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Association of Herpes Zoster Vaccination and Cardiovascular Risk in patients with Diabetes: Long-Term Insights from a Retrospective Cohort Study

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Association of Herpes Zoster Vaccination and Cardiovascular Risk in patients with Diabetes: Long-Term Insights from a Retrospective Cohort Study

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Abstract

Objectives: Herpes zoster (HZ) infection associated with higher risk of major adverse cardiovascular events (MACE), including stroke and coronary artery disease. This study aims to investigate the risk of MACE after HZ vaccination in patients with diabetes

Design: Retrospective cohort study.

Setting: Community-based population in the United States.

Participants: Utilizing the TrinetX database, the study included 4.9 million patients with diabetes from 2006 to 2022. It established two cohorts: 70,088 patients in the HZ vaccination (comprising any HZ vaccine, Shingrix or Zostavax) and 4,546,625 patients in the non-HZ vaccination group. After excluding patients with history of MACE, immune disease, and complications of HZ prior to the index date, the study cohort was reduced to 42,664 patients. Propensity Score Matching, accounting for age, sex, race, and disease comorbidities, was conducted to minimize study bias.

Interventions: HZ vaccination

Primary and secondary outcome measures: MACE outcomes, including stroke, coronary artery disease and all-cause mortality. Comparative risk analysis used hazard ratios (HR).

Results: Post-matching, the mean patient age was 63.5 years, with 48.8% females. The risk of MACE, CAD, stroke, and all-cause mortality was consistently lower among patients with any HZ vaccination compared to those without vaccination, as evidenced by hazard ratios (HR) and 95% confidence intervals (CI) of 0.62 (0.60–0.65), 0.70 (0.66–0.74), 0.76 (0.71–0.81), and 0.55 (0.52–0.57), respectively. These protective effects were consistent across different age groups, sexes, and types of diabetes

Conclusions: HZ vaccination associated with lower risk of MACE in patients with diabetes. Further prospective study is critically needed to confirm this finding.

Funding: This work was supported by grants from the Chung Shan Medical University Hospital (CSH-2020-C-016).

Strengths and Limitations of this study:

- This study utilized a large community database, providing robust and representative data for analysis
- This study boasts a long follow-up duration, allowing us to assess the impact of herpes zoster vaccination on MACE risk over an extended period.
- This study evaluated the risk of MACE after herpes zoster vaccination in diabetes patients
- This study is limited by the potential for residual confounding that cannot be entirely eliminated.

Introduction

Herpes zoster (HZ), commonly known as shingles, is a prevalent viral infection caused by the reactivation of the varicella-zoster virus, which remains latent in the body following an initial chickenpox infection.[1] Triggered typically by aging, immunosuppression, or stress, this reactivation manifests as painful, blistering skin eruptions localized to specific dermatomes.[2,3] Additionally, It is particularly noted for its complications, such as postherpetic neuralgia, which can cause prolonged discomfort.[4,5] Recent studies have shifted focus towards the broader impacts of HZ, especially its association with an increased risk of major adverse cardiovascular events (MACE), including stroke and myocardial infarction.[6–18] Importantly, research suggests that the risk of stroke is time-dependent following an HZ infection, with a significant elevation in the first month at 78%, reducing to 43% after 3 months, and further to 20% after 1 year, before leveling off to a non-significant 7% increase up to 3 years post-infection.[19] This time-dependent risk profile underscores the importance of timely intervention and prevention strategies.

Within the population of individuals with diabetes mellitus, the interplay between HZ infection and cardiovascular risk is of particular concern. Diabetes, a chronic condition characterized by elevated blood glucose levels, significantly heightens the risk of cardiovascular diseases, making this group particularly susceptible to the compounded effects of HZ infection.[19,20] The risk of cardiovascular events in patients with diabetes is two to threefold higher than in those without diabetes, underscoring the critical need for comprehensive strategies to mitigate these risks.[21,22] The exacerbation of cardiovascular complications by HZ may be mediated through vasculopathy, a process potentially involving direct viral invasion of intra- or extracranial arteries, culminating in vessel wall damage through inflammatory responses characterized by multinucleated giant cells and epithelioid macrophages.[23–27] Additionally, HZ may provoke an inflammatory environment within the vessel wall, fostering a pro-coagulation state, further underscoring the complex interrelation between HZ infection and cardiovascular morbidity in diabetes.[24,28,29]

The advent of HZ vaccines, such as the recombinant zoster vaccine (RZV or Shingrix) and the live attenuated zoster vaccine (LZV or Zostavax), offers a promising strategy for reducing the incidence of HZ and its associated complications.[30–32] These vaccines have demonstrated robust efficacy in the general population aged 50 years and older, reducing both the occurrence of HZ and the severity of postherpetic neuralgia.[33] Given the established link between HZ infection and an increased risk of cardiovascular events, it is plausible to hypothesize that HZ vaccination could also confer protective effects against MACE, particularly in the diabetes population. However, investigations into the cardiovascular advantages of HZ vaccination yield inconclusive outcomes, as existing studies predominantly assess risk within the general population.[34–37] This study is designed to address this gap through the utilization of a community-based dataset to examine the effects of HZ vaccination on the incidence of composite MACE specifically in individuals with diabetes. In undertaking this analysis, it aims to uncover the comprehensive protective potential of HZ vaccination, serving as a multifaceted preventative measure against both infectious diseases and cardiovascular complications in a population identified as high-risk.

Methods

Study population

This retrospective cohort study utilized data from the TriNetX database, which aggregates electronic medical records from healthcare organizations across the United States. The TriNetX database is a comprehensive repository of de-identified electronic health records from a diverse range of healthcare organizations, including hospitals, clinics, and medical practices. It encompasses data on patient demographics, diagnoses, procedures, medications, laboratory results, and other clinical variables. By leveraging the TriNetX platform, researchers gain access to real-world data on a large and geographically diverse patient population, enabling robust analyses and insights into various health conditions and interventions.

Cohort selection

Cases were defined as individuals diagnosed with diabetes mellitus who received HZ vaccination, including Shingrix or Zostavax, within 1 year of their diabetes diagnosis, with the index date set as the date of vaccination. This timeframe was chosen to minimize potential differences and biases between cases and controls. Conversely, the control group comprised patients with diabetes who did not receive any HZ vaccination during the study period, with the index date corresponding to the first date of diabetes diagnosis. This study was conducted over a significant duration, spanning from January 1, 2006, to December 12, 2022, covering a total of nearly 17 years.

Exclusion Criteria

Patients with a history of MACE before the index date were excluded to ensure that the study focused on incident cases of cardiovascular events rather than pre-existing conditions. Immune-compromised individuals were excluded because their underlying conditions might confound the relationship between HZ vaccination and MACE. These conditions, such as Human immunodeficiency Virus (HIV), malignancy, and immune diseases (rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis) can affect the immune response and potentially influence the risk of cardiovascular events. Excluding individuals with a prior diagnosis of HZ and its complications (post-herpetic neuralgia, Bell's palsy, Ramsay-Hunt syndrome) before the index date helped to ensure that only new cases of these conditions were considered during the study period, reducing potential bias in the analysis.

Study codes and disease comorbidities.

Study codes and disease comorbidities were detailed in supplemental Table 1. In summary, the coding for diabetes diagnosis utilized International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) codes of E10-E11, while patients who received HZ vaccination were identified with procedure code and medical prescription normalized Medical prescription (RxNorm). Furthermore, socioeconomic status and disease comorbidities such as hypertension, obesity, and chronic kidney disease were allocated specific codes for identification and analysis purposes. This comprehensive coding system facilitated the organization and interpretation of patient data, ensuring clarity and precision in the study's findings.

This study aimed to investigate the association between HZ vaccination and the incidence of MACE among individuals with diabetes aged 50 years and older. The focus on this age group was driven by their heightened risk of MACE and their alignment with vaccination guidelines.[38] The primary endpoint of this study is defined as the first occurrence of composite MACE, comprising acute myocardial infarction and coronary artery disease (CAD), as well as the diagnosis of stroke following the index date. Secondary endpoints include individual outcomes of CAD, stroke, and all-cause mortality.

Statistical Analysis

Descriptive statistics were employed to summarize the baseline characteristics of the study population, including age, sex, race, and disease comorbidities. To effectively match cases with controls, propensity score matching (PSM) was utilized, leveraging logistic regression analysis on user-identified covariates within the TriNetX platform to generate propensity scores for each subject. These scores facilitated patient matching using a greedy nearest-neighbour algorithm, with a caliper width set at 0.1 pooled standard deviations to ensure close matching. TriNetX incorporates a step to randomize the order of subjects to mitigate bias inherent to the matching process. The success of this matching, reflected through p-values, assures the comparability of covariates across the two cohorts. Following PSM, the incidence of MACE was analyzed using a Cox proportional hazards model to adjust for potential confounders, with the risk of outcomes presented as adjusted odds ratios (aOR) alongside 95% confidence intervals (CIs). Statistical significance was determined by two-sided p-values less than 0.05, reinforcing the rigor of the analytical approach conducted within the TriNetX platform.

Ethical Considerations

The patient data utilized in this study were fully de-identified to ensure privacy and confidentiality. This procedure was implemented to prevent the direct or indirect identification of individual patients, thereby safeguarding patient privacy in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations. The study protocol was approved by the Institutional Review Board of Chung Shan Medical University Hospital, identified by the reference number CS2-23159.

Results

This study included a total of 112 million patients (figure 1). Following the filtration process to identify patients with a diagnosis of diabetes, we narrowed the cohort down to 4.9 million patients. Among these, 68,178 patients were identified as cases, having received any HZ vaccination within 1 year diagnosis of diabetes, while 4,835,246 patients served as controls, having diabetes without any HZ vaccination. Further exclusion of patients with immune diseases and a history of MACE before the index date resulted in 45,960 cases for any HZ vaccination and 3,363,873 controls. Subsequently, we divided the study into four populations for evaluation, designated as N1 through N4. The matching of cases vaccinated with any HZ vaccine to non-HZ vaccinated controls yielded 45,958 pairs (N1). Meanwhile, matching cases vaccinated with Shingrix to non-HZ vaccinated controls resulted in 14,142 pairs (N2), and matching cases vaccinated with Zostavax to non-HZ vaccinated controls resulted in 11,285 pairs (N3). Finally, matching cases vaccinated with Shingrix against those vaccinated with Zostavax resulted 10,505 pairs (N4).

The discrepancy between the sum of populations N2 and N3 not equaling the total of N1 can be attributed to the specific inclusion criteria based on procedural and medication codes utilized to identify the vaccination status within our study cohorts. N1 encompasses a broader category of individuals vaccinated with any HZ vaccine, identified through a comprehensive set of codes, including CPT codes 90736 (Zostavax) and 90750 (Shingrix), as well as additional codes for unspecified zoster vaccines (459891000124012) and their respective RXNORM codes (1292422 for Zostavax and 1986821 for Shingrix). This allows for the inclusion of all individuals vaccinated against HZ, capturing a wider demographic. Conversely, N2 and N3 focus on narrower subsets, with N2 including only those vaccinated with Shingrix (via CPT code 90750 and RXNORM code 1986821) and N3 comprising individuals vaccinated with Zostavax (identified by CPT code 90736 and RXNORM code 1292422).

Table 1 presents baseline characteristics for both HZ vaccination cases and non-HZ vaccination controls. Prior to PSM, notable differences were observed in several comorbidities, including hypertensive diseases, obesity, heart disease, chronic kidney disease (CKD), neoplasm, and nicotine dependence. The mean age was 63.4 years, with 49.1% female and 58.9% white race. Disease comorbidities included patients with hypertensive disease accounting for 54.8%, overweight and obesity at 19.5%, other forms of heart disease at 12.3%, CKD at 7%, neoplasm at 8.3%, and nicotine dependence at 5.82%. Following the matching process, the disparity between cases and controls was significantly reduced, as evidenced by the standardized mean differences (SMD) being less than 0.1, detailed in Supplemental Tables 2-5.

Table 2 presents the risk of MACE among patients with HZ vaccination compared to those without vaccination. The risk of MACE, CAD, stroke, and all-cause mortality was consistently lower among patients with any HZ vaccination compared to those without vaccination, as evidenced by hazard ratios (HR) and 95% confidence intervals (CI) of 0.76 (0.72–0.79), 0.73 (0.69–0.78), 0.79 (0.74–0.84), and 0.54 (0.52–0.57), respectively. These findings underscore the potential protective effect of any HZ vaccination against adverse cardiovascular outcomes. In solitary use, both Shingrix and Zostavax demonstrated effectiveness in reducing the risk of MACE, CAD, stroke, and all-cause mortality compared to non-vaccination. For Shingrix, the risks were 0.84 (0.76–0.91) for MACE, 0.78 (0.69–0.88) for CAD, 0.87 (0.77–0.99) for stroke, and 0.53 (0.48–0.58) for all-cause mortality. Similarly, Zostavax showed HR and 95% CI of 0.81 (0.75–0.88) for MACE, 0.72 (0.65–0.80) for CAD, 0.90 (0.81–1.01) for stroke, and 0.58 (0.53–0.62) for all-cause mortality.

These results suggest that both Shingrix and Zostavax offer protective benefits against MACE when administered individually. When comparing Shingrix to Zostavax, interesting findings emerged. While a neutral result was observed for MACE and stroke, a notable difference was detected in CAD. The HR and 95% CI for CAD were 1.16 (1.01–1.34), indicating a higher risk of CAD among individuals receiving Shingrix compared to Zostavax. However, no significant differences were noted in stroke, all-cause mortality, or overall MACE between the two vaccines. This highlights the importance of considering specific cardiovascular outcomes when evaluating the comparative effectiveness of different HZ vaccines.

The stratification analysis of the risk of MACE among different groups revealed consistent findings across various demographic and clinical factors (table 3). Regardless of age, individuals aged 50-65 years and those over 65 years demonstrated a lower risk of MACE with HZ vaccination compared to non-vaccination, with HR and 95% CI of 0.80 (0.75–0.86) and 0.83 (0.78–0.89), respectively. Similarly, both females and males experienced a reduced risk of MACE with vaccination, with HR and 95% CI of 0.77 (0.72–0.83) and 0.74 (0.69–0.79), respectively. Furthermore, individuals with type 1 or type 2 diabetes also exhibited a lower risk of MACE with HZ vaccination compared to non-vaccination, with HR and 95% CI of 0.25 (0.08–0.75) for type 1 diabetes and 0.71 (0.68–0.75) for type 2 diabetes. These consistent protective effects across different age groups, sexes, and types of diabetes underscore the robustness of the association between HZ vaccination and reduced cardiovascular risk.

When considering the timing within the first year of vaccination, Table 4 illustrates a notable trend in the risk of MACE. The risk of MACE is observed to be the lowest in the first month following vaccination, with a HR and 95% CI of 0.21 (0.16–0.27). Subsequently, the risk of MACE is gradually increases over time, yet remains significantly lower compared to non-vaccination. At the end of the first year, the HR and 95% CI for MACE stand at 0.57 (0.52–0.62). In the long-term follow-up, as depicted in Supplementary table 6, the risk of MACE demonstrates consistent patterns across different time intervals. Over a follow-up period of up to 5 years, individuals with HZ vaccination exhibit a significantly lower risk of MACE compared to non-vaccinated counterparts, with a HR and 95% CI of 0.70 (0.66–0.74). However, the protective effects seem to wane with time. During follow-up periods of 5-10 years and beyond 10 years, the Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Major Adverse Cardiac Events (MACE) among vaccinated individuals are observed to be 0.93 (0.84–1.02) and 1.13 (0.92–1.39), respectively.

The protective efficacy of Shingrix demonstrates consistency, whether administered as a single dose or a two-dose regimen, when compared to a non-HZ vaccinated control group. Specifically, the hazard ratio (HZ) for individuals receiving one dose of Shingrix was 0.66 (95% CI: 0.59–0.73), while for those completing the two-dose regimen, the HZ was 0.73 (95% CI: 0.59–0.89), as detailed in Supplementary table 7.

Discussion

To the best of our knowledge, this study represents the first comprehensive investigation into the risk of MACE among patients with diabetes following HZ vaccination. Our findings reveal a significant decrease in the risk of MACE subsequent to HZ vaccination. This protective effect extends to other critical outcomes, including CAD, stroke, and all-cause mortality, demonstrating consistent benefits across multiple cardiovascular endpoints. Furthermore, our subgroup analysis highlights the robustness of the protective effect, as it remains consistent across different age groups, sexes, and types of diabetes. Interestingly, our study also indicates that the strongest protective effects appear to manifest within the first year following vaccination, but these effects appear to diminish over time. These findings underscore the potential additional benefits of HZ vaccination in reducing cardiovascular risk among individuals with diabetes.

HZ is increasingly being investigated for its potential link to CVD. Initial evidence suggesting HZ as a risk factor for CVD comes primarily from retrospective analyses,[6–18] which have documented a higher frequency of cardiovascular events—such as stroke and myocardial infarction—in individuals who have had HZ episodes compared to those who have not. Following these preliminary observations, further research aimed at confirming and expanding upon this association has been conducted through larger-scale studies across diverse global populations. This extensive research has shown an increased risk of cardiovascular events post-HZ infection, underscoring the necessity for increased clinical awareness and management of cardiovascular risk factors among those with a history of HZ.[34,37]

Several mechanisms have been proposed to elucidate the link between HZ infection and an increased risk of MACE. A primary mechanism believed to be implicated is vasculopathy, wherein the virus directly infects and spreads from the nerve to the cerebral artery, eliciting inflammation, pathological vascular remodeling, and subsequently heightening the risk of stroke.[25,39] Moreover, beyond the direct vascular effects, HZ infection may contribute to elevated blood pressure due to the pain and stress associated with the condition. This elevation in blood pressure could further exacerbate the risk of stroke, given that hypertension is a leading cause of stroke.

Within the existing literature, our study stands out for evaluating patients with the longest follow-up duration and focusing specifically on the diabetes population. Notably, three published studies have been identified, each presenting unique findings. Parameswaran et al.[34] and Yang et al.[37] reported positive HZ vaccination outcomes, while Minnasian et al.[35] found no significant advantage. These studies, characterized by retrospective designs, differ in their data sources, study populations, and methodologies, contributing to the heterogeneity in results.

The distinctive aspect of our study lies in the examination of patients aged between 50 and 65 years old, a demographic often underrepresented in similar analyses.[34,35,37] This age group, typically considered lower risk for MACE compared to those over 65, exhibited intriguing results in our study. Specifically, we observed a significantly reduced risk of MACE among diabetes patients aged 50-65 who received HZ vaccination, with a HR of 0.80 (95% CI: 0.75–0.86), as compared to non-vaccinated counterparts. This finding provides valuable insights into the effectiveness of HZ vaccination in reducing MACE risk among individuals who might benefit most from early preventive measures. Another unique aspect of our study is the inclusion of data on patients with type 1 diabetes who received HZ vaccination, a demographic that has been largely overlooked in previous literature. To our knowledge, this is the first study to report outcomes for individuals with type 1 diabetes following HZ vaccination. Our analysis revealed a noteworthy finding, indicating a significantly reduced risk of MACE among patients with type 1 diabetes who received HZ vaccination, with a HR of 0.25 (95% CI: 0.08–0.75). This novel insight underscores the potential benefits of HZ vaccination not only for individuals with type 2 diabetes but also for those with type 1 diabetes, highlighting the importance of considering this population in future vaccination strategies and guidelines.

Parameswaran and colleagues, utilizing Veteran Affairs data, observed a significant protective effect against stroke in elderly males following vaccination with both Zostavax and Shingrix.[34] Their study revealed that patients experienced a notably higher risk of stroke within the first month following recent HZ infection. However, individuals who received at least one zoster vaccination demonstrated a mitigation of this increased risk. Specifically, the odds ratio (OR) for stroke 30 days post-event was 0.57 (95% CI: 0.46–0.72) for Shingrix and 0.77 (95% CI: 0.65–0.91) for Zostavax. Similarly, Yang et al., analyzing US Medicare data, identified a 16% reduction in stroke risk among vaccine recipients aged 66 and older, with enhanced benefits observed in specific subgroups.[37]

Minnasian et al.'s study,[35] conducted within the Medicare population and focusing on patients older than 65 years, revealed a transiently heightened risk of stroke and myocardial infarction associated with HZ infection. Particularly noteworthy was the pronounced increase observed within the initial week following zoster diagnosis, with a 2.4-fold elevated rate of ischemic stroke (incidence rate [IR] 2.37, 95% CI 2.17–2.59) and a 1.7-fold increase in myocardial infarction rate (IR 1.68, 95% CI 1.47–1.92), followed by a gradual reduction over six months. However, the study did not find evidence of a reduction in the IR for ischemic stroke or myocardial infarction among HZ vaccine recipients in the first four weeks following zoster diagnosis. The lack of observed protective effects of the HZ vaccine may be attributed to the limited number of patients in the vaccinated groups, thereby restricting the study's power to adequately assess this outcome. Notably, only 9% of participants received the vaccine during the study period, underscoring the challenge of assessing vaccine effectiveness in real-world settings with low uptake rates. These disparities underscore the importance of considering study-specific factors, such as data sources and population characteristics, when interpreting and comparing research findings.

An additional significant discovery from our research is the most robust protective impact of HZ vaccination against MACE observed during the first year, with this protective effect extending over 5 years of follow-up. This outcome aligns with the observation that the highest risk of stroke occurs within the first year.[19] This phenomenon could be attributed to various potential mechanisms. Firstly, the vaccine may modulate the immune response, reducing systemic inflammation, a key contributor to atherosclerosis and cardiovascular events. Furthermore, by preventing HZ, the vaccine indirectly decreases cardiovascular stress, considering the association between HZ and a heightened risk of stroke and myocardial infarction, particularly in the first year following infection. This dual mechanism—lowering inflammation and averting HZ—accounts for the observed sustained, albeit gradually decreasing, protective effect over time.

Observing a greater number of events in the Zostavax vaccination group compared to the control group, while the HR remains less than 1, highlights the nuanced nature of HR as a measure of relative risk over time rather than a simple count of events (table 2). This phenomenon indicates that, after adjusting for the duration of follow-up and baseline risk factors, individuals in the Zostavax group experienced a lower rate of events at any given time compared to the non-vaccinated group. The HR less than 1 suggests a protective effect of the Zostavax vaccine, reflecting its efficacy in reducing the instantaneous risk of adverse outcomes, despite the apparent higher number of events when viewed without the context of time and population size adjustments. This underscores the importance of HR in providing a more accurate assessment of the vaccine's impact on health outcomes.

It is important to note that the discrepancies in total numbers between Table 2 and Table 3, as well as in other subgroups, are caused by the methodology employed in the TrinetX analyses. Each stratified analysis involves re-matching individuals based on specific criteria, leading to variations in sample sizes and the number of participants experiencing MACE across different tables or subgroups. This re-matching process is designed to ensure that comparisons within each stratification are appropriate and accurate, taking into account the varying characteristics of participants within each subgroup. Consequently, the figures for the total number of individuals and those experiencing MACE in one table cannot simply be summed to match the figures in another table, due to these inherent differences in sample composition and size resulting from the re-matching process.

An intriguing finding emerged from our study when directly comparing the effectiveness of Shingrix and Zostavax, as there is a notable scarcity of head-to-head comparisons in the existing literature, particularly regarding their impact on MACE outcomes. Interestingly, while the American Diabetes Association (ADA) recommends Shingrix vaccination for individuals aged 50 years and older with diabetes,[38] our study revealed superior outcomes associated with Zostavax. However, it is imperative to interpret these findings with caution, as our analysis is retrospective in nature and there exists a marked difference in the study timing between Zostavax and Shingrix. The reasons for this discrepancy are not fully elucidated but may relate to differences in vaccine composition and the resulting immune response. Zostavax, being a live attenuated vaccine, could potentially elicit a broader and more robust immune response compared to Shingrix, which is a recombinant subunit vaccine. Moreover, Zostavax offers the convenience of requiring only one injection for full protection, whereas Shingrix necessitates two injections. The variations in the immune response elicited by these vaccines may contribute to differences in their effectiveness in preventing MACE outcomes among individuals with diabetes.

Our study benefits from several strengths that enhance the reliability and significance of our findings. Firstly, leveraging data from the TriNetX database, which aggregates electronic medical records from 61 healthcare organizations across the US, provided a robust and extensive dataset for analysis. Secondly, employing a rigorous retrospective cohort study design enabled us to investigate the association between HZ vaccination and MACE among individuals with diabetes with clarity and precision. Additionally, our detailed analysis, including comprehensive stratification by age, sex, and diabetes type, allowed for a nuanced understanding of vaccine effectiveness across diverse subgroups. Lastly, our study's long-term follow-up, assessing MACE outcomes over up to 10 years post-vaccination, provides valuable insights into the enduring protection offered by HZ vaccination against cardiovascular events.

Despite its strengths, our study is not without limitations. Firstly, despite efforts to control for confounding variables, the potential for residual confounding cannot be entirely eliminated. Secondly, the generalizability of our findings may be restricted due to the reliance on data from a single database comprising healthcare organizations solely within the United States. Lastly, the retrospective nature of our study design precludes the establishment of causal relationships between HZ vaccination and MACE, warranting cautious interpretation of our results and emphasizing the need for further prospective investigations.

Further prospective study is crucial to comprehensively evaluate the effectiveness of HZ vaccination in individuals with diabetes. This prospective study should aim to assess vaccination outcomes in diabetes patients across various time intervals following vaccination, allowing for a comprehensive understanding of the long-term efficacy and safety profiles of different vaccines, including Shingrix and Zostavax. By conducting such studies, researchers can address existing gaps in the literature and provide more definitive evidence to guide clinical decision-making and vaccination strategies in this vulnerable population.

In conclusion, our retrospective cohort study provides valuable insights into the association between HZ vaccination and MACE among individuals with diabetes. Despite the inherent limitations of retrospective analyses, our findings suggest a potential protective effect of HZ vaccination against MACE, aligning with the ADA recommendation to vaccinate individuals aged 50 and older with diabetes against HZ. Our study underscores the importance of HZ vaccination as a potential strategy for reducing cardiovascular risk in this vulnerable population. Moreover, beyond its known benefits in reducing the risk of HZ, our findings suggest that HZ vaccination may also contribute to the reduction of MACE.

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Authorship contribution statement:
Edy Kornelius: Conceptualization, Methodology, Writing – Original Draft
Shi-Chang Lo: Conceptualization, Methodology
Chien-Ning Huang: Resources, Supervision, Data analysis
Chi-Chih Wang: Investigation, Review & Editing
Yu-Hsun Wang: Data curation, Investigation, Software, Visualization, Data Analysis
Yi-Sun Yang: Methodology, Data analysis, Writing – Review & Editing

Disclosure: all authors disclosed no conflict of interest.

Data sharing availability: This population-based study obtained data from the TrinetX platform (accessible at https://trinetx.com/), for which third-party restrictions apply to the availability of this data. The data were used under license for this study with restrictions that do not allow for data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs might be incurred, and a data-sharing agreement would be necessary.

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Figure legends

Figure 1. Detailed flow chart illustrating the division of participants into four groups based on Herpes Zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to non-vaccinated controls yielded 42,663 pairs (N1). Matching Shingrix vaccinated to non-vaccinated controls resulted in 11,955 pairs (N2), Zostavax vaccinated to non-vaccinated controls yielded 10,973 pairs (N3), and Shingrix vs. Zostavax vaccination resulted in 8,331 pairs (N4).

Table 1. Demographic Characteristics of Individuals Vaccinated and Not Vaccinated Against Herpes Zoster.

	Any HZ vaccine N = 45960	Non-HZ vaccine N = 3363873	SMD
Age	63.46 ± 7.76	63.30 ± 9.30	0.019
Sex			
Female	22594 (49.16)	1599758 (47.56)	0.032
Male	20606 (44.84)	1656250 (49.24)	0.088
Race			
White	27076 (58.91)	1950119 (57.97)	0.019
Black or African American	7218 (15.71)	563189 (16.74)	0.028
Asian	2928 (6.37)	142295 (4.23)	0.096
Social economic status			
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	513 (1.12)	8856 (0.26)	0.103
Comorbidities			
Hypertensive diseases	25190 (54.81)	463468 (13.78)	0.959
Overweight and obesity	8980 (19.54)	149819 (4.45)	0.477
Other forms of heart disease	5651 (12.30)	205284 (6.10)	0.216
Chronic kidney disease	3257 (7.09)	89980 (2.68)	0.206
Neoplasms	3815 (8.30)	83995 (2.50)	0.259
Nicotine dependence	2673 (5.82)	67311 (2.00)	0.198
Hypertensive chronic kidney disease	1175 (2.56)	26124 (0.78)	0.139
Alcohol related disorders	734 (1.60)	18739 (0.56)	0.101
Fibrosis and cirrhosis of liver	438 (0.95)	19169 (0.57)	0.044
Unspecified dementia	235 (0.51)	7108 (0.21)	0.05
Alcoholic liver disease	189 (0.41)	6594 (0.20)	0.039
Alzheimer's disease	144 (0.31)	3447 (0.10)	0.046
Dementia in other diseases classified elsewhere	161 (0.35)	3858 (0.12)	0.049
Hepatic failure, not elsewhere classified	140 (0.31)	5878 (0.18)	0.027
Chronic hepatitis, not elsewhere classified	21 (0.05)	730 (0.02)	0.013
Vascular dementia	61 (0.13)	1394 (0.04)	0.031
Rheumatoid arthritis with rheumatoid factor	22 (0.05)	1081 (0.03)	0.008

Any HZ vaccine: Shingrix or Zostavax; HZ: herpes zoster; SMD: standardized mean difference

Table 2. Risk of MACE exposed to HZ vaccine compared to non-HZ vaccine

	Exposure group		Comparison		
	N	No. of event	N	No. of event	HR (95% C.I.)
Any HZ vaccine vs non-HZ vaccine (N1 matched population)					
MACE	45,958	3,474	45,958	4,060	0.76 (0.72–0.79)
Coronary artery disease	45,958	1,902	45,958	2,331	0.73 (0.69–0.78)
Stroke	45,958	1,863	45,958	2,116	0.79 (0.74–0.84)
All-cause mortality	45,958	2,793	45,958	4,794	0.54 (0.52–0.57)
Shingrix vs non-HZ vaccine (N2 matched population)					
MACE	14,142	858	14,142	1,294	0.84 (0.76–0.91)
Coronary artery disease	14,142	468	14,142	770	0.78 (0.69–0.88)
Stroke	14,142	445	14,142	650	0.87 (0.77–0.99)
All-cause mortality	14,142	569	14,142	1,561	0.53 (0.48–0.58)
Zostavax vs non-HZ vaccine (N3 matched population)					
MACE	11,285	1,674	11,285	1,030	0.81 (0.75–0.88)
Coronary artery disease	11,285	910	11,285	616	0.72 (0.65–0.80)
Stroke	11,285	952	11,285	530	0.90 (0.81–1.01)
All-cause mortality	11,285	1,496	11,285	1,203	0.58 (0.53–0.62)
Shingrix vs Zostavax (N4 matched population)					
MACE	10,505	615	10,505	1,574	1.09 (0.98–1.21)
Coronary artery disease	10,505	335	10,505	859	1.16 (1.01–1.34)
Stroke	10,505	310	10,505	900	0.96 (0.83–1.11)
All-cause mortality	10,505	378	10,505	1,400	0.99 (0.87–1.12)

Any HZ vaccine: Shingrix or Zostavax; MACE: major adverse cardiovascular events; HZ: herpes zoster

Table 3. Stratification analysis of risk of MACE among different group in N1 matched population.

	Any vaccine		Non-HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Age					
50-65	28,258	1,634	28,258	1,968	0.80 (0.75–0.86)
>65	16,903	1,859	16,903	1,723	0.83 (0.78–0.89)
Sex					
Female	22,591	1,559	22,591	1,808	0.77 (0.72–0.83)
Male	20,603	1,665	20,603	1,995	0.74 (0.69–0.79)
Type 1 diabetes	230	10	230	16	0.25 (0.08–0.75)
Type 2 diabetes	42,503	2,945	42,503	3,588	0.71 (0.68–0.75)

If the patient's count is 1-10, the results indicate a count of 10.

N1 indicate any herpes zoster vaccination versus non-herpes zoster vaccination population

Any vaccine: Shingrix or Zostavax; MACE: major adverse cardiovascular events

Table 4. Risk of MACE among within 1 year follow-up period in N1 matched population.

	Exposure group		Comparison		
	N	No. of event	N	No. of event	HR (95% C.I.)
Follow-up period					
1 month	45,958	69	45,958	314	0.21 (0.16–0.27)
3 months	45,958	218	45,958	575	0.35 (0.30–0.41)
6 months	45,958	404	45,958	813	0.45 (0.40–0.50)
9 months	45,958	612	45,958	1,014	0.54 (0.48–0.59)
12 months	45,958	790	45,958	1,228	0.57 (0.52–0.62)

MACE: major adverse cardiovascular events

N1 indicate any herpes zoster vaccination versus non-herpes zoster vaccination population

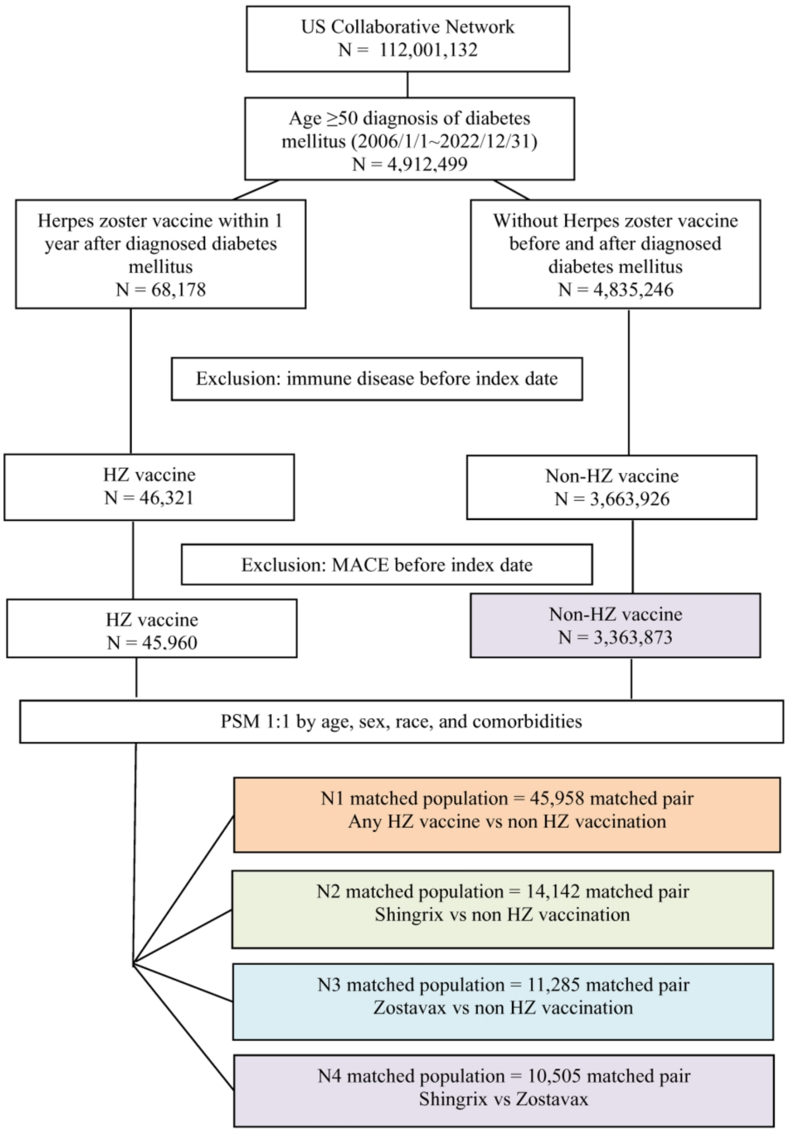

Figure 1. Detailed flow chart illustrating the division of participants into four groups based on Herpes Zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to non-vaccinated controls yielded 42,663 pairs (N1). Matching Shingrix vaccinated to non-vaccinated controls resulted in 11,955 pairs (N2), Zostavax vaccinated to non-vaccinated controls yielded 10,973 pairs (N3), and Shingrix vs. Zostavax vaccination resulted in 8,331 pairs (N4).

153x211mm (300 x 300 DPI)

Supplementary table 1. Detailed coding of this study.

Inclusion criteria: diabetes mellitus

- **Presence of ICD-10 CM codes:** E10 or E11
- ICD-10-CM: E11, Type 2 diabetes mellitus
- ICD-10-CM: E10, Type 1 diabetes mellitus

Herpes Zoster vaccine codes:

Procedure code:

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- UMLS:SNOMED:459891000124102 (Herpes zoster vaccination)
- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)

Medication code:

- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N1 population (any HZ vaccine):

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- UMLS:SNOMED:459891000124102 (Herpes zoster vaccination)
- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N2 population (Shingrix):

- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N3 population (Zostavax):

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)

N4 population (Shingrix VS Zostavax):

- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))
- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)

Outcomes:

Code for major adverse cardiovascular event (MACE)

Item	ICD-10-CM
Cardiovascular disease	
Coronary artery disease	
Acute myocardial infarction	I21
Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	I22
Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)	I23
Other acute ischemic heart diseases	I24
Stroke	
Nontraumatic subarachnoid hemorrhage	I60
Nontraumatic intracerebral hemorrhage	I61
Other and unspecified nontraumatic intracranial hemorrhage	I62
Cerebral infarction	I63

MACE: Major adverse cardiovascular event.

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

ICD-10-PCS: ICD-10 Procedure Coding System.

CPT: Current Procedural Terminology.

Codes of comorbidities

	ICD-10-CM
Socioeconomic status	
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	Z55-Z65
Comorbidities	
Hypertensive diseases	I10-I1A
Overweight and obesity	E66
Other forms of heart disease	I30-I5A
Chronic kidney disease	N18
Neoplasms	C00-D49
Nicotine dependence	F17.2
Hypertensive chronic kidney disease	I12
Alcohol related disorders	F10
Fibrosis and cirrhosis of liver	K74
Unspecified dementia	F03
Alcoholic liver disease	K70
Alzheimer's disease	G30
Dementia in other diseases classified elsewhere	F02
Hepatic failure, not elsewhere classified	K72
Chronic hepatitis, not elsewhere classified	K73
Vascular dementia	F01
Rheumatoid arthritis with rheumatoid factor	M05

Supplementary Table 2. Demographic Characteristics of Individuals with and without the Herpes Zoster Vaccine Before and After PSM (N1 matched population)

	Before PSM			After PSM		
	Any vaccine N = 45,960	Non-HZ vaccine N = 3,363,873	SMD	Any vaccine N1 = 45,958	Non-HZ vaccine N1 = 45,958	SMD
Age	63.46 ± 7.76	63.30 ± 9.30	0.019	63.46 ± 7.76	63.46 ± 7.85	0.001
Sex						
Female	22594 (49.16)	1599758 (47.56)	0.032	22592 (49.16)	22585 (49.14)	<0.001
Male	20606 (44.84)	1656250 (49.24)	0.088	20606 (44.84)	21544 (46.88)	0.041
Race						
White	27076 (58.91)	1950119 (57.97)	0.019	27076 (58.92)	27056 (58.87)	0.001
Black or African American	7218 (15.71)	563189 (16.74)	0.028	7218 (15.71)	7280 (15.84)	0.004
Asian	2928 (6.37)	142295 (4.23)	0.096	2926 (6.37)	2904 (6.32)	0.002
Social economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	513 (1.12)	8856 (0.26)	0.103	512 (1.11)	433 (0.94)	0.017
Comorbidities						
Hypertensive diseases	25190 (54.81)	463468 (13.78)	0.959	25188 (54.81)	25214 (54.86)	0.001
Overweight and obesity	8980 (19.54)	149819 (4.45)	0.477	8978 (19.54)	8969 (19.52)	<0.001
Other forms of heart disease	5651 (12.30)	205284 (6.10)	0.216	5651 (12.30)	5548 (12.07)	0.007
Chronic kidney disease	3257 (7.09)	89980 (2.68)	0.206	3256 (7.09)	3238 (7.05)	0.002
Neoplasms	3815 (8.30)	83995 (2.50)	0.259	3814 (8.30)	3820 (8.31)	<0.001
Nicotine dependence	2673 (5.82)	67311 (2.00)	0.198	2673 (5.82)	2647 (5.76)	0.002
Hypertensive chronic kidney disease	1175 (2.56)	26124 (0.78)	0.139	1175 (2.56)	1155 (2.51)	0.003
Alcohol related disorders	734 (1.60)	18739 (0.56)	0.101	734 (1.60)	667 (1.45)	0.012
Fibrosis and cirrhosis of liver	438 (0.95)	19169 (0.57)	0.044	438 (0.95)	414 (0.90)	0.005
Unspecified dementia	235 (0.51)	7108 (0.21)	0.050	235 (0.51)	219 (0.48)	0.005
Alcoholic liver disease	189 (0.41)	6594 (0.20)	0.039	189 (0.41)	186 (0.41)	0.001
Alzheimer's disease	144 (0.31)	3447 (0.10)	0.046	144 (0.31)	128 (0.28)	0.006
Dementia in other diseases classified elsewhere	161 (0.35)	3858 (0.12)	0.049	161 (0.35)	134 (0.29)	0.010
Hepatic failure, not elsewhere classified	140 (0.31)	5878 (0.18)	0.027	140 (0.31)	124 (0.27)	0.007
Chronic hepatitis, not elsewhere classified	21 (0.05)	730 (0.02)	0.013	21 (0.05)	15 (0.03)	0.007
Vascular dementia	61 (0.13)	1394 (0.04)	0.031	61 (0.13)	46 (0.10)	0.010
Rheumatoid arthritis with rheumatoid factor	22 (0.05)	1081 (0.03)	0.008	22 (0.05)	24 (0.05)	0.002

Any vaccine: Shingrix or Zostavax; HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference

Supplementary table 3. Demographic Characteristics of Individuals with Shingrix vaccination and without the Herpes Zoster Vaccination Before and After PSM (N2 matched population)

	Before PSM			After PSM		
	Shingrix N = 14,142	Non-HZ vaccine N = 3,363,856	SMD	Shingrix N2 = 14,142	Non-HZ vaccine N2 = 14,142	SMD
Age	65.08 ± 8.47	63.30 ± 9.30	0.201	65.08 ± 8.47	65.08 ± 8.55	<0.001
Sex						
Female	6857 (48.49)	1599752 (47.56)	0.019	6857 (48.49)	6880 (48.65)	0.003
Male	5945 (42.04)	1656239 (49.24)	0.145	5945 (42.04)	6534 (46.20)	0.084
Race						
White	8222 (58.14)	1950118 (57.97)	0.003	8222 (58.14)	8246 (58.31)	0.003
Black or African American	2320 (16.41)	563189 (16.74)	0.009	2320 (16.41)	2337 (16.53)	0.003
Asian	870 (6.15)	142285 (4.23)	0.087	870 (6.15)	845 (5.98)	0.007
Social economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	191 (1.35)	8856 (0.26)	0.122	191 (1.35)	166 (1.17)	0.016
Comorbidities						
Hypertensive diseases	8659 (61.23)	463464 (13.78)	1.124	8659 (61.23)	8672 (61.32)	0.002
Overweight and obesity	3347 (23.67)	149816 (4.45)	0.575	3347 (23.67)	3362 (23.77)	0.002
Other forms of heart disease	2088 (14.77)	205281 (6.10)	0.286	2088 (14.77)	2059 (14.56)	0.006
Chronic kidney disease	1443 (10.20)	89978 (2.68)	0.310	1443 (10.20)	1409 (9.96)	0.008
Neoplasms	1280 (9.05)	83993 (2.50)	0.284	1280 (9.05)	1276 (9.02)	0.001
Nicotine dependence	946 (6.69)	67311 (2.00)	0.231	946 (6.69)	932 (6.59)	0.004
Hypertensive chronic kidney disease	568 (4.02)	26124 (0.78)	0.213	568 (4.02)	545 (3.85)	0.008
Alcohol related disorders	275 (1.95)	18739 (0.56)	0.125	275 (1.95)	260 (1.84)	0.008
Fibrosis and cirrhosis of liver	158 (1.12)	19168 (0.57)	0.060	158 (1.12)	136 (0.96)	0.015
Unspecified dementia	111 (0.79)	7108 (0.21)	0.082	111 (0.79)	104 (0.74)	0.006
Alcoholic liver disease	82 (0.58)	6594 (0.20)	0.062	82 (0.58)	72 (0.51)	0.016
Alzheimer's disease	69 (0.49)	3447 (0.10)	0.071	69 (0.49)	65 (0.46)	0.004
Dementia in other diseases classified elsewhere	76 (0.54)	3858 (0.12)	0.074	76 (0.54)	71 (0.50)	0.005
Hepatic failure, not elsewhere classified	57 (0.40)	5877 (0.18)	0.043	57 (0.40)	47 (0.33)	0.012
Chronic hepatitis, not elsewhere classified	10 (0.07)	730 (0.02)	0.023	10 (0.07)	13 (0.09)	0.007
Vascular dementia	30 (0.21)	1394 (0.04)	0.048	30 (0.21)	24 (0.17)	0.010
Rheumatoid arthritis with rheumatoid factor	11 (0.08)	1081 (0.03)	0.019	11 (0.08)	10 (0.07)	0.003

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
If the patient's count is 1-10, the results indicate a count of 10.

Supplementary table 4. Demographic Characteristics of Individuals with Zostavax vaccination and without the Herpes Zoster Vaccination Before and After PSM (N3 matched population)

	Before PSM			After PSM		
	Zostavax N = 11,285	Non-HZ vaccine N = 3,363,856	SMD	Zostavax N3 = 11,285	Non-HZ vaccine N3 = 11,285	SMD
Age	65.18 ± 6.07	63.30 ± 9.30	0.239	65.18 ± 6.07	65.20 ± 6.18	0.004
Sex						
Female	5802 (51.41)	1599752 (47.56)	0.077	5802 (51.41)	5808 (51.47)	0.001
Male	5018 (44.47)	1656239 (49.24)	0.096	5018 (44.47)	5087 (45.08)	0.012
Race						
White	7009 (62.11)	1950118 (57.97)	0.085	7009 (62.11)	7005 (62.07)	0.001
Black or African American	1677 (14.86)	563189 (16.74)	0.052	1677 (14.86)	1679 (14.88)	<0.001
Asian	541 (4.79)	142285 (4.23)	0.027	541 (4.79)	544 (4.82)	0.001
Social economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	71 (0.63)	8856 (0.26)	0.055	71 (0.63)	62 (0.55)	0.010
Comorbidities						
Hypertensive diseases	5613 (49.74)	463464 (13.78)	0.837	5613 (49.74)	5620 (49.80)	0.001
Overweight and obesity	1355 (12.01)	149816 (4.45)	0.277	1355 (12.01)	1346 (11.93)	0.002
Other forms of heart disease	1215 (10.77)	205281 (6.10)	0.168	1215 (10.77)	1208 (10.70)	0.002
Chronic kidney disease	685 (6.07)	89978 (2.68)	0.167	685 (6.07)	690 (6.11)	0.002
Neoplasms	787 (6.97)	83993 (2.50)	0.212	787 (6.97)	767 (6.80)	0.007
Nicotine dependence	407 (3.61)	67311 (2.00)	0.097	407 (3.61)	419 (3.71)	0.006
Hypertensive chronic kidney disease	219 (1.94)	26124 (0.78)	0.101	219 (1.94)	218 (1.93)	0.001
Alcohol related disorders	0 (0.00)	3546 (0.11)	0.046	0 (0.00)	10 (0.09)	0.042
Fibrosis and cirrhosis of liver	116 (1.03)	18739 (0.56)	0.053	116 (1.03)	113 (1.00)	0.003
Unspecified dementia	56 (0.50)	19168 (0.57)	0.010	56 (0.50)	56 (0.50)	<0.001
Alcoholic liver disease	45 (0.40)	7108 (0.21)	0.034	45 (0.40)	38 (0.34)	0.010
Alzheimer's disease	22 (0.20)	6594 (0.20)	<0.001	22 (0.20)	24 (0.21)	0.004
Dementia in other diseases classified elsewhere	33 (0.29)	3447 (0.10)	0.043	33 (0.29)	31 (0.28)	0.003
Hepatic failure, not elsewhere classified	35 (0.31)	3858 (0.12)	0.042	35 (0.31)	37 (0.33)	0.003
Chronic hepatitis, not elsewhere classified	14 (0.12)	5877 (0.18)	0.013	14 (0.12)	15 (0.13)	0.002
Vascular dementia	10 (0.09)	730 (0.02)	0.029	10 (0.09)	10 (0.09)	<0.001
Rheumatoid arthritis with rheumatoid factor	10 (0.09)	1394 (0.04)	0.019	10 (0.09)	10 (0.09)	<0.001

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.

If the patient's count is 1-10, the results indicate a count of 10.

Supplementary table 5. Demographic Characteristics of Individuals with Shingrix vaccination and Zostavax Vaccination Before and After PSM (N4 matched population)

	Before PSM			After PSM		
	Shingrix N = 14,142	Zostavax N = 11,285	SMD	Shingrix N4 = 10,505	Zostavax N4 = 10,505	SMD
Age	65.08 ± 8.47	65.18 ± 6.07	0.013	65.33 ± 8.07	65.20 ± 6.08	0.018
Sex						
Female	6857 (48.49)	5802 (51.41)	0.059	5318 (50.62)	5402 (51.42)	0.016
Male	5945 (42.04)	5018 (44.47)	0.049	4314 (41.07)	4639 (44.16)	0.06[illegible]
Race						
White	8222 (58.14)	7009 (62.11)	0.081	6497 (61.85)	6358 (60.52)	0.02[illegible]
Black or African American	2320 (16.41)	1677 (14.86)	0.043	1559 (14.84)	1654 (15.75)	0.02[illegible]
Asian	870 (6.15)	541 (4.79)	0.060	523 (4.98)	540 (5.14)	0.00[illegible]
Social economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	191 (1.35)	71 (0.63)	0.073	70 (0.67)	70 (0.67)	<0.00[illegible]
Comorbidities						
Hypertensive diseases	8659 (61.23)	5613 (49.74)	0.233	5635 (53.64)	5605 (53.36)	0.00[illegible]
Overweight and obesity	3347 (23.67)	1355 (12.01)	0.308	1393 (13.26)	1354 (12.89)	0.01[illegible]
Other forms of heart disease	2088 (14.77)	1215 (10.77)	0.120	1234 (11.75)	1194 (11.37)	0.01[illegible]
Chronic kidney disease	1443 (10.20)	685 (6.07)	0.152	646 (6.15)	685 (6.52)	0.01[illegible]
Neoplasms	1280 (9.05)	787 (6.97)	0.077	756 (7.20)	775 (7.38)	0.00[illegible]
Nicotine dependence	946 (6.69)	407 (3.61)	0.140	403 (3.84)	406 (3.87)	0.00[illegible]
Hypertensive chronic kidney disease	568 (4.02)	219 (1.94)	0.122	209 (1.99)	219 (2.09)	0.00[illegible]
Alcohol related disorders	275 (1.95)	116 (1.03)	0.076	111 (1.06)	115 (1.10)	0.00[illegible]
Fibrosis and cirrhosis of liver	158 (1.12)	56 (0.50)	0.069	62 (0.59)	55 (0.52)	0.00[illegible]
Unspecified dementia	111 (0.79)	45 (0.40)	0.050	31 (0.30)	45 (0.43)	0.02[illegible]
Alcoholic liver disease	82 (0.58)	22 (0.20)	0.062	18 (0.17)	21 (0.20)	0.00[illegible]
Alzheimer's disease	69 (0.49)	33 (0.29)	0.031	34 (0.32)	32 (0.31)	0.00[illegible]
Dementia in other diseases classified elsewhere	76 (0.54)	35 (0.31)	0.035	35 (0.33)	35 (0.33)	<0.00[illegible]
Hepatic failure, not elsewhere classified	57 (0.40)	14 (0.12)	0.054	13 (0.12)	14 (0.13)	0.00[illegible]
Chronic hepatitis, not elsewhere classified	10 (0.07)	10 (0.09)	0.006	10 (0.10)	10 (0.10)	<0.00[illegible]
Vascular dementia	30 (0.21)	10 (0.09)	0.032	10 (0.10)	10 (0.10)	<0.00[illegible]
Rheumatoid arthritis with rheumatoid factor	11 (0.08)	10 (0.09)	0.004	10 (0.10)	10 (0.10)	<0.00[illegible]

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
If the patient's count is 1-10, the results indicate a count of 10.

Supplementary table 6. Risk of MACE among different follow-up period in N1 matched population.

	Exposure group		Comparison		
	N	No. of event	N	No. of event	HR (95% C.I.)
Follow-up period					
≤5 years	45,958	2,513	45,958	3,051	0.70 (0.66–0.74)
5-10 years	43,445	812	42,798	799	0.93 (0.84–1.02)
>10 years	42,633	149	41,999	238	1.13 (0.92–1.39)

MACE: major adverse cardiovascular events

N1 indicate any herpes zoster vaccination versus non-herpes zoster vaccination population

Supplementary table 7. Stratification analysis of risk of MACE in different Shingrix dosage

	All vaccine		Non-HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Shingrix 1 dose	10760	546	10760	990	0.66 (0.59–0.73)
Shingrix 2 doses	3237	167	3237	288	0.73 (0.59–0.89)

MACE: major adverse cardiovascular events; HZ: herpes zoster

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Association of Herpes Zoster Vaccination and Cardiovascular Risk in patients with Diabetes: Long-Term Insights from a Retrospective Cohort Study

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Abstract

Objectives: Herpes zoster (HZ) infection associated with higher risk of major adverse cardiovascular events (MACE), including stroke and coronary artery disease (CAD). Patients with diabetes are at an increased risk of MACE, highlighting the importance of studying this population to assess the potential protective effects of HZ vaccination. This study aims to investigate the risk of MACE after HZ vaccination in patients with diabetes

Design: Retrospective cohort study.

Setting: Community-based population in the United States.

Participants: Utilizing the TrinetX database, the study included 4.9 million patients with diabetes from 2006 to 2022. It established two cohorts: 68,178 patients in the HZ vaccination (comprising any HZ vaccine, Shingrix or Zostavax) and 4,835,246 patients in the no HZ vaccination group. After excluding patients with history of MACE, immune disease, and complications of HZ prior to the index date, the study cohort was reduced to 45,960 patients. Propensity Score Matching, accounting for age, sex, race, socioeconomic status and disease comorbidities, was conducted to minimize study bias.

Interventions: HZ vaccination

Primary and secondary outcome measures: MACE outcomes, defined as the first occurrence of CAD or stroke. Comparative risk analysis was conducted using hazard ratios (HR)

Results: Post-matching, the mean patient age was 63.5 years, with 49.2% females. The incidence rate of MACE was lower among vaccinated patients compared to no vaccinated individuals, with a HR of 0.76 (0.72–0.79). For secondary endpoints, the HRs were 0.73 (0.69–0.78) for CAD, 0.79 (0.74–0.84) for stroke, and 0.54 (0.52–0.57) for all-cause mortality. These protective effects remained consistent across different age groups, sexes, and diabetes types, supporting the potential benefit of HZ vaccination in reducing cardiovascular risk.

Conclusions: HZ vaccination associated with lower risk of MACE in patients with diabetes. Further prospective study is critically needed to confirm this finding.

Funding: This work was supported by grants from the Chung Shan Medical University Hospital (CSH-2020-C-016).

Strengths and Limitations of this study:

- This study utilized a large community database, providing robust and representative data for analysis
- This study boasts a long follow-up duration, allowing us to assess the impact of herpes zoster vaccination on MACE risk over an extended period.
- This study evaluated the risk of MACE after herpes zoster vaccination in diabetes patients
- This study is limited by the potential for residual confounding that cannot be entirely eliminated.

Introduction

Herpes zoster (HZ), commonly known as shingles, is a prevalent viral infection caused by the reactivation of the varicella-zoster virus, which remains latent in the body following an initial chickenpox infection.[1] Triggered typically by aging, immunosuppression, or stress, this reactivation manifests as painful, blistering skin eruptions localized to specific dermatomes.[2,3] Additionally, It is particularly noted for its complications, such as postherpetic neuralgia, which can cause prolonged discomfort.[4,5] Recent studies have shifted focus towards the broader impacts of HZ, especially its association with an increased risk of major adverse cardiovascular events (MACE), including stroke and myocardial infarction.[6–18] Importantly, research suggests that the risk of stroke is time-dependent following an HZ infection, with a significant elevation in the first month at 78%, reducing to 43% after 3 months, and further to 20% after 1 year, before leveling off to a non-significant 7% increase up to 3 years post-infection.[19] This time-dependent risk profile underscores the importance of timely intervention and prevention strategies.

Within the population of individuals with diabetes mellitus, the interplay between HZ infection and cardiovascular risk is of particular concern. Diabetes, a chronic condition characterized by elevated blood glucose levels, significantly heightens the risk of cardiovascular diseases, making this group particularly susceptible to the compounded effects of HZ infection.[19,20] The risk of cardiovascular events in patients with diabetes is two to threefold higher than in those without diabetes, underscoring the critical need for comprehensive strategies to mitigate these risks.[21,22] The exacerbation of cardiovascular complications by HZ may be mediated through vasculopathy, a process potentially involving direct viral invasion of intra- or extracranial arteries, culminating in vessel wall damage through inflammatory responses characterized by multinucleated giant cells and epithelioid macrophages.[23–27] Additionally, HZ may provoke an inflammatory environment within the vessel wall, fostering a pro-coagulation state, further underscoring the complex interrelation between HZ infection and cardiovascular morbidity in diabetes.[24,28,29]

The advent of HZ vaccines, such as the recombinant zoster vaccine (RZV or Shingrix) and the live attenuated zoster vaccine (LZV or Zostavax), offers a promising strategy for reducing the incidence of HZ and its associated complications.[30–32] These vaccines have demonstrated robust efficacy in the general population aged 50 years and older, reducing both the occurrence of HZ and the severity of postherpetic neuralgia.[33] Given the established link between HZ infection and an increased risk of cardiovascular events, it is plausible to hypothesize that HZ vaccination could also confer protective effects against MACE, particularly in the diabetes population. However, prior research on this topic has produced conflicting results. Some studies suggest a reduced risk of cardiovascular events following HZ vaccination, while others report no significant association.[34–37] The inconsistency in findings is partly due to differences in study designs, populations, and follow-up durations, leaving gaps in understanding the vaccine's impact, especially in high-risk populations like individuals with diabetes. This study aims to address these gaps by evaluating the association between HZ vaccination and the incidence of composite MACE in individuals with diabetes.

Methods

Study population

This retrospective cohort study utilized data from the TriNetX database, which aggregates electronic medical records from healthcare organizations across the United States. The TriNetX database is a comprehensive repository of de-identified electronic health records from a diverse range of healthcare organizations, including hospitals, clinics, and medical practices. It encompasses data on patient demographics, diagnoses, procedures, medications, laboratory results, and other clinical variables. The TriNetX database has been validated and has been widely used in many representative publications, supporting its credibility for research purposes.[38–40] The total number of patients available in the TriNetX network is 112 million.

Cohort selection

Cases were defined as individuals with age 50 or older, who diagnosed with diabetes mellitus who received HZ vaccination, including Shingrix or Zostavax, within 1 year of their diabetes diagnosis, with the index date set as the date of vaccination. This timeframe was chosen to minimize potential differences and biases between cases and controls. Conversely, the control group comprised patients with diabetes who did not receive any HZ vaccination during the study period, with the index date corresponding to the first date of diabetes diagnosis. This study was conducted from January 1, 2006, to December 12, 2022.

Exclusion Criteria

Patients with a history of MACE before the index date were excluded to ensure that the study focused on incident cases of cardiovascular events rather than pre-existing conditions. Immune-compromised individuals were excluded because their underlying conditions might confound the relationship between HZ vaccination and MACE. These conditions, such as Human immunodeficiency Virus (HIV), malignancy, and immune diseases (rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis) can affect the immune response and potentially influence the risk of cardiovascular events. Excluding individuals with a prior diagnosis of HZ and its complications (post-herpetic neuralgia, Bell's palsy, Ramsay-Hunt syndrome) before the index date helped to ensure that only new cases of these conditions were considered during the study period, reducing potential bias in the analysis.

Study codes and disease comorbidities.

Study codes and disease comorbidities were detailed in supplementary Table 1. In summary, the coding for diabetes diagnosis utilized International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) codes of E10-E11, while patients who received HZ vaccination were identified with procedure code and medical prescription normalized Medical prescription (RxNorm). Furthermore, disease comorbidities such as hypertension, obesity, and chronic kidney disease were allocated specific codes for identification and analysis purposes. This comprehensive coding system facilitated the organization and interpretation of patient data, ensuring clarity and precision in the study's findings. The definition of socioeconomic status (SES) in our study is based on ICD-10 coding (Z55-Z65), which includes factors related to education, employment, income, and social environment.

This study aimed to investigate the association between HZ vaccination and the incidence of MACE among individuals with diabetes aged 50 years and older. The focus on this age group was driven by their heightened risk of MACE and their alignment with vaccination guidelines.[41] The primary endpoint of this study is defined as the first occurrence of composite MACE, comprising coronary artery disease (CAD) or stroke following the index date. Secondary endpoints include individual outcomes of CAD, stroke, and all-cause mortality. Subgroup analysis was conducted by stratifying age, sex, and type of diabetes. Additionally, we also explored the risk of MACE within the first year of follow-up.

Propensity score matching

Propensity score matching (PSM) is a statistical technique used to balance cohorts in observational studies by adjusting for potential confounders. It ensures comparability between the HZ vaccine and no HZ vaccine groups when randomization is not feasible. This is achieved by estimating the probability, or "propensity score," of a patient belonging to one cohort based on observed covariates.

In this study, researchers defined two cohorts of interest (HZ vaccine vs. no HZ vaccine) and identified covariates—factors that may influence both treatment allocation and outcomes. These covariates include age, sex, race, socio-economic status (SES), and various comorbidities, such as hypertensive diseases, overweight and obesity, other forms of heart disease, chronic kidney disease, neoplasms, nicotine dependence, hypertensive chronic kidney disease, alcohol related disorders, fibrosis and cirrhosis of liver, unspecified dementia, alcoholic liver disease, Alzheimer's disease, dementia, hepatic failure, chronic hepatitis, vascular dementia, rheumatoid arthritis with rheumatoid factor.

Using logistic regression, the system calculates each patient's propensity score, which reflects the probability of belonging to a specific cohort given the covariates. The system employs a greedy nearest neighbor matching with a caliper of 0.1 pooled standard deviations, ensuring that patients in the smaller cohort are matched to those in the larger cohort based on the closest propensity scores within the defined range. This process generates balanced matched subsets.

After matching, the outcomes of interest are compared between these balanced subsets rather than the original cohorts, effectively minimizing the effects of confounding variables. PSM is implemented within a federated data network, pooling data from multiple healthcare organizations. To mitigate bias introduced by the order of data during matching, patient records are randomized prior to matching. Deterministic randomization is applied to ensure the reproducibility of the analyses. The PSM analysis for this study was conducted using the built-in tools provided by the TriNetX platform.

To evaluate the impact of HZ vaccination on MACE, we divided the study into four populations for analysis, designated as N1 through N4. The matching process involved four different comparisons: (1) cases vaccinated with any HZ vaccine matched to no HZ vaccinated controls (N1), (2) cases vaccinated with Shingrix matched to no HZ vaccinated controls (N2), (3) cases vaccinated with Zostavax matched to no HZ vaccinated controls (N3), and (4) cases vaccinated with Shingrix matched against those vaccinated with Zostavax (N4). This approach allowed us to assess both the overall effect of HZ vaccination and direct comparisons between vaccine types.

Statistical Analysis

TriNetX ensures data quality through rigorous checks and monitoring. The platform validates data formatting, ensuring proper representation of dates and required fields (e.g., patient identifiers), rejecting records with missing essential information. Referential integrity checks verify successful data integration across tables, while volume trends are monitored during data refreshes to maintain validity. Patient records must include at least one non-demographic fact to be included, as records with only demographic data are excluded. TriNetX collaborates with data providers by sharing regular feedback and data quality scorecards, enabling providers to assess their data quality and compare it with peers based on regional or population-specific benchmarks. Data quality is assessed at various stages: during onboarding of new providers, periodic data refreshes, significant pipeline changes, or troubleshooting requests. The process is dynamic, with ongoing improvements in metrics, collection methods, and evaluation procedures to enhance overall data reliability and operational efficiency.

TriNetX ensures cohort integrity by using a master patient index, tokenization, and data normalization to prevent duplicate patient records. It applies cross-site deduplication, distinct patient count algorithms, and real-time filtering to ensure each patient is counted only once, minimizing bias and maintaining data accuracy in research analyses.

Descriptive statistics were employed to summarize the baseline characteristics of the study population, including age, sex, race, SES, and disease comorbidities. Following PSM, the balance between matched cohorts was evaluated using standardized mean differences (SMD), where an SMD value of less than 0.1 was considered indicative of a well-matched cohort. The incidence of MACE was analyzed using a Kaplan-Meier survival curve with statistical significance determined using the log-rank test. Cox proportional hazard model was further applied to evaluate the association between group assignment and the risk of MACE and all-cause mortality, providing hazard ratios (HRs) with 95% confidence intervals. All analyses were performed using the TriNetX online platform, which utilizes R version 4.0.2 as its underlying statistical framework.

Patient and Public Involvement

The patient data utilized in this study were fully de-identified to ensure privacy and confidentiality. This procedure was implemented to prevent the direct or indirect identification of individual patients, thereby safeguarding patient privacy in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations. The study protocol was approved by the Institutional Review Board of Chung Shan Medical University Hospital, identified by the reference number CS2-23159.

Sensitivity Analysis

To address potential healthy vaccine bias, we conducted a post-hoc sensitivity analysis by identifying a subgroup of patients who received HZ vaccination at least one year after their diabetes diagnosis. This additional analysis aimed to determine whether delaying vaccination after diabetes diagnosis affected the primary outcomes.

Results

This study included a total of 112 million patients (figure 1). Following the filtration process to identify patients with a diagnosis of diabetes, we narrowed the cohort down to 4.9 million patients. Among these, 68,178 patients were identified as cases, having received any HZ vaccination within 1 year diagnosis of diabetes, while 4,835,246 patients served as controls, having diabetes without any HZ vaccination. Further exclusion of patients with immune diseases and a history of MACE before the index date resulted in 45,960 cases for any HZ vaccination and 3,363,873 controls. Subsequently, we divided the study into four populations for evaluation, designated as N1 through N4. The matching of cases vaccinated with any HZ vaccine to no HZ vaccinated controls yielded 45,958 pairs (N1). Meanwhile, matching cases vaccinated with Shingrix to no HZ vaccinated controls resulted in 14,142 pairs (N2), and matching cases vaccinated with Zostavax to no HZ vaccinated controls resulted in 11,285 pairs (N3). Finally, matching cases vaccinated with Shingrix against those vaccinated with Zostavax resulted 10,505 pairs (N4).

Table 1 presents baseline characteristics for both HZ vaccination cases and no HZ vaccination controls. Prior to PSM, notable differences were observed in several comorbidities, including hypertensive diseases, obesity, heart disease, chronic kidney disease (CKD), neoplasm, and nicotine dependence. The mean age was 63.5 years, with 49.1% female and 58.9% white race. Disease comorbidities included patients with hypertensive disease accounting for 54.8%, overweight and obesity at 19.5%, other forms of heart disease at 12.3%, CKD at 7.1%, neoplasm at 8.3%, and nicotine dependence at 5.8%. Patients with socioeconomic status issues accounted for 1.1% of the HZ vaccination group. Following the matching process, the disparity between cases and controls was significantly reduced, as evidenced by the standardized mean differences (SMD) being less than 0.1, detailed in Supplementary Tables 2-5.

Table 2 presents the risk of MACE among patients with HZ vaccination compared to those without vaccination. The risk of MACE, CAD, stroke, and all-cause mortality was consistently lower among patients with any HZ vaccination compared to those without vaccination, as evidenced by hazard ratios (HR) and 95% confidence intervals (CI) of 0.76 (0.72–0.79), 0.73 (0.69–0.78), 0.79 (0.74–0.84), and 0.54 (0.52–0.57), respectively. These findings underscore the potential protective effect of any HZ vaccination against adverse cardiovascular outcomes. In solitary use, both Shingrix and Zostavax demonstrated effectiveness in reducing the risk of MACE, CAD, stroke, and all-cause mortality compared to no vaccination. For Shingrix, the risks were 0.84 (0.76–0.91) for MACE, 0.78 (0.69–0.88) for CAD, 0.87 (0.77–0.99) for stroke, and 0.53 (0.48–0.58) for all-cause mortality. Similarly, Zostavax showed HR and 95% CI of 0.81 (0.75–0.88) for MACE, 0.72 (0.65–0.80) for CAD, 0.90 (0.81–1.01) for stroke, and 0.58 (0.53–0.62) for all-cause mortality.

These results suggest that both Shingrix and Zostavax offer protective benefits against MACE when administered individually. When comparing Shingrix to Zostavax, interesting findings emerged. While a neutral result was observed for MACE and stroke, a notable difference was detected in CAD. The HR and 95% CI for CAD were 1.16 (1.01–1.34), indicating a higher risk of CAD among individuals receiving Shingrix compared to Zostavax. However, no significant differences were noted in stroke, all-cause mortality, or overall MACE between the two vaccines. This highlights the importance of considering specific cardiovascular outcomes when evaluating the comparative effectiveness of different HZ vaccines.

The stratification analysis of the risk of MACE among different groups revealed consistent findings across various demographic and clinical factors (table 3). Regardless of age, individuals aged 50-65 years and those over 65 years demonstrated a lower risk of MACE with HZ vaccination compared to no vaccination, with HR and 95% CI of 0.80 (0.75–0.86) and 0.83 (0.78–0.89), respectively. Similarly, both females and males experienced a reduced risk of MACE with vaccination, with HR and 95% CI of 0.77 (0.72–0.83) and 0.74 (0.69–0.79), respectively. Furthermore, individuals with type 1 or type 2 diabetes also exhibited a lower risk of MACE with HZ vaccination compared to no vaccination, with HR and 95% CI of 0.25 (0.08–0.75) for type 1 diabetes and 0.71 (0.68–0.75) for type 2 diabetes. These consistent protective effects across different age groups, sexes, and types of diabetes underscore the robustness of the association between HZ vaccination and reduced cardiovascular risk.

When considering the timing within the first year of vaccination, Table 4 illustrates a notable trend in the risk of MACE. The risk of MACE is observed to be the lowest in the first month following vaccination, with a HR and 95% CI of 0.21 (0.16–0.27). Subsequently, the risk of MACE is gradually increases over time, yet remains significantly lower compared to no vaccination. At the end of the first year, the HR and 95% CI for MACE stand at 0.57 (0.52–0.62). In the long-term follow-up, as depicted in Supplementary table 6, the risk of MACE demonstrates consistent patterns across different time intervals. Over a follow-up period of up to 5 years, individuals with HZ vaccination exhibit a significantly lower risk of MACE compared to no vaccinated counterparts, with a HR and 95% CI of 0.70 (0.66–0.74). However, the protective effects seem to wane with time. During follow-up periods of 5-10 years and beyond 10 years, the HR and 95% CI for MACE among vaccinated individuals are observed to be 0.93 (0.84–1.02) and 1.13 (0.92–1.39), respectively.

The protective efficacy of Shingrix demonstrates consistency, whether administered as a single dose or a two-dose regimen, when compared to a no HZ vaccinated control group. Specifically, the HR for individuals receiving one dose of Shingrix was 0.66 (95% CI: 0.59–0.73), while for those completing the two-dose regimen, the HZ was 0.73 (95% CI: 0.59–0.89), as detailed in Supplementary table 7. Furthermore, a post-hoc sensitivity analysis was conducted by identifying a subgroup of patients who received HZ vaccination at least one year after their diabetes diagnosis. The results were consistent with our primary findings, confirming that the protective effect of HZ vaccination against MACE remained robust, regardless of the timing of vaccination relative to diabetes diagnosis (supplementary figure 1). Detailed results of this analysis are provided in Supplementary Tables 8 and 9.

The Kaplan-Meier survival curve (supplementary figure 2) illustrates the cumulative incidence of MACE over time, comparing HZ-vaccinated vs. no vaccinated patients and a head-to-head analysis of Shingrix vs. Zostavax. The curves show a lower cumulative incidence of MACE in vaccinated patients, suggesting a protective effect of HZ vaccination. In the Shingrix vs. Zostavax comparison, the results indicate a neutral effect between the two vaccines, with no significant difference in MACE risk.

Discussion

To the best of our knowledge, this study represents the first comprehensive investigation into the risk of MACE among patients with diabetes following HZ vaccination. Our findings reveal a significant decrease in the risk of MACE subsequent to HZ vaccination. This protective effect extends to other critical outcomes, including CAD, stroke, and all-cause mortality, demonstrating consistent benefits across multiple cardiovascular endpoints. Furthermore, our subgroup analysis highlights the robustness of the protective effect, as it remains consistent across different age groups, sexes, and types of diabetes. Interestingly, our study also indicates that the strongest protective effects appear to manifest within the first year following vaccination, but these effects appear to diminish over time. These findings underscore the potential additional benefits of HZ vaccination in reducing cardiovascular risk among individuals with diabetes.

HZ is increasingly being investigated for its potential link to cardiovascular disease. Initial evidence suggesting HZ as a risk factor for cardiovascular disease comes primarily from retrospective analyses,[6–18] which have documented a higher frequency of cardiovascular events—such as stroke and myocardial infarction—in individuals who have had HZ episodes compared to those who have not. Following these preliminary observations, further research aimed at confirming and expanding upon this association has been conducted through larger-scale studies across diverse global populations. This extensive research has shown an increased risk of cardiovascular events post-HZ infection, underscoring the necessity for increased clinical awareness and management of cardiovascular risk factors among those with a history of HZ.[34,37]

Several mechanisms have been proposed to elucidate the link between HZ infection and an increased risk of MACE. A primary mechanism believed to be implicated is vasculopathy, wherein the virus directly infects and spreads from the nerve to the cerebral artery, eliciting inflammation, pathological vascular remodeling, and subsequently heightening the risk of stroke.[25,42] Moreover, beyond the direct vascular effects, HZ infection may contribute to elevated blood pressure due to the pain and stress associated with the condition. This elevation in blood pressure could further exacerbate the risk of stroke, given that hypertension is a leading cause of stroke.

Within the existing literature, our study stands out for evaluating patients with the longest follow-up duration and focusing specifically on the diabetes population. Notably, three published studies have been identified, each presenting unique findings. Parameswaran et al.[34] and Yang et al.[37] reported positive HZ vaccination outcomes, while Minnasian et al.[35] found no significant advantage. These studies, characterized by retrospective designs, differ in their data sources, study populations, and methodologies, contributing to the heterogeneity in results.

The distinctive aspect of our study lies in the examination of patients aged between 50 and 65 years old, a demographic often underrepresented in similar analyses.[34,35,37] This age group, typically considered lower risk for MACE compared to those over 65, exhibited intriguing results in our study. Specifically, we observed a significantly reduced risk of MACE among diabetes patients aged 50-65 who received HZ vaccination, with a HR of 0.80 (95% CI: 0.75–0.86), as compared to no vaccinated counterparts. This finding provides valuable insights into the effectiveness of HZ vaccination in reducing MACE risk among individuals who might benefit most from early preventive measures. Another unique aspect of our study is the inclusion of data on patients with type 1 diabetes who received HZ vaccination, a demographic that has been largely overlooked in previous literature. To our knowledge, this is the first study to report outcomes for individuals with type 1 diabetes following HZ vaccination. Our analysis revealed a noteworthy finding, indicating a significantly reduced risk of MACE among patients with type 1 diabetes who received HZ vaccination, with a HR of 0.25 (95% CI: 0.08–0.75). This novel insight underscores the potential benefits of HZ vaccination not only for individuals with type 2 diabetes but also for those with type 1 diabetes, highlighting the importance of considering this population in future vaccination strategies and guidelines.

Parameswaran and colleagues, utilizing Veteran Affairs data, observed a significant protective effect against stroke in elderly males following vaccination with both Zostavax and Shingrix.[34] Their study revealed that patients experienced a notably higher risk of stroke within the first month following recent HZ infection. However, individuals who received at least one zoster vaccination demonstrated a mitigation of this increased risk. Specifically, the odds ratio (OR) for stroke 30 days post-event was 0.57 (95% CI: 0.46–0.72) for Shingrix and 0.77 (95% CI: 0.65–0.91) for Zostavax. Similarly, Yang et al., analyzing US Medicare data, identified a 16% reduction in stroke risk among vaccine recipients aged 66 and older, with enhanced benefits observed in specific subgroups.[37]

Minnasian et al.'s study,[35] conducted within the Medicare population and focusing on patients older than 65 years, revealed a transiently heightened risk of stroke and myocardial infarction associated with HZ infection. Particularly noteworthy was the pronounced increase observed within the initial week following zoster diagnosis, with a 2.4-fold elevated rate of ischemic stroke (incidence rate [IR] 2.37, 95% CI 2.17–2.59) and a 1.7-fold increase in myocardial infarction rate (IR 1.68, 95% CI 1.47–1.92), followed by a gradual reduction over six months. However, the study did not find evidence of a reduction in the IR for ischemic stroke or myocardial infarction among HZ vaccine recipients in the first four weeks following zoster diagnosis. The lack of observed protective effects of the HZ vaccine may be attributed to the limited number of patients in the vaccinated groups, thereby restricting the study's power to adequately assess this outcome. Notably, only 9% of participants received the vaccine during the study period, underscoring the challenge of assessing vaccine effectiveness in real-world settings with low uptake rates. These disparities underscore the importance of considering study-specific factors, such as data sources and population characteristics, when interpreting and comparing research findings.

An additional significant discovery from our research is the most robust protective impact of HZ vaccination against MACE observed during the first year, with this protective effect extending over 5 years of follow-up. This outcome aligns with the observation that the highest risk of stroke occurs within the first year.[19] This phenomenon could be attributed to various potential mechanisms. Firstly, the vaccine may modulate the immune response, reducing systemic inflammation, a key contributor to atherosclerosis and cardiovascular events. Furthermore, by preventing HZ, the vaccine indirectly decreases cardiovascular stress, considering the association between HZ and a heightened risk of stroke and myocardial infarction, particularly in the first year following infection. This dual mechanism—lowering inflammation and averting HZ—accounts for the observed sustained, albeit gradually decreasing, protective effect over time.

The discrepancy between the sum of populations N2 and N3 not equaling the total of N1 can be attributed to the specific inclusion criteria based on procedural and medication codes utilized to identify the vaccination status within our study cohorts. N1 encompasses a broader category of individuals vaccinated with any HZ vaccine, identified through a comprehensive set of codes, including CPT codes 90736 (Zostavax) and 90750 (Shingrix), as well as additional codes for unspecified zoster vaccines (459891000124012) and their respective RXNORM codes (1292422 for Zostavax and 1986821 for Shingrix). This allows for the inclusion of all individuals vaccinated against HZ, capturing a wider demographic. Conversely, N2 and N3 focus on narrower subsets, with N2 including only those vaccinated with Shingrix (via CPT code 90750 and RXNORM code 1986821) and N3 comprising individuals vaccinated with Zostavax (identified by CPT code 90736 and RXNORM code 1292422).

Observing a greater number of events in the Zostavax vaccination group compared to the control group, while the HR remains less than 1, highlights the nuanced nature of HR as a measure of relative risk over time rather than a simple count of events (table 2). This phenomenon indicates that, after adjusting for the duration of follow-up and baseline risk factors, individuals in the Zostavax group experienced a lower rate of events at any given time compared to the no vaccinated group. The HR less than 1 suggests a protective effect of the Zostavax vaccine, reflecting its efficacy in reducing the instantaneous risk of adverse outcomes, despite the apparent higher number of events when viewed without the context of time and population size adjustments. This underscores the importance of HR in providing a more accurate assessment of the vaccine's impact on health outcomes.

It is important to note that the discrepancies in total numbers between Table 2 and Table 3, as well as in other subgroups, are caused by the methodology employed in the TrinetX analyses. Each stratified analysis involves re-matching individuals based on specific criteria, leading to variations in sample sizes and the number of participants experiencing MACE across different tables or subgroups. This re-matching process is designed to ensure that comparisons within each stratification are appropriate and accurate, taking into account the varying characteristics of participants within each subgroup. Consequently, the figures for the total number of individuals and those experiencing MACE in one table cannot simply be summed to match the figures in another table, due to these inherent differences in sample composition and size resulting from the re-matching process.

An intriguing finding emerged from our study when directly comparing the effectiveness of Shingrix and Zostavax, as there is a notable scarcity of head-to-head comparisons in the existing literature, particularly regarding their impact on MACE outcomes. Interestingly, while the American Diabetes Association (ADA) recommends Shingrix vaccination for individuals aged 50 years and older with diabetes,[41] our study observed comparable outcomes between Zostavax and Shingrix, with a slight difference in CAD risk favoring Zostavax. However, it is imperative to interpret these findings with caution, as our analysis is retrospective in nature and there exists a marked difference in the study timing between Zostavax and Shingrix. The reasons for this discrepancy are not fully elucidated but may relate to differences in vaccine composition and the resulting immune response. Zostavax, being a live attenuated vaccine, could potentially elicit a broader and more robust immune response compared to Shingrix, which is a recombinant subunit vaccine. Moreover, Zostavax offers the convenience of requiring only one injection for full protection, whereas Shingrix necessitates two injections. The variations in the immune response elicited by these vaccines may contribute to differences in their effectiveness in preventing MACE outcomes among individuals with diabetes.

Our study benefits from several strengths that enhance the reliability and significance of our findings. Firstly, leveraging data from the TriNetX database, which aggregates electronic medical records from 61 healthcare organizations across the US, provided a robust and extensive dataset for analysis. Secondly, employing a rigorous retrospective cohort study design enabled us to investigate the association between HZ vaccination and MACE among individuals with diabetes with clarity and precision. Additionally, our detailed analysis, including comprehensive stratification by age, sex, and diabetes type, allowed for a nuanced understanding of vaccine effectiveness across diverse subgroups. Lastly, our study's long-term follow-up, assessing MACE outcomes over up to 10 years post-vaccination, provides valuable insights into the enduring protection offered by HZ vaccination against cardiovascular events.

Despite its strengths, our study is not without limitations. Firstly, despite efforts to control for confounding variables, the potential for residual confounding cannot be entirely eliminated. Variables such as lifestyle factors, medication adherence, and unmeasured comorbidities may contribute to residual confounding. Secondly, the generalizability of our findings may be restricted due to the reliance on data from a single database comprising healthcare organizations solely within the United States. Lastly, the retrospective nature of our study design precludes the establishment of causal relationships between HZ vaccination and MACE, warranting cautious interpretation of our results and emphasizing the need for further prospective investigations.

Further prospective study is crucial to comprehensively evaluate the effectiveness of HZ vaccination in individuals with diabetes. This prospective study should aim to assess vaccination outcomes in diabetes patients across various time intervals following vaccination, allowing for a comprehensive understanding of the long-term efficacy and safety profiles of different vaccines, including Shingrix and Zostavax. By conducting such studies, researchers can address existing gaps in the literature and provide more definitive evidence to guide clinical decision-making and vaccination strategies in this vulnerable population.

In conclusion, our retrospective cohort study provides valuable insights into the association between HZ vaccination and MACE among individuals with diabetes. Despite the inherent limitations of retrospective analyses, our findings suggest a potential protective effect of HZ vaccination against MACE, aligning with the ADA recommendation to vaccinate individuals aged 50 and older with diabetes against HZ. Our study underscores the importance of HZ vaccination as a potential strategy for reducing cardiovascular risk in this vulnerable population. Moreover, beyond its known benefits in reducing the risk of HZ, our findings suggest that HZ vaccination may also contribute to the reduction of MACE.

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Authorship contribution statement:
Edy Kornelius: Guarantor, Conceptualization, Methodology, Writing – Original Draft
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Yi-Sun Yang: Methodology, Data analysis, Writing – Review & Editing

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Data sharing availability: This population-based study obtained data from the TrinetX platform (accessible at https://trinetx.com/), for which third-party restrictions apply to the availability of this data. The data were used under license for this study with restrictions that do not allow for data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs might be incurred, and a data-sharing agreement would be necessary.

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Figure legends

Figure 1. Detailed flow chart illustrating the division of participants into four groups based on Herpes Zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to no vaccinated controls yielded 45,958 pairs (N1). Matching Shingrix vaccinated to no vaccinated controls resulted in 14,142 pairs (N2), Zostavax vaccinated to no vaccinated controls yielded 11,285 pairs (N3), and Shingrix vs. Zostavax vaccination resulted in 10,505 pairs (N4).

Supplementary Figure 1. Flowchart illustrating the sensitivity analysis of this study, evaluating herpes zoster vaccination administered exclusively one year after a diabetes mellitus diagnosis. Patients were divided into four groups based on Herpes Zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to no vaccinated controls yielded 138,083 pairs (N1). Matching Shingrix vaccinated to no vaccinated controls resulted in 45,904 pairs (N2), Zostavax vaccinated to no vaccinated controls yielded 33,350 pairs (N3), and Shingrix vs. Zostavax vaccination resulted in 27,171 pairs (N4).

Supplementary Figure 2. Kaplan-Meier survival curves depicting the cumulative incidence of MACE over time, comparing herpes zoster (HZ)-vaccinated versus non-vaccinated patients, along with a head-to-head analysis of Shingrix versus Zostavax. (A) Any HZ vaccine vs. no vaccine; (B) Shingrix vs. no vaccine; (C) Zostavax vs. no vaccine; and (D) Shingrix vs. Zostavax.

Table 1. Demographic characteristics of unmatched individuals vaccinated versus unvaccinated against herpes zoster.

	Any HZ vaccine N = 45960	No HZ vaccine N = 3363873	SMD
Age	63.46 ± 7.76	63.30 ± 9.30	0.019
Sex			
Female	22594 (49.16)	1599758 (47.56)	0.032
Male	20606 (44.84)	1656250 (49.24)	0.088
Race			
White	27076 (58.91)	1950119 (57.97)	0.019
Black or African American	7218 (15.71)	563189 (16.74)	0.028
Asian	2928 (6.37)	142295 (4.23)	0.096
Social economic status			
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	513 (1.12)	8856 (0.26)	0.103
Comorbidities			
Hypertensive diseases	25190 (54.81)	463468 (13.78)	0.959
Overweight and obesity	8980 (19.54)	149819 (4.45)	0.477
Other forms of heart disease	5651 (12.30)	205284 (6.10)	0.216
Chronic kidney disease	3257 (7.09)	89980 (2.68)	0.206
Neoplasms	3815 (8.30)	83995 (2.50)	0.259
Nicotine dependence	2673 (5.82)	67311 (2.00)	0.198
Hypertensive chronic kidney disease	1175 (2.56)	26124 (0.78)	0.139
Alcohol related disorders	734 (1.60)	18739 (0.56)	0.101
Fibrosis and cirrhosis of liver	438 (0.95)	19169 (0.57)	0.044
Unspecified dementia	235 (0.51)	7108 (0.21)	0.05
Alcoholic liver disease	189 (0.41)	6594 (0.20)	0.039
Alzheimer's disease	144 (0.31)	3447 (0.10)	0.046
Dementia in other diseases classified elsewhere	161 (0.35)	3858 (0.12)	0.049
Hepatic failure, not elsewhere classified	140 (0.31)	5878 (0.18)	0.027
Chronic hepatitis, not elsewhere classified	21 (0.05)	730 (0.02)	0.013
Vascular dementia	61 (0.13)	1394 (0.04)	0.031
Rheumatoid arthritis with rheumatoid factor	22 (0.05)	1081 (0.03)	0.008

Any HZ vaccine: Shingrix or Zostavax; HZ: herpes zoster; SMD: standardized mean difference.

Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Table 2. Risk of MACE Among Patients Receiving HZ Vaccination Compared to No-Vaccination and Head-to-Head Comparison of Shingrix vs. Zostavax

	Exposure group		Comparison			
	N	No. of event	N	No. of event	HR (95% C.I.)	p value
Any HZ vaccine vs no HZ vaccine						
(N1 matched population)						
MACE	45,958	3,474	45,958	4,060	0.76 (0.72–0.79)	<0.001
Coronary artery disease	45,958	1,902	45,958	2,331	0.73 (0.69–0.78)	<0.001
Stroke	45,958	1,863	45,958	2,116	0.79 (0.74–0.84)	<0.001
All-cause mortality	45,958	2,793	45,958	4,794	0.54 (0.52–0.57)	<0.001
Shingrix vs no HZ vaccine						
(N2 matched population)						
MACE	14,142	858	14,142	1,294	0.84 (0.76–0.91)	<0.001
Coronary artery disease	14,142	468	14,142	770	0.78 (0.69–0.88)	<0.001
Stroke	14,142	445	14,142	650	0.87 (0.77–0.99)	0.035
All-cause mortality	14,142	569	14,142	1,561	0.53 (0.48–0.58)	<0.001
Zostavax vs no HZ vaccine						
(N3 matched population)						
MACE	11,285	1,674	11,285	1,030	0.81 (0.75–0.88)	<0.001
Coronary artery disease	11,285	910	11,285	616	0.72 (0.65–0.80)	<0.001
Stroke	11,285	952	11,285	530	0.90 (0.81–1.01)	0.065
All-cause mortality	11,285	1,496	11,285	1,203	0.58 (0.53–0.62)	<0.001
Shingrix vs Zostavax						
(N4 matched population)						
MACE	10,505	615	10,505	1,574	1.09 (0.98–1.21)	0.104
Coronary artery disease	10,505	335	10,505	859	1.16 (1.01–1.34)	0.036
Stroke	10,505	310	10,505	900	0.96 (0.83–1.11)	0.582
All-cause mortality	10,505	378	10,505	1,400	0.99 (0.87–1.12)	0.824

Any HZ vaccine: Shingrix or Zostavax; MACE: major adverse cardiovascular events; HZ: herpes zoster.

The p-value is derived from the log-rank test.

Table 3. Stratification analysis of risk of MACE among different group in N1 matched population.

	Any HZ vaccine		No HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Age					
50-65	28,258	1,634	28,258	1,968	0.80 (0.75–0.86)
>65	16,903	1,859	16,903	1,723	0.83 (0.78–0.89)
Sex					
Female	22,591	1,559	22,591	1,808	0.77 (0.72–0.83)
Male	20,603	1,665	20,603	1,995	0.74 (0.69–0.79)
Type 1 diabetes	230	10	230	16	0.25 (0.08–0.75)
Type 2 diabetes	42,503	2,945	42,503	3,588	0.71 (0.68–0.75)

If the patient's count is 1-10, the results indicate a count of 10.

N1 indicate any herpes zoster vaccination versus no herpes zoster vaccination population

Any vaccine: Shingrix or Zostavax; MACE: major adverse cardiovascular events

Table 4. Risk of MACE within a one-year follow-up period in the N1 matched population.

	HZ vaccine		No HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Follow-up period					
1 month	45,958	69	45,958	314	0.21 (0.16–0.27)
3 months	45,958	218	45,958	575	0.35 (0.30–0.41)
6 months	45,958	404	45,958	813	0.45 (0.40–0.50)
9 months	45,958	612	45,958	1,014	0.54 (0.48–0.59)
12 months	45,958	790	45,958	1,228	0.57 (0.52–0.62)

MACE: major adverse cardiovascular events; HZ: herpes zoster

N1 indicate any herpes zoster vaccination versus non-herpes zoster vaccination population

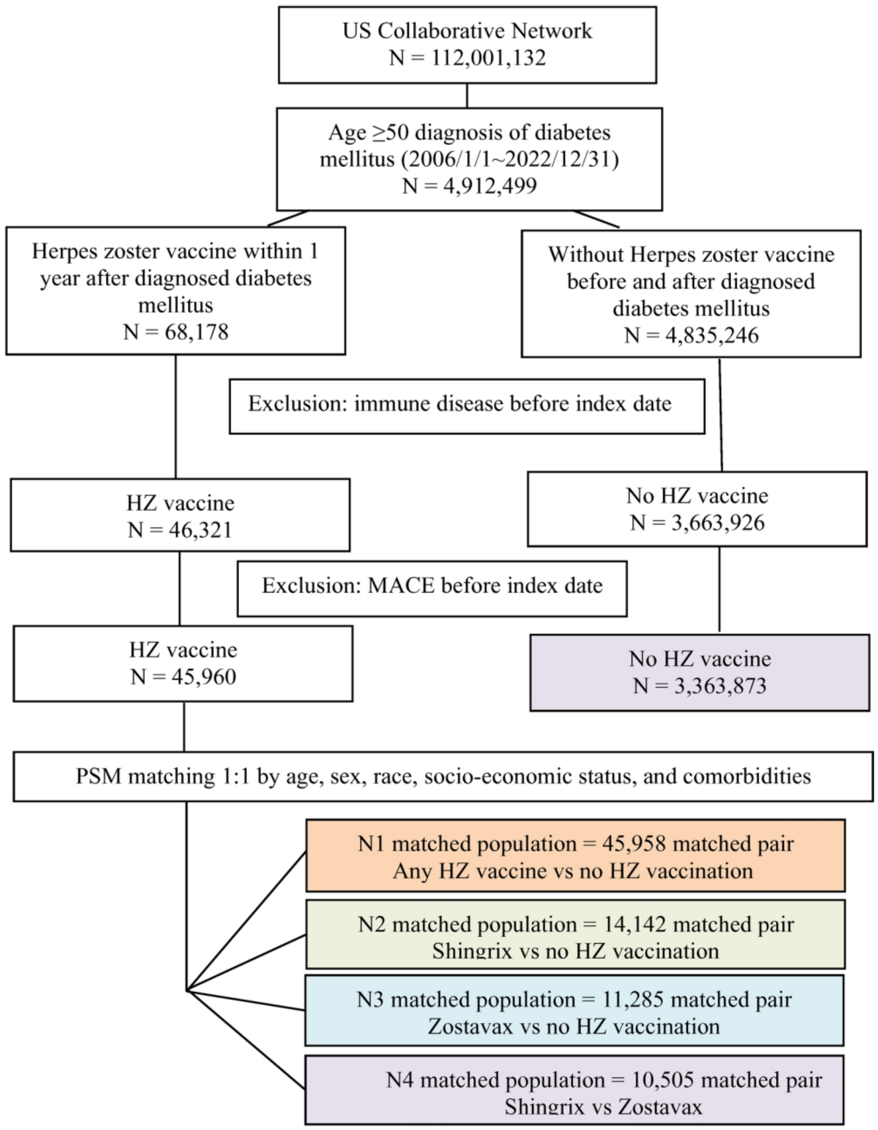

Figure 1. Detailed flow chart illustrating the division of participants into four groups based on Herpes Zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to no vaccinated controls yielded 45,958 pairs (N1). Matching Shingrix vaccinated to no vaccinated controls resulted in 14,142 pairs (N2), Zostavax vaccinated to no vaccinated controls yielded 11,285 pairs (N3), and Shingrix vs. Zostavax vaccination resulted in 10,505 pairs (N4).

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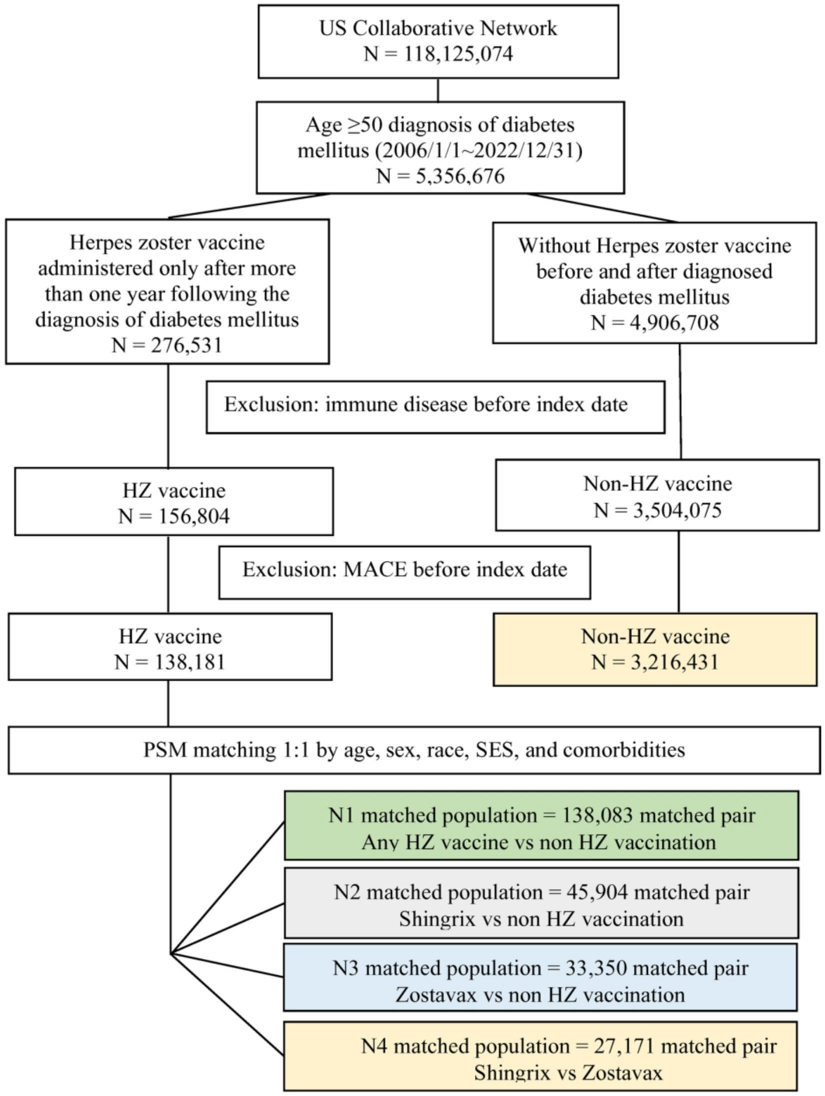

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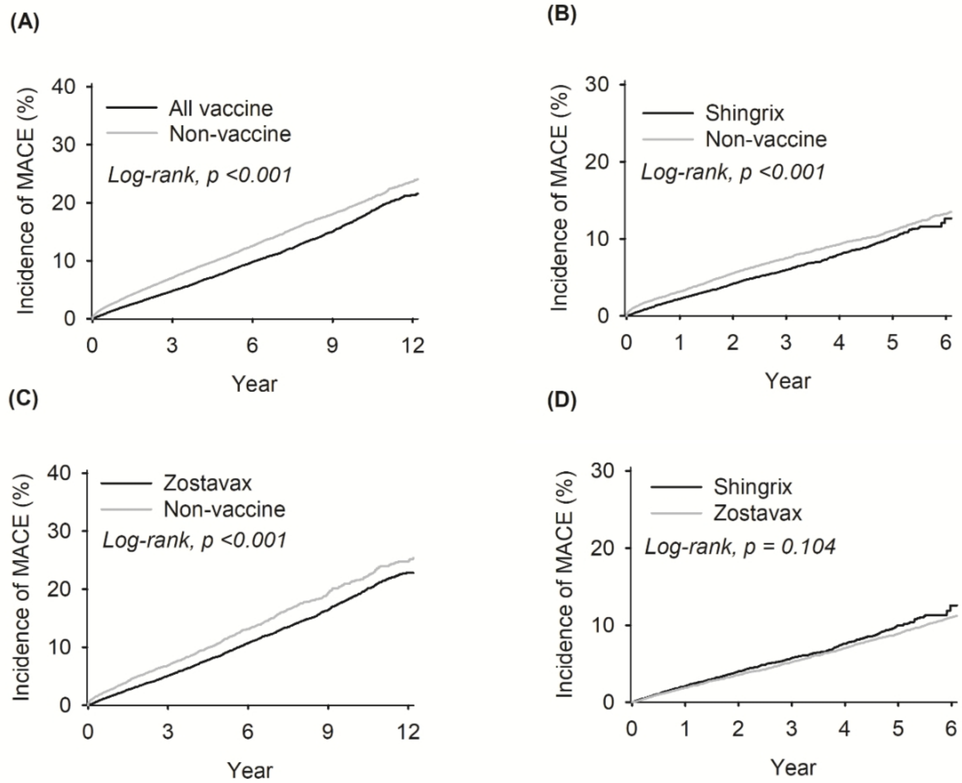

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Supplementary table 1. Detailed coding of this study.

Inclusion criteria: diabetes mellitus

- **Presence of ICD-10 CM codes:** E10 or E11
- ICD-10-CM: E11, Type 2 diabetes mellitus
- ICD-10-CM: E10, Type 1 diabetes mellitus

Herpes Zoster vaccine codes:

Procedure code:

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- UMLS:SNOMED:459891000124102 (Herpes zoster vaccination)
- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)

Medication code:

- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N1 population (any HZ vaccine):

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- UMLS:SNOMED:459891000124102 (Herpes zoster vaccination)
- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N2 population (Shingrix):

- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N3 population (Zostavax):

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)

N4 population (Shingrix VS Zostavax):

- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))
- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)

Outcomes:

Code for major adverse cardiovascular event (MACE)

Item	ICD-10-CM
Cardiovascular disease	
Coronary artery disease	
Acute myocardial infarction	I21
Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	I22
Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)	I23
Other acute ischemic heart diseases	I24
Stroke	
Nontraumatic subarachnoid hemorrhage	I60
Nontraumatic intracerebral hemorrhage	I61
Other and unspecified nontraumatic intracranial hemorrhage	I62
Cerebral infarction	I63

MACE: Major adverse cardiovascular event.

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

ICD-10-PCS: ICD-10 Procedure Coding System.

CPT: Current Procedural Terminology.

Codes of comorbidities

	ICD-10-CM
Socioeconomic status	
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	Z55-Z65
Comorbidities	
Hypertensive diseases	I10-I1A
Overweight and obesity	E66
Other forms of heart disease	I30-I5A
Chronic kidney disease	N18
Neoplasms	C00-D49
Nicotine dependence	F17.2
Hypertensive chronic kidney disease	I12
Alcohol related disorders	F10
Fibrosis and cirrhosis of liver	K74
Unspecified dementia	F03
Alcoholic liver disease	K70
Alzheimer's disease	G30
Dementia in other diseases classified elsewhere	F02
Hepatic failure, not elsewhere classified	K72
Chronic hepatitis, not elsewhere classified	K73
Vascular dementia	F01
Rheumatoid arthritis with rheumatoid factor	M05

Supplementary Table 2. Demographic Characteristics of Individuals with and without the Herpes Zoster Vaccine Before and After PSM (N1 matched population)

	Before PSM			After PSM		
	Any HZ vaccine N = 45,960	No-HZ vaccine N = 3,363,873	SMD	Any HZ vaccine N1 = 45,958	No-HZ vaccine N1 = 45,958	SMD
Age	63.46 ± 7.76	63.30 ± 9.30	0.019	63.46 ± 7.76	63.46 ± 7.85	0.001
Sex						
Female	22594 (49.16)	1599758 (47.56)	0.032	22592 (49.16)	22585 (49.14)	<0.001
Male	20606 (44.84)	1656250 (49.24)	0.088	20606 (44.84)	21544 (46.88)	0.041
Race						
White	27076 (58.91)	1950119 (57.97)	0.019	27076 (58.92)	27056 (58.87)	0.001
Black or African American	7218 (15.71)	563189 (16.74)	0.028	7218 (15.71)	7280 (15.84)	0.004
Asian	2928 (6.37)	142295 (4.23)	0.096	2926 (6.37)	2904 (6.32)	0.002
Socio-economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	513 (1.12)	8856 (0.26)	0.103	512 (1.11)	433 (0.94)	0.017
Comorbidities						
Hypertensive diseases	25190 (54.81)	463468 (13.78)	0.959	25188 (54.81)	25214 (54.86)	0.001
Overweight and obesity	8980 (19.54)	149819 (4.45)	0.477	8978 (19.54)	8969 (19.52)	<0.001
Other forms of heart disease	5651 (12.30)	205284 (6.10)	0.216	5651 (12.30)	5548 (12.07)	0.007
Chronic kidney disease	3257 (7.09)	89980 (2.68)	0.206	3256 (7.09)	3238 (7.05)	0.002
Neoplasms	3815 (8.30)	83995 (2.50)	0.259	3814 (8.30)	3820 (8.31)	<0.001
Nicotine dependence	2673 (5.82)	67311 (2.00)	0.198	2673 (5.82)	2647 (5.76)	0.002
Hypertensive chronic kidney disease	1175 (2.56)	26124 (0.78)	0.139	1175 (2.56)	1155 (2.51)	0.003
Alcohol related disorders	734 (1.60)	18739 (0.56)	0.101	734 (1.60)	667 (1.45)	0.012
Fibrosis and cirrhosis of liver	438 (0.95)	19169 (0.57)	0.044	438 (0.95)	414 (0.90)	0.005
Unspecified dementia	235 (0.51)	7108 (0.21)	0.050	235 (0.51)	219 (0.48)	0.005
Alcoholic liver disease	189 (0.41)	6594 (0.20)	0.039	189 (0.41)	186 (0.41)	0.001
Alzheimer's disease	144 (0.31)	3447 (0.10)	0.046	144 (0.31)	128 (0.28)	0.006
Dementia in other diseases classified elsewhere	161 (0.35)	3858 (0.12)	0.049	161 (0.35)	134 (0.29)	0.010
Hepatic failure, not elsewhere classified	140 (0.31)	5878 (0.18)	0.027	140 (0.31)	124 (0.27)	0.007
Chronic hepatitis, not elsewhere classified	21 (0.05)	730 (0.02)	0.013	21 (0.05)	15 (0.03)	0.007
Vascular dementia	61 (0.13)	1394 (0.04)	0.031	61 (0.13)	46 (0.10)	0.010
Rheumatoid arthritis with rheumatoid factor	22 (0.05)	1081 (0.03)	0.008	22 (0.05)	24 (0.05)	0.002

Any vaccine: Shingrix or Zostavax; HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.

Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary table 3. Demographic Characteristics of Individuals with Shingrix vaccination and without the Herpes Zoster Vaccination Before and After PSM (N2 matched population)

	Before PSM			After PSM		
	Shingrix N = 14,142	No HZ vaccine N = 3,363,856	SMD	Shingrix N2 = 14,142	No HZ vaccine N2 = 14,142	SMD
Age	65.08 ± 8.47	63.30 ± 9.30	0.201	65.08 ± 8.47	65.08 ± 8.55	<0.001
Sex						
Female	6857 (48.49)	1599752 (47.56)	0.019	6857 (48.49)	6880 (48.65)	0.003
Male	5945 (42.04)	1656239 (49.24)	0.145	5945 (42.04)	6534 (46.20)	0.084
Race						
White	8222 (58.14)	1950118 (57.97)	0.003	8222 (58.14)	8246 (58.31)	0.003
Black or African American	2320 (16.41)	563189 (16.74)	0.009	2320 (16.41)	2337 (16.53)	0.003
Asian	870 (6.15)	142285 (4.23)	0.087	870 (6.15)	845 (5.98)	0.007
Socio-economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	191 (1.35)	8856 (0.26)	0.122	191 (1.35)	166 (1.17)	0.016
Comorbidities						
Hypertensive diseases	8659 (61.23)	463464 (13.78)	1.124	8659 (61.23)	8672 (61.32)	0.002
Overweight and obesity	3347 (23.67)	149816 (4.45)	0.575	3347 (23.67)	3362 (23.77)	0.002
Other forms of heart disease	2088 (14.77)	205281 (6.10)	0.286	2088 (14.77)	2059 (14.56)	0.006
Chronic kidney disease	1443 (10.20)	89978 (2.68)	0.310	1443 (10.20)	1409 (9.96)	0.008
Neoplasms	1280 (9.05)	83993 (2.50)	0.284	1280 (9.05)	1276 (9.02)	0.001
Nicotine dependence	946 (6.69)	67311 (2.00)	0.231	946 (6.69)	932 (6.59)	0.004
Hypertensive chronic kidney disease	568 (4.02)	26124 (0.78)	0.213	568 (4.02)	545 (3.85)	0.008
Alcohol related disorders	275 (1.95)	18739 (0.56)	0.125	275 (1.95)	260 (1.84)	0.008
Fibrosis and cirrhosis of liver	158 (1.12)	19168 (0.57)	0.060	158 (1.12)	136 (0.96)	0.013
Unspecified dementia	111 (0.79)	7108 (0.21)	0.082	111 (0.79)	104 (0.74)	0.006
Alcoholic liver disease	82 (0.58)	6594 (0.20)	0.062	82 (0.58)	72 (0.51)	0.010
Alzheimer's disease	69 (0.49)	3447 (0.10)	0.071	69 (0.49)	65 (0.46)	0.004
Dementia in other diseases classified elsewhere	76 (0.54)	3858 (0.12)	0.074	76 (0.54)	71 (0.50)	0.005
Hepatic failure, not elsewhere classified	57 (0.40)	5877 (0.18)	0.043	57 (0.40)	47 (0.33)	0.012
Chronic hepatitis, not elsewhere classified	10 (0.07)	730 (0.02)	0.023	10 (0.07)	13 (0.09)	0.007
Vascular dementia	30 (0.21)	1394 (0.04)	0.048	30 (0.21)	24 (0.17)	0.010
Rheumatoid arthritis with rheumatoid factor	11 (0.08)	1081 (0.03)	0.019	11 (0.08)	10 (0.07)	0.003

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
If the patient's count is 1-10, the results indicate a count of 10.
Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary table 4. Demographic Characteristics of Individuals with Zostavax vaccination and without the Herpes Zoster Vaccination Before and After PSM (N3 matched population)

	Before PSM			After PSM		
	Zostavax N = 11,285	No HZ vaccine N = 3,363,856	SMD	Zostavax N3 = 11,285	No HZ vaccine N3 = 11,285	SMD
Age	65.18 ± 6.07	63.30 ± 9.30	0.239	65.18 ± 6.07	65.20 ± 6.18	0.004
Sex						
Female	5802 (51.41)	1599752 (47.56)	0.077	5802 (51.41)	5808 (51.47)	0.001
Male	5018 (44.47)	1656239 (49.24)	0.096	5018 (44.47)	5087 (45.08)	0.012
Race						
White	7009 (62.11)	1950118 (57.97)	0.085	7009 (62.11)	7005 (62.07)	0.001
Black or African American	1677 (14.86)	563189 (16.74)	0.052	1677 (14.86)	1679 (14.88)	<0.001
Asian	541 (4.79)	142285 (4.23)	0.027	541 (4.79)	544 (4.82)	0.001
Socio-economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	71 (0.63)	8856 (0.26)	0.055	71 (0.63)	62 (0.55)	0.010
Comorbidities						
Hypertensive diseases	5613 (49.74)	463464 (13.78)	0.837	5613 (49.74)	5620 (49.80)	0.001
Overweight and obesity	1355 (12.01)	149816 (4.45)	0.277	1355 (12.01)	1346 (11.93)	0.002
Other forms of heart disease	1215 (10.77)	205281 (6.10)	0.168	1215 (10.77)	1208 (10.70)	0.002
Chronic kidney disease	685 (6.07)	89978 (2.68)	0.167	685 (6.07)	690 (6.11)	0.002
Neoplasms	787 (6.97)	83993 (2.50)	0.212	787 (6.97)	767 (6.80)	0.007
Nicotine dependence	407 (3.61)	67311 (2.00)	0.097	407 (3.61)	419 (3.71)	0.006
Hypertensive chronic kidney disease	219 (1.94)	26124 (0.78)	0.101	219 (1.94)	218 (1.93)	0.001
Alcohol related disorders	0 (0.00)	3546 (0.11)	0.046	0 (0.00)	10 (0.09)	0.042
Fibrosis and cirrhosis of liver	116 (1.03)	18739 (0.56)	0.053	116 (1.03)	113 (1.00)	0.003
Unspecified dementia	56 (0.50)	19168 (0.57)	0.010	56 (0.50)	56 (0.50)	<0.001
Alcoholic liver disease	45 (0.40)	7108 (0.21)	0.034	45 (0.40)	38 (0.34)	0.011
Alzheimer's disease	22 (0.20)	6594 (0.20)	<0.001	22 (0.20)	24 (0.21)	0.004
Dementia in other diseases classified elsewhere	33 (0.29)	3447 (0.10)	0.043	33 (0.29)	31 (0.28)	0.004
Hepatic failure, not elsewhere classified	35 (0.31)	3858 (0.12)	0.042	35 (0.31)	37 (0.33)	0.003
Chronic hepatitis, not elsewhere classified	14 (0.12)	5877 (0.18)	0.013	14 (0.12)	15 (0.13)	0.002
Vascular dementia	10 (0.09)	730 (0.02)	0.029	10 (0.09)	10 (0.09)	<0.001
Rheumatoid arthritis with rheumatoid factor	10 (0.09)	1394 (0.04)	0.019	10 (0.09)	10 (0.09)	<0.001

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
If the patient's count is 1-10, the results indicate a count of 10.
Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary table 5. Demographic Characteristics of Individuals with Shingrix vaccination and Zostavax Vaccination Before and After PSM (N4 matched population)

	Before PSM			After PSM		
	Shingrix N = 14,142	Zostavax N = 11,285	SMD	Shingrix N4 = 10,505	Zostavax N4 = 10,505	SMD
Age	65.08 ± 8.47	65.18 ± 6.07	0.013	65.33 ± 8.07	65.20 ± 6.08	0.018
Sex						
Female	6857 (48.49)	5802 (51.41)	0.059	5318 (50.62)	5402 (51.42)	0.016
Male	5945 (42.04)	5018 (44.47)	0.049	4314 (41.07)	4639 (44.16)	0.063
Race						
White	8222 (58.14)	7009 (62.11)	0.081	6497 (61.85)	6358 (60.52)	0.027
Black or African American	2320 (16.41)	1677 (14.86)	0.043	1559 (14.84)	1654 (15.75)	0.024
Asian	870 (6.15)	541 (4.79)	0.060	523 (4.98)	540 (5.14)	0.007
Socio-economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	191 (1.35)	71 (0.63)	0.073	70 (0.67)	70 (0.67)	<0.001
Comorbidities						
Hypertensive diseases	8659 (61.23)	5613 (49.74)	0.233	5635 (53.64)	5605 (53.36)	0.006
Overweight and obesity	3347 (23.67)	1355 (12.01)	0.308	1393 (13.26)	1354 (12.89)	0.011
Other forms of heart disease	2088 (14.77)	1215 (10.77)	0.120	1234 (11.75)	1194 (11.37)	0.012
Chronic kidney disease	1443 (10.20)	685 (6.07)	0.152	646 (6.15)	685 (6.52)	0.011
Neoplasms	1280 (9.05)	787 (6.97)	0.077	756 (7.20)	775 (7.38)	0.007
Nicotine dependence	946 (6.69)	407 (3.61)	0.140	403 (3.84)	406 (3.87)	0.00[illegible]
Hypertensive chronic kidney disease	568 (4.02)	219 (1.94)	0.122	209 (1.99)	219 (2.09)	0.007
Alcohol related disorders	275 (1.95)	116 (1.03)	0.076	111 (1.06)	115 (1.10)	0.004
Fibrosis and cirrhosis of liver	158 (1.12)	56 (0.50)	0.069	62 (0.59)	55 (0.52)	0.009
Unspecified dementia	111 (0.79)	45 (0.40)	0.050	31 (0.30)	45 (0.43)	0.022
Alcoholic liver disease	82 (0.58)	22 (0.20)	0.062	18 (0.17)	21 (0.20)	0.007
Alzheimer's disease	69 (0.49)	33 (0.29)	0.031	34 (0.32)	32 (0.31)	0.001
Dementia in other diseases classified elsewhere	76 (0.54)	35 (0.31)	0.035	35 (0.33)	35 (0.33)	<0.001
Hepatic failure, not elsewhere classified	57 (0.40)	14 (0.12)	0.054	13 (0.12)	14 (0.13)	0.003
Chronic hepatitis, not elsewhere classified	10 (0.07)	10 (0.09)	0.006	10 (0.10)	10 (0.10)	<0.001
Vascular dementia	30 (0.21)	10 (0.09)	0.032	10 (0.10)	10 (0.10)	<0.001
Rheumatoid arthritis with rheumatoid factor	11 (0.08)	10 (0.09)	0.004	10 (0.10)	10 (0.10)	<0.001

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
If the patient's count is 1-10, the results indicate a count of 10.
Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary table 6. Risk of MACE among different follow-up period in N1 matched population.

	HZ vaccine		No HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Follow-up period					
≤5 years	45,958	2,513	45,958	3,051	0.70 (0.66–0.74)
5-10 years	43,445	812	42,798	799	0.93 (0.84–1.02)
>10 years	42,633	149	41,999	238	1.13 (0.92–1.39)

MACE: major adverse cardiovascular events; HZ: herpes zoster

N1 indicate any herpes zoster vaccination versus no herpes zoster vaccination population

Supplementary table 7. Stratification analysis of risk of MACE in different Shingrix dosage

	HZ vaccine		No HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Shingrix 1 dose	10760	546	10760	990	0.66 (0.59–0.73)
Shingrix 2 doses	3237	167	3237	288	0.73 (0.59–0.89)

MACE: major adverse cardiovascular events; HZ: herpes zoster

Supplementary Table 8. Demographic characteristics of individuals who received the herpes zoster vaccine more than one year after a diabetes mellitus diagnosis (N1 matched population)

	Before PSM			After PSM		
	Any HZ vaccine N = 138,181	No HZ vaccine N = 3,216,431	SMD	Any HZ vaccine N = 138,083	No HZ vaccine N = 138,083	SMD
Age	65.35 ± 7.40	63.04 ± 9.20	0.277	65.34 ± 7.40	65.41 ± 7.64	0.009
Sex						
Female	69821 (50.53)	1526559 (47.46)	0.061	69755 (50.52)	69332 (50.21)	0.006
Male	62075 (44.92)	1585168 (49.28)	0.087	62045 (44.93)	62124 (44.99)	0.001
Race						
White	78496 (56.81)	1785703 (55.52)	0.026	78454 (56.82)	79342 (57.46)	0.013
Black or African American	24018 (17.38)	514062 (15.98)	0.038	24006 (17.39)	23554 (17.06)	0.009
Asian	11428 (8.27)	161438 (5.02)	0.131	11392 (8.25)	11038 (7.99)	0.009
Social economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	1699 (1.23)	8086 (0.25)	0.114	1680 (1.22)	1501 (1.09)	0.012
Comorbidities						
Hypertensive diseases	87294 (63.17)	440309 (13.69)	1.182	87196 (63.15)	87436 (63.32)	0.004
Overweight and obesity	28615 (20.71)	145078 (4.51)	0.503	28533 (20.66)	27819 (20.15)	0.013
Other forms of heart disease	20106 (14.55)	190683 (5.93)	0.287	20091 (14.55)	20527 (14.87)	0.009
Chronic kidney disease	14749 (10.67)	84559 (2.63)	0.327	14677 (10.63)	14119 (10.23)	0.013
Neoplasms	13620 (9.86)	82826 (2.58)	0.305	13560 (9.82)	13404 (9.71)	0.004
Nicotine dependence	7419 (5.37)	62447 (1.94)	0.183	7410 (5.37)	7549 (5.47)	0.004
Hypertensive chronic kidney disease	5882 (4.26)	25680 (0.80)	0.222	5867 (4.25)	5190 (3.76)	0.025
Alcohol related disorders	1645 (1.19)	18062 (0.56)	0.068	1645 (1.19)	1521 (1.10)	0.008
Fibrosis and cirrhosis of liver	1628 (1.18)	18742 (0.58)	0.064	1619 (1.17)	1597 (1.16)	0.001
Unspecified dementia	848 (0.61)	6458 (0.20)	0.065	848 (0.61)	823 (0.60)	0.002
Alcoholic liver disease	423 (0.31)	6556 (0.20)	0.020	422 (0.31)	349 (0.25)	0.010
Alzheimer's disease	518 (0.38)	3077 (0.10)	0.058	518 (0.38)	508 (0.37)	0.001
Dementia in other diseases classified elsewhere	593 (0.43)	3474 (0.11)	0.062	591 (0.43)	565 (0.41)	0.003
Hepatic failure, not elsewhere classified	227 (0.16)	5726 (0.18)	0.003	227 (0.16)	205 (0.15)	0.004
Chronic hepatitis, not elsewhere classified	56 (0.04)	743 (0.02)	0.010	56 (0.04)	62 (0.05)	0.002
Vascular dementia	230 (0.17)	1240 (0.04)	0.040	229 (0.17)	201 (0.15)	0.005
Rheumatoid arthritis with rheumatoid factor	62 (0.05)	973 (0.03)	0.008	62 (0.05)	39 (0.03)	0.009

Any vaccine: Shingrix or Zostavax; HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary Table 9. Risk of MACE in individuals who received the herpes zoster (HZ) vaccine compared to those who did not, with vaccination administered more than one year after a diabetes mellitus diagnosis.

	Exposure group		Comparison		
	N	No. of event	N	No. of event	HR (95% C.I.)
Any HZ vaccine vs no HZ vaccine (N1 matched population)					
MACE	138,083	17,009	138,083	27,096	0.58 (0.57–0.59)
Coronary artery disease	138,083	6,313	138,083	8,772	0.67 (0.65–0.69)
Stroke	138,083	5,999	138,083	7,656	0.74 (0.71–0.76)
All-cause mortality	138,083	8,027	138,083	16,215	0.48 (0.46–0.49)
Shingrix vs no HZ vaccine (N2 matched population)					
MACE	45,904	5,063	45,904	9,926	0.62 (0.60–0.65)
Coronary artery disease	45,904	1,970	45,904	3,241	0.75 (0.71–0.80)
Stroke	45,904	1,831	45,904	2,831	0.79 (0.74–0.84)
All-cause mortality	45,904	2,180	45,904	5,965	0.48 (0.46–0.51)
Zostavax vs no HZ vaccine (N3 matched population)					
MACE	33,350	8,024	33,350	6,280	0.61 (0.59–0.63)
Coronary artery disease	33,350	2,980	33,350	2,014	0.71 (0.67–0.75)
Stroke	33,350	3,072	33,350	1,805	0.82 (0.77–0.87)
All-cause mortality	33,350	3,995	33,350	3,751	0.48 (0.46–0.50)
Shingrix vs Zostavax (N4 matched population)					
MACE	27,171	2,259	27,171	6,916	0.99 (0.94–1.04)
Coronary artery disease	27,171	900	27,171	2,555	1.08 (0.99–1.17)
Stroke	27,171	852	27,171	2,601	0.97 (0.89–1.06)
All-cause mortality	27,171	851	27,171	3,556	0.91 (0.84–0.99)

Any HZ vaccine: Shingrix or Zostavax; MACE: major adverse cardiovascular events; HZ: herpes zoster

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Association of herpes zoster vaccination and cardiovascular risk in patients with diabetes: long-term insights from a retrospective cohort study

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Abstract

Objectives: Herpes zoster (HZ) infection associated with higher risk of major adverse cardiovascular events (MACE), including stroke and coronary artery disease (CAD). Patients with diabetes are at an increased risk of MACE, highlighting the importance of studying this population to assess the potential protective effects of HZ vaccination. This study aims to investigate the risk of MACE after HZ vaccination in patients with diabetes

Design: Retrospective cohort study.

Setting: Community-based population in the United States.

Participants: Utilizing the TrinetX database, the study included 4.9 million patients with diabetes from 2006 to 2022. It established two cohorts: 68,178 patients in the HZ vaccination (comprising any HZ vaccine, Shingrix or Zostavax) and 4,835,246 patients in the no HZ vaccination group. After excluding patients with history of MACE, immune disease, and complications of HZ prior to the index date, the study cohort was reduced to 45,960 patients. Propensity Score Matching, accounting for age, sex, race, socioeconomic status and disease comorbidities, was conducted to minimize study bias.

Interventions: HZ vaccination.

Outcome measures: MACE outcomes, defined as the first occurrence of CAD or stroke. Comparative risk analysis was conducted using hazard ratios (HRs).

Results: Post-matching, the mean patient age was 63.5 years, with 49.2% females. The incidence rate of MACE was lower among vaccinated patients compared to unvaccinated individuals, with a HR of 0.76 (0.72–0.79). For secondary endpoints, the HRs were 0.73 (0.69–0.78) for CAD, 0.79 (0.74–0.84) for stroke, and 0.54 (0.52–0.57) for all-cause mortality. These protective effects remained consistent across different age groups, sexes, and diabetes types, supporting the potential benefit of HZ vaccination in reducing cardiovascular risk.

Conclusions: HZ vaccination is associated with a lower risk of MACE in patients with diabetes. Further prospective studies are critically needed to confirm this finding.

Strengths and limitations of this study

- This study utilized a large community-based database, providing robust and representative data for analysis.
- This study includes a long follow-up duration, allowing us to assess the impact of herpes zoster vaccination on MACE risk over an extended period.
- This study evaluated the risk of MACE after herpes zoster vaccination in patients with diabetes.
- This study is limited by the potential for unmeasured confounding that cannot be entirely eliminated.

INTRODUCTION

Herpes zoster (HZ), commonly known as shingles, is a prevalent viral infection caused by the reactivation of the varicella-zoster virus, which remains latent in the body following an initial chickenpox infection.[1] Triggered typically by aging, immunosuppression, or stress, this reactivation manifests as painful, blistering skin eruptions localized to specific dermatomes.[2,3] Additionally, It is particularly noted for its complications, such as postherpetic neuralgia, which can cause prolonged discomfort.[4,5] Recent studies have shifted focus towards the broader impacts of HZ, especially its association with an increased risk of major adverse cardiovascular events (MACE), including stroke and myocardial infarction.[6–18] Importantly, research suggests that the risk of stroke is time-dependent following an HZ infection, with a significant elevation in the first month at 78%, reducing to 43% after 3 months, and further to 20% after 1 year, before leveling off to a non-significant 7% increase up to 3 years post-infection.[19] This time-dependent risk profile underscores the importance of timely intervention and prevention strategies.

Within the population of individuals with diabetes mellitus, the interplay between HZ infection and cardiovascular risk is of particular concern. Diabetes, a chronic condition characterized by elevated blood glucose levels, significantly heightens the risk of cardiovascular diseases, making this group particularly susceptible to the compounded effects of HZ infection.[19,20] The risk of cardiovascular events in patients with diabetes is two to threefold higher than in those without diabetes, underscoring the critical need for comprehensive strategies to mitigate these risks.[21,22] The exacerbation of cardiovascular complications by HZ may be mediated through vasculopathy, a process potentially involving direct viral invasion of intra- or extracranial arteries, culminating in vessel wall damage through inflammatory responses characterized by multinucleated giant cells and epithelioid macrophages.[23–27] Additionally, HZ may provoke an inflammatory environment within the vessel wall, fostering a pro-coagulation state, further underscoring the complex interrelation between HZ infection and cardiovascular morbidity in diabetes.[24,28,29]

The advent of HZ vaccines, such as the recombinant zoster vaccine (RZV or Shingrix) and the live attenuated zoster vaccine (LZV or Zostavax), offers a promising strategy for reducing the incidence of HZ and its associated complications.[30–32] These vaccines have demonstrated robust efficacy in the general population aged 50 years and older, reducing both the occurrence of HZ and the severity of postherpetic neuralgia.[33] Given the established link between HZ infection and an increased risk of cardiovascular events, it is plausible to hypothesize that HZ vaccination could also confer protective effects against MACE, particularly in the diabetes population. However, prior research investigating the relationship between HZ vaccination and cardiovascular events has yielded mixed outcomes. Specifically, Parameswaran and colleagues,[34] utilizing Veteran Affairs data, observed a significant protective effect against stroke in elderly male vaccine recipients (both Zostavax and Shingrix). Their study noted that patients faced a higher stroke risk within the first month following recent HZ infection, but individuals who received at least one zoster vaccination demonstrated a mitigation of this elevated risk, with odds ratios (OR) of 0.57 (95% CI: 0.46–0.72) for Shingrix and 0.77 (95% CI: 0.65–0.91) for Zostavax at 30 days post-event. In contrast, Minnasian et al.,[35] using Medicare data from individuals older than 65 years, identified a transiently heightened risk of stroke and myocardial infarction associated with HZ infection—most pronounced within the first week following zoster diagnosis—yet did not detect a reduction in the incidence of these events in HZ vaccine recipients within the initial four weeks post-infection. Yang et al.,[36,37] in separate analyses of the US Medicare population, found a 16% reduction in stroke risk among vaccine recipients aged 66 and older, with enhanced benefits noted in specific subgroups. These varying findings may stem from differences population demographics (e.g., age ranges, underlying comorbidities), and follow-up durations (e.g., short-term vs. long-term surveillance). Despite these efforts, it remains unclear whether HZ vaccination consistently confers a true protective effect, particularly among high-risk individuals such as those with diabetes, where the burden of cardiovascular disease is already elevated. Thus, a critical gap remains in establishing whether HZ vaccination offers meaningful cardiovascular benefits in patients with diabetes, underscoring the need for more targeted research in this domain.

METHODS

Study population

This retrospective cohort study utilized data from the TriNetX database, which aggregates electronic medical records from healthcare organizations across the United States. The TriNetX database is a comprehensive repository of de-identified electronic health records from a diverse range of healthcare organizations, including hospitals, clinics, and medical practices. It encompasses data on patient demographics, diagnoses, procedures, medications, laboratory results, and other clinical variables. The TriNetX database has been validated and has been widely used in many representative publications, supporting its credibility for research purposes.[38–40] The total number of patients available in the TriNetX network is 112 million.

Cohort selection

Cases were defined as individuals with aged 50 or older, diagnosed with diabetes mellitus, who received HZ vaccination, including Shingrix or Zostavax, within 1 year of their diabetes diagnosis, with the index date set as the date of vaccination. This timeframe was chosen to minimize potential differences and biases between cases and controls. Conversely, the control group comprised patients with diabetes who did not receive any HZ vaccination during the study period, with the index date corresponding to the first date of diabetes diagnosis. This study was conducted from January 1, 2006, to December 12, 2022.

Exclusion criteria

Patients with a history of MACE before the index date were excluded to ensure that the study focused on incident cases of cardiovascular events rather than pre-existing conditions. Immunocompromised individuals were excluded because their underlying conditions might confound the relationship between HZ vaccination and MACE. These conditions, such as human immunodeficiency virus (HIV), malignancy, and immune diseases (rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis) can affect the immune response and potentially influence the risk of cardiovascular events. Excluding individuals with a prior diagnosis of HZ and its complications (post-herpetic neuralgia, Bell's palsy, Ramsay-Hunt syndrome) before the index date helped to ensure that only new cases of these conditions were considered during the study period, reducing potential bias in the analysis.

Study codes and disease comorbidities.

Study codes and disease comorbidities were detailed in Supplementary Table 1. In summary, the coding for diabetes diagnosis utilized International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) codes of E10-E11, while patients who received HZ vaccination were identified with procedure code and medical prescription normalized medical prescription (RxNorm). Furthermore, disease comorbidities such as hypertension, obesity, and chronic kidney disease (CKD) were allocated specific codes for identification and analysis purposes. This comprehensive coding system facilitated the organization and interpretation of patient data, ensuring clarity and precision in the study's findings. The definition of socioeconomic status (SES) in our study is based on ICD-10 coding (Z55-Z65), which includes factors related to education, employment, income, and social environment.

This study aimed to investigate the association between HZ vaccination and the incidence of MACE among individuals with diabetes aged 50 years and older. The focus on this age group was driven by their heightened risk of MACE and their alignment with vaccination guidelines.[41] The primary endpoint of this study is defined as the first occurrence of composite MACE, comprising coronary artery disease (CAD) or stroke following the index date. Secondary endpoints include individual outcomes of CAD, stroke, and all-cause mortality. Subgroup analysis was conducted by stratifying age, sex, and type of diabetes. Additionally, we explored the risk of MACE within the first year of follow-up.

Propensity score matching

Propensity score matching (PSM) is a statistical technique used to balance cohorts in observational studies by adjusting for potential confounders. It ensures comparability between the HZ vaccine and no HZ vaccine groups when randomization is not feasible. This is achieved by estimating the probability, or "propensity score," of a patient belonging to one cohort based on observed covariates.

In this study, researchers defined two cohorts of interest (HZ vaccine vs. no HZ vaccine) and identified covariates—factors that may influence both treatment allocation and outcomes. These covariates include age, sex, race, SES, and various comorbidities, such as hypertensive diseases, overweight and obesity, other forms of heart disease, CKD, neoplasms, nicotine dependence, hypertensive chronic kidney disease, alcohol related disorders, fibrosis and cirrhosis of liver, unspecified dementia, alcoholic liver disease, Alzheimer's disease, dementia, hepatic failure, chronic hepatitis, vascular dementia, rheumatoid arthritis with rheumatoid factor.

Using logistic regression, the system calculates each patient's propensity score, which reflects the probability of belonging to a specific cohort given the covariates. The system employs a greedy nearest neighbor matching with a caliper of 0.1 pooled standard deviations, ensuring that patients in the smaller cohort are matched to those in the larger cohort based on the closest propensity scores within the defined range. This process generates balanced matched subsets.

After matching, the outcomes of interest are compared between these balanced subsets rather than the original cohorts, effectively minimizing the effects of confounding variables. PSM is implemented within a federated data network, pooling data from multiple healthcare organizations. To mitigate bias introduced by the order of data during matching, patient records are randomized prior to matching. Deterministic randomization is applied to ensure the reproducibility of the analyses. The PSM analysis for this study was conducted using the built-in tools provided by the TriNetX platform.

To evaluate the impact of HZ vaccination on MACE, we divided the study into four populations for analysis, designated as model 1 through model 4. The matching process involved four different comparisons: (1) cases vaccinated with any HZ vaccine matched to no HZ vaccinated controls (model 1), (2) cases vaccinated with Shingrix matched to no HZ vaccinated controls (model 2), (3) cases vaccinated with Zostavax matched to no HZ vaccinated controls (model 3), and (4) cases vaccinated with Shingrix matched against those vaccinated with Zostavax (model 4). This approach allowed us to assess both the overall effect of HZ vaccination and direct comparisons between vaccine types.

Statistical analysis

TriNetX ensures data quality through rigorous checks and monitoring. The platform validates data formatting, ensuring proper representation of dates and required fields (e.g., patient identifiers), rejecting records with missing essential information. Referential integrity checks verify successful data integration across tables, while volume trends are monitored during data refreshes to maintain validity. Patient records must include at least one non-demographic fact to be included, as records with only demographic data are excluded. TriNetX collaborates with data providers by sharing regular feedback and data quality scorecards, enabling providers to assess their data quality and compare it with peers based on regional or population-specific benchmarks. Data quality is assessed at various stages: during onboarding of new providers, periodic data refreshes, significant pipeline changes, or troubleshooting requests. The process is dynamic, with ongoing improvements in metrics, collection methods, and evaluation procedures to enhance overall data reliability and operational efficiency.

TriNetX ensures cohort integrity by using a master patient index, tokenization, and data normalization to prevent duplicate patient records. It applies cross-site deduplication, distinct patient count algorithms, and real-time filtering to ensure each patient is counted only once, minimizing bias and maintaining data accuracy in research analyses.

Descriptive statistics were employed to summarize the baseline characteristics of the study population, including age, sex, race, SES, and disease comorbidities. Following PSM, the balance between matched cohorts was evaluated using standardized mean differences (SMD), where an SMD value of less than 0.1 was considered indicative of a well-matched cohort. The incidence of MACE was analyzed using a Kaplan-Meier survival curve with statistical significance determined using the log-rank test. A Cox proportional hazards model was further applied to evaluate the association between group assignment and the risk of MACE and all-cause mortality, providing hazard ratios (HRs) with 95% confidence intervals. All analyses were performed using the TriNetX online platform, which utilizes R version 4.0.2 as its underlying statistical framework.

Sensitivity analysis

To address potential healthy vaccine bias, we conducted a post-hoc sensitivity analysis by identifying a subgroup of patients who received HZ vaccination at least one year after their diabetes diagnosis. This additional analysis aimed to determine whether delaying vaccination after diabetes diagnosis affected the primary outcomes.

Ethical considerations

The patient data utilized in this study were fully de-identified to ensure privacy and confidentiality. This procedure was implemented to prevent the direct or indirect identification of individual patients, thereby safeguarding patient privacy in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations. The study protocol was approved by the Institutional Review Board of Chung Shan Medical University Hospital, identified by the reference number CS2-23159.

Patient and public involvement

None.

RESULTS

This study included a total of 112 million patients (Figure 1). Following the filtration process to identify patients with a diagnosis of diabetes, we narrowed the cohort down to 4.9 million patients. Among these, 68,178 patients were identified as cases, having received any HZ vaccination within 1 year of diagnosis of diabetes, while 4,835,246 patients served as controls, having diabetes without any HZ vaccination. Further exclusion of patients with immune diseases and a history of MACE before the index date resulted in 45,960 cases for any HZ vaccination and 3,363,873 controls. Subsequently, we divided the study into four populations for evaluation, designated as model 1 through model 4. The matching of cases vaccinated with any HZ vaccine to no HZ vaccinated controls yielded 45,958 pairs (model 1). Meanwhile, matching cases vaccinated with Shingrix to no HZ vaccinated controls resulted in 14,142 pairs (model 2), and matching cases vaccinated with Zostavax to no HZ vaccinated controls resulted in 11,285 pairs (model 3). Finally, matching cases vaccinated with Shingrix against those vaccinated with Zostavax resulted in 10,505 pairs (model 4).

Table 1 presents baseline characteristics for both HZ vaccination cases and no HZ vaccination controls. Prior to PSM, notable differences were observed in several comorbidities, including hypertensive diseases, obesity, heart disease, CKD, neoplasm, and nicotine dependence. The mean age was 63.5 years, with 49.1% female and 58.9% white race. Disease comorbidities included patients with hypertensive disease accounting for 54.8%, overweight and obesity at 19.5%, other forms of heart disease at 12.3%, CKD at 7.1%, neoplasm at 8.3%, and nicotine dependence at 5.8%. Patients with SES issues accounted for 1.1% of the HZ vaccination group. Following the matching process, the disparity between cases and controls was significantly reduced, as evidenced by the SMD being less than 0.1, detailed in Supplementary Tables 2-5.

Table 2 presents the risk of MACE among patients with HZ vaccination compared to those without vaccination. The risk of MACE, CAD, stroke, and all-cause mortality was consistently lower among patients with any HZ vaccination compared to those without vaccination, as evidenced by hazard ratios (HR) and 95% confidence intervals (CI) of 0.76 (0.72–0.79), 0.73 (0.69–0.78), 0.79 (0.74–0.84), and 0.54 (0.52–0.57), respectively. These findings underscore the potential protective effect of any HZ vaccination against adverse cardiovascular outcomes. When used individually, both Shingrix and Zostavax demonstrated effectiveness in reducing the risk of MACE, CAD, stroke, and all-cause mortality compared to no vaccination. For Shingrix, the risks were 0.84 (0.76–0.91) for MACE, 0.78 (0.69–0.88) for CAD, 0.87 (0.77–0.99) for stroke, and 0.53 (0.48–0.58) for all-cause mortality. Similarly, Zostavax showed HR and 95% CI of 0.81 (0.75–0.88) for MACE, 0.72 (0.65–0.80) for CAD, 0.90 (0.81–1.01) for stroke, and 0.58 (0.53–0.62) for all-cause mortality.

These results suggest that both Shingrix and Zostavax offer protective benefits against MACE when administered individually. When comparing Shingrix to Zostavax, interesting findings emerged. While a neutral result was observed for MACE and stroke, a notable difference was detected in CAD. The HR and 95% CI for CAD were 1.16 (1.01–1.34), indicating a higher risk of CAD among individuals receiving Shingrix compared to Zostavax. However, no significant differences were noted in stroke, all-cause mortality, or overall MACE between the two vaccines. This highlights the importance of considering specific cardiovascular outcomes when evaluating the comparative effectiveness of different HZ vaccines.

The stratification analysis of the risk of MACE among different groups revealed consistent findings across various demographic and clinical factors (Table 3). Regardless of age, individuals aged 50-65 years and those over 65 years demonstrated a lower risk of MACE with HZ vaccination compared to no vaccination, with HR and 95% CI of 0.80 (0.75–0.86) and 0.83 (0.78–0.89), respectively. Similarly, both females and males experienced a reduced risk of MACE with vaccination, with HR and 95% CI of 0.77 (0.72–0.83) and 0.74 (0.69–0.79), respectively. Furthermore, individuals with type 1 or type 2 diabetes also exhibited a lower risk of MACE with HZ vaccination compared to no vaccination, with HR and 95% CI of 0.25 (0.08–0.75) for type 1 diabetes and 0.71 (0.68–0.75) for type 2 diabetes. These consistent protective effects across different age groups, sexes, and types of diabetes underscore the robustness of the association between HZ vaccination and reduced cardiovascular risk.

When considering the timing within the first year of vaccination, Table 4 illustrates a notable trend in the risk of MACE. The risk of MACE is observed to be the lowest in the first month following vaccination, with a HR and 95% CI of 0.21 (0.16–0.27). Subsequently, the risk of MACE gradually increases over time, yet remains significantly lower compared to no vaccination. At the end of the first year, the HR and 95% CI for MACE stand at 0.57 (0.52–0.62). In the long-term follow-up, as depicted in Supplementary Table 6, the risk of MACE demonstrates consistent patterns across different time intervals. Over a follow-up period of up to 5 years, individuals with HZ vaccination exhibit a significantly lower risk of MACE compared to unvaccinated counterparts, with a HR and 95% CI of 0.70 (0.66–0.74). However, the protective effects seem to wane with time. During follow-up periods of 5-10 years and beyond 10 years, the HR and 95% CI for MACE among vaccinated individuals are observed to be 0.93 (0.84–1.02) and 1.13 (0.92–1.39), respectively.

The protective efficacy of Shingrix demonstrates consistency, whether administered as a single dose or a two-dose regimen, when compared to a no HZ vaccinated control group. Specifically, the HR for individuals receiving one dose of Shingrix was 0.66 (95% CI: 0.59–0.73), while for those completing the two-dose regimen, the HR was 0.73 (95% CI: 0.59–0.89), as detailed in Supplementary Table 7. Furthermore, a post-hoc sensitivity analysis was conducted by identifying a subgroup of patients who received HZ vaccination at least one year after their diabetes diagnosis. The results were consistent with our primary findings, confirming that the protective effect of HZ vaccination against MACE remained robust, regardless of the timing of vaccination relative to diabetes diagnosis (Supplementary Figure 1). Detailed results of this analysis are provided in Supplementary Tables 8 and 9.

The Kaplan-Meier survival curve (Supplementary Figure 2) illustrates the cumulative incidence of MACE over time, comparing HZ-vaccinated vs. unvaccinated patients and a head-to-head analysis of Shingrix vs. Zostavax. The curves show a lower cumulative incidence of MACE in vaccinated patients, suggesting a protective effect of HZ vaccination. In the Shingrix vs. Zostavax comparison, the results indicate a neutral effect between the two vaccines, with no significant difference in MACE risk.

DISCUSSION

To the best of our knowledge, this study represents the first comprehensive investigation into the risk of MACE among patients with diabetes following HZ vaccination. Our findings reveal a significant decrease in the risk of MACE subsequent to HZ vaccination. This protective effect extends to other critical outcomes, including CAD, stroke, and all-cause mortality, demonstrating consistent benefits across multiple cardiovascular endpoints. Furthermore, our subgroup analysis highlights the robustness of the protective effect, as it remains consistent across different age groups, sexes, and types of diabetes. Interestingly, our study also indicates that the strongest protective effects appear to manifest within the first year following vaccination, but these effects appear to diminish over time. These findings underscore the potential additional benefits of HZ vaccination in reducing cardiovascular risk among individuals with diabetes.

HZ is increasingly being investigated for its potential link to cardiovascular disease. Initial evidence suggesting HZ as a risk factor for cardiovascular disease comes primarily from retrospective analyses,[6–18] which have documented a higher frequency of cardiovascular events—such as stroke and myocardial infarction—in individuals who have had HZ episodes compared to those who have not. Following these preliminary observations, further research aimed at confirming and expanding upon this association has been conducted through larger-scale studies across diverse global populations. This extensive research has shown an increased risk of cardiovascular events post-HZ infection, underscoring the necessity for increased clinical awareness and management of cardiovascular risk factors among those with a history of HZ.[34,37]

Several mechanisms have been proposed to elucidate the link between HZ infection and an increased risk of MACE. A primary mechanism believed to be implicated is vasculopathy, wherein the virus directly infects and spreads from the nerve to the cerebral artery, eliciting inflammation, pathological vascular remodeling, and subsequently heightening the risk of stroke.[25,42] Moreover, beyond the direct vascular effects, HZ infection may contribute to elevated blood pressure due to the pain and stress associated with the condition. This elevation in blood pressure could further exacerbate the risk of stroke, given that hypertension is a leading cause of stroke.

Within the existing literature, our study stands out for evaluating patients with the longest follow-up duration and focusing specifically on the diabetes population. Notably, three published studies have been identified, each presenting unique findings. Parameswaran et al.[34] and Yang et al.[37] reported positive HZ vaccination outcomes, while Minnasian et al.[35] found no significant advantage. These studies, characterized by retrospective designs, differ in their data sources, study populations, and methodologies, contributing to the heterogeneity in results.

The distinctive aspect of our study lies in the examination of patients aged between 50 and 65 years old, a demographic often underrepresented in similar analyses.[34,35,37] This age group, typically considered lower risk for MACE compared to those over 65, exhibited intriguing results in our study. Specifically, we observed a significantly reduced risk of MACE among diabetes patients aged 50-65 who received HZ vaccination, with a HR of 0.80 (95% CI: 0.75–0.86), as compared to unvaccinated counterparts. This finding provides valuable insights into the effectiveness of HZ vaccination in reducing MACE risk among individuals who might benefit most from early preventive measures. Another unique aspect of our study is the inclusion of data on patients with type 1 diabetes who received HZ vaccination, a demographic that has been largely overlooked in previous literature. To our knowledge, this is the first study to report outcomes for individuals with type 1 diabetes following HZ vaccination. Our analysis revealed a noteworthy finding, indicating a significantly reduced risk of MACE among patients with type 1 diabetes who received HZ vaccination, with a HR of 0.25 (95% CI: 0.08–0.75). This novel insight underscores the potential benefits of HZ vaccination not only for individuals with type 2 diabetes but also for those with type 1 diabetes, highlighting the importance of considering this population in future vaccination strategies and guidelines.

Parameswaran and colleagues, utilizing Veteran Affairs data, observed a significant protective effect against stroke in elderly males following vaccination with both Zostavax and Shingrix.[34] Their study revealed that patients experienced a notably higher risk of stroke within the first month following recent HZ infection. However, individuals who received at least one zoster vaccination demonstrated a mitigation of this increased risk. Specifically, the odds ratio (OR) for stroke 30 days post-event was 0.57 (95% CI: 0.46–0.72) for Shingrix and 0.77 (95% CI: 0.65–0.91) for Zostavax. Similarly, Yang et al., analyzing US Medicare data, identified a 16% reduction in stroke risk among vaccine recipients aged 66 and older, with enhanced benefits observed in specific subgroups.[37]

Minnasian et al.'s study,[35] conducted within the Medicare population and focusing on patients older than 65 years, revealed a transiently heightened risk of stroke and myocardial infarction associated with HZ infection. Particularly noteworthy was the pronounced increase observed within the initial week following zoster diagnosis, with a 2.4-fold elevated rate of ischemic stroke (incidence rate [IR] 2.37, 95% CI 2.17–2.59) and a 1.7-fold increase in myocardial infarction rate (IR 1.68, 95% CI 1.47–1.92), followed by a gradual reduction over six months. However, the study did not find evidence of a reduction in the IR for ischemic stroke or myocardial infarction among HZ vaccine recipients in the first four weeks following zoster diagnosis. The lack of observed protective effects of the HZ vaccine may be attributed to the limited number of patients in the vaccinated groups, thereby restricting the study's power to adequately assess this outcome. Notably, only 9% of participants received the vaccine during the study period, underscoring the challenge of assessing vaccine effectiveness in real-world settings with low uptake rates. These disparities underscore the importance of considering study-specific factors, such as data sources and population characteristics, when interpreting and comparing research findings.

An additional significant discovery from our research is the most robust protective impact of HZ vaccination against MACE observed during the first year, with this protective effect extending over 5 years of follow-up. This outcome aligns with the observation that the highest risk of stroke occurs within the first year.[19] This phenomenon could be attributed to various potential mechanisms. Firstly, the vaccine may modulate the immune response, reducing systemic inflammation, a key contributor to atherosclerosis and cardiovascular events. Furthermore, by preventing HZ, the vaccine indirectly decreases cardiovascular stress, considering the association between HZ and a heightened risk of stroke and myocardial infarction, particularly in the first year following infection. This dual mechanism—lowering inflammation and averting HZ—accounts for the observed sustained, albeit gradually decreasing, protective effect over time.

The discrepancy between the sum of populations model 2 and model 3 not equaling the total of model 1 can be attributed to the specific inclusion criteria based on procedural and medication codes utilized to identify the vaccination status within our study cohorts. Model 1 encompasses a broader category of individuals vaccinated with any HZ vaccine, identified through a comprehensive set of codes, including CPT codes 90736 (Zostavax) and 90750 (Shingrix), as well as additional codes for unspecified zoster vaccines (459891000124012) and their respective RXNORM codes (1292422 for Zostavax and 1986821 for Shingrix). This allows for the inclusion of all individuals vaccinated against HZ, capturing a wider demographic. Conversely, Model 2 and model 3 focus on narrower subsets, with model 2 including only those vaccinated with Shingrix (via CPT code 90750 and RXNORM code 1986821) and model 3 comprising individuals vaccinated with Zostavax (identified by CPT code 90736 and RXNORM code 1292422).

Observing a greater number of events in the Zostavax vaccination group compared to the control group, while the HR remains less than 1, highlights the nuanced nature of HR as a measure of relative risk over time rather than a simple count of events (Table 2). This phenomenon indicates that, after adjusting for the duration of follow-up and baseline risk factors, individuals in the Zostavax group experienced a lower rate of events at any given time compared to the no vaccinated group. The HR less than 1 suggests a protective effect of the Zostavax vaccine, reflecting its efficacy in reducing the instantaneous risk of adverse outcomes, despite the apparent higher number of events when viewed without the context of time and population size adjustments. This underscores the importance of HR in providing a more accurate assessment of the vaccine's impact on health outcomes.

It is important to note that the discrepancies in total numbers between Table 2 and Table 3, as well as in other subgroups, are caused by the methodology employed in the TrinetX analyses. Each stratified analysis involves re-matching individuals based on specific criteria, leading to variations in sample sizes and the number of participants experiencing MACE across different tables or subgroups. This re-matching process is designed to ensure that comparisons within each stratification are appropriate and accurate, taking into account the varying characteristics of participants within each subgroup. Consequently, the figures for the total number of individuals and those experiencing MACE in one table cannot simply be summed to match the figures in another table, due to these inherent differences in sample composition and size resulting from the re-matching process.

An intriguing finding emerged from our study when directly comparing the effectiveness of Shingrix and Zostavax, as there is a notable scarcity of head-to-head comparisons in the existing literature, particularly regarding their impact on MACE outcomes. Interestingly, while the American Diabetes Association (ADA) recommends Shingrix vaccination for individuals aged 50 years and older with diabetes,[41] our study observed comparable outcomes between Zostavax and Shingrix, with a slight difference in CAD risk favoring Zostavax. However, it is imperative to interpret these findings with caution, as our analysis is retrospective in nature and there exists a marked difference in the study timing between Zostavax and Shingrix. The reasons for this discrepancy are not fully elucidated but may relate to differences in vaccine composition and the resulting immune response. Zostavax, being a live attenuated vaccine, could potentially elicit a broader and more robust immune response compared to Shingrix, which is a recombinant subunit vaccine. Moreover, Zostavax offers the convenience of requiring only one injection for full protection, whereas Shingrix necessitates two injections. The variations in the immune response elicited by these vaccines may contribute to differences in their effectiveness in preventing MACE outcomes among individuals with diabetes.

Our study benefits from several strengths that enhance the reliability and significance of our findings. Firstly, leveraging data from the TriNetX database, which aggregates electronic medical records from 61 healthcare organizations across the US, provided a robust and extensive dataset for analysis. Secondly, employing a rigorous retrospective cohort study design enabled us to investigate the association between HZ vaccination and MACE among individuals with diabetes with clarity and precision. Additionally, our detailed analysis, including comprehensive stratification by age, sex, and diabetes type, allowed for a nuanced understanding of vaccine effectiveness across diverse subgroups. Lastly, our study's long-term follow-up, assessing MACE outcomes over up to 10 years post-vaccination, provides valuable insights into the enduring protection offered by HZ vaccination against cardiovascular events.

Despite its strengths, our study is not without limitations. Firstly, despite efforts to control for confounding variables, the potential for residual confounding cannot be entirely eliminated. Variables such as lifestyle factors, medication adherence, and unmeasured comorbidities may contribute to unmeasured confounding. Secondly, the generalizability of our findings may be restricted due to the reliance on data from a single database comprising healthcare organizations solely within the United States. Lastly, the retrospective nature of our study design precludes the establishment of causal relationships between HZ vaccination and MACE, warranting cautious interpretation of our results and emphasizing the need for further prospective investigations.

Further prospective studies are crucial to comprehensively evaluate the effectiveness of HZ vaccination in individuals with diabetes. Such prospective research should aim to assess vaccination outcomes in diabetes patients across various time intervals following vaccination, allowing for a comprehensive understanding of the long-term efficacy and safety profiles of different vaccines, including Shingrix and Zostavax. By conducting such studies, researchers can address existing gaps in the literature and provide more definitive evidence to guide clinical decision-making and vaccination strategies in this vulnerable population.

In conclusion, our retrospective cohort study provides valuable insights into the association between HZ vaccination and MACE among individuals with diabetes. Despite the inherent limitations of retrospective analyses, our findings suggest a potential protective effect of HZ vaccination against MACE, aligning with the ADA recommendation to vaccinate individuals aged 50 and older with diabetes against HZ. Our study underscores the importance of HZ vaccination as a potential strategy for reducing cardiovascular risk in this vulnerable population. Moreover, beyond its known benefits in reducing the risk of HZ, our findings suggest that HZ vaccination may also contribute to lowering the risk of MACE.

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Competing interests: None declared.

Data availability statement: This population-based study obtained data from the TrinetX platform (accessible at https://trinetx.com/), for which third-party restrictions apply to the availability of this data. The data were used under license for this study with restrictions that do not allow for data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs might be incurred, and a data-sharing agreement would be necessary.

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Figure legends

Figure 1. Detailed flow chart illustrating the division of participants into four groups based on herpes zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to no vaccinated controls yielded 45,958 pairs (model 1). Matching Shingrix vaccinated to no vaccinated controls resulted in 14,142 pairs (model 2), Zostavax vaccinated to no vaccinated controls yielded 11,285 pairs (model 3), and Shingrix vs. Zostavax vaccination resulted in 10,505 pairs (model 4).

Supplementary Figure 1. Flowchart illustrating the sensitivity analysis of this study, evaluating herpes zoster vaccination administered exclusively one year after a diabetes mellitus diagnosis. Patients were divided into four groups based on Herpes Zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to no vaccinated controls yielded 138,083 pairs (model 1). Matching Shingrix vaccinated to no vaccinated controls resulted in 45,904 pairs (model 2), Zostavax vaccinated to no vaccinated controls yielded 33,350 pairs (model 3), and Shingrix vs. Zostavax vaccination resulted in 27,171 pairs (model 4).

Supplementary Figure 2. Kaplan-Meier survival curves depicting the cumulative incidence of MACE over time, comparing herpes zoster (HZ)-vaccinated versus non-vaccinated patients, along with a head-to-head analysis of Shingrix versus Zostavax. (A) Any HZ vaccine vs. no vaccine; (B) Shingrix vs. no vaccine; (C) Zostavax vs. no vaccine; and (D) Shingrix vs. Zostavax.

Table 1. Demographic characteristics of unmatched individuals vaccinated versus unvaccinated against herpes zoster

	Any HZ vaccine (N = 45960)	No HZ vaccine (N = 3363873)	SMD
Age	63.46 ± 7.76	63.30 ± 9.30	0.019
Sex			
Female	22594 (49.16)	1599758 (47.56)	0.032
Male	20606 (44.84)	1656250 (49.24)	0.088
Race			
White	27076 (58.91)	1950119 (57.97)	0.019
Black or African American	7218 (15.71)	563189 (16.74)	0.028
Asian	2928 (6.37)	142295 (4.23)	0.096
Social economic status			
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	513 (1.12)	8856 (0.26)	0.103
Comorbidities			
Hypertensive diseases	25190 (54.81)	463468 (13.78)	0.959
Overweight and obesity	8980 (19.54)	149819 (4.45)	0.477
Other forms of heart disease	5651 (12.30)	205284 (6.10)	0.216
Chronic kidney disease	3257 (7.09)	89980 (2.68)	0.206
Neoplasms	3815 (8.30)	83995 (2.50)	0.259
Nicotine dependence	2673 (5.82)	67311 (2.00)	0.198
Hypertensive chronic kidney disease	1175 (2.56)	26124 (0.78)	0.139
Alcohol related disorders	734 (1.60)	18739 (0.56)	0.101
Fibrosis and cirrhosis of liver	438 (0.95)	19169 (0.57)	0.044
Unspecified dementia	235 (0.51)	7108 (0.21)	0.05
Alcoholic liver disease	189 (0.41)	6594 (0.20)	0.039
Alzheimer's disease	144 (0.31)	3447 (0.10)	0.046
Dementia in other diseases classified elsewhere	161 (0.35)	3858 (0.12)	0.049
Hepatic failure, not elsewhere classified	140 (0.31)	5878 (0.18)	0.027
Chronic hepatitis, not elsewhere classified	21 (0.05)	730 (0.02)	0.013
Vascular dementia	61 (0.13)	1394 (0.04)	0.031
Rheumatoid arthritis with rheumatoid factor	22 (0.05)	1081 (0.03)	0.008

Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Any HZ vaccine: Shingrix or Zostavax; HZ: herpes zoster; SMD: standardized mean difference.

Table 2. Risk of MACE among patients receiving HZ vaccination compared to no-vaccination and head-to-head comparison of Shingrix vs. Zostavax

	Exposure group		Comparison			
	N	No. of event	N	No. of event	HR (95% C.I.)	p value
Any HZ vaccine vs no HZ vaccine						
(Model 1 matched population)						
MACE	45,958	3,474	45,958	4,060	0.76 (0.72–0.79)	<0.001
Coronary artery disease	45,958	1,902	45,958	2,331	0.73 (0.69–0.78)	<0.001
Stroke	45,958	1,863	45,958	2,116	0.79 (0.74–0.84)	<0.001
All-cause mortality	45,958	2,793	45,958	4,794	0.54 (0.52–0.57)	<0.001
Shingrix vs no HZ vaccine						
(Model 2 matched population)						
MACE	14,142	858	14,142	1,294	0.84 (0.76–0.91)	<0.001
Coronary artery disease	14,142	468	14,142	770	0.78 (0.69–0.88)	<0.001
Stroke	14,142	445	14,142	650	0.87 (0.77–0.99)	0.035
All-cause mortality	14,142	569	14,142	1,561	0.53 (0.48–0.58)	<0.001
Zostavax vs no HZ vaccine						
(Model 3 matched population)						
MACE	11,285	1,674	11,285	1,030	0.81 (0.75–0.88)	<0.001
Coronary artery disease	11,285	910	11,285	616	0.72 (0.65–0.80)	<0.001
Stroke	11,285	952	11,285	530	0.90 (0.81–1.01)	0.065
All-cause mortality	11,285	1,496	11,285	1,203	0.58 (0.53–0.62)	<0.001
Shingrix vs Zostavax						
(Model 4 matched population)						
MACE	10,505	615	10,505	1,574	1.09 (0.98–1.21)	0.104
Coronary artery disease	10,505	335	10,505	859	1.16 (1.01–1.34)	0.036
Stroke	10,505	310	10,505	900	0.96 (0.83–1.11)	0.582
All-cause mortality	10,505	378	10,505	1,400	0.99 (0.87–1.12)	0.824

The p-value is derived from the log-rank test.

Any HZ vaccine: Shingrix or Zostavax; MACE: major adverse cardiovascular events; HZ: herpes zoster.

Table 3. Stratification analysis of risk of MACE among different group in model 1 matched population

	Any HZ vaccine		No HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Age					
50-65	28,258	1,634	28,258	1,968	0.80 (0.75–0.86)
>65	16,903	1,859	16,903	1,723	0.83 (0.78–0.89)
Sex					
Female	22,591	1,559	22,591	1,808	0.77 (0.72–0.83)
Male	20,603	1,665	20,603	1,995	0.74 (0.69–0.79)
Type 1 diabetes	230	10	230	16	0.25 (0.08–0.75)
Type 2 diabetes	42,503	2,945	42,503	3,588	0.71 (0.68–0.75)

If the patient's count is 1-10, the results indicate a count of 10.

Model 1 indicate any herpes zoster vaccination versus no herpes zoster vaccination population.

Any vaccine: Shingrix or Zostavax; MACE: major adverse cardiovascular events.

Table 4. Risk of MACE within a one-year follow-up period in the model 1 matched population

	HZ vaccine		No HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Follow-up period					
1 month	45,958	69	45,958	314	0.21 (0.16–0.27)
3 months	45,958	218	45,958	575	0.35 (0.30–0.41)
6 months	45,958	404	45,958	813	0.45 (0.40–0.50)
9 months	45,958	612	45,958	1,014	0.54 (0.48–0.59)
12 months	45,958	790	45,958	1,228	0.57 (0.52–0.62)

Model 1 indicates any herpes zoster vaccination versus non-herpes zoster vaccination population.

MACE: major adverse cardiovascular events; HZ: herpes zoster.

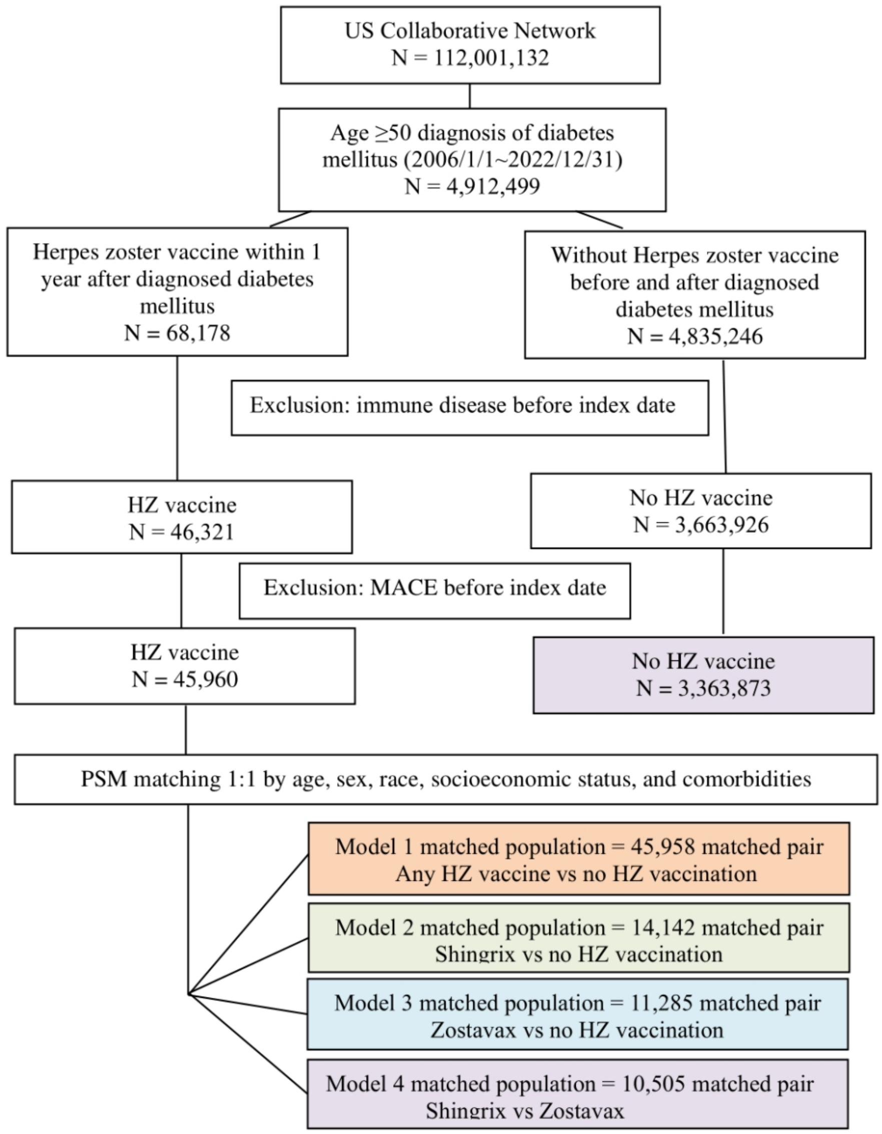
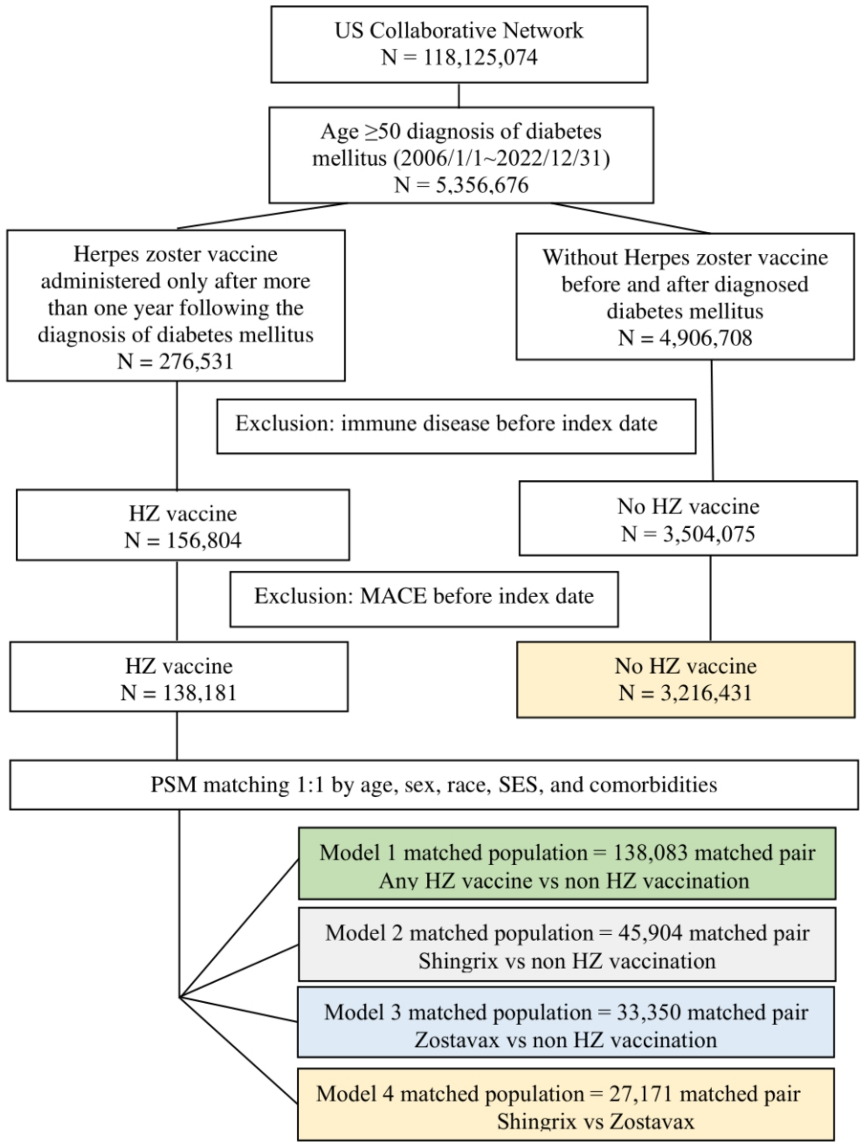


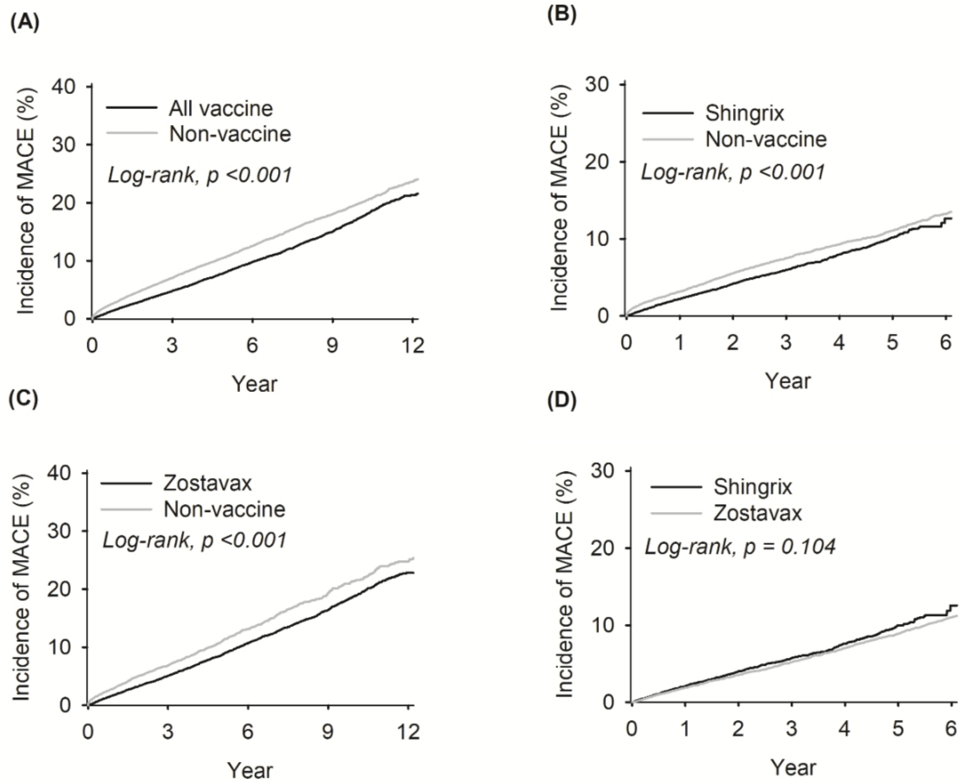
Figure 1. Detailed flow chart illustrating the division of participants into four groups based on Herpes Zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to no vaccinated controls yielded 45,958 pairs (model 1). Matching Shingrix vaccinated to no vaccinated controls resulted in 14,142 pairs (model 2), Zostavax vaccinated to no vaccinated controls yielded 11,285 pairs (model 3), and Shingrix vs. Zostavax vaccination resulted in 10,505 pairs (model 4)

145x180mm (200 x 200 DPI)



Supplementary Figure 1. Flowchart illustrating the sensitivity analysis of this study, evaluating herpes zoster vaccination administered exclusively one year after a diabetes mellitus diagnosis. Patients were divided into four groups based on Herpes Zoster (HZ) vaccination status. Matching of any HZ vaccinated cases to no vaccinated controls yielded 138,083 pairs (model 1). Matching Shingrix vaccinated to no vaccinated controls resulted in 45,904 pairs (model 2), Zostavax vaccinated to no vaccinated controls yielded 33,350 pairs (model 3), and Shingrix vs. Zostavax vaccination resulted in 27,171 pairs (model 4).

143x181mm (200 x 200 DPI)



146x116mm (220 x 220 DPI)

Supplementary table 1. Detailed coding of this study.

Inclusion criteria: diabetes mellitus

- **Presence of ICD-10 CM codes:** E10 or E11
- ICD-10-CM: E11, Type 2 diabetes mellitus
- ICD-10-CM: E10, Type 1 diabetes mellitus

Herpes Zoster vaccine codes:

Procedure code:

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- UMLS:SNOMED:459891000124102 (Herpes zoster vaccination)
- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)

Medication code:

- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N1 population (any HZ vaccine):

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- UMLS:SNOMED:459891000124102 (Herpes zoster vaccination)
- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N2 population (Shingrix):

- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))

N3 population (Zostavax):

- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)

N4 population (Shingrix VS Zostavax):

- UMLS:CPT:90750 (Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use)
- NLM:RXNORM:1986821 (varicella zoster virus glycoprotein E (Shingrix))
- UMLS:CPT:90736 (Zoster (shingles) vaccine (HZV), live, for subcutaneous injection)
- NLM:RXNORM:1292422 (varicella-zoster virus vaccine live (Oka-Merck) strain (Zostavax)

Outcomes:

Code for major adverse cardiovascular event (MACE)

Item	ICD-10-CM
Cardiovascular disease	
Coronary artery disease	
Acute myocardial infarction	I21
Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	I22
Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)	I23
Other acute ischemic heart diseases	I24
Stroke	
Nontraumatic subarachnoid hemorrhage	I60
Nontraumatic intracerebral hemorrhage	I61
Other and unspecified nontraumatic intracranial hemorrhage	I62
Cerebral infarction	I63

MACE: Major adverse cardiovascular event.

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

ICD-10-PCS: ICD-10 Procedure Coding System.

CPT: Current Procedural Terminology.

Codes of comorbidities

	ICD-10-CM
Socioeconomic status	
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	Z55-Z65
Comorbidities	
Hypertensive diseases	I10-I1A
Overweight and obesity	E66
Other forms of heart disease	I30-I5A
Chronic kidney disease	N18
Neoplasms	C00-D49
Nicotine dependence	F17.2
Hypertensive chronic kidney disease	I12
Alcohol related disorders	F10
Fibrosis and cirrhosis of liver	K74
Unspecified dementia	F03
Alcoholic liver disease	K70
Alzheimer's disease	G30
Dementia in other diseases classified elsewhere	F02
Hepatic failure, not elsewhere classified	K72
Chronic hepatitis, not elsewhere classified	K73
Vascular dementia	F01
Rheumatoid arthritis with rheumatoid factor	M05

Supplementary Table 2. Demographic Characteristics of Individuals with and without the Herpes Zoster Vaccine Before and After PSM (N1 matched population)

	Before PSM			After PSM		
	Any HZ vaccine N = 45,960	No-HZ vaccine N = 3,363,873	SMD	Any HZ vaccine N1 = 45,958	No-HZ vaccine N1 = 45,958	SMD
Age	63.46 ± 7.76	63.30 ± 9.30	0.019	63.46 ± 7.76	63.46 ± 7.85	0.001
Sex						
Female	22594 (49.16)	1599758 (47.56)	0.032	22592 (49.16)	22585 (49.14)	<0.001
Male	20606 (44.84)	1656250 (49.24)	0.088	20606 (44.84)	21544 (46.88)	0.041
Race						
White	27076 (58.91)	1950119 (57.97)	0.019	27076 (58.92)	27056 (58.87)	0.001
Black or African American	7218 (15.71)	563189 (16.74)	0.028	7218 (15.71)	7280 (15.84)	0.004
Asian	2928 (6.37)	142295 (4.23)	0.096	2926 (6.37)	2904 (6.32)	0.002
Socio-economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	513 (1.12)	8856 (0.26)	0.103	512 (1.11)	433 (0.94)	0.017
Comorbidities						
Hypertensive diseases	25190 (54.81)	463468 (13.78)	0.959	25188 (54.81)	25214 (54.86)	0.001
Overweight and obesity	8980 (19.54)	149819 (4.45)	0.477	8978 (19.54)	8969 (19.52)	<0.001
Other forms of heart disease	5651 (12.30)	205284 (6.10)	0.216	5651 (12.30)	5548 (12.07)	0.007
Chronic kidney disease	3257 (7.09)	89980 (2.68)	0.206	3256 (7.09)	3238 (7.05)	0.002
Neoplasms	3815 (8.30)	83995 (2.50)	0.259	3814 (8.30)	3820 (8.31)	<0.001
Nicotine dependence	2673 (5.82)	67311 (2.00)	0.198	2673 (5.82)	2647 (5.76)	0.002
Hypertensive chronic kidney disease	1175 (2.56)	26124 (0.78)	0.139	1175 (2.56)	1155 (2.51)	0.003
Alcohol related disorders	734 (1.60)	18739 (0.56)	0.101	734 (1.60)	667 (1.45)	0.012
Fibrosis and cirrhosis of liver	438 (0.95)	19169 (0.57)	0.044	438 (0.95)	414 (0.90)	0.005
Unspecified dementia	235 (0.51)	7108 (0.21)	0.050	235 (0.51)	219 (0.48)	0.005
Alcoholic liver disease	189 (0.41)	6594 (0.20)	0.039	189 (0.41)	186 (0.41)	0.001
Alzheimer's disease	144 (0.31)	3447 (0.10)	0.046	144 (0.31)	128 (0.28)	0.006
Dementia in other diseases classified elsewhere	161 (0.35)	3858 (0.12)	0.049	161 (0.35)	134 (0.29)	0.010
Hepatic failure, not elsewhere classified	140 (0.31)	5878 (0.18)	0.027	140 (0.31)	124 (0.27)	0.007
Chronic hepatitis, not elsewhere classified	21 (0.05)	730 (0.02)	0.013	21 (0.05)	15 (0.03)	0.007
Vascular dementia	61 (0.13)	1394 (0.04)	0.031	61 (0.13)	46 (0.10)	0.010
Rheumatoid arthritis with rheumatoid factor	22 (0.05)	1081 (0.03)	0.008	22 (0.05)	24 (0.05)	0.002

Any vaccine: Shingrix or Zostavax; HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary table 3. Demographic Characteristics of Individuals with Shingrix vaccination and without the Herpes Zoster Vaccination Before and After PSM (N2 matched population)

	Before PSM			After PSM		
	Shingrix N = 14,142	No HZ vaccine N = 3,363,856	SMD	Shingrix N2 = 14,142	No HZ vaccine N2 = 14,142	SMD
Age	65.08 ± 8.47	63.30 ± 9.30	0.201	65.08 ± 8.47	65.08 ± 8.55	<0.001
Sex						
Female	6857 (48.49)	1599752 (47.56)	0.019	6857 (48.49)	6880 (48.65)	0.003
Male	5945 (42.04)	1656239 (49.24)	0.145	5945 (42.04)	6534 (46.20)	0.084
Race						
White	8222 (58.14)	1950118 (57.97)	0.003	8222 (58.14)	8246 (58.31)	0.003
Black or African American	2320 (16.41)	563189 (16.74)	0.009	2320 (16.41)	2337 (16.53)	0.003
Asian	870 (6.15)	142285 (4.23)	0.087	870 (6.15)	845 (5.98)	0.007
Socio-economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	191 (1.35)	8856 (0.26)	0.122	191 (1.35)	166 (1.17)	0.016
Comorbidities						
Hypertensive diseases	8659 (61.23)	463464 (13.78)	1.124	8659 (61.23)	8672 (61.32)	0.002
Overweight and obesity	3347 (23.67)	149816 (4.45)	0.575	3347 (23.67)	3362 (23.77)	0.002
Other forms of heart disease	2088 (14.77)	205281 (6.10)	0.286	2088 (14.77)	2059 (14.56)	0.006
Chronic kidney disease	1443 (10.20)	89978 (2.68)	0.310	1443 (10.20)	1409 (9.96)	0.008
Neoplasms	1280 (9.05)	83993 (2.50)	0.284	1280 (9.05)	1276 (9.02)	0.001
Nicotine dependence	946 (6.69)	67311 (2.00)	0.231	946 (6.69)	932 (6.59)	0.004
Hypertensive chronic kidney disease	568 (4.02)	26124 (0.78)	0.213	568 (4.02)	545 (3.85)	0.008
Alcohol related disorders	275 (1.95)	18739 (0.56)	0.125	275 (1.95)	260 (1.84)	0.008
Fibrosis and cirrhosis of liver	158 (1.12)	19168 (0.57)	0.060	158 (1.12)	136 (0.96)	0.015
Unspecified dementia	111 (0.79)	7108 (0.21)	0.082	111 (0.79)	104 (0.74)	0.006
Alcoholic liver disease	82 (0.58)	6594 (0.20)	0.062	82 (0.58)	72 (0.51)	0.010
Alzheimer's disease	69 (0.49)	3447 (0.10)	0.071	69 (0.49)	65 (0.46)	0.004
Dementia in other diseases classified elsewhere	76 (0.54)	3858 (0.12)	0.074	76 (0.54)	71 (0.50)	0.005
Hepatic failure, not elsewhere classified	57 (0.40)	5877 (0.18)	0.043	57 (0.40)	47 (0.33)	0.012
Chronic hepatitis, not elsewhere classified	10 (0.07)	730 (0.02)	0.023	10 (0.07)	13 (0.09)	0.007
Vascular dementia	30 (0.21)	1394 (0.04)	0.048	30 (0.21)	24 (0.17)	0.010
Rheumatoid arthritis with rheumatoid factor	11 (0.08)	1081 (0.03)	0.019	11 (0.08)	10 (0.07)	0.003

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
If the patient's count is 1-10, the results indicate a count of 10.
Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary table 4. Demographic Characteristics of Individuals with Zostavax vaccination and without the Herpes Zoster Vaccination Before and After PSM (N3 matched population)

	Before PSM			After PSM		
	Zostavax N = 11,285	No HZ vaccine N = 3,363,856	SMD	Zostavax N3 = 11,285	No HZ vaccine N3 = 11,285	SMD
Age	65.18 ± 6.07	63.30 ± 9.30	0.239	65.18 ± 6.07	65.20 ± 6.18	0.004
Sex						
Female	5802 (51.41)	1599752 (47.56)	0.077	5802 (51.41)	5808 (51.47)	0.001
Male	5018 (44.47)	1656239 (49.24)	0.096	5018 (44.47)	5087 (45.08)	0.012
Race						
White	7009 (62.11)	1950118 (57.97)	0.085	7009 (62.11)	7005 (62.07)	0.001
Black or African American	1677 (14.86)	563189 (16.74)	0.052	1677 (14.86)	1679 (14.88)	<0.001
Asian	541 (4.79)	142285 (4.23)	0.027	541 (4.79)	544 (4.82)	0.001
Socio-economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	71 (0.63)	8856 (0.26)	0.055	71 (0.63)	62 (0.55)	0.010
Comorbidities						
Hypertensive diseases	5613 (49.74)	463464 (13.78)	0.837	5613 (49.74)	5620 (49.80)	0.001
Overweight and obesity	1355 (12.01)	149816 (4.45)	0.277	1355 (12.01)	1346 (11.93)	0.002
Other forms of heart disease	1215 (10.77)	205281 (6.10)	0.168	1215 (10.77)	1208 (10.70)	0.002
Chronic kidney disease	685 (6.07)	89978 (2.68)	0.167	685 (6.07)	690 (6.11)	0.002
Neoplasms	787 (6.97)	83993 (2.50)	0.212	787 (6.97)	767 (6.80)	0.007
Nicotine dependence	407 (3.61)	67311 (2.00)	0.097	407 (3.61)	419 (3.71)	0.006
Hypertensive chronic kidney disease	219 (1.94)	26124 (0.78)	0.101	219 (1.94)	218 (1.93)	0.001
Alcohol related disorders	0 (0.00)	3546 (0.11)	0.046	0 (0.00)	10 (0.09)	0.042
Fibrosis and cirrhosis of liver	116 (1.03)	18739 (0.56)	0.053	116 (1.03)	113 (1.00)	0.003
Unspecified dementia	56 (0.50)	19168 (0.57)	0.010	56 (0.50)	56 (0.50)	<0.001
Alcoholic liver disease	45 (0.40)	7108 (0.21)	0.034	45 (0.40)	38 (0.34)	0.010
Alzheimer's disease	22 (0.20)	6594 (0.20)	<0.001	22 (0.20)	24 (0.21)	0.004
Dementia in other diseases classified elsewhere	33 (0.29)	3447 (0.10)	0.043	33 (0.29)	31 (0.28)	0.003
Hepatic failure, not elsewhere classified	35 (0.31)	3858 (0.12)	0.042	35 (0.31)	37 (0.33)	0.003
Chronic hepatitis, not elsewhere classified	14 (0.12)	5877 (0.18)	0.013	14 (0.12)	15 (0.13)	0.002
Vascular dementia	10 (0.09)	730 (0.02)	0.029	10 (0.09)	10 (0.09)	<0.001
Rheumatoid arthritis with rheumatoid factor	10 (0.09)	1394 (0.04)	0.019	10 (0.09)	10 (0.09)	<0.001

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
If the patient's count is 1-10, the results indicate a count of 10.
Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary table 5. Demographic Characteristics of Individuals with Shingrix vaccination and Zostavax Vaccination Before and After PSM (N4 matched population)

	Before PSM			After PSM		
	Shingrix N = 14,142	Zostavax N = 11,285	SMD	Shingrix N4 = 10,505	Zostavax N4 = 10,505	SMD
Age	65.08 ± 8.47	65.18 ± 6.07	0.013	65.33 ± 8.07	65.20 ± 6.08	0.018
Sex						
Female	6857 (48.49)	5802 (51.41)	0.059	5318 (50.62)	5402 (51.42)	0.016
Male	5945 (42.04)	5018 (44.47)	0.049	4314 (41.07)	4639 (44.16)	0.06[illegible]
Race						
White	8222 (58.14)	7009 (62.11)	0.081	6497 (61.85)	6358 (60.52)	0.02[illegible]
Black or African American	2320 (16.41)	1677 (14.86)	0.043	1559 (14.84)	1654 (15.75)	0.02[illegible]
Asian	870 (6.15)	541 (4.79)	0.060	523 (4.98)	540 (5.14)	0.00[illegible]
Socio-economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	191 (1.35)	71 (0.63)	0.073	70 (0.67)	70 (0.67)	<0.001
Comorbidities						
Hypertensive diseases	8659 (61.23)	5613 (49.74)	0.233	5635 (53.64)	5605 (53.36)	0.00[illegible]
Overweight and obesity	3347 (23.67)	1355 (12.01)	0.308	1393 (13.26)	1354 (12.89)	0.01[illegible]
Other forms of heart disease	2088 (14.77)	1215 (10.77)	0.120	1234 (11.75)	1194 (11.37)	0.01[illegible]
Chronic kidney disease	1443 (10.20)	685 (6.07)	0.152	646 (6.15)	685 (6.52)	0.01[illegible]
Neoplasms	1280 (9.05)	787 (6.97)	0.077	756 (7.20)	775 (7.38)	0.00[illegible]
Nicotine dependence	946 (6.69)	407 (3.61)	0.140	403 (3.84)	406 (3.87)	0.00[illegible]
Hypertensive chronic kidney disease	568 (4.02)	219 (1.94)	0.122	209 (1.99)	219 (2.09)	0.00[illegible]
Alcohol related disorders	275 (1.95)	116 (1.03)	0.076	111 (1.06)	115 (1.10)	0.00[illegible]
Fibrosis and cirrhosis of liver	158 (1.12)	56 (0.50)	0.069	62 (0.59)	55 (0.52)	0.00[illegible]
Unspecified dementia	111 (0.79)	45 (0.40)	0.050	31 (0.30)	45 (0.43)	0.02[illegible]
Alcoholic liver disease	82 (0.58)	22 (0.20)	0.062	18 (0.17)	21 (0.20)	0.00[illegible]
Alzheimer's disease	69 (0.49)	33 (0.29)	0.031	34 (0.32)	32 (0.31)	0.00[illegible]
Dementia in other diseases classified elsewhere	76 (0.54)	35 (0.31)	0.035	35 (0.33)	35 (0.33)	<0.001
Hepatic failure, not elsewhere classified	57 (0.40)	14 (0.12)	0.054	13 (0.12)	14 (0.13)	0.00[illegible]
Chronic hepatitis, not elsewhere classified	10 (0.07)	10 (0.09)	0.006	10 (0.10)	10 (0.10)	<0.001
Vascular dementia	30 (0.21)	10 (0.09)	0.032	10 (0.10)	10 (0.10)	<0.001
Rheumatoid arthritis with rheumatoid factor	11 (0.08)	10 (0.09)	0.004	10 (0.10)	10 (0.10)	<0.001

HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.

If the patient's count is 1-10, the results indicate a count of 10.

Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary table 6. Risk of MACE among different follow-up period in N1 matched population.

	HZ vaccine		No HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Follow-up period					
≤5 years	45,958	2,513	45,958	3,051	0.70 (0.66–0.74)
5-10 years	43,445	812	42,798	799	0.93 (0.84–1.02)
>10 years	42,633	149	41,999	238	1.13 (0.92–1.39)

MACE: major adverse cardiovascular events; HZ: herpes zoster

N1 indicate any herpes zoster vaccination versus no herpes zoster vaccination population

Supplementary table 7. Stratification analysis of risk of MACE in different Shingrix dosage

	HZ vaccine		No HZ vaccine		
	N	No. of event	N	No. of event	HR (95% C.I.)
Shingrix 1 dose	10760	546	10760	990	0.66 (0.59–0.73)
Shingrix 2 doses	3237	167	3237	288	0.73 (0.59–0.89)

MACE: major adverse cardiovascular events; HZ: herpes zoster

Supplementary Table 8. Demographic characteristics of individuals who received the herpes zoster vaccine more than one year after a diabetes mellitus diagnosis (N1 matched population)

	Before PSM			After PSM		
	Any HZ vaccine N = 138,181	No HZ vaccine N = 3,216,431	SMD	Any HZ vaccine N = 138,083	No HZ vaccine N = 138,083	SMD
Age	65.35 ± 7.40	63.04 ± 9.20	0.277	65.34 ± 7.40	65.41 ± 7.64	0.009
Sex						
Female	69821 (50.53)	1526559 (47.46)	0.061	69755 (50.52)	69332 (50.21)	0.006
Male	62075 (44.92)	1585168 (49.28)	0.087	62045 (44.93)	62124 (44.99)	0.001
Race						
White	78496 (56.81)	1785703 (55.52)	0.026	78454 (56.82)	79342 (57.46)	0.013
Black or African American	24018 (17.38)	514062 (15.98)	0.038	24006 (17.39)	23554 (17.06)	0.009
Asian	11428 (8.27)	161438 (5.02)	0.131	11392 (8.25)	11038 (7.99)	0.009
Social economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	1699 (1.23)	8086 (0.25)	0.114	1680 (1.22)	1501 (1.09)	0.012
Comorbidities						
Hypertensive diseases	87294 (63.17)	440309 (13.69)	1.182	87196 (63.15)	87436 (63.32)	0.004
Overweight and obesity	28615 (20.71)	145078 (4.51)	0.503	28533 (20.66)	27819 (20.15)	0.013
Other forms of heart disease	20106 (14.55)	190683 (5.93)	0.287	20091 (14.55)	20527 (14.87)	0.009
Chronic kidney disease	14749 (10.67)	84559 (2.63)	0.327	14677 (10.63)	14119 (10.23)	0.013
Neoplasms	13620 (9.86)	82826 (2.58)	0.305	13560 (9.82)	13404 (9.71)	0.004
Nicotine dependence	7419 (5.37)	62447 (1.94)	0.183	7410 (5.37)	7549 (5.47)	0.004
Hypertensive chronic kidney disease	5882 (4.26)	25680 (0.80)	0.222	5867 (4.25)	5190 (3.76)	0.025
Alcohol related disorders	1645 (1.19)	18062 (0.56)	0.068	1645 (1.19)	1521 (1.10)	0.008
Fibrosis and cirrhosis of liver	1628 (1.18)	18742 (0.58)	0.064	1619 (1.17)	1597 (1.16)	0.001
Unspecified dementia	848 (0.61)	6458 (0.20)	0.065	848 (0.61)	823 (0.60)	0.002
Alcoholic liver disease	423 (0.31)	6556 (0.20)	0.020	422 (0.31)	349 (0.25)	0.010
Alzheimer's disease	518 (0.38)	3077 (0.10)	0.058	518 (0.38)	508 (0.37)	0.001
Dementia in other diseases classified elsewhere	593 (0.43)	3474 (0.11)	0.062	591 (0.43)	565 (0.41)	0.003
Hepatic failure, not elsewhere classified	227 (0.16)	5726 (0.18)	0.003	227 (0.16)	205 (0.15)	0.004
Chronic hepatitis, not elsewhere classified	56 (0.04)	743 (0.02)	0.010	56 (0.04)	62 (0.05)	0.002
Vascular dementia	230 (0.17)	1240 (0.04)	0.040	229 (0.17)	201 (0.15)	0.005
Rheumatoid arthritis with rheumatoid factor	62 (0.05)	973 (0.03)	0.008	62 (0.05)	39 (0.03)	0.009

Any vaccine: Shingrix or Zostavax; HZ: herpes zoster; PSM: propensity score matching; SMD: standardized mean difference.
Age is presented as mean ± standard deviation, while sex, race, socioeconomic status, and comorbidities are presented as sample numbers and percentages.

Supplementary Table 9. Risk of MACE in individuals who received the herpes zoster (HZ) vaccine compared to those who did not, with vaccination administered more than one year after a diabetes mellitus diagnosis.

	Exposure group		Comparison		
	N	No. of event	N	No. of event	HR (95% C.I.)
Any HZ vaccine vs no HZ vaccine (N1 matched population)					
MACE	138,083	17,009	138,083	27,096	0.58 (0.57–0.59)
Coronary artery disease	138,083	6,313	138,083	8,772	0.67 (0.65–0.69)
Stroke	138,083	5,999	138,083	7,656	0.74 (0.71–0.76)
All-cause mortality	138,083	8,027	138,083	16,215	0.48 (0.46–0.49)
Shingrix vs no HZ vaccine (N2 matched population)					
MACE	45,904	5,063	45,904	9,926	0.62 (0.60–0.65)
Coronary artery disease	45,904	1,970	45,904	3,241	0.75 (0.71–0.80)
Stroke	45,904	1,831	45,904	2,831	0.79 (0.74–0.84)
All-cause mortality	45,904	2,180	45,904	5,965	0.48 (0.46–0.51)
Zostavax vs no HZ vaccine (N3 matched population)					
MACE	33,350	8,024	33,350	6,280	0.61 (0.59–0.63)
Coronary artery disease	33,350	2,980	33,350	2,014	0.71 (0.67–0.75)
Stroke	33,350	3,072	33,350	1,805	0.82 (0.77–0.87)
All-cause mortality	33,350	3,995	33,350	3,751	0.48 (0.46–0.50)
Shingrix vs Zostavax (N4 matched population)					
MACE	27,171	2,259	27,171	6,916	0.99 (0.94–1.04)
Coronary artery disease	27,171	900	27,171	2,555	1.08 (0.99–1.17)
Stroke	27,171	852	27,171	2,601	0.97 (0.89–1.06)
All-cause mortality	27,171	851	27,171	3,556	0.91 (0.84–0.99)

Any HZ vaccine: Shingrix or Zostavax; MACE: major adverse cardiovascular events; HZ: herpes zoster