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Article

Interpreting Robustness in Observational Real-World Evidence: Hydrochlorothiazide and Reported Nonmelanoma Skin Cancer History as an Empirical Case

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Abstract: Background: We used the association between hydrochlorothiazide (HCTZ) and nonmelanoma skin cancer (NMSC) to examine how adjustment, comparator choice, and assumptions about bias affect the interpretation of observational real-world evidence. Methods: We analyzed pooled pre-pandemic National Health and Nutrition Examination Survey data from 2009 through March 2020. Survey-weighted models estimated the cross-sectional prevalence-odds association between current/recent HCTZ use, defined from the past-30-day prescription medication inventory, and reported NMSC history. We adjusted for measured covariates, varied the adjustment set, compared HCTZ-only with angiotensin-converting enzyme inhibitor (ACEI)-only current users, and added a general healthcare-access measure. Differential outcome-ascertainment quantitative bias analysis (QBA) used the primary adjusted model. A separate post-hoc analysis examined generic unmeasured confounding of the crude association. Results: Among 30,413 adults, 2,839 were current/recent HCTZ users and 476 reported an NMSC history. The crude positive association was substantially attenuated after measured-covariate adjustment (odds ratio [OR], 1.733; 95% confidence interval [CI], 1.240–2.421 vs OR, 0.976; 95% CI, 0.686–1.389). Estimates were similar when hypertension was omitted (OR, 1.016), when HCTZ-only users were compared with ACEI-only users (OR, 1.053), and when a general healthcare-access measure was added (OR, 0.969). Differential outcome-ascertainment QBA yielded ORs of 0.880–1.038 across valid S1–S4 scenarios. The sensitivity and specificity assumptions were illustrative rather than empirically calibrated for NHANES-reported NMSC; the CIs excluded bias-parameter and measurement-structure uncertainty. Conclusions: The association changed markedly after measured adjustment. Additional analyses gave similar estimates but examined different model choices, populations, and potential biases. Current/recent use could not be shown to precede historical NMSC, so these data cannot answer the cumulative-dose causal safety question addressed by temporally ordered longitudinal studies.

Keywords: real-world evidence; quantitative bias analysis; hydrochlorothiazide; nonmelanoma skin cancer; pharmacoepidemiology; sensitivity analysis

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1. Introduction

Hydrochlorothiazide (HCTZ) is widely used to treat hypertension, making reports of associations with keratinocyte cancer an important pharmacoepidemiologic problem. Observational studies have reported positive associations, often stronger for squamous cell carcinoma than basal cell carcinoma and at higher cumulative exposure [1–4]. Active-comparator cohorts and systematic reviews report associations that vary by cumulative

dose, duration, cancer subtype, population, comparator, and geography [5–9]. Studies using accumulated dispensing histories and incident subtype-specific outcomes address a different question from a recent medication inventory paired with historical aggregate disease.

Observational drug–outcome estimates may be sensitive to design choices, measured and unmeasured confounding, and outcome ascertainment [10–12]. Quantitative bias analysis can assess the consequences of specified assumptions but cannot identify the true bias or establish causality in a noncausal design [11–12].

The National Health and Nutrition Examination Survey (NHANES) links reported prescription medications, health history, and participant characteristics in a nationally representative complex survey. Its past-30-day inventory identifies current/recent HCTZ use rather than cumulative or lifetime exposure, while its cancer questionnaire records reported historical aggregate nonmelanoma skin cancer (NMSC) rather than incident, subtype-specific disease. Current/recent use cannot be shown to precede the reported NMSC history.

Our objective was to estimate the survey-weighted cross-sectional prevalence-odds association between current/recent HCTZ use and reported NMSC history among U.S. adults represented by pooled pre-pandemic NHANES data. We examined how the estimate changed with measured adjustment, alternative model specifications, an HCTZ-only versus ACEI-only current-user comparison, and adjustment for healthcare access. Separate bias analyses examined differential outcome ascertainment and generic unmeasured confounding.

2. Methods

2.1. Study Design and Population

We conducted a cross-sectional analysis of pooled, pre-pandemic National Health and Nutrition Examination Survey (NHANES) data from 2009 through March 2020, comprising four conventional 2-year cycles (2009–2016) and the 2017–March 2020 prepandemic release. NHANES uses a stratified, multistage probability design to represent the noninstitutionalized U.S. population. Questionnaire, examination, and prescription-medication data were linked at the participant level. The pooled source population comprised 55,999 participants; restriction to adults aged at least 20 years yielded 32,498 candidates. The primary complete-case analysis required classifiable exposure and outcome, complete prespecified covariates, and a positive finite survey weight, leaving 30,413 participants (93.58%). Sequential exclusions were unclassifiable NMSC outcome (n=56), missing BMI (n=1,953), missing diabetes status (n=16), missing hypertension status (n=39), and missing smoking status (n=21), totaling 2,085 exclusions (6.42%).

2.2. Exposure, Outcome, Covariates, and Estimand

Current/recent HCTZ use was operationalized from the past-30-day prescription medication inventory. Standardized generic drug names were searched using a case-insensitive whole-ingredient match for hydrochlorothiazide; participants were classified as users when any single-ingredient or combination product matched; the comparator comprised participants with no HCTZ identified in that inventory. Reported history of nonmelanoma skin cancer (NMSC) required a positive cancer-history screen (MCQ220) and code 32 in MCQ230A–D; melanoma (code 25) and skin cancer of unknown kind (code 33) were not classified as NMSC. The outcome was an aggregate historical report and did not distinguish squamous-cell from basal-cell carcinoma.

The prespecified adjustment set comprised continuous age, sex, race/ethnicity, continuous body mass index, reported diabetes (modeled as no diabetes, borderline diabetes, or diabetes), reported hypertension, and smoking status. Smoking status was classified as never (<100 lifetime cigarettes), former (≥100 lifetime cigarettes and not currently smoking), or current (≥100 lifetime cigarettes and currently smoking every day or some days). These harmonized measures addressed major recorded demographic and

clinical differences. Race/ethnicity was treated as a demographic covariate, not as a measure of skin phenotype, ultraviolet exposure, or genetic ancestry. The available covariates were insufficient for causal identification.

The estimand was the survey-weighted cross-sectional prevalence odds ratio for reported NMSC history comparing current/recent HCTZ users with participants with no HCTZ identified in the current/recent inventory. Pairing a past-30-day medication measure with a historical outcome does not establish exposure precedence or cumulative/lifetime HCTZ use; the estimand is neither incident risk nor a causal safety effect.

2.3. Survey Design and Primary Analysis

Examination weights were pooled in proportion to the duration represented by each release. Survey designs specified masked variance strata, primary sampling units, the combined weight, and nesting of sampling units within strata. Four 2-year releases plus the 3.2-year prepandemic release represented 11.2 years, giving study-specific cycle-weight multipliers of 2/11.2 and 3.2/11.2, respectively.

Survey-weighted generalized linear models used a quasibinomial family with logit link. We fitted an unadjusted model containing HCTZ exposure and a primary model containing exposure plus all prespecified covariates. Exponentiated HCTZ coefficients were reported as prevalence odds ratios (ORs). Design-based standard errors and two-sided 95% confidence intervals used the t distribution with model residual survey degrees of freedom (75 for the primary model).

2.4. Sensitivity Analyses

First, we omitted hypertension from the otherwise unchanged primary model, without assigning hypertension a causal role. Second, a restricted current-user comparison contrasted mutually exclusive HCTZ-only users (n=1,712) with angiotensin-converting enzyme inhibitor (ACEI)-only users (n=3,038), with ACEI as the reference. Eleven prespecified exact ACEI generic ingredients were used, dual current users were excluded, and the primary covariate set was retained. This analysis changed both the population and medication contrast; it was not a longitudinal active-comparator new-user design. Third, the primary model was extended with a three-level usual-place-of-care/general healthcare-access proxy (yes, no, or more than one usual place of care) (n=30,410; residual survey df=73), which did not measure dermatologist contact, skin examination, biopsy, or cumulative surveillance. We also compared continuous, categorical (20–39 [reference], 40–59, 60–74, and ≥75 years), and natural-spline (splines::ns(Age, df=3)) age specifications in the primary analytical sample.

The primary adjusted model also anchored a deterministic, fixed-parameter differential outcome-ascertainment QBA based on the standard relationship between latent disease probability and observed outcome probability under sensitivity and specificity assumptions [13–14]: $q_i = (1 - Sp_i) + (Se_i + Sp_i - 1)p_i$, where p_i is latent disease probability and q_i is reported-positive probability. Exposure-group-specific parameters, NHANES-weighted maximum pseudo-likelihood, design-based sandwich covariance, and t(75)-based intervals were study-specific implementation choices.

Prespecified scenarios S0–S4 varied fixed exposure-group-specific outcome-ascertainment assumptions to examine how sensitivity differences affected the estimate. S0 was a nondifferential benchmark; S1–S3 progressively increased assumed sensitivity among HCTZ users, and S4 reversed the sensitivity contrast. The assumed operating characteristics were illustrative/stress-test values rather than empirically calibrated values for NHANES-reported NMSC. Sensitivities derived from assumed high- and low-surveillance mixtures, with specificity held near perfect, provided graded illustrative differential-ascertainment contrasts, not validated operating characteristics for NHANES-reported NMSC. Confidence intervals represented sampling uncertainty conditional on fixed parameters and excluded bias-parameter and measurement-structure uncertainty. Prespecified convergence and parameter-domain checks determined validity. Table 3 reports the fixed parameters and results for S0–S4. The prespecified differential-specificity

stress-test S5 (HCTZ/non-HCTZ Se, 0.7625/0.7250; Sp, 0.995/0.999) failed the dual-start convergence criterion because the second starting point produced singular convergence; no effect estimate was retained and no rescue or reparameterization was applied.

A separate post-hoc generic unmeasured-confounding sensitivity analysis used the crude OR as its analytical anchor. Given the low survey-weighted outcome prevalence, the OR was used as a study-specific rare-outcome approximation to a risk ratio. The E-value applied the risk-ratio-scale formulation of VanderWeele and Ding [15] to provide a single equal-strength association threshold. Rule-out boundaries and a 55-scenario Array used binary-confounder formulations from Schneeweiss [16] to examine hypothetical confounder prevalence and association strength. Rule-out analyses used marginal confounder prevalences of 0.10, 0.25, and 0.50 and a null target of 1. The confounder–outcome RR ranged from 1.01 to 10.00 in increments of 0.01; the corresponding exposure–confounder OR was solved within the strict Fréchet probability bounds, using survey-weighted HCTZ prevalence 0.08044946. The Array varied confounder prevalence among non-HCTZ users (0.10, 0.25, 0.50), its increase among HCTZ users (Δ = 0, 0.10, 0.25, 0.50), and the confounder–reported-NMSC RR (1, 1.5, 2, 3, 5). It divided the crude association by a scenario-specific binary-confounder bias factor and retained only combinations with implied confounder prevalence among HCTZ users no greater than 0.95. The generic factor was hypothetical and was not equated with ultraviolet exposure, skin phenotype/photosusceptibility, surveillance intensity, or measured covariates. The generic unmeasured-confounding sensitivity analysis examined the crude association, whereas the differential outcome-ascertainment QBA used the primary adjusted model. The two analyses addressed different potential sources of bias and were not applied sequentially.

2.5. Missing Data and Reproducibility

The primary analysis used complete cases; multiple imputation was not performed. A feasibility assessment identified at most 520 additional participants (1.68% of a survey-eligible, exposure/outcome-defined frame of 30,933) as potentially recoverable through covariate imputation, but no imputed analysis was conducted. Analyses were implemented in R version 4.6.1 (2026-06-24) using versioned scripts, analytical datasets, model outputs, and tabulated results retained for reproduction. The critical packages used for manuscript reproduction were survey version 4.5 for complex-survey estimation and haven version 2.5.5 for NHANES XPT import.

3. Results

3.1. Analytical Sample and Participant Characteristics

The primary analytical sample included 30,413 adults: 2,839 current/recent HCTZ users and 27,574 participants with no HCTZ identified in the current/recent medication inventory. Reported NMSC history was present in 476 participants. HCTZ users were older on average and more often had hypertension, diabetes, and former smoking (Table 1). In total, 93.58% of the 32,498 adult candidates were retained.

Table 1. Characteristics of the Primary Analytical Sample by Current/recent HCTZ Use

Characteristic	Overall (N=30,413)	Non-HCTZ (N=27,574)	HCTZ (N=2,839)
Age, years	47.6 (0.26)	46.4 (0.26)	61.5 (0.31)
Sex			
Male	14,686 (48.1%)	13,522 (48.8%)	1,164 (40.1%)
Female	15,727 (51.9%)	14,052 (51.2%)	1,675 (59.9%)
Race/ethnicity			
Non-Hispanic White	11,757 (65.1%)	10,672 (64.7%)	1,085 (68.8%)
Mexican American	4,223 (8.5%)	3,942 (8.8%)	281 (4.7%)
Other Hispanic	3,196 (6.4%)	2,956 (6.6%)	240 (4.1%)

Non-Hispanic Black	6,965 (11.4%)	5,949 (10.9%)	1,016 (17.4%)
Other race	4,272 (8.7%)	4,055 (9.0%)	217 (5.0%)
BMI, kg/m²	29.2 (0.09)	29.0 (0.09)	32.5 (0.21)
Diabetes			
No diabetes	25,566 (87.6%)	23,666 (88.9%)	1,900 (72.5%)
Borderline diabetes	758 (2.3%)	612 (2.0%)	146 (4.9%)
Diabetes	4,089 (10.2%)	3,296 (9.1%)	793 (22.6%)
Hypertension			
No	19,279 (67.8%)	19,111 (73.2%)	168 (5.8%)
Yes	11,134 (32.2%)	8,463 (26.8%)	2,671 (94.2%)
Smoking			
Never	17,327 (56.6%)	15,802 (56.8%)	1,525 (53.6%)
Former	7,089 (24.7%)	6,177 (23.9%)	912 (34.1%)
Current	5,997 (18.7%)	5,595 (19.3%)	402 (12.2%)
Study outcome			
Reported history of NMSC	476 (2.4%)	402 (2.3%)	74 (3.9%)

Categorical values are unweighted n (survey-weighted %); age and BMI are survey-weighted mean (SE). Estimates account for the NHANES complex survey design. Current/recent HCTZ use was defined from prescription medication use reported in the past 30 days. NMSC denotes reported history of nonmelanoma skin cancer. The primary analytical sample was restricted to complete cases. BMI, body mass index; HCTZ, hydrochlorothiazide; NHANES, National Health and Nutrition Examination Survey; SE, standard error.

3.2. Primary Measured Adjustment

The crude positive survey-weighted cross-sectional prevalence-odds association between current/recent HCTZ use and reported NMSC history was OR 1.733 (95% CI, 1.240–2.421). After adjustment for the prespecified covariates, the estimate was OR 0.976 (95% CI, 0.686–1.389) (Table 2).

Table 2. Primary Association and Sensitivity Analyses for Current/recent HCTZ Use and Reported NMSC History

Analysis	Comparison/specification	N	OR	95% CI
Crude association	HCTZ vs non-HCTZ	30,413	1.733	1.240–2.421
Primary adjusted association	HCTZ vs non-HCTZ; primary adjustment set	30,413	0.976	0.686–1.389
Alternative adjustment	Primary adjustment set excluding hypertension	30,413	1.016	0.724–1.425
Active-comparator sensitivity	HCTZ-only vs ACEI-only current users	4,750	1.053	0.619–1.791
Healthcare-access sensitivity	Primary model plus 3-level usual-place-of-care variable (HUQ030)	30,410	0.969	0.680–1.380
Categorical age	Primary model with categorical age	30,413	0.968	0.682–1.373
Natural-spline age	Primary model with natural-spline age	30,413	0.964	0.679–1.369

Notes: Values are odds ratios (ORs) with 95% confidence intervals (CIs) from NHANES survey-weighted logistic regression. The outcome was reported history of nonmelanoma skin cancer (NMSC), and exposure was current/recent hydrochlorothiazide (HCTZ) use.

The primary model adjusted for age, sex, race/ethnicity, body mass index, diabetes, hypertension, and smoking. The alternative model omitted hypertension from the adjustment set. Age-specification sensitivity models replaced the continuous age term with categorical or natural-spline terms and retained the other primary covariates.

The active-comparator sensitivity analysis compared mutually exclusive HCTZ-only with ACEI-only current users. The healthcare-access sensitivity analysis additionally adjusted for the three-level usual-place-of-care variable HUQ030.

ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; CI, confidence interval; HCTZ, hydrochlorothiazide; NMSC, nonmelanoma skin cancer; OR, odds ratio.

3.3. Model Specification, Active Comparator, and Healthcare Access

The OR was 1.016 when hypertension was omitted, 1.053 in the HCTZ-only versus ACEI-only current-user comparison, and 0.969 after adding the general healthcare-access measure (Table 2). Categorical and natural-spline age models yielded ORs of 0.968 and 0.964, respectively, in the same 30,413 participants. Table 2 reports the confidence intervals and analytical sample sizes.

3.4. Differential Outcome-Ascertainment QBA

The nondifferential benchmark S0 yielded OR 0.981 (95% CI, 0.675–1.424), and valid differential scenarios S1–S4 ranged from OR 0.880 to 1.038 (Table 3).

Table 3. Differential Outcome-Ascertainment Quantitative Bias Analysis for Current/recent HCTZ Use and Reported NMSC History

Scenario	Ascertainment assumption	Sensitivity		Specificity		QBA-adjusted OR (95% CI)
		HCTZ	non-HCTZ	HCTZ	non-HCTZ	
S0	**Nondifferential baseline**	0.7250	0.7250	0.999	0.999	0.981 (0.675–1.424)
S1	Minimal differential surveillance	0.7375	0.7250	0.999	0.999	0.962 (0.663–1.397)
S2	Moderate differential surveillance	0.7625	0.7250	0.999	0.999	0.928 (0.640–1.345)
S3	Strong surveillance stress test	0.8000	0.7250	0.999	0.999	0.880 (0.608–1.274)
S4	Reverse surveillance	0.7250	0.7625	0.999	0.999	1.038 (0.715–1.506)

1. Deterministic, scenario-based quantitative bias analysis (QBA). Sensitivity (Se) and specificity (Sp) denote assumed operating characteristics for reported nonmelanoma skin cancer (NMSC) ascertainment among hydrochlorothiazide (HCTZ) and non-HCTZ participants.

The QBA starting estimate was the primary adjusted OR, 0.976 (95% CI 0.686–1.389), based on N=30,413.

3. Sensitivity and specificity are prespecified fixed illustrative assumptions, not empirically calibrated operating characteristics for NHANES-reported NMSC. Estimates and confidence intervals are conditional on those fixed assumptions; intervals do not include bias-parameter or measurement-structure uncertainty.

The additional prespecified differential-specificity stress-test scenario S5 was non-estimable, as described in Methods.

3.5. Post-Hoc Generic Unmeasured-Confounding Analysis

The post-hoc generic unmeasured-confounding analysis was anchored to the crude OR of 1.733 (95% CI, 1.240–2.421), treated as a rare-outcome approximation to an RR. It examined how hypothetical unmeasured confounding could change the crude association rather than quantifying residual confounding of the adjusted estimate.

The E-values were 2.859 for the point estimate and 1.785 for the confidence limit closest to the null. At a U–NMSC RR of 10, the exposure–U ORs required to move the crude point estimate to the null were 3.161, 3.089, and 9.155 for marginal P(U) values of 0.10, 0.25, and 0.50, respectively (Table 4).

Table 4. Post-hoc Generic Unmeasured-Confounding Sensitivity Analysis Anchored to the Crude Association

Analysis	Assumptions	Result
E-value	Crude OR treated as a rare-outcome approximation to RR	Point estimate: 2.859 Closest confidence limit: 1.785
Rule-out analysis	Marginal P(U): 0.10, 0.25, 0.50 U–NMSC RR: 1.01–10.00	At U–NMSC RR = 10, required exposure–U OR: 3.161, 3.089, and 9.155 for P(U) = 0.10, 0.25, and 0.50, respectively
Array analysis	Baseline P(U) among non-HCTZ users: 0.10, 0.25, 0.50 Δ: 0, 0.10, 0.25, 0.50 U–NMSC RR: 1, 1.5, 2, 3, 5	55 valid scenarios Scenario-conditional association range: 0.713–1.733 Estimates ≤1: 3/55

Notes: U denotes a hypothetical binary confounder, and Δ denotes the increase in its prevalence among HCTZ users relative to non-HCTZ users. Array scenarios with an implied U prevalence >0.95 among HCTZ users were excluded. OR, odds ratio; RR, risk ratio; CI, confidence interval.

Across 55 valid Array scenarios, the scenario-conditional association ranged from 0.713 to 1.733, with 3 of 55 estimates at or below 1 (Table 4). The three estimates at or below 1 occurred when baseline P(U) was 0.10, the U–NMSC RR was 3 or 5, and Δ was 0.50 (0.945 and 0.713, respectively), or when baseline P(U) was 0.25, the U–NMSC RR was 5, and Δ was 0.50 (0.866).

4. Discussion

4.1. Principal Findings

In this survey-weighted cross-sectional study, the crude positive association between current/recent HCTZ use and reported NMSC history was substantially attenuated after adjustment for measured covariates (OR, 1.733 to 0.976). Omitting hypertension, changing the age specification, comparing HCTZ-only with ACEI-only users, and adding a general healthcare-access measure yielded estimates close to the primary adjusted estimate. These results concern a cross-sectional prevalence-odds association and do not establish a causal safety effect.

4.2. Measured Adjustment and Sensitivity Analyses

HCTZ users differed in age and other measured characteristics (Table 1).

The adjusted estimates were similar with continuous, categorical, and natural-spline age terms (Table 2). Thus, the estimate was not materially dependent on a single continuous linear age term.

Omitting hypertension assessed dependence on its inclusion in the adjustment set without establishing its causal role or removing indication confounding. The HCTZ-only versus ACEI-only comparison changed both the current-user population and medication contrast; it was not a longitudinal new-user design [17]. Adding the usual-place-of-care measure adjusted for one aspect of healthcare access, while dermatologist contact, skin examination, biopsy, and cumulative surveillance remained unmeasured.

4.3. Outcome Ascertainment and Generic Unmeasured Confounding

Reported historical NMSC may be influenced by opportunities for detection and diagnosis, as well as recall and reporting. Examination and screening can alter opportunities for skin-cancer diagnosis [18–19], but these sources do not establish HCTZ-specific ascertainment differences or NHANES sensitivity and specificity. The differential outcome-ascertainment QBA assessed how the adjusted association changed under specified exposure-group-specific ascertainment assumptions. The results for valid S1–S4 scenarios were similar to the primary adjusted result, but the tested values were not empirically calibrated for NHANES-reported NMSC. The intervals represented sampling uncertainty conditional on fixed parameters and omitted parameter and measurement-structure uncertainty.

The generic unmeasured-confounding sensitivity analysis examined the crude association before measured-covariate adjustment (Table 4). It examined how hypothetical unmeasured confounding could change the crude association, rather than quantifying residual confounding of the adjusted estimate. The E-value gave an equal-strength RR threshold, whereas the rule-out and Array analyses incorporated assumptions about confounder prevalence and its associations with exposure and outcome. These analyses do not identify an actual confounder or show that a hypothetical binary confounder generated the observed crude-to-adjusted attenuation. Their interpretation depends on the rare-outcome OR-as-RR approximation.

4.4. Relation to Previous Evidence

Positive observational literature has commonly examined cumulative HCTZ exposure and incident keratinocyte cancers in prescription-linked studies. Danish registry data reported dose-related associations stronger for SCC than BCC [1]; Spanish and UK studies evaluated cumulative exposure and incident subtype-specific outcomes [2–3]. These studies and reviews report associations that vary by dose, duration, subtype, population, and comparator [4–9].

Our study examined current/recent use from a past-30-day inventory and reported history of aggregate NMSC at a single assessment. The data provide neither cumulative exposure nor exposure precedence, and they do not provide incident, pathology-confirmed SCC/BCC outcomes; the comparator indicates no HCTZ identified currently or recently rather than lifetime nonuse. These prevalence-odds findings therefore neither replicate nor contradict longitudinal cumulative-dose evidence.

4.5. Implications for Real-World Evidence

In this study, similar estimates arose from analyses that changed different model choices, populations, or bias assumptions. QBA results require an explicit target bias, analytical anchor, parameter source, and account of uncertainty [11–12]. Neither the sensitivity analyses nor QBA supplied the missing exposure chronology or cumulative-dose information.

The NHANES complex survey design, explicit estimand, reproducible exposure and outcome definitions, and retained analytical scripts and model outputs were strengths of the study. Complete-case analysis retained 93.58% of adult candidates, although this does not make missingness ignorable. Generalizability is limited to the noninstitutionalized U.S. adults represented by the pooled pre-pandemic NHANES periods.

5. Conclusion

The positive crude prevalence-odds association between current/recent HCTZ use and reported NMSC history was substantially attenuated after measured-covariate adjustment. Additional model, comparator, healthcare-access, and ascertainment analyses yielded similar estimates while addressing different questions. Generic unmeasured-confounding analyses separately assessed the crude association. Current/recent use could not be shown to precede historical NMSC; these data cannot answer the cumulative-dose causal safety question, which is better addressed by temporally ordered longitudinal studies with incident, subtype-specific outcomes.

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