declined the existence of adverse effects of water fluoridation on other health outcomes
165	that are related to functional limitation, including bone fracture, cancer, and cognitive

166	ability. ^{23,28–31} Assumption 3 might be challenging because the population supplied with
167	fluoridated tap water in England has increased with time. Also, local characteristics are
168	potential confounders because local public bodies make decisions on community water
169	fluoridation. ³² We addressed the cohort effect confounding by restricting study participants to
170	those born in a specific range of years (between 1945-1965) so that to exclude participants
171	that lived their childhood prior to water fluoridation was introduced in the UK, and also
172	statistically controlled for it in the model. The region effect confounding was addressed by
173	adjusting for regional fixed effects and sensitivity analysis ^{22,28–31} Accordingly, the exogenous-
174	variation in the coverage of fluoridated water would be useful as an IV to investigate the
175	effect of tooth loss on instrumental activities of daily living (IADL) limitation with an-
176	assumption that tooth loss is the only way that fluoridated water can affect functional
177	capacity. The present study aimed to investigate the causal effect of the number of teeth on-
178	functional capacity among adults aged ≥50 years old in England, whereby employing the
179	exogenous variation in fluoridated water as an IV.
180	

181 METHODS

182 Study participants

We conducted a secondary analysis using the data of the English Longitudinal Study of
Ageing (ELSA).) wave 7, which was conducted between 2014–2015. ELSA is a sizeable

185	longitudinal panel study targeting a representative sample of the population aged 50 years or
186	older in England. Further details about ELSA are available elsewhere. ³³ We used ELSA wave
187	7, which was conducted between 2014–2015 and is the only wave that measured the number
188	of remaining teeth. To reduce bias due to the cohort effect and effectively utilize the variation
189	in tap water fluoride in childhood, the data of 5,631 individuals born in 1945–1965 without
190	missing information on variables were analyzed. ³² ELSA received ethical approval for all
191	waves from NHS Research Ethics Committees under the National Research and Ethics-
192	Service (NRES). The present study was approved by the ethical committee at Tokyo Medical
193	and Dental University.
194	
195	Dependent variable: instrumental activities of daily living
196	IADL, which reduces at an early stage of declining functional capacity, was used to evaluate
197	whether oral health could be one strategy to prevent loss of functional competence. They
198	reflect instrumental self-maintenance by assessing the presence of limitations in the following
199	six activities: preparing a hot meal, shopping for groceries, making telephone calls, taking
200	medications, doing work around the house or garden, and managing money such as paying
201	bills and keeping track of expenses. An aggregate binary variable indicating limitations in
202	any of these six activities was used as the dependent variable to evaluate the impact of tooth
203	loss on daily function, as the daily life of older people is negatively affected when any of the

204	IADL components are compromised. This dichotomized outcome has been used in a previous
205	study. ³
206	IADL was used to assess functional capacity. They reflect instrumental self-maintenance by-
207	assessing the presence of limitations in the following six activities: preparing a hot meal,
208	shopping for groceries, making telephone calls, taking medications, doing work around the
209	house or garden, and managing money such as paying bills and keeping track of expenses.
210	IADL relates to autonomy in everyday life and requires interplay of higher physical and
211	cognitive function ³³ , therefore could be influenced by tooth loss. An aggregate binary-
212	variable indicating limitations in any of these six activities was used as the dependent-
213	variable.
214	
215	Exposure variable: the number of teeth
216	The number of remaining teeth was assessed through the following question: "Adults usually
217	have up to 32 natural teeth, but over time people lose some of them. How many natural teeth
218	have you got?." Respondents were asked to choose the answer from the following options:
219	"None at all," "Between 1 and 9 natural teeth," "Between 10 and 19 natural teeth," and "20
220	or more natural teeth." The variable was used as continuous in analyses with the middle
221	number allocated to each category (i.e., 0, 4.5, 14.5, and 26, respectively). Thereby, the

222 <u>estimated effect size was scaled at the level of retaining one more tooth.</u>

223

224 Instrumental variable

225 We used the total annual likelihood of being exposed to naturally/artificially fluoridated 226 water between 5 and 20 years of age as the IV for the number of teeth. A similar This approach has been previously used in a previous study, 34 , and the age range was selected to 227 228 covercorrespond to the period of eruption and post-eruptive maturation of the enamel of permanent teeth, including third molar, that is when they are more prone to the preventive 229 effect of fluoride.35 230 231 Figure 21 illustrates the trajectories of population coverage with naturally/artificially fluoridated water in each region. We obtained county-level information on the number of 232 233 population covered by naturally/artificially fluoridated water and the year of the initiation of 234 artificial water fluoridation from a previous report.²¹in 2012 and the year of the initiation ofartificial WF from a previous report.²¹ As residential information of ELSA participants was 235 236 only available for the region of residence at the time of regional level in the survey dataset, we 237 used this variable as a proxy of the region they resided in childhood and aggregated the information on <u>water fluoridation</u>WF to a regional level. The proportion of people covered by 238 239 water fluoridation WF in each region every year was calculated based on the population size in 2012.³⁶ The concentration of fluoride was targeted at 1.0 ppm for artificial water 240 241 fluoridation WF, while that of natural water fluoridation WF varied between 0.5–1.5 ppm.

242	Further detail of the calculation is described in Supplementary Method S1.
243	
244	Covariates
245	To consider differences by year of birth and region of residence, fixed effects of year of birth,
246	sex (men, women), and regional fixed effects were adjusted for. As several examples shown
247	in Supplementary Table S2, there might be differences in general health issues,
248	socioeconomic status, and other unmeasured factors by year of birth and region of residence.
249	Given that the analysis exploited the variation in the number of remaining teeth in adulthood
250	derived by differential exposure to tap water fluoride in childhood, we considered individual
251	general health variables as mediators rather than confounders; and we did not include them in
252	the covariates. The balancing tests showed that the difference in childhood socioeconomic
253	status by the instrument is small (standardized differences were close to or smaller than 0.1,
254	Supplementary Table S3); and we controlled them in the sensitivity analysis.
255	Year of birth (categorized in groups of five years), sex (men, women), and regional fixed-
256	effects were adjusted for. Since the instrument was constructed as a function of year of birth-
257	in each region of residence, this leaves as identifying variation the interaction of cohort and
258	region.
259	

260 Statistical analyses

261 Linear probability model (LPM) was fitted by Two-Stage-Least-Squares (2SLS) estimation. Formally, let subscripts ig denote individual i living in a region g. Teethig, Fluorideig, 262 263 <u>Yobig</u> Ageig, and Sexig are participants's number of teeth, exposure to fluoridated water when 264 aged 5-20 years, year of birthage, and sex, respectively. RegionFixed, indicates dummy variables for each region. vig is an error term. Accordingly, our first-stage regression can be 265 266 written as: Teeth_{ia} $= \alpha_0 + \alpha_1 Fluoride_{ig} + \alpha_2 \underline{Yob_{ig}} Age_{ig} + \alpha_3 Sex_{ig} + \alpha_4 \underline{Region_g} + \underline{v_{ig}} RegionFixed_{g} + v_{ig}$ 267 Let $Teeth_{ig}$ be the participant *i*'s number of teeth predicted by the first-stage regression, and 268 $IADL_{ig}$ be a binary variable equals to 1 if the participant *i* had any limitation in IADL. <u>*e*_{ig} is</u> 269 270 an error term. The second-stage regression is then: $= \beta_0 + \beta_1 \widehat{Teeth}_{ig} + \beta_2 \underbrace{Yob}_{ig} Age_{ig} + \beta_3 Sex_{ig} + \beta_4 \underbrace{Region_g + e_{ig}}_{d_g^-} + e_{ig}$ *IADL_{ig}* 271 The coefficient β_1 indicates the percentage points change in the probability of limitation in 272 IADL percaused by retaining one more tooth.³⁷³⁷ Analysis using each IADL item asTo-273 consider the dependent variable was also performed number of teeth assigned to investigate 274 which specific components were affected. 275 276 277 Sensitivity analysis 278 Four sets of each category, a sensitivity analyses were analysis was performed: 1) by assigning

279	mean or median of the clinically examined number of teeth respective to age, sex, and self-
280	reported number of teeth in Adult Dental Health Survey 2009. ³⁸ to evaluate whether As the
281	results are robust to data included only one wave of the allocationsurvey, there could be an-
282	identification issue if we include the fixed effect of the midpointevery single year of
283	categorical responses; 2) controlling the cohort effects for linear function and restricted
284	cubicbirth. To address this, further sensitivity analysis was performed by adding spline
285	function, respectively; 3) adjusting for participants' educational qualification and their
286	parents' yearsterms for the year of education; 4) stratification analysis by age group (50-64
287	and 65–70 years old). birth. STATA MP version 1615.1 (Stata Corp., College Station, TX,
288	USA) was utilized for all analyses.
289	
290	RESULTS
291	Among the 9666 respondents of ELSA wave 7, 39 living outside of England, 174 aged less-
292	than 50 years, and 16 with missing information on the variables were excluded. Accordingly,
293	data on 9437 respondents were analyzed (average age = 67.7 years, 44.7% men).
294	——————————————————————————————————————
295	region. The fraction of the population covered by fluoridated water in 2012 ranged from 0
296	(South East and South West) to 0.675 (West Midlands). The average year of initiation of
297	artificial WF ranged from 1968 (North East and Yorkshire and The Humber) to 1980 (West

298 Midlands).

299	Table 2 describes the main characteristics of the respondents by the number of
300	remaining natural teeth. The overall prevalence of the IADL limitation was $11.918.0\%$ and
301	was higher among people with fewer teeth. Exposure The extent of exposure to fluoridated
302	water when aged 5-20 years was greater among people with more natural teeth in later
303	adulthood.
304	Table 3 shows the estimated causal effects of tooth loss on IADL. The first-stage
305	regression showed that exposure to the extent of fluoridated water was significantly associated
306	with having more natural teeth (Coefficient = $0.7261.076$; 95% confidence interval, CI:
307	0. <u>311700</u> , 1. <u>1</u> 452). More specifically, one <u>-unit increment in the instrument, which is</u>
308	equivalent to one additional year of exposure to fluoridated water during the age of 5 to 20
309	years, was associated with having $0.726 + 1.08$ more teeth on average at an older age. The first-
310	stage F-statistic was <u>11.749</u> 31.487, indicating that the IV was sufficiently strong to predict
311	the number of teeth. ³⁹ The second-stage regression showed that retaining one more tooth
312	reduced the probability of limitation in IADL by 3.1.9 (95% CI: 0.2, 6.04, 3.5) percentage
313	points. Similar estimates were obtained when changing the number of teeth assigned to each
314	category (Appendix Table A.1). Adjusting for the year of birth with spline terms resulted in-
315	similar findings (Appendix Table A.2).
316	The second-stage estimates for each component of IADL are shown in

317	Supplementary Figure S4. With the exception of "taking medications" and "managing
318	money", the point estimates were negative, that is, having more natural teeth was associated
319	with lower probability of each IADL limitation, though only the association with "shopping
320	for groceries" was significant.
321	Similar estimates were obtained when changing the number of teeth assigned to each
322	category (Supplementary Table S5). The results did not change when adjusting for the year of
323	birth with different functions or adjusting for individual educational level (Supplementary
324	Table S6). Further stratification analysis by age showed similar point estimates in aged 50-64
325	year-olds, while the first-stage regression was not significant in those aged 65-70 years old.
326	
327	DISCUSSION
328	The present natural experimental study showed that investigated the extent to which the
329	number of remaining teeth predicted by the differential exposure to tap water fluoride in
330	childhood was associated with a lower probability of having limitations in IADL. Under the
331	assumptions supported by previous literature, our affected functional capacity, using-
332	exogenous variation in exposure to water fluoridation as a natural experiment that predicted a
333	higher tooth count among people with compared to those without exposure to fluoridated
334	water. Our findings suggest that having one more tooth (due to exposure to fluoridated water-
335	earlier in life) reduced the probability of having a limitation in IADL by $3.1.9$ percentage
1	

points among adults aged $\geq 50-70$ years old in England.

337	Under the monotonicity assumption, IV analyses estimate the local average
338	treatment (LATE) effect among compliers. ³⁷ In the present study, the monotonicity
339	assumption, that is, no one loses their teeth because of being exposed to fluoridated water in
340	childhood, is supported by previous biological and epidemiological studies. ⁴⁰ As our
341	instrument is a continuous scale, the inferential target population consists of all individuals
342	used in the analysis contributing with unknown weights. ³⁷ Given that the preventive effect of
343	water fluoridation is more prominent in high-risk populations (i.e., living in deprivation), ⁴¹
344	our results might primarily reflect the effect of teeth on IADL among people from lower
345	socioeconomic backgrounds. The 2SLS estimate (3.1 percentage points difference) was larger
346	than the OLS estimation (0.7 percentage points difference), which may suggest that the
346 347	than the OLS estimation (0.7 percentage points difference), which may suggest that the impact of tooth loss is more significant among people from lower socioeconomic
347	impact of tooth loss is more significant among people from lower socioeconomic
347 348	impact of tooth loss is more significant among people from lower socioeconomic backgrounds. It is possible that the lack of resources and limited access to care among the
347 348 349	 impact of tooth loss is more significant among people from lower socioeconomic backgrounds. It is possible that the lack of resources and limited access to care among the deprived population⁴² might accelerate the impact of tooth loss on IADL. Our estimates
347 348 349 350	 impact of tooth loss is more significant among people from lower socioeconomic. backgrounds. It is possible that the lack of resources and limited access to care among the deprived population⁴² might accelerate the impact of tooth loss on IADL. Our estimates might overestimate the effect of tooth loss on IADL limitation, as the IV estimator can be
347 348 349 350 351	 impact of tooth loss is more significant among people from lower socioeconomic. backgrounds. It is possible that the lack of resources and limited access to care among the deprived population⁴² might accelerate the impact of tooth loss on IADL. Our estimates might overestimate the effect of tooth loss on IADL limitation, as the IV estimator can be more biased than the OLS estimator when the IV is only weakly correlated with the exposure

355	the average treatment effect in the older adult population in England.
356	IADL reflects coordination of higher physical and cognitive functions. ⁴⁵ Thus, the
357	pathway of the association between tooth loss and general physical and cognitive function is
358	also relevant. Low dietary intake due to tooth loss ^{10,46} could result in decline in functional
359	capacity. Lower social interaction, which is a risk factor for the onset of disability, ¹² would
360	also explain the link between tooth loss and IADL, because tooth loss is associated with low
361	social function. ⁴⁷ Further, as a marker of lifetime experience of oral diseases and treatment,
362	tooth loss is related to past dental caries and periodontal diseases, and the latter in particular
363	could partly reflect past oral inflammation. ¹¹ The difference in tooth loss induced by water
364	fluoridation, which we exploited in the analysis, would mainly reflect the differential dental
365	caries experience rather than periodontal diseases. Thus, the pathway through periodontal
366	inflammation might be less likely to explain our findings. The component-specific analysis
367	resulted in "shopping for groceries" and "doing work around the house or garden" having the
368	two largest point estimates, although only the former was significant. These reflect the two
369	most demanding physical tasks from the IADL items included in the study. ⁴⁸ This might
370	suggest that tooth loss affects functional capacity at an early stage of the decline. While the
371	present study provides evidence for a causal relationship between tooth loss and functional
372	capacity, the plausibility and extent of the different pathways would need further
373	investigations in the framework of strong causal inference.

374	Previous studies have shown associations, that is, people with fewer teeth being
375	more likely to have disabilities or limitations in functional capacity, ⁶⁻⁹ thereby providing
376	evidence that tooth loss may be useful as an early marker of decline in functional capacity.
377	The present study added the causal evidence to the literature, that is, retaining natural teeth
378	prevents a limitation in IADL. Other observational studies have reported that having
379	recommended levels of physical exercise, ⁴⁹ social participation, ⁵⁰ and living in a walk-up
380	residence, i.e., having to walk upstairs ⁵¹ was associated with 0.53–0.74 times lower odds of
381	having a limitation in IADL. Considering the prevalence of IADL limitation in the present
382	study participants, the estimated causal effect of retaining one more tooth (3.1 percentage
383	points difference) is equivalent to 0.72 in terms of odds ratio scale. The estimated effect size
384	might be larger than the population average because of the reasons described above. Given
385	the high prevalence of tooth loss, this could be a relevant target for interventions to promote
386	functional capacity and avoid or delay limitations in IADLs. The health gain from retaining
387	natural teeth might not be limited to oral health outcomes. We assumed a linear relationship
388	between the number of remaining teeth and IADL, but the marginal effect of losing a tooth
389	might be different for people that have lost many teeth. Further research, such as studies
390	using clinically examined tooth count to consider a potential non-linear effect of tooth loss as
391	well as cost-effectiveness evaluation of interventions incorporating oral and general health
392	outcomes, are needed.

393	While we addressed and evaluated potential violations of the assumptions, the results
394	need to be interpreted with caution. Assumption 1, the relevance of the instrument, is
395	supported by previous literature ^{23–27} and the results from the first-stage regression.
396	Assumption 2, the exclusion restriction, is at least partly supported by previous
397	literature, ^{23,24,26–31} although it is not possible to prove perfectly. Assumption 3, the exogenous
398	condition, could be violated if the cohort and region effects were not fully controlled in the
399	model. We carefully addressed this issue by restricting participants to the cohorts born during
400	1945–1965 and also controlling the cohort effect with various functions. The results were
401	mostly similar; however, estimates were not significant in further stratification analysis by
402	age group, possibly because of reduced sample size and smaller variation in the instrument
403	among those aged 65–70. As for the region effect confounding, we have adjusted for regional
404	characteristics by including a fixed effect in the models, but it is still possible that the timing
405	of the initiation of water fluoridation is associated with local authorities' characteristics. The
406	political situation in the local community might have influenced the decision; ³² however, it is
407	difficult to be controlled for in the model. We evaluated the regional difference within the
408	data availability; we compared area deprivation between counties with and without water
409	fluoridation and found that the median rank of Index of Multiple Deprivation ⁵² was not
410	significantly different between them ($P = 0.720$). The results did not change when adjusting
411	for participants' educational qualifications and parents' years of education. Nevertheless,

412	unknown but plausible confounders might exist and influence the results.
413	Another assumption is that the participants had lived in the same region in their
414	childhood as in the time of the survey. The assumption may well have been violated as the
415	participants are 50 years old or older because, in England, about 1 to 3% of the population
416	migrated to other regions in 2014.53 We were not able to evaluate this potential
417	misclassification due to lack of data. We believe the misclassification to be non-differential
418	because people would be less likely to decide their region of residence based on whether
419	there is water fluoridation. Therefore, it would have decreased both the reduced-form and the
420	first-stage estimators; and the direction of the bias on the IV estimator (ratio of the reduced-
421	form estimator to the first-stage estimator) might be over or underestimated.
422	Other methodological limitations include that we did not have any information on
423	other sources of fluoride (e.g., toothpaste). Thus, our estimation might be biased if the
424	utilization of fluoride resources differs by regions; however, the frequency of tooth brushing
425	was not different by region in Adult Dental Health Survey 2009. ³⁸ Moreover, data on the
426	number of teeth and IADL was self-reported; however, high accuracy of self-reports for
427	number of teeth has been reported previously. ⁵⁴
428	Few previous studies have applied natural experimental design to investigate the causal
429	relationship between oral and general health outcomes. The present natural experimental
430	study exploited the historical and geographical variation in community water fluoridation and

431	found that retaining one more natural tooth due to exposure to fluoridated water in childhood
432	was associated with a lower probability of limitations in IADL. The present study is the
433	first to report the causal effect of tooth loss on having a limitation in IADL. We obtained the
434	causal effect using representative data of people aged ≥50 years in England. Few oral health
435	studies have applied IV estimation. Through employing schooling reforms as IV for-
436	education, previous research established the causal effect of education on receiving-
437	periodontal treatment in Norway ⁴⁰ and reducing edentulousness in the UK. ⁴¹ Lowered
438	socioeconomic circumstances after a huge earthquake and tsunami were shown to cause-
439	increased tooth loss in Japan, ⁴² while Glied and Neidell (2010) used geographical variation in
440	WF in the US to estimate the effect of teeth on earnings. ³⁴ -
441	IADL reflects coordination of higher physical and cognitive function. ³³ The pathway
442	of the association between tooth loss and general physical and cognitive function is also
443	relevant. Tooth loss predicts poor dietary intake9,43; therefore, poor nutrition could partly-
444	explain our results. Social interaction, which is a risk factor for the onset of disability, ¹¹ could
445	also partly explain the link between tooth loss and IADL, because tooth loss is associated
446	with poor social function.44 Further, as a marker of lifetime experience of oral diseases and
447	treatment, tooth loss is related to past dental caries and periodontal diseases, and the latter in
448	particular could partly reflect past oral inflammation. ⁴⁰ However, as our IV estimates distilled
449	
	the effect of tooth loss following dental caries (i.e., the difference in tooth loss induced by

450	water fluoridation), the pathway through periodontal diseases might be less likely to explain-
451	our findings. We have further ran the analysis with each IADL item as the dependent variable
452	(Appendix Figure A.3). "Shopping for groceries" and "doing work around the house or
453	garden" had the two largest point estimates, although only the former was significant. These-
454	reflect the two most demanding physical tasks from the IADL items included in the study.45-
455	This might suggest that tooth loss affects functional capacity at an early stage of the decline.
456	While the present study provides evidence for a causal relationship between tooth loss and
457	functional capacity, the plausibility and extent of the different pathways would need further
458	investigations in the framework of strong causal inference.
459	————Our study has important public health implications. One billion of the world-
460	population are living with disabilities. ³ In the UK alone, 2.5 million older people had-
461	disabilities in 2015, and it is projected to rise by 25% in the next 20 years, ⁴⁶ further-
462	challenging public healthcare systems and expenditure.4 Previous studies showed
463	associations, that is people with fewer teeth being more likely to have disabilities or-
464	limitations in functional capacity, ⁵⁻⁸ thereby providing evidence that tooth loss may be useful-
465	as an early marker of decline in functional capacity. This study has gone a step further and
466	demonstrated causation in that association, which means that retaining natural teeth actually-
467	prevents a decline in functional capacity. To put our estimates into context, we looked at the-
468	effect on IADL limitation of a well-established risk factor such as the lack of physical

469	exercise. ⁴⁷ -Taking into account the high prevalence of tooth loss -61% of older adults aged-
470	65 years or more were without functional dentition in the UK in 2009 ⁴⁸ — and extrapolating-
471	our results (that are provided per natural tooth) into the aforementioned groups that have-
472	respectively 32 and at least 12 teeth missing, it is evident that promoting good oral health and
473	the retention of natural teeth should be considered a priority area of population health.
474	——————————————————————————————————————
475	local average treatment effect, which is the average effect among people whose exposure was
476	changed by the IV (i.e., those whose tooth loss was prevented by WF). ³⁷ The effect of
477	fluoride on preventing dental caries may be larger among the high-risk population (i.e., living-
478	in deprivation). ⁴⁹ Thus, our results might primarily reflect the effect of teeth on IADL among
479	people from lower socioeconomic backgrounds, that is, the groups that have worse health and
480	function. The OLS estimation showed that one additional remaining tooth was significantly-
481	associated with a lower probability of having a limitation in IADL by 0.6 percentage points-
482	(95% CI: 0.6, 0.7 percentage points) (Table 3), which was smaller than the 2SLS estimation.
483	It should be noted that our estimates might overestimate the effect of tooth loss on IADL-
484	limitation, as the IV estimate can be more biased than OLS when the IV is only weakly-
485	correlated with the exposure variable. ⁵⁰ Second, we have assumed that the study participants-
486	did not move from their region of birth. This assumption may well have been violated as the
487	participants are 50 years old or older. Also, although we have adjusted for regional-
I.	

488	characteristics by including a fixed effect in the models, it is possible that the timing of the
489	initiation of WF is associated with local authorities' characteristics. However, we could not
490	find any evidence/report against our assumption, i.e., that showed local authorities'
491	characteristics to be associated with the timing of WF. Third, as the data included only one-
492	wave of the survey, we were not able to adjust for the fixed effect of year of birth by every-
493	single year. Instead, we have adjusted for the fixed effect of the year of birth categorized in-
494	groups of five years. However, in sensitivity analyses we further confirmed that the results-
495	remained similar when adjusting for spline of the year of birth. Fourth, we did not include
496	any information on other sources of fluoride (e.g., toothpaste). Thus, our estimation might be-
497	biased if the utilization of fluoride resources differs by regions; however, the frequency of
498	tooth brushing was not different by region in Adult Dental Health Survey 2009.38-
499	Additionally, data on the number of teeth and IADL was self-reported.
500	Using a natural experiment methodology with the consumption of fluoridated water-
501	as an instrumental variable, we found a causal effect of natural teeth on functional capacity-
502	among adults aged \geq 50 years old in England. Retaining one more natural tooth reduced the
503	probability of limitation in instrumental activities of daily living by 1.9 percentage points.
504	Preventive oral health strategies can potentially improve independent living in later life.
505	

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27

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to Review Only

	Total population in 2012 ^a	PopulationNumber of population covered by <u>fluoridatednatural/ar</u> tificial water fluoridation-in 2012 b	Fraction of population covered by <u>fluoridatednatural/artif</u> icial water fluoridation in 2012 ^b	YearAverage year of initiating artificial water fluoridation ^b in- different parts of- the region ^b
Governmental region				
North East	2 <u>-</u> 602 <u>-</u> 300	965 <u>-</u> 000	0.371	1968
North West	7 <u>-</u> -084 <u>-</u> 300	257000	0.036	1969
Yorkshire and The Humber	5 316 _ 700	136000	0.026	1968
East Midlands	4 <u>,</u> -567 <u>,</u> 700	580000	0.127	1972
West Midlands	5 <u>-</u> 642 <u>-</u> 600	3810000	0.675	1980
East of England	5 <u>-</u> 907 <u>-</u> 300	198000	0.034	1977
London	8 ₂ -308 ₂ 400	180 <u>-</u> 000 ^a	0.022	-
South East	8 ₂ -724 <u>3</u> 700	0	0.000	-
South West	5 <u></u> -339 <u></u> 600	0	0.000	-

TT 1 1 1	C1 · · ·	C (1/	···· 1	a • 1 /•	1 .
Table I	Characteristics	of natural/ar	titicial water	· fluoridation	by region
1 4010 1.	Characteristics	or matural/ar	unional water	indonidution	by region

a Source: Office for National Statistics. Population estimates (2012)

b Source: The British Fluoridation Society. The extent of water fluoridation, 3rd ed. One in a Million: the facts about water fluoridation (2012). https://www.bfsweb.org/one-in-a-million

c Average year is shown because the year of initiation differed among the parts of the region

$\underline{n = 234}$ $\underline{n (\%)}$ $\underline{175 (74.8\%)}$ $\underline{59 (25.2\%)}$ $\underline{120 (51.3\%)}$	<u>n = 290</u> <u>n (%)</u> <u>217 (74.8%)</u> <u>73 (25.2%)</u>	<u>n = 719</u> <u>n (%)</u> <u>584 (81.2%)</u>	$\frac{n = 4,388}{n (\%)}$ 3,987 (90.9%)	of teeth ^a <u>Mean</u>
<u>175 (74.8%)</u> <u>59 (25.2%)</u> <u>120 (51.3%)</u>	<u>217 (74.8%)</u>	<u>584 (81.2%)</u>		Mean
<u>59 (25.2%)</u> <u>120 (51.3%)</u>			2 087 (00 00/)	
<u>59 (25.2%)</u> <u>120 (51.3%)</u>			2.087(00.00/)	
120 (51.3%)	<u>73 (25.2%)</u>		<u>,70/ (70.770)</u>	22.8 (7.0)
		<u>135 (18.8%)</u>	<u>401 (9.1%)</u>	<u>19.1 (9.3)</u>
	<u>128 (44.1%)</u>	<u>286 (39.8%)</u>	<u>1,271 (29.0%)</u>	<u>21.0 (8.5)</u>
<u>76 (32.5%)</u>	<u>88 (30.3%)</u>	<u>243 (33.8%)</u>	<u>1,398 (31.9%)</u>	22.3 (7.4)
<u>30 (12.8%)</u>	<u>61 (21.0%)</u>	<u>128 (17.8%)</u>	<u>1,007 (22.9%)</u>	<u>23.1 (6.6)</u>
<u>8 (3.4%)</u>	<u>13 (4.5%)</u>	<u>62 (8.6%)</u>	<u>712 (16.2%)</u>	<u>24.5 (4.7)</u>
<u>92 (39.3%)</u>	<u>161 (55.5%)</u>	<u>337 (46.9%)</u>	<u>1,921 (43.8%)</u>	<u>22.2 (7.5)</u>
142 (60.7%)	<u>129 (44.5%)</u>	<u>382 (53.1%)</u>	<u>2,467 (56.2%)</u>	22.5 (7.3)
<u>26 (11.1%)</u>	18 (6.2%)	<u>57 (7.9%)</u>	237 (5.4%)	20.9 (8.5)
38 (16.2%)	<u>52 (17.9%)</u>	<u>93 (12.9%)</u>	<u>521 (11.9%)</u>	21.5 (8.2)
<u>37 (15.8%)</u>	<u>40 (13.8%)</u>	<u>74 (10.3%)</u>	<u>423 (9.6%)</u>	<u>21.4 (8.4)</u>
43 (18.4%)	23 (7.9%)	75 (10.4%)	460 (10.5%)	21.9 (8.1)
20 (8.5%)	38 (13.1%)	83 (11.5%)	490 (11.2%)	22.4 (7.2)
<u>18 (7.7%)</u>	<u>36 (12.4%)</u>	100 (13.9%)	<u>552 (12.6%)</u>	22.6 (6.9)
13 (5.6%)	26 (9.0%)	59 (8.2%)	417 (9.5%)	23.0 (6.7)
27 (11.5%)	35 (12.1%)	112 (15.6%)	760 (17.3%)	23.1 (6.6)
12 (5.1%)	22 (7.6%)	66 (9.2%)	528 (12.0%)	23.6 (6.0)
0.328 (0.748 <u>)</u>	<u>0.260 (0.652)</u>	0.381 (0.862)	<u>0.401 (0.925)</u>	Ξ
	<u>43 (18.4%)</u> <u>20 (8.5%)</u> <u>18 (7.7%)</u> <u>13 (5.6%)</u> <u>27 (11.5%)</u> <u>12 (5.1%)</u>	$\begin{array}{c} \underline{43\ (18.4\%)}\\ \underline{20\ (8.5\%)}\\ \underline{18\ (7.7\%)}\\ \underline{13\ (5.6\%)}\\ \underline{27\ (11.5\%)}\\ \underline{12\ (5.1\%)}\\ \underline{22\ (7.6\%)}\\ 22\ (7.6\%)$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

	$\frac{\text{No teeth}}{(n = 955)}$		$\frac{1-9 \text{ teeth}}{(n=779)}$		$\frac{10-19 \text{ teeth}}{(n = 1,566)}$		$\frac{20 + \text{ teeth}}{(n = 6, 137)}$		Number of teeth*	
	n	<mark>⁰∕₀</mark>	Ħ	<mark>⁰∕₀</mark>	n	<mark>⁰∕₀</mark>	Ħ	<mark>⁰∕₀</mark>	Mean	SD
Having IADL limitation										
- No	589	61.7%	532	68.3%	1-206	77.0%	5-416	88.3%	20.8	(8.7)

-Yes	366	38.3%	247	31.7%	360	23.0%	721	11.7%	14.9	(10.7)
Year of birth										
	38 4	4 0.2%	219	28.1%	308	19.7%	401	6.5%	12.2	(10.6)
-1935-1939	196	20.5%	138	17.7%	271	17.3%	554	9.0%	16.4	(10.3)
- <u>1940-1944</u>	141	14.8%	132	16.9%	268	17.1%	79 4	12.9%	18.9	(9.5)
- <u>1945-1949</u>	120	12.6%	128	16.4%	286	18.3%	1-271	20.7%	21.0	(8.5)
- 1950-195 4	76	8.0%	88	11.3%	243	15.5%	1-398	22.8%	22.3	(7.4)
- <u>1955-1965</u>	38	4 .0%	74	9.5%	190	12.1%	1 719	28.0%	23.7	(6.0)
Sex										
- <u>Men</u>	363	38.0%	407	52.2%	725	4 6.3%	2-727	44.4%	19.8	(9.2)
-Women	592	62.0%	372	4 7.8%	8 41	53.7%	3-410	55.6%	19.7	(9.5)
Governmental region										
-North East	100	10.5%	58	7.4%	116	7.4%	306	5.0%	17.1	(10.4)
-North West	138	14.5%	103	13.2%	186	11.9%	690	11.2%	18.9	(9.8)
-Yorkshire and The Humber	136	14.2%	85	10.9%	152	9.7%	579	9.4%	18.6	(10.1)
-East Midlands	125	13.1%	72	9.2%	178	11.4%	62 4	10.2%	19.2	(9.7)
-West Midlands	117	12.3%	92	11.8%	167	10.7%	680	11.1%	19.5	(9.6)
-East of England	87	9.1%	104	13.4%	210	13.4%	805	13.1%	20.3	(8.8)
-London	57	6.0%	60	7.7%	126	8.0%	585	9.5%	20.9	(8.5)
-South East	107	11.2%	119	15.3%	245	15.6%	1-107	18.0%	20.9	(8.6)
-South West	88	9.2%	86	11.0%	186	11.9%	761	12.4%	20.4	(8.8)
Extent of being exposed to	0.165	(0.443)	0.157	(0.447)	0.223	(0.624)	0.307	(0.803)		
fluoridated water be	0.100	(0.115)	5.157	(0.117)	5.225	(0.021)	0.007	(0.005)		

Abbreviations: IADL, instrumental activity of daily living, SD, standard deviation

a No teeth was coded 0, 1-9 teeth was coded 5, 10-19 teeth was coded 14.5, and 20+ teeth was coded 26

b Total of the annual proportion of people covered by fluoridated water in the region of residence between 5

and 20 years of age-

c Values are expressed as mean (SD)

<u>31)</u> 9437)- -	Coef.	95% CI	F-statistic
PLS estimation			
Number of remaining teeth ^a	-0.006	-0.007, -0.006	
SLS estimation			
Second-stage regression			
Number of remaining teeth ^a	-0.019	- 0.035, -0.00 4	
First-stage regression			
Extent of being exposed to fluoridated water ^b	1.076	0.700, 1.452	31.487
educed form estimation		,	
Extent of being exposed to fluoridated water ^b	-0.021	-0.037, -0.005	
	<u>Coef. (95</u>		statistic
LS estimation	<u></u>	<u></u>	
Number of remaining teeth	<u>-0.007 (-0.0</u>	<u>08, -0.006)</u>	
SLS estimation			
Second-stage regression			
Number of remaining teeth	<u> </u>	<u>60, -0.002)</u>	<u>-</u>
First-stage regression			
Extent of being exposed to fluoridated water	0.726 (0.1	<u>311, 1.142)</u>	11.749
educed-form estimation			
Extent of being exposed to fluoridated water	-0.023 (-0.04	41, -0.004)	E.
iations: CI, confidence interval; 2SLS, two-stag	e least square,	OLS, ordinary le	ast squares
d for the fixed effects of year of birth, sex, and	governmental r	region of residence	e
	-	-	
o teeth was coded 0, 1–9 teeth was coded 5, 10-	–19 teeth was c	coded 14.5, and \geq	20 teeth was

Table 3. Causal effect of the number of teeth on the instrumental activity of daily living, IADL (N =

5 and 20 years of age

Total of the annual proportion of people covered by fluoridated water in the region of residence between 5 and 20 years of age-

FIGURE LEGEND

Figure 1. Criteria for a valid instrumental variable (left side) and corresponding assumptions in the present study (right side).

Figure 2. Figure 1. Trajectory of population covered by naturally/artificially fluoridated water

SUPPLEMENTAL INFORMATION LEGENDS

Supplementary Method S1. The detail of the instrumental variable in the present study

Supplementary Appendix Table S2. Difference in general health issue and educational status by year of

birth and region

Supplementary Table S3. Balancing test for participants' socioeconomic status in childhood

Supplementary Figure S4A.1. Causal effect of the number of teeth on the instrumental activity of daily-

living-

Appendix Table A.2. Causal effect of the number of teeth on the instrumental activity of daily living-

Appendix Figure A.3. Causal effect of number of teeth on each item of instrumental activity of daily living,

<u>IADL (N = 5,631)</u>—

Supplementary Table S6. Sensitivity analysis by different adjustment for cohort and regional confounders