**Online Supplement**

# Increased Health Care Resource Utilization and Costs Associated with Herpes Zoster Among Patients Aged ≥50 Years with Chronic Obstructive Pulmonary Disease in the United States

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## Table S1. Definitions

| Item | Definition |
|---|---|
| COPD diagnosis (modified from Dalal et al[1]) | ≥1 of the following:<br>• 1 claim for an inpatient stay with COPD as a primary diagnosis (ICD-9: 491, 492, 496; ICD-10: J41, J42, J43, J44)[a]<br>• 1 claim for an outpatient visit with COPD as a primary diagnosis and a second outpatient visit with a diagnosis of COPD (in any position) on a separate date<br>• 1 claim with a diagnosis of COPD (in any position) and a filled prescription for a COPD maintenance treatment (LAMA, LABA, ICS/LABA, LABA/LAMA, ICS/LABA/LAMA) |
| HZ diagnosis | ≥1 claim associated with a diagnosis of HZ (ICD-9: 053 excluding 053.1; ICD-10: B02 excluding B02.2) |
| PHN | Both of the following:<br>• ≥1 claim associated with a diagnosis of PHN (ICD-9: 053.1; ICD-10: B02.2) or HZ ≥90 days after HZ index date<br>• ≥1 claim for a pain medication[b] (non-opioid analgesics, opioid analgesics, anticonvulsants, tricyclic antidepressants, other antidepressants, baclofen, capsaicin cream, clonidine, diclofenac cream, gabapentin, lidocaine, mexiletine, lidocaine patch, pamidronate, prilocaine cream, or tizanidine) or intervention[b] (acupuncture, anesthetic agent, neurostimulators, nerve destruction by neurolytic agent, or nerve decompression) >90 days after the PHN or HZ claim |
| HZO | ≥1 of the following:<br>• ≥1 claim associated with a diagnosis of HZO (ICD-9: 053.21, 053.22, 053.29; ICD-10: B02.31, B02.32, B02.33, B02.34, B02.39)<br>• ≥1 claim associated with a diagnosis of eye complications within 30 days of the HZ diagnosis: unspecified chorioretinitis (ICD-9: 363.20; ICD-10: H30.93), unspecified iridocyclitis (ICD-9: 364.3; ICD-10: H20.9), blindness and low vision (ICD-9: 369; ICD-10: H54), keratitis (ICD-9: 370; ICD-10: H16), scleritis and episcleritis (ICD-9: 379.0x; ICD-10: H15.0, H15.1), mydriasis (ICD-9: 379.43; ICD-10: H57.04) |
| CCI components[2] | MI, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, connective tissue disorder, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes (type 1 or 2), hemiplegia, moderate or severe renal disease, diabetes (type 1 or 2) with end-organ damage, any malignant tumor, metastatic solid tumor, leukemia, lymphoma, AIDS |
| Autoimmune comorbidities potentially associated with increased risk of HZ | Rheumatoid arthritis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), systemic lupus erythematosus, multiple sclerosis, psoriasis, chronic kidney disease, Wegener's granulomatosis, polymyalgia rheumatica, giant cell arteritis, ankylosing spondylitis, idiopathic pulmonary fibrosis, sarcoidosis, scleroderma, psoriatic arthritis |

| | |
|---|---|
| Immunosuppressive conditions | • SOT (ie lung transplant, combined heart-lung transplantation, heart transplantation, transplant of intestine, liver transplant, transplant of pancreas, transplant of kidney)<br>• HSCT (ie allogenic bone marrow transplant, allogenic stem cell transplant, autologous bone marrow transplant, autologous stem cell transplant)<br>• Use of chemotherapy for solid and hematological malignancies in prior 6 months<br>• Use of immunosuppressants<br>• Patients with rheumatoid arthritis (and/or other autoimmune conditions) receiving biologics<br>• Patients with symptomatic HIV disease (ie AIDS) |
| COPD exacerbations | • An exacerbation was recorded as a separate episode if it occurred following a 14-day period free of any exacerbation claim. Exacerbation claims occurring ≤14 days from another were considered the same episode, for which the most severe claim determined the severity<br>• Moderate exacerbation: an outpatient or ED visit associated with a diagnosis of COPD as a primary or any secondary diagnosis and ≥1 dispensing for a systemic corticosteroid or antibiotic within 7 days of such a visit (this temporal restriction was used to differentiate use of antibiotics and systemic corticosteroid for other reasons that were not related to the COPD exacerbation)<br>• Severe exacerbation: an inpatient stay with a claim associated with a diagnosis of COPD as a primary diagnosis |
| Stroke | ≥1 claim associated with a diagnosis of stroke (ICD-9: 430, 431, 432, 433.x1, 434.x1; ICD-10: I60.9, I61.9, I63.019, I63.119, I63.139, I63.20, I63.219, I63.22, I63.239, I63.30, I63.40, I63.50, I63.59) |
| TIA | ≥1 claim associated with a diagnosis of TIA (ICD-9: 435; ICD-10: G45) |
| MI | ≥1 claim associated with a diagnosis of MI (ICD-9: 410; ICD-10: I21) |

[a]The protocol specified that only ICD-10 codes J43 and J44 (along with ICD-9: 491, 492, 496) would be used to define the COPD diagnosis. Upon internal discussions and feasibility counts, it was decided to add ICD-10 codes J41 and J42

[b]Although pain medications/interventions were used to help identify PHN, pharmacy costs were not included as these could not be guaranteed to have been used to treat PHN

COPD=chronic obstructive pulmonary disease; ICD-9=International Classification of Diseases, Ninth Revision; ICD-10=International Classification of Diseases, Tenth Revision; LAMA=long-acting muscarinic antagonist; LABA=long-acting beta agonist; ICS=inhaled corticosteroids; HZ=herpes zoster; PHN=post-herpetic neuralgia; HZO=herpes zoster ophthalmicus; CCI=Charlson-Quan Comorbidity Index; MI=myocardial infarction; AIDS=acquired immunodeficiency syndrome; SOT=solid organ transplant; HSCT=hematopoietic stem cell transplant; HIV=human immunodeficiency virus; ED=emergency department; TIA=transient ischemic attack

**References:**

1. Dalal AA, Liu F, Riedel AA. Cost trends among commercially insured and Medicare Advantage-insured patients with chronic obstructive pulmonary disease: 2006 through 2009. *Int J Chron Obstruct Pulmon Dis*. 2011;6:533-542. doi: 10.2147/COPD.S24591.

2. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi: 10.1093/aje/kwq433.

**Table S2. All-Cause and COPD-Related[a] Mean Costs for Patients in the COPD+/HZ– and COPD+/HZ+ Cohorts with Costs >$0 in Each Category During the First Year[b] of Observation**

| | All-cause costs, mean ± SD, $ PPPM | | COPD-related[a] costs, mean ± SD, $ PPPM | |
|---|---|---|---|---|
| | **COPD+/HZ– (n=35,360)** | **COPD+/HZ+ (n=3,415)** | **COPD+/HZ– (n=35,360)** | **COPD+/HZ+ (n=3,415)** |
| Total HRU | 3,846 ± 8,034 (n=34,464) | 4,142 ± 7,616 (n=3,414) | 1,358 ± 3,226 (n=32,054) | 1,613 ± 4,058 (n=3,262) |
| Medical services | 3,386 ± 7,900 (n=34,147) | 3,591 ± 7,399 (n=3,414) | 1,407 ± 3,442 (n=27,240) | 1,588 ± 4,181 (n=2,983) |
| Inpatient | 7,997 ± 13,118 (n=4,537) | 7,223 ± 10,652 (n=374) | 3,678 ± 5,555 (n=3,449) | 3,703 ± 5,051 (n=305) |
| ED | 1,695 ± 3,088 (n=14,990) | 1,782 ± 3,344 (n=1,860) | 1,611 ± 2,790 (n=8,291) | 1,655 ± 3,304 (n=1,167) |
| Outpatient | 1,468 ± 4,397 (n=33,929) | 1,691 ± 4,623 (n=3,408) | 425 ± 1,566 (n=25,105) | 502 ± 2,269 (n=2,869) |
| Other[c] | 180 ± 475 (n=22,910) | 193 ± 464 (n=2,505) | 171 ± 385 (n=9,529) | 197 ± 426 (n=1,194) |
| Pharmacy | 535 ± 1,110 (n=31,679) | 598 ± 1,521 (n=3,142) | 202 ± 241 (n=25,766) | 196 ± 549 (n=2,687) |

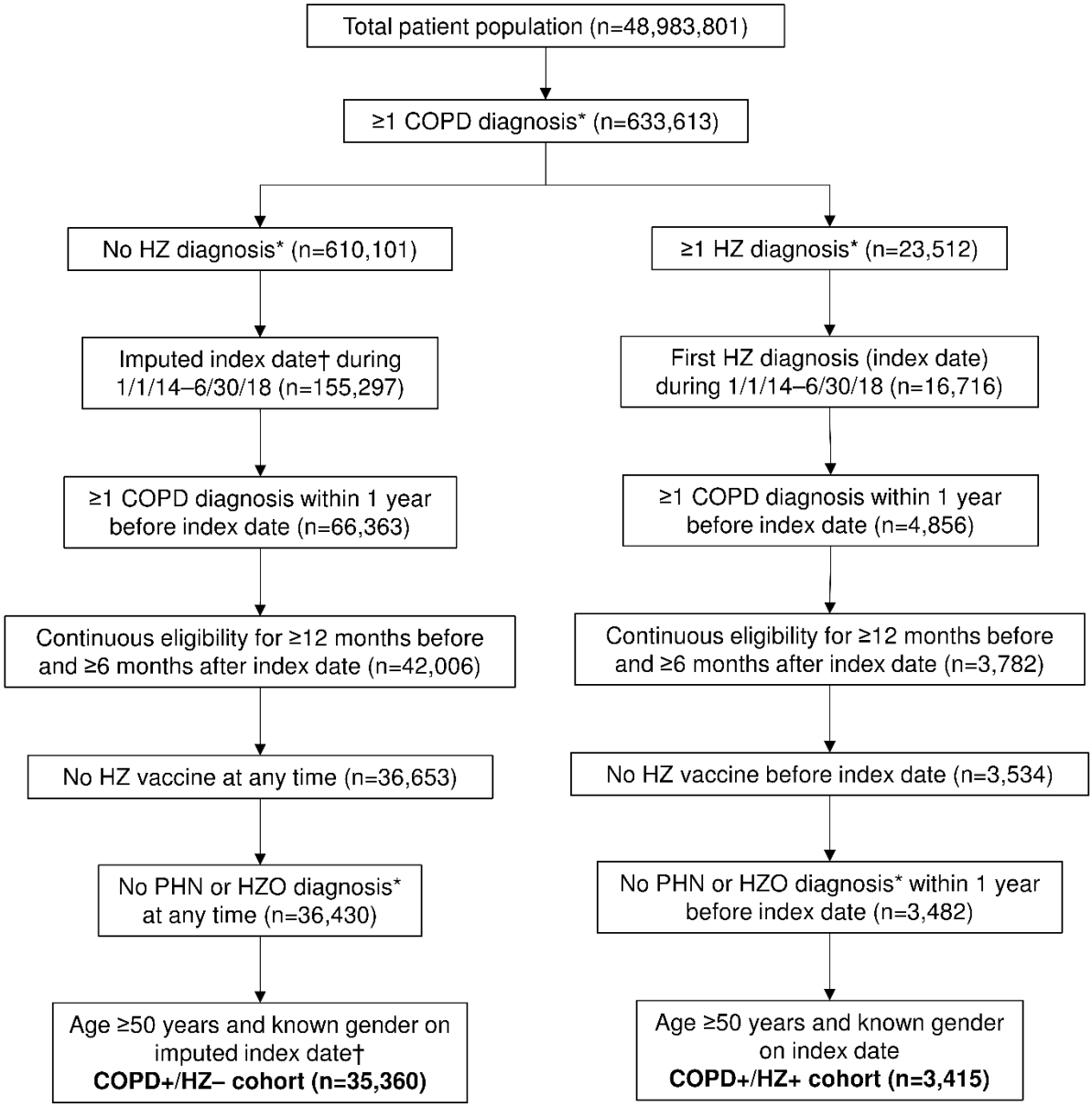
[a]Claim associated with a COPD diagnosis in any position or order, ie as a primary or coexisting condition (COPD-related pharmacy costs were estimated using pharmacy claims associated with a filled prescription of COPD maintenance medication or COPD rescue medication)
[b]Mean observation periods: COPD+/HZ–: 10.9 ± 1.8 months; COPD+/HZ+: 11.4 ± 1.4 months
[c]Including skilled nursing facilities, home care services, hospice, vision care, durable medical equipment, services and supplies, and transportation services
COPD=chronic obstructive pulmonary disease; COPD+/HZ–=patients with chronic obstructive pulmonary disease but without herpes zoster; COPD+/HZ+=patients with chronic obstructive pulmonary disease and herpes zoster; SD=standard deviation; PPPM=per person per month; n=number of patients; HRU=healthcare resource utilization; ED=emergency department

**Table S3. Mean Costs Associated with HZ, PHN, and HZO – Among All Patients in the COPD+/HZ+ Cohort and Only Among Those with Costs >$0 in Each Category During the First Year[a] of Observation**

| | HZ-related[b] costs, mean ± SD, $ PPPM | | PHN-related[b] costs, mean ± SD, $ PPPM | | HZO-related[b] costs, mean ± SD, $ PPPM | |
|---|---|---|---|---|---|---|
| | All patients (n=3,415) | Patients with costs >$0 | All patients (n=3,415) | Patients with costs >$0 | All patients (n=3,415) | Patients with costs >$0 |
| Total HRU | 244 ± 1,056 | 245 ± 1,059 (n=3,395) | –[c] | –[c] | –[c] | –[c] |
| Medical services | 239 ± 1,056 | 241 ± 1,061 (n=3,378) | 56 ± 481 | 332 ± 1,134 (n=574) | 24 ± 542 | 321 ± 1,952 (n=258) |
| Inpatient | 62 ± 512 | 1,908 ± 2,141 (n=111) | 14 ± 224 | 1,936 ± 1,805 (n=25) | 4 ± 115 | 2,070 ± 1,609 (n=7) |
| ED | 105 ± 705 | 557 ± 1,545 (n=645) | 25 ± 359 | 1,093 ± 2,127 (n=78) | 15 ± 523 | 1,438 ± 4,958 (n=36) |
| Outpatient | 61 ± 528 | 68 ± 560 (n=3,027) | 14 ± 140 | 91 ± 342 (n=539) | 3 ± 36 | 54 ± 143 (n=189) |
| Other[d] | 11 ± 136 | 188 ± 542 (n=194) | 2 ± 44 | 165 ± 348 (n=46) | 2 ± 38 | 59 ± 207 (n=108) |
| Pharmacy | 5 ± 16 | 8 ± 18 (n=2,410) | –[c] | –[c] | –[c] | –[c] |

[a]Mean observation period: 11.4 ± 1.4 months
[b]HZ-, PHN-, and HZO-related HRU and costs were estimated using claims associated with a diagnosis of HZ, PHN, or HZO, respectively (see Supplemental Table S1)
[c]Pharmacy costs were not included for PHN or HZO because the treatment of these conditions is highly variable (based on symptom severity)
[d]Including skilled nursing facilities, home care services, hospice, vision care, durable medical equipment, services and supplies, and transportation services
HZ=herpes zoster; PHN=post-herpetic neuralgia; HZO=herpes zoster ophthalmicus; COPD+/HZ+=patients with chronic obstructive pulmonary disease and herpes zoster; SD=standard deviation; PPPM=per person per month; n=number of patients; HRU=healthcare resource utilization; ED=emergency department

## Figure S1. Study Flow Chart

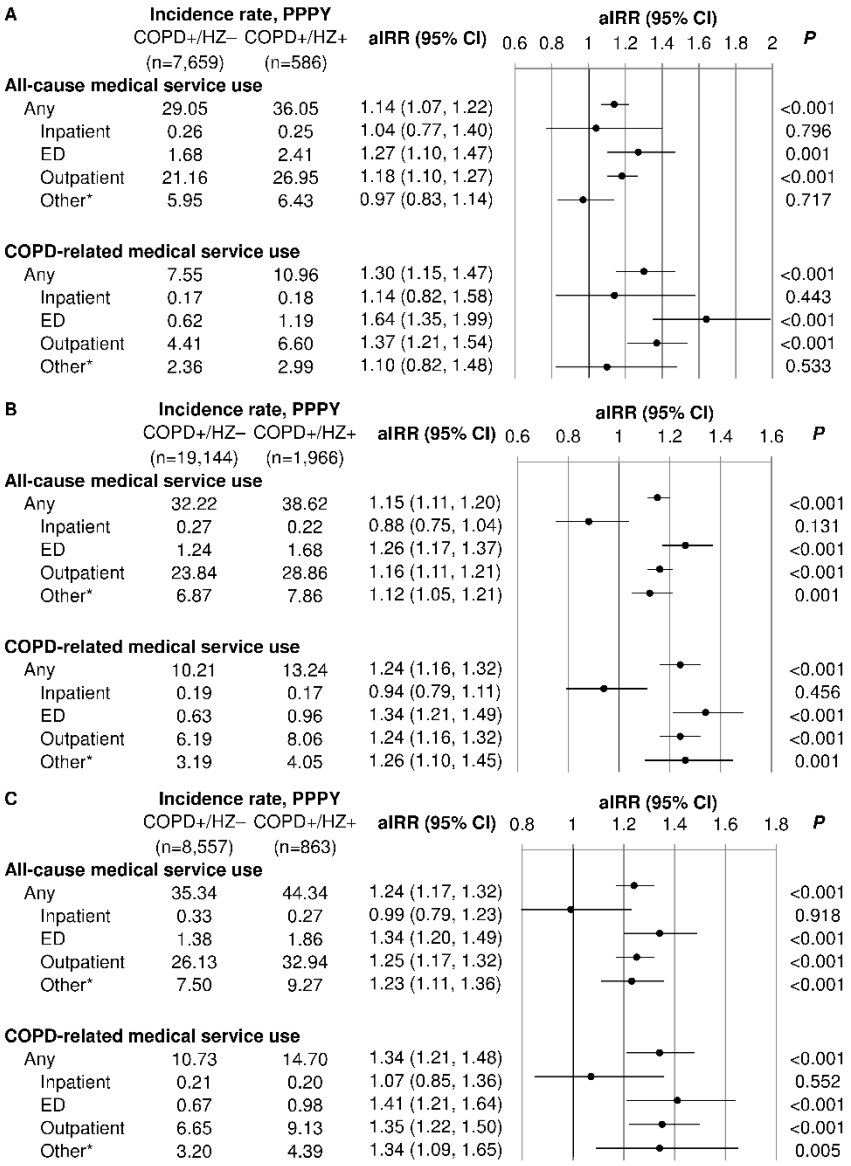



*See Supplemental Table S1 for ICD codes

†Index date for the COPD+/HZ– cohort was assigned such that the distribution of time in the pre-index period was similar to that in the COPD+/HZ+ cohort

n=number of patients; COPD=chronic obstructive pulmonary disease; HZ=herpes zoster; PHN=post-herpetic neuralgia; HZO=herpes zoster ophthalmicus; COPD+/HZ–=patients with chronic obstructive pulmonary disease but without herpes zoster; COPD+/HZ+=patients with chronic obstructive pulmonary disease and herpes zoster; ICD=International Classification of Diseases

**Figure S2. Incidence Rates and aIRRs[a] of All-Cause and COPD-Related[b] Medical Service Use for Patients in the COPD+/HZ– and COPD+/HZ+ Cohorts During the First Year[c] of Observation (A) Age 50–64 Years (B) Age 65–79 Years (C) Age ≥80 Years**




[a]Calculated using generalized linear models assuming a negative binomial distribution and log link, accounting for the propensity score of being in the COPD+/HZ+ cohort and relevant baseline characteristics

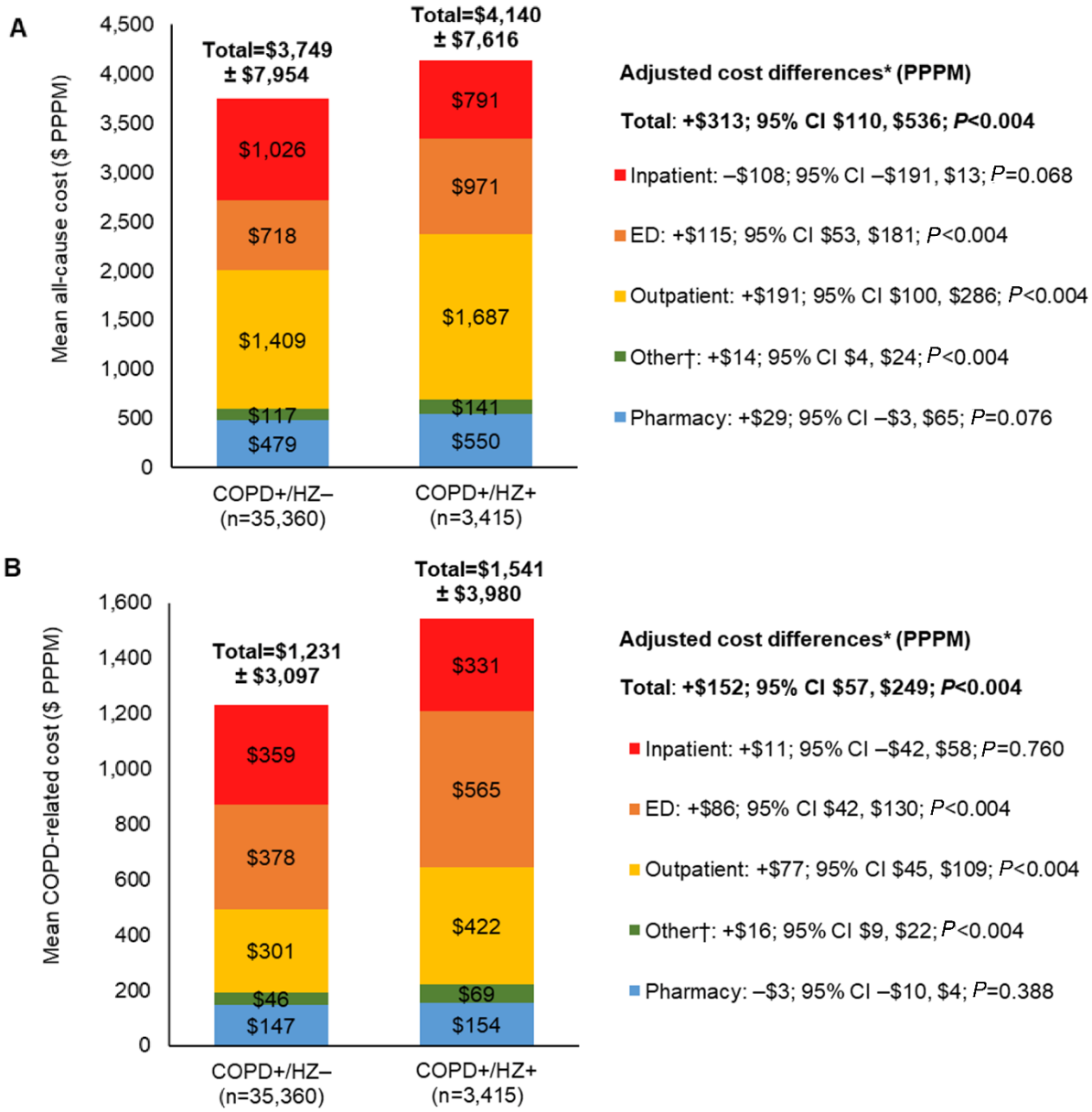
[b]Claim associated with a COPD diagnosis in any position or order, ie as a primary or coexisting condition

[c]Mean observation periods: age 50–64 years: COPD+/HZ–: 10.9 ± 1.8 months; COPD+/HZ+: 11.4 ± 1.5 months; age 65–79 years: 11.0 ± 1.8 and 11.4 ± 1.4 months, respectively; age ≥80 years: 10.8 ± 1.9 and 11.4 ± 1.4 months, respectively

*Including skilled nursing facilities, home care services, hospice, vision care, durable medical equipment, services and supplies, and transportation services.

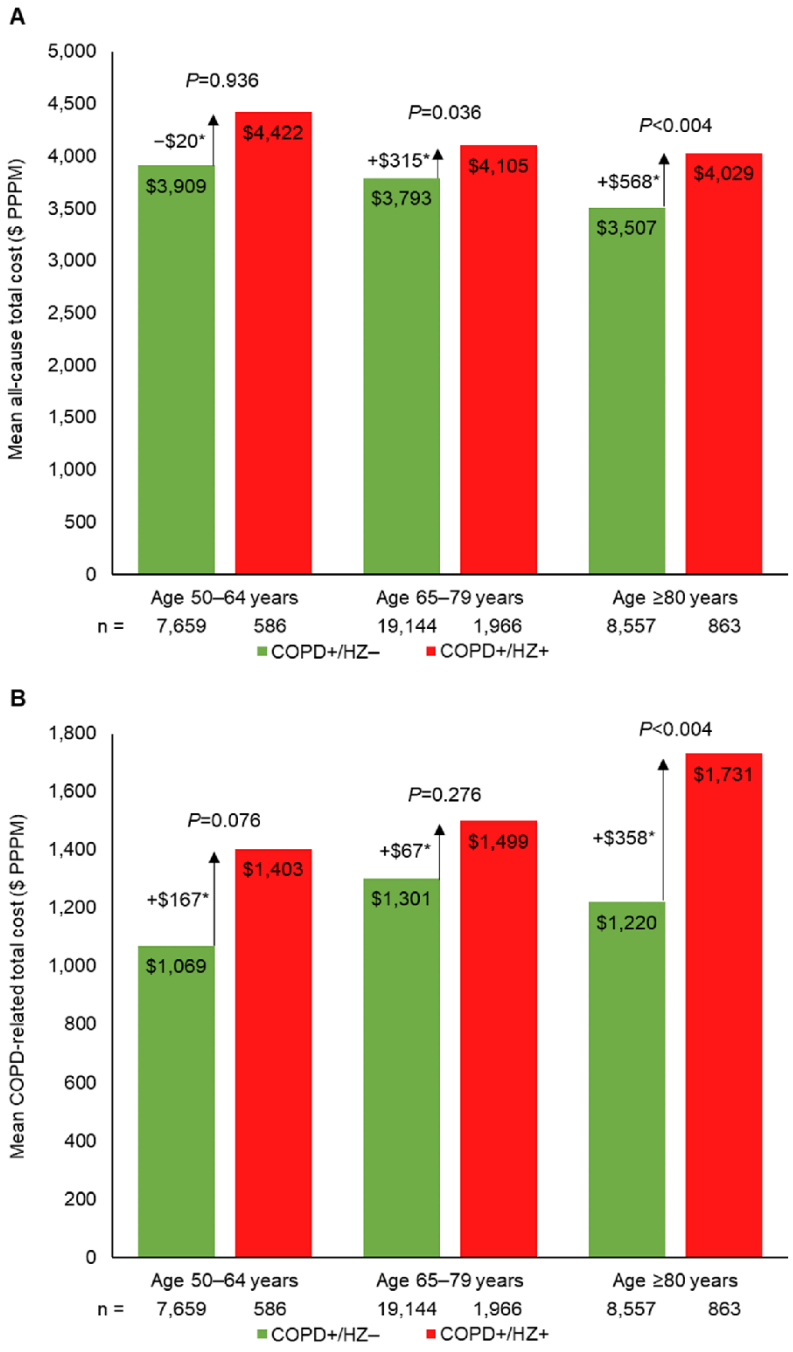
aIRR=adjusted incidence rate ratio; COPD=chronic obstructive pulmonary disease; COPD+/HZ–=patients with chronic obstructive pulmonary disease but without herpes zoster; COPD+/HZ+=patients with chronic obstructive pulmonary disease and herpes zoster; PPPY= per person per year; CI=confidence interval; *P*=*P*-value; n=number of patients; ED=emergency department

**Figure S3. Costs (Total and by HRU Category) for Patients in the COPD+/HZ– and COPD+/HZ+ Cohorts During the First Year[a] of Observation (A) All-Cause Costs (B) COPD-Related[b] Costs**




[a]Mean observation periods: COPD+/HZ–: 10.9 ± 1.8 months; COPD+/HZ+: 11.4 ± 1.4 months
[b]Claim associated with a COPD diagnosis in any position or order, ie as a primary or coexisting condition (COPD-related pharmacy costs were estimated using pharmacy claims associated with a filled prescription of COPD maintenance medication or COPD rescue medication)
*Cost differences were estimated using the two-part modelling approach
†Including skilled nursing facilities, home care services, hospice, vision care, durable medical equipment, services and supplies, and transportation services
HRU=healthcare resource utilization; COPD+/HZ–=patients with chronic obstructive pulmonary disease but without herpes zoster; COPD+/HZ+=patients with chronic obstructive pulmonary disease and herpes zoster; COPD=chronic obstructive pulmonary disease; PPPM=per person per month; CI=confidence interval; *P*=*P*-value; ED=emergency department; n=number of patients

**Figure S4. Mean Total Costs for Patients in the COPD+/HZ– and COPD+/HZ+ Cohorts by Age Category During the First Year[a] of Observation (A) All-Cause (B) COPD-Related[b]**



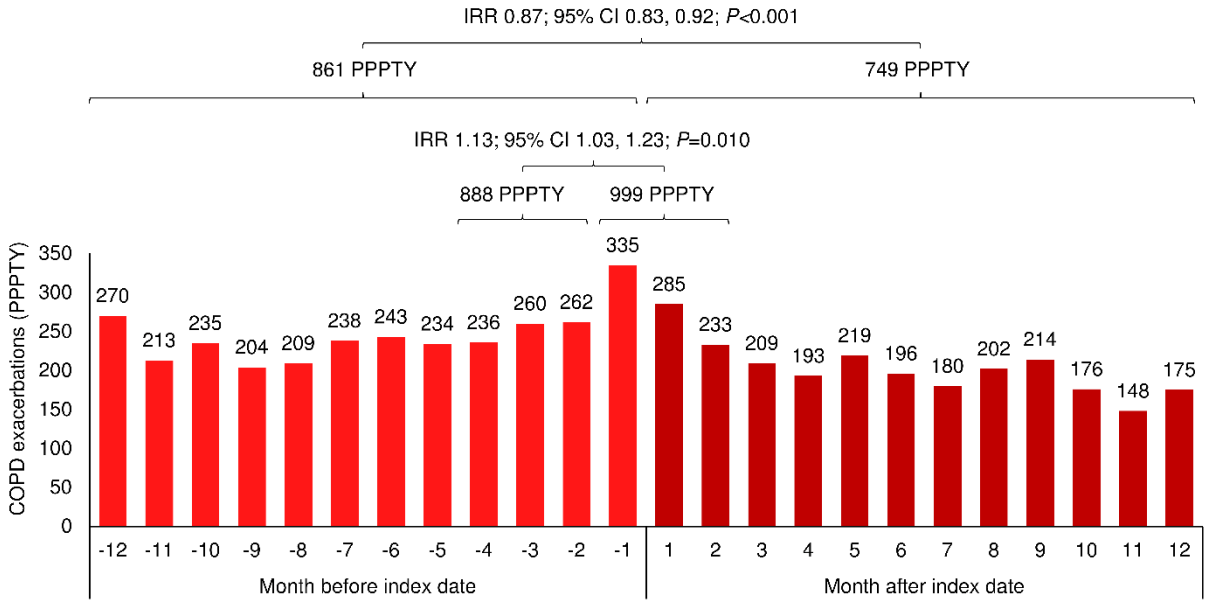

[a]Mean observation periods are as in Supplemental Figure S2

[b]Claim associated with a COPD diagnosis in any position or order, ie as a primary or coexisting condition (COPD-related pharmacy costs were estimated using pharmacy claims associated with a filled prescription of COPD maintenance medication or COPD rescue medication)

*Cost differences were estimated using the two-part modeling approach

COPD+/HZ–=patients with chronic obstructive pulmonary disease but without herpes zoster; COPD+/HZ+=patients with chronic obstructive pulmonary disease and herpes zoster; COPD=chronic obstructive pulmonary disease; PPPM=per person per month; *P*=*P*-value; n=number of patients

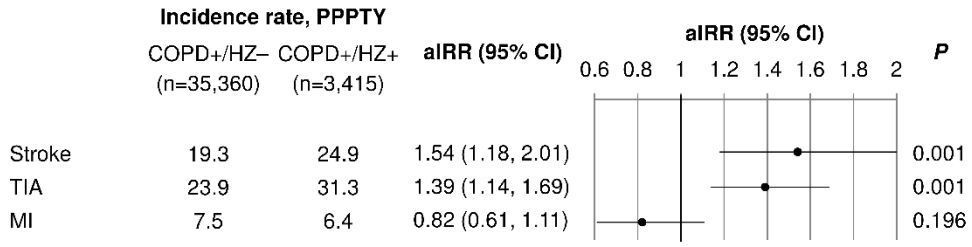
**Figure S5. Incidence Rates of COPD Moderate/Severe Exacerbations[a] in the COPD+/HZ+ Cohort During the 12 Months Before and the 12 Months After the Index Date**




[a]See definition in Supplemental Table S1

COPD=chronic obstructive pulmonary disease; COPD+/HZ+=patients with chronic obstructive pulmonary disease and herpes zoster; IRR=incidence rate ratio; CI=confidence interval; *P*=*P*-value; PPPTY=per person per thousand years

## Figure S6. Incidence Rates and aIRRs[a] of Vascular Events in the COPD+/HZ– and COPD+/HZ+ Cohorts During the Whole Observation Period[b]




[a]aIRRs for stroke and TIA were calculated using generalized linear models assuming a negative binomial distribution and log link, accounting for the propensity score of being in the COPD+/HZ+ cohort and relevant baseline characteristics. The aIRR for MI was calculated using the same method but assuming a Poisson distribution and log link

[b]Mean observation periods: stroke: COPD+/HZ–: 25.3 ± 14.1 months; COPD+/HZ+: 25.3 ± 14.9 months; TIA: 25.1 ± 14.1 and 25.1 ± 14.9 months, respectively; MI: 26.0 ± 14.2 and 26.0 ± 14.8 months, respectively

aIRR=adjusted incidence rate ratio; COPD+/HZ–=patients with chronic obstructive pulmonary disease but without herpes zoster; COPD+/HZ+=patients with chronic obstructive pulmonary disease and herpes zoster; PPPTY=per person per thousand years; CI=confidence interval; *P*=*P*-value; n=number of patients; TIA=transient ischemic attack; MI=myocardial infarction

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 2–3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3–5 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 3–5 |
| | | (b) For matched studies, give matching criteria and number of exposed and unexposed | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5–6 |

| | | | |
|---|---|---|---|
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 3–5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6–9 |
| Study size | 10 | Explain how the study size was arrived at | Figure S1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6–9 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6–9 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6–9 |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | |
| | | (*e*) Describe any sensitivity analyses | 8 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 9; Figure S1 |
| | | (b) Give reasons for non-participation at each stage | Figure S1 |
| | | (c) Consider use of a flow diagram | Figure S1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9; Table 1 |

| | | | |
|---|---|---|---|
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) Summarise follow-up time (eg, average and total amount) | Figures 3–4; S2–S6; Tables S2–S3 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 9–12 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 9–12; Figures 3–4; S2–S6 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11; Figure S5 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 12 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 15–16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of | 12–15 |

| | | | |
|---|---|---|---|
| | | analyses, results from similar studies, and other relevant evidence | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 12–15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Title Page |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.