MAJOR ARTICLE

# Incidence of Herpes Zoster and Persistent Post-Zoster Pain in Adults With or Without Diabetes in the United States

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***Background.*** This study was designed to assess the association between diabetes and herpes zoster (HZ) and persistent post-zoster pain (PPZP).

***Methods.*** We used a United States-based, 2005–2009 retrospective observational study of medical and pharmacy claims from adults in 3 large national databases. Incidence rate ratios were used to compare HZ incidence by diabetes status. Multivariate regressions assessed the age and sex-adjusted risk of diabetes on HZ and PPZP as a function of immune competence. National projections of HZ and PPZP cases were obtained.

***Results.*** Among 51 million enrollees (~88 million person-years [PYs] at risk), we identified 420 515 HZ cases. Patients with diabetes represented 8.7% of the PYs analyzed but accounted for 14.5% of the HZ cases and 20.3% of the PPZP cases. The crude incidence of HZ was 78% higher (7.96 vs 4.48 cases/1000 PY; $P < .01$) and the rate of PPZP was 50% higher (5.97% vs 3.93%; $P < .01$) in individuals with diabetes than without. Individuals with diabetes had 45% higher adjusted risk of HZ (hazard ratio [HR] = 1.45; 95% confidence intervals [CIs], 1.43–1.46) and 18% higher adjusted odds of PPZP (odds ratio = 1.18; 95% CI, 1.13–1.24). The risk of HZ associated with diabetes among immune-compromised individuals was weaker (HR = 1.10; 95% CI, 1.07–1.14) and the risk of PPZP was no longer significant. Every year, approximately 1.2 million HZ cases occur in US adults, 13% of these occur in individuals with diabetes.

***Conclusions.*** Diabetes is a risk factor for HZ and PPZP in the US adult population. This association is stronger in immune-competent individuals.

***Keywords.*** diabetes; herpes zoster; incidence; post-herpetic pain; risk.

Herpes zoster (HZ) is the neurocutaneous manifestation of reactivation of varicella-zoster virus (VZV) that is latent in sensory ganglia as a result of primary VZV infection (varicella) [1]. Herpes zoster causes significant morbidity, especially in older and immune-compromised patients, and results in a significant societal burden because of healthcare costs [2, 3], productivity losses [4, 5], negative effects on quality of life [6], and death [7]. The occurrence of HZ is closely related to a decline in VZV-specific, cell-mediated immunity (VZV-CMI) [8], which occurs progressively with aging and is commonly depressed in immune-compromised patients, thereby explaining the higher HZ incidence rates that accompany aging and immune compromise [1, 8].

Diabetes has been found to be associated with an increased incidence of certain viral infections, such as hepatitis B infection [9], and the severity of influenza may be greater in individuals with diabetes [10]. In general, infections in people with diabetes have a poorer prognosis [10]. Some measures of CMI are depressed in individuals with diabetes; for example, T-cell dysregulation, which is very characteristic of diabetes, might result in an increased incidence of HZ [11–13]. Clinical evidence regarding whether diabetes is a risk factor for HZ is conflicting. One large study utilizing a managed care database in Israel found that the incidence of HZ

Received 4 February 2014; accepted 27 May 2014.

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**Open Forum Infectious Diseases**



DOI: 10.1093/ofid/ofu049

was increased in individuals with diabetes compared with a well chosen control group of individuals without diabetes [14]. In addition, 2 studies from Asia, a hospital-based study from Japan, and a population-based study from Taiwan found an increased incidence of HZ among individuals with diabetes [15, 16]. However, in 3 other studies, diabetes was not associated with an increased risk of HZ [17–19].

To further investigate the association between diabetes and HZ incidence and the rate of persistent post-zoster pain in a US population, we analyzed medical and pharmacy claims for a 5-year period from 3 large databases that encompassed the age, socioeconomic spectrum, and payer sources of the US adult population, stratified by immune function.

## METHODS

### Data Sources

We used data from 3 large administrative claims databases from Truven Health MarketScan Research Databases, each of which represented a different population: (1) privately insured, based on nation-wide commercially insured working adults and their dependents; (2) Medicare-eligible retirees with Medicare supplemental insurance; and (3) Medicaid (a government program for low-income qualifying individuals) from 12 states. Combined, these 3 databases had over 55 million enrollees in any given year (30 million [commercial], 22 million [Medicaid], and 3 million [Medicare]). The study population consisted of adults aged 18–64 years from Commercial and Medicaid insurance populations, and those aged 65 years or older from Medicare. The study period was from January 1, 2005 through December 31, 2009. Medicaid enrollees who had Medicare dual-eligibility or lacked drug coverage were excluded from the analysis.

### Definitions

Diabetes status, immune status, and HZ diagnosis were each based on the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) with at least 1 claim with ICD-9-CM-specific codes in medical outpatient or inpatient claims for each of the conditions (Table A1). For cancer, we required 2 claims on separate dates. This study used the following conditions as proxies for immune compromise: any cancer except for skin (with or without immune suppressive treatment), human immunodeficiency virus (HIV) infection, solid-organ transplant, bone marrow or stem cell transplant, or the following conditions if there were outpatient pharmacy claims for concomitant use of immune suppressants: rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, and psoriasis. The study population was also stratified by gender and age group (18–49 years, 50–59 years, 60–64 years, and ≥65 years). Age group stratification was based on the Advisory Committee on Immunization Practices (Centers for Disease and Control and Prevention) recommendations for HZ vaccination, which are for immune-competent individuals aged ≥60 years and has the potential for an additional recommendation for individuals 50–59 years in accordance with recent licensure of a zoster vaccine for this age group [20]. Because of the use of different age-related data sources, we further stratified ≥60 years into 60–64 years or ≥65 years (ie, enrollees with Medicare supplemental insurance consisted of individuals ≥65 years).

### Diabetes Prevalence

For comparison purposes with national estimates, we estimated the 2009 prevalence of diabetes (ICD-9-CM: 250.xx) overall and by sex, age group, and only in those enrollees with continuous enrollment in 2009.

### Incidence of Herpes Zoster

Two cohorts were created based on medical claims associated with diagnosis codes for diabetes. All enrollees had had at least 6 months continuous enrollment in the database to confirm they did not have HZ when the study assessment began, which was from the end date of the 6-month, continuous enrollment period (index date). Patients were dichotomized into 2 cohorts: those with diabetes vs those without diabetes. For patients with diabetes, the study assessment began 6 months after the first observed diabetes diagnosis.

Herpes zoster cases were based on principal or secondary ICD-9-CM diagnosis codes: 053.xx. We excluded prevalent HZ patients if they had any of these diagnosis codes during the 6 months before the index date. We also excluded patients if their first observed HZ diagnosis after the index date was postherpetic trigeminal neuralgia (ICD-9-CM: 053.12) or postherpetic polyneuropathy (ICD-9-CM: 053.13), because these codes indicated that they were not incident HZ episodes. Patients were censored at the end of follow-up period or the occurrence of HZ, whichever came first.

Herpes zoster incidence was calculated stratified by sex, age group, and immune status in individuals with and without diabetes. Concomitant immune status, based on conditions and treatments as described above, was determined for the 6 months before the index date. Incidence rates were calculated as the number of new HZ cases per 1000 person-years (PYs), and 95% confidence intervals (CIs) were provided based on Poisson distribution. We also estimated the incidence rate ratio (IRR) to quantify HZ incidence differences by diabetes status. The 95% CI of IRR was estimated based on Mantel-Haenszel combined estimate.

### Rates of Persistent Post-Zoster Pain

We estimated the 6-month rates of persistent pain after the identification of incident HZ cases. Therefore, only patients with HZ and at least 6 months of continuous enrollment after

the HZ diagnosis were included in this subset analysis. For this purpose, we considered HZ patients having persistent post-zoster pain if they met any of the following 3 criteria: (1) a diagnosis of postherpetic trigeminal neuralgia (ICD-9-CM: 053.12) or postherpetic polyneuropathy (ICD-9-CM: 053.13); (2) a diagnosis of HZ with other nervous system complications (ICD-9-CM: 053.19) and more than a 30-day supply of medications typically used to treat post-zoster pain (as listed in Table A2); or (3) a diagnosis of neuralgia, neuritis, or radiculitis (ICD-9-CM: 729.2) that first appeared after the HZ diagnosis (ie, no claims preceding the diagnosis of HZ for the entire analyzed period for each individual, of at least 6 months). Because this study relied on claims data, we did not have any clinical information about the severity of the pain.

Rates of persistent post-zoster pain were estimated among the eligible HZ cases by sex, age group, and immune status in individuals with and without diabetes. These rates were reported as percentages, and 95% CIs were estimated based on the Wilson score interval. Differences in rates between individuals with and without diabetes were tested using Fisher's exact tests.

### Multivariate Regression Models

We first developed Cox proportional hazard regression models to assess the adjusted risk of diabetes on HZ. Models were performed in 3 population groups: all, immune competent, and immune compromised. Hazard ratios (HRs) and 95% CIs were reported. We also developed separate multiple logistic regression models to assess the adjusted risk of diabetes on persistent post-zoster pain among persons with HZ in these 3 populations. Odds ratios (ORs) and 95% CIs were reported. In addition to diabetes, all models had gender and age groups as covariates.

### National Projections of Herpes Zoster Cases by Diabetes Status

To estimate the annual number of HZ cases in the US adult population, we multiplied our HZ incidence estimates by the corresponding US population stratified by known diabetes status and age group [21, 22]. To quantify uncertainty due to stochastic variation in our HZ incidence estimates and national diabetes prevalence, we ran a Monte Carlo simulation with 20 000 iterations using the means and standard errors of inputs with normal distribution assumptions (Crystal Ball, Fusion Edition, version 11.1 and Excel 2007 software packages). All data analyses and statistical procedures were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

## RESULTS

After applying inclusion and exclusion criteria, the study population consisted of approximately 51 million adult individuals: 4.5 million with diabetes and 46.5 million without diabetes, during the study period of 2005 through 2009 (Table A3). In those with diabetes, the mean age was 54.6 years, 50.1% were female, and 5.1% were immune compromised. In those without diabetes, the mean age was 42.0 years; 54.3% were female and 2.7% were immune compromised. Immune-compromised patients were older than immune-competent individuals. Among immune-compromised individuals, those with diabetes were also older than those without diabetes (Table A3). In 2009, the overall prevalence of diabetes in our study population was 8.3%, 7.6% in females and 9.1% in males. The prevalence of diabetes was associated with age and ranged from 3.9% to 17.2% in enrollees aged 18–49 and ≥65 years, respectively (data not shown).

The study population consisted of approximately 88 million PYs and identified 420 515 HZ cases (Table 1). Although individuals with diabetes represented 8.7% of the PYs analyzed, they accounted for 14.5% of the HZ cases. The incidence of HZ was 78% higher in individuals with diabetes than in those without diabetes (7.96 vs 4.48 cases/1000 PY; IRR = 1.78; 95% CI, 1.76–1.79). The incidence of HZ in females with diabetes was significantly higher than in males with diabetes (9.17 cases/1000 PY, 95% CI 9.07–9.25 vs 6.76/1000 PY, 95% CI 6.68–6.85). This relationship was also observed for individuals without diabetes (female: 5.17 cases/1000 PY, 95% CI 5.15–5.20 vs male: 3.66/1000 PY, 95% CI 3.64–3.68). The incidence of HZ was higher in all age groups in individuals with diabetes than in those without diabetes. Younger individuals with diabetes had incidence rates of HZ comparable to those in older individuals without diabetes. Incidence rate ratios of HZ between patients with and without diabetes were highest in age groups 18–49 years and ≥65 years.

Immune-compromised patients accounted for 2.9% of both the study population and the PYs assessed (1.48 million individuals [Table A3] and 2.5 million PYs [Table 1], respectively). The incidence of HZ in immune-compromised patients was 1.7 and 2.6 times that of immune-competent patients with diabetes (13.12 cases/1000 PY, 95% CI 12.75–13.49 vs 7.70/1000 PY, 95% CI 7.63–7.76) and without diabetes (11.05 cases/1000 PY, 95% CI 10.91–11.19 vs 4.30/1000 PY, 95% CI 4.28–4.31), respectively (Table 1). As with immune-competent individuals, female and older immunocompromised individuals also experienced higher incidences of HZ than males and younger age groups, independent of diabetes status. However, the HZ IRRs between persons with and without diabetes were always lower among immune-compromised patients than in immune-competent individuals. In addition, diabetes was not associated with a higher risk of HZ in immune-compromised patients aged ≥60 years.

We identified 308 857 HZ cases with at least 6-months' follow-up data claims, that is, 73.4% of all the identified HZ cases (Table 2). For persistent post-herpetic pain cases, criteria 1, 2, and 3 identified 24%, 56%, and 20% of the cases in diabetic and 24%, 52%, and 24% of the cases in nondiabetic individuals, respectively (data not shown in table). Therefore, criterion 3 for

**Table 1. Incidence Rates of Herpes Zoster by Diabetes and Concomitant Immune-Compromised Status, 2005–2009**

| | Diabetic Individuals | | | | Nondiabetics Individuals | | | | Difference | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Herpes Zoster Cases | Person-Years (PY) | Cases/ 1000 PY | 95% Confidence Interval [CI]* | Herpes Zoster Cases | Person-Years (PY) | Cases/ 1000 PY | 95% CI* | Incidence Rate Ratio | 95% CI** |
| Total study population | | | | | | | | | | |
| Enrollees in group | 61 142 | 7 681 336 | 7.96 | (7.90–8.02) | 359 373 | 80 266 547 | 4.48 | (4.46–4.49) | 1.78 | (1.76–1.79) |
| Sex | | | | | | | | | | |
| Females | 35 071 | 3 826 046 | 9.17 | (9.07–9.26) | 224 735 | 43 431 997 | 5.17 | (5.15–5.20) | 1.77 | (1.75–1.79) |
| Males | 26 071 | 3 855 290 | 6.76 | (6.68–6.85) | 134 638 | 36 834 550 | 3.66 | (3.64–3.68) | 1.85 | (1.83–1.87) |
| Age group | | | | | | | | | | |
| 18–49 years | 12 441 | 2 464 386 | 5.05 | (4.96–5.14) | 169 277 | 51 819 510 | 3.27 | (3.25–3.28) | 1.55 | (1.52–1.57) |
| 50–59 years | 22 284 | 2 821 550 | 7.90 | (7.79–8.00) | 104 908 | 17 041 888 | 6.16 | (6.12–6.19) | 1.28 | (1.26–1.30) |
| 60–64 years | 9619 | 993 001 | 9.69 | (9.49–9.88) | 31 838 | 4 396 777 | 7.24 | (7.16–7.32) | 1.34 | (1.31–1.37) |
| ≥65 years | 16 798 | 1 402 399 | 11.98 | (11.80–12.16) | 53 350 | 7 008 371 | 7.61 | (7.55–7.68) | 1.57 | (1.55–1.60) |
| Immune competent | | | | | | | | | | |
| Enrollees in group | 56 261 | 7 309 166 | 7.70 | (7.63–7.76) | 335 809 | 78 133 941 | 4.30 | (4.28–4.31) | 1.79 | (1.78–1.81) |
| Sex | | | | | | | | | | |
| Females | 32 308 | 3 632 648 | 8.89 | (8.80–8.99) | 209 521 | 42 154 331 | 4.97 | (4.95–4.99) | 1.79 | (1.77–1.81) |
| Males | 23 953 | 3 676 518 | 6.52 | (6.43–6.60) | 126 288 | 35 979 610 | 3.51 | (3.49–3.53) | 1.86 | (1.83–1.88) |
| Age group | | | | | | | | | | |
| 18–49 years | 11 670 | 2 394 113 | 4.87 | (4.79–4.96) | 162 206 | 50 979 189 | 3.18 | (3.17–3.20) | 1.53 | (1.50–1.56) |
| 50–59 years | 20 682 | 2 694 694 | 7.68 | (7.57–7.78) | 97 670 | 16 397 987 | 5.96 | (5.92–5.99) | 1.29 | (1.27–1.31) |
| 60–64 years | 8803 | 933 587 | 9.43 | (9.23–9.63) | 28 881 | 4 169 442 | 6.93 | (6.85–7.01) | 1.36 | (1.33–1.39) |
| ≥65 years | 15 106 | 1 286 772 | 11.74 | (11.55–11.93) | 47 052 | 6 587 323 | 7.14 | (7.08–7.21) | 1.64 | (1.61–1.67) |
| Immune compromised | | | | | | | | | | |
| Enrollees in group | 4881 | 372 169 | 13.12 | (12.75–13.49) | 23 564 | 2 132 606 | 11.05 | (10.91–11.19) | 1.19 | (1.15–1.22) |
| Sex | | | | | | | | | | |
| Females | 2763 | 193 398 | 14.29 | (13.76–14.83) | 15 214 | 1 277 666 | 11.91 | (11.72–12.10) | 1.20 | (1.15–1.25) |
| Males | 2118 | 178 772 | 11.85 | (11.35–12.36) | 8350 | 854 940 | 9.77 | (9.56–9.98) | 1.21 | (1.16–1.27) |
| Age group | | | | | | | | | | |
| 18–49 years | 771 | 70 273 | 10.97 | (10.21–11.77) | 7071 | 840 321 | 8.41 | (8.22–8.61) | 1.30 | (1.21–1.40) |
| 50–59 years | 1602 | 126 856 | 12.63 | (12.02–13.26) | 7238 | 643 902 | 11.24 | (10.98–11.50) | 1.12 | (1.06–1.19) |
| 60–64 years | 816 | 59 414 | 13.73 | (12.81–14.71) | 2957 | 227 335 | 13.01 | (12.54–13.49) | 1.06 | (0.98–1.14) |
| ≥65 years | 1692 | 115 627 | 14.63 | (13.94–15.35) | 6298 | 421 048 | 14.96 | (14.59–15.33) | 0.98 | (0.93–1.03) |

* 95% confidence interval (CI) was based on Poisson distribution.

** 95% CI of incidence rate ratio was based on Mantel–Haenszel combined estimate.

identification of persistent post-zoster pain was the least common criteria used to define cases and was less frequent among diabetic individuals than among nondiabetic individuals (20% vs 24%). Overall, observed rates of persistent post-zoster pain were approximately 50% higher in individuals with diabetes than in those without diabetes (5.97% vs 3.93%; $P < .01$). Persistent pain was more frequent in females and older age groups than in males and younger age groups, regardless of their diabetes status. Rate differences in post-zoster pain between patients with and without diabetes decreased with increasing age, and no difference was observed in individuals aged ≥65 years. Rates of persistent post-zoster pain were higher in immune compromised than in immune-competent individuals, regardless of diabetes status. However, rate differences between immune-compromised and immune-competent individuals were lower in patients with diabetes (7.46%, 95% CI 6.63–8.38 vs 5.84%, 95% CI 5.62–6.08) than in patients without diabetes (6.25%, 95% CI 5.89–6.62 vs 3.77%, 95% CI 3.70–3.85).

In the Cox regression analysis controlling for age and gender, the adjusted risk of HZ was 45% higher in persons with diabetes than in those without diabetes (HR = 1.45; 95% CI, 1.43–1.46) (Table 3). Females had a 41% higher risk of HZ than males (HR = 1.41; 95% CI, 1.39–1.41), and individuals aged ≥65 years had a 28% higher risk of HZ than those aged 50–59 years (HR = 1.28; 95% CI, 1.26–1.29). These trends were similar when the analysis was limited to immune-competent individuals.

**Table 2. Six-Month Rates of Persistent Post-Zoster Pain by Diabetes and Concomitant Immune-Compromised Status, 2005–2009**

| | Herpes Zoster Cases | | % Herpes Zoster Cases With Persistent Post-Zoster Pain | | | | |
|---|---|---|---|---|---|---|---|
| | Diabetic Individuals | Nondiabetic Individuals | Diabetic Individuals | | Nondiabetic Individuals | | Difference |
| | *N* | *N* | % | 95% Confidence Interval [CI] | % | 95% CI | *P* Value* |
| Total study population | | | | | | | |
| Enrollees in group | 44 460 | 264 397 | 5.97 | (5.75–6.19) | 3.93 | (3.86–4.01) | <.01 |
| Sex | | | | | | | |
| Females | 25 569 | 165 776 | 6.12 | (5.83–6.42) | 4.07 | (3.98–4.17) | <.01 |
| Males | 18 891 | 98 621 | 5.77 | (5.44–6.11) | 3.69 | (3.57–3.81) | <.01 |
| Age group | | | | | | | |
| 18–49 years | 7685 | 111 980 | 3.55 | (3.16–3.99) | 1.85 | (1.77–1.93) | <.01 |
| 50–59 years | 15 125 | 78 084 | 4.70 | (4.38–5.05) | 3.60 | (3.47–3.73) | <.01 |
| 60–64 years | 8862 | 32 200 | 5.26 | (4.81–5.74) | 4.69 | (4.47–4.93) | .03 |
| ≥65 years | 12 788 | 42 133 | 9.42 | (8.92–9.93) | 9.50 | (9.22–9.78) | .80 |
| Immune competent | | | | | | | |
| Enrollees in group | 40 998 | 247 371 | 5.84 | (5.62–6.08) | 3.77 | (3.70–3.85) | <.01 |
| Sex | | | | | | | |
| Females | 23 582 | 154 677 | 6.06 | (5.76–6.37) | 3.94 | (3.85–4.04) | <.01 |
| Males | 17 416 | 92 694 | 5.55 | (5.22–5.90) | 3.49 | (3.37–3.61) | <.01 |
| Age group | | | | | | | |
| 18–49 years | 7203 | 107 475 | 3.49 | (3.09–3.93) | 1.79 | (1.71–1.87) | <.01 |
| 50–59 years | 14 069 | 73 031 | 4.56 | (4.23–4.92) | 3.49 | (3.36–3.62) | <.01 |
| 60–64 years | 8155 | 29 507 | 5.15 | (4.69–5.65) | 4.65 | (4.41–4.89) | .07 |
| ≥65 years | 11 571 | 37 358 | 9.36 | (8.84–9.90) | 9.34 | (9.05–9.64) | .94 |
| Immune compromised | | | | | | | |
| Enrollees in group | 3462 | 17 026 | 7.46 | (6.63–8.38) | 6.25 | (5.89–6.62) | <.01 |
| Sex | | | | | | | |
| Females | 1987 | 11 099 | 6.85 | (5.82–8.04) | 5.91 | (5.49–6.37) | .09 |
| Males | 1475 | 5927 | 8.28 | (6.98–9.79) | 6.87 | (6.26–7.54) | .05 |
| Age group | | | | | | | |
| 18–49 years | 482 | 4505 | 4.56 | (3.03–6.80) | 3.31 | (2.83–3.87) | .15 |
| 50–59 years | 1056 | 5053 | 6.55 | (5.20–8.20) | 5.17 | (4.59–5.81) | .06 |
| 60–64 years | 707 | 2693 | 6.52 | (4.92–8.58) | 5.20 | (4.42–6.10) | .14 |
| ≥65 years | 1217 | 4775 | 9.94 | (8.38–11.75) | 10.75 | (9.90–11.66) | .43 |

* *P* value for the difference between the risks was based on Fisher's exact test.

In a separate regression analysis restricted to immune-compromised individuals, those with diabetes had a 10% higher risk of HZ (HR = 1.10; 95% CI, 1.07–1.14). Female gender and older age were again associated with higher risk of HZ.

In the logistic regression analysis on 308 857 individuals with HZ, the adjusted odds of persistent post-zoster pain was 18% higher in persons with diabetes than in those without diabetes (OR = 1.18; 95% CI, 1.13–1.24) (Table 3). Post-zoster persistent pain was 8% more likely in females than in males (OR = 1.08; 95% CI, 1.04–1.12) and was 2.65 times more likely at ≥65 years than between 50–59 years (OR = 2.65; 95% CI, 2.53–2.77). In a separate logistic regression analysis on 20 488 immune-compromised individuals with HZ, diabetes and sex were not significant predictors of persistent pain (diabetes OR = 1.10; 95% CI, 0.95–1.27; females OR = 0.91; 95% CI, 0.81–1.02), but age remained as a significant predictor of persistent pain.

Based on this study, the projected HZ cases among adults in the US during the study period was 1.2 million cases/year (Table 4). Individuals aged 18–49 years, 50–59 years, 60–64 years, and ≥65 years accounted for 38%, 22%, 11%, and 29% of HZ cases, respectively. Individuals with diabetes were projected to account for 13.5% of all HZ cases among adults in the United States (Table 4).

## DISCUSSION

We found that the incidence of HZ among individuals with diabetes was higher than among those without (7.96 vs 4.48 cases/

**Table 3. Adjusted Risk of Herpes Zoster and Persistent Post-Zoster Pain by Diabetes Status and Demographic Characteristics***

| | Herpes Zoster | | Persistent Post-Zoster Pain, If Herpes Zoster | |
|---|---|---|---|---|
| | Hazard Ratio | 95% Confidence Interval [CI] | Odds Ratio | 95% CI |
| Total study population | | | | |
| Diabetes | | | | |
| Yes | 1.45 | (1.43–1.46) | 1.18 | (1.13–1.24) |
| No | Ref. | | Ref. | |
| Sex | | | | |
| Females | 1.40 | (1.39–1.41) | 1.08 | (1.04–1.12) |
| Males | Ref. | | Ref. | |
| Age group | | | | |
| 18–49 years | 0.55 | (0.54–0.55) | 0.52 | (0.49–0.55) |
| 50–59 years | Ref. | | Ref. | |
| 60–64 years | 1.20 | (1.18–1.21) | 1.28 | (1.21–1.36) |
| ≥65 years | 1.28 | (1.26–1.29) | 2.65 | (2.53–2.77) |
| Immune competent | | | | |
| Diabetes | | | | |
| Yes | 1.47 | (1.45–1.48) | 1.19 | (1.13–1.25) |
| No | Ref. | | Ref. | |
| Sex | | | | |
| Females | 1.40 | (1.39–1.41) | 1.10 | (1.06–1.14) |
| Males | Ref. | | Ref. | |
| Age group | | | | |
| 18–49 years | 0.55 | (0.55–0.56) | 0.52 | (0.49–0.55) |
| 50–59 years | Ref. | | Ref. | |
| 60–64 years | 1.19 | (1.17–1.20) | 1.31 | (1.23–1.39) |
| ≥65 years | 1.24 | (1.23–1.26) | 2.69 | (2.56–2.81) |
| Immune compromised | | | | |
| Diabetes | | | | |
| Yes | 1.10 | (1.07–1.14) | 1.10 | (0.95–1.27) |
| No | Ref. | | Ref. | |
| Sex | | | | |
| Females | 1.27 | (1.24–1.31) | 0.91 | (0.81–1.02) |
| Males | Ref. | | Ref. | |
| Age group | | | | |
| 18–49 years | 0.75 | (0.73–0.78) | 0.62 | (0.51–0.75) |
| 50–59 years | Ref. | | Ref. | |
| 60–64 years | 1.15 | (1.11–1.20) | 1.01 | (0.84–1.21) |
| ≥65 years | 1.33 | (1.29–1.38) | 2.03 | (1.77–2.33) |

* Note: Hazard ratios were used for reporting adjusted risk of herpes zoster (HZ). Three separate Cox proportional hazard regression models were run. Each model's study populations was as follows: total study population ($n = 51\,007\,975$) in first model, immune competent only ($n = 49\,528\,378$) in second model, and immune compromised only ($n = 1\,479\,597$) in third model.

Odds ratios were used for reporting adjusted risk of persistent post-zoster pain among individuals with HZ. Three separate binary multivariate logistic regression models were run. Each model's study populations was as follows: individuals with HZ ($n = 308\,857$) in first model, immune-competent individuals with HZ ($n = 288\,369$) in second model, and immune-compromised individuals with HZ ($n = 20\,488$) in third model.

For all regression models, the independent variables were diabetes, gender, and age groups. Abbreviation: Ref., reference category.

1000 PYs) and that diabetes was associated with a 45% adjusted risk of HZ. We also found higher rates of persistent post-zoster pain in individuals with diabetes than those without (5.97% vs 3.93%) and that diabetes was associated with an 18% adjusted risk of persistent post-zoster pain.

Comparisons between HZ incidence and persistent post-zoster pain rates across studies are difficult because of the following: (1) differences in insured populations, and inclusions and exclusions for HZ diagnosis; (2) differences in coding algorithms and coding accuracy; (3) data sources and timing; and (4) nature of the

**Table 4. Projected Annual Number of Herpes Zoster Cases by Diabetes Status in the United States During the Period 2005–2009***

| Age Group | US Population (Million) | Diabetes Prevalence (%) | Diabetic Individuals | | | Nondiabetic Individuals | | | All Individuals |
|---|---|---|---|---|---|---|---|---|---|
| | | | Projected Population (Million) | HZ Incidence (Cases/1000 PY) | HZ Cases | Projected Population (Million) | HZ Incidence (Cases/1000 PY) | HZ Cases | HZ Cases |
| 18–49 years | 136.33 | 2.7 (0.03) | 3.68 (0.41) | 5.05 (0.04) | 18 608 (2079) | 132.64 (0.41) | 3.27 (0.01) | 433 340 (1720) | 451 947 (1318) |
| 50–59 years | 41.49 | 10.5 (0.09) | 4.36 (0.37) | 7.90 (0.06) | 34 417 (2941) | 37.13 (0.37) | 6.16 (0.02) | 228 574 (2392) | 262 991 (988) |
| 60–64 years | 16.57 | 10.5 (0.09) | 1.74 (0.15) | 9.69 (0.10) | 16 858 (1447) | 14.83 (0.15) | 7.24 (0.04) | 107 399 (1231) | 124 257 (726) |
| ≥65 years | 40.26 | 18.4 (0.09) | 7.41 (0.36) | 11.98 (0.09) | 88 724 (4352) | 32.85 (0.36) | 7.61 (0.03) | 250 050 (2935) | 338 775 (2014) |
| All adults | 234.64 | | 17.19 (0.67) | | 158 606 (5817) | 217.45 (0.67) | | 1 019 364 (4317) | 1 177 970 (2697) |

Abbreviations: HZ, herpes zoster; PY, person-years.

* Note: Parentheses contain standard error estimates.

Data sources: US population, Census Bureau; Diabetes prevalence: Health, United States 2010; HZ incidence: current study.

Note: Diabetes prevalence estimates are for physician-diagnosed diabetes (obtained by self-report and excludes women having diabetes only during pregnancy). Diabetes prevalence estimates from Health, United States 2010 are specific for the following age groups: 20–44, 45–64, and ≥65 years. Minor assumptions were made in this study to provide diabetes prevalence estimates for slightly different age groups.

follow-up mechanisms (ie, clinical trial or observational studies). Our HZ incidence estimates fell within the range of 3–15 cases/1000 PYs reported in previous studies [5, 23–25].

Reported rates of postherpetic pain have ranged from 3% to 34% [5, 23, 24]. We found rates for persistent post-zoster pain of 5.97% and 3.93% in individuals with or without diabetes, respectively, which are in the lower range of previous studies. The identification of persistent post-zoster pain using the ICD-9-CM diagnosis system in medical claims, rather than from review of medical records, is known to underestimate the real frequency [26].

In our study, HZ was 45% more likely (adjusted HR = 1.45) in individuals with diabetes than those without after adjustments for age or sex. Several observational studies have previously assessed the relationship between diabetes and HZ [14, 23, 25, 27–29]. A case-control study in Israel found that diabetes was associated with a 53% increase in the odds for HZ (OR = 1.53, $P < .05$), but it did not find that the increased risk correlated with the level of glycosylated hemoglobin (hemoglobin $A_{1c}$) or insulin requirement [14]. An observational study of US adults younger than 65 years of age found that diabetes was associated with a 6% increase in the odds for HZ (OR = 1.06, $P < .05$) after controlling for sex, number of claims, and 9 other serious chronic conditions [28]. A 2006 study based on electronic medical records in Navarra, Spain found that having diabetes was associated with a 2 times risk increase of HZ [27]. Another population-based retrospective cohort analysis conducted in a health maintenance organization with over one quarter of Israel's population also found that diabetes was associated with a 17% increase in the risk for HZ (HR = 1.53, $P < .05$) after controlling for sex, age, socioeconomic status, history of cancer, HIV treatment, and use of antitumor necrosis factor-α therapy [29].

Two US cohort studies that analyzed the association of diabetes and HZ in older populations (≥60 years) as secondary objectives found much smaller positive relationships between diabetes and HZ incidence (HRs 1.06 and 1.05, respectively, both $P < .05$) [23, 25]. In our study, when performing a subanalysis focusing on individuals ≥60 years (data not shown), we observed a similar positive, but larger relationship (HR = 1.60, $P < .05$). The current study confirmed that the incidence of HZ and persistent post-zoster pain increases with advancing age and the presence of reduced immunity [5, 15, 30–33]. We also found that the risk of HZ in females was 41% and 27% higher than immune-competent and immune-compromised males, respectively. This relationship has been reported by some [5, 24, 31, 32, 34–40] but not all previous studies [15].

Approximately 7.9% of the US adult population was reported to have diabetes in 2008 [22]. In our entire study sample, the prevalence of diabetes was 8.3% in 2009. We found concomitant diabetes to be more common in patients with HZ (14.5%) and persistent post-zoster pain (20.3%) (calculations not shown). These findings may be explained by the lower VZV-CMI

responses to HZ reactivation observed in patients with diabetes [41]. Approximately 10% of HZ cases in the current study occurred in immunocompromised patients, which is similar to a previous report [5]. The incidence of HZ was higher in individuals with diabetes than individuals without it, across all age groups. For example, individuals with diabetes aged 18–49 years had an overall incidence of HZ that was comparable to older individuals aged 50–59 years without diabetes. We also found that the increased risk of HZ among individuals with diabetes was more evident in immune-competent persons than in those with the selected immune-compromising conditions (increased risk 47% vs 10%, respectively). This could indicate that the effect on VZV-CMI imposed by diabetes is less than that due to the other immune-compromising conditions. Likewise, there was no added risk of developing HZ in individuals ≥60 years with diabetes compared with concomitant immune compromise (Table 2), again suggesting that the VZV-CMI depression associated with both concomitant immune compromise and aging is so great that any impact of that associated with diabetes is not measurable. As observed for HZ, rates of persistent post-zoster pain in younger individuals with diabetes (ie, 18–49 years and 50–59 years) generally mirrored rates in older individuals without diabetes (ie, 50–59 years and ≥65 years, respectively). Also the association between diabetes and persistent post-zoster pain was stronger in the immune competent than the immune compromised.

Strengths of our study are the analysis of claims data from almost 51 million US adults contributing to over 88 million PYs, a 5-year period (2005–2009), which allowed us to analyze almost 435 000 HZ episodes over this interval from 3 types of medical insurance programs. In addition, the inclusion of 3 different data sources and insured populations—commercial, Medicaid, and supplemental Medicare—enhances the validity of generalizing our incidence estimates to the general US adult population. Based on our incidence estimates, we estimated that approximately 1.2 million HZ cases occurred annually in the US from 2005 to 2009, with 13.5% of HZ cases occurring in individuals with diabetes.

A major limitation of this study is its dependence on claims data, which derive from ICD-9-CM codes completed by medical coders for billing purposes and the lack of medical record review. In contrast to medical records, ICD-9-CM codes lack relevant clinical details with which to validate diagnosis, timing, and severity of both diabetes and HZ or use of specific medications. For example, because we used medical claims, in which the distinction between type 1 and type 2 diabetes is not always available, any attempt to stratify diabetes by type would have been inaccurate [42].

Another limitation of using medical claims or medical records as data sources is the potential for care-seeking bias. For example, patients with diabetes may be more likely than those without diabetes to have (1) an established relationship with healthcare providers and (2) more ready access to care, or (3) they could seek healthcare due to symptomatic hyperglycemia secondary to an HZ episode. Such a bias would increase the observed relative risk of HZ in patients with diabetes. It is possible that the overall incidence of HZ might have been greater if cases in individuals not visiting a medical care provider for mild cases or lack of access to healthcare were included. Based on the results of this study, we cannot concluded whether the observed higher risk of HZ and post-zoster pain associated with diabetes is due (1) to biological underlying conditions and its physiologic implications such as response to zoster infection or (2) to differences in healthcare-seeking behaviors. However, independent of the underlying reasons, HZ and persistent post-zoster pain were more commonly diagnosed in individuals with diabetes than in those without diabetes, thereby delineating a public health consideration.

Some study design decisions could have affected our results. For example, we included individuals with continuous enrollment in the database for 6 months. In addition, our calculation of persistent post-zoster pain rates only included individuals with a diagnosis with HZ who had 6 months of follow-up data. If persons with diabetes had an enrollment period with undiagnosed diabetes, this period was excluded from the incidence calculations. By limiting reporting to up to 6-month rates for persisting pain after HZ, we ignored late-onset pain or long-lasting pain. In addition, it is known that up to 30% of persons with diabetes have not been diagnosed. Therefore, we may have underestimated diabetes prevalence and thereby falsely reduced the true relative risk of HZ in the persons with diabetes. The number of cases identified by criterion 3 (ie, unspecified neuralgia, neuritis, or radiculitis, if diagnosis only followed zoster diagnosis) of post-zoster pain among HZ cases was less frequent in diabetic than in nondiabetic individuals (20% vs 24% of all post-zoster pain cases). This finding suggests that diabetic neuropathy was not misclassified as postherpetic pain. However, although we do not know the overall specificity for each of the criteria used, criteria 3 likely had the lowest specificity of the 3 criteria because the ICD codes used for the basis of this criterion were not zoster-specific. The imposed minimum of a 6-month period without claims for unspecified neuralgia, neuritis, or radiculitis preceding the diagnosis of HZ, however, had reduced the risk of misclassification. Finally, we did not exclude individuals who were vaccinated against HZ during the study period. Early information on zoster vaccination was not believed to be accurate [43], and the rate of vaccination at this time period (2009 last study year) was felt to be too low (~1.9%) [44] to influence the findings in this analysis.

In summary, this study identified diabetes as a risk factor for HZ and persistent post-zoster pain among adult individuals seeking care in the United States. Younger individuals with diabetes seem to have incidence rates of HZ overall comparable to older individuals without diabetes. Clinical, public

health, and economic benefit assessments of interventions to mitigate the higher risks of HZ in individuals with diabetes are warranted.

## Acknowledgments

We thank Margaret Kelly (GlaxoSmithKline group of companies) and Julia Donnelly (freelance publication manager on behalf of GlaxoSmithKline group of companies) for their valuable editorial assistance.

***Disclaimer.*** J. A. S., S. Y. C., Q. L., S. J. B., and M. J. L. are the guarantors of this publication, ie, take full responsibility for the work as a whole, including decisions on study design, data collection and analysis, decision where to publish, and preparation of the manuscript. All these decisions were taken solely and collectively by the authors.

***Financial support.*** This study was funded by GlaxoSmithKline.

***Potential conflicts of interest.*** J. A. S. is employed by the GlaxoSmithKline group of companies. At the time of this study, J. A. S. worked at GlaxoSmithKline Vaccines. S. Y. C. and Q. L. are employees of Evidera (an independent research organization contracted to execute the study). S. J. B. is employed by the GlaxoSmithKline group of companies, at GlaxoSmithKline Vaccines. M. J. L. acted as a consultant for GlaxoSmithKline on the study, has received research grants from GlaxoSmithKline, and chairs an adjudication committee for GlaxoSmithKline. M. J. L. shares intellectual property with Merck, Sharpe & Dohme on the herpes zoster vaccine and performs clinical research with Merck funds.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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## APPENDIX

**Table A1. ICD-9 Conditions/Procedures Codes Used in This Study**

| Disease/Condition | ICD-9-CM Diagnosis Codes/ Procedure Codes | Description |
|---|---|---|
| Diabetes | 250.xx | Diabetes mellitus |
| Herpes zoster (HZ) | 053.xx | HZ |
| Persistent post-zoster pain[a] | 053.12 | Postherpetic trigeminal neuralgia |
| | 053.13 | Postherpetic polyneuropathy |
| | 053.19 | Zoster with other nervous system complications |
| | 729.2x | Neuralgia, neuritis, or radiculitis |
| Cancer | 140.xx-171.xx, 174.xx-208.xx | Malignant neoplasm except for other malignant neoplasm of skin (172.xx, 173.xx) |
| | 99.25, 99.28 | Injection or infusion of cancer chemotherapeutic substance or biological response modifier as an antineoplastic agent |
| Human immunodeficiency virus (HIV) | 042, 079.53, V08 | HIV |
| Solid-organ transplant | V42.0, 55.6x | Kidney transplant |
| | V42.1, 33.6, 37.51 | Heart transplant |
| | V42.6, 33.5x, 33.6 | Lung transplant |
| | V42.7, 50.5x | Liver transplant |
| Bone marrow or stem cell transplant | V42.81, V42.82, 41.0x | Bone marrow or stem cell transplant |
| Rheumatoid arthritis | 714.xx | Rheumatoid arthritis |
| Inflammatory bowel disease | 555.x | Regional enteritis |
| | 556.x | Ulcerative colitis |
| Lupus | 710 | Systemic lupus erythematosus |
| Multiple sclerosis (MS) | 340.x | MS |
| Psoriasis | 696.x | Psoriasis and similar disorders |

[a] Note: For the purpose of this study, persistent post-zoster pain was defined by any of the following 3 criteria: (1) a diagnosis of postherpetic trigeminal neuralgia or postherpetic polyneuropathy; (2) a diagnosis of HZ with other nervous system complications and more than a 30-day supply of medications typically used to treat post-zoster pain, as listed in Table A2; or a diagnosis of neuralgia, neuritis, or radiculitis (ICD-9-CM: 729.2) that first appeared after the HZ diagnosis.

**Table A2. Medications for Persistent Post-Zoster Pain**

| Drug Group | Drug Included |
|---|---|
| Opioids | Codeine, hydrocodone, oxycodone, pentazocine, propoxyphene, tramadol, fentanyl, hydromorphone, meperidine, morphine, butorphanol, oxymorphone, levorphanol, methadone |
| Other analgesic medications | Acetaminophen and combinations, aspirin and combinations |
| Nonsteroidal anti-inflammatory drugs | Ibuprofen and combinations, naproxen and combinations, indomethacin, diclofenac, nabumetone, etodolac, meloxicam, sulindac, piroxicam, oxaprozin, ketoprofen, tolmetin, ketorolac tromethamine, celecoxib, valdecoxib, diflunisal |
| Anticonvulsants | Gabapentin, pregabalin |
| Lidoderm | Lidocaine patch 5% |
| Other topical anesthetic | Capsaicin (topical) |
| Serotonin-norepinephrine reuptake inhibitors (SNRI) | Duloxetine |
| Tricyclic antidepressants (TCA) | Amitriptyline and combinations, desipramine, nortriptyline doxepin, imipramine |

**Table A3. Demographic Characteristics of Study Population by Diabetes and Immune Status During 2005–2009**

| | Individuals With Diabetes | Individuals Without Diabetes |
|---|---|---|
| Total study population | | |
| Number of enrollees | 4 540 014 | 46 467 961 |
| Females (%) | 50.1 | 54.3 |
| Age (years): mean (standard deviation [SD]) | 54.6 (13.6) | 42.0 (15.6) |
| Age group (years) (%) | | |
| 18–49 years | 33.5 | 69.1 |
| 50–59 years | 32.9 | 17.9 |
| 60–64 years | 14.5 | 5.5 |
| ≥65 years | 19.0 | 7.6 |
| Immune competent | | |
| Number of enrollees | 4 307 621 | 45 220 757 |
| Females (%) | 50.0 | 54.2 |
| Age (years): mean (SD) | 54.3 (13.6) | 41.7 (15.5) |
| Age group (years) (%) | | |
| 18–49 years | 34.3 | 69.8 |
| 50–59 years | 33.1 | 17.6 |
| 60–64 years | 14.3 | 5.3 |
| ≥65 years | 18.3 | 7.2 |
| Immune compromised | | |
| Number of enrollees | 232,393 | 1 247 204 |
| Females (%) | 51.8 | 59.5 |
| Age (years): mean (SD) | 60.0 (13.2) | 52.6 (15.6) |
| Age group (years) (%) | | |
| 18–49 years | 19.5 | 41.4 |
| 50–59 years | 30.2 | 26.9 |
| 60–64 years | 17.7 | 11.9 |
| ≥65 years | 32.5 | 19.8 |