Target Trial Emulation for Causal Inference Using Targeted Maximum Likelihood Estimation: An Application to Chronic Oral Diseases and Incident Dementia in the UK Biobank

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Abstract

Chronic, inflammatory oral diseases have increasingly been suggested as a potential modifiable risk factor for dementia, yet causal relationships remain unclear. Prior literature has relied heavily on traditional case control and proportional hazards models that inadequately control for time-varying confounders. In this paper, we employ Longitudinal Targeted Maximum Likelihood Estimation (LTMLE), a modern causal inference method which yields more robust estimates under time-varying confounding than traditional methods. Additionally, we leverage a target trial (TTE) framework to explicitly define potential outcomes under a wider range of treatment histories than has been considered previously. Using data from the UK Biobank, including $161,061$ participants aged ≥ 60, we estimate the causal effect of oral disease exposure timing on the 25-year incident dementia risk. Using LTMLE to control for demographic, behavioral, and comorbidity covariates, we find that those exposed at baseline, 5 years, and 10 years into the study demonstrate a consistent 20 - 22% increased 25-year risk of dementia compared to those not exposed (RRs: 1.20 - 1.22; 95% CIs 1.00 - 1.47). Overall, our findings are consistent with a causal relationship between long-term oral disease exposure and elevated dementia risk, underscoring the importance of early oral intervention and further research into oral disease-modifying treatment.

1 Introduction

Dementia remains a leading cause of disability among older adults, affecting an estimated 57 million individuals worldwide and ranking as the seventh leading cause of death worldwide (World Health Organization, 2025). Despite extensive research, effective disease-modifying treatments remain limited. As such, in recent years, public health emphasis has shifted towards prevention and risk reduction throughout the life course.

Chronic, inflammatory oral diseases have increasingly been suggested as a potential modifiable risk factor for dementia (Tonsekar et al., 2017). Conditions such as dental caries, periodontal disease, and other inflammatory diseases affect over 3.5 billion people worldwide, disproportionately burdening older adults and socioeconomically disadvantaged populations (Jain et al., 2024; Wu et al., 2025). Nonetheless, oral diseases are highly modifiable through preventative dental care and oral hygiene practices, making them a potential target for dementia risk reduction.

Several biological mechanisms have been proposed linking chronic oral diseases and dementia. One such mechanism proposes that inflammatory oral infections contribute to systemic inflammation, characterized by elevated pro-inflammatory cytokines and immune activation, which in turn may promote neuroinflammation and downstream neurodegeneration (Villar et al., 2024; Loughman et al., 2023). Other mechanisms have been proposed involving the direct microbial invasion of oral pathogens, most notably Porphyromonas gingivalis, into the brain (Villar et al., 2024; Dominy et al., 2019).

Due to the lack of ethical randomized controlled trials that can be performed, the question of causality has largely been approached through observational epidemiological research (Hernán and Robins, 2016). However, results thus far have largely been inconclusive. Overall, authors have repeatedly cited high-dimensional, time-varying residual confounding and reverse causality as two major biases in causal estimation (Asher et al., 2022; Agarwal et al., 2024).

In early studies, estimates have varied widely, with some reporting positive associations, and others reporting null or conditional effects. A retrospective cohort study in California, for example, identified positive associations between tooth count and decreased dementia risk in men, but not women (Paganini-Hill et al., 2012), while another cohort study in France identified associations in lower educated subjects but not higher educated subjects (Arrivé et al., 2012). Another cross-sectional study in Finland reported associations between tooth loss and decreased mental recall scores, but not verbal fluency (Asher et al., 2021).

While in recent years result heterogeneity across studies has subsided, an overwhelming reliance on proportional hazards models and case-control designs has emerged. Among numerous studies which reported positive associations in longitudinal cohort studies across the United States (Demmer et al., 2020; Beydoun et al., 2024), the United Kingdom (Zhang et al., 2023), Germany (Laugisch et al.), Korea (Yoo et al., 2023; Kim et al., 2020), and Taiwan (Lee et al., 2017; Cardoso et al., 2019) all employed either a proportional hazards model or a case-control design as their primary form of analysis.

While these methods are well established and accessible, they present major limitations for causal inference in longitudinal settings. Foremost is their inadequate handling of temporal relationships: Numerous comorbidities including diabetes, cardiovascular disease, autoimmune conditions, and metabolic conditions have been implicated to influence both chronic oral disease and dementia prevalence through strict timing-dependent relationships (Holmstrup et al., 2017; Cao et al., 2024). Without modification, traditional case-control designs and regression-based approaches rely on time-static covariates which are ineffective at accounting for exposure-confounder feedback (Daniel et al., 2013; Clare et al., 2019). Likewise, proportional hazards models assume the proportional hazards assumption for correct model specification, an assumption that is rarely plausible in high-dimensional, long-term settings with complex temporal relationships (Stensrud and Hernán, 2025). As such, meta analyses have noted a substantial need for more robust causal

methodology in the oral disease and dementia setting (Asher et al., 2022).

In this paper, we address the gaps in the literature by employing Longitudinal Targeted Maximum Likelihood Estimation (LTMLE), a modern causal inference framework which controls for time-varying confounding under high-dimensional settings (Schuler and Rose, 2017). LTMLE offers a doubly-robust approach, combining the outcome model established by G-computation with a treatment model to yield a counterfactual estimator which is unbiased if either the treatment or the outcome model is specified correctly. Our usage of LTMLE provides causal estimates which are more robust to time-varying confounding than the prior literature. Further, we also leverage the target trial (TTE) framework proposed by Hernan and Robins to explicitly define potential outcomes under a wider range of treatment histories than has previously been considered (Hernán and Robins, 2016). While traditional studies have estimated time-static odds ratios (OR) or instantaneous hazard ratios (HR), we provide the estimation of well-defined counterfactual risks under oral health exposure regimes, allowing our study to more closely replicate a randomized controlled trial.

Overall, our study leverages a target trial framework and LTMLE to estimate the causal effect of oral disease exposure timing on the 25-year incident dementia risk in the UK Biobank.

2 Methods

2.1 Study Population and Inclusion Criteria

Study data was obtained from the UK Biobank, a prospective biomedical database comprising half a million participants aged 40-69 (Sudlow et al., 2015). Participants were recruited from 2006 to 2010 and reported baseline assessments including demographics, physical measurements, and medical histories. All participants were subsequently followed through online questionnaires and linkage to electronic medical records. To ensure the study population represents those at risk of dementia and oral infection, only subjects aged 60 or older were included and subjects who were diagnosed with dementia or oral disease at least 5 years prior to baseline were excluded. Further, to ensure the validity of our data, subjects missing any covariate information were excluded. After exclusion, our study population comprised a total of $N = 161061$ subjects.

2.2 Data Structure and Censoring

In order to ensure a sufficient number of captured exposure events during follow-up, we aligned the study time origin to five years prior to the UK Biobank assessment date. Exposure, outcome, and time-varying comorbidities obtained through medical histories during this 5-year pre-assessment period were incorporated into the longitudinal data and were treated as occurring after the augmented index date. Baseline covariates, however, were measured at the original UK Biobank assessment date and were used as a proxy for time-static covariates at the index date.

From the study index date, participants were followed-up until either 1) dropout of electronic follow-up, 2) death, or 3) administrative censoring on January 1st, 2026. We discretize the time

axis into 5 intervals of 5 years each, originating from the index date. The maximum follow-up of 25 years reflects the maximum observed difference between a participant's index date and their censoring date. A visualization of the study's timeline is presented in Figure 1.

We denote time with $t \in \{0, 1, \ldots, 4\}$, where $t = 0$ corresponds to events observed within the first 5 years following the index date and each subsequent t represents a 5-year interval thereafter.

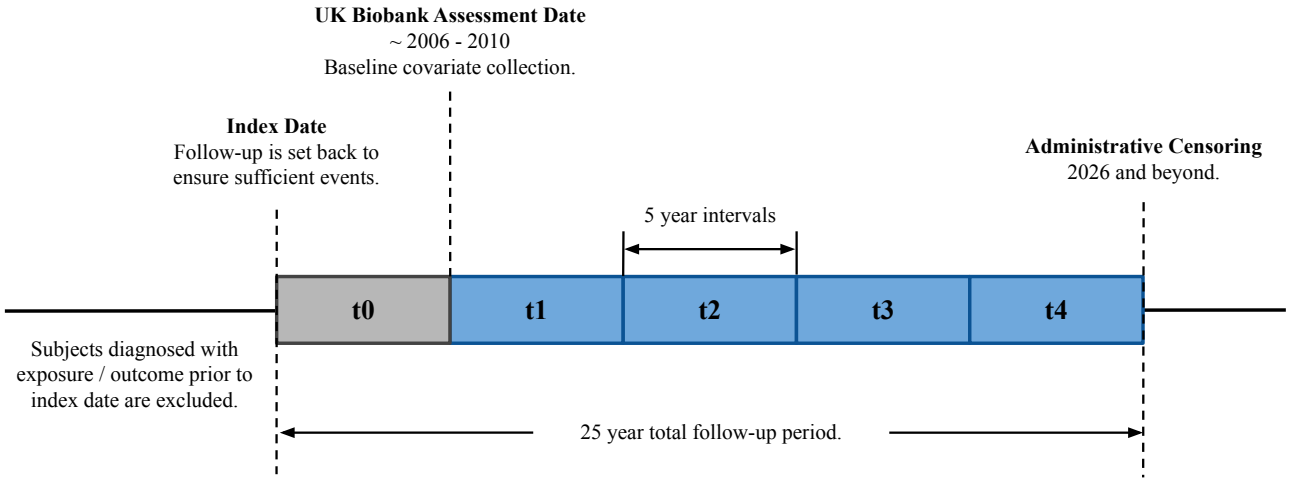

Figure 1: Study timeline

2.3 Assessment Definitions

Oral disease exposure was identified from electronically linked ICD-10 codes, recorded as the date of first diagnosis. Primary exposure records included K02 (dental caries), K03 (diseases of hard tissues of teeth), K04 (diseases of pulp and periapical tissues), K05 (gingivitis and periodontal diseases), K12 (stomatitis and related lesions), and K13 (diseases of lip and oral mucosa). Exposure was defined as a binary, time-varying indicator $A_t, t \in \{0, 1 \ldots, 4\}$, where $A_t = 1$ indicates a diagnosis occurring at or before time t, and $A_t = 0$ indicates no prior diagnosis at or before time t.

Dementia outcomes were obtained using dementia ICD-10 codes F00 (dementia in Alzheimer's disease), F01 (Vascular dementia), F02 (Dementia in other diseases classified elsewhere), and F03 (unspecified dementia). Dementia was similarly defined as a binary indicator $Y_t, t \in \{0, 1 \ldots, 4\}$, where $Y_t = 1$ indicates a prior or current diagnosis.

2.4 Covariates

Baseline covariates included sex, household income, body mass index, disability status, physical activity level, alcohol intake level, and smoking status. We denote baseline covariates with W.

As time-varying covariates, we included comorbid conditions identified from ICD-10 records including diabetes, hypertension, cardiovascular disease, obesity, renal failure, rheumatoid arthri-

tis, and chronic obstructive pulmonary disease. In addition to comorbid conditions, we included age as a time-varying covariate. We again denote time-varying covariates with binary indicators $L_t, t \in \{0, 1 \ldots, 4\}$.

2.5 Censoring and Observed Data Structure

Participants were censored at time t if they 1) dropped out of electronic follow-up, 2) died, or 3) reached the administrative censoring date of January 1st, 2026. We denote censoring with a binary indicator $C_t, t \in \{0, 1 \ldots, 4\}$.

Thus, the observed data for each participant is given by N independent and identically distributed observations

$$O = (W, L_0, A_0, Y_0, C_0, ..., L_4, A_4, Y_4, C_4).$$

2.6 Target Trial Emulation

We emulate a target trial to estimate the causal effect of oral disease exposure timing on the 25-year risk of incident dementia. In particular, we consider the following set of counterfactual exposure sequences $\bar{a} = (A_0, \ldots, A_4)$.

$$\begin{aligned}
\text{Disease at Baseline (Early Exposure):} \quad & \bar{a}^{(0)} = (1, 1, 1, 1, 1), \\
\text{Disease at Year 5 (Early/Mid Exposure):} \quad & \bar{a}^{(1)} = (0, 1, 1, 1, 1), \\
\text{Disease at Year 10 (Mid Exposure):} \quad & \bar{a}^{(2)} = (0, 0, 1, 1, 1), \\
\text{Disease at Year 15 (Mid/Late Exposure):} \quad & \bar{a}^{(3)} = (0, 0, 0, 1, 1), \\
\text{Disease at Year 20 (Late Exposure):} \quad & \bar{a}^{(4)} = (0, 0, 0, 0, 1), \\
\text{No Disease (No Exposure):} \quad & \bar{a}^{(5)} = (0, 0, 0, 0, 0).
\end{aligned}$$

Under each exposure regime $\bar{a}$, we estimate $Y(\bar{a})$, the counterfactual outcome that would have been observed under $\bar{a}$. Using Longitudinal Targeted Maximum Likelihood Estimation, we estimate the mean counterfactual outcome probability

$$\Psi(P) = \mathbb{E}[Y(\bar{a})].$$

Further, given two counterfactual regimes $\bar{a}$ and $\bar{a}'$, we derive the average treatment effect (ATE), and the risk ratio (RR).

$$\text{ATE} = \mathbb{E}[Y(\bar{a})] - \mathbb{E}[Y(\bar{a}')], \quad \text{RR} = \frac{\mathbb{E}[Y(\bar{a})]}{\mathbb{E}[Y(\bar{a}')]}.$$

2.7 Longitudinal Targeted Maximum Likelihood Estimation

Briefly, Longitudinal Targeted Maximum Likelihood Estimation is an emerging causal inference method which extends the traditional g-computation result in order to establish a more efficient, targeted outcome model. Given a correctly specified outcome model $Q_t(W, \bar{L}_t, \bar{A}_t, \bar{Y}_{t-1}) = \mathbb{E}[Y_t \mid W, \bar{L}_t, \bar{A}_t, \bar{Y}_{t-1}]$, we can estimate the mean counterfactual outcome over the population with the

g-computation result,

$$\hat{\Psi}_{\text{G-comp}} = \frac{1}{N}\sum_{i=1}^{N} \hat{Q}_0\Big(W, \bar{L}_0, \bar{A}_0 = \bar{a}_0\Big).$$

where $\hat{Q}_0$ is defined recursively from

$$\hat{Q}_t\Big(W, \bar{L}_t, \bar{A}_t\Big) = \mathbb{E}[\hat{Q}_{t+1}(W, \bar{L}_{t+1}, \bar{A}_{t+1}) \mid \bar{L}_t, \bar{A}_t]$$

with $\hat{Q}_T = Y_T$. The targeting step of LTMLE identifies a targeted outcome model $\hat{Q}_t^*$ by updating $\hat{Q}_t$,

$$\text{logit}(\hat{Q}_t^*) = \text{logit}(\hat{Q}_t) + \epsilon H_t$$

where H_t is derived from the treatment model

$$g_t(a_t \mid W, \bar{L}_t, \bar{A}_{t-1}, \bar{Y}_{t-1}) = P(A_t = a_t \mid W, \bar{L}_t, \bar{A}_{t-1}, \bar{Y}_{t-1})$$

and

$$H_t = \frac{\mathbb{I}(\bar{A}_t = \bar{a}_t)}{\prod_{s=0}^{t} \hat{g}_s(A_s \mid W, \bar{L}_s, \bar{A}_{s-1}, \bar{Y}_{s-1})}.$$

The targeted outcome model $\hat{Q}_t^*$ is then selected to solve the estimating equation,

$$\frac{1}{N}\sum_{i=1}^{N} H_t(O_i)(Y_i - \hat{Q}_t^*(O_i)) = 0$$

which guarantees that $\hat{Q}_t^*$ is consistent and asymptotically efficient. Finally, the mean counterfactual outcome can be derived using the plug-in estimator from g-computation.

$$\Psi_{\text{LTMLE}} = \frac{1}{N}\sum_{i=1}^{N} \hat{Q}_0^*\Big(W, \bar{L}_0, \bar{A}_0 = \bar{a}_0\Big).$$

2.8 Implementation

We used Longitudinal Targeted Maximum Estimation to estimate the causal effect of oral disease exposure timing on the 25-year incident dementia risk. For computational scalability, we specified logistic regressions for both the outcome regression and treatment mechanism, rather than more computationally intensive flexible learner algorithms. To stabilize our estimates to extreme treatment probabilities, we set a fixed truncation bound at 0.01. 95% confidence intervals were derived from variance estimates of the efficient influence function.

We first provided empirical diagnostics to assess support for each counterfactual exposure regime as estimated through the treatment mechanism. Formally, we require that

$$g(A_t = a_t \mid W = w, \bar{L}_t = \bar{\ell}_t, \bar{A}_{t-1} = \bar{a}_{t-1}, \bar{Y}_t = \bar{y}_t) > 0$$

for all observed $w, \bar{\ell}_t, \bar{a}_{t-1}, \bar{y}_{t-1}$. Following established practices, we set $\delta = 0.01$ as the threshold for adequate support. Exposure regimes with a significant portion of cumulative treatment

probabilities below δ were considered unsupported and were interpreted with caution.

We then employed LTMLE to estimate mean counterfactual outcome probabilities across all supported exposure regimes. For comparison, we contrasted LTMLE estimates with naive estimates based on the unadjusted proportion of outcome events among individuals who followed each regime. We additionally provided causal contrasts between exposure regimes, including average treatment effects (ATE) and risk ratios (RR). Finally, we conducted sensitivity analyses to evaluate robustness to variations to truncation bounds and time discretization procedures. All statistical analyses were implemented using the ltmle package in R (version 4.4.0).

3 Results

3.1 Study Population and Descriptive Statistics

A descriptive summary of baseline covariates, stratified by incident dementia is presented in Table 1. A summary of the cumulative number of observed censor, exposure, outcome, and comorbid events over time is presented in Table 2. Over the 25-year study period, a total of 6221 participants were diagnosed with dementia and 8439 participants were diagnosed with oral disease.

Overall, participants who were diagnosed with dementia were older at recruitment (mean 65.56 [2.73] vs 63.98 [2.82]) and more likely to be male (57.2% vs 50.8%). Additionally, participants diagnosed with dementia were generally lower income (44.8% vs 32.4% income <£18000), more likely to report disability (13.7% vs 6.2%), and had poorer smoking habits (9.3% vs 8.0% baseline smokers) compared to healthy participants. Baseline BMI was similar across groups while alcohol intake levels were higher among health participants.

Across the 25-year follow-up period, a total of 26407 participants were censored. Among the included comorbid conditions, hypertension (86953 diagnoses), renal failure (24616) and diabetes (20880) were most prevalent.

Baseline Characteristics Stratified by Incident Dementia

Variable	Level	No Incident Dementia (N = 155380)	Incident Dementia (N = 6221)
Age at Recruitment (years), Mean (SD)		63.98 (2.82)	65.56 (2.73)
Sex, n (%)	Female	76402 (49.2%)	2660 (42.8%)
	Male	78978 (50.8%)	3561 (57.2%)
Household Income (£), n (%)	Less than 18,000	50322 (32.4%)	2784 (44.8%)
	18,000 to 30,999	51112 (32.9%)	2033 (32.7%)
	31,000 to 51,999	33582 (21.6%)	970 (15.6%)
	Greater than 52,000	20364 (13.1%)	434 (7.0%)
Body Mass Index, Mean (SD)		27.51 (4.46)	27.66 (4.65)
Disability Status, n (%)	YES	9654 (6.2%)	852 (13.7%)
	NO	145726 (93.8%)	5369 (86.3%)
Physical Activity (days/week), n (%)	0	17528 (11.3%)	832 (13.4%)
	1-2	32292 (20.8%)	1138 (18.3%)
	3-4	40972 (26.4%)	1534 (24.7%)
	5+	64588 (41.6%)	2717 (43.7%)
Alcohol Intake, n (%)	Never	43769 (28.2%)	2129 (34.2%)
	Occasionally	36448 (23.5%)	1412 (22.7%)
	Three or four times a week	35898 (23.1%)	1264 (20.3%)
	Daily	39265 (25.3%)	1416 (22.8%)
Smoking Status, n (%)	Never	76855 (49.5%)	2775 (44.6%)
	Previous	66060 (42.5%)	2866 (46.1%)
	Current	12465 (8.0%)	580 (9.3%)

Table 1: Baseline characteristics stratified by incident dementia.

Cumulative Number of Subjects with Observed Event within n Years of Baseline

Years	Censored	Oral Infection	Dementia	Diabetes	Hypertension	CVD	Obesity	RF	RA	COPD
5	0	2354	84	11155	59197	9037	4655	3557	2517	3973
10	0	5142	525	13696	67793	11206	8308	7840	3155	5985
15	4390	7404	2509	17793	78913	13834	13685	15957	4330	9936
20	12599	8435	6000	20840	86882	16421	17746	24517	5160	13134
25	26407	8439	6221	20880	86953	16540	17759	24616	5165	13175

Abbreviations: CVD = Cardiovascular Disease; RA = Rheumatoid Arthritis; RF = Renal Failure; COPD = Chronic Obstructive Pulmonary Disease.

Table 2: Cumulative number of subjects with observed event within n years of baseline.

3.2 Assessing Support Across Exposure Regimes

To evaluate the support for each counterfactual exposure regime in our data, we examined the distribution of cumulative treatment probabilities estimated by the exposure mechanism $g_t(a_t \mid W, \bar{L}_t, \bar{A}_{t-1}, \bar{Y}_{t-1})$ across all observed covariate patterns (see Figure 2). Following the established literature, we set $\delta = 0.01$ as the threshold for adequate support.

Overall, the counterfactual regimes corresponding to disease at year 15 and disease at year 20 exhibited limited support, with a significant portion of cumulative treatment probabilities below the established threshold $\delta = 0.01$. To preserve the reliability of our results, we interpreted estimates on these regimes with caution, and excluded them from future analyses. The remaining counterfactual regimes corresponding to disease at baseline, disease at year 5, disease at year 10, and no disease were consistently supported, with a majority of cumulative treatment probabilities above $\delta = 0.01$. As such, we confidently included these regimes in our remaining analyses.

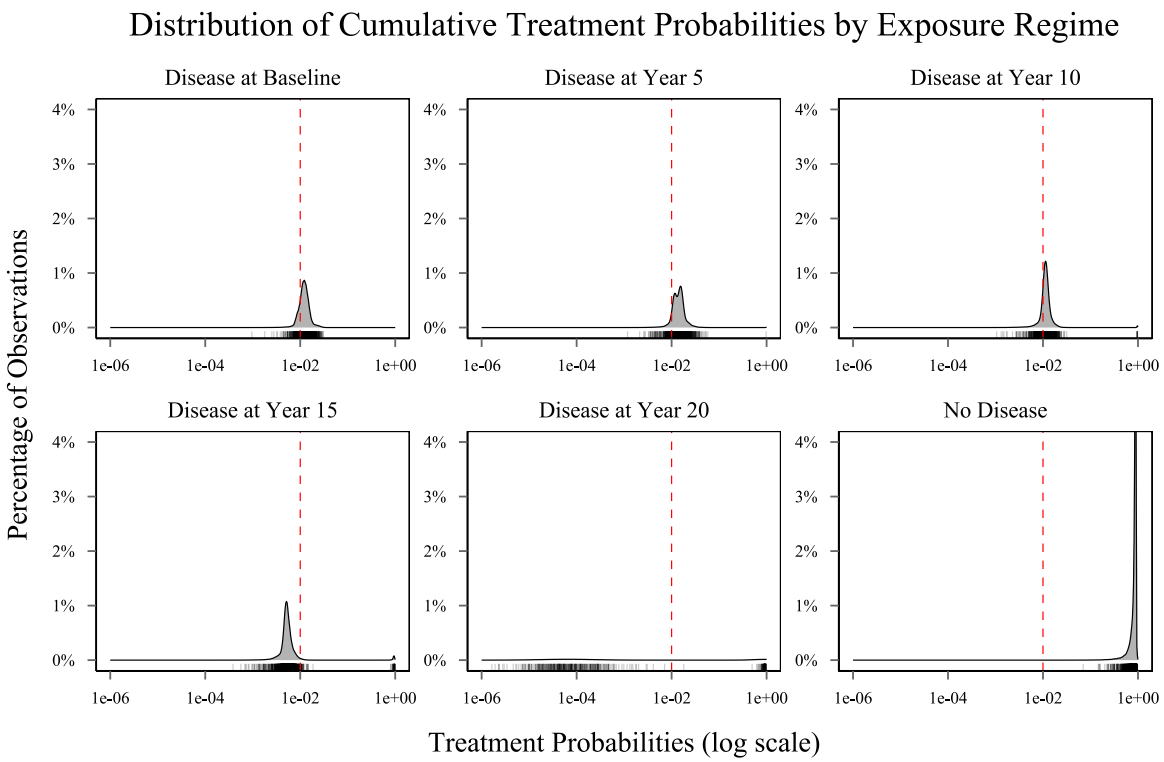

Figure 2: Distribution of cumulative treatment probabilities by exposure regime.

3.3 LTMLE Results

Using Longitudinal Targeted Maximum Likelihood Estimation, we estimated the 25-year counterfactual dementia risk under each supported exposure regime (see Figure 3). We further compared the LTMLE estimates with naive estimates based on the simple proportion of outcome events among those who followed each regime. Under the no disease counterfactual regime, the estimated 25-year dementia risk was 4.14% (95% CI: 4.04% - 4.25%). However, under regimes corresponding to oral disease exposure earlier in follow-up (disease at baseline, disease at year 5, and disease at year 10), the estimated dementia risks were consistently higher. Both the point estimates and confidence intervals remained consistent within early exposure regimes, while the confidence interval around the no disease estimate was significantly tighter. Likewise, point estimates within early exposure regimes remained consistent with unadjusted estimates, while the no disease point estimate was modestly higher than the unadjusted estimate.

Table 3 contrasts the LTMLE estimates for counterfactual regimes corresponding with early exposure regimes with the no disease regime. Overall, earlier exposure timing corresponded to an approximate 0.8% to 0.9% absolute increase in the 25-year dementia risk relative to the no disease regime. These absolute risk difference estimates, however, were not statistically significant and should be interpreted with caution. Risk ratio estimates comparing early exposure regimes with no disease regimes, however, were statistically significant. Overall, risk ratios ranged from approximately 1.20 to 1.22, indicating a 20 - 22% relative increase in dementia associated with early oral disease exposure beginning at baseline, year 5, or year 10.

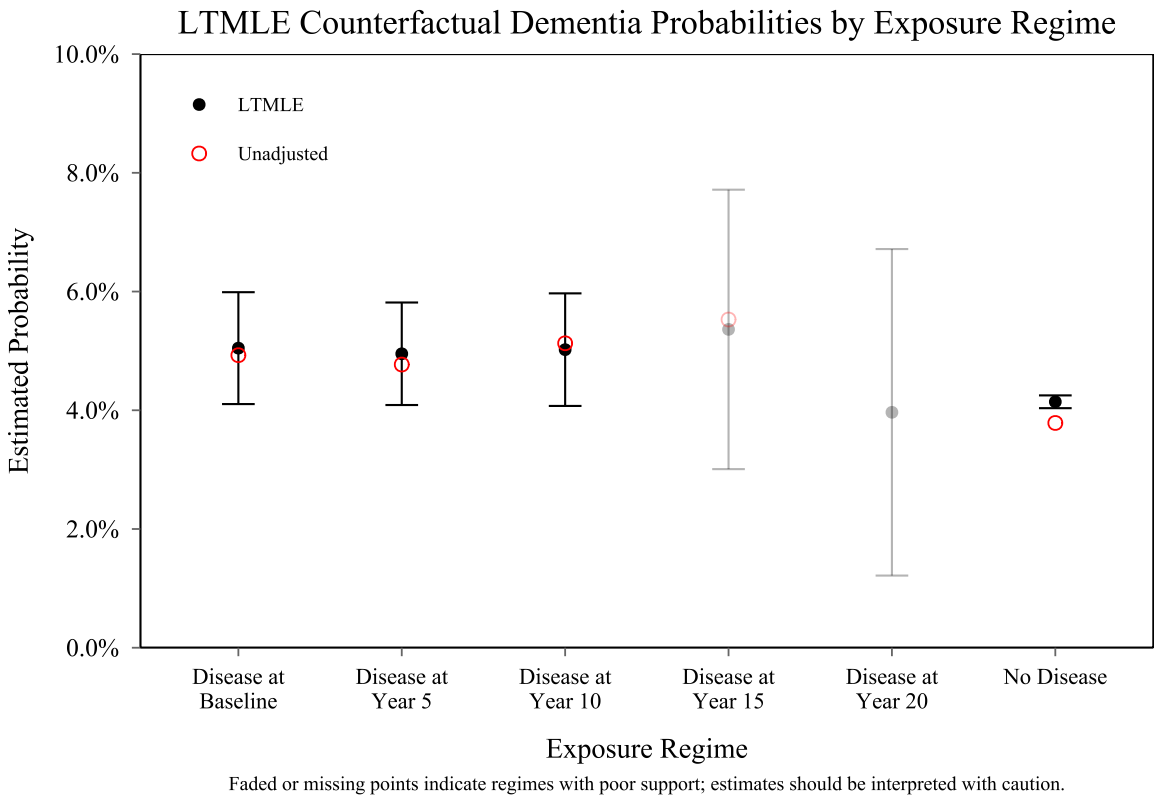

Figure 3: LTMLE counterfactual dementia probabilities by exposure regime.

Comparison of 25-year Dementia Probabilities across Supported Exposure Regimes

Contrast (Regime A vs B)	Risk under A (%)	Risk under B (%)	Risk Difference (%)	Risk Ratio
Disease at Baseline vs No Disease	5.05% (4.10%, 5.99%)	4.14% (4.04%, 4.25%)	0.90% (-0.04%, 1.85%)	1.218 (1.009, 1.471)
Disease at Year 5 vs No Disease	4.95% (4.09%, 5.82%)	4.14% (4.04%, 4.25%)	0.81% (-0.06%, 1.68%)	1.195 (1.002, 1.426)
Disease at Year 10 vs No Disease	5.02% (4.07%, 5.97%)	4.14% (4.04%, 4.25%)	0.88% (-0.08%, 1.83%)	1.212 (1.002, 1.466)

95% Confidence intervals in parentheses. Exposure regimes with poor support were excluded.

Table 3: Comparison of 25-year dementia probabilities across supported exposure regimes.

3.4 Sensitivity Analyses

To assess the robustness of our results to positivity-related instability, we repeated the LTMLE analyses under varying truncation bounds on the treatment mechanism $g_t(a_t \mid W, \bar{L}_t, \bar{A}_{t-1}, \bar{Y}_{t-1})$ (see Table 4). While the estimated risk under the no disease regime remained consistent across all truncation bounds, the estimated risk under the disease at baseline regime decreased modestly as truncation increased. Likewise, stronger truncation bounds resulted in lower risk ratios and risk differences and wider confidence intervals, consistent with the bias-variance trade-off that is observed in prior literature.

We further evaluated the robustness of our results to the choice of time discretization procedure by repeating LTMLE analyses under varying interval sizes (see Table 5). Overall, point estimates remained consistent across 4, 5, and 6 year intervals, with confidence intervals slightly widening as the interval size decreased. By contrast, the 3-year interval procedure demonstrated a modestly higher risk ratio and risk difference, and produced substantially wider confidence intervals. Generally, our results are consistent with the expected increase in model instability which results from the decreased sample size per interval.

LTMLE Estimates by Truncation Bound Used

Truncation Bound	Percent Truncated (%)	Disease at Baseline Risk (%)	No Disease Risk (%)	Risk Difference (%)	Risk Ratio
0.008	0%	5.04% (4.11 – 5.97)	4.14% (4.04 – 4.25)	0.90% (-0.04 – 1.83)	1.22 (1.01 – 1.47)
0.010	7%	5.05% (4.10 – 5.99)	4.14% (4.04 – 4.25)	0.90% (-0.04 – 1.85)	1.22 (1.01 – 1.47)
0.012	25%	5.03% (4.02 – 6.03)	4.14% (4.04 – 4.25)	0.88% (-0.13 – 1.89)	1.21 (0.99 – 1.48)
0.014	53%	4.98% (3.87 – 6.09)	4.14% (4.04 – 4.25)	0.84% (-0.27 – 1.95)	1.20 (0.96 – 1.50)

95% Confidence intervals in parentheses

Table 4: LTMLE estimates by truncation bound used.

LTMLE Estimates by Time Discretization Procedure Used

Interval Size (Years)	Number of Intervals	Disease at Baseline Risk (%)	No Disease Risk (%)	Risk Difference (%)	Risk Ratio
3	8	5.50% (2.55 – 8.45)	4.21% (4.10 – 4.33)	1.29% (-1.66 – 4.23)	1.30 (0.76 – 2.23)
4	6	5.10% (3.91 – 6.29)	4.18% (4.07 – 4.29)	0.91% (-0.28 – 2.11)	1.22 (0.96 – 1.54)
5	5	5.05% (4.10 – 5.99)	4.14% (4.04 – 4.25)	0.90% (-0.04 – 1.85)	1.22 (1.01 – 1.47)
6	4	4.97% (4.15 – 5.80)	4.12% (4.01 – 4.22)	0.86% (0.03 – 1.68)	1.21 (1.02 – 1.43)

95% Confidence intervals in parentheses

Table 5: LTMLE estimates by time discretization procedure used.

4 Discussion

In this study, we employed a modern Target Trial Emulation approach using Targeted Maximum Likelihood Estimation to estimate the causal effect of oral disease exposure timing on the 25-year incident dementia risk. After controlling for time-varying confounding, we found that those exposed at baseline, 5 years, and 10 years into the study demonstrated a consistent 20 - 22% increased 25-year risk of dementia compared to those not exposed (RRs: 1.20 - 1.22; 95% CIs 1.00 - 1.47). Overall, our findings provide evidence supporting a modest causal effect between long-term oral disease and elevated dementia risk. Moreover, the consistency of effect sizes across early exposure regimes suggests that cumulative disease burden over the first 10 years of follow-up may be a more relevant factor to long-term dementia risk than the precise timing of disease onset. Collectively, these results are consistent with much of the established literature reporting positive associations (Asher et al., 2022).

Before interpreting our results further, several limitations should be noted. Although our effect estimates were positive in direction, our confidence intervals remained borderline significant. We addressed this, in part, through sensitivity analyses on truncation bounds and time discretization procedures, demonstrating that the direction and magnitude of effect estimates remained stable despite changes to varying modeling specifications.

Further, in order to obtain more complete data, we aligned the study index time to five years prior to the UK Biobank assessment date, and used baseline covariates measured at assessment as a proxy for time-static covariates at the index time. It is plausible that covariates may change during this pre-assessment interval, possibly introducing non-differential measurement error. Moreover, oral disease exposure, dementia outcome, and comorbid conditions were defined using electronically linked ICD-10 codes. Therefore, while our definitions were likely to identify severe cases, it is possible that more moderate or subclinical conditions were misclassified. If non-differential, this misclassification would likely bias our results to the null, but the possibility of differential misclassification due to behavior or healthcare utilization cannot be excluded.

In addition, we treated death as a censoring event rather than as a competing risk. However, in older populations especially, death may preclude dementia diagnosis, potentially leading to bias if the risk of death is not modeled alongside dementia risk. Further, due to computational constraints working within the UK Biobank Research Analysis Program, we specified both the outcome and treatment mechanisms using logistic regressions. More complex flexible learner algorithms such as random forest, gradient boosting, and neural networks may have reduced the risk of model misspecification. Moreover, the UK Biobank cohort has been established to exhibit volunteer bias, with participants who are generally healthier than the broader population. As such, selection bias may limit the generalizability of our results to more disadvantaged populations. Finally, despite extensive adjustment of demographic, behavioral, and comorbidity covariates, it is plausible that residual confounding may still exist through alternate pathways. For example, dietary patterns, oral hygiene behavior, and genetic covariates were not adjusted for and may confound our results.

Nonetheless, our study has notable strengths. Firstly, our use of the UK Biobank cohort enabled the inclusion of over 150,000 participants with up to 25 years of follow-up, allowing us to provide a more statistically rigorous analysis than many prior studies limited by smaller samples and shorter follow-up durations. Moreover, we leveraged a novel target trial framework, allowing us to define potential outcomes under a wider range of treatment histories than has been previously considered. While most prior studies estimated either odds ratios comparing exposed and unexposed populations or instantaneous hazards ratios under a proportional hazards assumption, we estimated the counterfactual 25-year dementia risks under explicit 5-year consecutive exposure regimes. This approach enabled us to evaluate the effect of varying exposure timings rather than the effect of a single binary exposure classification.

In addition, we leveraged Longitudinal Targeted Maximum Likelihood Estimation to estimate population-level counterfactual risks which are robust to time-varying confounding and model misspecification than traditional methods. Compared to traditional case control designs and proportional hazards models employed in prior studies, LTMLE enabled a semi-parametric approach better suited to high-dimensional, longitudinal settings. Moreover, by modeling comorbid conditions as time-varying covariates, we were better able to adjust for exposure-confounder feedback and the temporal ordering of disease processes than would have been possible with conventional analyses.

To the best of our knowledge, this study is among the first to apply LTMLE to analyze oral disease and dementia. Thus, our study serves not only to analyze causal effect within a specific research scope, but to also highlight the feasibility of applying LTMLE to clinical data and encourage its broader adoption in epidemiologic research.

In summary, our findings provide evidence consistent with a modest causal relationship between long-term oral disease exposure and incident dementia. Our results underscore the importance of early oral disease prevention and treatment as a preventative measure which individuals may take to minimize the risk of dementia.

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