brain sciences

MDPI

*Article*

# Association Between Upper Respiratory Tract Infections and Parkinson's Disease in Korean Populations: A Nested Case–Control Study Using a National Health Screening Cohort

**Hyuntaek Rim [1], Hyo Geun Choi [2,3], Jee Hye Wee [4], Joo Hyun Park [5], Mi Jung Kwon [6], Ho Suk Kang [7], Hoang Nguyen [8], In Bok Chang [1], Joon Ho Song [1] and Ji Hee Kim [1,*]**

[1] Department of Neurosurgery, Hallym University College of Medicine, Anyang 14068, Republic of Korea; coldwings@naver.com (H.R.); nscib71@hanmail.net (I.B.C.); song@hallym.or.kr (J.H.S.)
[2] Department of Otorhinolaryngology-Head and Neck Surgery, Suseoseoul ENT Clinic, Seoul 06349, Republic of Korea; pupen@naver.com
[3] MD Analytics, Seoul 06349, Republic of Korea
[4] Department of Otorhinolaryngology-Head and Neck Surgery, Hallym University College of Medicine, Anyang 14068, Republic of Korea; weejh07@hanmail.net
[5] Department of Otorhinolaryngology-Head and Neck Surgery, Dongguk University Ilsan Hospital, Goyang 10326, Republic of Korea; parkzzu19@naver.com
[6] Department of Pathology, Hallym University College of Medicine, Anyang 14068, Republic of Korea; mulank@hanmail.net
[7] Division of Gastroenterology, Department of Internal Medicine, Hallym University College of Medicine, Anyang 14068, Republic of Korea; hskang76@hallym.or.kr
[8] Department of Chemistry and Biochemistry, University of California San Diego, San Diego, CA 92093, USA; hon005@ucsd.edu
* Correspondence: kimjihee.ns@gmail.com; Tel.: +82-31-380-3771; Fax: +82-31-386-9474

## Abstract

Background: Although several epidemiological studies have suggested a potential association between infections and Parkinson's disease (PD), relatively few have specifically examined the relationship between upper respiratory tract infections (URIs) and PD, apart from coronavirus disease 2019 (COVID-19). Objectives: We investigated whether a history of URI was associated with the diagnosis of PD among Korean individuals aged ≥40 years, using data from the Korean National Health Insurance Service–Health Screening Cohort. Methods: A total of 5844 patients newly diagnosed with PD were identified and matched with 23,376 control participants at a 1:4 ratio based on age, sex, income, and geographical region. Conditional logistic regression analyses were performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for PD, adjusting for potential confounders including smoking, alcohol consumption, body mass index, blood pressure, comorbidity scores, blood glucose, and serum cholesterol levels. Results: Overall, no significant association was found between a history of URI and PD when considering a two-year exposure window. However, in the one-year window analysis, individuals with a history of URI had a modestly reduced odds of PD (≥1, ≥2, or ≥3 episodes: (adjusted OR: 0.93, 95% CI: 0.88–0.97, aOR: 0.91, 95% CI: 0.87–0.96 and aOR: 0.92, 95% CI: 0.87–0.98, respectively). Subgroup analyses revealed that the inverse association was more pronounced among women, older adults (≥65 years), and those with higher comorbidity scores. No clear dose–response trend was observed across increasing frequencies of URI diagnoses. Conclusions: Our findings suggest that the apparent protective association between recent URI history and PD is unlikely to be causal and may instead reflect confounding by medication use or reverse causation related to the prodromal phase of PD. These results should therefore be interpreted with caution and regarded as hypothesis-generating. Further prospective studies incorporating detailed prescription data and long-term follow-up are warranted to clarify the role of infections and anti-inflammatory medications in the pathogenesis of PD.

check for updates

Academic Editors: Santiago Perez-Lloret, Matilde Otero-Losada and Francisco Capani

Received: 28 July 2025
Revised: 21 August 2025
Accepted: 27 August 2025
Published: 28 August 2025

**Citation:** Rim, H.; Choi, H.G.; Wee, J.H.; Park, J.H.; Kwon, M.J.; Kang, H.S.; Nguyen, H.; Chang, I.B.; Song, J.H.; Kim, J.H. Association Between Upper Respiratory Tract Infections and Parkinson's Disease in Korean Populations: A Nested Case–Control Study Using a National Health Screening Cohort. *Brain Sci.* **2025**, *15*, 939. https://doi.org/10.3390/brainsci15090939

**Copyright:** © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

**Keywords:** infection; neurodegenerative disease; neuroinflammation; Parkinson's disease; pathogenesis; upper respiratory tract infection

## 1. Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the midbrain and the accumulation of misfolded alpha-synuclein aggregates, known as Lewy bodies, in various brain regions. It typically presents with motor symptoms such as resting tremor, rigidity, bradykinesia, and postural instability. Non-motor symptoms, arising from dysfunction across multiple neurotransmitter systems in both central and peripheral nervous systems [1], include psychiatric and autonomic disturbances, cognitive impairment, sleep disorders, olfactory dysfunction, and pain [2–4]. PD affects approximately 7.5 million people worldwide, with a prevalence that increases markedly with age [5]. Despite extensive research, the precise etiology and pathogenesis of neuronal degeneration in PD remain incompletely understood.

Upper respiratory tract infections (URIs) are among the most common human illnesses, encompassing a broad range of conditions affecting the nasal cavity, sinuses, pharynx, larynx, and large airways [6]. Most acute URIs are viral in origin, primarily caused by rhinoviruses, though they may occasionally result in bacterial complications or spread to adjacent organs [7]. The primary symptoms of URIs are usually mild and include nasal congestion, rhinorrhea, sneezing, sore throat, cough, malaise, fatigue, and low-grade fever. URIs occur globally and annually, with some progressing to more severe manifestations that require hospitalization [8]. Antiviral agents are currently approved only for select pathogens, such as influenza viruses, whereas antibiotic therapy is generally reserved for bacterial complications, such as acute otitis media and sinusitis.

Current understanding of PD pathogenesis implicates several overlapping mechanisms, including aberrant protein handling, oxidative stress, mitochondrial dysfunction, excitotoxicity, and programmed cell death (apoptosis) [9]. Increasing evidence also suggests that neuroinflammatory processes play a critical role in the cascade leading to neuronal degeneration. In both human patients with PD and corresponding animal models, sustained inflammatory responses, T-cell infiltration, and glial cell activation have been consistently observed and are thought to substantially contribute to dopaminergic neuronal loss [10,11].

In this context, both bacterial and viral infections have been identified as potential environmental risk factors for PD, primarily through their ability to induce chronic microglial activation and inflammation [12]. A wide range of bacterial species—including *Helicobacter pylori*, *Escherichia coli*, *Proteus mirabilis*, *Mycobacterium tuberculosis*, *Porphyromonas gingivalis*, *Clostridium difficile*, and *Chlamydia pneumoniae*—which cause infections in the lungs, skin, and gastrointestinal tract, have been associated with the onset and, to a lesser extent, progression of PD [13–16]. Similarly, several viruses have been implicated in PD development, including influenza virus, coxsackievirus, Japanese encephalitis virus, West Nile Equine Encephalitic virus (WEEV), herpesviruses, hepatitis C virus (HCV), human immunodeficiency virus (HIV), and SARS-CoV-2 [17–19].

However, compared to better-studied pathogens such as influenza, relatively few studies have investigated the association between PD and URIs caused by other viral or bacterial agents [20–23]. In this study, we examined whether individuals with a history of multiple URIs were at increased risk for subsequent PD compared with the general population.

## 2. Methods

### *2.1. Ethics*

This study was approved by the Ethics Committee of Hallym University (IRB No.: 2019-10-023) on 22 December 2022. The requirement for written informed consent was waived by the Institutional Review Board. All analyses were conducted in accordance with the relevant guidelines and regulations of the Hallym University Ethics Committee.

### *2.2. Study Design and Population*

We conducted a retrospective cohort study using data from the Korean National Health Insurance Service (NHIS)–Health Screening Cohort, covering the period from 1 January 2002 to 31 December 2019. The study population included newly diagnosed patients with PD and matched controls. Among the 514,866 participants with 895,300,177 medical claim codes, individuals diagnosed with PD more than twice during the study period were classified into the PD group ($n$ = 9437); while the remaining participants were assigned to the control group ($n$ = 505,429).

To exclude potential pre-existing PD cases, participants diagnosed with PD in 2002–2003 ($n$ = 641) and those without fasting blood glucose data ($n$ = 2) were excluded from the PD group. In the control group, participants with only a single PD diagnosis were excluded ($n$ = 2082).

To reduce selection bias and maximize the control sample, each patient with PD was matched to four control participants based on age, sex, income, and geographical region. Controls were randomly ordered and selected sequentially. The index date for each patient with PD was defined as the date of the first PD diagnosis, and the same index date was assigned to their matched controls. A total of 8794 participants in the PD group and 35,176 participants in the control group were included in the final analysis (Figure 1).

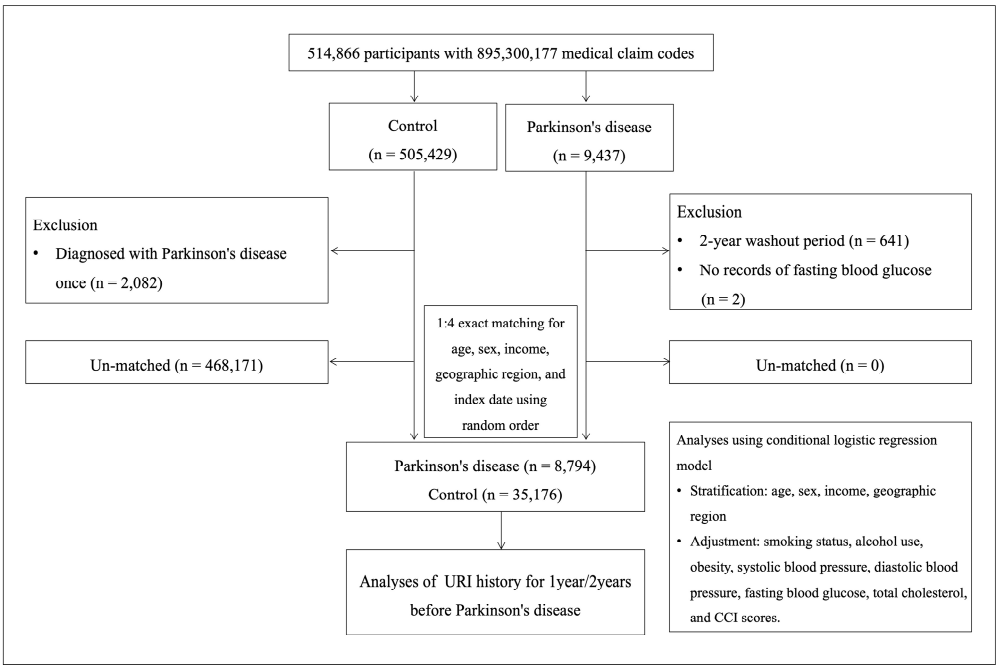



**Figure 1.** Flowchart illustrating the participant selection process. Among the 514,866 participants, 8794 participants with Parkinson's disease were matched with 35,176 controls based on age, sex, income, and geographic region.

### 2.3. Exposure

URIs were defined using specific ICD-10 codes: J00 (acute nasopharyngitis) and all codes from J02 (acute pharyngitis) to J069 (acute upper respiratory tract infection) [24]. Individuals with at least one registered diagnosis of URI during the study period were considered to have a history of URI.

### 2.4. Outcome

PD was defined using ICD-10 code G20 (Parkinson's disease). To improve diagnostic accuracy, we required at least two separate physician-recorded diagnoses of PD at different clinic visits. Although this approach increases diagnostic validity, it may exclude subclinical or misdiagnosed cases, which could result in underestimation of the true association. We selected exposure windows of 1 year and 2 years prior to PD diagnosis to focus on short-term infection history, as longer windows would likely overlap with the prodromal phase of PD and introduce greater uncertainty in temporal inference.

### 2.5. Covariates

Potential confounding variables were selected based on previous literature and included demographic factors (age, sex, geographical region, and income) and comorbidities (smoking status, alcohol use, obesity, systolic (SBP) and diastolic blood pressure (DBP), fasting blood glucose, and total cholesterol). The Charlson Comorbidity Index (CCI), which quantifies multimorbidity using 17 comorbidities, was used as a continuous variable ranging from 0 (no comorbidities) to 29 (multiple comorbidities).

Age was categorized into 10 groups in 5-year intervals starting from age 40. Income was stratified into five levels, from class 1 (lowest) to class 5 (highest). Geographical regions were classified as urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) or rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju). Smoking status was categorized as nonsmoker, a past smoker, or current smoker. Alcohol intake was recorded as $<1$ time/week or $\geq 1$ time/week. Obesity was assessed using body mass index (BMI, $kg/m^2$) and categorized using Asia-Pacific criteria from the Western Pacific Regional Office (WPRO) 2000: $<18.5$ (underweight), 18.5–22.9 (normal), 23–24.9 (overweight), 25–29.9 (obese I), and $\geq 30$ (obese II). SBP (mmHg), DBP (mmHg), fasting blood glucose (mg/dL), and total cholesterol (mg/dL) were also measured.

### 2.6. Statistical Analyses

Standardized differences were used to compare baseline characteristics between the PD and control groups (Table 1). Conditional logistic regression was applied to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between URI and PD, adjusting for matched variables (age, sex, income, and geographical region).

Model 1 was adjusted for smoking status, alcohol use, obesity, and CCI scores. Model 2 was further adjusted for SBP, DBP, fasting blood glucose, and total cholesterol (Table 2). URI history was categorized as $\geq 1$, $\geq 2$, or $\geq 3$ events within the previous year, and $\geq 1$ event within the previous 2 years. Subgroup analyses were performed across all covariates (Tables 2–5).

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-tailed $p$ value $< 0.05$ was considered statistically significant.

## 3. Results

The proportions of participants in the PD and control groups were well balanced across age, sex, income, and geographical region, as ensured by the matching process (all

standardized differences = 0.00, Table 1). Compared with controls, participants with PD were more likely to be nonsmokers, consume less alcohol, and have higher DBP, fasting glucose levels, and CCI scores (Table 1).

**Table 1.** General characteristics of participants.

| Characteristics | Total Participants | | |
|---|---|---|---|
| | PD | Control | Standardized Difference |
| Age (years old) (*n*, %) | | | 0.00 |
| 40–44 | 5 (0.06) | 20 (0.06) | |
| 45–49 | 66 (0.75) | 264 (0.75) | |
| 50–54 | 224 (2.55) | 896 (2.55) | |
| 55–59 | 498 (5.66) | 1992 (5.66) | |
| 60–64 | 883 (10.04) | 3532 (10.04) | |
| 65–69 | 1347 (15.32) | 5388 (15.32) | |
| 70–74 | 1950 (22.17) | 7800 (22.17) | |
| 75–79 | 2122 (24.13) | 8488 (24.13) | |
| 80–84 | 1293 (14.70) | 5172 (14.70) | |
| 85+ | 406 (4.62) | 1624 (4.62) | |
| Sex (*n*, %) | | | 0.00 |
| Male | 4204 (47.81) | 16,816 (47.81) | |
| Female | 4590 (52.19) | 18,360 (52.19) | |
| Income (*n*, %) | | | 0.00 |
| 1 (lowest) | 1624 (18.47) | 6496 (18.47) | |
| 2 | 952 (10.83) | 3808 (10.83) | |
| 3 | 1172 (13.33) | 4688 (13.33) | |
| 4 | 1691 (19.23) | 6764 (19.23) | |
| 5 (highest) | 3355 (38.15) | 13,420 (38.15) | |
| Geographic region (*n*, %) | | | 0.00 |
| Urban | 3326 (37.82) | 13,304 (37.82) | |
| Rural | 5468 (62.18) | 21,872 (62.18) | |
| Obesity † (*n*, %) | | | 0.02 |
| Underweight | 318 (3.62) | 1283 (3.65) | |
| Normal | 3098 (35.23) | 12,521 (35.60) | |
| Overweight | 2308 (26.25) | 9289 (26.41) | |
| Obese I | 2772 (31.52) | 10,988 (31.24) | |
| Obese II | 298 (3.39) | 1095 (3.11) | |
| Smoking status (*n*, %) | | | 0.09 |
| Nonsmoker | 6765 (76.93) | 25,888 (73.60) | |
| Past smoker | 1200 (13.65) | 5142 (14.62) | |
| Current smoker | 829 (9.43) | 4146 (11.79) | |
| Alcohol use (*n*, %) | | | 0.10 |
| <1 time a week | 6243 (70.99) | 23,295 (66.22) | |
| ≥1 time a week | 2551 (29.01) | 11,881 (33.78) | |
| Systolic blood pressure (*n*, %) | | | 0.00 |
| <120 mmHg | 2122 (24.13) | 8156 (23.19) | |
| 120–139 mmHg | 3967 (45.11) | 17,428 (49.55) | |
| ≥140 mmHg | 2705 (30.76) | 9592 (27.27) | |
| Diastolic blood pressure (*n*, %) | | | 0.11 |
| <80 mmHg | 3651 (41.52) | 16,604 (47.20) | |
| 80–89 mmHg | 3090 (35.14) | 12,529 (35.62) | |
| ≥90 mmHg | 2053 (23.35) | 6043 (17.18) | |
| Fasting blood glucose (*n*, %) | | | 0.11 |
| <100 mg/dL | 4613 (52.46) | 20,128 (57.22) | |
| 100–125 mg/dL | 2918 (33.18) | 11,078 (31.49) | |
| ≥126 mg/dL | 1263 (14.36) | 3970 (11.29) | |

**Table 1.** *Cont.*

| Characteristics | Total Participants | | |
|---|---|---|---|
| | PD | Control | Standardized Difference |
| Fasting blood glucose (*n*, %) | | | 0.11 |
| <100 mg/dL | 4613 (52.46) | 20,128 (57.22) | |
| 100–125 mg/dL | 2918 (33.18) | 11,078 (31.49) | |
| ≥126 mg/dL | 1263 (14.36) | 3970 (11.29) | |
| Total cholesterol (*n*, %) | | | 0.05 |
| <200 mg/dL | 5169 (58.78) | 19,833 (56.38) | |
| 200–239 mg/dL | 2501 (28.44) | 10,815 (30.75) | |
| ≥240 mg/dL | 1124 (12.78) | 4528 (12.87) | |
| CCI score (*n*, %) | | | 0.29 |
| 0 | 2649 (30.12) | 16,827 (47.84) | |
| 1 | 2030 (23.08) | 6867 (19.52) | |
| ≥2 | 4115 (46.79) | 11,482 (32.64) | |
| The number of URIs (Mean, Standard deviation) | | | |
| within 1 year | 1.72 (3.89) | 1.67 (3.28) | 0.01 |
| within 2 years | 3.50 (6.75) | 3.35 (5.66) | 0.02 |

CCI, Charlson comorbidity index; PD, Parkinson's disease; URI, upper respiratory tract infection. † Obesity (BMI, body mass index, kg/m$^2$) was categorized as <18.5 (underweight), ≥18.5 to <23 (normal), ≥23 to <25 (overweight), ≥25 to <30 (obese I), and ≥30 (obese II).

The mean number of URIs within 1 year was 1.72 in the PD group and 1.67 in the control group. Within 2 years, the means were 3.5 and 3.35, respectively. These differences were statistically significant ($p < 0.05$ for both comparisons, Table 1).

A significant inverse association was observed between a history of URI within 1 year prior to the index date and the subsequent diagnosis of PD. Specifically, participants with ≥1 URI had an adjusted OR of 0.93 (95% CI: 0.88–0.97, Table 2); those with ≥2 URIs had an OR of 0.91 (95% CI: 0.87–0.96, Table 3); and those with ≥3 URIs had an OR of 0.92 (95% CI: 0.87–0.98, Table 4). Participants who experienced ≥1, ≥2, or ≥3 URIs consistently demonstrated a decreased odds of PD even after various stratifications (Tables 2–4).

However, no significant associations were observed in certain subgroups, including participants aged <65 years, males, individuals with high income, rural residents, those who were underweight or of normal weight, past and current smokers, those consuming alcohol ≥1 time per week, individuals with high blood pressure, and those with a CCI score of 0. The remaining subgroups showed a consistent inverse relationship between URI and the development of PD (Tables 2–4).

When URI history within 2 years prior to the index date was examined, the inverse association between URI and PD was no longer statistically significant (adjusted OR: 0.97, 95% CI: 0.92–1.01, Table 5). Subgroup analysis also revealed no significant associations, except among participants with a CCI core of 1 (Table 5).

**Table 2.** Crude and adjusted odds ratios for the association between ≥1 event of URI history within 1 year and PD.

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| Total (*n* = 43,970) | | | | | | | | |
| No URI | 4706/8794 (53.5%) | 18,170/35,176 (51.7%) | 1 | | 1 | | 1 | |
| ≥1 URI | 4088/8794 (46.5%) | 17,006/35,176 (48.4%) | 0.93 (0.89–0.97) | 0.002 * | 0.92 (0.88–0.96) | 0.001 * | 0.93 (0.88–0.97) | 0.001 * |

**Table 2.** *Cont.*

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| Age < 65 years old (*n* = 8380) | | | | | | | | |
| No URI | 948/1676 (56.6%) | 3665/6704 (54.7%) | 1 | | 1 | | 1 | |
| ≥1 URI | 728/1676 (43.4%) | 3039/6704 (45.3%) | 0.93 (0.83–1.03) | 0.163 | 0.93 (0.88–0.98) | 0.005 * | 0.90 (0.80–1.00) | 0.059 |
| Age ≥ 65 years old (*n* = 35,590) | | | | | | | | |
| No URI | 3758/7118 (52.8%) | 14,505/28,472 (50.9%) | 1 | | 1 | | 1 | |
| ≥1 URI | 3360/7118 (47.2%) | 13,967/28,472 (49.1%) | 0.93 (0.88–0.98) | 0.005 * | 0.94 (0.89–0.99) | 0.014 * | 0.93 (0.88–0.98) | 0.009 * |
| Men (*n* = 21,020) | | | | | | | | |
| No URI | 2308/4204 (54.9%) | 9215/16,816 (54.8%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1896/4204 (45.1%) | 7601/16,816 (45.2%) | 1.00 (0.93–1.07) | 0.906 | 1.00 (0.94–1.08) | 0.905 | 0.99 (0.92–1.06) | 0.722 |
| Women (*n* = 22,950) | | | | | | | | |
| No URI | 2398/4590 (52.2%) | 8955/18,360 (48.8%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2192/4590 (47.8%) | 9405/18,360 (51.2%) | 0.87 (0.82–0.93) | <0.001 * | 0.88 (0.82–0.94) | <0.001 * | 0.88 (0.82–0.94) | <0.001 * |
| Low income (*n* = 18,740) | | | | | | | | |
| No URI | 2044/3748 (54.5%) | 7757/14,992 (51.7%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1704/3748 (45.5%) | 7235/14,992 (48.3%) | 0.89 (0.83–0.96) | 0.002 * | 0.90 (0.84–0.97) | 0.005 * | 0.88 (0.82–0.95) | 0.001 * |
| High income (*n* = 25,230) | | | | | | | | |
| No URI | 2662/5046 (52.8%) | 10,413/20,184 (51.6%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2384/5046 (47.3%) | 9771/20,184 (48.4%) | 0.95 (0.90–1.02) | 0.139 | 0.96 (0.90–1.02) | 0.213 | 0.95 (0.90–1.02) | 0.148 |
| Urban residents (*n* = 16,630) | | | | | | | | |
| No URI | 1864/3326 (56.0%) | 1864/3326 (56.0%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1462/3326 (44.0%) | 1462/3326 (44.0%) | 0.88 (0.82–0.95) | 0.001 * | 0.89 (0.82–0.96) | 0.002 * | 0.88 (0.81–0.95) | 0.001 * |
| Rural residents (*n* = 27,340) | | | | | | | | |
| No URI | 2842/5468 (52.0%) | 11,132/21,872 (50.9%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2626/5468 (48.0%) | 10,740/21,872 (49.1%) | 0.96 (0.90–1.02) | 0.154 | 0.97 (0.91–1.02) | 0.251 | 0.95 (0.90–1.01) | 0.122 |
| Underweight (*n* = 1601) | | | | | | | | |
| No URI | 179/318 (56.3%) | 720/1283 (56.1%) | 1 | | 1 | | 1 | |
| ≥1 URI | 139/318 (43.7%) | 563/1283 (43.9%) | 0.99 (0.78–1.27) | 0.956 | 1.02 (0.79–1.31) | 0.871 | 0.98 (0.76–1.26) | 0.876 |
| Normal weight (*n* = 15,619) | | | | | | | | |
| No URI | 1659/3098 (53.6%) | 6563/12,521 (52.4%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1439/3098 (46.5%) | 5958/12,521 (47.6%) | 0.96 (0.88–1.03) | 0.258 | 0.96 (0.89–1.04) | 0.357 | 0.96 (0.88–1.04) | 0.264 |
| Overweight (*n* = 11,597) | | | | | | | | |
| No URI | 1235/2308 (53.5%) | 4718/9289 (50.8%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1073/2308 (46.5%) | 4571/9289 (49.2%) | 0.90 (0.82–0.98) | 0.019 * | 0.90 (0.82–0.99) | 0.025 * | 0.91 (0.84–0.99) | 0.022 * |
| Obese (*n* = 15,153) | | | | | | | | |
| No URI | 1633/3070 (53.2%) | 6169/12,083 (51.1%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1437/3070 (46.8%) | 5914/12,083 (48.9%) | 0.92 (0.85–0.99) | 0.034 * | 0.92 (0.85–1.00) | 0.049 * | 0.91 (0.84–0.99) | 0.022 * |
| Nonsmokers (*n* = 32,653) | | | | | | | | |
| No URI | 3585/6765 (53.0%) | 13,021/25,888 (50.3%) | 1 | | 1 | | 1 | |
| ≥1 URI | 3180/6765 (47.0%) | 12,867/25,888 (49.7%) | 0.90 (0.85–0.95) | <0.001 * | 0.91 (0.86–0.96) | <0.001 * | 0.91 (0.86–0.96) | <0.001 * |
| Past and current smokers (*n* = 11,317) | | | | | | | | |
| No URI | 1121/2029 (55.3%) | 5149/9288 (55.4%) | 1 | | 1 | | 1 | |
| ≥1 URI | 908/2029 (44.8%) | 4139/9288 (44.6%) | 1.01 (0.91–1.11) | 0.877 | 1.01 (0.92–1.12) | 0.784 | 0.99 (0.89–1.09) | 0.765 |
| Alcohol use < 1 time a week (*n* = 29,538) | | | | | | | | |
| No URI | 3288/6243 (52.7%) | 11,775/23,295 (50.6%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2955/6243 (47.3%) | 11,520/23,295 (49.5%) | 0.92 (0.87–0.97) | 0.003 * | 0.93 (0.88–0.98) | 0.011 * | 0.92 (0.87–0.98) | 0.005 * |
| Alcohol use ≥ 1 time a week (*n* = 14,432) | | | | | | | | |
| No URI | 1418/2551 (55.6%) | 6395/11,881 (53.8%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1133/2551 (44.4%) | 5486/11,881 (46.2%) | 0.93 (0.85–1.02) | 0.105 | 0.93 (0.85–1.02) | 0.105 | 0.93 (0.85–1.01) | 0.090 |

**Table 2.** *Cont.*

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| SBP < 140 mmHg and DBP < 90 mmHg (*n* = 30,119) | | | | | | | | |
| No URI | 2937/5669 (51.8%) | 12,343/24,450 (50.5%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2732/5669 (48.2%) | 12,107/24,450 (49.5%) | 0.95 (0.90–1.00) | 0.072 | 0.95 (0.90–1.01) | 0.077 | 0.93 (0.88–0.99) | 0.024 * |
| SBP ≥ 140 mmHg or DBP ≥ 90 mmHg (*n* = 13,851) | | | | | | | | |
| No URI | 1769/3125 (56.6%) | 5827/10,726 (54.3%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1356/3125 (43.4%) | 4899/10,726 (45.7%) | 0.91 (0.84–0.99) | 0.024 * | 0.93 (0.86–1.01) | 0.096 | 0.93 (0.86–1.01) | 0.074 |
| Fasting blood glucose < 100 mg/dL (*n* = 24,741) | | | | | | | | |
| No URI | 2409/4613 (52.2%) | 10,164/20,128 (50.5%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2204/4613 (47.8%) | 9964/20,128 (49.5%) | 0.93 (0.88–0.99) | 0.035 * | 0.94 (0.88–1.00) | 0.043 * | 0.93 (0.87–0.99) | 0.021 * |
| Fasting blood glucose ≥ 100 mg/dL (*n* = 19,229) | | | | | | | | |
| No URI | 2297/4181 (54.9%) | 8006/15,048 (53.2%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1884/4181 (45.1%) | 7042/15,048 (46.8%) | 0.93 (0.87–1.00) | 0.047 * | 0.93 (0.87–1.00) | 0.056 | 0.92 (0.86–0.99) | 0.024 * |
| Total cholesterol < 200 mg/dL (*n* = 25,002) | | | | | | | | |
| No URI | 2765/5169 (53.5%) | 10,264/19,833 (51.8%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2404/5169 (46.5%) | 9569/19,833 (48.3%) | 0.93 (0.88–0.99) | 0.026 * | 0.94 (0.89–1.01) | 0.072 | 0.93 (0.88–0.99) | 0.034 * |
| Total cholesterol ≥ 200 mg/dL (*n* = 18,968) | | | | | | | | |
| No URI | 1941/3625 (53.5%) | 1941/3625 (53.5%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1684/3625 (46.5%) | 1684/3625 (46.5%) | 0.92 (0.86–0.99) | 0.029 * | 0.92 (0.86–0.99) | 0.033 * | 0.91 (0.85–0.98) | 0.016 * |
| CCI scores = 0 (*n* = 19,476) | | | | | | | | |
| No URI | 1404/2649 (53.0%) | 8765/16,827 (52.1%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1245/2649 (47.0%) | 8062/16,827 (47.9%) | 0.96 (0.89–1.05) | 0.383 | 0.97 (0.90–1.06) | 0.537 | 0.97 (0.89–1.05) | 0.402 |
| CCI score = 1 (*n* = 8897) | | | | | | | | |
| No URI | 1090/2030 (53.7%) | 3479/6867 (50.7%) | 1 | | 1 | | 1 | |
| ≥1 URI | 940/2030 (46.3%) | 3388/6867 (49.3%) | 0.89 (0.80–0.98) | 0.016 * | 0.89 (0.80–0.98) | 0.022 * | 0.88 (0.80–0.98) | 0.015 * |
| CCI score ≥ 2 (*n* = 15,597) | | | | | | | | |
| No URI | 2212/4115 (53.8%) | 5926/11,482 (51.6%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1903/4115 (46.3%) | 5556/11,482 (48.4%) | 0.92 (0.85–0.99) | 0.018 * | 0.91 (0.85–0.98) | 0.009 * | 0.90 (0.84–0.97) | 0.005 * |

CCI, Charlson Comorbidity Index; DBP, Diastolic blood pressure; PD, Parkinson's disease; SBP, Systolic blood pressure; URI, upper respiratory tract infection. * Conditional or unconditional logistic regression analysis, significance at $p < 0.05$. † Stratified model for age, sex, income, and geographic region. ‡ Model 1 was adjusted for smoking status, alcohol use, obesity, and CCI scores. § Model 2 was adjusted for model 1 plus total cholesterol, SBP, DBP, and fasting blood glucose.

**Table 3.** Crude and adjusted odds ratios for the association between ≥2 events of URI history within 1 year and PD.

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| Total (*n* = 43,970) | | | | | | | | |
| No URI | 6168/8794 (70.1%) | 24,047/35,176 (68.4%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 2626/8794 (29.9%) | 11,129/35,176 (31.6%) | 0.92 (0.87–0.97) | 0.001 * | 0.91 (0.87–0.96) | 0.001 * | 0.91 (0.87–0.96) | 0.001 * |
| Age < 65 years old (*n* = 8380) | | | | | | | | |
| No URI | 1237/1676 (73.8%) | 4858/6704 (72.5%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 439/1676 (26.2%) | 1846/6704 (27.5%) | 0.93 (0.83–1.05) | 0.270 | 0.93 (0.82–1.05) | 0.263 | 0.90 (0.79–1.02) | 0.096 |
| Age ≥ 65 years old (*n* = 35,590) | | | | | | | | |
| No URI | 4931/7118 (69.3%) | 19,189/28,472 (67.4%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 2187/7118 (30.7%) | 9283/28,472 (32.6%) | 0.92 (0.87–0.97) | 0.002 * | 0.92 (0.87–0.98) | 0.005 * | 0.92 (0.87–0.97) | 0.003 * |
| Men (*n* = 21,020) | | | | | | | | |
| No URI | 3011/4204 (71.6%) | 11,980/16,816 (71.2%) | 1 | | 1 | | 1 | |

**Table 3.** *Cont.*

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| ≥2 URIs | 1193/4204 (28.4%) | 4836/16,816 (28.8%) | 0.98 (0.91–1.06) | 0.626 | 0.99 (0.92–1.07) | 0.770 | 0.97 (0.90–1.05) | 0.413 |
| Women (*n* = 22,950) | | | | | | | | |
| No URI | 3157/4590 (68.8%) | 12,067/18,360 (65.7%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1433/4590 (31.2%) | 6293/18,360 (34.3%) | 0.87 (0.81–0.93) | <0.001 * | 0.88 (0.82–0.94) | <0.001 * | 0.87 (0.81–0.94) | <0.001 * |
| Low income (*n* = 18,740) | | | | | | | | |
| No URI | 2653/3748 (70.8%) | 10,245/14,992 (68.3%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1095/3748 (29.2%) | 4747/14,992 (31.7%) | 0.89 (0.82–0.96) | 0.004 * | 0.89 (0.83–0.97) | 0.006 * | 0.87 (0.81–0.95) | 0.001 * |
| High income (*n* = 25,230) | | | | | | | | |
| No URI | 3515/5046 (69.7%) | 13,802/20,184 (68.4%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1531/5046 (30.3%) | 6382/20,184 (31.6%) | 0.94 (0.88–1.01) | 0.080 | 0.95 (0.89–1.01) | 0.120 | 0.94 (0.88–1.01) | 0.087 |
| Urban residents (*n* = 16,630) | | | | | | | | |
| No URI | 2380/3326 (71.6%) | 9219/13,304 (69.3%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 946/3326 (28.4%) | 4085/13,304 (30.7%) | 0.90 (0.82–0.98) | 0.011 * | 0.90 (0.83–0.98) | 0.016 * | 0.89 (0.82–0.97) | 0.008 * |
| Rural residents (*n* = 27,340) | | | | | | | | |
| No URI | 3788/5468 (69.3%) | 14,828/21,872 (67.8%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1680/5468 (30.7%) | 7044/21,872 (32.2%) | 0.93 (0.88–1.00) | 0.036 * | 0.94 (0.88–1.00) | 0.054 | 0.93 (0.87–0.99) | 0.022 * |
| Underweight (*n* = 1601) | | | | | | | | |
| No URI | 224/318 (70.4%) | 915/1283 (71.3%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 94/318 (29.6%) | 368/1283 (28.7%) | 1.04 (0.80–1.37) | 0.756 | 1.07 (0.82–1.41) | 0.623 | 1.04 (0.79–1.37) | 0.790 |
| Normal weight (*n* = 15,619) | | | | | | | | |
| No URI | 2193/3098 (70.8%) | 8702/12,521 (69.5%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 905/3098 (29.2%) | 3819/12,521 (30.5%) | 0.94 (0.86–1.03) | 0.162 | 0.95 (0.87–1.03) | 0.219 | 0.94 (0.86–1.02) | 0.143 |
| Overweight (*n* = 11,597) | | | | | | | | |
| No URI | 1615/2308 (70.0%) | 6234/9289 (67.1%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 693/2308 (30.0%) | 3055/9289 (32.9%) | 0.88 (0.79–0.97) | 0.009 * | 0.88 (0.80–0.97) | 0.011 * | 0.87 (0.79–0.96) | 0.006 * |
| Obese (*n* = 15,153) | | | | | | | | |
| No URI | 2136/3070 (69.6%) | 8196/12,083 (67.8%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 934/3070 (30.4%) | 3887/12,083 (32.2%) | 0.92 (0.85–1.00) | 0.064 | 0.92 (0.85–1.01) | 0.066 | 0.91 (0.84–0.99) | 0.036 * |
| Nonsmokers (*n* = 32,653) | | | | | | | | |
| No URI | 4716/6765 (69.7%) | 17,404/25,888 (67.2%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 2049/6765 (30.3%) | 8484/25,888 (32.8%) | 0.89 (0.84–0.94) | <0.001 * | 0.90 (0.85–0.96) | 0.001 * | 0.90 (0.85–0.95) | <0.001 * |
| Past and current smokers (*n* = 11,317) | | | | | | | | |
| No URI | 1452/2029 (71.6%) | 6643/9288 (71.5%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 577/2029 (28.4%) | 2645/9288 (28.5%) | 1.00 (0.90–1.11) | 0.971 | 1.00 (0.90–1.11) | 0.994 | 0.97 (0.87–1.08) | 0.567 |
| Alcohol use < 1 time a week (*n* = 29,538) | | | | | | | | |
| No URI | 4326/6243 (69.3%) | 15,618/23,295 (67.0%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1917/6243 (30.7%) | 7677/23,295 (33.0%) | 0.90 (0.85–0.96) | 0.001 * | 0.91 (0.86–0.97) | 0.002 * | 0.90 (0.85–0.96) | 0.001 * |
| Alcohol use ≥ 1 time a week (*n* = 14,432) | | | | | | | | |
| No URI | 1842/2551 (72.2%) | 8429/11,881 (71.0%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 709/2551 (27.8%) | 3452/11,881 (29.1%) | 0.94 (0.85–1.03) | 0.202 | 0.94 (0.85–1.04) | 0.215 | 0.94 (0.85–1.03) | 0.202 |
| SBP < 140 mmHg and DBP < 90 mmHg (*n* = 30,119) | | | | | | | | |
| No URI | 3912/5669 (69.0%) | 16,491/24,450 (67.5%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1757/5669 (31.0%) | 7959/24,450 (32.6%) | 0.93 (0.87–0.99) | 0.024 * | 0.93 (0.88–0.99) | 0.027 * | 0.92 (0.86–0.98) | 0.007 * |
| SBP ≥ 140 mmHg or DBP ≥ 90 mmHg (*n* = 13,851) | | | | | | | | |
| No URI | 2256/3125 (72.2%) | 7556/10,726 (70.5%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 869/3125 (27.8%) | 3170/10,726 (29.6%) | 0.92 (0.84–1.00) | 0.059 | 0.93 (0.85–1.02) | 0.117 | 0.93 (0.85–1.01) | 0.092 |
| Fasting blood glucose < 100 mg/dL (*n* = 24,741) | | | | | | | | |
| No URI | 3184/4613 (69.0%) | 13,599/20,128 (67.6%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1429/4613 (31.0%) | 6529/20,128 (32.4%) | 0.93 (0.87–1.00) | 0.056 | 0.94 (0.87–1.00) | 0.063 | 0.93 (0.86–0.99) | 0.034 * |
| Fasting blood glucose ≥ 100 mg/dL (*n* = 19,229) | | | | | | | | |
| No URI | 2984/4181 (71.4%) | 10,448/15,048 (69.4%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1197/4181 (28.6%) | 4600/15,048 (30.6%) | 0.91 (0.84–0.98) | 0.016 * | 0.91 (0.84–0.98) | 0.016 * | 0.90 (0.83–0.97) | 0.005 * |

**Table 3.** *Cont.*

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| Total cholesterol < 200 mg/dL (*n* = 25,002) | | | | | | | | |
| No URI | 3614/5169 (69.9%) | 13,573/19,833 (68.4%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1555/5169 (30.1%) | 6260/19,833 (31.6%) | 0.93 (0.87–1.00) | 0.041 * | 0.94 (0.88–1.01) | 0.092 | 0.93 (0.87–1.00) | 0.041 * |
| Total cholesterol ≥ 200 mg/dL (*n* = 18,968) | | | | | | | | |
| No URI | 2554/3625 (70.5%) | 10,474/15,343 (68.3%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1071/3625 (29.5%) | 4869/15,343 (31.7%) | 0.90 (0.83–0.98) | 0.011 * | 0.90 (0.83–0.97) | 0.009 * | 0.89 (0.82–0.96) | 0.004 * |
| CCI scores = 0 (*n* = 19,476) | | | | | | | | |
| No URI | 1853/2649 (70.0%) | 11,669/16,827 (69.4%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 796/2649 (30.1%) | 5158/16,827 (30.7%) | 0.97 (0.89–1.06) | 0.532 | 0.99 (0.90–1.08) | 0.787 | 0.98 (0.9–1.07) | 0.664 |
| CCI score = 1 (*n* = 8897) | | | | | | | | |
| No URI | 1440/2030 (70.9%) | 4590/6867 (66.8%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 590/2030 (29.1%) | 2277/6867 (33.2%) | 0.83 (0.74–0.92) | 0.001 * | 0.82 (0.74–0.92) | 0.001 * | 0.82 (0.73–0.91) | <0.001 * |
| CCI score ≥ 2 (*n* = 15,597) | | | | | | | | |
| No URI | 2875/4115 (69.9%) | 7788/11,482 (67.8%) | 1 | | 1 | | 1 | |
| ≥2 URIs | 1240/4115 (30.1%) | 3694/11,482 (32.2%) | 0.91 (0.84–0.98) | 0.016 * | 0.90 (0.84–0.98) | 0.010 * | 0.90 (0.83–0.97) | 0.006 * |

CCI, Charlson Comorbidity Index; DBP, Diastolic blood pressure; PD, Parkinson's disease; SBP, Systolic blood pressure; URI, upper respiratory tract infection. * Conditional or unconditional logistic regression analysis, significance at $p < 0.05$. † Stratified model for age, sex, income, and geographic region. ‡ Model 1 was adjusted for smoking status, alcohol use, obesity, and CCI scores. § Model 2 was adjusted for model 1 plus total cholesterol, SBP, DBP, and fasting blood glucose.

**Table 4.** Crude and adjusted odds ratios for the association between ≥3 events of URI history within 1 year and PD.

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| Total (*n* = 43,970) | | | | | | | | |
| No URI | 7005/8794 (79.7%) | 27,600/35,176 (78.5%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 1789/8794 (20.3%) | 7576/35,176 (21.5%) | 0.93 (0.88–0.99) | 0.015 * | 0.92 (0.87–0.98) | 0.006 * | 0.92 (0.87–0.98) | 0.008 * |
| Age < 65 years old (*n* = 8380) | | | | | | | | |
| No URI | 1411/1676 (84.2%) | 5541/6704 (82.7%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 265/1676 (15.8%) | 1163/6704 (17.4%) | 0.89 (0.77–1.04) | 0.135 | 0.90 (0.77–1.04) | 0.151 | 0.87 (0.75–1.01) | 0.074 |
| Age ≥ 65 years old (*n* = 35,590) | | | | | | | | |
| No URI | 5594/7118 (78.6%) | 22,059/28,472 (77.5%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 1524/7118 (21.4%) | 6413/28,472 (22.5%) | 0.94 (0.88–1.00) | 0.044 * | 0.94 (0.88–1.00) | 0.067 | 0.94 (0.88–1.00) | 0.041 * |
| Men (*n* = 21,020) | | | | | | | | |
| No URI | 3399/4204 (80.9%) | 13,544/16,816 (80.5%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 805/4204 (19.2%) | 3272/16,816 (19.5%) | 0.98 (0.90–1.07) | 0.651 | 0.99 (0.91–1.08) | 0.853 | 0.98 (0.89–1.06) | 0.581 |
| Women (*n* = 22,950) | | | | | | | | |
| No URI | 3606/4590 (78.6%) | 14,056/18,360 (76.6%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 984/4590 (21.4%) | 4304/18,360 (23.4%) | 0.89 (0.82–0.96) | 0.004 * | 0.89 (0.83–0.97) | 0.005 * | 0.89 (0.82–0.96) | 0.003 * |
| Low income (*n* = 18,740) | | | | | | | | |
| No URI | 2997/3748 (80.0%) | 11,766/14,992 (78.5%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 751/3748 (20.0%) | 3226/14,992 (21.5%) | 0.91 (0.84–1.00) | 0.047 * | 0.92 (0.84–1.01) | 0.072 | 0.91 (0.83–0.99) | 0.032 * |
| High income (*n* = 25,230) | | | | | | | | |
| No URI | 4008/5046 (79.4%) | 15,834/20,184 (78.5%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 1038/5046 (20.6%) | 4350/20,184 (21.6%) | 0.94 (0.87–1.02) | 0.128 | 0.95 (0.88–1.02) | 0.168 | 0.94 (0.87–1.01) | 0.104 |

**Table 4.** *Cont.*

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| Urban residents (*n* = 16,630) | | | | | | | | |
| No URI | 2677/3326 (80.5%) | 10,464/13,304 (78.7%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 649/3326 (19.5%) | 2840/13,304 (21.4%) | 0.89 (0.81–0.98) | 0.020 * | 0.90 (0.82–0.99) | 0.031 * | 0.89 (0.80–0.98) | 0.014 * |
| Rural residents (*n* = 27,340) | | | | | | | | |
| No URI | 4328/5468 (79.2%) | 17,136/21,872 (78.4%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 1140/5468 (20.9%) | 4736/21,872 (21.7%) | 0.95 (0.89–1.02) | 0.195 | 0.96 (0.89–1.03) | 0.252 | 0.95 (0.88–1.02 | 0.148 |
| Underweight (*n* = 1601) | | | | | | | | |
| No URI | 255/318 (80.2%) | 1042/1283 (81.2%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 63/318 (19.8%) | 241/1283 (18.8%) | 1.07 (0.78–1.46) | 0.676 | 1.09 (0.80–1.49) | 0.585 | 1.05 (0.77–1.44) | 0.769 |
| Normal weight (*n* = 15,619) | | | | | | | | |
| No URI | 2496/3098 (80.6%) | 9934/12,521 (79.3%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 602/3098 (19.4%) | 2587/12,521 (20.7%) | 0.93 (0.84–1.02) | 0.129 | 0.94 (0.85–1.03) | 0.189 | 0.92 (0.84–1.02) | 0.122 |
| Overweight (*n* = 11,597) | | | | | | | | |
| No URI | 1833/2308 (79.4%) | 7155/9289 (77.0%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 475/2308 (20.6%) | 2134/9289 (23.0%) | 0.87 (0.78–0.97) | 0.014 * | 0.87 (0.78–0.97) | 0.015 * | 0.86 (0.77–0.96) | 0.010 * |
| Obese (*n* = 15,153) | | | | | | | | |
| No URI | 2421/3070 (78.9%) | 9469/12,083 (78.4%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 649/3070 (21.1%) | 2614/12,083 (21.6%) | 0.97 (0.88–1.07) | 0.554 | 0.97 (0.88–1.07) | 0.550 | 0.96 (0.87–1.06) | 0.143 |
| Nonsmokers (*n* = 32,653) | | | | | | | | |
| No URI | 5355/6765 (79.2%) | 20,129/25,888 (77.8%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 1410/6765 (20.8%) | 5759/25,888 (22.3%) | 0.92 (0.86–0.98) | 0.013 * | 0.93 (0.87–0.99) | 0.032 * | 0.92 (0.86–0.99) | 0.017 * |
| Past and current smokers (*n* = 11,317) | | | | | | | | |
| No URI | 1650/2029 (81.3%) | 7471/9288 (80.4%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 379/2029 (18.7%) | 1817/9288 (19.6%) | 0.94 (0.84–1.07) | 0.362 | 0.95 (0.84–1.07) | 0.397 | 0.92 (0.81–1.05) | 0.208 |
| Alcohol use < 1 time a week (*n* = 29,538) | | | | | | | | |
| No URI | 4945/6243 (79.2%) | 18,091/23,295 (77.7%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 1298/6243 (20.8%) | 5204/23,295 (22.3%) | 0.91 (0.85–0.98) | 0.009 * | 0.92 (0.86–0.99) | 0.022 * | 0.91 (0.85–0.98) | 0.008 * |
| Alcohol use ≥ 1 time a week (*n* = 14,432) | | | | | | | | |
| No URI | 2060/2551 (80.8%) | 9509/11,881 (80.0%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 491/2551 (19.3%) | 2372/11,881 (20.0%) | 0.96 (0.86–1.06) | 0.410 | 0.96 (0.86–1.07) | 0.419 | 0.95 (0.85–1.06) | 0.389 |
| SBP < 140 mmHg and DBP < 90 mmHg (*n* = 30,119) | | | | | | | | |
| No URI | 4471/5669 (78.9%) | 19,009/24,450 (77.8%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 1198/5669 (21.1%) | 5441/24,450 (22.3%) | 0.94 (0.87–1.00) | 0.067 | 0.94 (0.87–1.00) | 0.065 | 0.92 (0.86–0.99) | 0.021 * |
| SBP ≥ 140 mmHg or DBP ≥ 90 mmHg (*n* = 13,851) | | | | | | | | |
| No URI | 2534/3125 (81.1%) | 8591/10,726 (80.1%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 591/3125 (18.9%) | 2135/10,726 (19.9%) | 0.94 (0.85–1.04) | 0.219 | 0.96 (0.87–1.06) | 0.426 | 0.95 (0.86–1.06) | 0.351 |
| Fasting blood glucose < 100 mg/dL (*n* = 24,741) | | | | | | | | |
| No URI | 3655/4613 (79.2%) | 15,699/20,128 (78.0%) | 1 | | 1 | | | |
| ≥3 URIs | 958/4613 (20.8%) | 4429/20,128 (22.0%) | 0.93 (0.86–1.01) | 0.066 | 0.93 (0.86–1.01) | 0.083 | 0.92 (0.85–1.00) | 0.048 * |
| Fasting blood glucose ≥ 100 mg/dL (*n* = 19,229) | | | | | | | | |
| No URI | 3350/4181 (80.1%) | 11,901/15,048 (79.1%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 831/4181 (19.9%) | 3147/15,048 (20.9%) | 0.94 (0.86–1.02) | 0.143 | 0.94 (0.86–1.02) | 0.152 | 0.92 (0.85–1.01) | 0.067 |
| Total cholesterol < 200 mg/dL (*n* = 25,002) | | | | | | | | |
| No URI | 4130/5169 (79.9%) | 15,669/19,833 (79.0%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 1039/5169 (20.1%) | 4164/19,833 (21.0%) | 0.95 (0.88–1.02) | 0.158 | 0.96 (0.89–1.04) | 0.295 | 0.95 (0.88–1.02) | 0.158 |
| Total cholesterol ≥ 200 mg/dL (*n* = 18,968) | | | | | | | | |
| No URI | 2875/3625 (79.3%) | 11,931/15,343 (77.8%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 750/3625 (20.7%) | 3412/15,343 (22.2%) | 0.91 (0.83–1.00) | 0.043 * | 0.90 (0.83–0.99) | 0.028 * | 0.90 (0.82–0.98) | 0.018 * |

**Table 4.** *Cont.*

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| CCI scores = 0 (*n* = 19,476) | | | | | | | | |
| No URI | 2104/2649 (79.4%) | 13,397/16,827 (79.6%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 2104/2649 (79.4%) | 13,397/16,827 (79.6%) | 1.01 (0.91–1.12) | 0.821 | 1.03 (0.93–1.14) | 0.524 | 1.03 (0.93–1.14) | 0.587 |
| CCI score = 1 (*n* = 8897) | | | | | | | | |
| No URI | 1616/2030 (79.6%) | 5307/6867 (77.3%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 414/2030 (20.4%) | 1560/6867 (22.7%) | 0.87 (0.77–0.98) | 0.027 * | 0.88 (0.78–0.99) | 0.034 * | 0.87 (0.77–0.99) | 0.029 * |
| CCI score ≥ 2 (*n* = 15,597) | | | | | | | | |
| No URI | 3285/4115 (79.8%) | 8896/11,482 (77.5%) | 1 | | 1 | | 1 | |
| ≥3 URIs | 830/4115 (20.2%) | 2586/11,482 (22.5%) | 0.87 (0.80–0.95) | 0.002 * | 0.86 (0.79–0.94) | 0.001 * | 0.86 (0.78–0.94) | 0.001 * |

CCI, Charlson Comorbidity Index; DBP, Diastolic blood pressure; PD, Parkinson's disease; SBP, Systolic blood pressure; URI, upper respiratory tract infection. * Conditional or unconditional logistic regression analysis, significance at $p < 0.05$. † Stratified model for age, sex, income, and geographic region. ‡ Model 1 was adjusted for smoking status, alcohol use, obesity, and CCI scores. § Model 2 was adjusted for model 1 plus total cholesterol, SBP, DBP, and fasting blood glucose.

**Table 5.** Crude and adjusted odds ratios for the association between ≥1 event of URI history within 2 years and PD.

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| Total (*n* = 43,970) | | | | | | | | |
| No URI | 3149/8794 (35.8%) | 12,374/35,176 (35.2%) | 1 | | 1 | | 1 | |
| ≥1 URI | 5645/8794 (64.2%) | 22,802/35,176 (64.8%) | 0.97 (0.93–1.02) | 0.267 | 0.96 (0.91–1.01) | 0.093 | 0.97 (0.92–1.01) | 0.162 |
| Age < 65 years old (*n* = 8380) | | | | | | | | |
| No URI | 643/1676 (38.4%) | 2556/6704 (38.1%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1033/1676 (61.6%) | 4148/6704 (61.9%) | 0.99 (0.89–1.11) | 0.857 | 1.00 (0.89–1.11) | 0.945 | 0.96 (0.85–1.07) | 0.449 |
| Age ≥ 65 years old (*n* = 35,590) | | | | | | | | |
| No URI | 2506/7118 (35.2%) | 9818/28,472 (34.5%) | 1 | | 1 | | 1 | |
| ≥1 URI | 4612/7118 (64.8%) | 18,654/28,472 (65.5%) | 0.97 (0.92–1.02) | 0.250 | 0.98 (0.93–1.03) | 0.425 | 0.97 (0.92–1.02) | 0.256 |
| Men (*n* = 21,020) | | | | | | | | |
| No URI | 1608/4204 (38.3%) | 6475/16,816 (38.5%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2596/4204 (61.8%) | 10,341/16,816 (61.5%) | 1.01 (0.94–1.08) | 0.761 | 1.02 (0.95–1.10) | 0.526 | 1.00 (0.93–1.07) | 0.986 |
| Women (*n* = 22,950) | | | | | | | | |
| No URI | 1541/4590 (33.6%) | 5899/18,360 (32.1%) | 1 | | 1 | | 1 | |
| ≥1 URI | 3049/4590 (66.4%) | 12,461/18,360 (67.9%) | 0.94 (0.87–1.00) | 0.062 | 0.94 (0.88–1.01) | 0.092 | 0.94 (0.87–1.00) | 0.061 |
| Low income (*n* = 18,740) | | | | | | | | |
| No URI | 1373/3748 (36.6%) | 5362/14,992 (35.8%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2375/3748 (63.4%) | 9630/14,992 (64.2%) | 0.96 (0.89–1.04) | 0.321 | 0.97 (0.90–1.05) | 0.477 | 0.95 (0.88–1.02) | 0.153 |
| High income (*n* = 25,230) | | | | | | | | |
| No URI | 1776/5046 (35.2%) | 7012/20,184 (34.7%) | 1 | | 1 | | 1 | |
| ≥1 URI | 3270/5046 (64.8%) | 13,172/20,184 (65.3%) | 0.98 (0.92–1.05) | 0.543 | 0.99 (0.93–1.06) | 0.734 | 0.98 (0.92–1.04) | 0.488 |
| Urban residents (*n* = 16,630) | | | | | | | | |
| No URI | 1264/3326 (38.0%) | 4897/13,304 (36.8%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2062/3326 (62.0%) | 8407/13,304 (63.2%) | 0.95 (0.88–1.03) | 0.202 | 0.95 (0.88–1.03) | 0.235 | 0.94 (0.87–1.02) | 0.133 |
| Rural residents (*n* = 27,340) | | | | | | | | |
| No URI | 1885/5468 (34.5%) | 7477/21,872 (34.2%) | 1 | | 1 | | 1 | |
| ≥1 URI | 3583/5468 (65.5%) | 14,395/21,872 (65.8%) | 0.99 (0.93–1.05) | 0.688 | 1.00 (0.94–1.06) | 0.998 | 0.98 (0.92–1.05) | 0.553 |
| Underweight (*n* = 1601) | | | | | | | | |
| No URI | 135/318 (42.5%) | 505/1283 (39.4%) | 1 | | 1 | | 1 | |
| ≥1 URI | 183/318 (57.6%) | 778/1283 (60.6%) | 0.88 (0.69–1.13) | 0.314 | 0.90 (0.70–1.16) | 0.437 | 0.88 (0.68–1.13) | 0.309 |

**Table 5.** *Cont.*

| Characteristics | No. of PD | No. of Control | Odds Ratios for PD (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (Exposure/Total, %) | (Exposure/Total, %) | Crude † | *p*-Value | Model 1 †,‡ | *p*-Value | Model 2 †,§ | *p*-Value |
| Normal weight (*n* = 15,619) | | | | | | | | |
| No URI | 1083/3098 (35.0%) | 4525/12,521 (36.1%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2015/3098 (65.0%) | 7996/12,521 (63.9%) | 1.05 (0.97–1.14) | 0.220 | 1.06 (0.98–1.15) | 0.153 | 1.05 (0.96–1.14) | 0.103 |
| Overweight (*n* = 11,597) | | | | | | | | |
| No URI | 823/2308 (35.7%) | 3160/9289 (34.0%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1485/2308 (64.3%) | 6129/9289 (66.0%) | 0.93 (0.85–1.02) | 0.138 | 0.93 (0.85–1.03) | 0.166 | 0.92 (0.84–1.02) | 0.103 |
| Obese (*n* = 15,153) | | | | | | | | |
| No URI | 1108/3070 (36.1%) | 4184/12,083 (34.6%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1962/3070 (63.9%) | 7899/12,083 (65.4%) | 0.94 (0.86–1.02) | 0.129 | 0.94 (0.87–1.03) | 0.178 | 0.93 (0.85–1.01) | 0.077 |
| Nonsmokers (*n* = 32,653) | | | | | | | | |
| No URI | 2366/6765 (35.0%) | 8689/25,888 (33.6%) | 1 | | 1 | | 1 | |
| URI ≥ 1 | 4399/6765 (65.0%) | 17,199/25,888 (66.4%) | 0.94 (0.89–0.99) | 0.029 * | 0.95 (0.90–1.01) | 0.086 | 0.95 (0.89–1.00) | 0.054 |
| Past and current smokers (*n* = 11,317) | | | | | | | | |
| No URI | 783/2029 (38.6%) | 3685/9288 (39.7%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1246/2029 (61.4%) | 5603/9288 (60.3%) | 1.05 (0.95–1.15) | 0.367 | 1.06 (0.96–1.17) | 0.285 | 1.02 (0.92–1.13) | 0.692 |
| Alcohol use < 1 time a week (*n* = 29,538) | | | | | | | | |
| No URI | 2190/6243 (35.1%) | 7914/23,295 (34.0%) | 1 | | 1 | | 1 | |
| ≥1 URI | 4053/6243 (64.9%) | 15,381/23,295 (66.0%) | 0.95 (0.90–1.01) | 0.102 | 0.97 (0.91–1.03) | 0.255 | 0.95 (0.90–1.01) | 0.109 |
| Alcohol use ≥ 1 time a week (*n* = 14,432) | | | | | | | | |
| No URI | 959/2551 (37.6%) | 4460/11,881 (37.5%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1592/2551 (62.4%) | 7421/11,881 (62.5%) | 0.95 (0.90–1.01) | 0.109 | 1.00 (0.92–1.10) | 0.969 | 0.99 (0.90–1.08) | 0.822 |
| SBP < 140 mmHg and DBP < 90 mmHg (*n* = 30,119) | | | | | | | | |
| No URI | 1902/5669 (33.6%) | 8295/24,450 (33.9%) | 1 | | 1 | | 1 | |
| ≥1 URI | 3767/5669 (66.5%) | 16,155/24,450 (66.1%) | 1.02 (0.96–1.08) | 0.591 | 1.02 (0.96–1.08) | 0.541 | 1.00 (0.94–1.06) | 0.989 |
| SBP ≥ 140 mmHg or DBP ≥ 90 mmHg (*n* = 13,851) | | | | | | | | |
| No URI | 1247/3125 (39.9%) | 4079/10,726 (38.0%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1878/3125 (60.1%) | 6647/10,726 (62.0%) | 0.92 (0.85–1.00) | 0.058 | 0.95 (0.87–1.03) | 0.186 | 0.93 (0.86–1.01) | 0.094 |
| Fasting blood glucose < 100 mg/dL (*n* = 24,741) | | | | | | | | |
| No URI | 1587/4613 (34.4%) | 6898/20,128 (34.3%) | 1 | | 1 | | 1 | |
| ≥1 URI | 3026/4613 (65.6%) | 13,230/20,128 (65.7%) | 0.99 (0.93–1.06) | 0.865 | 1.00 (0.93–1.07) | 0.961 | 0.99 (0.92–1.06) | 0.677 |
| Fasting blood glucose ≥ 100 mg/dL (*n* = 19,229) | | | | | | | | |
| No URI | 1562/4181 (37.4%) | 5476/15,048 (36.4%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2619/4181 (62.6%) | 9572/15,048 (63.6%) | 0.96 (0.89–1.03) | 0.248 | 0.96 (0.90–1.04) | 0.309 | 0.94 (0.88–1.01) | 0.101 |
| Total cholesterol < 200 mg/dL (*n* = 25,002) | | | | | | | | |
| No URI | 1861/5169 (36.0%) | 7019/19,833 (35.4%) | 1 | | 1 | | 1 | |
| ≥1 URI | 3308/5169 (64.0%) | 12,814/19,833 (64.6%) | 0.97 (0.91–1.04) | 0.411 | 0.99 (0.93–1.06) | 0.761 | 0.97 (0.91–1.04) | 0.419 |
| Total cholesterol ≥ 200 mg/dL (*n* = 18,968) | | | | | | | | |
| No URI | 1288/3625 (35.5%) | 5355/15,343 (34.9%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2337/3625 (64.5%) | 9988/15,343 (65.1%) | 0.97 (0.90–1.05) | 0.474 | 0.97 (0.90–1.05) | 0.443 | 0.95 (0.88–1.03) | 0.234 |
| CCI scores = 0 (*n* = 19,476) | | | | | | | | |
| No URI | 1288/3625 (35.5%) | 5355/15,343 (34.9%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2337/3625 (64.5%) | 9988/15,343 (65.1%) | 1.03 (0.94–1.12) | 0.566 | 1.04 (0.95–1.13) | 0.394 | 0.96 (0.94–0.99) | 0.559 |
| CCI score = 1 (*n* = 8897) | | | | | | | | |
| No URI | 735/2030 (36.2%) | 2326/6867 (33.9%) | 1 | | 1 | | 1 | |
| ≥1 URI | 1295/2030 (63.8%) | 4541/6867 (66.1%) | 0.90 (0.81–1.00) | 0.052 | 0.91 (0.82–1.01) | 0.075 | 0.90 (0.81–1.00) | 0.045 * |
| CCI score ≥ 2 (*n* = 15,597) | | | | | | | | |
| No URI | 1477/4115 (35.9%) | 3999/11,482 (34.8%) | 1 | | 1 | | 1 | |
| ≥1 URI | 2638/4115 (64.1%) | 7483/11,482 (65.2%) | 0.95 (0.89–1.03) | 0.218 | 0.94 (0.87–1.02) | 0.124 | 0.93 (0.87–1.01) | 0.074 |

CCI, Charlson Comorbidity Index; DBP, Diastolic blood pressure; PD, Parkinson's disease; SBP, Systolic blood pressure; URI, upper respiratory tract infection. * Conditional or unconditional logistic regression analysis, significance at $p < 0.05$. † Stratified model for age, sex, income, and geographic region. ‡ Model 1 was adjusted for smoking status, alcohol use, obesity, and CCI scores. § Model 2 was adjusted for model 1 plus total cholesterol, SBP, DBP, and fasting blood glucose.

## 4. Discussion

This study identified a modest inverse association between the occurrence of URI within 1 year and the subsequent diagnosis of PD. However, when the observation period was extended to 2 years, the association was no longer statistically significant. These findings were generally consistent across stratified analyses, suggesting that the observed relationship is relatively robust.

Historical evidence linking infections to PD dates back to the H1N1 influenza pandemic in 1918, which was associated with cases of encephalitis lethargica and post-encephalic parkinsonism [25]. Since then, both epidemiological and experimental studies have suggested that systemic inflammation caused by infections may play a role in the etiology and progression of PD [26]. Elevated levels of systemic inflammatory markers, such as interleukin-1β, interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, have been reported in both patients with PD and animal models [26,27].

A cohort study evaluating antibody titers against common pathogens found higher seropositivity to cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpesvirus, *Borrelia burgdorferi*, *Chlamydophila pneumoniae*, and *Helicobacter pylori* in patients with PD compared with healthy controls [28]. A recent meta-analysis of cohort and case–control studies further confirmed that infections with *H. pylori*, *C. pneumoniae*, HCV, or *Malassezia* yeast were positively associated with the risk of PD [5].

Infections with other pathogenic microorganisms, including hepatitis B virus, influenza virus, measles, varicella-zoster virus, pertussis, scarlet fever, rheumatic fever, and diphtheria, have also been increasingly recognized as potential risk factors for PD [22,29]. In contrast, certain infections may not increase PD risk and may even exert a protective effect. A population-based case–control study reported an inverse association between PD and childhood infections such as chickenpox, mumps, and measles [22].

Whereas most prior studies have focused on specific pathogens such as influenza, HCV, and *H. pylori*, few have examined the broader category of URI in relation to PD risk [5,23,30–41]. Moreover, although many observational studies have explored the association between early- and mid-life infections and PD development, the short-term effects of recent infections have not been well characterized. Interest in the potential short- and long-term cognitive and neurological sequelae of coronavirus disease 2019 (COVID-19) has further emphasized the importance of studying the neuroinflammatory consequences of recent viral exposure.

In this nationwide nested case–control study using physician-coded diagnoses, we found statistically significant inverse association between a history of URIs and PD diagnosis within a 1-year period. Specifically, those with $\geq$1, $\geq$2, or $\geq$3 episodes of URI had 7% (95% CI: 0.88–0.97), 9% (95% CI: 0.87–0.96), and 8% (95% CI: 0.87–0.98) lower odds of developing PD, respectively. However, no significant association was observed when URI exposure was assessed over a 2-year window.

These findings suggest that the protective effect may not be driven by specific pathogens but rather by broader immunological mechanisms, such as systemic inflammation or treatment responses. Although secondary bacterial infections and some viral infections may necessitate antimicrobial or antiviral treatment, the management of URIs is generally supportive. In outpatient settings, clinicians typically prescribe analgesics and antipyretics to alleviate symptoms resulting from local and systemic inflammatory responses. Consequently, one possible explanation for the reduced diagnosis of PD among individuals with recent URIs may involve the protective role of anti-inflammatory medications commonly used to treat such infections.

Indeed, several animal studies have reported consistent findings and described multiple mechanisms through which non-steroidal anti-inflammatory drugs (NSAIDs)—commonly

prescribed for pain, fever, and inflammation—may confer neuroprotection in PD. These mechanisms include reducing dopaminergic neuronal loss by downregulating gene-1 expression, which may be associated with the suppression of microglial inactivation. NSAIDs have also been shown to attenuate nuclear factor kappa B (NF-κB) activity, enhance reactive oxygen species (ROS) scavenging, decrease superoxide anion generation, and limit the depletion of dopamine metabolites such as 3,4-dihydroxyphenylacetic acid and homovanillic acid, all of which may contribute to neuroprotection [42–44].

Despite accumulating evidence supporting the neuroprotective potential of NSAIDs [45–49], findings remain inconsistent. Several animal studies have shown that COX-2 inhibitors fail to exert neuroprotective effects or reduce neuronal cell death [50]. Similarly, epidemiological studies have yielded conflicting results, reporting both decreased [50] and increased risks of PD associated with NSAID use [51]. In principle, the Korean NHIS claims database contains comprehensive prescription records, which could enable direct evaluation of this hypothesis. However, extraction and validation of medication data require at least 6 to 12 months, and such analyses are therefore beyond the scope of the present study. We acknowledge this limitation and highlight that the observed inverse association may reflect medication effects rather than infections per se. Future studies incorporating prescription records and prospective data are warranted to clarify the neuroinflammatory and neuroprotective roles of these agents in PD pathogenesis.

The subgroup results provide additional insights. The absence of an association in participants with a CCI score of 0 suggests that the effect is not universal but may depend on comorbid health status. The stronger association observed in women may reflect sex-specific immune responses or differences in healthcare-seeking behavior. Associations limited to overweight and obese individuals may indicate an interaction between acute infection and the chronic low-grade inflammation characteristic of obesity. Finally, the restriction of the association to older adults (≥65 years) may be related to immunosenescence, which alters immune responses to infections. Importantly, we observed no clear monotonic dose–response pattern (≥1, ≥2, ≥3 URIs), which further weakens any argument for causality.

The major strength of this study is the use of data from the Korean NHIS, which encompasses nearly the entire Korean population. This enabled a nationwide study design with a large sample size and near-complete follow-up. Moreover, as a population-based study conducted within a single country, it is likely that diagnostic coding practices were consistently applied over time. The use of prospectively recorded diagnoses for both URI and PD also minimizes the risk of selection and measurement bias that may arise in observational studies relying on retrospective data.

Several limitations should be considered. First, reliance on ICD-10 codes may have led to misclassification of both URIs and PD. Although we required at least two PD diagnoses to improve specificity, this may have excluded patients with only one diagnosis, some of whom could have had subclinical or early PD. Second, the retrospective design precludes causal inference. In particular, reverse causation must be strongly considered. The prodromal phase of PD may begin 10–20 years before clinical diagnosis [52] and is characterized by non-motor features such as autonomic dysfucntion, impaired cough reflex, and altered healthcare-seeking behaviors. These prodromal features could reduce the likelihood of URI diagnoses before PD onset [53]. Notably the inverse association was observed only within the 1-year window but not at 2 years, strongly suggesting that our finding reflects early disease processes rather than a causal protective effect of infections. Third, residual and unmeasured confounding (e.g., genetic susceptibility, lifestyle factors) may have influenced the results. Nevertheless, our study adjusted for key known risk factors for PD, including age and smoking, and further accounted for additional factors

such as alcohol use, blood pressure, BMI, cholesterol, and fasting blood glucose, which were obtained during standardized health screenings. Fourth, surveillance bias and differences in health-seeking behavior could also partly explain the observed associations, as individuals who seek more medical care may have higher chances of receiving both URI and PD diagnoses. Fifth, although we observed a modest inverse association within 1 year, the effect size was small and not consistent across all subgroups, underscoring the need for cautious interpretation. Lastly, we were unable to conduct formal statistical interaction testing (e.g., URI sex or URI age group terms) due to dataset constraints, which represents an additional limitation. The absence of consistent dose–response trends across increasing URI frequency also suggests caution in interpreting the results. Future prospective cohort studies with detailed symptom tracking are warranted to clarify the temporal relationship and potential biological mechanisms linking infections to PD.

## 5. Conclusions

Our study provides epidemiological evidence of a potential short-term inverse association between URI history and PD diagnosis. This association does not imply causality, and its clinical significance may be limited. Nonetheless, these findings may help generate new hypothesis and underscore the importance of further research exploring the role of infections and inflammation in PD pathogenesis. Future studies incorporating prescription data and prospective designs are needed to clarify the relationship between infections, medications, and PD.

**Author Contributions:** H.G.C. and J.H.K.: study concept and design, data acquisition and interpretation, critical revision of the manuscript. J.H.W., J.H.P., M.J.K., H.S.K., H.N., I.B.C. and J.H.S.: drafting of the figures, critical revision of the manuscript. H.R.: data interpretation, drafting of the manuscript and figures. All authors have read and agreed to the published version of the manuscript.

**Funding:** This study was supported in part by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT). (No. NRF-2022R1F1A1071120).

**Institutional Review Board Statement:** This study was approved by the Ethics Committee of Hallym University (IRB No.: 2019-10-023) on 22 December 2022. The requirement for written informed consent was approved by the Ethics Committee. All analyses were conducted in accordance with the relevant guidelines and regulations of the Ethics Committee of Hallym University.

**Informed Consent Statement:** This study was conducted using de-identified claims data from the Korean National Health Insurance Service–Health Screening Cohort. Because all data were anonymized, informed consent from individual participants was not required. The study protocol was approved by the Institutional Review Board, and the requirement for written informed consent was waived.

**Data Availability Statement:** The data used for this study are available from the Korean National Health Insurance Sharing Service (https://nhiss.nhis.or.kr) subject to their requirements and fees. For data requests for this study, please contact the corresponding author (kimjihee.ns@gmail.com).

**Conflicts of Interest:** Author Hyo Geun Choi was employed by the company MD Analytics. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

1. Chaudhuri, K.R.; Schapira, A.H. Non-motor symptoms of Parkinson's disease: Dopaminergic pathophysiology and treatment. *Lancet Neurol.* **2009**, *8*, 464–474. [CrossRef]
2. Federico, A.; Maier, A.; Vianello, G.; Mapelli, D.; Trentin, M.; Zanette, G.; Picelli, A.; Gandolfi, M.; Tamburin, S. Screening for mild cognitive impairment in Parkinson's disease: Comparison of the Italian versions of three neuropsychological tests. *Park. Dis.* **2015**, *2015*, 681976. [CrossRef]

3. Varalta, V.; Picelli, A.; Fonte, C.; Amato, S.; Melotti, C.; Zatezalo, V.; Saltuari, L.; Smania, N. Relationship between Cognitive Performance and Motor Dysfunction in Patients with Parkinson's Disease: A Pilot Cross-Sectional Study. *BioMed Res. Int.* **2015**, *2015*, 365959. [CrossRef]
4. Schrag, A.; Sauerbier, A.; Chaudhuri, K.R. New clinical trials for nonmotor manifestations of Parkinson's disease. *Mov. Disord.* **2015**, *30*, 1490–1504. [CrossRef] [PubMed]
5. Wang, H.; Liu, X.; Tan, C.; Zhou, W.; Jiang, J.; Peng, W.; Zhou, X.; Mo, L.; Chen, L. Bacterial, viral, and fungal infection-related risk of Parkinson's disease: Meta-analysis of cohort and case–control studies. *Brain Behav.* **2020**, *10*, e01549. [CrossRef]
6. Jain, N.; Lodha, R.; Kabra, S. Upper respiratory tract infections. *Indian J. Pediatr.* **2001**, *68*, 1135–1138. [CrossRef]
7. Thomas, M.; Bomar, P.A. Upper respiratory tract infection. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2018.
8. Desforges, M.; Le Coupanec, A.; Dubeau, P.; Bourgouin, A.; Lajoie, L.; Dubé, M.; Talbot, P.J. Human coronaviruses and other respiratory viruses: Underestimated opportunistic pathogens of the central nervous system? *Viruses* **2019**, *12*, 14. [CrossRef]
9. Hirsch, E.C.; Hunot, S. Neuroinflammation in Parkinson's disease: A target for neuroprotection? *Lancet Neurol.* **2009**, *8*, 382–397. [CrossRef]
10. Hirsch, E.C.; Vyas, S.; Hunot, S. Neuroinflammation in Parkinson's disease. *Park. Relat. Disord.* **2012**, *18*, S210–S212. [CrossRef] [PubMed]
11. Lv, Y.; Zhang, Z.; Hou, L.; Zhang, L.; Zhang, J.; Wang, Y.; Liu, C.; Xu, P.; Liu, L.; Gai, X.; et al. Phytic acid attenuates inflammatory responses and the levels of NF-κB and p-ERK in MPTP-induced Parkinson's disease model of mice. *Neurosci. Lett.* **2015**, *597*, 132–136. [CrossRef] [PubMed]
12. Alam, Q.; Zubair Alam, M.; Mushtaq, G.; Damanhouri, G.A.; Rasool, M.; Amjad Kamal, M.; Haque, A. Inflammatory process in Alzheimer's and Parkinson's diseases: Central role of cytokines. *Curr. Pharm. Des.* **2016**, *22*, 541–548. [CrossRef]
13. Alby, K.; Nachamkin, I. Gastrointestinal infections. *Microbiol. Spectr.* **2016**, *4*, 10-1128. [CrossRef]
14. Cookson, M.R. Mechanisms of mutant LRRK2 neurodegeneration. In *Leucine-Rich Repeat Kinase 2 (LRRK2)*; Springer: Berlin/Heidelberg, Germany, 2017; pp. 227–239.
15. Deusenbery, C.; Wang, Y.; Shukla, A. Recent innovations in bacterial infection detection and treatment. *ACS Infect. Dis.* **2021**, *7*, 695–720. [CrossRef]
16. Cannon, T.; Gruenheid, S. Microbes and Parkinson's disease: From associations to mechanisms. *Trends Microbiol.* **2022**, *30*, 749–760. [CrossRef]
17. Schultz, D.R.; Barthal, J.S.; Garrett, G. Western equine encephalitis with rapid onset of parkinsonism. *Neurology* **1977**, *27*, 1095. [CrossRef]
18. Jang, H.; Boltz, D.A.; Webster, R.G.; Smeyne, R.J. Viral parkinsonism. *Biochim. Biophys. Acta (BBA)-Mol. Basis Dis.* **2009**, *1792*, 714–721. [CrossRef]
19. Sulzer, D.; Antonini, A.; Leta, V.; Nordvig, A.; Smeyne, R.J.; Goldman, J.E.; Al-Dalahmah, O.; Zecca, L.; Sette, A.; Bubacco, L.; et al. COVID-19 and possible links with Parkinson's disease and parkinsonism: From bench to bedside. *NPJ Park. Dis.* **2020**, *6*, 18. [CrossRef]
20. Martyn, C.; Osmond, C. Parkinson's disease and the environment in early life. *J. Neurol. Sci.* **1995**, *132*, 201–206. [CrossRef] [PubMed]
21. Vlajinac, H.; Dzoljic, E.; Maksimovic, J.; Marinkovic, J.; Sipetic, S.; Kostic, V. Infections as a risk factor for Parkinson's disease: A case–control study. *Int. J. Neurosci.* **2013**, *123*, 329–332. [CrossRef] [PubMed]
22. Harris, M.A.; Tsui, J.K.; Marion, S.A.; Shen, H.; Teschke, K. Association of Parkinson's disease with infections and occupational exposure to possible vectors. *Mov. Disord.* **2012**, *27*, 1111–1117. [CrossRef] [PubMed]
23. Cocoros, N.M.; Svensson, E.; Szépligeti, S.K.; Vestergaard, S.V.; Szentkúti, P.; Thomsen, R.W.; Borghammer, P.; Sørensen, H.T.; Henderson, V.W. Long-term risk of Parkinson disease following influenza and other infections. *JAMA Neurol.* **2021**, *78*, 1461–1470. [CrossRef]
24. Choi, H.G.; Park, B.; Sim, S.; Ahn, S.-H.; Passi, A.G. Tonsillectomy does not reduce upper respiratory infections: A national cohort study. *PLoS ONE* **2016**, *11*, e0169264. [CrossRef]
25. Von Economo, C. Encephalitis Lethargica, Us Sequelae and Treatment. *South. Med. J.* **1931**, *24*, 1014. [CrossRef]
26. Ferrari, C.C.; Tarelli, R. Parkinson′ s disease and systemic inflammation. *Park. Dis.* **2011**, *2011*, 436813.
27. Sawada, H.; Oeda, T.; Umemura, A.; Tomita, S.; Hayashi, R.; Kohsaka, M.; Yamamoto, K.; Sudoh, S.; Sugiyama, H.; Hashimoto, K. Subclinical elevation of plasma C-reactive protein and illusions/hallucinations in subjects with Parkinson's disease: Case–control study. *PLoS ONE* **2014**, *9*, e85886. [CrossRef]
28. Bu, X.-L.; Wang, X.; Xiang, Y.; Shen, L.-L.; Wang, Q.-H.; Liu, Y.-H.; Jiao, S.-S.; Wang, Y.-R.; Cao, H.-Y.; Yi, X.; et al. The association between infectious burden and Parkinson's disease: A case-control study. *Park. Relat. Disord.* **2015**, *21*, 877–881. [CrossRef]

29. Sasco, A.J.; Paffenbarger, R.S., Jr. Measles infection and Parkinson's disease. *Am. J. Epidemiol.* **1985**, *122*, 1017–1031. [CrossRef] [PubMed]
30. Levine, K.S.; Leonard, H.L.; Blauwendraat, C.; Iwaki, H.; Johnson, N.; Bandres-Ciga, S.; Ferrucci, L.; Faghri, F.; Singleton, A.B.; Nalls, M.A. Virus exposure and neurodegenerative disease risk across national biobanks. *Neuron* **2023**, *111*, 1086–1093. e2. [CrossRef] [PubMed]
31. Dardiotis, E.; Tsouris, Z.; Mentis, A.-F.A.; Siokas, V.; Michalopoulou, A.; Sokratous, M.; Dastamani, M.; Bogdanos, D.P.; Deretzi, G.; Kountouras, J. H. pylori and Parkinson's disease: Meta-analyses including clinical severity. *Clin. Neurol. Neurosurg.* **2018**, *175*, 16–24. [CrossRef] [PubMed]
32. Poskanzer, D.C.; Schwab, R.S. Cohort analysis of Parkinson's syndrome: Evidence for a single etiology related to subclinical infection about 1920. *J. Chronic Dis.* **1963**, *16*, 961–973. [CrossRef]
33. Dourmashkin, R. What caused the 1918–30 epidemic of encephalitis lethargica? *J. R. Soc. Med.* **1997**, *90*, 515–520. [CrossRef] [PubMed]
34. Bond, M.; Bechter, K.; Müller, N.; van Elst, L.T.; Meier, U.-C. A role for pathogen risk factors and autoimmunity in encephalitis lethargica? *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2021**, *109*, 110276. [CrossRef]
35. Estupinan, D.; Nathoo, S.; Okun, M.S. The demise of Poskanzer and Schwab's influenza theory on the pathogenesis of Parkinson's disease. *Park. Dis.* **2013**, *2013*, 167843. [CrossRef]
36. Smeyne, R.J.; Noyce, A.J.; Byrne, M.; Savica, R.; Marras, C. Infection and risk of Parkinson's disease. *J. Park. Dis.* **2021**, *11*, 31–43. [CrossRef]
37. Wu, W.Y.; Kang, K.H.; Chen, S.S.; Chiu, S.H.; Yen, A.F.; Fann, J.Y.; Su, C.W.; Liu, H.C.; Lee, W.M.; Fu, H.H.; et al. Hepatitis C virus infection: A risk factor for P arkinson's disease. *J. Viral Hepat.* **2015**, *22*, 784–791. [CrossRef]
38. Abushouk, A.I.; El-Husseny, M.W.A.; Magdy, M.; Ismail, A.; Attia, A.; Ahmed, H.; Pallanti, R.; Negida, A. Evidence for association between hepatitis C virus and Parkinson's disease. *Neurol. Sci.* **2017**, *38*, 1913–1920. [CrossRef]
39. McGee, D.J.; Lu, X.-H.; Disbrow, E.A. Stomaching the possibility of a pathogenic role for Helicobacter pylori in Parkinson's disease. *J. Park. Dis.* **2018**, *8*, 367–374. [CrossRef] [PubMed]
40. Lotz, S.K.; Blackhurst, B.M.; Reagin, K.L.; Funk, K.E. Microbial infections are a risk factor for neurodegenerative diseases. *Front. Cell. Neurosci.* **2021**, *15*, 691136. [CrossRef] [PubMed]
41. Limphaibool, N.; Iwanowski, P.; Holstad, M.J.V.; Kobylarek, D.; Kozubski, W. Infectious etiologies of parkinsonism: Pathomechanisms and clinical implications. *Front. Neurol.* **2019**, *10*, 652. [CrossRef]
42. Maharaj, D.; Saravanan, K.; Maharaj, H.; Mohanakumar, K.; Daya, S. Acetaminophen and aspirin inhibit superoxide anion generation and lipid peroxidation, and protect against 1-methyl-4-phenyl pyridinium-induced dopaminergic neurotoxicity in rats. *Neurochem. Int.* **2004**, *44*, 355–360. [CrossRef]
43. Aubin, N.; Curet, O.; Deffois, A.; Carter, C. Aspirin and salicylate protect against MPTP-induced dopamine depletion in mice. *J. Neurochem.* **1998**, *71*, 1635–1642. [CrossRef]
44. Sairam, K.; Saravanan, K.S.; Banerjee, R.; Mohanakumar, K.P. Non-steroidal anti-inflammatory drug sodium salicylate, but not diclofenac or celecoxib, protects against 1-methyl-4-phenyl pyridinium-induced dopaminergic neurotoxicity in rats. *Brain Res.* **2003**, *966*, 245–252. [CrossRef]
45. Teismann, P.; Ferger, B. Inhibition of the cyclooxygenase isoenzymes COX-1 and COX-2 provide neuroprotection in the MPTP-mouse model of Parkinson's disease. *Synapse* **2001**, *39*, 167–174. [CrossRef] [PubMed]
46. Teismann, P.; Tieu, K.; Choi, D.-K.; Wu, D.-C.; Naini, A.; Hunot, S.; Vila, M.; Jackson-Lewis, V.; Przedborski, S. Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 5473–5478. [CrossRef] [PubMed]
47. Sánchez-Pernaute, R.; Ferree, A.; Cooper, O.; Yu, M.; Brownell, A.-L.; Isacson, O. Selective COX-2 inhibition prevents progressive dopamine neuron degeneration in a rat model of Parkinson's disease. *J. Neuroinflamm.* **2004**, *1*, 6. [CrossRef]
48. Wang, T.; Pei, Z.; Zhang, W.; Liu, B.; Langenbach, R.; Lee, C.; Wilson, B.; Reece, J.M.; Miller, D.S.; Hong, J.S. MPP+-induced COX-2 activation and subsequent dopaminergic neurodegeneration. *FASEB J.* **2005**, *19*, 1134–1136. [CrossRef]
49. Carrasco, E.; Casper, D.; Werner, P. Dopaminergic neurotoxicity by 6-OHDA and MPP+: Differential requirement for neuronal cyclooxygenase activity. *J. Neurosci. Res.* **2005**, *81*, 121–131. [CrossRef]
50. Przybyłkowski, A.; Kurkowska-Jastrzębska, I.; Joniec, I.; Ciesielska, A.; Członkowska, A.; Członkowski, A. Cyclooxygenases mRNA and protein expression in striata in the experimental mouse model of Parkinson's disease induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine administration to mouse. *Brain Res.* **2004**, *1019*, 144–151. [CrossRef] [PubMed]
51. Bornebroek, M.; de Lau, L.M.; Haag, M.D.; Koudstaal, P.J.; Hofman, A.; Stricker, B.H.; Breteler, M.M. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. *Neuroepidemiology* **2007**, *28*, 193–196. [CrossRef]

52. Bloem, B.R.; Okun, M.S.; Klein, C. Parkinson's disease. *Lancet* **2021**, *397*, 2284–2303. [CrossRef]
53. Schrag, A.; Horsfall, L.; Walters, K.; Noyce, A.; Petersen, I. Prediagnostic presentations of Parkinson's disease in primary care: A case-control study. *Lancet Neurol.* **2015**, *14*, 57–64. [CrossRef] [PubMed]

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.