HHS Public Access

Author manuscript

J Allergy Clin Immunol. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

J Allergy Clin Immunol. 2016 March ; 137(3): 734–743.e1. doi:10.1016/j.jaci.2015.06.017.

Hospitalizations and Outpatient Visits for Rhinovirus - Associated Acute Respiratory Illness in Adults

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Abstract

Background—Rhinovirus is linked to asthma exacerbations and chronic obstructive pulmonary disease exacerbations in adults. The severity and rates of rhinovirus acute respiratory illnesses (ARI) in adults are uncertain.

Objectives—We determined rhinovirus-associated ARI rates in adults presenting for care in multiple settings and identified factors associated with rhinovirus detection.

Methods—This prospective, population-based cohort enrolled Tennessee residents ≥18 years old in the emergency department (ED), outpatient clinics, or hospitalized for ARI December 2008-May 2010. Nasal/throat swabs were collected and tested for rhinovirus and other viruses by RT-PCR. Rates of ED visits and hospitalizations were calculated and rhinovirus-positive and -negative patients were compared.

Results—Among 2351 enrollees, rhinovirus was detected in 247 (11%). There were 7 rhinovirus-associated ED visits and 3 hospitalizations per 1000 adults annually. Patients with rhinovirus, compared to virus-negative ARI, were more likely to present with wheezing (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.23-2.35, p<0.001), to be a current smoker (OR

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Clinical Implications. Rhinovirus is associated with 7 ED visits and 3 hospitalizations per 1000 adults annually and particularly impacts adults who smoke, live with a smoker, or have underlying respiratory disease.

2.31, CI 1.68-3.19) or live with a smoker (OR 1.72, CI 1.10-2.67), have a history of chronic respiratory disease (OR 1.61, CI 1.17-2.22), and were less likely to be hospitalized versus seen in the outpatient setting (OR 0.58, CI 0.41-0.83).

Conclusion—Rhinovirus is associated with a substantial number of ED visits and hospitalizations for ARI in adults. There may be modifiable factors that can reduce the likelihood of presenting with rhinovirus-associated ARI.

Keywords

Rhinovirus; acute respiratory illness; adults; hospitalized; emergency department; smoking

Introduction

Human rhinoviruses, first identified in culture in 1956, are members of the *Picornaviridae* family(1, 2). More than 150 serotypes or genotypes of rhinovirus have been identified to date(1, 3-5), and most known serotypes fall into one of three main species: rhinovirus A, rhinovirus B, or rhinovirus C(6-20). Rhinoviruses are the most frequent cause of the common cold in adults and children. Rhinoviruses are also associated with lower respiratory illness(21-30) and with a significant burden of disease in infants and young children(21, 31).

Rhinoviruses are frequently associated with exacerbations of asthma and chronic obstructive pulmonary disease (COPD) in adults(22, 23, 26, 32-38). The recently described rhinovirus C has been associated with wheezing and more severe respiratory symptoms in children(39, 40), but these findings have been inconsistent and data are limited in adults(41, 42). The impact of the novel rhinovirus C on US adults has not been established, and the association of rhinovirus C with asthma and COPD is unclear.

We analyzed a large, prospective cohort of US adults, originally recruited during an Influenza surveillance study, who presented to outpatient clinics, emergency departments (ED), or were hospitalized with ARI or fever. We sought to establish the role of rhinovirus in this cohort and determine associations between severity of disease, wheezing, and viral infection.

Methods

Study Population

Adults ≥18 years of age who were seen in the hospital, emergency department (ED), or outpatient clinics with acute respiratory symptoms or fever from December 2008 through May 2010 in middle Tennessee(43, 44)(43, 44) were invited to participate in an influenza surveillance study(43-46). Seasonal influenza surveillance began in 2008 and continued through 2011. The specific study months were selected for rhinovirus analyses since there was year-round enrollment during that period because of pandemic influenza, and rhinoviruses are known to be associated with symptomatic infections year-round. Enrollment was restricted to residents of Nashville, TN (Davidson County) and 11 surrounding counties. Institutional Review Boards of the participating surveillance hospitals approved the study. Two to five days each week, study nurses identified patients at each

study site with ARI symptoms or fever/feverishness. When influenza was circulating, surveillance was performed 5 days per week. In the clinic and ED, only patients presenting during the day were enrolled. Hospitalized patients could be enrolled if they had been admitted within 24 hours. Written informed consent was obtained from the patient. Demographic and clinical information from each patient was collected on a standardized questionnaire(43). History of underlying medical conditions, health insurance status, symptom duration, past medical history, microbiology laboratory results, laboratory results, hospital course, and discharge diagnoses were obtained from the medical record. A maximum of 10 ICD-9 discharge diagnosis codes were recorded for each hospitalization. For the purposes of this study, patients were classified as having “obstructive wheezing illness” if the medical record documented physician-diagnosed asthma, COPD, or patient reported wheezing. After testing for influenza, samples were frozen for future use. If patients agreed to future use, samples were thawed for testing for human rhinovirus, in addition to respiratory syncytial virus (RSV)(44) and human metapneumovirus (MPV). (44, 47)

Samples

At the time of enrollment, nasal and throat swabs were collected, combined into a single tube of transport media (Remel M4RT), transported immediately to the lab on ice, divided into aliquots and stored at −80°C until processed. RNA was extracted from 200 μl of medium on a Roche MagNApure LC automated nucleic acid extraction instrument and real-time RT-PCR for the detection of rhinovirus was performed as previously described(48-51) using primers and probe sequences from a highly conserved human rhinovirus 5’-non-coding region (NCR) capable of detecting all rhinovirus prototype strains(49). Samples positive for rhinovirus were then cloned and sequenced. A 548-nucleotide sequence which encompassed the VP4/VP2 region(51) was amplified, directly sequenced(52), and compared to published GenBank sequences to determine species. MPV and RSV were tested for by RT-PCR using primers/probes previously described(53, 54).

Statistical Analysis

Proportions of rhinovirus positive and rhinovirus subspecies samples were summarized by viral status, and by inpatient/outpatient/ED status. If a patient presented to the ED but was then hospitalized, they were included in the hospitalized group. Demographic and clinical variables were summarized using median and inter-quartile range (IQR) for continuous variables and counts/percentages for categorical variables. Logistic regression with restricted cubic splines for seasonal variation was used to provide time-smoothed estimates of the probability of rhinovirus positive and rhinovirus-C positive (among rhinovirus positive samples) across time. The number of ARI hospital and ED visits in the county was determined using the Tennessee Hospital Discharge Database System (HDDS) (https://health.state.tn.us/statistics/specialprojects.htm#hdds)(55), which receives information from UB-92 (HCFA-1450) forms on all inpatient discharges and other selected patient visits from Tennessee hospitals. Each form contains information on patient diagnoses, procedures performed on the patient, charges for services provided, and selected patient demographics. Estimated Davidson County-based population rates were extrapolated from the study by multiplying the proportion of rhinovirus positive samples in our study hospitalized and ED

enrollees by the number of ARI hospital and ED visits in the county, and divided by the estimated county population, obtained from the CDC website, vintage release of the bridged-race estimates (http://www.cdc.gov/nchs/nvss/bridged_race.htm)(56). Population-based rates were estimated only for Davidson County because this county contributed the majority of the samples and population data was readily available. Data were separated by county for population-based rate estimates; however, other analyses included data from all participating counties to maximize power.

Key disease outcomes of interest included hospitalization and obstructive wheezing illness (medical record documentation of physician-diagnosed asthma, COPD, or patient reported wheezing). We tested the association between rhinovirus detection and study outcomes using logistic regression, both with and without covariate adjustment. Rhinovirus status was categorized into 3 levels: rhinovirus positive only (no other virus co-detected), rhinovirus plus other study virus positive, and rhinovirus negative. This definition provided a clean comparison of rhinovirus positive samples that lack co-detection to study virus negative samples (negative for rhinovirus, influenza, MPV, and RSV). Multinomial logistic regression was used to model viral status as a function of disease outcomes both with and without covariate adjustment. A similar subset analysis (both with and without covariate adjustment) was conducted among rhinovirus-A and rhinovirus-C positive samples. Due to sample size restrictions, the subset analysis of rhinovirus (A and C) only adjusted for age, sex, and smoking. A separate logistic regression model was used to evaluate associations between all potential confounders and hospitalization in the subset population of rhinovirus positive samples (A, B, C, and non- sequenced samples). Odds ratios and corresponding 95% confidence intervals are reported for all models.

Biologically relevant covariates chosen *a priori* included age, sex, smoking status (current smoker, lives with smoker, and never or previously smoked), public insurance, cardiac disease, supplemental oxygen use, respiratory disease (including asthma, COPD, other), and chronic steroid use (use of chronic oral steroids). The age variable was used to model a restricted cubic spline with four knots. Multinomial logistic regression was used to model viral status as a function of wheezing or hospitalization in a multivariable model, adjusting for covariates. This model provides an estimated odds ratio for each variable in the model for comparing the odds of rhinovirus-positive only versus virus negative, and for comparing the odds of rhinovirus plus other virus positive versus virus negative. The model provides both sets of odds ratios in one comprehensive model, which is more efficient than fitting two separate logistic regression models.

Secondary analyses were conducted with rhinovirus status as a binary variable corresponding to either rhinovirus-positive or rhinovirus-negative. Models with this variable included additional covariates for other viruses such as RSV, MPV, and influenza, in efforts to account for any co-infections in the evaluation of the association of rhinovirus with disease severity.

Results

Subjects were enrolled from December 2008 through May 2010. There were a total of 2351 specimens available for testing. Four hundred seventy-two (20.1%) were from patients in the ED, 1231 (52.4%) from hospitalized subjects and 648 (27.6%) from clinic outpatients.

Two hundred and forty seven of the 2351 specimens (10.5%) tested positive for rhinovirus. Six samples represented co-detection with another virus, including three with influenza, one with RSV, and one with MPV. There were 1628 samples available for testing from Davidson County residents alone.

In Davidson County, rhinovirus was associated with 11.8% of ED visits, 8.9% of hospitalizations, and 14.1% of outpatient visits, translating to 6.9 ED visits and 3.0 hospitalizations per 1000 adults per year (**Table 1**). Among the 180 Davidson County residents who tested positive for rhinovirus, 46.6% had rhinovirus A, 3.8% rhinovirus B, 24.4% rhinovirus C, and 25% had rhinovirus that could not be sequenced. Rates by site are listed in **Table 1**. (See **Supplemental Figure 1.)**

Demographic factors among virus positive subjects enrolled in all 12 Tennessee counties were also examined. **Table 2** compares features of rhinovirus-positive only and other virus positive (influenza, MPV, or RSV) subjects. The six co-detections were omitted from analyses comparing clinical symptoms. Compared to rhinovirus-positive and other virus positive, those with no study virus detected were more likely to be male (p=0.04), older (p<0.001), and non-smokers (p<0.001).

Rhinovirus A was the most common species detected in all settings (46.2%), followed by those not sequenced (27.1%), C (21.5%), and B (5.3%). The proportion of samples with rhinovirus significantly differed throughout the 18-month duration of the study ($p < 0.001$; **Fig1a),** however when the seasonal patterns of rhinovirus A and rhinovirus C were compared, there was not a statistically significant difference by species during the 18-month study period ($p = 0.15$; **Fig 1b).** Prevalence of rhinovirus A peaked during September 2009 (**Fig 1a**), and rhinovirus C showed similar prevalence throughout the study (**Fig 1b**).

Rhinovirus and hospitalization

Those with rhinovirus only detected were less likely to be hospitalized than seen in the outpatient setting, compared to those with no virus detected (OR: 0.58, CI: 0.41, 0.83; **Figure 2a**). Patients positive for other viruses also had decreased odds for hospitalization, but this association was not statistically significant (OR: 0.8, CI: 0.56, 1.16; **Figure 2a**). For the subset analysis of rhinovirus species, there was not a significant association between rhinovirus A or rhinovirus C and hospitalization (OR: 0.81, CI: 0.39, 1.69, $p = 0.57$) after adjusting for age, smoking status and sex. However, neither of the confidence intervals for other viruses or rhinovirus A/C ruled out clinically meaningful odds ratios.

Rhinovirus and wheeze

Rhinovirus positive subjects had greater odds of wheezing compared to virus negative subjects (OR: 1.7, CI: 1.23, 2.35; **Fig 3a**), after adjusting for covariates described above

(p<0.001). Subjects who were positive for other viruses also had increased odds of wheeze (OR: 2.38, CI: 1.70, 3.34) compared to virus negative subjects. In the multivariable model, other variables associated with wheezing included smoking status [p<0.001, current smoker (OR: 1.73, CI: 1.36, 2.20) and lives with smoker (OR: 1.40, CI: 1.02, 1.93)], and underlying chronic respiratory disease (OR: 3.68, CI: 2.88, 4.70, p < 0.001; **Fig 3**). There was not a significant association between rhinovirus species (A versus C) and wheezing (OR: 1.44, CI: 0.68, 3.08), though the precision of the CI did not rule out meaningful odds ratios.

Risk factors for rhinovirus among adults presenting with ARI/fever in various settings

Chronic smokers and those living with smokers were at increased odds of being rhinovirus-positive. In the multinomial logistic regression model, smoking status (p < 0.001; **Fig 4a**), chronic respiratory disease (p = 0.016), and age (**Fig 4b**; p = 0.003), were significantly associated with increased odds of rhinovirus detection, after adjusting for age, sex, smoking status, public insurance, cardiac disease, supplemental oxygen use, respiratory disease, chronic steroid use, and living with children under the age of 18. Individuals who were currently smoking had 2.31-fold greater odds of having rhinovirus (CI: 1.68, 3.19) and those living with a smoker had 1.72-fold greater odds of being rhinovirus-positive (CI: 1.10, 2.67), compared to people who never or previously smoked (**Fig 4a**). Subjects with chronic respiratory disease had 1.61-fold greater odds of rhinovirus infection (CI: 1.17, 2.22) compared to patients without chronic respiratory illness. Although younger individuals were more likely to be infected with rhinovirus (**Fig 4c**), we were not able to find a significant association of rhinovirus status and living with children under the age of 18 (p = 0.28; **Fig 4a**).

Neither current smokers (OR: 1.18, CI: 0.84, 1.67) nor those living with a smoker (OR: 1.23, CI: 0.79, 1.93) significantly increased odds of being other virus-positive compared to patients who never or previously smoked (**Fig 4b**), though the CI did not rule out meaningful odds ratios. Chronic respiratory disease was not significantly associated with being other virus-positive (OR: 1.03, CI: 0.73, 1.46). In contrast, chronic oral steroid use was associated with greater odds of other virus-positive (OR: 1.52, CI: 1.03, 2.25) relative to virus negative status (**Fig 4b**).

Secondary analyses of rhinovirus as a binary variable (rhinovirus positive, rhinovirus negative) with adjustment for other viruses did not reveal any notable findings beyond what is reported above. Results of these models are not shown.

Discussion

Our findings confirm that rhinovirus is prevalent in US adults presenting with acute respiratory illness or fever to the hospital, ED, or outpatient clinics. The rhinovirus-associated rate of hospitalization was 3 per 1000 per year, and the rate of ED visits was 6.9 per 1000 per year. Proportions of rhinovirus-associated ARI in Davidson County were 8.9% of hospitalizations, 11.8% of ED visits, and 14.1% of outpatient visits. Few of these represented co-detections with other common respiratory viruses. There have been few prospective studies on rhinovirus in adults, and no known published rates of rhinovirus-associated hospitalization or ED visits in US adults. In a 2011 study, the proportion of

rhinovirus in adults and children hospitalized with ARI in Thailand was found to be to be 16%, compared with 9.6% of outpatients(57). However the outpatient population was a convenience sample without other clinical data, and patients were mostly hospitalized. Thus, the proportion of rhinovirus may be different in the general population seeking medical care. A few other studies have reported proportion of adults with rhinovirus-associated ARI to be from 4%-23%; however these either examined specimens that had tested negative for other viruses(58), had small sample sizes(59), or selected for subjects presenting with fever(41, 60), thus likely underestimating rhinovirus prevalence. The rates of rhinovirus-associated hospitalization we detected were generally lower than those reported in a similarly-designed study of young children in this same geographic region (5 per 1000/year overall for children aged 0-5 years)(61). This is consistent with the fact that respiratory virus detection, in general, is less common in adults compared with children. Typical HRV detection after initial infection persists 7-11 days, rarely up to 28 days in the immunocompetent host(62). The aforementioned Thai study found increased prevalence of rhinovirus in children compared to adults(57) and another study found that rhinovirus-associated symptoms were more severe among children when compared with adults(63). Adults have likely had prior exposure to more rhinoviruses, hence it is likely they become symptomatic less often and when symptomatic shed less virus than children. When infected with rhinovirus, it is likely to be the complications associated with ARI and underlying medication conditions that cause patients to seek care. It is possible that more adults in Davidson County had rhinovirus-associated ARI but did not present to any clinical setting for evaluation.

In studies published to date of adults and children with rhinovirus C, the proportion of rhinovirus attributable to rhinovirus C ranged from 8 to 81% (13, 15, 20, 32, 63-73). In our study, the proportion of rhinovirus C was 1.9% in hospitalized, 3.0% ED, and 3.8% in outpatient settings. A recent US study found, among 72 adults seeking care with rhinovirus-associated respiratory illness, those with RV-A or RV-B had greater illness severity; however, this association disappeared after controlling for confounders(42). While overall rhinovirus peaked in September, rhinovirus C displayed no clear seasonal pattern. One longitudinal pediatric study in the same region over a 21-year period found HRV-C to be more prevalent during winter(74), as did a surveillance study in the Middle East(72). However, others have found rhinovirus C to circulate with a similar bimodal peak to that identified for the HRVs in general(32, 72, 75), or to be evenly distributed year-round(71). Lee et al. found that single rhinovirus infections (excluding co-detections with other common respiratory viruses like RSV and influenza) were 5- to 10-fold more likely to cause moderate to severe illness during winter months compared with summer, despite increased overall rhinovirus prevalence during spring and fall(76) suggesting the need to further study correlations between season and symptom severity.

Several demographic and clinical variables were significantly associated with hospitalization and wheezing. In our study, hospitalization (versus outpatient visit) was more likely in males, older subjects, those taking chronic oral steroids, and those who used supplemental oxygen at home. Hospitalization was less likely among subjects with rhinovirus compared to those subjects that were study virus negative, perhaps due to the fact that patients were hospitalized with other comorbid conditions. Wark et al. found that viral and bacterial infection in acute asthma and COPD increased length of hospitalization as well as risk for

hospital readmission(77). However, that study only enrolled adults hospitalized with acute asthma or COPD, and there were no outpatients for assessment. Another study found that rhinovirus infections were frequently followed by secondary bacterial infections in adults with COPD, with sputum viral load peaking at day 5-9 and bacterial load on day 15(78). Our study did not test for bacterial respiratory infections. Thus, it is possible that patients had milder respiratory symptoms with rhinovirus, followed by prolonged or more severe symptoms with subsequent bacterial infection prompting clinical care, or that patients presented with a bacterial infection and incidentally were positive for rhinovirus. In general, in this study, rhinovirus was not associated with severe disease unless there was respiratory compromise at baseline.

Wheezing outcome was more likely in patients who had rhinovirus, another virus, underlying respiratory disease, or increasing age up to 45 years. A previous study examining hospitalized patients with severe asthma exacerbations described differing proportions of certain demographic and clinical factors by age group(79). In that study, younger patients hospitalized with acute asthma exacerbation were more likely to have pets and smoke; middle-aged patients had high rates of aspirin intolerance; and older patients were more likely to have hypertension, cardiac disease, diabetes, and COPD. Continuous inhaled corticosteroid use increased with age category(79). Our study was designed differently, with enrollment of patients seeking care for any ARI/fever in various clinical settings. We did not collect information on continuous inhaled corticosteroids. McCullough et al. found no differences in RV species detection among 72 adults with rhinovirus-associated respiratory symptoms and underlying pulmonary comorbidities (primarily asthma/COPD), nor were pulmonary comorbidities associated with rhinovirus-associated illness severity in that study(42). Other studies of asthma exacerbations in children and adults(22, 23, 26, 32-38) clearly show an association with rhinovirus detection. Of interest in our study, with increasing age beyond 45 years, wheezing was a less likely diagnosis, perhaps related to other diseases increasing in prevalence with age.

Because rhinovirus was the most common virus detected among these adults seeking clinical care, and because asymptomatic or mild infection with rhinovirus also occurs(28, 80), we sought to determine factors that may predispose a patient to present with symptoms from rhinovirus. Notably, having rhinovirus detected during an ARI/fever visit was more likely among those who smoked or lived with smokers, those with underlying respiratory disease, and adults around the age of 60. One smaller study found that adults hospitalized with a rhinovirus-associated asthma exacerbation were more likely to be smokers(25). Proud et al. recently studied primary human bronchial epithelial cells and identified a potential mechanism for this relationship: cigarette smoke modulated the expression of rhinovirus-induced airway epithelial host defense genes(81). Another group also found that cigarette smoke decreased innate responses of epithelial cells to rhinovirus infection, further supporting our results. Hudy recently reported that cigarette smoke exposure specifically reduces chromatin accessibility and inhibits viral signaling via NF-κB, IRF-1, STAT-1, and MDA5, concluding that cigarette smoke exposure can simultaneously modulate multiple pathways linked to innate immune responses to rhinovirus infection(82). One study of the elderly found that smoking and chronic medical conditions were risk factors for lower respiratory complications with rhinovirus(83). Our study confirms these findings in a large-

scale, prospective study of adults presenting to the hospital, ED, or clinics with ARI. With regards to the elderly population, it has recently been reported that RSV and MPV symptomatically infect this group with rates similar to that for influenza(44). We now report that rates of rhinovirus-associated ARI in this population are also prominent in this age group and are particularly prevalent among those who smoke or live with smokers, those with underlying respiratory disease, and those approximately 60 years old. These groups should be targeted with interventions.

Limitations

Despite the strengths of this large, multi-site, prospective study, there are limitations. First, we did not test for bacterial respiratory tract infection. However, we tested for multiple common respiratory viruses. Next, information on inhaled corticosteroids was not collected because the study was originally designed for influenza surveillance and not specifically for asthma. The timing of symptom onset to enrollment and sample collection varied between subjects. Finally, this study represents a single geographic region over a one-and-a-half year period encompassing the novel influenza A H1N1 pandemic, thus rates may not be representative of all years and regions. However, we enrolled patients from 12 counties and the proportions of rhinovirus detected were similar to other reports that did not calculate population-based rates. Our rate calculations relied on the assumption that the percent of infections in persons we enrolled would be similar to percent in persons with acute respiratory illness ED and hospital discharge diagnoses. Despite these limitations, studies that use direct patient testing to estimate rates are needed to help define the burden of disease and focus future preventive and treatment measures.

In conclusion, we estimate that rates of hospitalization or ED visits associated with rhinovirus in Davidson County, TN were 3.0 and 6.9, respectively per 1000 people per year. We found that rhinovirus positive subjects were more likely to wheeze compared to virus negative subjects. Finally, smoking and living with a smoker increased the odds of rhinovirus detection. This evidence suggests that there are modifiable factors that may decrease the odds of rhinovirus-associated clinical visits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank the patients, nurses, providers, and technicians for their support in making this study possible.

Funding sources:

The Vanderbilt VANTAGE Core provided technical assistance for this work. VANTAGE is supported in part by CTSA Grant (5UL1 RR024975-03), the Vanderbilt Ingram Cancer Center (P30 CA68485), the Vanderbilt Vision Center (P30 EY08126), and NIH/NCRR (G20 RR030956). Supported by UL1 TR000445 (NCATS/NIH), AI101629 (NIH/NIAID) and U18 1P000184 (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences, the National Institutes of Health, or the Centers for Disease Control.

Abbreviations

RV	rhinovirus
ARI	acute respiratory illness
ED	emergency department

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Capsule Summary

Rhinoviruses are commonly detected among adults with acute respiratory illness presenting for medical care in the acute clinical setting. Certain factors are associated with rhinovirus detection in this population.

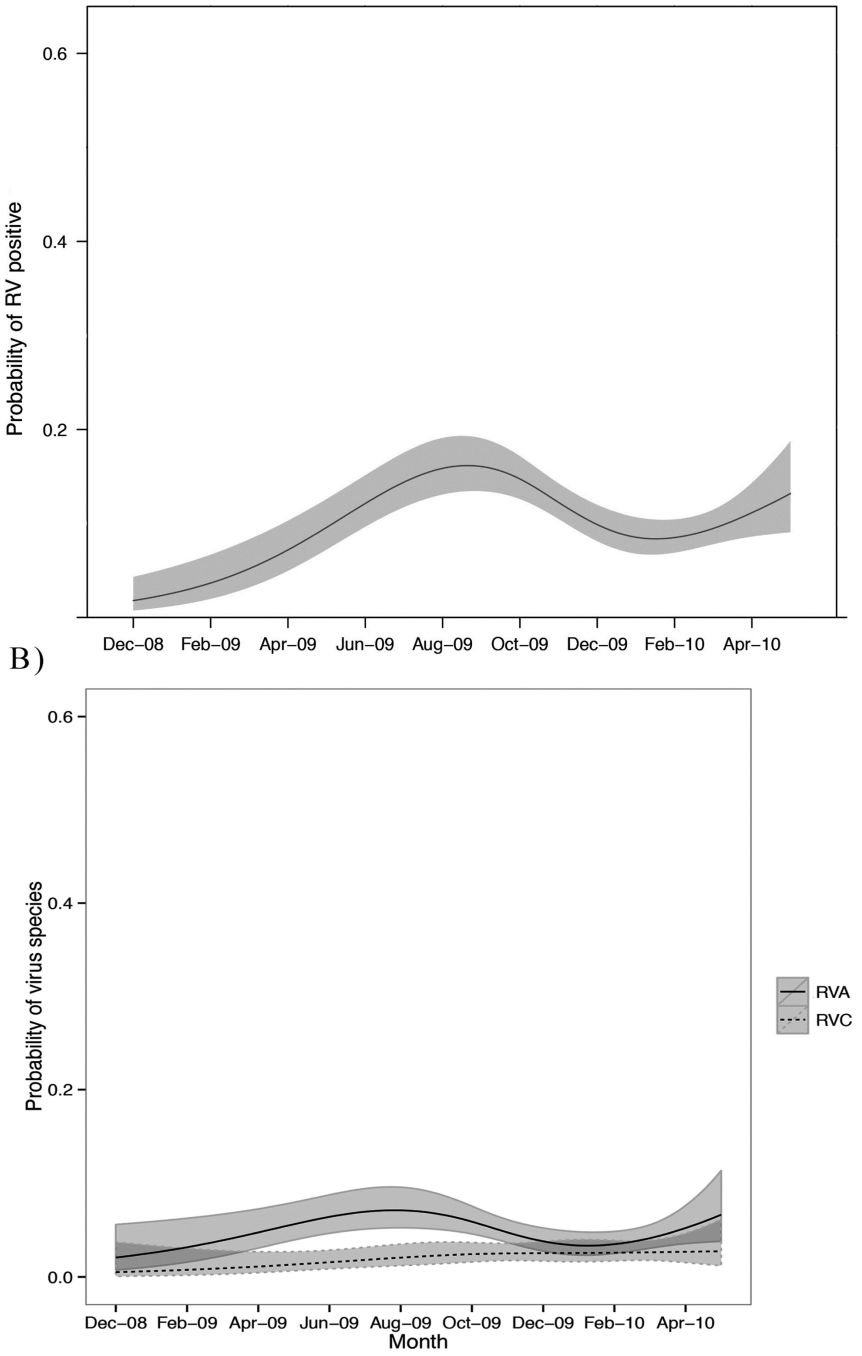

Figure 1. Seasonal prevalence

Among adults seeking care for respiratory illness or fever, rhinovirus (RV) detection differs significantly by month. A) When all rhinovirus-associated episodes are examined, virus prevalence is highest during August and September of 2009 ($p < 0.001$). This graph shows the probability of a rhinovirus-positive ARI. B) When probability of rhinovirus C ARI is compared to rhinovirus A, peaks of rhinovirus A are seen during August 2009 and April 2010; however, differences are not statistically significant ($p = 0.16$). Shaded regions represent 95% confidence intervals.

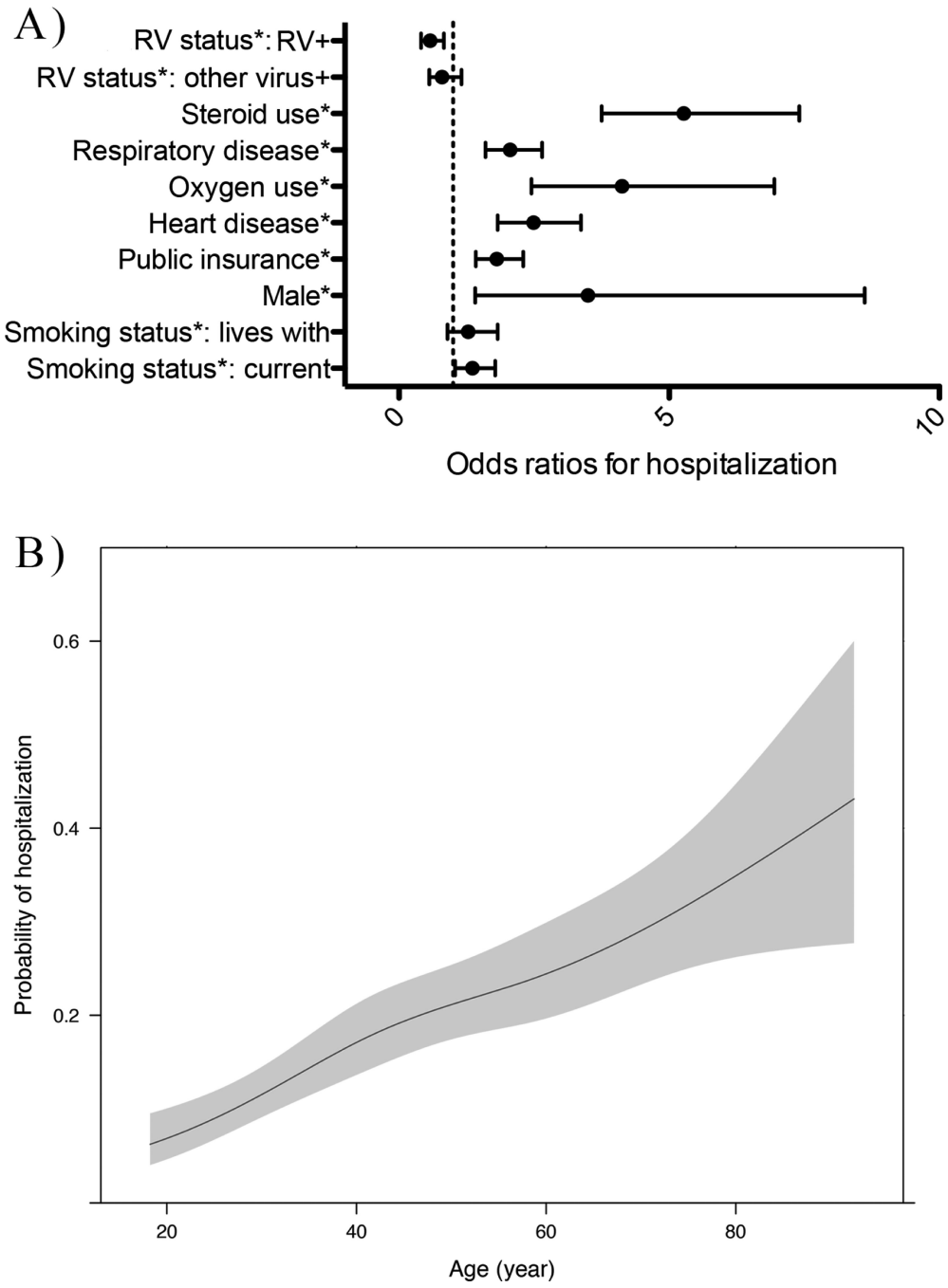

Figure 2. Hospitalization

Virus status does not account for hospitalization of subjects. A) Odds ratios and confidence intervals of hospitalized subjects compared to outpatients and emergency department visits adjusted for viral status ($p = 0.009$), sex ($p < 0.001$), smoking status ($p = 0.05$), public insurance ($p < 0.001$), cardiac disease ($p < 0.001$), oxygen use ($p < 0.001$), chronic respiratory disease ($p < 0.001$), chronic steroid use ($p < 0.001$), and B) age ($p < 0.001$). Older adults had an increased probability of hospitalization.

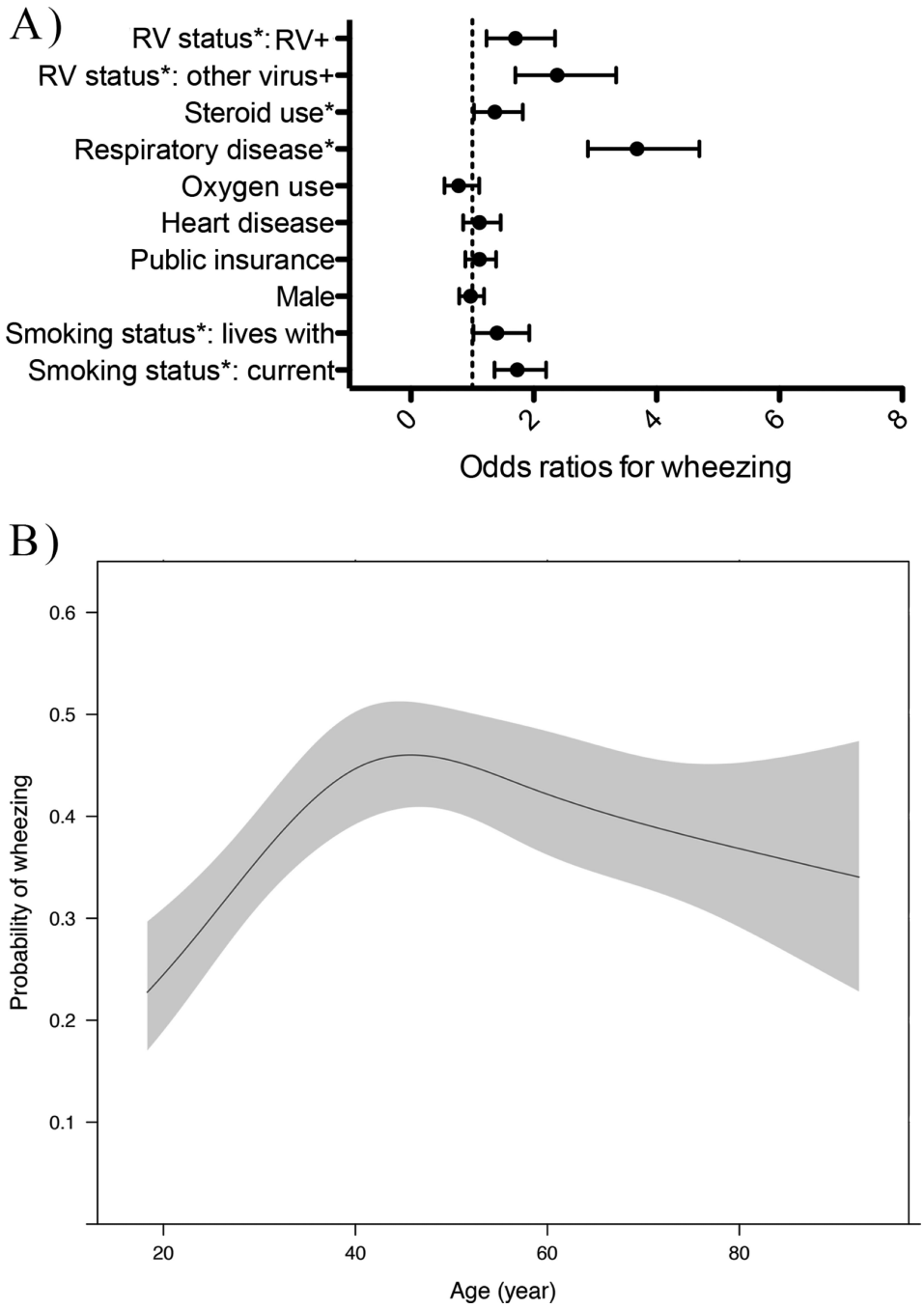

Figure 3. Wheezing

Rhinovirus (RV) status is associated with increased odds of wheezing. A) Odds ratios and confidence intervals of subjects with wheeze compared to those without wheeze are shown, adjusted for rhinovirus ($p < 0.001$), other virus positive (Influenza, metapneumovirus, respiratory syncytial virus; $p < 0.001$), sex, smoking status ($p < 0.001$), public insurance, cardiac disease, oxygen use, chronic respiratory disease ($p < 0.001$) and chronic steroid use. B) Age is also associated with wheeze ($p < 0.001$), the probability of wheeze increases with age until approximately 45 years old, then gradually decreases.

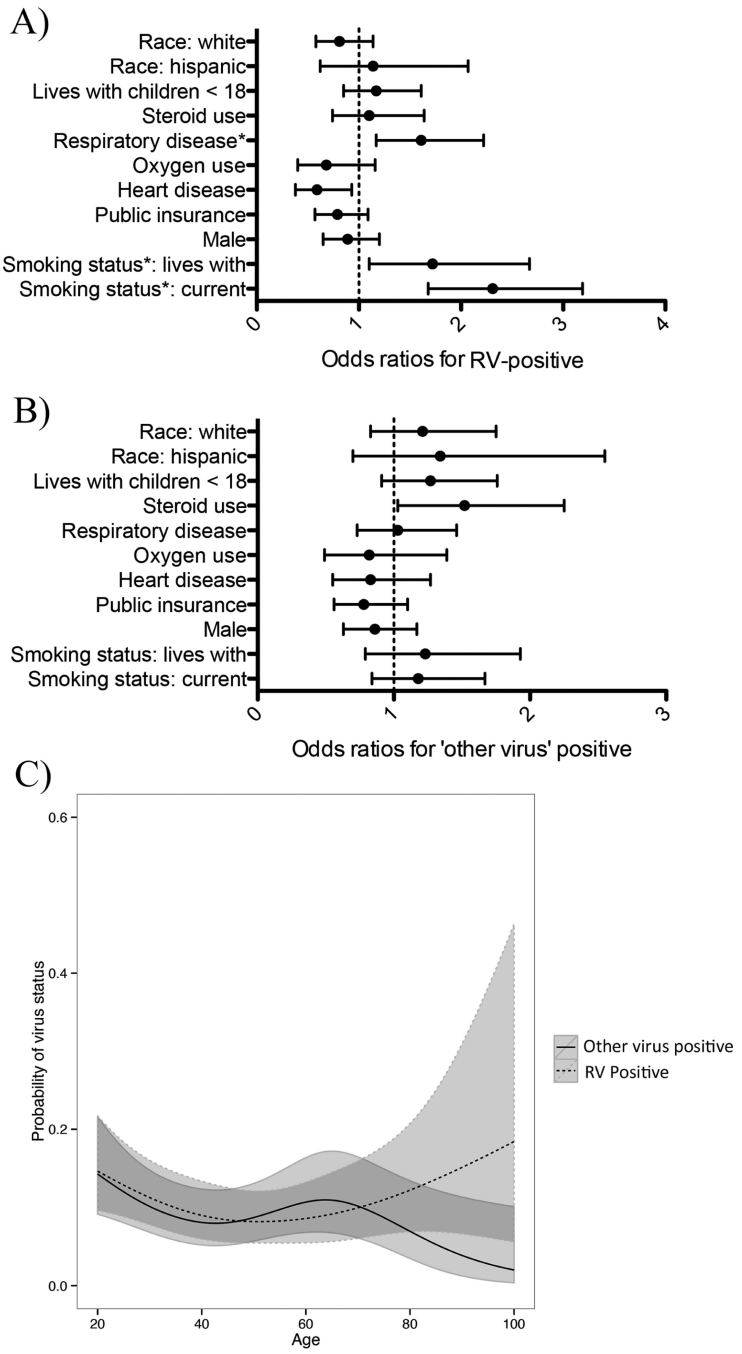

Figure 4. Rhinovirus-positive and 'other virus' positive subjects

A) Smoking status ($p < 0.001$) and chronic respiratory disease ($p = 0.02$) increase odds of being rhinovirus (RV) positive compared to being virus negative. B) Odds ratios for subjects that are 'other virus' positive compared to virus negative, and C) probability of being rhinovirus-positive (dashed line) or 'other virus' positive (solid line) with age ($P = 0.003$). Odds ratios (midpoint) and confidence intervals are shown. Values were adjusted for age,

race, smoking status, public insurance, cardiac disease, oxygen use, chronic respiratory disease, chronic steroid use, and living with children under the age of 18.

Table 1

Number of rhinovirus-positive subjects by site from Davidson County.

	Emergency Department % (n) [rate]	Inpatient % (n) [rate]	Outpatient % (n)
Davidson County *	n =364	n = 795	n =469
Rhinovirus-positive	11.8% (43) **[6.9]**	8.9% (71) **[3.0]**	14.1% (66)
Rhinovirus A	4.9% (18) **[2.78]**	4.7% (37) **[1.49]**	6.2% (29)
Rhinovirus B	0.8% (3) **[0.46]**	0.2% (2) **[0.08]**	0.4% (2)
Rhinovirus C	3.0% (11) **[1.70]**	1.9% (15) **[0.60]**	3.8% (18)
Not sequenced	3.0% (11) **[1.70]**	2.1% (17) **[0.68]**	3.6% (17)

* Percents given, with counts in parentheses and rates in bold (rate/1000 subjects/year). Rates were only available for the emergency department and inpatient settings in Davidson County.

Table 2

Demographic features of human rhinovirus-positive, other virus positive and rhinovirus-negative subjects, excluding co-infections.

	Rhinovirus positive % (n = 252)	Other virus positive % (n = 259)	Virus negative % (n = 1840)	p value
Male	34.0 % (86)	34.0% (89)	40.0% (746)	0.04
Race				0.29
Black	29.7% (74)	24.1% (62)	24.3% (508)	
White	63.1% (1573)	68.9% (177)	68.7% (1437)	
Hispanic/other	7.2% (18)	7.0% (18)	5.9% (123)	
Public insurance	42.0% (98)	38.0% (84)	46.0% (695)	0.11
Age	*29* **45** *59*	*30* **47** *62*	*37* **52** *65*	< 0.001
Lives with children < 18	38.0% (96)	35.0% (90)	30.0% (554)	0.08
Smoking status				<0.001
Current smoker	41.0% (102)	28.0% (73)	25.0% (458)	
Lives with smoker	14.0% (36)	13.0% (33)	11.0% (206)	

* Percent and total number of subjects shown, median and quartiles given for ‘age’. Unadjusted p-values determined using Pearsons test, except for ‘age’, which was determined using a Wilcoxon test.