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CLINICAL RESEARCH
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Live zoster vaccination and cardiovascular outcomes: a nationwide, South Korean study

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Abstract

Background and Aims Despite the potential association between herpes zoster infection and cardiovascular events, limited studies have investigated the relationship between live zoster vaccination and cardiovascular outcomes. This large-scale, population-based cohort study with a long-term follow-up aimed to investigate the association between live zoster vaccination and the risk of various cardiovascular events.

Methods Data on comprehensive information of individuals aged ≥50 years from South Korea ($n = 2\,207\,784$) were included from 1 January 2012, to 31 December 2021. National insurance information from the Korea Health Insurance Review and Assessment Service, the national health examination results from the Korean National Health Insurance Service, and the live zoster vaccination data from the Korea Disease Control and Prevention Agency were merged. The risk of incident cardiovascular outcomes after live zoster vaccination was assessed compared with unvaccinated individuals. The primary outcome was the risk of cardiovascular diseases based on International Classification of Diseases, Tenth Revision code diagnosis. In propensity score–based overlap weighted cohorts, Cox proportional hazard models were used to estimate hazard ratios (HRs) for overall and specific cardiovascular outcomes, while calculating restricted mean survival time (RMST) for each outcome. The observation period was from 1 January 2012, to 31 January 2024. Multiple stratification analyses were performed.

Results After applying propensity score–based overlap weighting, 1 271 922 individuals were included [mean age, 61.3 years (standard deviation, 3.4); 548 986 (43.2%) male; median follow-up time, 6.0 years] in overlap-weighted cohort. Live zoster vaccination was associated with lower risks of overall cardiovascular events [HR 0.77, 95% confidence interval (CI) 0.76–0.78], particularly major adverse cardiovascular events [0.74 (0.71–0.77)], heart failure [0.74 (0.70–0.77)], cerebrovascular disorders [0.76 (0.74–0.78)], ischaemic heart disease [0.78 (0.76–0.80)], thrombotic disorders [0.78 (0.74–0.83)], and dysrhythmia [0.79 (0.77–0.81)]. The RMST difference for overall cardiovascular events following live zoster vaccination was 95.14 days per decade (95% CI 94.99–95.30). The protective association persisted up to 8 years, with the greatest reduction observed 2–3 years post-vaccination. The decrease in cardiovascular disease risk was more pronounced among males, individuals aged <60 years, those with unhealthy lifestyle habits, and those from low-income households and rural residents.

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Conclusions These findings suggest that live zoster vaccination may be beneficial as a public health strategy with potential implications for cardiovascular disease burden in the general population. This strategy may help address health disparities and mortality linked to cardiovascular complications.

Structured Graphical Abstract

Key Question

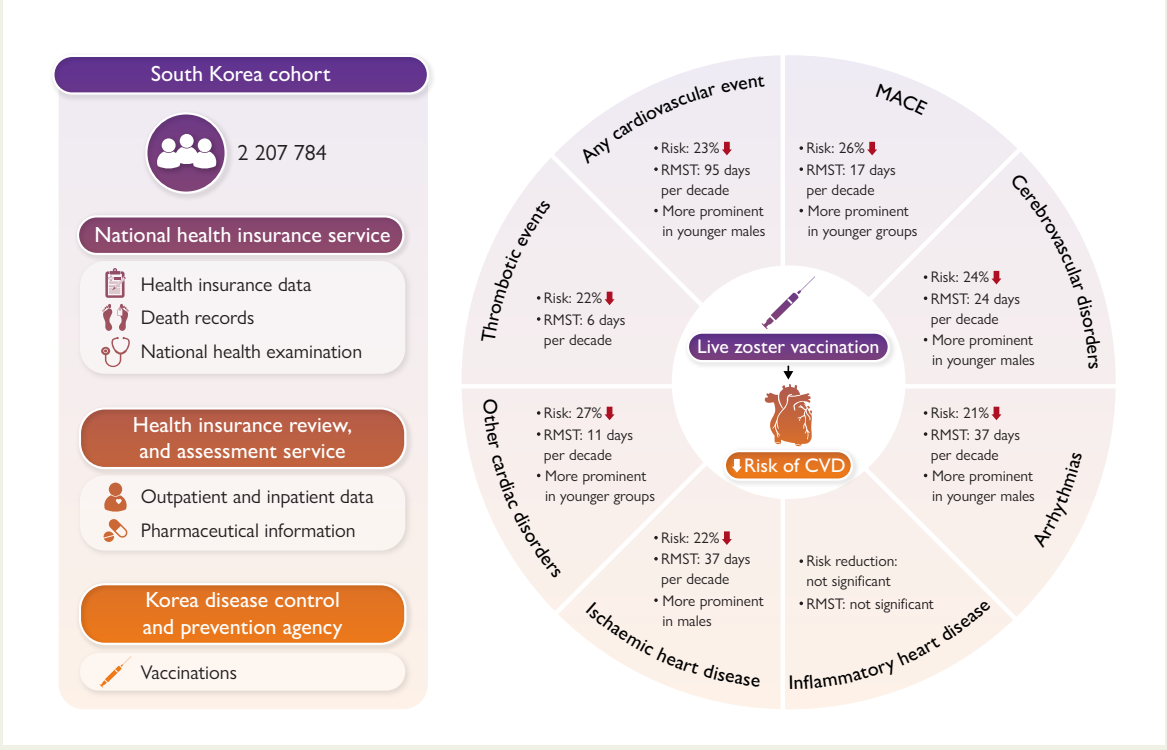
Herpes zoster is known to increase cardiovascular risk. Does live zoster vaccination reduce long-term cardiovascular risk?

Key Finding

Live zoster vaccination was associated with lower rates of various cardiovascular events, including major cardiovascular events, heart failure, stroke, thrombotic events, arrhythmias, and ischaemic heart disease. This association lasted up to 8 years and was stronger for males, individuals aged <60 years, those with unhealthy lifestyles, lower income, and rural residence.

Take Home Message

This comprehensive, long-term study underscores the potential benefits of live zoster vaccination. This might impact on public health policies.



Keywords Cardiovascular disease • Herpes zoster • Live zoster vaccine • Vaccination

Introduction

Herpes zoster (HZ) results from the reactivation of the latent varicella-zoster virus (VZV), manifesting as a painful rash, particularly in individuals with compromised immune systems.[1] The majority of HZ cases, approximately two-thirds, occur in individuals aged over 49 years.[1] The condition can result in severe complications such as postherpetic neuralgia and HZ ophthalmicus, often requiring hospitalization, with morbidity increasing with advancing age.[2] Without vaccination, the lifetime risk of developing HZ is estimated to be 30%.[3] Individuals aged over 65 years are known to experience high case fatality rates, underscoring the critical importance of vaccination within this demographic.[1]

Two HZ vaccines, the live zoster vaccine and the recombinant zoster vaccine, are licensed and administered globally to individuals aged over 49 years.[4] Previous studies have indicated the effectiveness of both vaccines in preventing HZ, particularly the live zoster vaccine, which has shown efficacy in individuals with comorbidities such as heart disease, diabetes, lung disease, and chronic kidney disease.[4]

Among the various complications associated with HZ, cardiovascular events are frequently recognized as potential complications of HZ infection. Associations between stroke and cardiovascular events following HZ infection have been suggested, indicating a potential association with acute myocardial infarction (MI) and stroke.[5] However, only a few studies have suggested that the live zoster vaccine might lower the risk of

cardiovascular disease. These studies are limited by their small sample sizes, leaving uncertainty regarding the role of vaccination in preventing MI or stroke.[6]

Therefore, our objective was to investigate the association between live zoster vaccine and all cardiovascular events, which are known to occur following HZ infection using a large-scale, population-based cohort. Our dataset encompasses a long-term follow-up period, enabling the identification of the association between vaccination and all cardiovascular outcomes. Considering the demographic shift towards an increasingly aged population[7] and rising numbers of immunocompromised individuals,[8] both the risk of HZ infection and the burden of cardiovascular disease have become critical issues. Through this study, we aimed to investigate whether the live zoster vaccine can reduce the risk of cardiovascular events, particularly in the vulnerable older population.[9] This study will aid in identifying the long-term safety and benefits of vaccination, potentially contributing to public healthcare initiatives.

Methods

Data source

This study utilized a large-scale, nationwide, population-based cohort design: a South Korean nationwide cohort (total $n = 2\,207\,784$). As South Korea is based on a universal health insurance system, we merged the national insurance information (outpatient and inpatient data, pharmaceutical information, and death records) from the Korea Health Insurance Review and Assessment Service, the national health examination results from the Korean National Health Insurance Service, and the live zoster vaccination data from the Korea Disease Control and Prevention Agency. The study protocol was approved by the Korea Healthcare Bigdata of the Ministry of Health and Welfare (no. 2022-00061), the Korea Health Insurance Review and Assessment Service, the Korean National Health Insurance Service, and the Korea Disease Control and Prevention Agency. Under the terms of the approval, patient consent was not required to use routine health records for our study. To ensure confidentiality, all patient-related information was anonymized by the Korea Healthcare Bigdata of the Ministry of Health and Welfare.

This cohort is a nationwide, large-scale, general population-based cohort in South Korea, encompassing 98% of the South Korean population.[10,11] Detailed information on the cohort is provided in Supplementary data online, *Methods*. We included all Korean individuals aged ≥50 years who received the live zoster vaccine between 1 January 2012, and 31 December 2021. Additionally, as an unvaccinated control, we applied propensity score–based overlap-weighting algorithm with the nationwide population of Koreans aged ≥50 years who did not receive the live zoster vaccination. We excluded individuals who met the following criteria: (i) insufficient socioeconomic information or died before enrolment; (ii) missing data from the national health examination; and (iii) previous history of cardiovascular events before HZ vaccination (excluded $n = 528\,951$). Thus, the final sample had 1 678 833 participants. The observation period was from 1 January 2012, to 31 January 2024.

Exposures and outcomes

We obtained data on the live zoster vaccinations from the Korea Disease Control and Prevention Agency.[12] In this cohort, 1 093 860 individuals received live zoster vaccine from 1 January 2012 to 31 December 2021. In South Korea, the live zoster vaccine is administered according to a single-dose schedule. We classified individuals into vaccinated and unvaccinated cohorts based on their immunization status with this single-dose live zoster vaccine.[12,13]

The primary outcome was the onset of cardiovascular events as follows: (i) cerebrovascular diseases such as stroke and transient ischaemic accident (TIA); (ii) dysrhythmia such as atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmia, and atrial flutter; (iii) inflammatory heart diseases such as pericarditis and myocarditis; (iv) ischaemic heart diseases such as acute coronary disease, MI, and angina; (v) other cardiac disorders such as heart failure, cardiac arrest, and cardiogenic shock; (vi) thrombotic disorders such as arterial thromboembolism, pulmonary embolism, and deep vein thrombosis; and (vii) major adverse cardiovascular events (MACEs). Major adverse cardiovascular events refers to all-cause mortality, stroke, and MI.[14] A composite of any cardiovascular outcome was defined as the first incident occurrence of any of the cardiovascular outcomes investigated in this study. We provided a list of the International Classification of Diseases, Tenth Revision (ICD-10) codes and medications used to define each disease in this study (see Supplementary data online, *Table S1*).

Covariates

The demographic characteristics of the participants were sourced from the health insurance database as follows: age (50–54, 55–59, 60–64, and ≥65 years), sex (male and female), region of residence (urban and rural), and household income [low (0–39 percentile), middle (40–79 percentile), and high (80–100 percentile)]. The information on body mass index (BMI) [underweight and normal (<23.0 kg/m^2), overweight (23.0–24.9 kg/m^2), and obese (≥25.0 kg/m^2)], fasting blood glucose (<100 and ≥100 mg/dL), blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), and glomerular filtration rate (<60, 60–89, and ≥90 mL/min/1.73 m^2) were included from the fasting serum samples of national health examination. Charlson comorbidity index score, history of medication usage for diabetes, hyperlipidaemia, hypertension, smoking status (non-, former, and current smoker), alcoholic drinks (<1, 1–2, 3–4, and ≥5 days per week), and aerobic physical activity [sufficient (≥600 Mmetabolic Equivalent Task scores) and insufficient] were collected based on ICD-10 code and/or results of national health examination with medical interview. The national health examination data have been matched with the most recent data available up to or including the index date. Furthermore, complete case methods were adopted to exclude individuals, including those missing from all covariates.

Overlap-weighted cohort

Based on the literature and expert knowledge, we illustrated the hypothesized causal relationship in Supplementary data online, *Figure S1A* using a directed acyclic graph representing the effect of all covariates on vaccination and cardiovascular disease.[15–17] We identified sex, age, region of residence, household income, BMI, smoking status, alcohol consumption, physical activity, and Charlson comorbidity index as potential confounders. To ensure a balanced comparison between the vaccinated and unvaccinated groups, we adjusted for these variables in a multivariable logistic regression model to estimate the propensity score for vaccination. Additionally, to address the issue of extreme propensity scores, we employed a propensity score–based overlap weighting algorithm.[18,19] The adequacy of overlap weighting was evaluated by comparing standardized mean differences (SMDs), with an SMD <0.1 considered no significant imbalance between the two groups.[10] Through these methods of effectively balancing the confounding influence of covariates between the two groups, we were able to reduce the relationship between confounders and vaccination assignment, thereby controlling for confounding.[20] The causal relationships between covariates, exposure, and outcomes, adjusted for confounders, are illustrated in Supplementary data online, *Figure S1B*.[21] Following overlap weighting, 1 271 922 individuals were included in the study (*Figure 1*; Supplementary data online, *Table S2*).

Statistical analysis

In this study, live zoster vaccination was designated as the exposure variable. The primary outcome was the new onset of any cardiovascular event after at least 30 days following vaccination.[22] Secondary outcomes encompassed seven subtypes of cardiovascular events, including cerebrovascular diseases, dysrhythmia, inflammatory heart disease, ischaemic heart disease, other cardiac disorders, thrombotic disorders, and MACE. In the study, the

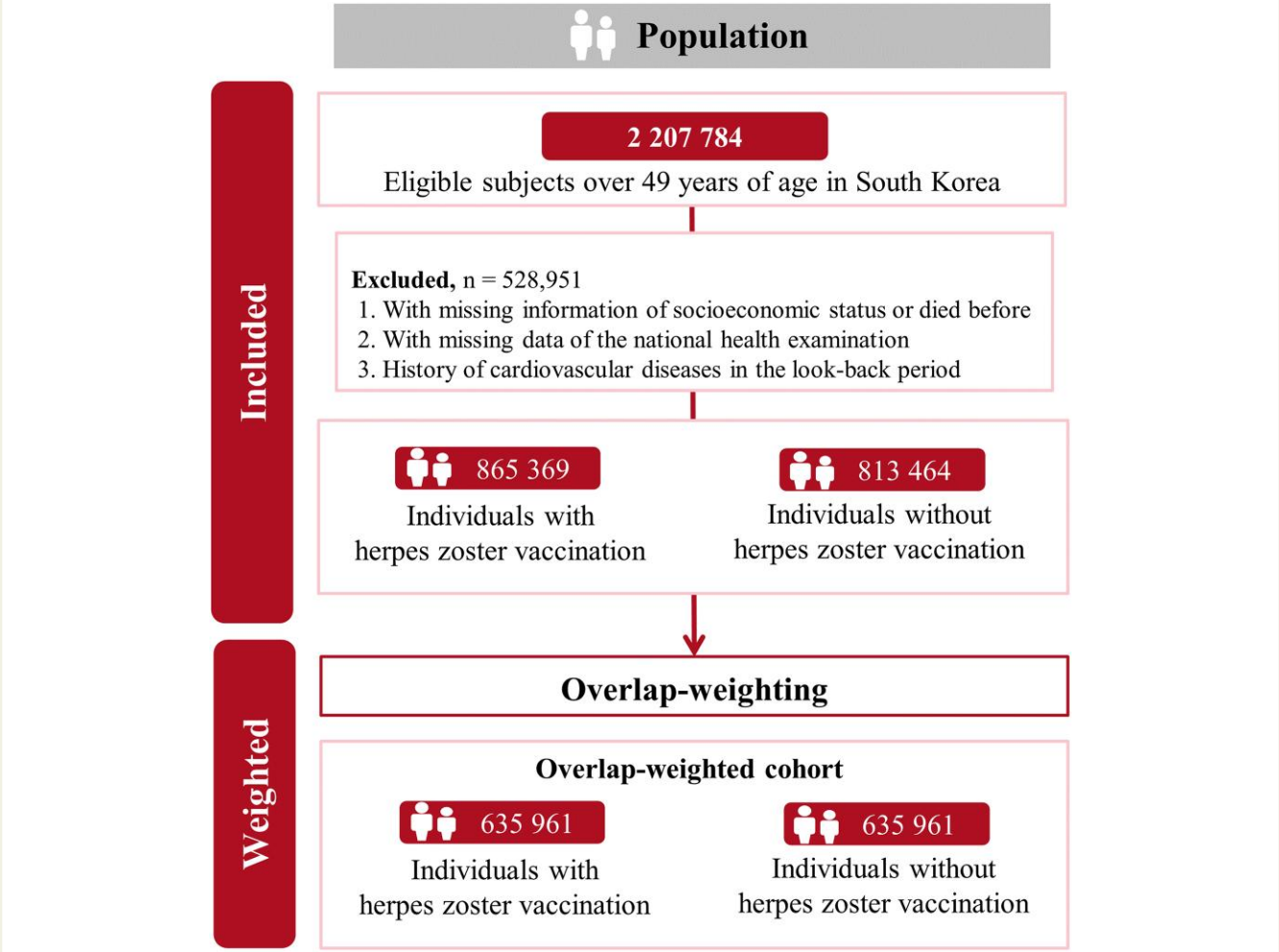


Figure 1 Study design

date of the live zoster vaccination was designated as the individual index date (T_0) among the vaccinated group. To address immortal time bias, we generated randomization by assigning random values based on a uniform distribution to the unvaccinated control group. The control participants were then assigned a T_0 in the order of these random values, corresponding to the distribution of T_0 in the vaccinated group.[19,23,24] The follow-up period ended upon new-onset cardiovascular events, reaching 31 January 2024, or in the event of the subject's death.

Cox proportional hazards regression models were used to calculate cause-specific hazard ratios (HRs) and their 95% confidence intervals (CIs), censoring participants at all-cause death.[25,26] The proportional hazards assumption was met on examination of log-minus-log survival plots using a Kaplan–Meier method. For more interpretable analysis, we estimated restricted mean survival time (RMST) over a 10-year period for both groups.[27] The RMST difference (95% CIs), which represents the number of days between the vaccinated and unvaccinated groups, is an absolute measure of survival time and provides an independent value for each outcome.[28] Also, we executed stratification analyses according to sex, age, region of residence, household income, BMI, smoking status, alcohol consumption, physical activity, and previous medication use for diabetes, hyperlipidaemia, and hypertension. We further assessed the time persistence effect of cardiovascular events following live zoster vaccination using point estimates at specific time intervals (<1, 1–2, 2–3, 3–5, 5–8, and ≥8 years). We provided justification for the sensitivity analyses in Supplementary data online, *Table S3*. We used SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) to perform all statistical analyses in this study. A two-sided *P*-value of <.05 was considered statistically significant.

Sensitivity analysis

We assessed the proportion of the association between live zoster vaccination and cardiovascular events that is mediated by HZ complications. HZ complications are defined as postherpetic polyneuropathy and other neurological or systemic complications (see Supplementary data online, *Table S1*). Counterfactual mediation analysis was performed to quantify the indirect effect (the association of vaccination with the outcome that is mediated by HZ complications), direct effect (the association of vaccination with the outcome that is not mediated by HZ complications), and total effect (the direct and indirect effects). We employed competing risks regression models to investigate the association of exposure on the incidence of cardiovascular events while accounting for the competing risk of death from non-cardiovascular causes. Fine–Gray sub-distribution hazard models were utilized to calculate sub-distribution HRs and their corresponding 95% CIs. The cumulative incidence functions of cardiovascular events were estimated considering non-cardiovascular death as a competing risk (see Supplementary data online, *Figure S2*). To enhance the robustness and explanatory of the results, we analysed HRs for any cardiovascular event and MACE in the full unweighted cohort. Additionally, we conducted

an analysis in the overlap-weighted cohort, defining any cardiovascular events while excluding sinus tachycardia and sinus bradycardia.

Patient and public involvement

No patients were involved in formulating the research question or study design. The study design and implementation were conducted without consultation. However, we plan to disseminate the results of this study to all study participants and wider relevant communities upon request.

Results

A total of 2 207 784 individuals with a mean age of 61.8 [standard deviation (SD), 3.6] years were included, of which 46.1% ($n = 1\,018\,230$) were male (see Supplementary data online, *Table S4*). After applying propensity score–based overlap weighting, 635 961 individuals were allocated to each of the vaccinated and unvaccinated group. The overlap-weighted cohort had a mean age of 61.3 (SD, 3.4) years, and 43.2% (548 986/1 271 922) were male. SMDs of all covariates in the overlap-weighted cohort were smaller than 0.1 (*Table 1*). The median follow-up time was 6.0 (95% CI 3.3–8.2) years.

Figure 2 shows that individuals with live zoster vaccination had a significantly lower HR for overall cardiovascular disease outcomes than unvaccinated individuals [HR 0.77 (95% CI 0.76–0.78)]. Among the specific cardiovascular disease categories, the lowest hazard was observed for MACE [HR 0.74 (95% CI 0.71–0.77)], followed by heart failure [HR 0.74 (95% CI 0.70–0.77)], cerebrovascular disorders [HR 0.76 (95% CI 0.74–0.78)], ischaemic heart disease [HR 0.78 (95% CI 0.76–0.80)], thrombotic disorders [HR 0.78 (95% CI 0.74–0.83)], and dysrhythmia [HR 0.79 (95% CI 0.77–0.81)]. Detailed analysis results are presented in Supplementary data online, *Table S5*. Over a 10-year follow-up period, the RMST for any cardiovascular events was 95.14 (95% CI 94.99–95.30) days greater in individuals vaccinated with live zoster vaccine compared with unvaccinated individuals. The RMST difference between vaccinated and unvaccinated individuals was most pronounced for ischaemic heart disease [36.63 (95% CI 36.51–36.75) days], followed by dysrhythmia [35.61 (95% CI 35.50–35.73) days], cerebrovascular disorders [24.35 (95% CI 24.23–24.47) days], MACE [16.51 (95% CI 16.41–16.61) days], other cardiac disorders [11.19 (95% CI 11.11–11.28) days], and thrombotic disorders [6.19 (95% CI 6.19–6.25) days].

Stratification analysis results, shown in *Figure 3* and Supplementary data online, *Tables S6* and *S7*, indicate that for any cardiovascular disease, males showed greater differences in HR compared with females [males: HR 0.73 (95% CI 0.71–0.74); females: HR 0.80 (95% CI 0.79–0.82); $P_{\text{interaction}}$ <.001]. Age groups under 60 years had a more significant risk reduction compared with those over 60 years [<60 years: HR 0.73 (95% CI 0.71–0.75); ≥60 years: HR 0.84 (95% CI 0.82–0.85); $P_{\text{interaction}}$ <.001]. Significant disparities were observed based on socioeconomic status and region of residence. Individuals living in rural areas presented larger differences in cardiovascular outcomes compared with those living in urban areas [urban: HR 0.80 (95% CI 0.78–0.81); rural: HR 0.75 (95% CI 0.73–0.76); $P_{\text{interaction}}$ <.001], and the lower HRs were more pronounced among individuals with low household income compared with those with high household income [low: HR 0.74 (95% CI 0.72–0.76); high: HR 0.80 (95% CI 0.78–0.82); $P_{\text{interaction}}$ <.001]. Individuals with obesity (BMI ≥25.0 kg/m^2) showed more substantially lowered HR in cardiovascular outcomes following vaccination [<23.0 kg/m^2: HR 0.79 (95% CI 0.77–0.81); 23.0–24.9 kg/m^2: HR, 0.77 (95% CI 0.75–0.79); and ≥25.0 kg/m^2: HR 0.75 (95% CI 0.74–0.77); $P_{\text{interaction}}$ <.001]. When comparing individuals by lifestyle habits, those with unhealthy lifestyles such as smoking, excessive alcohol consumption, and insufficient physical activity had similarly lowered HR in cardiovascular events compared with those with healthy lifestyles. Individuals using medication for diabetes, hyperlipidaemia, and hypertension presented similarly lowered HR individuals who were not on medication. Similar patterns were observed for each disease category (see Supplementary data online, *Tables S7–S14*).

The temporal pattern of lowered HR for cardiovascular outcomes following live zoster vaccination showed a U-shaped curve (*Figure 4*). The lowered HR was observed from the first year, with the most pronounced difference in hazard occurring during 2–3 years post-vaccination [<1 year: HR 0.80 (95% CI 0.78–0.82); 1–2 years: HR 0.74 (95% CI 0.72–0.77); 2–3 years: HR 0.74 (95% CI 0.71–0.76); and 3–5 years: HR 0.80 (95% CI 0.78–0.82)]. The lowered HR became less pronounced after 5 years [5–8 years: HR 0.88 (95% CI 0.83–0.93)], though differences in HRs remained apparent for up to 8 years. Similar patterns were observed in the detailed disease categories (see Supplementary data online, *Tables S15–S22*).

In sensitivity analysis, the total, direct, and indirect effects of vaccination on cardiovascular risks were examined. For any cardiovascular event, an odds ratio of the total effect was 0.65 (95% CI 0.41–0.97). While for the indirect effect, representing the association between vaccination and the outcome mediated by HZ complications, it was 0.32 (95% CI 0.10–0.58), and for the direct effect (not mediated by HZ complications), it was 2.03 (95% CI 1.30–4.90) (see Supplementary data online, *Table S23*). We observed similar patterns through other sensitivity analyses (see Supplementary data online, *Tables S24–S26*).

Discussion

This is the first study to investigate the relationship between live zoster vaccination and its association with reduced risk of cardiovascular outcomes, utilizing a large-scale and nationwide cohort in South Korea comprising over 2 million participants. The main findings of this study are as follows: (i) live zoster vaccination was associated with lower risk of overall cardiovascular events; (ii) the lowered HR for cardiovascular outcomes was observed over time, with the most pronounced difference noted 2–3 years post-vaccination, with diminishing differences after 8 years; (iii) males, individuals aged <60 years, individuals with unhealthy lifestyles, those with low and middle incomes, and rural residents showed more prominently lowered HR in cardiovascular outcomes following live zoster vaccination (*Structured Graphical Abstract*).

Comparisons with previous studies

While several studies have investigated cardiovascular outcomes such as stroke,[5,29–31] MI,[5,30] MACE,[30] coronary heart disease,[30] heart failure,[32] and dysrhythmia,[33] only a few explored the association between live zoster vaccination and the subsequent risk of cardiovascular outcomes.[5,6] Previous studies consistently reported increased risk of cardiovascular diseases following HZ or VZV infection. Risks of stroke, MI, MACE, coronary heart disease, and heart failure were found to increase ∼1.5-fold to two-fold following infection. A recent study revealed that HZ infection could increase the risk of coronary heart disease and stroke for up to 5–8 years, although no significant increase was observed 1–4 years post-infection.[30] Studies that examined the association between live zoster vaccination and cardiovascular outcomes had conflicting conclusions. One study suggested that all types of stroke could be reduced through live zoster vaccination, indicating a 15% reduction in stroke risk compared with the unvaccinated population.[6] However, another study concluded that the beneficial effect of

Table 1 Baseline characteristics for propensity score–based overlap weighted cohort in South Korea

Characteristic	Overlap-weighted cohort (N = 1 271 922)		
	Vaccinated (n = 635 961)	Unvaccinated (n = 635 961)	SMD[a]
Mean age (SD), years	61.3 (3.4)	61.6 (3.4)	
Age, *n* (%)			<.001
50–54 years	18 465 (2.9)	18 078 (2.8)	
55–59 years	157 199 (24.7)	156 090 (24.5)	
60–64	334 944 (52.7)	336 077 (52.9)	
≥65 years	125 353 (19.7)	125 716 (19.8)	
Sex, *n* (%)			<.001
Male	274 493 (43.2)	274 493 (43.2)	
Female	361 468 (56.8)	361 468 (56.8)	
Region of residence, *n* (%)			<.001
Urban	300 948 (47.3)	300 841 (47.3)	
Rural	335 013 (52.7)	335 120 (52.7)	
Household income, *n* (%)			<.001
Low (0–39th percentile)	182 512 (28.7)	183 169 (28.8)	
Middle (40–79th percentile)	231 270 (36.4)	232 022 (36.5)	
High (80–100th percentile)	222 179 (34.9)	220 770 (34.7)	
Charlson comorbidity index score, *n* (%)			<.001
0	546 915 (86.0)	548 295 (86.2)	
1	70 955 (11.2)	71 078 (11.2)	
≥2	18 091 (2.8)	16 588 (2.6)	
BMI group, *n* (%)			<.001
Underweight (<18.5 kg/m^2)	173 783 (27.3)	172 586 (27.1)	
Normal (18.5–22.9 kg/m^2)	175 096 (27.5)	175 642 (27.6)	
Overweight (23.0–24.9 kg/m^2)	254 866 (40.1)	256 870 (40.4)	
Obese (≥25.0 kg/m^2)	32 216 (5.1)	30 863 (4.9)	
Smoking status, *n* (%)			<.001
Never	440 503 (69.3)	441 724 (69.5)	
Former	156 894 (24.7)	157 153 (24.7)	
Current	38 564 (6.1)	37 084 (5.8)	
Alcohol consumption, *n* (%)			<.001
<1 day/week	347 391 (54.6)	350 653 (55.1)	
1–2 days/week	255 693 (40.2)	254 416 (40.0)	
3–4 days/week	21 486 (3.4)	20 312 (3.2)	
≥5 days/week	11 391 (1.8)	10 580 (1.7)	
Aerobic physical activity, *n* (%)			.004
Insufficient	486 292 (76.5)	487 371 (76.6)	
Sufficient	149 669 (23.5)	148 590 (23.4)	

Continued

Table 1 *Continued*

Characteristic	Overlap-weighted cohort ($N = 1\,271\,922$)		
	Vaccinated ($n = 635\,961$)	Unvaccinated ($n = 635\,961$)	SMD[a]
Unadjusted covariates, *n* (%)			
Previous medication history			
Medication use for diabetes	80 120 (12.6)	77 118 (12.1)	.014
Medication use for hyperlipidaemia	85 637 (13.5)	83 364 (13.1)	.011
Medication use for hypertension	188 723 (29.7)	187 403 (29.5)	.005
Blood pressure			.004
SBP <140 mmHg and DBP <90 mmHg	471 319 (74.1)	472 529 (74.3)	
SBP ≥140 mmHg or DBP ≥90 mmHg	164 642 (25.9)	163 432 (25.7)	
Fasting blood glucose			<.001
<100 mg/dL	333 013 (52.4)	333 148 (52.4)	
≥100 mg/dL	302 948 (47.6)	302 813 (47.6)	
Glomerular filtration rate			<.001
<60 mL/min/1.73 m^2	30 055 (4.7)	29 171 (4.6)	
60–89 mL/min/1.73 m^2	330 897 (52.0)	332 272 (52.3)	
≥90 mL/min/1.73 m^2	275 009 (43.2)	274 518 (43.2)	

DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]An SMD <0.1 indicates no significant imbalance. All SMDs were <0.1 in the propensity score–based overlap weighted cohort.

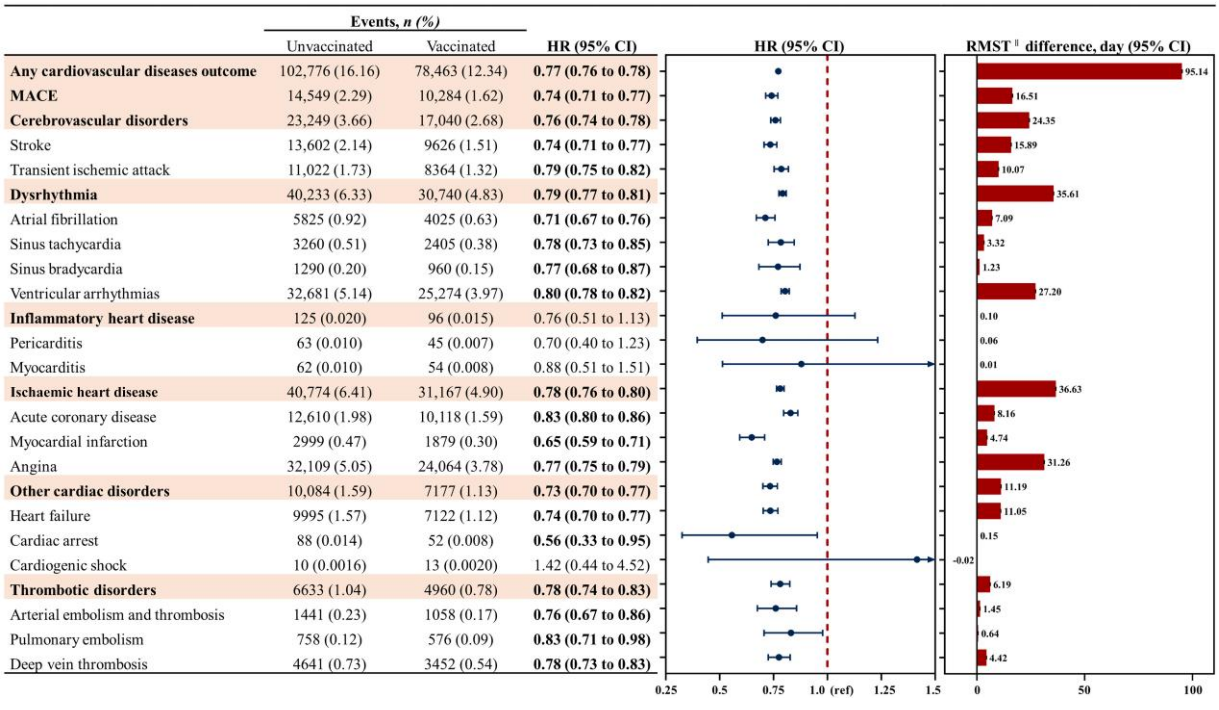


Figure 2 Hazard ratio (95% confidence interval) and restricted mean survival time for incident risk of overall cardiovascular events after zoster vaccination in the overlap-weighted cohort. ‖Estimated restricted mean survival time up to 10 years

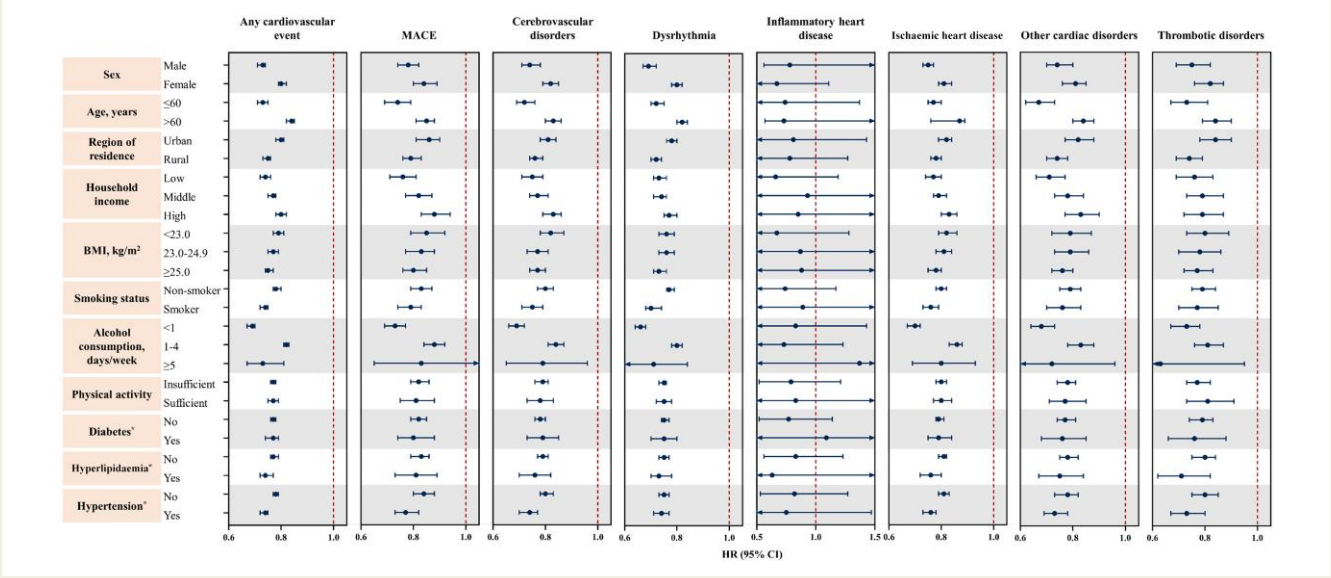


Figure 3 Stratification analysis for the incident risk of overall cardiovascular events after zoster vaccination in the overlap-weighted cohort. *History of medication use

vaccination on reducing the risk of MI and stroke remains unclear,[5] possibly due to its small sample size of vaccinated individuals. Additionally, these studies had relatively short follow-up periods, which hindered the identification of the long-term effects of live zoster vaccination on overall cardiovascular outcomes. Therefore, we aimed to investigate the association of live zoster vaccination with overall cardiovascular events, categorizing them into 18 types of diseases, with a follow-up period up to a maximum of 12 years. Unlike previous studies that solely compared vaccinated and unvaccinated individuals to identify the protective effect of live zoster vaccination on stroke, we conducted a stratification analysis. We compared individuals infected with HZ after live zoster vaccination with those not vaccinated before infection. Furthermore, while previous studies only included a few variables to calculate the adjusted HR, we incorporated diverse factors such as health conditions, economic status, and behaviours (smoking, alcohol drinks, and physical activity). Thus, there is a need to investigate the risk of cardiovascular outcomes following live zoster vaccination with large-scale and national-based cohorts.

Plausible underlying mechanisms

Several factors may contribute to reduced overall cardiovascular outcomes following live zoster vaccination. Primarily, vaccination prevents HZ infection, which has been associated with an increased risk of cardiovascular events through various mechanisms. VZV vasculopathy is caused by a productive viral infection of blood vessels.[34] Following the initial infection, the virus can propagate via neural pathways upon vaccination, affecting both the intracranial and extracranial blood vessels.[35] VZV vasculopathy leads to vascular injury and can cause ischaemic and haemorrhagic cerebrovascular and cardiovascular events.[5] Moreover, VZV-related inflammation is associated with a hypercoagulable state and endovascular inflammation,[36] which can result in the rupture of atherosclerotic plaques and the formation of thrombi, leading to MI and other thrombotic diseases.[37] Additionally, severe HZ infection has been linked to a higher risk of heart failure.[32] Furthermore, HZ can involve the vagus nerve and its ganglia, potentially leading to autonomic dysfunction.[33] As vagus nerve impairment is associated with dysrhythmia and sudden cardiac death, HZ infection, which can cause vagus nerve impairment, may trigger cardiac dysrhythmia. Vaccination may prevent HZ complications, which in turn leads to a reduction in cardiovascular events associated with VZV vasculopathy.

A lower hazard of overall cardiovascular events was observed in both age groups, with a more pronounced reduction in younger individuals. A previous study reported that older age groups experienced less efficacy from live zoster vaccination, possibly due to a decreased biological response to vaccination in older individuals.[3] The observed age-dependent variation in vaccine effectiveness can be attributed to immunosenescence, the progressive decline of immune function with age.[38] This phenomenon may explain the enhanced protective effect against cardiovascular events in younger individuals, whose immune systems generally exhibit more robust responses to vaccination. Additionally, males had a lower risk of cardiovascular events following vaccination. A previous cohort study and meta-analysis reported that females have a higher risk of HZ infection,[39] with a less protective effect of the vaccine against HZ infection in females.[3]

Our study showed a long-term protective effect of vaccination, with the greatest protection observed 2–3 years following vaccination and a gradual reduction after 8 years. A recent cohort analysis reported that the risk of cardiovascular events remained elevated for more than a decade after any infection, indicating that acute infection can influence cardiovascular health for an extended period.[40] Similarly, a previous study suggested that vascular changes caused by VZV vasculopathy can be chronic and persist for years.[41] Previous studies have shown that the effectiveness of the live zoster vaccination diminishes after 10 years, but it still protects against HZ infection for 2–3 years.[3,4] This is consistent with our finding that vaccinated individuals have a lower risk of HZ infection for several years than unvaccinated individuals. Consequently, the long-term risk of cardiovascular events could be reduced in vaccinated individuals, as they are less likely to be infected with HZ during vaccine-induced protection. The declined protective effect after 8 years can be explained by several factors. Previous studies have shown decreasing effectiveness over time. Vaccine effectiveness

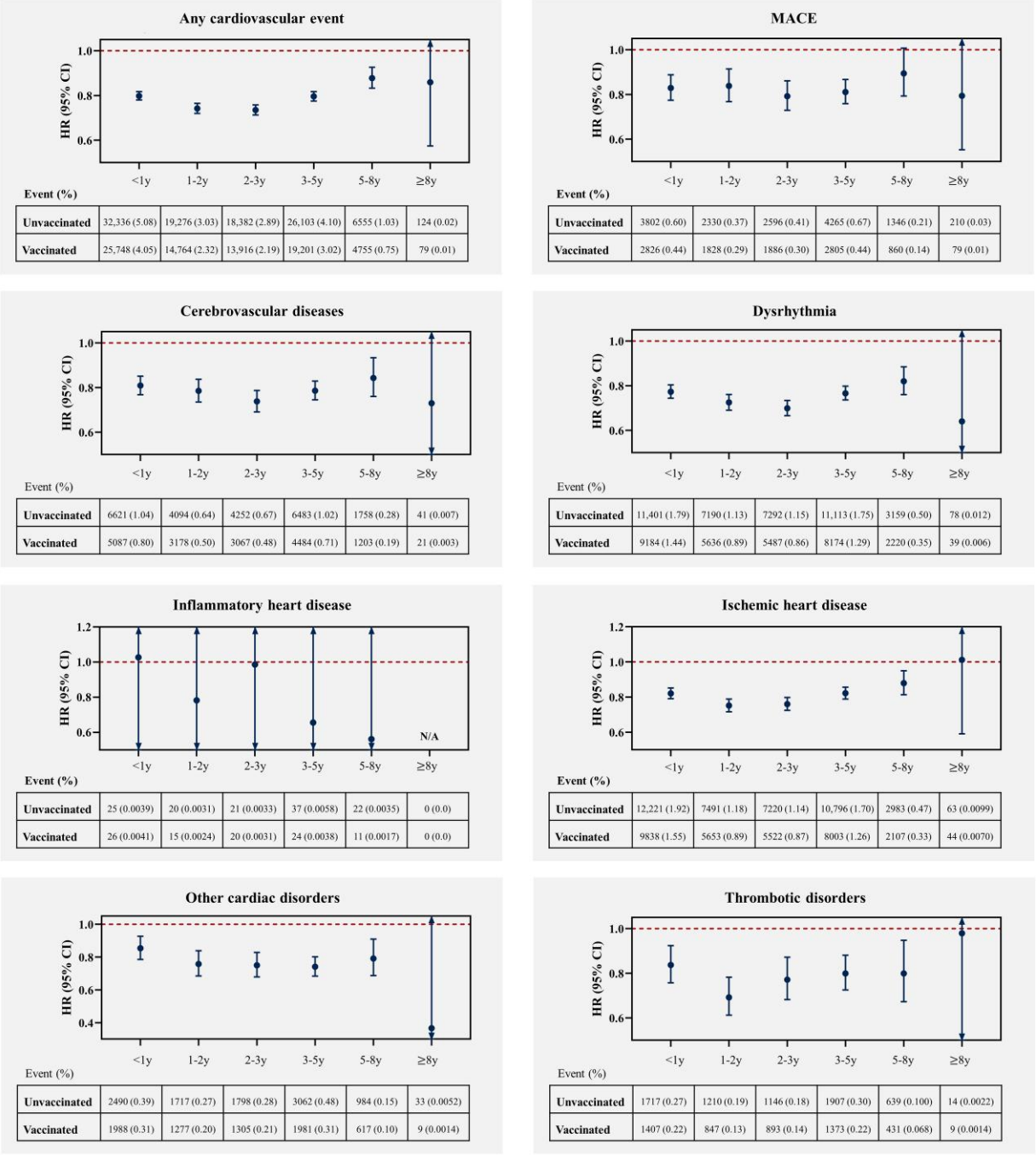


Figure 4 Time persistence association with the development of overall cardiovascular events after zoster vaccination

drops to ~27%–31% by the eighth year post-vaccination and further declines to ~15% after 10 years.[3,42] The immune response stimulated by the vaccine naturally diminishes over time, and as vaccinated individuals aged, immunosenescence occurs thus leading to waning of protective effect.[42]

Strengths and limitations

This study is the first to comprehensively analyse the long-term reduction in risk of all cardiovascular events following live zoster vaccination. We investigated the association between live zoster vaccination and 18 categories of cardiovascular diseases over a maximum 12-year follow-up period with diverse stratification analyses.

Although our study has several strengths, it also has some limitations. First, the generalizability of our findings to other racial and ethnic populations can be restricted, as our data are based on an Asian cohort. It is important to note that the risk factors and incidence rates of cardiovascular events can vary significantly across different ethnic groups,[9] and the immune response to live zoster vaccination may also differ among these populations.[43] Second, while we excluded individuals with a

history of cardiovascular events before the index date, our study is limited by the absence of data before 2012. Consequently, we could not account for individuals with a more distant history of cardiovascular events, potentially leading to underlying bias in our analyses. However, we excluded all individuals with missing data to mitigate the underlying bias. Third, despite adjusting for a wide range of covariates, residual confounding factors still exist that could influence the results. For example, other vaccines, such as the 23-valent polysaccharide pneumococcal and influenza vaccines, have been reported to reduce the risk of stroke potentially.[44] However, we were unable to incorporate this information into our analysis. Fourth, our study relied on the assumption that individuals who use medication for a specific disease are likely to have that disease. However, this assumption may not always hold true due to various factors, including poor compliance with medication, limited access to healthcare, under-diagnosis, and sub-optimal management of chronic diseases. As a result, certain populations may not receive appropriate medication despite having a disease. Fifth, the gradual changes in the association between vaccination and cardiovascular outcomes after 8 years should be interpreted cautiously. This trend may be attributed to the small sample size of individuals with more than 8 years of follow-up, resulting in a large CI. Further studies with extended follow-up periods are necessary to accurately investigate the long-term association between vaccination and cardiovascular outcomes. Sixth, the live zoster vaccine is contraindicated for specific populations, including immunocompromised individuals, those receiving immunosuppressive therapy, patients with active but untreated tuberculosis, pregnant women, and recipients of haematopoietic stem cell transplants.[45] Further research is necessary to evaluate the association between the recombinant zoster vaccine and cardiovascular outcomes, as it is not contraindicated in most of these groups. However, given the recent approval of the recombinant zoster vaccine in South Korea in 2022, long-term data are currently unavailable, necessitating additional studies to address this knowledge gap. Last, although we have conducted diverse sensitivity analyses and thorough statistical evaluations, cautious interpretation is necessary.

Clinical and policy implications

Our data, analysed from a large-scale, population-based cohort, suggest that live zoster vaccination was associated with lower rates of cardiovascular disease in the general population, even among those without known risk factors for cardiovascular diseases. Furthermore, people with unhealthy lifestyles, such as smoking, excessive alcohol consumption, insufficient physical activity, and obesity, also showed an association with lower risks of cardiovascular diseases in relation to live zoster vaccination. As these factors are known to be behavioural risk factors of cardiovascular diseases,[46] live zoster vaccination in these groups was associated with cardiovascular disease outcomes. Interestingly, individuals residing in rural areas showed a stronger association than those in urban areas. Previously, disparities between people with different socioeconomic statuses were identified in outcomes of MI, heart failure, and stroke.[47,48] Earlier research suggested that challenges in accessing hospital care for both emergent care and chronic disease management might be attributed to the increased risk of cardiovascular disease and could impact these disparities. Similarly, people with low socioeconomic status showed a stronger association than those with high socioeconomic status. This implies that a vaccination policy may be associated with lower risks of cardiovascular events among people with challenges in accessing routine healthcare from cardiovascular events. Moreover, previous studies reported that individuals with HZ infection had a higher mortality rate from acute MI and MACE compared with those without HZ infection.[49] By reducing the incidence of HZ infection, vaccination may indirectly decrease the number of deaths attributable to these cardiovascular complications.

Conclusions

In this first comprehensive study, we utilized a large-scale, population-based, nationwide cohort database in South Korea to investigate the association between live zoster vaccination and subsequent cardiovascular outcomes. Live zoster vaccination was associated with lower risks of overall cardiovascular events, particularly MACE, heart failure, cerebrovascular disorders (stroke and TIA), thrombotic disorders (arterial embolism and thrombosis, and deep vein thrombosis), dysrhythmia (atrial fibrillation, sinus tachycardia, sinus bradycardia, and ventricular arrhythmia), and ischaemic heart disease (MI and angina). The association between live zoster vaccination and lower rates of cardiovascular diseases was observed up to 8 years following vaccination, with the most prominent association observed between 2 and 3 years. Males and younger individuals showed more notable associations with lower cardiovascular outcomes. Notably, even individuals with unhealthy lifestyles, with low-income households, and those living in rural areas benefited from the protective effect. Therefore, the findings suggest that implementing live zoster vaccination strategies may be associated with favourable cardiovascular outcomes across different population groups.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

Data are available on reasonable request. Study protocol and statistical code are available from D.K.Y. (email: yonkkang@gmail.com). Data set is available from the National Health Insurance Service of Korea (NHIS), Korea Health Insurance Review and Assessment Service (HIRA), and Korea Disease Control and Prevention Agency (KDCA) through a data use agreement.

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Ethical Approval

The study protocol was approved by the Korea Healthcare Bigdata of the Ministry of Health and Welfare (no. 2022-00061), the Korea Health Insurance Review and Assessment Service, the Korean National Health Insurance Service, and the Korea Disease Control and Prevention Agency and the Institutional Review Board at Kyung Hee University. Under the terms of the approval, patient consent was not required to use routine health records for our study.

Pre-registered Clinical Trial Number

Not applicable.

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