ELECTRONIC-CIGARETTE USE AND RESPIRATORY SYMPTOMS IN ADOLESCENTS

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ABSTRACT

Background: Rates of adolescent electronic (e-) cigarette use are increasing, but there has been little study of the chronic effects of use. Components of e-cigarette aerosol have known pulmonary toxicity.

Methods: Associations of self-reported use of e-cigarettes with chronic bronchitic symptoms (chronic cough, phlegm or bronchitis) and of wheeze in the previous 12 months were examined in 2086 Southern California Children's Health Study participants completing questionnaires in 11th and 12th grade in 2014.

Results: Ever e-cigarette use was reported by 502 (24.0%), of whom 201 (9.6%) used e-cigarettes during the last 30 days (current users). Risk of bronchitic symptoms was increased by almost two-fold among past users (odds ratio (OR) 1.85 [95% confidence interval (CI) 1.37,2.49]), compared to never users, and by 2.02-fold (95%CI 1.42,2.88) among current users. Risk increased with frequency of current use (OR 1.66 (95%CI 1.02,2.68) for 1-2 days and 2.52 (95%CI 1.56,4.08) for 3 or more days in past 30 days) compared with never users. Associations were attenuated by adjustment for lifetime number of cigarettes smoked and secondhand smoke exposure. However, risk of bronchitic symptoms among past e-cigarette users remained elevated after adjustment for relevant potential confounders, and was also observed among never cigarette users (OR 1.70 [95%CI 1.11,2.59]). There were no statistically significant associations of e-cigarette use with wheeze after adjustment for cigarette use.

Conclusions: Adolescent e-cigarette users had increased rates of chronic bronchitic symptoms. Further investigation is needed to determine the long-term effects of e-cigarettes on respiratory health.

BACKGROUND

Use of electronic (e-) cigarettes, including vape pens, e-hookah, e-cigars, or other electronic nicotine delivery systems has increased rapidly worldwide in recent years. In the United States, prevalence of e-cigarette use in the previous 30 days among high school students (9^{th} to 12^{th} grade) in the U.S. National Youth Tobacco Survey increased from 1.5% in 2011 to 16.0% in 2015[1] and in 2014 was estimated to be a $2 billion (and rapidly growing) market.[2] The diversity of e-cigarette products, in particular of products with flavorings, is also increasing at a rapid rate. As of January 2014, there were 466 distinct brands of electronic nicotine products and at least 7764 unique flavors.[2]

There has been little study of the chronic health effects of e-cigarettes.[3, 4] However, e-cigarettes produce exposures with known toxicity to the lung. These include flavorings, volatile aldehydes, and oxidant metals present in e-cigarette aerosol.[5-8] In *in vitro* study of human airway epithelial cells and in mouse lungs, e-cigarette vapor produced oxidative stress and inflammatory effects, and decreased cell viability.[9] Moreover, e-cigarettes deliver an aerosol of ultrafine particles to the distal airways and alveoli.[10] Therefore, the lung is a likely target organ for health effects of e-cigarettes. Two recent cross-sectional studies of children found an association of e-cigarette use with increased prevalence of bronchitic symptoms[11] and asthma.[12]

Detailed prospective information has been collected on respiratory symptoms in the Southern California Children's Health Study (CHS),[13] a cohort with low rates of cigarette smoking and rapidly increasing use of e-cigarettes. We evaluated the associations of e-cigarette use with wheeze and chronic bronchitic symptoms, which are both common and account for substantial

morbidity in children.[14] These symptoms have been shown in the CHS and other studies to be associated with smoking and exposure to secondhand tobacco smoke (SHS), ambient air pollution, and other respiratory irritants.[14-19]

METHODS

Population: Participants were initially recruited into the CHS cohort in 2002-2003, when they were in kindergarten or 1st grade, from entire classrooms in schools in 12 communities in southern California.[13] (See supplemental material). The cohort was followed annually through 2008, then every two years through 2014. We now report findings from the 2014 survey, when students were in 11th and 12th grade (N=2097, 87% of 2412 members of the cohort attending schools in the study communities). Of these, 2086 provided information on e-cigarette use and either wheeze or bronchitic symptoms. Mean age of this sample was 17.3 years, standard deviation 0.6. Participants completed self-administered questionnaires at school with study staff supervision.

The study was approved by the University of Southern California Institutional Review Board. Written informed consent was obtained prior to data collection.

Outcomes: A child was considered to have had chronic bronchitic symptoms during the previous year, based on the report of a daily cough for 3 months in a row, congestion or phlegm other than when accompanied by a cold, or bronchitis in the previous 12 months, as previously described.[15] Wheeze was assessed based on a report of wheezing or whistling in the chest during the previous

12 months. Information on wheeze severity in the past 12 months was collected, based on any attacks of wheeze, sleep disturbance due to wheeze or wheezing severe enough to limit speech to only one or two words at a time between breaths.[20] Analyses were based on subjects with complete information on e-cigarette use, including 1922 subjects also not missing information and not reporting "don't know" regarding bronchitic symptoms, and 2083 subjects not missing wheeze information. Information on these conditions was collected at each visit during the prior prospective follow-up of the cohort, as previously described.[21]

Tobacco product use: The 2014 questionnaire assessed use of tobacco products, including cigarette, cigar, pipe, hookah, and e-cigarettes, based on questions modified from the National Youth Tobacco Survey.[22] Students were asked the age at which they had first tried cigarettes or e-cigarettes and the number of days they had used the product in the past 30 days. Participants who had "never tried" a product were classified as "never users". Those who had used a product, but not in the last 30 days, were classified as "past users." Participants who had used a product on at least one of the past 30 days were classified as "current users" of that product. Frequency of current e-cigarette use was categorized as 1-2 days or 3 or more days. In addition, participants reported number of cigarettes smoked in the previous month and the lifetime number of cigarettes smoked. Lifetime number of cigarettes smoked was categorized as 0 (never smokers), >0-10, 11-99 and >99 cigarettes.

Covariate information: Asthma was based on participant's self-report of ever having had asthma.[20] A parent-completed questionnaire at study entry assessed sociodemographic characteristics, including child's date of birth, gender, ethnicity (Hispanic, Non-Hispanic White,

other), parental education (highest level of education of either parent, categorized as <12th grade, high school diploma or GED, some college, college degree, or some graduate school or higher), and acculturation based on language of questionnaire (Spanish or English) completed. Information on housing conditions (including a history of mildew or mold or of water damage or flooding in the home while the child lived there, of a gas stove, cockroaches or carpeting in the home),and ownership of a dog or cat, was collected and updated periodically over the course of follow-up by parent or child-completed questionnaire.

Information on SHS exposure inside the home of the child was collected in each questionnaire over the course of follow-up. In 2014, perception of harm of e-cigarette use was assessed by asking whether the participant thought it would be bad for his/her health, and was classified based on whether the participant strongly agreed, agreed, disagreed or strongly disagreed.

Statistical analysis: Logistic regression was used to evaluate the association of bronchitic symptoms and current wheeze with e-cigarette use. Dummy variables were created to assess effects of past and current use, compared to never use, and of frequency of use among current users. The linear trend in effects of frequency of current e-cigarette use was assessed across three categories of use (never users, 1-2 and 3 or more days in the previous 30 days). Confounding was assessed by including relevant covariates in the model to see if the estimated e-cigarette effect changed by more than 10%. The estimate of e-cigarette associations with the outcomes examined changed more after adjustment for lifetime number of cigarettes smoked than adjustment for other smoking variables (categories of never, past and current smoking and number of cigarettes smoked in past 30 days). Therefore, models were adjusted for lifetime

number of cigarettes. In sensitivity analyses, associations of e-cigarettes with bronchitic symptoms and wheeze were adjusted for these same conditions in 2010 (before there was widespread use of e-cigarettes) and were restricted to children without symptoms in 2010. Based on previous epidemiological literature on associations of respiratory irritants with bronchitic symptoms in children,[23] interaction terms of e-cigarette use with a dog or cat at home were examined for this outcome. For each outcome, the interactions of gender, ethnicity (Hispanic and Non-Hispanic White) and asthma (in separate models) with e-cigarette use were also evaluated by calculating a likelihood ratio test for models with and without the interaction across categories of e-cigarette use. In all models, missing data were assumed to occur at random. (See supplement for additional analytical details).

All analyses assumed a two-sided alternative hypothesis at 0.05 level of significance and were conducted using STATA version 13.1.

RESULTS

There were 502 participants (24.0%) who had ever used e-cigarettes; 301 (14.4%) were past and 201 (9.6%) current users. Among current users, 107 (53.3%) used e-cigarettes on 1-2 days monthly and 94 (46.8%) on 3 or more days. Among past and current e-cigarette users, 132 (44.2%) and 81 (40.5%), respectively, were never cigarette users.

Compared to Hispanic White participants, non-Hispanic White youth were more likely to have bronchitic symptoms or wheeze (Table 1). Parental education greater than high school was associated with greater risk of both outcomes. SHS exposure in the home was associated with

increased risk of bronchitic symptoms but not of wheeze. Current and non-current use of cigarettes was associated with greater risk of each outcome.

A report of bronchitic symptoms or wheeze on the 2010 questionnaire (before e-cigarettes were widely available to this cohort) was each associated with both outcomes on the current (2014) questionnaire (eTable 1). Other covariates positively associated with both bronchitic symptoms and wheeze included ever asthma (in 2014), hookah, cigar and pipe use, having a pet cat and a history of water damage or flooding in the home. Effect estimates for current use of each combustible tobacco product were consistently larger than for past use. Parental completion of the enrollment questionnaire in Spanish was inversely associated with both outcomes. A pet dog in the home was associated only with bronchitic symptoms, and mold or mildew in the home were associated only with wheeze.

Bronchitic symptoms were associated with both past [OR 1.85 (95% CI 1.37, 2.49)] and current use of e-cigarettes [OR 2.02 (95% CI 1.42, 2.88)]. These estimated effects were robust to adjustment for sociodemographic characteristics (Figure 1). They were attenuated by additional adjustment for lifetime number of cigarettes smoked and SHS exposure in the home [OR 1.71, (95% CI 1.20, 2.43) for past and 1.41 (95% CI 0.92, 2.17) for current use]. Further adjustment for other tobacco product use, other sociodemographic characteristics and housing conditions listed in eTable 1 did not appreciably change the estimated effect size and the association with past e-cigarette use remained significant (results not shown). We examined interactions of e-cigarette use with gender, ethnicity (Hispanic and non-Hispanic White), asthma and with a dog or cat in the home, none of which was statistically significant.[23]

The risk of bronchitic symptoms increased with number of days used in the previous 30 days, (OR 1.66 (95% CI 1.02, 2.68) for 1-2 days and OR 2.52 (95% CI 1.56, 4.08) for 3 or more days), compared to never e-cigarette users (Figure 2; p for trend <0.001). This association with e-cigarette use frequency was not confounded by demographic characteristics, but was attenuated by additional adjustment for SHS exposure and lifetime number of cigarettes smoked (OR 1.37 (95% CI 0.79, 2.37) for 1-2 days and OR 1.64 (95% CI 0.88, 3.05) for 3 or more days of use) and the trend was no longer significant (p for trend 0.09).

In sensitivity analyses restricted to never cigarette smokers, the risks of bronchitic symptoms associated with past and current e-cigarette use were not as large as observed in the unadjusted analysis of all study participants but were unchanged by adjustment for demographic characteristics and SHS exposure [OR 1.70 (95% CI 1.11, 2.59) for past and OR 1.52 (95% CI 0.89, 2.61)] for current e-cigarette use after adjustment (Figure 3). Effect estimates were similar in magnitude to those observed in models of the entire population adjusted for lifetime smoking history shown in Figure 1. In additional sensitivity analyses the pattern of effect estimates for the association of bronchitic symptoms with e-cigarette use were similar after adjustment for bronchitic symptoms in 2010 and in analyses restricted to adolescents with no bronchitic symptoms in 2010 (results not shown).

Wheeze was associated with current [OR 1.86 (95% CI 1.28, 2.71)] but not with past use of e-cigarettes [OR 1.02 (95% CI 0.70, 1.49)]; Figure 4 (left panel). The effect of current e-cigarette use was not confounded by sociodemographic characteristics but was markedly attenuated by

adjustment for SHS exposure and lifetime number of cigarettes smoked [OR 1.24 (95% CI 0.78, 1.98)], and after adjustment the association of past use of e-cigarettes with wheeze became negative [OR 0.70 (95% CI 0.45, 1.10)]. The magnitude of effect estimates for e-cigarette exposure in analyses restricted to never smokers were similar to those found in the entire population after adjustment for sociodemographic characteristics, smoking history and SHS exposure [Figure 4 (right panel)]. The frequency of current use of e-cigarettes was not associated with wheeze in either unadjusted or adjusted models (results not shown). In additional sensitivity analyses, we examined associations of e-cigarette use with more severe wheeze in the past year, based on attacks of wheeze, sleep disturbance or shortness of breath due to wheeze; the pattern of associations was similar to that observed with any wheeze in the previous year (results not shown).

DISCUSSION

Bronchitic symptoms were associated with use of e-cigarettes among adolescents. Associations with past, but not current, use remained statistically significant after adjustment for use of cigarettes and other combustible tobacco products, sociodemographic characteristics and respiratory risk factors in the home, including SHS exposure. Bronchitic symptoms were also associated with frequency of current use, based on number of days of e-cigarette use in the past month, but these effect estimates were markedly attenuated and not statistically significant after adjustment for lifetime number of cigarettes smoked and SHS exposure. There were no significant associations of wheeze, a marker of allergic airway disease, with use of e-cigarettes. These findings contribute data to the ongoing debate about the health effects of e-cigarettes that has largely occurred in the absence of evidence either of safety or of harm, and the results are

potentially informative for clinicians asked to advise patients and parents about the hazards of e-cigarette use.

Bronchitis and chronic bronchitic symptoms are common and have been associated with substantial clinical morbidity and economic cost.[14, 24-26] Bronchitis or questionnaire based report of persistent cough and phlegm are relatively imprecise outcomes and likely represent a heterogeneous complex of conditions, including chronic, indolent respiratory illness, asthma exacerbation or chronic airway inflammation. These outcomes might also reflect repeated acute exacerbations, including acute bronchitis that has been reported to persist for several weeks and to have a marked impact on quality of life, in adults and in children.[14, 27] Bronchitis and bronchitic symptoms have shown robust associations with diverse respiratory hazards in previous epidemiologic studies,[15, 17-19] including with childhood smoking and exposure to SHS.[17, 18] The magnitude of estimated effect we observed was only a little smaller than that previously reported to occur as a result of occasional smoking in an adolescent population.[28] Therefore, if causal, the observed association between bronchitic symptoms and e-cigarettes could have clinical, public health, economic and policy implications.

Results were consistent with those of a cross-sectional study of Chinese adolescents, among whom a greater than two-fold increased risk of bronchitic symptoms associated with e-cigarette use was observed among never smokers.[11] These associations are plausible based on the known pulmonary toxicity of e-cigarette aerosol composition, including glycerol vapor, nicotine and other irritants that have been associated with bronchitic and other respiratory symptoms.[3, 6-8, 29-33] Flavorings, including diacetyl and related diketone compounds that have a sweet or buttery

flavor, have caused bronchiolitis obliterans, an obstructive lung disease, in exposed workers and in animal models.[5] These diketone flavoring compounds have been measured in e-cigarette liquids at concentrations of public health concern.[34, 35] E-cigarette solutions produced cytotoxicity and pro- inflammatory effects that varied markedly across brands and solutions, depending at least in part on flavoring, in *in vitro* models using cells relevant to the lung.[36, 37] A case report of lipoid pneumonia was attributed to recurrent exposure to glycerin-based oils found in e-cigarette nicotine vapor.[38]

A previous study of Korean high school students found increased risk of asthma and more severe asthma in the previous year to be associated with e-cigarette use.[12] E-cigarette aerosol exposure also increased allergen-induced airway inflammation and hyper-responsiveness in an experimental study in mice.[39] In addition, acute effects of e-cigarette vapor inhalation on fractional excretion of nitric oxide, a marker of airway inflammation, have been observed (although the direction of effect has not been consistent).[10 40] However, we found no association of e-cigarette use with wheeze or wheeze severity, markers of asthma activity. It is possible that youth with asthma were more likely to self-select not to use e-cigarettes because of their disease. However, history of asthma neither confounded nor modified the association of e-cigarette use with bronchitic symptoms, which might be expected to be subject to similar self-selection.

The study has several strengths, including well-characterized covariates of respiratory symptoms in a large ethnically diverse sample of adolescents. Limitations to the inference of a causal relationship between past e-cigarette use and bronchitic symptoms include the possibility that residual confounding by smoking could have explained the association with past use, if cigarette

smoking were not accurately measured, as associations of bronchitic symptoms with e-cigarette use were attenuated by adjustment for smoking history. However, low rates of smoking in this cohort and substantial numbers of e-cigarette users who were never smokers made it possible to disentangle the independent associations of each exposure. It is unlikely that cigarette use explained the results, as an association of bronchitic symptoms with past use of e-cigarettes was also observed among never smokers and was similar in magnitude to the estimated effects of past e-cigarette use adjusted for cigarette use in the entire population sample. Effects were also robust to additional adjustment for a large number of sociodemographic factors, other combustible tobacco product use, asthma and other housing characteristics (listed in Tables 1 and e1). Although the adjusted association of bronchitic symptoms with current e-cigarette use was not statistically significant, the strength of the association was only modestly weaker than with past users and the difference in estimates for past and current use was not statistically significant. It is also possible that those adolescents who experienced symptoms after trying e-cigarettes chose to stop, becoming past users.

It is possible that study participants with pre-existing symptoms and an interest in using tobacco products might have used e-cigarettes because of a perception that they were less toxic than cigarettes. However, adjustment for perception of e-cigarette harm did not confound the association of past e-cigarette use with bronchitic symptoms.

Only the 2014 questionnaire asked about use of e-cigarettes and tobacco products other than cigarettes. However, information on bronchitic symptoms collected in 2010 tracked over time (as shown in eTable 1), so adjusting the observed cross-sectional associations for bronchitic

symptoms in previous years provided an opportunity to account for unmeasured determinants of symptoms. Because there was little adolescent e-cigarette use in the United States in 2010 and likely little use of other tobacco products (at cohort average age 13), by adjusting for 2010 symptoms it was possible to assess prospectively the change in symptoms associated with e-cigarette use. It is, therefore, more likely that the observed (2014) relationship of bronchitic symptoms with e-cigarette use was causal, because the e-cigarette effect estimates were unchanged after adjustment for 2010 symptoms and after restriction to adolescents with no bronchitic symptoms in 2010. However, the prevalence of 2010 bronchitic symptoms was also associated with (subsequent) e-cigarette use. Therefore, the possibility that the 2014 cross-sectional associations could be explained by unmeasured confounders associated with e-cigarette use cannot be excluded. Further longitudinal follow-up of this and other cohort studies of respiratory health in children, and complementary experimental studies, are needed to elucidate these relationships.

Several public health and research organizations, including the Forum of International Respiratory Societies, the American Association for Cancer Research and the American Society of Clinical Oncology,[41] have proposed regulation to restrict or ban e-cigarettes until there is more evidence of the safety of e-cigarette use.[42] The Food and Drug Administration recently finalized a rule to extend its authority over all tobacco products, including e-cigarettes.[43] This rule will prohibit the sale of e-cigarette products to persons under the age of 18 years and will prohibit sale of e-cigarettes in vending machines and the distribution of free samples. Our results suggest that reducing e-cigarette use in youth may reduce morbidity. However, because e-cigarette use is

still new, there has been little study of its chronic effects. Additional epidemiological and toxicological investigation of effects of chronic e-cigarette exposure is urgently needed.

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Table 1: Association of selected demographic characteristics and tobacco product use with bronchitis and wheeze, Children's Health Study

Characteristic		N (% of column total)*	Bronchitis N (% of row total)**	OR (95% CI)	Current Wheeze N/(% of row total)**	OR (95% CI)
Total		2086	368 (19.2)**		255 (12.3)**	
Gender	Female	1034 (49.6)	188 (19.8)	Reference	136 (13.2)	Reference
	Male	1052 (50.4)	180 (18.6)	0.93 (0.74, 1.16)	133 (12.6)	0.95 (0.74, 1.23)
Ethnicity	Non-Hispanic White	732 (35.1)	160 (23.2)	1.56 (1.22, 1.99)	118 (16.1)	1.66 (1.26, 2.19)
	Hispanic White	1078 (51.7)	161 (16.3)	Reference	112 (10.4)	Reference
	Other	276 (13.2)	47 (19.5)	1.25 (0.87, 1.79)	39 (14.1)	1.42 (0.96, 2.09)
Parental Education	<12th grade	387 (20.1)	47 (13.4)	Reference	28 (7.3)	Reference
	12th grade	312 (16.2)	59 (20.4)	1.66 (1.09, 2.53)	42 (13.5)	2.00 (1.21, 3.30)
	Some college	720 (37.4)	137 (20.4)	1.66 (1.16, 2.38)	110 (15.3)	2.31 (1.49, 3.57)
	College degree	258 (13.4)	57 (24.0)	2.04 (1.33, 3.13)	43 (16.7)	2.56 (1.54, 4.24)
	Some graduate school	246 (12.8)	42 (18.4)	1.47 (0.93, 2.31)	33 (13.4)	1.98 (1.16, 3.37)
Secondhand smoke in home	No	1964 (94.3)	332 (18.3)	Reference	252 (12.9)	Reference
	Yes	119 (5.7)	36 (32.1)	2.11(1.39, 3.19)	17 (14.3)	1.13 (0.67, 1.92)
Cigarette use	Never	1693 (81.3)	271 (17.3)	Reference	196 (11.6)	Reference
	Past	271 (13.0)	58 (24.2)	1.53 (1.11, 2.11)	46 (17.0)	1.56 (1.10, 2.21)
	Current	119 (5.71)	39 (35.5)	2.63 (1.74, 3.98)	27 (22.7)	2.24 (1.42, 3.52)

*Denominator (N=2086 with information on e-cigarette use and either outcome) varies due to missing values in covariates.
**N=1922 for bronchitic symptoms with complete outcome information, N=2083 for wheeze

Figure 1: Association of current and past e-cigarette use with bronchitis, adjusted for sociodemographic characteristics, smoking history and secondhand tobacco smoke exposure (N=1922)

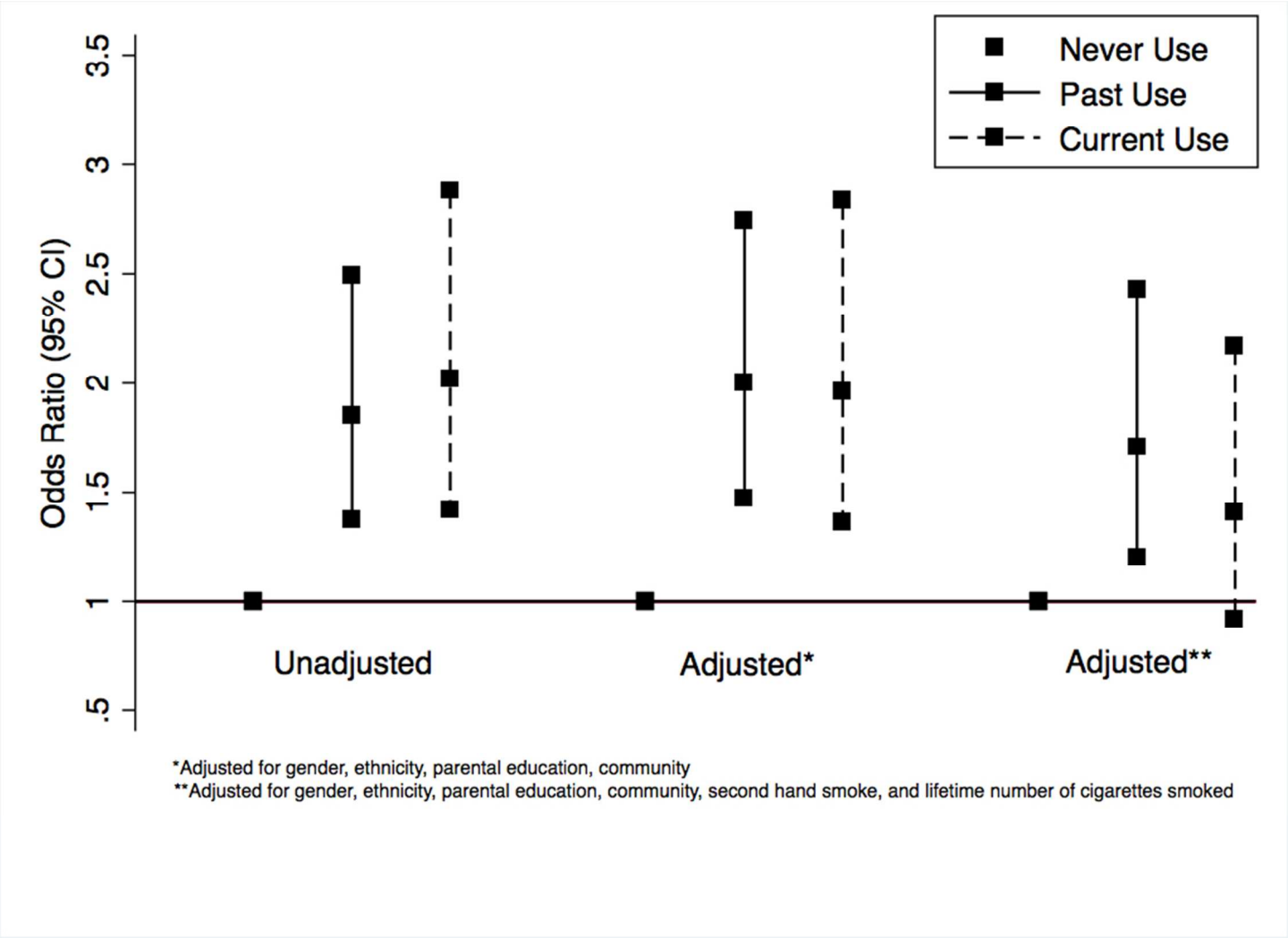


Figure 2: Association of number of days of current e-cigarette use in prior month with bronchitis, adjusted for sociodemographic characteristics, smoking history and secondhand tobacco smoke exposure, Children's Health Study (N=1640)

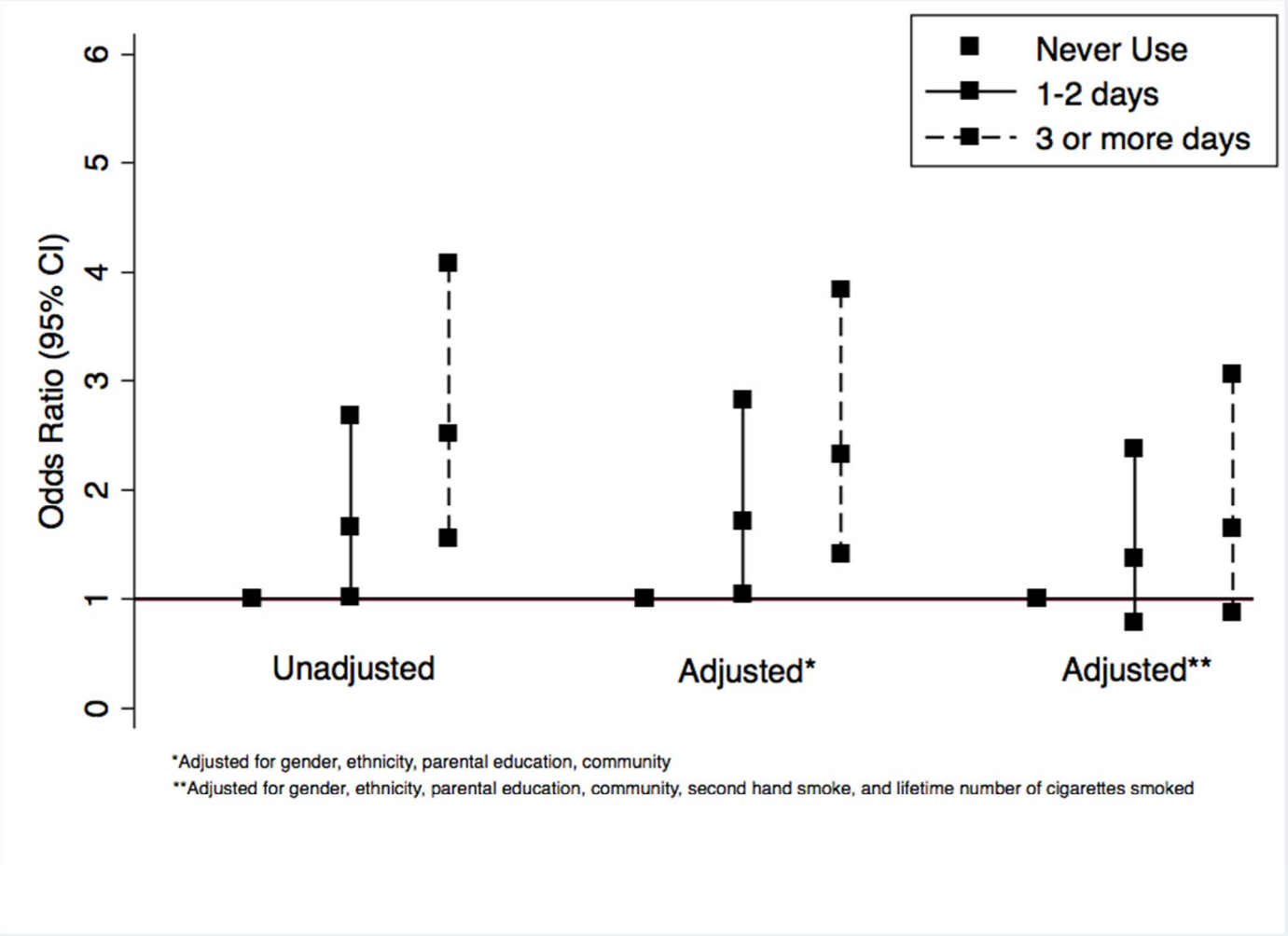


Figure 3: Association of current and past e-cigarette use with bronchitis among never smokers, adjusted for sociodemographic characteristics, smoking history and secondhand tobacco smoke exposure (N=1570)

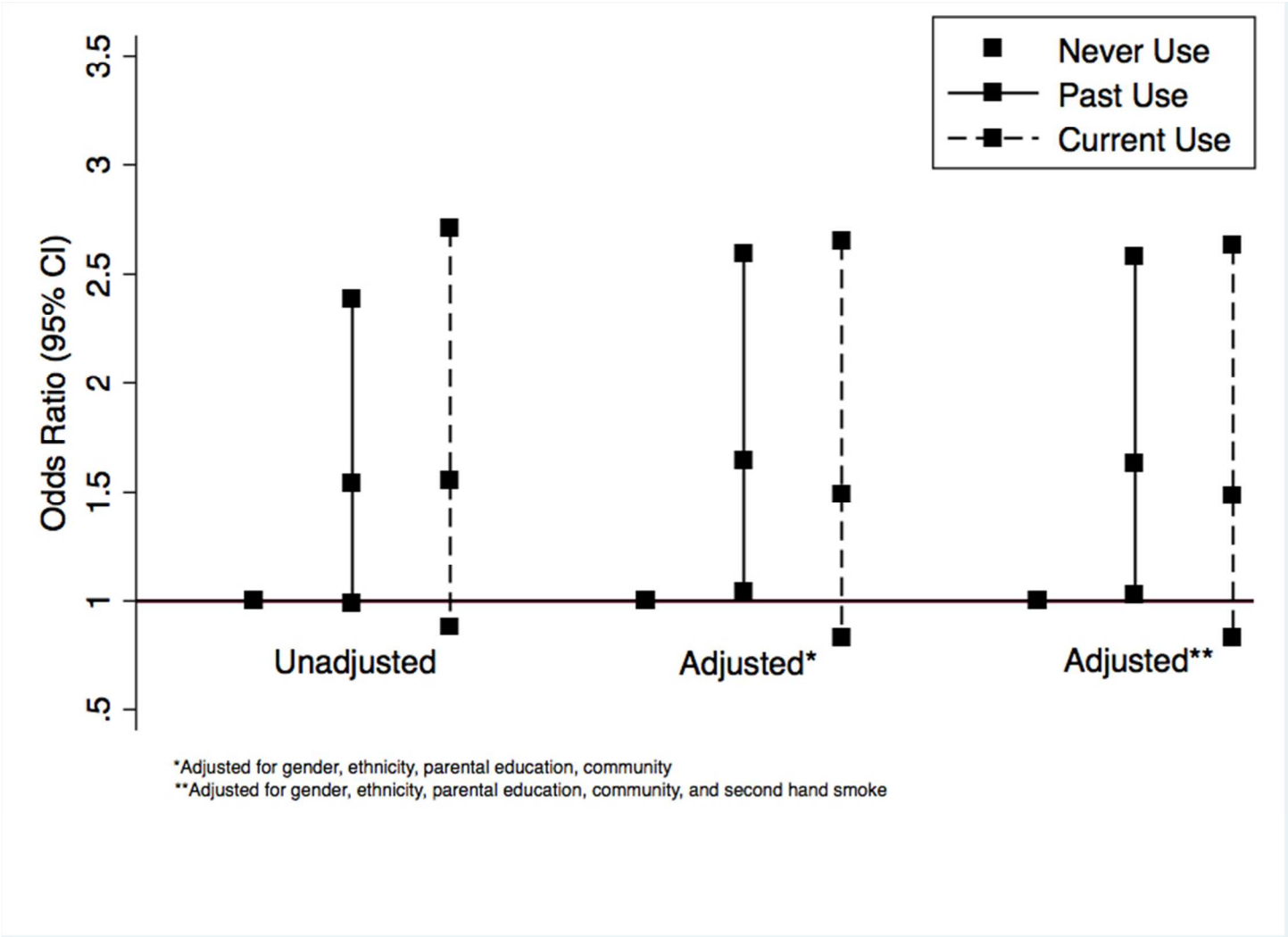
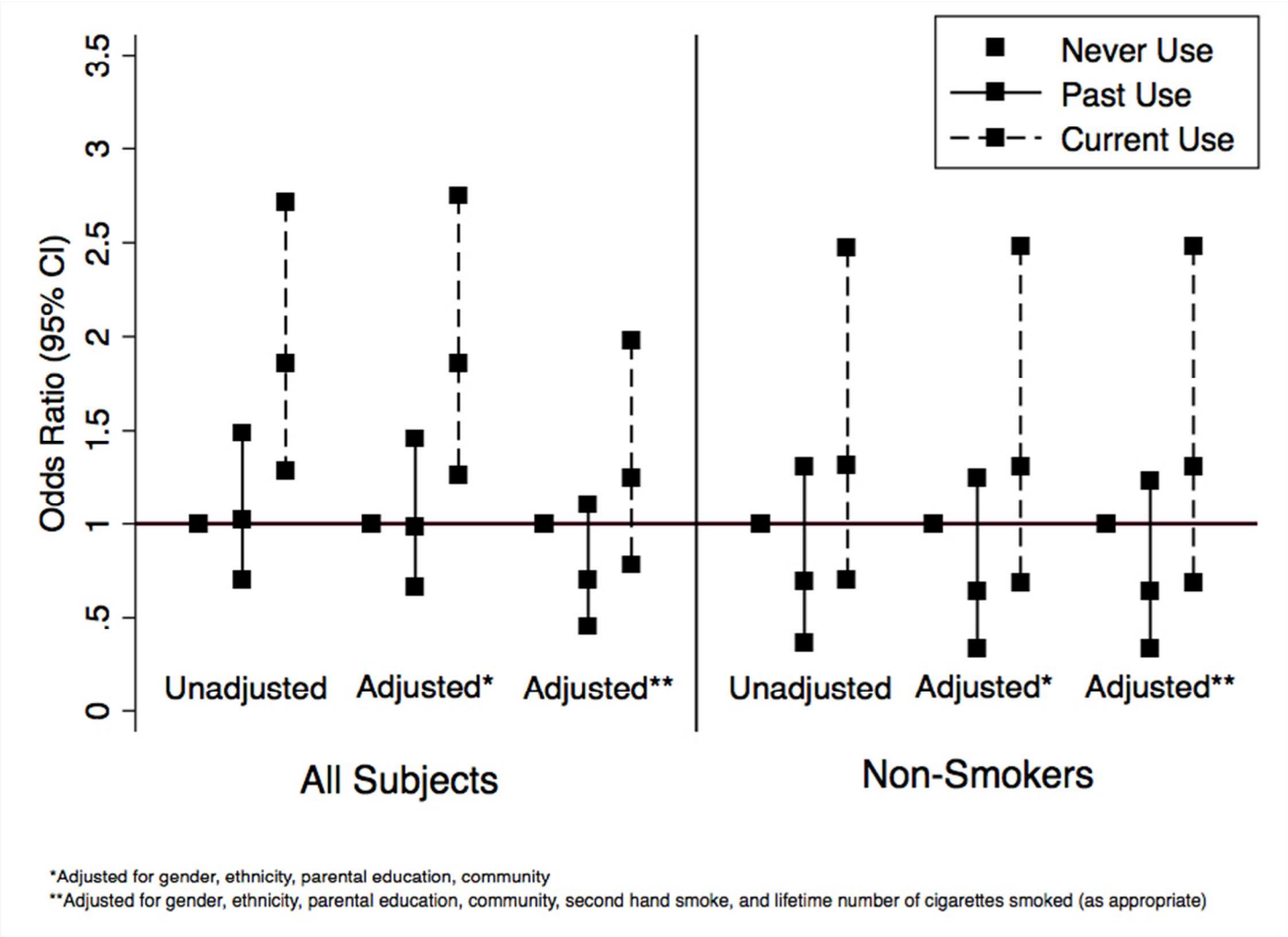


Figure 4: Association of current and past e-cigarette use with wheeze, adjusted for sociodemographic characteristics, smoking history and secondhand tobacco smoke exposure (Left panel, N=2083), and restricted to never smokers (Right panel; N=1689)



ELECTRONIC-CIGARETTE USE AND RESPIRATORY SYMPTOMS IN ADOLESCENTS

ONLINE SUPPLEMENT

Population: Participants were originally recruited from school districts in13 Southern California communities (Anaheim, Alpine, Glendora, Lake Arrowhead (Lake Gregory), Lake Elsinore, Long Beach, Mira Loma, Riverside, San Bernardino, San Dimas, Santa Barbara, Santa Maria, Upland), but the Long Beach school district declined to participate in the current survey.

Statistical analysis: Confounding by use of combustible tobacco products other than cigarettes (cigar, pipe or hookah) and by other household characteristics was assessed by including each potential confounding characteristic one at a time in models adjusted for sociodemographic characteristics, number of lifetime cigarettes smoked and SHS exposure. A missing indicator was included for covariates with missing data so as to be able to compare e-cigarette effect estimates across models with different covariates.

eTable 1: Association of additional covariates with bronchitis and wheeze, Children's Health Study

Characteristic		N (% of column total)*	Bronchitic symptoms N (row %)** N=1922	OR (95% CI)	Current Wheeze N (row%)** N=2083	OR (95% CI)
Bronchitic symptoms (2010)	No	1199 (77.4)	159 (14.2)	Reference	113 (9.5)	Reference
	Yes	350 (22.6)	120 (37.0)	3.56 (2.69, 4.72)	82 (23.4)	2.93 (2.14, 4.01)
Current Wheeze (2010)	No	1636 (86.8)	240 (15.9)	Reference	115 (7.0)	Reference
	Yes	248 (13.2)	88 (38.6)	3.33 (2.46, 4.49)	118 (47.6)	12.0 (8.76, 16.4)
Asthma ever	No	1588 (76.2)	221 (15.1)	Reference	92 (5.8)	Reference
	Yes	496 (23.8)	147 (32.0)	2.64 (2.07, 3.37)	177 (35.8)	9.04 (6.84, 12.0)
Hookah use	Never	1518 (72.8)	233 (16.6)	Reference	160 (10.6)	Reference
	Past	343 (16.5)	71 (22.8)	1.49 (1.11, 2.01)	57 (16.7)	1.70 (1.22, 2.35)
	Current	223 (10.7)	64 (31.7)	2.34 (1.68, 3.25)	52 (23.3)	2.58 (1.81, 3.66)
Cigar use	Never	1810 (86.9)	287 (17.2)	Reference	212 (11.7)	Reference
	Past	197 (9.5)	52 (28.4)	1.91 (1.35, 2.70)	34 (17.3)	1.57 (1.06, 2.33)
	Current	76 (3.7)	29 (42.7)	3.58 (2.18, 5.89)	22 (29.0)	3.07 (1.83, 5.14)
Pipe use	Never	2023 (97.1)	348 (18.7)	Reference	252 (12.5)	Reference
	Past	45 (2.2)	14 (33.3)	2.18 (1.14, 4.18)	11 (24.4)	2.27 (1.14, 4.54)
	Current	15 (0.7)	5 (38.5)	2.72 (0.89, 8.38)	5 (33.3)	3.51 (1.19, 10.3)
Perception of harm of e-cigarette	Strongly Agree	1326 (64.0)	229 (18.6)	Reference	173 (13.1)	Reference
	Agree	455 (22.0)	76 (18.6)	1.01 (0.75, 1.34)	51 (11.2)	0.84 (0.60, 1.18)
	Disagree	291 (14.0)	60 (22.3)	1.26 (0.91, 1.74)	44 (15.2)	1.19 (0.83, 1.70)
Parent questionnaire l language	English	1558 (74.8)	308 (21.5)	Reference	236 (15.2)	Reference
	Spanish	526 (25.2)	60 (12.4)	0.52 (0.39, 0.70)	33 (6.3)	0.38 (0.26, 0.55)
Cat	No	1583 (81.5)	254 (17.4)	Reference	193 (12.2)	Reference
	Yes	359 (18.5)	93 (27.7)	1.82 (1.38, 2.40)	62 (17.3)	1.50 (1.10, 2.05)
Dog	No	1337 (68.9)	220 (17.8)	Reference	183 (13.7)	Reference
	Yes	605 (31.2)	127 (22.5)	1.34 (1.05, 1.71)	72 (11.9)	0.85 (0.64, 1.14)
Water damage	No	1646 (85.6)	274 (18.1)	Reference	189 (11.5)	Reference
	Yes	277 (14.4)	64 (24.6)	1.48 (1.09, 2.02)	61 (22.1)	2.18 (1.58, 3.01)
Mold/mildew	No	1378 (75.4)	233 (18.2)	Reference	161 (11.7)	Reference
	Yes	449 (24.6)	85 (20.7)	1.18 (0.89, 1.55)	73 (16.3)	1.47 (1.09, 1.99)
Gas stove	No	289 (15.0)	49 (18.0)	Reference	47 (16.3)	Reference
	Yes	1636 (85.0)	295 (19.5)	1.11 (0.79, 1.55)	207 (12.7)	0.75 (0.53, 1.06)
Cockroaches	No	1734 (91.1)	311 (19.4)	Reference	235 (13.6)	Reference
	Yes	169 (8.9)	30 (19.4)	1.00 (0.66, 1.52)	19 (11.3)	0.81 (0.49, 1.34)
Carpet	No	137 (7.1)	21 (16.7)	Reference	18 (13.1)	Reference
	Yes	1799 (92.3)	322 (19.4)	1.20 (0.74, 1.95)	237 (13.2)	1.01 (0.60, 1.68)

*Denominator (N=2086 with information on e-cigarette use and either outcome) varies due to missing values in covariates.

**N=1922 for bronchitic symptoms with complete outcome information, N=2083 for wheeze