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Research Article

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Posted Date: November 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11383974/v1

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Additional Declarations: No competing interests reported.

Discordant associations of herpes zoster vaccination with mortality and vascular events in adults with hypertension, diabetes and hyperlipidemia

A propensity score matched TriNetX cohort study

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Abstract

Background: Reported mortality associations after herpes zoster vaccination may not reflect the direction of associations with vascular events. We examined mortality, individual vascular diagnoses, and their timing in adults with coexisting hypertension, diabetes, and hyperlipidemia.

Methods: This exploratory retrospective study used aggregate TriNetX results for patients aged ≥50 years at qualifying vaccination or immunization encounters on or after 1 January 2021. Zoster vaccine recipients were matched 1:1 to patients with Z23-coded immunization encounters and no recorded zoster vaccination at any time (36,988 per group). We examined platform-exported Cox estimates, Kaplan-Meier curves, and fixed-time estimates; non-fatal Kaplan-Meier estimates were interpreted as net risk rather than competing-risk cumulative incidence.

Results: Recorded mortality was lower in the zoster cohort (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.47–0.55), whereas cerebrovascular disease (HR 1.20, 95% CI 1.13–1.29) and myocardial infarction (HR 1.14, 95% CI 1.05–1.25) had higher recorded hazards. Three-year mortality estimates were 2.52% versus 5.01%, and mortality curves separated within 30–90 days and hazards were nonproportional. The death-inclusive composite HR was 0.94 (95% CI 0.90–0.98), with three-year estimates of 9.63% versus 9.88%. All 41 evaluable matched standardized mean differences were below 0.10.

Conclusions: Lower recorded mortality did not coincide with lower recorded vascular event hazards. Reporting individual endpoints and mortality timing alongside a death-inclusive composite provides a more complete account of these associations. Residual confounding, comparator selection, and limitations of aggregate follow-up data preclude causal conclusions about cardiovascular benefit or harm.

Keywords: herpes zoster vaccination; cardiometabolic multimorbidity; mortality; cardiovascular outcomes; propensity score matching; electronic health records

Background

Interest in the cardiovascular consequences of adult vaccination has grown, alongside evidence linking infection with vascular events. Randomized evidence supports influenza vaccination after myocardial infarction (MI) [1], and observational studies have associated herpes zoster infection with stroke and myocardial infarction [2]. Whether zoster vaccination is associated with fewer vascular events beyond its established prevention indications remains an important question in cardiovascular epidemiology.

Observational studies in diabetes, chronic disease, and a nationwide South Korean population have reported favorable cardiovascular associations after zoster vaccination [3–5]. However, mortality and vascular endpoints do not always move in the same direction. Shih et al. reported lower mortality without significantly lower major adverse cardiovascular events in patients receiving Janus kinase inhibitors [6], whereas a chronic kidney disease study reported lower cardiovascular and mortality risks [7]. The clinical population, vaccine definition, comparator, and endpoint composition may influence the associations observed.

Therefore, a favorable mortality association alone is insufficient to describe cardiovascular outcomes. Death-inclusive composites can conceal differences between individual endpoints [10], whereas death limits the opportunity to record later non-fatal events [11]. Vaccination-related differences in frailty, recent illness, and preventive care engagement may persist after adjustment for routine electronic health record variables [8,9]. An immunization-encounter comparator offers a clinically relevant care-seeking context but does not remove these differences.

We examined recorded zoster vaccination versus Z23-coded immunization encounters among patients aged ≥50 years with coexisting hypertension, diabetes, and hyperlipidemia and no specified vascular diagnoses in the eligibility exclusion group. Our question was whether mortality and individual vascular associations were concordant and how the mortality pattern developed early after the index. We present relative associations, fixed-time absolute estimates, and a death-inclusive composite. This analysis characterizes an observed endpoint pattern rather than estimating a causal vaccine effect or validating a mechanism of bias.

Methods

Study design and data source

This exploratory retrospective matched cohort study used the TriNetX Global Collaborative Network. The primary analysis was run on 10 August 2026 at 12:56 pm, as recorded in the export metadata. The network then comprised 208,930,984 patients from 189 healthcare organizations, with 181 online for analysis. These totals describe network coverage, not the study sample; the run date is not an independently verified end date for clinical data coverage. The retained results screen reports that one or more healthcare organizations did not return results. Therefore, the counts reflect the returned analysis rather than complete participation by all network organizations. Patient-level records were not downloaded. Reporting is mapped to STROBE and RECORD in Additional file 1 [13,14].

Eligibility and exposure definitions

Eligibility required hypertension (ICD-10-CM I10–I1A), diabetes mellitus (E08–E13), and hyperlipidemia (E78.5) in a condition group occurring on or before a qualifying immunization event. The qualifying zoster vaccine or comparator Z23 event had an age restriction of ≥50 years and occurred on or after 1 January 2021. The same pre-immunization or same-day condition group excluded myocardial infarction (I21–I22), cerebrovascular disease (I60–I69), and vascular dementia (F01.50). Thus, the retained query specifies before-or-same-day eligibility rather than a separately verified fixed pre-index washout period. Figure 1 summarizes the available cohort counts; exported query definitions are supplied in Additional file 1.

Zoster vaccination was identified by CPT 90750 or 90736, combining recombinant and live vaccine codes. The comparator was an encounter coded Z23, with no recorded zoster vaccination at any time. This exclusion also incorporates vaccinations occurring after index and can introduce future-dependent selection. Z23 does not specify a vaccine product; this comparison therefore cannot estimate the effect of zoster vaccination against any alternative vaccine. Dose number, series completion and product-specific effects were not analyzed.

Matching and follow-up

Propensity score matching was performed within TriNetX at a 1:1 ratio. The study analysis description specifies nearest-neighbor matching with a caliper of 0.1; the retained output does not establish whether the caliper was applied on the probability or logit scale. The exported characteristics comprise age, sex, race, ethnicity, medication categories, diagnosis groups, and procedures (Additional file 1, Table S1). Standardized mean differences (SMDs) were used to assess the measured balance; absolute values <0.10 were considered acceptable. Exact index-month and healthcare-organization alignment were not available.

The saved input screen specifies an analysis window from day 1 to day 1,825 after the index and Kaplan–Meier censoring after the last fact in each patient record. The interface defines the index as the first day on which the selected index criteria are satisfied. However, the displayed selection includes condition-group criteria; it does not establish that the index equals the first qualifying vaccine or immunization encounter. The main curves are displayed through day 1,095, whereas event totals and overall HRs cover the configured full window. Individual censoring dates and the specific treatment of death in nonfatal analyses cannot be reconstructed from aggregate curves. Recorded follow-up summaries are reported by group, not as endpoint-specific person-time. [AUTHOR TO VERIFY WHICH SELECTED CRITERIA ACTUALLY DEFINED INDEX IN THE SAVED ANALYSIS.]

Outcomes and analysis populations

The retained outcome configuration defines myocardial infarction as ICD-10-CM I21 or I22, cerebrovascular disease as I60-I69, vascular dementia as F01.50, and mortality using the platform Deceased term. The composite joins all four components with OR and is analyzed as time to the first recorded qualifying component. I60-I69 is a broad cerebrovascular disease definition, not an ischemic-stroke-only phenotype; F01.50 is a specific vascular dementia code rather than all dementia diagnoses. For these five endpoints, the displayed MOA, Kaplan-Meier, and number-of-instances modules select the exclusion of patients with the outcome before the analysis window. This exploratory report does not assert prospective prespecification of an outcome hierarchy.

The analysis populations were endpoint-specific. Myocardial infarction, cerebrovascular disease, and vascular dementia analyses retained 36,988 patients per group. The platform excluded 110 zoster-cohort patients and 167 comparators from both mortality and the composite because the outcome preceded the analysis window, yielding 36,878 and 36,821 analyzed patients. The arithmetic is consistent, but individual records are unavailable to determine the clinical or temporal explanation for the mortality exclusions. All denominators are reported explicitly.

Statistical analysis

We used platform-exported Cox HRs and 95% confidence intervals (CIs), log-rank tests, and proportionality tests. Kaplan-Meier estimates at days 30, 90, 365, and 1,095 were evaluated at the last exported step at or before each horizon. The marginal curve confidence limits were retained. Between-group differences were descriptive percentage-point contrasts; paired covariance was unavailable; therefore, difference CIs and equivalence tests were not calculated. For non-fatal outcomes, 1 minus Kaplan-Meier survival is a net-risk quantity and not a competing-risk cumulative incidence [11]. Numbers at risk were unavailable and not inferred.

Because mortality hazards were nonproportional, the overall mortality HR is a follow-up-dependent summary association, not a constant effect. Outcomes were assessed without multiplicity adjustment and are interpreted as exploratory. Conditional estimates, $1-S(t)/S(L)$, with $L=30$ or 90 days and $t=365$ or 1,095 days from the original index, describe later portions of each endpoint-specific curve. They are not rematched survivor cohorts or landmark Cox analyses. An overlapping 2020-inclusive cohort is reported in the supplement as a descriptive cohort-version comparison, not independent validation; no interaction test was available. A candidate appendicitis negative control was excluded from inference because its saved OR expression also includes a pelvis X-ray term and its prior-outcome exclusion setting differs across analysis modules (Additional file 1). Patient-level competing-risk models and valid endpoint-specific incidence rates cannot be recovered from these aggregate files.

Results

Study population and measured balance

There were 36,989 eligible zoster recipients and 531,448 eligible comparators; 36,988 patients per group were retained after matching (Figure 1). The mean age was 59.95 versus 59.99 years, and 51.6% versus 50.5% were male. All 41 evaluable matched SMDs were <0.10 (maximum 0.046); four invariant characteristics had undefined SMDs. The selected baseline characteristics are shown in Table 1 and all exported characteristics in Additional file 1, Table S1 and Figure S1.

The comparator was older before matching (mean 67.25 versus 59.95 years), indicating a substantial change in comparator composition. The mean follow-up was 1,012 versus 1,071 days and the median follow-up was 1,033 versus 1,142 days. Matching on measured characteristics did not establish identical follow-up, calendar timing, or outcome capture.

Mortality and vascular associations

Table 2 presents endpoint-specific denominators, event totals, and associations. Recorded mortality occurred in 905 zoster recipients and 1,875 comparators (HR 0.51, 95% CI 0.47–0.55). By contrast, cerebrovascular disease occurred in 1,951 versus 1,772 patients (HR 1.20, 95% CI 1.13–1.29), and myocardial infarction in 1,018 versus 964 (HR 1.14, 95% CI 1.05–1.25). Vascular dementia was uncommon (43 versus 31 events; HR 1.50, 95% CI 0.94–2.38). These event totals span the full exported analysis window.

The death-inclusive composite occurred in 3,387 and 3,916 patients (HR 0.94, 95% CI 0.90–0.98; log-rank P=0.008). At three years, the composite Kaplan-Meier estimates were 9.63% versus 9.88%, a descriptive difference of −0.25 percentage points. Mortality estimates were 2.52% versus 5.01%, a difference of −2.50 percentage points. Cerebrovascular net-risk estimates were 5.54% versus 4.30%, and myocardial infarction estimates were 2.91% versus 2.41% (Figure 2; Additional File 1, Table S2 and Figure S2). These fixed-time contrasts and full-window Cox HRs summarize the different features of the follow-up. The small composite contrast does not establish an equivalence. Marginal component estimates cannot be added or subtracted to recover the first-event contributions to the composite.

Early mortality separation and exploratory analyses

Mortality estimates differed on day 30 (0.04% versus 0.16%) and day 90 (0.13% versus 0.46%; Figure 3A). The mortality proportionality test was significant (P=0.002), whereas the composite test was not (P=0.77). Figure 3B shows the differing associations across the endpoints.

Day-90 conditional estimates to day 1,095 were 2.38% versus 4.57% for mortality, 5.24% versus 3.94% for cerebrovascular disease, 2.80% versus 2.21% for myocardial infarction, and 9.13% versus 9.00% for the composite. These are descriptive ratios of the marginal survival curves, not adjusted landmark estimates or evidence that early selection has been removed (Additional File 1: Table S3). The overlapping calendar cohort and appendicitis export audit are documented in Additional File 1. The historical July time-window labels do not establish verified landmarks or pre-exposure analyses and are not pooled with primary results.

Discussion

Principal finding and clinical relevance

The central finding was a difference in the direction of recorded mortality and vascular associations among patients with hypertension, diabetes, and hyperlipidemia. Zoster vaccination was associated with lower mortality but higher hazards of myocardial infarction and cerebrovascular diagnoses relative to immunization-encounter comparators. The death-inclusive composite showed a modest relative association and a small descriptive three-year absolute contrast. Reading these endpoints together changes the clinical interpretation: the mortality association alone does not describe the vascular event pattern, and the composite does not show the direction of every component.

Relationship to previous studies

The endpoint pattern differs from the favorable cardiovascular associations reported in diabetes and chronic disease cohorts [3,4], the South Korean population study [5], and the chronic kidney disease cohort [7]. Differences in eligibility, vaccine products, comparator construction, and outcomes prevent direct attribution of this contrast to the population or to any single analytic choice. Shih et al. already reported lower mortality without significantly lower MACE in Janus kinase inhibitor-treated patients [6]; our study does not claim the first observation of mortality–vascular discordance. Its contribution is the combined presentation of mortality timing, individual vascular diagnoses, absolute estimates, and a death-inclusive composite in a population with three coexisting cardiometabolic conditions, using an immunization-encounter comparator.

Interpreting the direction and timing of associations

The mortality curves were separated within the first 30–90 days. Such early divergence makes differences present around the qualifying encounter relevant to interpretation, including frailty-related vaccination deferral, recent illness, and engagement with preventive care [8,9]. However, timing alone neither proves healthy vaccinee bias nor identifies how much of the mortality association it explains. Mortality hazards were nonproportional; therefore, the overall HR should not be interpreted as a stable association throughout follow-

up. The conditional curve estimates show that later mortality estimates also differed; however, they do not recreate an adjusted survivor analysis or resolve selection around the index.

The higher recorded vascular hazards cannot establish vaccine-induced harm. Differences in diagnostic opportunity, clinical utilization, coding, and healthcare organizations are possible explanations. Death can alter the opportunity to record subsequent diagnoses, but the aggregate curves do not quantify a competing-risk mechanism. Nonfatal 1−Kaplan-Meier estimates are not competing-risk cumulative incidence [11]. The death-inclusive composite offers another description of the first-event experience but does not substitute for patient-level competing-risk analysis or identify the relative contribution of each component [10]. A causal explanation for the endpoint pattern remains unresolved.

Strengths and limitations

The strengths include a large matched cohort with explicit cardiometabolic eligibility, transparent measured-balance assessment, endpoint-specific denominators, and presentation of both timing and absolute estimates. The Z23 comparator places both groups in an immunization-related clinical context; however, its vaccine-product heterogeneity limits clinical specificity. Moreover, the exclusion of zoster vaccination at any time uses information after the index to select comparators. Matching does not remove this structural selection issue or unmeasured differences in frailty, illness severity, socioeconomic circumstances, and healthcare engagement. The mixed recombinant and live vaccine codes do not support product-specific conclusions.

Other limitations include incomplete diagnosis and mortality capture, rare vascular dementia events, exploratory comparisons without multiplicity adjustment, unequal recorded follow-up, and unavailable alignment by calendar month or healthcare organization. The results screen indicates that some organizations did not return results; the extent and direction of any resulting selection are unknown. The saved input screen confirms the window, outcome expressions, and last-record censoring, but the operative index selection and matching caliper scale remain unverified. Mortality and composite pre-window exclusions are arithmetically consistent, but their temporal and clinical explanation remains unresolved. Numbers at risk, endpoint-specific person-time, paired uncertainty for fixed-time differences, and competing-risk estimates are unavailable. No valid negative-control

analysis is presented: the candidate appendicitis expression includes an unrelated imaging term and module settings differ. These limitations cannot be corrected by conditional curve calculations.

Implications for cardiovascular research

For cardiovascular readers, the practical contribution is the endpoint-specific interpretation of observational vaccination results. Mortality timing and individual vascular estimates should be presented alongside composites, with a clear distinction between full-window HRs and fixed-time estimates. Our results do not establish cardiovascular protection or vascular harm and do not warrant changes to zoster-prevention recommendations [12]. Studies intended to estimate causal effects would require index-time eligibility, explicit handling of subsequent vaccination, product-defined comparators, better measurement of frailty and utilization, aligned calendar and organizational settings, and patient-level event histories. A justified and consistently implemented negative control could strengthen that work, but is not a substitute for those design features.

Conclusions

In this matched cohort of patients aged ≥50 years with hypertension, diabetes, and hyperlipidemia, recorded zoster vaccination was associated with lower mortality but higher hazards of myocardial infarction and cerebrovascular diagnoses relative to Z23-coded immunization encounters. Early mortality separation and different endpoint directions warrant joint reporting of mortality timing, individual vascular outcomes, and absolute estimates. The analysis characterizes observational associations; it does not establish a causal cardiovascular benefit, vaccine-induced vascular harm, or a specific mechanism underlying the discordance.

Abbreviations

CI, confidence interval; CPT, current procedural terminology; EHR, electronic health record; HR, hazard ratio; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; KM, Kaplan–Meier; MACE, major adverse cardiovascular events; MI, myocardial infarction; PH, proportional hazards; SMD, standardized mean difference.

Declarations

Ethics approval and consent to participate

This study used de-identified aggregate TriNetX results without patient contact. [AUTHOR TO INSERT THE EXACT FEMH IRB DETERMINATION, APPROVAL OR EXEMPTION DATE, REFERENCE NUMBER AND CONSENT STATUS FROM THE ISSUED LETTER. The previous manuscript cites consultation number -39325; the determination letter was not available for verification.]

Consent for publication

Not applicable. No identifiable individual information was presented.

‘Clinical trial number

Not applicable.

Availability of data and materials

TriNetX patient-level records are subject to institutional access and data use restrictions and were not downloaded. Machine-readable aggregate estimates and processing codes supporting the reported figures and tables are included in Additional file 2. The cohort definitions and retained-output limitations are described in Additional file 1. Independent access to the underlying network requires an appropriate institutional TriNetX agreement, and aggregate files do not permit patient-level reconstruction.

Competing interests

The authors declare no competing interests.

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Ai-Hsien Li: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review and editing. Yen-Wen Wu: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. Chih-Dao Chen: Formal analysis, Validation, Writing – review & editing. Yi-Yao Chang: Formal analysis, Validation, Writing – review & editing. Jung-Cheng Hsu: Supervision, Validation, Writing – review & editing. Kuan-Ming Chiu: Supervision, Validation, Writing – review & editing.

Acknowledgements

Not applicable.

Use of generative AI

ChatGPT (OpenAI) assisted with manuscript editing, processing of aggregate exports, figure preparation, and consistency checks. No patient-level data were entered into the tool. [AUTHORS TO COMPLETE FINAL VERIFICATION OF THE RESULTS, REFERENCES AND INTERPRETATIONS AND CONFIRM RESPONSIBILITY BEFORE SUBMISSION.]

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Tables

Table 1 Selected characteristics before and after matching

Characteristic	Before matching Zoster / comparator	After matching Zoster / comparator	Matched SMD
Patients	36,989 / 531,448	36,988 / 36,988	NA
Age at Index	59.95 (7.17) / 67.25 (9.05)	59.95 (7.17) / 59.99 (7.38)	0.005
Male	19,080 (51.6%) / 257,464 (48.4%)	19,079 (51.6%) / 18,689 (50.5%)	0.021
White	24,406 (66.0%) / 354,783 (66.8%)	24,405 (66.0%) / 24,339 (65.8%)	0.004
Black or African American	7,809 (21.1%) / 99,723 (18.8%)	7,809 (21.1%) / 7,963 (21.5%)	0.010
Hispanic or Latino	3,707 (10.0%) / 38,701 (7.3%)	3,707 (10.0%) / 3,657 (9.9%)	0.005
Cardiovascular Medications	36,322 (98.2%) / 487,583 (91.7%)	36,321 (98.2%) / 36,436 (98.5%)	0.024
Immunological Agents	30,087 (81.3%) / 383,139 (72.1%)	30,086 (81.3%) / 30,084 (81.3%)	0.000
Diseases of the circulatory system	36,988 (100.0%) / 531,448 (100.0%)	36,987 (100.0%) / 36,988 (100.0%)	0.007
Diseases of the nervous system	28,105 (76.0%) / 371,250 (69.9%)	28,104 (76.0%) / 28,453 (76.9%)	0.022

Values are mean (SD) or n (%). The full 45-characteristic export is in Additional file 1, Table S1. All 41 evaluable matched SMDs were <0.10, and four invariant characteristics had undefined values. Hypertension, diabetes, and hyperlipidemia were eligibility requirements. Follow-up was not a baseline covariate.

Table 2 Outcome specific associations and three year estimates

Outcome	Events / analyzed N Zoster then comparator	HR (95% CI)	3-year KM % Zoster / comparator	Difference (pp)
Death or first vascular outcome	3,387 / 36,878 3,916 / 36,821	0.94 (0.90-0.98)	9.63 / 9.88	-0.25
All-cause mortality	905 / 36,878 1,875 / 36,821	0.51 (0.47-0.55)	2.52 / 5.01	-2.50
Cerebrovascular disease	1,951 / 36,988 1,772 / 36,988	1.20 (1.13-1.29)	5.54 / 4.30	+1.24
Myocardial infarction	1,018 / 36,988 964 / 36,988	1.14 (1.05-1.25)	2.91 / 2.41	+0.50
Vascular dementia	43 / 36,988 31 / 36,988	1.50 (0.94-2.38)	0.10 / 0.09	+0.01

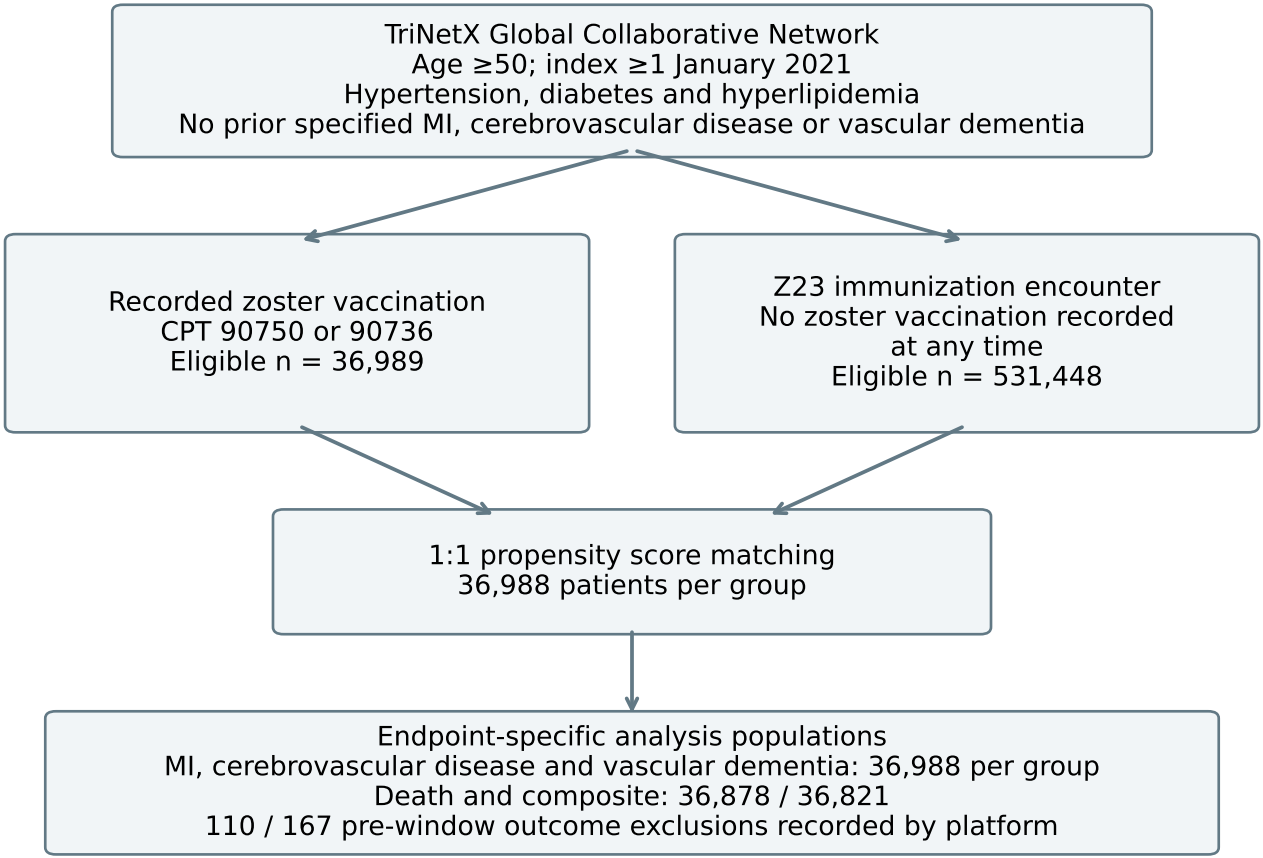
Event counts and Cox HRs span the full exported analysis window; KM estimates were evaluated at 1,095 days. Differences used unrounded inputs and had no paired CI or equivalence test. Non-fatal KM values are net-risk estimates, not competing-risk cumulative incidence. Mortality violated proportional hazards (P=0.002). For mortality and composite, 110/167 platform pre-window exclusions produced the reported denominators; their clinical explanation remains unresolved.

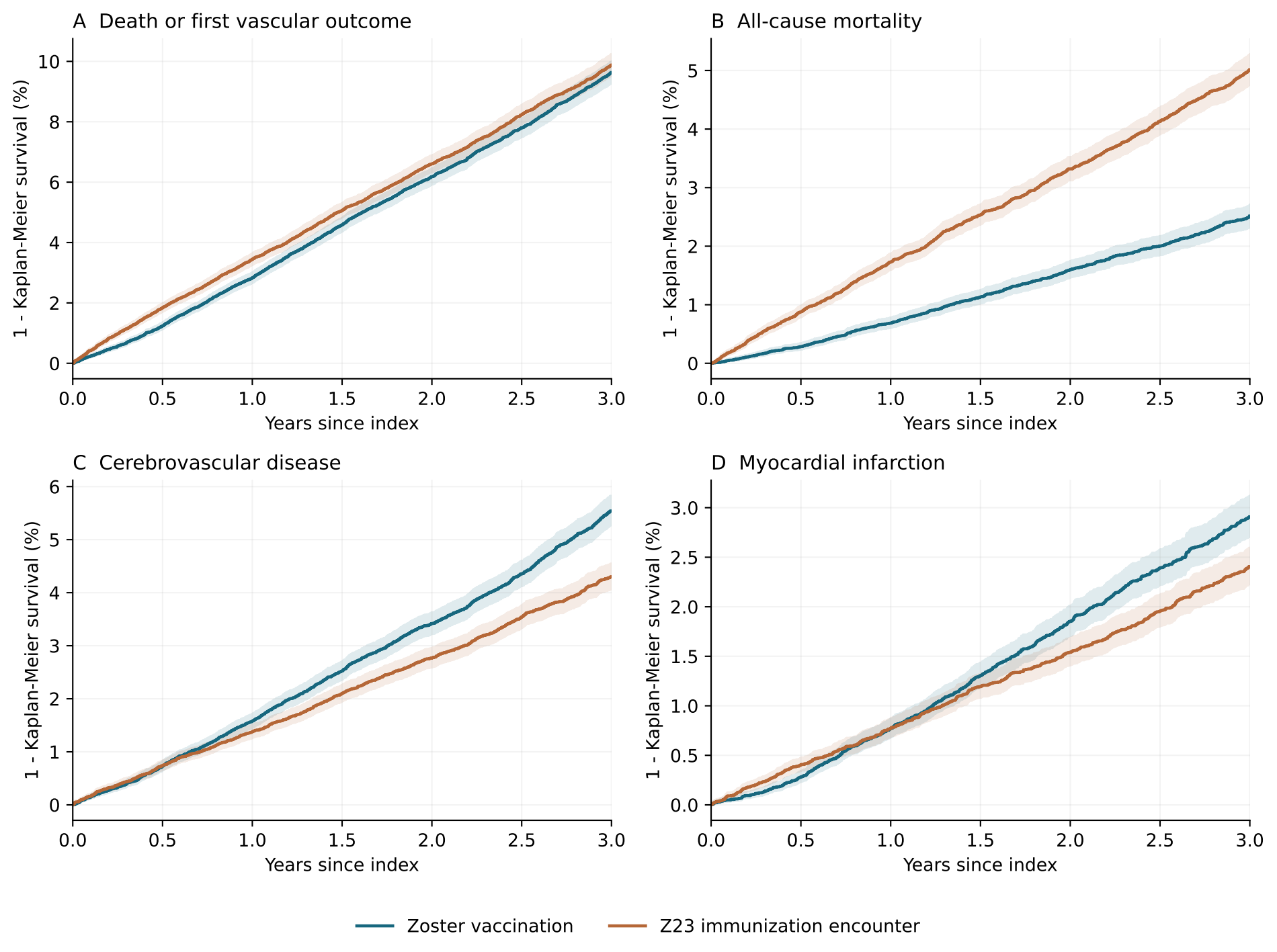
Figure legends

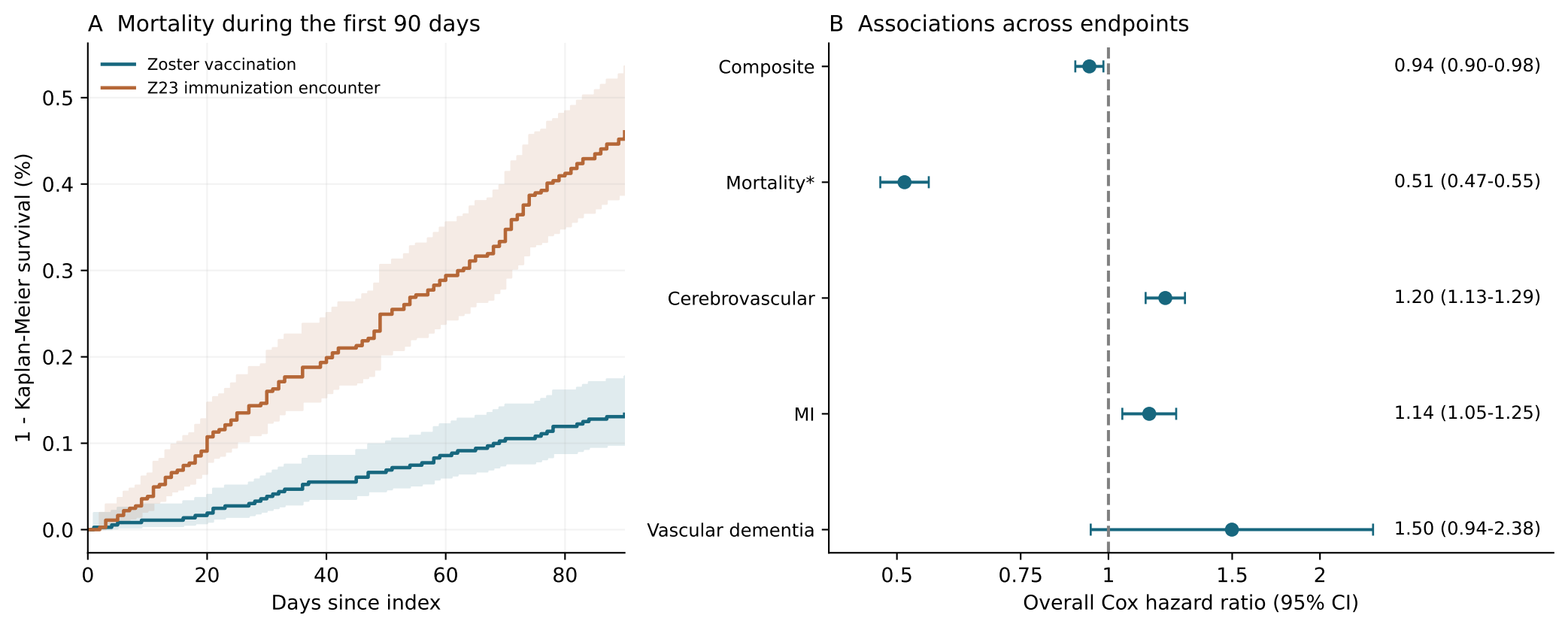
Figure 1. Cohort construction and endpoint-specific analysis of the populations. The eligibility and matching counts were reproduced from the retained study results. Intermediate exclusion-stage counts were not available for this study. Mortality and composite exclusion numbers were platform-reported and did not establish a clinical explanation for exclusions.

Figure 2. Mortality and vascular outcome curves over three years. Panels show the death-inclusive composite (A), all-cause mortality (B), cerebrovascular disease (C), and myocardial infarction (D). Shading denotes exported marginal 95% confidence limits. Non-fatal curves show 1-KM net-risk estimates, not competing-risk cumulative incidence. Numbers at risk were unavailable and were not reconstructed.

Figure 3. Early mortality timing and endpoint-specific relative associations. Panel A shows the first 90 days of the mortality curve with the exported marginal confidence limit. Panel B shows the overall Cox HRs and 95% CIs across the full exported analysis window. Mortality violated proportional hazards (P=0.002); its HR should not be interpreted as an effect. The timing and direction did not identify a causal mechanism.


TriNetX Global Collaborative Network
Age ≥50; index ≥1 January 2021
Hypertension, diabetes and hyperlipidemia
No prior specified MI, cerebrovascular disease or vascular dementia
Recorded zoster vaccination
CPT 90750 or 90736
Eligible n = 36,989
Z23 immunization encounter
No zoster vaccination recorded
at any time
Eligible n = 531,448
1:1 propensity score matching
36,988 patients per group
Endpoint-specific analysis populations
MI, cerebrovascular disease and vascular dementia: 36,988 per group
Death and composite: 36,878 / 36,821
110 / 167 pre-window outcome exclusions recorded by platform


A Death or first vascular outcome
1 - Kaplan-Meier survival (%)
Years since index
B All-cause mortality
1 - Kaplan-Meier survival (%)
Years since index
C Cerebrovascular disease
1 - Kaplan-Meier survival (%)
Years since index
D Myocardial infarction
1 - Kaplan-Meier survival (%)
Years since index
Zoster vaccination
Z23 immunization encounter



*Mortality PH test P = 0.002; HR is not a constant effect.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20261012BMCCVDManuscripttables.docx
- FigureS1covariatebalance.pdf
- FigureS2absoluteestimates.pdf