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

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**Title**

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

**Short running title**

Tooth loss and functional capacity

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**Impact statement**

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 England, whereby exploiting the exogenous geographical and historical variation in childhood exposure to tap water fluoride. Retaining one more tooth reduced the probability of having a limitation in the instrumental activity of daily living by 3.1 percentage points. Our findings support the causal evidence between tooth loss and functional capacity.

## Abstract

**BACKGROUND/OBJECTIVES:** Tooth loss is associated with reduced functional capacity, but so far, there is no relevant causal evidence reported. We investigated the causal effect of tooth loss on the instrumental activities of daily living (IADL) among older adults in England.

**DESIGN:** Natural experiment study with instrumental variable analysis.

**SETTING:** The English Longitudinal Study of Aging (ELSA) combined with the participants' childhood exposure to water fluoride due to the community water fluoridation.

**PARTICIPANTS:** 5,631 adults in England born in 1945–1965 participated in the ELSA wave 7 survey (conducted in 2014–2015; average age: 61.0 years, 44.6% men).

**EXPOSURE:** The number of natural teeth predicted by the exogenous geographical and historical variation in exposure to water fluoride from age 5 to 20 years old (instrumental variable).

**MAIN OUTCOME:** Having any limitations in IADL (preparing a hot meal, shopping for groceries, making telephone calls, taking medications, doing work around the house or garden, or managing money).

**RESULTS:** Linear probability model with Two-Stage Least Squares estimation was fitted. Being exposed to fluoridated water was associated with having more natural teeth in later life (coefficient: 0.726; 95% CI: 0.311, 1.142; F = 11.749). Retaining one more natural tooth reduced the probability of having a limitation in IADL by 3.1 percentage points (coefficient: −0.031; 95% CI: −0.060, −0.002).

**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 mechanism of the observed causal relationship is needed.

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

## INTRODUCTION

Instrumental activities of daily living (IADL) represent functional competence for independent living in a community and significantly impact the quality of life in older people.[1] A hierarchical model has been proposed for functional competence, and declines in higher-level competence predict future declines in lower-level domains.[2] As a decline in IADL is associated with dementia[3] and death,[4] maintaining IADL is essential for individuals in early old age and throughout aging society while it also leads to lower medical and long-term care costs.[4,5]

Studies have reported a longitudinal association between oral conditions and a decline in functional capacity and disability.[6–9] More specifically, physical and cognitive decline is more remarkable among edentate (i.e., people with no natural teeth) older people in England compared to their dentate counterparts.[9] Having more natural teeth is associated with delaying the onset of disability and death among the Japanese older population.[6] Relevant mechanisms include low nutritional status due to tooth loss[10] and increased risk of cardiovascular disease due to inflammation from past periodontal disease.[11] Social interactions could be another pathway because lack of social interaction increases the risk of disability[12] and is also associated with having fewer teeth, which in turn is clearly linked to worse oral function and quality of life.[13]

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

and functional capacity, there is hardly any robust evidence towards a *causal relationship* (i.e., tooth loss *affects* functional capacity). Residual confounding is one of the most challenging issues in the interpretation of association results from observational studies, and further studies distilling out the causal effect are needed.[14] Adverse environment/conditions in early life could be one example of residual confounding; they have been associated with chewing ability,[15] number of teeth in adulthood,[16,17] and functional capacity.[18] Moreover, it is impossible to measure all potential confounders, including unknown ones.

Randomized controlled trial (RCT) is conventionally considered a gold standard to establish causal evidence; however, its generalizability to populations is limited, and it is not well suited to investigate long-term consequences.[19] Beyond the RCT, causal estimates can also be obtained from certain observational study designs.[20] Natural experiments can be utilized as sources of exogenous variations that were not manipulated by researchers, thereby addressing reverse causation and (unmeasured) confounding.

In England, 10% of the population is exposed to artificially/naturally fluoridated water, but the fraction of the population covered by fluoridated water and the year of initiation varies geographically.[21] Thus, the likelihood of exposure to tap water fluoride is influenced by year of birth and region lived in childhood. Exploiting quasi-experimental variation in tooth loss due to this regional variation, we aimed to investigate the causal effect of the number of teeth on functional capacity of the late adulthood population in England.

## METHODS

*Assumptions in the present study*

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

existence of adverse effects of water fluoridation on other health outcomes related to functional limitation, including bone fracture, cancer, and cognitive ability.[23,28–31] Assumption 3 might be challenging because the population supplied with fluoridated tap water in England has increased with time. Also, local characteristics are potential confounders because local public bodies make decisions on community water fluoridation.[32] We addressed the cohort effect confounding by restricting study participants to those born in a specific range of years (between 1945-1965) so that to exclude participants that lived their childhood prior to water fluoridation was introduced in the UK, and also statistically controlled for it in the model. The region effect confounding was addressed by adjusting for regional fixed effects and sensitivity analysis.

*Study participants*

We conducted a secondary analysis using the data of the English Longitudinal Study of Ageing (ELSA). ELSA is a sizeable longitudinal panel study targeting a representative sample of the population aged 50 years or older in England. Further details about ELSA are available elsewhere.[33] We used ELSA wave 7, which was conducted between 2014–2015 and is the only wave that measured the number of remaining teeth. To reduce bias due to the cohort effect and effectively utilize the variation in tap water fluoride in childhood, the data of 5,631 individuals born in 1945–1965 without missing information on variables were

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

*Dependent variable: instrumental activities of daily living*

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

*Exposure variable: the number of teeth*

The number of remaining teeth was assessed through the following question: *"Adults usually have up to 32 natural teeth, but over time people lose some of them. How many natural teeth 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

2012.[36] The concentration of fluoride was targeted at 1.0 ppm for artificial water fluoridation, while that of natural water fluoridation varied between 0.5–1.5 ppm. Further detail of the calculation is described in Supplementary Method S1.

*Covariates*

To consider differences by year of birth and region of residence, fixed effects of year of birth, sex (men, women), and regional fixed effects were adjusted for. As several examples shown in Supplementary Table S2, there might be differences in general health issues, socioeconomic status, and other unmeasured factors by year of birth and region of residence. Given that the analysis exploited the variation in the number of remaining teeth in adulthood derived by differential exposure to tap water fluoride in childhood, we considered individual general health variables as mediators rather than confounders; and we did not include them in the covariates. The balancing tests showed that the difference in childhood socioeconomic status by the instrument is small (standardized differences were close to or smaller than 0.1, Supplementary Table S3); and we controlled them in the sensitivity analysis.

*Statistical analyses*

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*. $Teeth_{ig,}$ $Fluoride_{ig,}$ $Yob_{ig,}$

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. $v_{ig}$ is an error term. Accordingly, our first-stage regression can be written as:

$$Teeth_{ig} = \alpha_0 + \alpha_1 Fluoride_{ig} + \alpha_2 Yob_{ig} + \alpha_3 Sex_{ig} + \alpha_4 Region_g + v_{ig}$$

Let $\widehat{Teeth}_{ig}$ be the participant *i*'s number of teeth predicted by the first-stage regression, and $IADL_{ig}$ be a binary variable equals 1 if the participant *i* had any limitation in IADL. $e_{ig}$ is an error term. The second-stage regression is then:

$$IADL_{ig} = \beta_0 + \beta_1 \widehat{Teeth}_{ig} + \beta_2 Yob_{ig} + \beta_3 Sex_{ig} + \beta_4 Region_g + e_{ig}$$

The coefficient $\beta_1$ indicates the percentage points change in the probability of limitation in IADL per retaining one more tooth.[37] Analysis using each IADL item as the dependent variable was also performed to investigate which specific components were affected.

*Sensitivity analysis*

Four sets of sensitivity analyses were performed: 1) assigning mean or median of the clinically examined number of teeth respective to age, sex, and self-reported number of teeth in Adult Dental Health Survey 2009 [38] to evaluate whether the results are robust to the 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' educational qualification and their parents' years of education; 4) stratification analysis by

age group (50–64 and 65–70 years old). STATA MP version 16.1 (Stata Corp., College Station, TX, USA) was utilized for all analyses.

## RESULTS

Table 1 summarizes the details of naturally/artificially fluoridated water in each region. The fraction of the population covered by fluoridated water in 2012 ranged from 0 (South East and South West) to 0.675 (West Midlands). The average year of initiation of artificial WF ranged from 1968 (North East and Yorkshire and The Humber) to 1980 (West Midlands).

Table 2 describes the main characteristics of the respondents by the number of natural teeth. The overall prevalence of the IADL limitation was 11.9% and was higher among people with fewer teeth. Exposure to fluoridated water when aged 5–20 years was greater among people with more natural teeth in later adulthood.

Table 3 shows the estimated causal effects of tooth loss on IADL. The first-stage regression showed that exposure to fluoridated water was significantly associated with having more natural teeth (Coefficient = 0.726; 95% confidence interval, CI: 0.311, 1.142). More specifically, one-unit increment in the instrument, which is equivalent to one additional year of exposure to fluoridated water during the age of 5 to 20 years, was associated with having 0.726 more teeth on average at an older age. The first-stage F-statistic was 11.749, indicating that the IV was sufficiently strong to predict the number of teeth.[39] The second-stage

regression showed that retaining one more tooth reduced probability of limitation in IADL by 3.1 (95% CI: 0.2, 6.0) percentage points.

The second-stage estimates for each component of IADL are shown in Supplementary Figure S4. With the exception of "taking medications" and "managing money", the point estimates were negative, that is, having more natural teeth was associated with lower probability of each IADL limitation, though only the association with "shopping for groceries" was significant.

Similar estimates were obtained when changing the number of teeth assigned to each category (Supplementary Table S5). The results did not change when adjusting for the year of birth with different functions or adjusting for individual educational level (Supplementary Table S6). Further stratification analysis by age showed similar point estimates in aged 50–64 year-olds, while the first-stage regression was not significant in those aged 65–70 years old.

## DISCUSSION

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 probability of having limitations in IADL. Under the assumptions supported by previous 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.

Under the monotonicity assumption, IV analyses estimate the local average treatment (LATE) effect among compliers.[37] In the present study, the monotonicity assumption, that is, no one loses their teeth because of being exposed to fluoridated water in childhood, is supported by previous biological and epidemiological studies.[40] As our instrument is a continuous scale, the inferential target population consists of all individuals used in the analysis contributing with unknown weights.[37] Given that the preventive effect of water fluoridation is more prominent in high-risk populations (i.e., living in deprivation),[41] our results might primarily reflect the effect of teeth on IADL among people from lower socioeconomic backgrounds. The 2SLS estimate (3.1 percentage points difference) was larger 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 backgrounds. It is possible that the lack of resources and limited access to care among the deprived population[42] 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 variable.[43] The analytical population was younger than the entire ELSA participants. A previous study in the US found that the impact of tooth loss was more considerable among younger people.[44] For these reasons, the effect sizes in the present study might be larger than the average treatment effect in the older adult population in England.

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

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

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

Another assumption is that the participants had lived in the same region in their childhood as in the time of the survey. The assumption may well have been violated as the participants are 50 years old or older because, in England, about 1 to 3% of the population migrated to other regions in 2014.[53] We were not able to evaluate this potential misclassification due to lack of data. We believe the misclassification to be non-differential because people would be less likely to decide their region of residence based on whether there is water fluoridation. Therefore, it would have decreased both the reduced-form and the first-stage estimators; and the direction of the bias on the IV estimator (ratio of the reduced-form estimator to the first-stage estimator) might be over or underestimated.

Other methodological limitations include that we did not have any information on other sources of fluoride (e.g., toothpaste). Thus, our estimation might be biased if the utilization of fluoride resources differs by regions; however, the frequency of tooth brushing was not different by region in Adult Dental Health Survey 2009.[38] Moreover, data on the number of teeth and IADL was self-reported; however, high accuracy of self-reports for number of teeth has been reported previously.[54]

Few previous studies have applied natural experimental design to investigate the causal relationship between oral and general health outcomes. The present natural experimental study exploited the historical and geographical variation in community water fluoridation and found that retaining one more natural tooth due to exposure to fluoridated

water in childhood was associated with a lower probability of limitations in IADL. Preventive oral health strategies can potentially improve independent living in later life.

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372 design, interpretation of data, and critically revised the manuscript. All authors gave final
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Table 1. Characteristics of natural/artificial water fluoridation by region

| | 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 | - |

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

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

| | No teeth n = 234 | 1-9 teeth n = 290 | 10-19 teeth n = 719 | 20+ teeth n = 4,388 | Number 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 | 20 ( 8.5%) | 38 (13.1%) | 83 (11.5%) | 490 (11.2%) | 22.4 (7.2) |
| East of England | 18 ( 7.7%) | 36 (12.4%) | 100 (13.9%) | 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 fluoridated water [bc] | 0.328 (0.748) | 0.260 (0.652) | 0.381 (0.862) | 0.401 (0.925) | - |

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) | - |

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 ≥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 the exposure | 1. Childhood exposure to tap water fluoride prevents tooth loss in adulthood |
| 2. Instrumental variable affects the outcome only through the exposure but not otherwise | 2. Childhood exposure to tap water fluoride affects instrumental activity of daily living in adulthood only via preventing tooth loss but not through other pathways |
| 3. Independent of all unobserved variables that affect the outcome | 3. Factors influenced the decision on community water fluoridation do not affect 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)

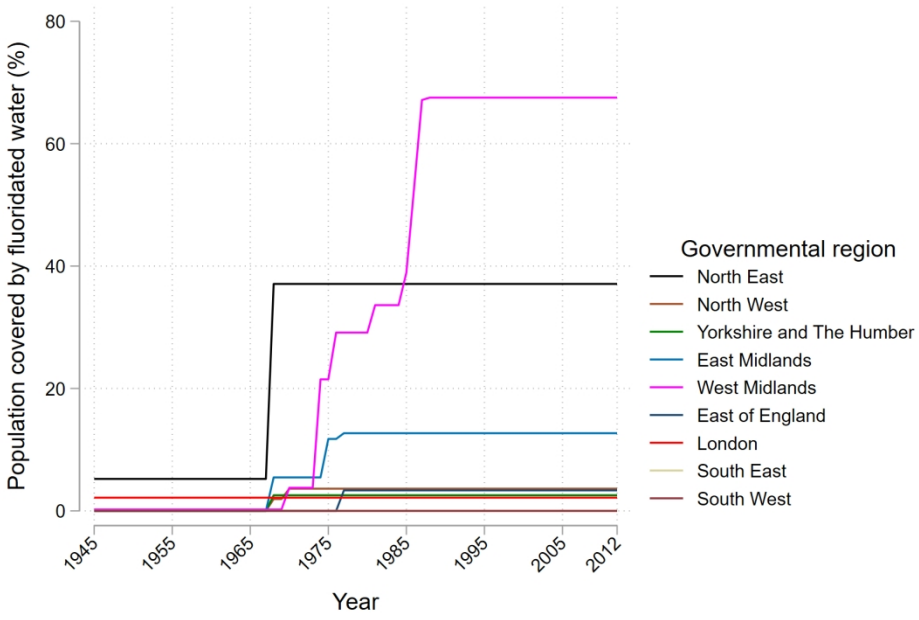


Figure 2. Trajectory of population covered by naturally/artificially fluoridated water

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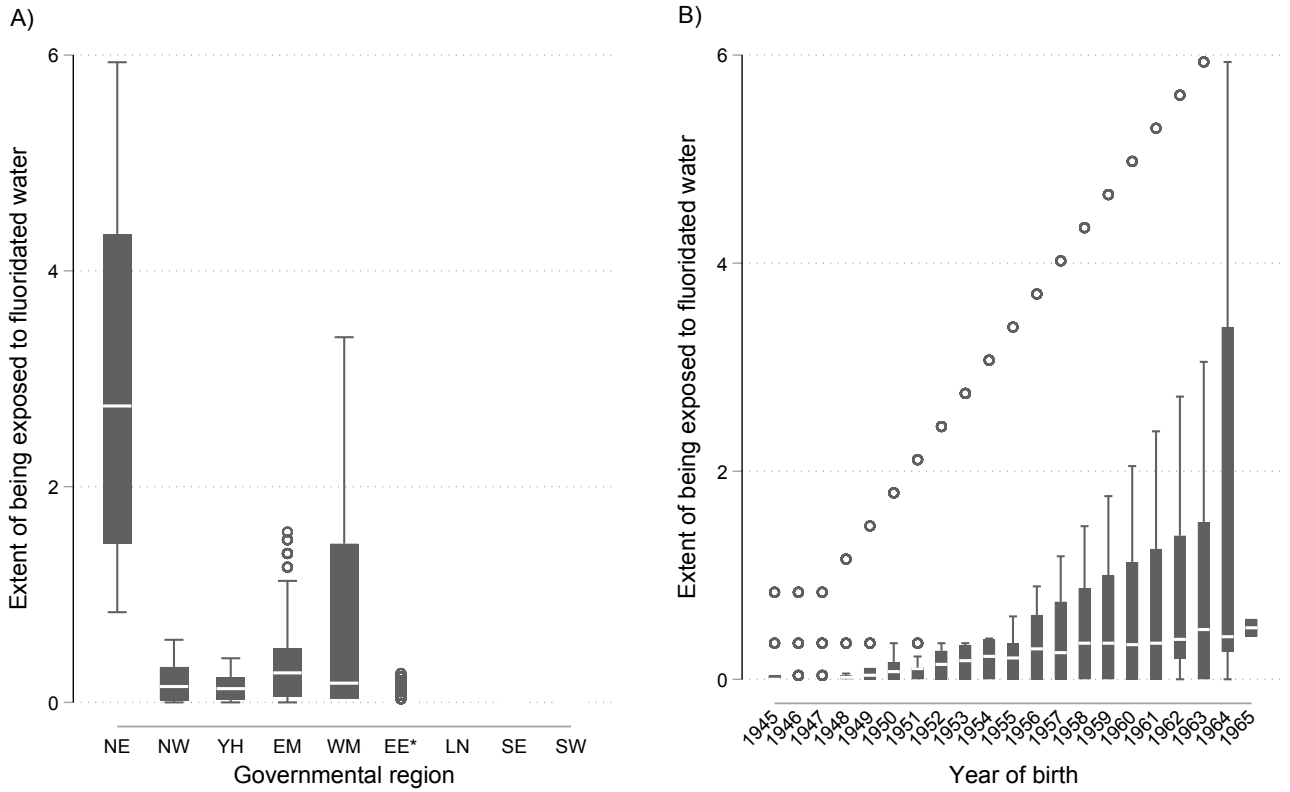
# SUPPLEMENTARY INFORMATION

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. Thus, the likelihood for individual 1 being exposed to 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 fluoridation has not been implemented, but 2.2% of the population were supplied naturally fluoridated

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.

Supplementary Method S1 Table. Instrumental variable for hypothetical four individuals

| | Individual 1 Born in West Midlands | | Individual 2 Born in West Midlands | | Individual 3 Born in London | | Individual 4 Born in London | |
|---|---|---|---|---|---|---|---|---|
| Year | Age | Fluoride coverage | Age | Fluoride coverage | Age | Fluoride coverage | Age | Fluoride coverage |
| 1950 | 0 | | | | 0 | | | |
| 1951 | 1 | | | | 1 | | | |
| 1952 | 2 | | | | 2 | | | |
| 1953 | 3 | | | | 3 | | | |
| 1954 | 4 | | | | 4 | | | |
| 1955 | 5 | 0.002 | | | 5 | 0.022 | | |
| 1956 | 6 | 0.002 | | | 6 | 0.022 | | |
| 1957 | 7 | 0.002 | | | 7 | 0.022 | | |
| 1958 | 8 | 0.002 | | | 8 | 0.022 | | |
| 1959 | 9 | 0.002 | | | 9 | 0.022 | | |
| 1960 | 10 | 0.002 | 0 | | 10 | 0.022 | 0 | |
| 1961 | 11 | 0.002 | 1 | | 11 | 0.022 | 1 | |
| 1962 | 12 | 0.002 | 2 | | 12 | 0.022 | 2 | |
| 1963 | 13 | 0.002 | 3 | | 13 | 0.022 | 3 | |
| 1964 | 14 | 0.002 | 4 | | 14 | 0.022 | 4 | |
| 1965 | 15 | 0.002 | 5 | 0.002 | 15 | 0.022 | 5 | 0.022 |
| 1966 | 16 | 0.002 | 6 | 0.002 | 16 | 0.022 | 6 | 0.022 |
| 1967 | 17 | 0.002 | 7 | 0.002 | 17 | 0.022 | 7 | 0.022 |
| 1968 | 18 | 0.002 | 8 | 0.002 | 18 | 0.022 | 8 | 0.022 |
| 1969 | 19 | 0.002 | 9 | 0.002 | 19 | 0.022 | 9 | 0.022 |
| 1970 | 20 | 0.038 | 10 | 0.038 | 20 | 0.022 | 10 | 0.022 |
| 1971 | | | 11 | 0.038 | | | 11 | 0.022 |
| 1972 | | | 12 | 0.038 | | | 12 | 0.022 |
| 1973 | | | 13 | 0.038 | | | 13 | 0.022 |
| 1974 | | | 14 | 0.215 | | | 14 | 0.022 |
| 1975 | | | 15 | 0.215 | | | 15 | 0.022 |
| 1976 | | | 16 | 0.291 | | | 16 | 0.022 |
| 1977 | | | 17 | 0.291 | | | 17 | 0.022 |
| 1978 | | | 18 | 0.291 | | | 18 | 0.022 |
| 1979 | | | 19 | 0.291 | | | 19 | 0.022 |
| 1980 | | | 20 | 0.291 | | | 20 | 0.022 |
| Total | | 0.068 | | 2.047 | | 0.352 | | 0.352 |

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

| | 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) ≥3

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

| | Unadjusted model | | | Adjusted model[a] | | |
|---|---|---|---|---|---|---|
| | Extent of being exposed to fluoridated water | | | Extent of being exposed to fluoridated 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 |

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.

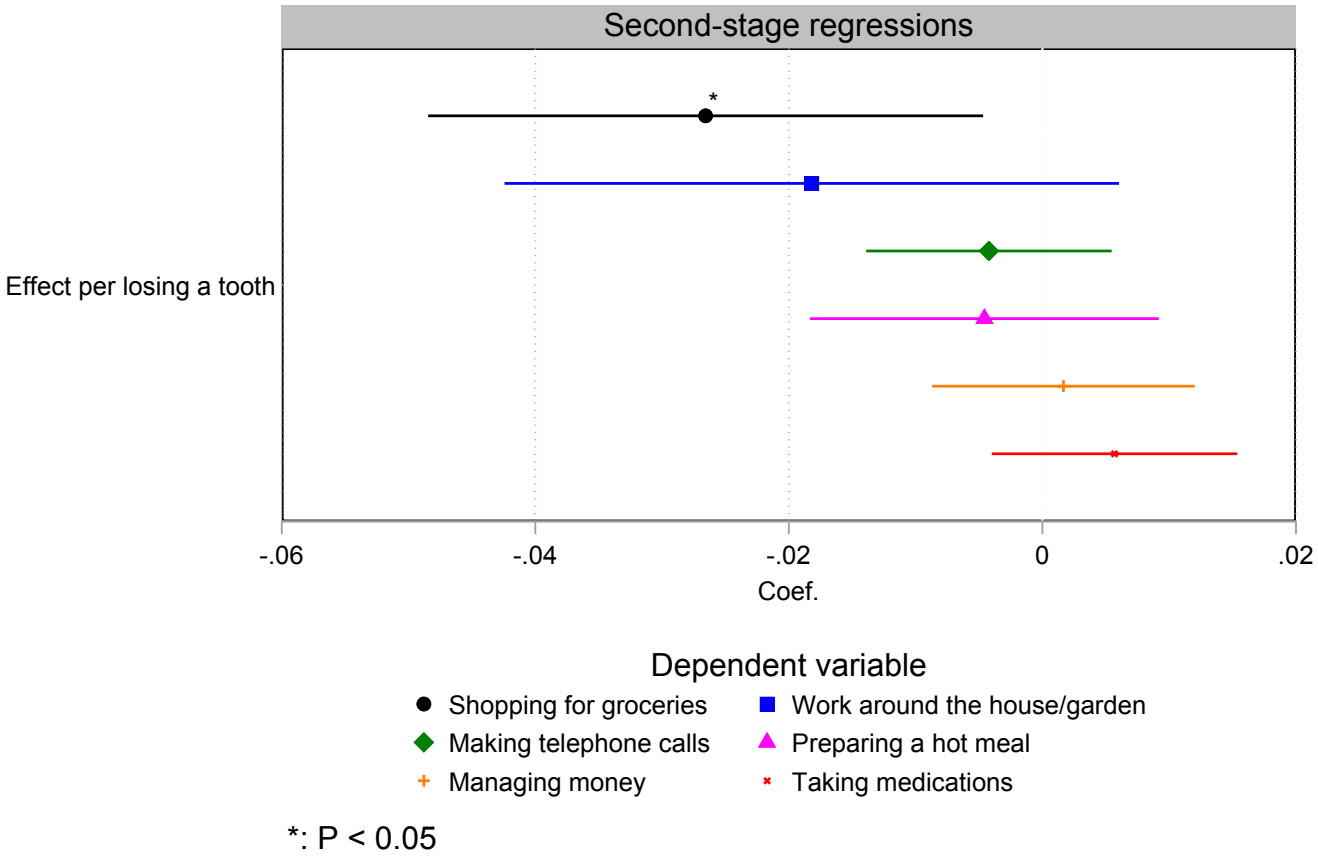
a adjusted for region fixed effect and year of birth fixed effect

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

| | 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-stage least square, OLS, ordinary least squares

Adjusted for the fixed effects of year of birth, 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

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

| | 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 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)

**Title**

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

**Short running title**

Tooth loss and functional capacity

**Authors**

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**Impact statement**

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 England, whereby exploiting the exogen~~e~~ous geographical and historical variation in ~~the~~ childhood exposure to tap water fluoride. Retaining ~~Our findings suggest that having~~ one more tooth ~~due to exposure to fluoridated water in childhood causally~~ reduced the probability of having a limitation in the instrumental activity of daily living~~IADL~~ by 3.1~~.9~~ percentage points. Our findings support the causal evidence between tooth loss and functional capacity ~~in later life~~.

## Abstract

**BACKGROUND/OBJECTIVES:** Tooth loss is associated with reduced functional capacity, but so far, there is no relevant causal evidence reported. We investigated the causal effect of tooth loss on the instrumental activities of daily living (IADL) among older adults ~~aged ≥50 years~~ in England.

**DESIGN:** Natural experiment study with instrumental variable analysis.

**SETTING:** The English Longitudinal Study of Aging (ELSA) combined with the participants' childhood exposure to water fluoride due to the community water fluoridation.

**PARTICIPANTS:** 5,631~~9,437~~ adults in England born in 1945~~23~~–1965 ~~who~~ participated in the ELSA wave 7 survey (conducted in 2014–2015; average age: 61.0~~67.7~~ years, 44.6~~7~~% men).

**EXPOSURE:** The number of natural teeth predicted by the exogenous geographical and historical variation in exposure to water fluoride from age 5 to 20 years old (instrumental variable).

**MAIN OUTCOME:** Having any limitations in IADL (preparing a hot meal, shopping for groceries, making telephone calls, taking medications, doing work around the house or garden, or managing money).

**RESULTS:** Linear probability model with Two-Stage Least Squares estimation was fitted. Being exposed to fluoridated water was associated with having more natural teeth in later life (coefficient: 0.726~~1.08~~; 95% CI: 0.311~~70~~, 1.142~~45~~; F = 11.749~~31.49~~). Retaining one more natural tooth reduced the probability of having a limitation in IADL by 3.1~~.9~~ percentage points (coefficient: −0.031~~9~~; 95% CI: −0.060~~035~~, −0.002~~4~~).

**CONCLUSION:** Preventing tooth loss maintains functional capacity among older adults ~~aged ≥50 years~~ in England. Given the high prevalence of tooth loss, this effect is considerable. Further research on the mechanism of the observed causal relationship is needed.

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

## INTRODUCTION –

Instrumental activities of daily living (IADL) represent~~Maintaining~~ functional competence~~capacity is essential~~ for independent living in a community and significantly impact the quality of~~later~~ life in older people.[1] A hierarchical model has been proposed for functional competence, and declines in higher-level competence predict future declines in lower-level domains.[2] As a decline in IADL is associated with dementia[3] and death,[4] maintaining IADL is essential for individuals in early old age and throughout aging society while it also leads to lower medical and long-term care costs.[4,5]

Studies have reported a longitudinal association between oral conditions and a decline in functional capacity and disability.[6–9] More specifically, physical and cognitive decline is more remarkable among edentate (i.e., people with no natural teeth) older people in England compared to their dentate counterparts.[9] Having more natural teeth is associated with delaying the onset of disability and death among the Japanese older population.[6] Relevant mechanisms include low nutritional status due to tooth loss[10] and increased risk of cardiovascular disease due to inflammation from past periodontal disease.[11] Social interactions could be another pathway because lack of social interaction increases the risk of disability[12] and is also associated with having fewer teeth, which in turn is clearly linked to worse oral function and quality of life.[13]

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

and functional capacity, there is hardly any robust evidence towards a *causal relationship* (i.e., tooth loss *affects* functional capacity). Residual confounding is one of the most challenging issues in the interpretation of association results from observational studies, and further studies distilling out the causal effect are needed.[14] Adverse environment/conditions in early life could be one example of residual confounding; they have been associated with chewing ability,[15] number of teeth in adulthood,[16,17] and functional capacity.[18] Moreover, it is impossible to measure all potential confounders, including unknown ones.

Randomized controlled trial (RCT) is conventionally considered a gold standard to establish causal evidence; however, its generalizability to populations is limited, and it is not well suited to investigate long-term consequences.[19] Beyond the RCT, causal estimates can also be obtained from certain observational study designs.[20] Natural experiments can be utilized as sources of exogenous variations that were not manipulated by researchers, thereby addressing reverse causation and (unmeasured) confounding.

In England, 10% of the population is exposed to artificially/naturally fluoridated water, but the fraction of the population covered by fluoridated water and the year of initiation varies geographically.[21] ~~Declines in higher-level functional competence predict future disability and death.[2] A billion of the world population are living with disabilities,[3] and the high prevalence of disability strains public healthcare systems and expenditures [4].~~ ~~Therefore, determining preventive factors of the initial decline in functional capacity is~~

~~important in an aging society.~~

~~Studies have reported a longitudinal association between oral conditions and decline in functional capacity and disability.[5–8] More specifically, physical and cognitive decline is greater among edentate (i.e., people with no natural teeth) older people in England compared to their dentate counterparts.[8] Having more natural teeth is associated with delaying the onset of disability and death among the Japanese older population.[5] Tooth loss due to dental caries or periodontal disease leads to poor nutritional status.[9] Inflammation related to past periodontal disease may increase the risk of cardiovascular disease.[10] Social interactions could be another pathway because lack of social interaction increases the risk of disability[11] and is also associated with having fewer teeth, which in turn is clearly linked to worse oral function and quality of life.[12]~~

~~In contrast to this accumulating evidence on the *association* between oral conditions and functional capacity, there is hardly any robust evidence towards a *causal relationship* (i.e., tooth loss *affects* functional capacity). Residual confounding is one of the most challenging issues in the interpretation of association results from observational studies, and further studies distilling out the causal effect are needed.[13] Adverse environment/conditions in early life could be one example of residual confounding; they have been associated with chewing ability,[14] number of teeth in adulthood,[15,16] and functional capacity.[17] Moreover, it is impossible to measure all potential confounders, including the unknown ones.~~

~~The randomized controlled trial (RCT) is conventionally considered a gold standard to establish causal evidence; however, its generalizability to populations is limited, and it is not well suited to investigate long-term consequences.[18] Beyond the RCT, causal estimates can also be obtained from certain observational study designs.[19] Natural experiments can be utilized as sources of exogenous variations that were not manipulated by researchers, thereby addressing reverse causation and (unmeasured) confounding. Such exogenous variation can be exploited as an instrumental variable (IV) for the exposure of interest.[20] The IV needs to be: 1) independent of all confounders that affect the exposure and the outcome; 2) associated with the exposure; 3) affecting the outcome only through the exposure.[20]~~

~~In England, 10% of the population is exposed to artificially/naturally fluoridated water, but the fraction of the population covered by fluoridated water and the year of initiation varies geographically.[21]~~ Thus, the likelihood of exposure to tap water fluoride is influenced by year of birth and region lived in childhood. Exploiting quasi-experimental variation in tooth loss due to this regional variation, we aimed to investigate the causal effect of the number of teeth on functional capacity of the late adulthood population in England.

## METHODS

*Assumptions in the present study*

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

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

## ~~METHODS~~

*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

longitudinal panel study targeting a representative sample of the population aged 50 years or older in England. Further details about ELSA are available elsewhere.[33] We used ELSA wave 7, which was conducted between 2014–2015 and is the only wave that measured the number of remaining teeth. To reduce bias due to the cohort effect and effectively utilize the variation in tap water fluoride in childhood, the data of 5,631 individuals born in 1945–1965 without missing information on variables were analyzed.[32] ~~ELSA received ethical approval for all waves from NHS Research Ethics Committees under the National Research and Ethics Service (NRES).~~ The present study was approved by the ethical committee at Tokyo Medical and Dental University.

*Dependent variable: instrumental activities of daily living*

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

IADL components are compromised. This dichotomized outcome has been used in a previous study.[3]

~~IADL was used to assess functional capacity. They reflect instrumental self-maintenance by assessing the presence of limitations in the following six activities: preparing a hot meal, shopping for groceries, making telephone calls, taking medications, doing work around the house or garden, and managing money such as paying bills and keeping track of expenses. IADL relates to autonomy in everyday life and requires interplay of higher physical and cognitive function[33], therefore could be influenced by tooth loss. An aggregate binary variable indicating limitations in any of these six activities was used as the dependent variable.~~

*Exposure variable: the number of teeth*

The number of remaining teeth was assessed through the following question: *"Adults usually have up to 32 natural teeth, but over time people lose some of them. How many natural teeth have you got?."* Respondents were asked to choose the answer from the following options: *"None at all," "Between 1 and 9 natural teeth," "Between 10 and 19 natural teeth,"* and *"20 or more natural teeth."* The variable was used as continuous in analyses with the middle number allocated to each category (i.e., 0, 4.5, 14.5, and 26, respectively). Thereby, the estimated effect size was scaled at the level of retaining one more tooth.

*Instrumental variable*

We used the total annual likelihood of being exposed to naturally/artificially fluoridated 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 cover~~correspond 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 effect of fluoride.[35]

Figure 2~~1~~ illustrates the trajectories of population coverage with naturally/artificially fluoridated water in each region. We obtained county-level information on the number of population covered by naturally/artificially fluoridated water and the year of the initiation of artificial water fluoridation from a previous report.[21]~~in 2012 and the year of the initiation of artificial WF from a previous report.[21]~~ As residential information of ELSA participants was only available for the region of residence at the time of~~regional level in~~ the survey~~dataset~~, we used this variable as a proxy of the region they resided in childhood and aggregated the information on water fluoridation~~WF~~ to a regional level. The proportion of people covered by 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 fluoridation~~WF~~, while that of natural water fluoridation~~WF~~ varied between 0.5–1.5 ppm.

Further detail of the calculation is described in Supplementary Method S1.

*Covariates*

To consider differences by year of birth and region of residence, fixed effects of year of birth, sex (men, women), and regional fixed effects were adjusted for. As several examples shown in Supplementary Table S2, there might be differences in general health issues, socioeconomic status, and other unmeasured factors by year of birth and region of residence. Given that the analysis exploited the variation in the number of remaining teeth in adulthood derived by differential exposure to tap water fluoride in childhood, we considered individual general health variables as mediators rather than confounders; and we did not include them in the covariates. The balancing tests showed that the difference in childhood socioeconomic status by the instrument is small (standardized differences were close to or smaller than 0.1, Supplementary Table S3); and we controlled them in the sensitivity analysis.

~~Year of birth (categorized in groups of five years), sex (men, women), and regional fixed effects were adjusted for. Since the instrument was constructed as a function of year of birth in each region of residence, this leaves as identifying variation the interaction of cohort and region.~~

*Statistical analyses*

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*. $Teeth_{ig}$, $Fluoride_{ig}$, $Yob_{ig}$ ~~$Age_{ig}$~~, and $Sex_{ig}$ are participants's ~~s~~ number of teeth, exposure to fluoridated water when aged 5-20 years, year of birth ~~age~~, and sex, respectively. $Region$ ~~$Fixed_g$~~ indicates dummy variables for each region. $v_{ig}$ is an error term. Accordingly, our first-stage regression can be written as:

$$Teeth_{ig} = \alpha_0 + \alpha_1 Fluoride_{ig} + \alpha_2 Yob_{ig} \text{ ~~} Age_{ig} \text{ ~~} + \alpha_3 Sex_{ig} + \alpha_4 Region_g + v_{ig} \text{ ~~} RegionFixed_g \text{ ~~} + v_{ig}$$

Let $\widehat{Teeth}_{ig}$ be the participant *i*'s number of teeth predicted by the first-stage regression, and $IADL_{ig}$ be a binary variable equals ~~to~~ 1 if the participant *i* had any limitation in IADL. $e_{ig}$ is an error term. The second-stage regression is then:

$$IADL_{ig} = \beta_0 + \beta_1 \widehat{Teeth}_{ig} + \beta_2 Yob_{ig} \text{ ~~} Age_{ig} \text{ ~~} + \beta_3 Sex_{ig} + \beta_4 Region_g + e_{ig} \text{ ~~} RegionFixed_g \text{ ~~} + e_{ig}$$

The coefficient $\beta_1$ indicates the percentage points change in the probability of limitation in IADL per ~~caused by~~ retaining one more tooth.[37] ~~37~~ Analysis using each IADL item as ~~To consider~~ the dependent variable was also performed ~~number of teeth assigned~~ to investigate which specific components were affected.

*Sensitivity analysis*

Four sets of ~~each category, a~~ sensitivity analyses were ~~analysis was~~ performed: 1) ~~by~~ assigning

mean or median of the clinically examined number of teeth respective to age, sex, and self-reported number of teeth in Adult Dental Health Survey 2009 ~~.~~[38] to evaluate whether~~As~~ the results are robust to ~~data included only one wave of~~ the allocation~~survey, there could be an identification issue if we include the fixed effect~~ of the midpoint~~every single year~~ of categorical responses; 2) controlling the cohort effects for linear function and restricted cubic~~birth. To address this, further sensitivity analysis was performed by adding~~ spline function, respectively; 3) adjusting for participants' educational qualification and their parents' years~~terms for the year~~ of education; 4) stratification analysis by age group (50–64 and 65–70 years old).~~birth.~~ STATA MP version 16~~15~~.1 (Stata Corp., College Station, TX, USA) was utilized for all analyses.

**RESULTS**

~~Among the 9666 respondents of ELSA wave 7, 39 living outside of England, 174 aged less than 50 years, and 16 with missing information on the variables were excluded. Accordingly, data on 9437 respondents were analyzed (average age = 67.7 years, 44.7% men).~~

Table 1 summarizes the details of naturally/artificially fluoridated water in each region. The fraction of the population covered by fluoridated water in 2012 ranged from 0 (South East and South West) to 0.675 (West Midlands). The average year of initiation of artificial WF ranged from 1968 (North East and Yorkshire and The Humber) to 1980 (West

Midlands).

Table 2 describes the main characteristics of the respondents by the number of remaining natural teeth. The overall prevalence of the IADL limitation was 11.918.0% and was higher among people with fewer teeth. ExposureThe extent of exposure to fluoridated water when aged 5–20 years was greater among people with more natural teeth in later adulthood.

Table 3 shows the estimated causal effects of tooth loss on IADL. The first-stage regression showed that exposure tothe extent of fluoridated water was significantly associated with having more natural teeth (Coefficient = 0.7261.076; 95% confidence interval, CI: 0.311700, 1.1452). More specifically, one-unit increment in the instrument, which is equivalent to one additional year of exposure to fluoridated water during the age of 5 to 20 years, was associated with having 0.7261.08 more teeth on average at an older age. The first-stage F-statistic was 11.74931.487, indicating that the IV was sufficiently strong to predict the number of teeth.[39] The second-stage regression showed that retaining one more tooth reduced the probability of limitation in IADL by 3.1.9 (95% CI: 0.2, 6.04, 3.5) percentage points. Similar estimates were obtained when changing the number of teeth assigned to each category (Appendix Table A.1). Adjusting for the year of birth with spline terms resulted in similar findings (Appendix Table A.2).

The second-stage estimates for each component of IADL are shown in

Supplementary Figure S4. With the exception of "taking medications" and "managing money", the point estimates were negative, that is, having more natural teeth was associated with lower probability of each IADL limitation, though only the association with "shopping for groceries" was significant.

Similar estimates were obtained when changing the number of teeth assigned to each category (Supplementary Table S5). The results did not change when adjusting for the year of birth with different functions or adjusting for individual educational level (Supplementary Table S6). Further stratification analysis by age showed similar point estimates in aged 50–64 year-olds, while the first-stage regression was not significant in those aged 65–70 years old.

## DISCUSSION

The present natural experimental study showed that ~~investigated the extent to which~~ the number of remaining teeth predicted by the differential exposure to tap water fluoride in childhood was associated with a lower probability of having limitations in IADL. Under the assumptions supported by previous literature, our ~~*affected* functional capacity, using exogenous variation in exposure to water fluoridation as a natural experiment that predicted a higher tooth count among people with compared to those without exposure to fluoridated water. Our~~ findings suggest that having one more tooth ~~(due to exposure to fluoridated water earlier in life)~~ reduced the probability of having a limitation in IADL by 3.1~~.9~~ percentage

points among adults aged ≥50–70 years old in England.

Under the monotonicity assumption, IV analyses estimate the local average treatment (LATE) effect among compliers.[37] In the present study, the monotonicity assumption, that is, no one loses their teeth because of being exposed to fluoridated water in childhood, is supported by previous biological and epidemiological studies.[40] As our instrument is a continuous scale, the inferential target population consists of all individuals used in the analysis contributing with unknown weights.[37] Given that the preventive effect of water fluoridation is more prominent in high-risk populations (i.e., living in deprivation),[41] our results might primarily reflect the effect of teeth on IADL among people from lower socioeconomic backgrounds. The 2SLS estimate (3.1 percentage points difference) was larger 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 backgrounds. It is possible that the lack of resources and limited access to care among the deprived population[42] 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 variable.[43] The analytical population was younger than the entire ELSA participants. A previous study in the US found that the impact of tooth loss was more considerable among younger people.[44] For these reasons, the effect sizes in the present study might be larger than

the average treatment effect in the older adult population in England.

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

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

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

unknown but plausible confounders might exist and influence the results.

Another assumption is that the participants had lived in the same region in their childhood as in the time of the survey. The assumption may well have been violated as the participants are 50 years old or older because, in England, about 1 to 3% of the population migrated to other regions in 2014.[53] We were not able to evaluate this potential misclassification due to lack of data. We believe the misclassification to be non-differential because people would be less likely to decide their region of residence based on whether there is water fluoridation. Therefore, it would have decreased both the reduced-form and the first-stage estimators; and the direction of the bias on the IV estimator (ratio of the reduced-form estimator to the first-stage estimator) might be over or underestimated.

Other methodological limitations include that we did not have any information on other sources of fluoride (e.g., toothpaste). Thus, our estimation might be biased if the utilization of fluoride resources differs by regions; however, the frequency of tooth brushing was not different by region in Adult Dental Health Survey 2009.[38] Moreover, data on the number of teeth and IADL was self-reported; however, high accuracy of self-reports for number of teeth has been reported previously.[54]

Few previous studies have applied natural experimental design to investigate the causal relationship between oral and general health outcomes. The present natural experimental study exploited the historical and geographical variation in community water fluoridation and

found that retaining one more natural tooth due to exposure to fluoridated water in childhood was associated with a lower probability of limitations in IADL. ~~The present study is the first to report the causal effect of tooth loss on having a limitation in IADL. We obtained the causal effect using representative data of people aged ≥50 years in England. Few oral health studies have applied IV estimation. Through employing schooling reforms as IV for education, previous research established the causal effect of education on receiving periodontal treatment in Norway[40] and reducing edentulousness in the UK.[41] Lowered socioeconomic circumstances after a huge earthquake and tsunami were shown to cause increased tooth loss in Japan,[42] while Glied and Neidell (2010) used geographical variation in WF in the US to estimate the effect of teeth on earnings.[34]~~

~~IADL reflects coordination of higher physical and cognitive function.[33] The pathway of the association between tooth loss and general physical and cognitive function is also relevant. Tooth loss predicts poor dietary intake[9,43]; therefore, poor nutrition could partly explain our results. Social interaction, which is a risk factor for the onset of disability,[11] could also partly explain the link between tooth loss and IADL, because tooth loss is associated with poor social function.[44] Further, as a marker of lifetime experience of oral diseases and treatment, tooth loss is related to past dental caries and periodontal diseases, and the latter in particular could partly reflect past oral inflammation.[10] However, as our IV estimates distilled the effect of tooth loss following dental caries (i.e., the difference in tooth loss induced by~~

water fluoridation), the pathway through periodontal diseases might be less likely to explain our findings. We have further ran the analysis with each IADL item as the dependent variable (Appendix Figure A.3). "Shopping for groceries" and "doing work around the house or garden" had the two largest point estimates, although only the former was significant. These reflect the two most demanding physical tasks from the IADL items included in the study.[45] This might suggest that tooth loss affects functional capacity at an early stage of the decline. While the present study provides evidence for a causal relationship between tooth loss and functional capacity, the plausibility and extent of the different pathways would need further investigations in the framework of strong causal inference.

Our study has important public health implications. One billion of the world population are living with disabilities.[3] In the UK alone, 2.5 million older people had disabilities in 2015, and it is projected to rise by 25% in the next 20 years,[46] further challenging public healthcare systems and expenditure.[4] Previous studies showed associations, that is people with fewer teeth being more likely to have disabilities or limitations in functional capacity,[5–8] thereby providing evidence that tooth loss may be useful as an early marker of decline in functional capacity. This study has gone a step further and demonstrated causation in that association, which means that retaining natural teeth actually prevents a decline in functional capacity. To put our estimates into context, we looked at the effect on IADL limitation of a well-established risk factor such as the lack of physical

exercise.[47] Taking into account the high prevalence of tooth loss – 61% of older adults aged 65 years or more were without functional dentition in the UK in 2009[48] – and extrapolating our results (that are provided per natural tooth) into the aforementioned groups that have respectively 32 and at least 12 teeth missing, it is evident that promoting good oral health and the retention of natural teeth should be considered a priority area of population health.

The present study has methodological limitations. First, the IV analyses estimate local average treatment effect, which is the average effect among people whose exposure was changed by the IV (i.e., those whose tooth loss was prevented by WF).[37] The effect of fluoride on preventing dental caries may be larger among the high-risk population (i.e., living in deprivation).[49] Thus, our results might primarily reflect the effect of teeth on IADL among people from lower socioeconomic backgrounds, that is, the groups that have worse health and function. The OLS estimation showed that one additional remaining tooth was significantly associated with a lower probability of having a limitation in IADL by 0.6 percentage points (95% CI: 0.6, 0.7 percentage points) (Table 3), which was smaller than the 2SLS estimation. It should be noted that our estimates might overestimate the effect of tooth loss on IADL limitation, as the IV estimate can be more biased than OLS when the IV is only weakly correlated with the exposure variable.[50] Second, we have assumed that the study participants did not move from their region of birth. This assumption may well have been violated as the participants are 50 years old or older. Also, although we have adjusted for regional

~~characteristics by including a fixed effect in the models, it is possible that the timing of the initiation of WF is associated with local authorities' characteristics. However, we could not find any evidence/report against our assumption, i.e., that showed local authorities' characteristics to be associated with the timing of WF. Third, as the data included only one wave of the survey, we were not able to adjust for the fixed effect of year of birth by every single year. Instead, we have adjusted for the fixed effect of the year of birth categorized in groups of five years. However, in sensitivity analyses we further confirmed that the results remained similar when adjusting for spline of the year of birth. Fourth, we did not include any information on other sources of fluoride (e.g., toothpaste). Thus, our estimation might be biased if the utilization of fluoride resources differs by regions; however, the frequency of tooth brushing was not different by region in Adult Dental Health Survey 2009.[38] Additionally, data on the number of teeth and IADL was self-reported.~~

~~Using a natural experiment methodology with the consumption of fluoridated water as an instrumental variable, we found a causal effect of natural teeth on functional capacity among adults aged ≥50 years old in England. Retaining one more natural tooth reduced the probability of limitation in instrumental activities of daily living by 1.9 percentage points.~~

Preventive oral health strategies can potentially improve independent living in later life.

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

| | Total population in 2012 [a] | Population ~~Number of population~~ covered by fluoridated ~~natural/artificial~~ water ~~fluoridation~~ in 2012 [b] | Fraction of population covered by fluoridated ~~natural/artificial~~ water ~~fluoridation~~ in 2012 [b] | Year ~~Average year~~ of initiating artificial water fluoridation [b] ~~in different parts of the region~~ [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 Humber | 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 | - |

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

Table 2. IADL and other characteristics of the respondents, by number of natural teeth (N = 5,631) ~~9437)~~

| | No teeth n = 234 | 1-9 teeth n = 290 | 10-19 teeth n = 719 | 20+ teeth n = 4,388 | Number 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 | 20 ( 8.5%) | 38 (13.1%) | 83 (11.5%) | 490 (11.2%) | 22.4 (7.2) |
| East of England | 18 ( 7.7%) | 36 (12.4%) | 100 (13.9%) | 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 fluoridated water [bc] | 0.328 (0.748) | 0.260 (0.652) | 0.381 (0.862) | 0.401 (0.925) | - |

| | ~~No teeth (n = 955)~~ | | ~~1-9 teeth (n = 779)~~ | | ~~10-19 teeth (n = 1,566)~~ | | ~~20+ teeth (n = 6,137)~~ | | ~~Number of teeth[a]~~ | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ~~n~~ | ~~%~~ | ~~n~~ | ~~%~~ | ~~n~~ | ~~%~~ | ~~n~~ | ~~%~~ | ~~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 | | | | | | | | | | |
| - 1923–1934 | 384 | 40.2% | 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) |
| - 1940–1944 | 141 | 14.8% | 132 | 16.9% | 268 | 17.1% | 794 | 12.9% | 18.9 | (9.5) |
| - 1945–1949 | 120 | 12.6% | 128 | 16.4% | 286 | 18.3% | 1 271 | 20.7% | 21.0 | (8.5) |
| - 1950–1954 | 76 | 8.0% | 88 | 11.3% | 243 | 15.5% | 1 398 | 22.8% | 22.3 | (7.4) |
| - 1955–1965 | 38 | 4.0% | 74 | 9.5% | 190 | 12.1% | 1 719 | 28.0% | 23.7 | (6.0) |
| Sex | | | | | | | | | | |
| - Men | 363 | 38.0% | 407 | 52.2% | 725 | 46.3% | 2 727 | 44.4% | 19.8 | (9.2) |
| - Women | 592 | 62.0% | 372 | 47.8% | 841 | 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% | 624 | 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 fluoridated water [bc] | 0.165 | (0.443) | 0.157 | (0.447) | 0.223 | (0.624) | 0.307 | (0.803) | — | — |

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)~~9437)~~

| — | ~~Coef.~~ | ~~95% CI~~ | ~~F-statistic~~ |
|---|---|---|---|
| ~~OLS estimation~~ | | | |
| ~~Number of remaining teeth [a]~~ | ~~−0.006~~ | ~~−0.007, −0.006~~ | |
| ~~2SLS estimation~~ | | | |
| ~~Second-stage regression~~ | | | |
| ~~Number of remaining teeth [a]~~ | ~~−0.019~~ | ~~−0.035, −0.004~~ | |
| ~~First-stage regression~~ | | | |
| ~~Extent of being exposed to fluoridated water [b]~~ | ~~1.076~~ | ~~0.700, 1.452~~ | ~~31.487~~ |
| ~~Reduced-form estimation~~ | | | |
| ~~Extent of being exposed to fluoridated water [b]~~ | ~~−0.021~~ | ~~−0.037, −0.005~~ | |

| | 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) | - |

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 ≥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

~~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.**~~**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 S4**~~**A.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, IADL (N = 5,631)—

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