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Systemic Hormonal Contraceptive Use and Rhinitis Among Adult Women: An All of Us Database Analysis

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ABSTRACT

Objectives: The role of sex hormones in the pathogenesis of allergic and inflammatory conditions such as rhinitis has been receiving increased attention, with evidence supporting an inflammation-modulating role of estrogen and progesterone in the nasal mucosa. However, the specific influence of hormonal contraceptives in rhinitis has been sparsely studied. As such, we sought to investigate the association of systemic hormonal contraceptives with both allergic (AR) and nonallergic rhinitis (NAR) using a national data set of adults in the United States.

Methods: This study was conducted using data from 46,205 female participants aged 20–40 in the *All of Us* Research Program. Rhinitis diagnoses, systemic hormonal contraceptive use, and covariate data were extracted for all participants. These variables were included in multivariable logistic regression models assessing the association of any systemic hormonal contraceptive use with rhinitis, both AR and NAR. Separate models were conducted to examine the association of progestin-only contraceptives (POCs) and estrogen-containing contraceptives (ECCs) on the odds of rhinitis. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Results: Systemic hormonal contraceptives were associated with AR (OR: 1.32; 95% CI: 1.20–1.44) but not NAR (OR: 1.20; 95% CI: 0.90–1.56) after controlling for covariates. When analyzing POCs and ECCs separately, both were associated with AR compared to those not taking any systemic hormonal contraceptives (OR: 1.29; 95% CI: 1.12–1.48 for POC, OR: 1.35; 95% CI: 1.21–1.51 for ECC) but were not significantly associated with NAR (OR: 1.04; 95% CI: 0.66–1.57 for POC, OR: 1.33; 95% CI: 0.95–1.81 for ECC).

Conclusion: Systemic hormonal contraceptive use was independently associated with AR, with no significant difference between POCs and ECCs, while not being associated with NAR. Our findings may support a hormonal role in the pathogenesis of AR, but further research is needed to establish causation and understand the underlying mechanisms linking systemic hormonal contraceptive use to AR.

Level of Evidence: 3.

1 | Introduction

Rhinitis encompasses a range of nasal symptoms such as congestion, rhinorrhea, sneezing, and itching caused by inflammation or dysfunction of the nasal mucosa [1]. It is divided into two main types: allergic rhinitis (AR), which involves an immune response mediated by immunoglobulin E (IgE) to allergens, and nonallergic rhinitis (NAR), which includes various disorders featuring rhinitis symptoms without allergen sensitization [1, 2]. In the pathogenesis of AR and other inflammation-mediated conditions such as asthma, the role of sex hormones has been attracting increased attention in the literature. Studies have described the effects of these hormones on systemic inflammation, with testosterone and progesterone primarily acting as anti-inflammatory agents, while estrogen has been shown to have mixed proinflammatory and anti-inflammatory roles [3–5]. Interestingly, within the nasal mucosa, both estrogen and progesterone have been shown to have proinflammatory roles through mechanisms including eosinophil recruitment, cytokine production, and degranulation [6–8]. This is supported by literature illustrating a positive association of estrogen-related traits with the incidence of asthma and AR [9–11].

Conventional paradigms of rhinitis have indicated that any rhinitis related to a hormonal cause, such as rhinitis of pregnancy and hormone-induced rhinitis, is inherently characterized as nonallergic [2]. However, given the role of hormones as mediators of inflammation, we believe that this notion is an oversimplification of the complex mechanisms underlying hormonal effects on the nasal mucosa. Recent literature investigating the role of sex hormones in asthma, a disease with a similar pathophysiology as AR, supports the link between sex hormones and the development of asthma [12–15] and warrants a re-evaluation regarding the role of hormones in both AR and NAR. Given that AR is mediated by inflammation through IgE, and that the most common subtypes of NAR, such as vasomotor rhinitis, are not mediated by inflammation [16], we instead hypothesize that female sex hormones are associated with AR rather than NAR.

In this study, we sought to better understand whether exogenous sex hormones in the form of systemic hormonal contraceptives are associated with rhinitis. We also aimed to determine whether estrogen-containing contraceptives (ECCs), usually containing both estrogen and progestin, have an increased risk of rhinitis compared to progestin-only contraceptives (POCs) due to the differing systemic inflammatory effects of estrogen and progesterone. The literature on this topic is relatively sparse. One study investigating the influence of female sex hormones on AR suggested that oral contraceptives may have conflicting effects depending on the specific rhinitis symptom, with a positive association with sneezing while having a negative association with nasal blockage [17]. However, this study was conducted in Austria with a small sample size of 23 patients, limiting its generalizability. To our knowledge, there has been no additional literature investigating the association between systemic hormonal contraceptives and rhinitis. Although some studies have investigated the association of hormone replacement therapy and rhinitis among postmenopausal women [18, 19], none have studied systemic hormonal contraceptives and rhinitis among premenopausal women, a population with a vastly different hormonal state.

Thus, our study aims to further investigate this association using a large national data set from the *All of Us* Research Program (AoURP). Understanding the association between systemic hormonal contraceptives and rhinitis is crucial for optimizing therapeutic strategies for patients on exogenous systemic hormones with comorbid rhinitis. This study may also lend additional evidence to the currently sparse body of literature linking female sex hormones with inflammatory conditions and diseases of the nasal mucosa. Our study is the first to investigate the association between systemic hormonal contraceptives and rhinitis in the United States (U.S.).

2 | Methods

This study utilized data from AoURP's Controlled Tier Dataset v7, available to authorized users on the Researcher Workbench. AoURP is a national data set aggregating participant data through numerous sources, including surveys, electronic health records, biosamples, and physical measurements, with a focus on participants who have been underrepresented in biomedical research [20]. Participants are enrolled via partner health care provider organizations, including academic centers, Veterans Affairs medical centers, and community health centers. Because AoURP is a de-identified public data set, this study was determined exempt by the institutional review board.

For our study, we selected participants with a self-reported female biological sex. To more specifically isolate systemic hormonal contraceptive use as the variable of interest, we only included participants 20–40 years old and excluded any participants who were pregnant at the time of data collection, had a history of oophorectomy, or had reached menopause. For these participants, we then extracted data regarding rhinitis diagnosis as the primary outcome, including both AR and NAR. Medical diagnoses in AoURP are derived from participant medical records via Systemized Nomenclature of Medicine (SNOMED) and International Classification of Diseases (ICD)-9 and ICD-10 codes. AoURP then converts these source codes into a single standardized vocabulary. We extracted data from AoURP regarding rhinitis diagnosis as the primary outcome by including any condition from the standardized vocabulary that included the term "rhinitis." Rhinitis diagnoses were then subclassified as AR if the condition included the terms "allergic" or "allergy," and all other diagnoses were categorized as NAR. These subclassifications were then manually reviewed to ensure accurate grouping. Covariates considered in this analysis included demographics (age, race/ethnicity), socioeconomic status (income, education, and insurance status), smoking history, and relevant comorbidities (asthma, gastroesophageal reflux disease [GERD]) [21, 22]. Any individual with missing outcome or covariate data was excluded from the current study.

Our primary exposure was systemic hormonal contraceptive use, determined using the "Hormonal contraceptives for systemic use" variable within the AoURP Workbench. Since this variable includes any lifetime exposure to systemic hormonal contraceptives queried from the electronic health record, we only included hormonal contraceptive use that was started prior to the date of rhinitis diagnosis in patients with rhinitis. We additionally only included contraceptives with

high systemic absorption, namely, pills, patches, and injections. Systemic hormonal contraceptives were then manually classified into POC or ECC based on the listed drug name. Participants with intrauterine devices, vaginal rings, inserts, creams, and sprays were included in the group with no systemic hormonal contraceptive use based on data showing poorer systemic absorption of hormone with these methods of contraception [23–25]. Participants taking emergency contraceptive pills without ongoing use of other systemic hormonal contraceptive were likewise included in this group due to the single-use nature of emergency contraception. To assess the validity of these categorizations, we also conducted a sensitivity analysis removing participants taking contraceptives with low systemic absorption from the analysis altogether (included in the Supporting Informations).

Although systemic hormonal contraceptives should only include drugs that are either progestin-only or a combination of estrogen and progestin, some estrogen-only drugs were classified as systemic hormonal contraceptives in AoURP. This could be due to misclassification within the data or mislabeled combined hormonal contraceptives. We opted to include these estrogen-only drugs in the analysis grouped with the ECCs and conducted a sensitivity analysis excluding these drugs (included in the Supporting Informations).

2.1 | Statistical Analysis

Participant characteristics stratified by rhinitis diagnosis and type of rhinitis (AR or NAR) were determined by calculating proportions for categorical variables and means and standard deviations for continuous variables. Chi-square or t-test, as appropriate, was used to compare participant characteristics between those with and without rhinitis and across different types of rhinitis. Covariates were included in multivariable logistic regression models to examine the independent associations of systemic hormonal contraceptive use with rhinitis, controlling for participant characteristics. We conducted two different analyses controlling for covariates: one examining the association between any systemic hormonal contraceptive use and rhinitis diagnosis, and the other assessing the association between systemic hormonal contraceptive use—categorized as either POC or ECC—and rhinitis, with no hormonal contraceptive use as the reference group. We used rhinitis diagnosis as the outcome variable and conducted separate models for both AR and NAR as the outcome variables. Adjusted odds ratios (aOR) and 95% confidence intervals for the associations of the exposure and outcome variables were calculated. A p value of <0.05 was used to denote statistical significance. Analyses were conducted using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria) within the *All of Us* Researcher Workbench cloud analysis environment.

3 | Results

Characteristics of the study cohort by rhinitis status and type are detailed in Table 1. We identified a total of 46,205 participants who met our inclusion and exclusion criteria. In our full cohort of participants, 2202 (4.8%) used POCs and 3477 (7.5%) used ECCs. Participants had an average age of 30.9 and were predominantly Non-Hispanic White (52.8%), had some college education (57.7%), and were insured through private/employer plans (60.6%). After stratification by rhinitis status and type, 4606 participants had rhinitis, of which 4254 (92.4%) had AR, and 351 (7.6%) had NAR. Compared to those without rhinitis, participants with rhinitis had a higher proportion of participants on POCs (4.4% vs. 8.0%, $p<0.001$ for AR; 4.4% vs. 6.3%, $p<0.001$ for NAR) and ECCs (6.9% vs. 12.7%, $p<0.001$ for AR; 6.9% vs. 13.7%, $p<0.001$ for NAR). Regarding covariates, participants with rhinitis were generally older ($p<0.001$), predominantly White ($p<0.001$), and had completed higher levels of education ($p<0.001$). They were also more likely to have health coverage (private/employer plans or Medicare/Medicaid) ($p<0.001$) and to have diagnoses of asthma ($p<0.001$) and GERD ($p<0.001$).

Results of a multivariable logistic regression analysis assessing the association between any systemic hormonal contraceptive use and rhinitis are described in Table 2. After controlling for covariates, participants with systemic hormonal contraceptive use had a significantly elevated odds of AR (OR: 1.32; 95% CI: 1.20–1.44) but not NAR (OR: 1.20; 95% CI: 0.90–1.56) compared to those not taking systemic hormonal contraceptives.

Table 3 details the results of the multivariable logistic regression model after stratifying systemic hormonal contraceptive use into either POC or ECC. Compared to participants not on systemic hormonal contraceptives, those on either POCs or ECCs were more likely to have a diagnosis of AR (OR: 1.29; 95% CI: 1.12–1.48 for POCs and OR: 1.35; 95% CI: 1.21–1.51 for ECCs) but not NAR (OR: 1.04; 95% CI: 0.66–1.57 for POCs and OR: 1.33; 95% CI: 0.95–1.81 for ECCs). In our sensitivity analysis removing estrogen-only drugs that were labeled as systemic hormonal contraceptives in AoURP, results were unchanged with participants taking either POCs (OR: 1.25; 95% CI: 1.09–1.43) or ECCs (OR: 1.44; 95% CI: 1.28–1.62) more likely to have a diagnosis of AR compared to those not taking systemic hormonal contraceptives, while not being associated with NAR (OR: 0.95; 95% CI: 0.59–1.47 for POCs and OR: 1.32; 95% CI: 0.92–1.84 for ECCs) (Table S1). Likewise, results were unchanged when removing participants on hormonal contraceptives with low systemic absorption from the analysis, with POCs and ECCs being associated with a higher odds of AR (OR: 1.27; 95% CI: 1.10–1.45 for POCs and OR: 1.39; 95% CI: 1.25–1.55 for ECCs) but not NAR (OR: 0.97; 95% CI: 0.60–1.48 for POCs and OR: 1.38; 95% CI: 0.99–1.88 for ECCs) (Table S2).

4 | Discussion

Our study found an association between systemic hormonal contraceptive use and AR among U.S. adults aged 20–40 after controlling for covariates. On further analysis, we additionally found that both POCs and ECCs were independently associated with AR compared to no systemic hormonal contraceptive use. However, systemic hormonal contraceptives were not associated with NAR. Moreover, given the significant overlap in odds ratio confidence intervals between POCs and ECCs in Table 3, there is no difference between POCs and ECCs in

TABLE 1 | Baseline characteristics of cohort for systemic hormonal contraceptive analysis after inclusion/exclusion criteria.

			Rhinitis	
	Full cohort (*N* = 46,205)	**No rhinitis (*N* = 41,600)**	**Allergic rhinitis (*N* = 4254)**	**Nonallergic rhinitis (*N* = 351)**
Hormonal contraceptives for systemic use[b], *n* (%)				
None	40,526 (87.7%)	36,874 (88.6%)	3371 (79.2%)	281 (80.1%)
Progestin only	2202 (4.8%)	1838 (4.4%)	342 (8.0%)	22 (6.3%)
Estrogen-containing	3477 (7.5%)	2888 (6.9%)	541 (12.7%)	48 (13.7%)
p	—	—	< 0.001[a]	< 0.001[a]
Age, mean (SD)	30.9 (5.4)	30.7 (5.4)	31.9 (5.3)	32.3 (5.4)
p	—	—	< 0.001[a]	< 0.001[a]
Race/Ethnicity, *n* (%)				
Non-Hispanic White	24,374 (52.8%)	21,665 (52.1%)	2498 (58.7%)	211 (60.1%)
Non-Hispanic Black	7243 (15.7%)	6558 (15.8%)	636 (15.0%)	49 (14.0%)
Hispanic	10,147 (22.0%)	9280 (22.3%)	803 (18.9%)	64 (18.2%)
Other	4441 (9.6%)	4097 (9.8%)	317 (7.5%)	27 (7.7%)
p	—	—	< 0.001[a]	0.026[a]
Annual income (USD), *n* (%)				
Less than 10,000	8393 (18.2%)	7657 (18.4%)	688 (16.2%)	48 (13.7%)
10,000–25,000	6365 (13.8%)	5743 (13.8%)	586 (13.8%)	36 (10.3%)
25,000–35,000	5283 (11.4%)	4759 (11.4%)	485 (11.4%)	39 (11.1%)
35,000–50,000	5746 (12.4%)	5140 (12.4%)	552 (13.0%)	54 (15.4%)
50,000–75,000	6607 (14.3%)	5892 (14.2%)	660 (15.5%)	55 (15.7%)
75,000–150,000	9345 (20.2%)	8347 (20.1%)	917 (21.6%)	81 (23.1%)
More than 150,000	4466 (9.7%)	4062 (9.8%)	366 (8.6%)	38 (10.8%)
p	—	—	< 0.001[a]	0.051
Education, *n* (%)				
Less than high school	2288 (5.0%)	2139 (5.1%)	141 (3.3%)	Hidden[c]
High school or GED	7566 (16.4%)	6898 (16.6%)	627 (14.7%)	Hidden[c]
Some college	26,674 (57.7%)	23,874 (57.4%)	2574 (60.5%)	226 (64.4%)
Advanced degree	9677 (20.9%)	8689 (20.9%)	912 (21.4%)	76 (21.7%)
p	—	—	< 0.001[a]	0.003[a]
Health insurance, *n* (%)				
None	3327 (7.2%)	3180 (7.6%)	134 (3.1%)	Hidden[c]
Medicare/medicaid	12,326 (26.7%)	11,008 (26.5%)	1224 (28.8%)	94 (26.8%)
Private/employer	28,019 (60.6%)	25,076 (60.3%)	2712 (63.8%)	231 (65.8%)
Other	2533 (5.5%)	2336 (5.6%)	184 (4.3%)	Hidden[c]
p	—	—	< 0.001[a]	0.011[a]
Smoking history, *n* (%)				
No	34,878 (75.5%)	31,328 (75.3%)	3282 (77.2%)	268 (26.4%)

(Continues)

TABLE 1 | (Continued)

			Rhinitis	
	Full cohort (*N* = 46,205)	**No rhinitis (*N* = 41,600)**	**Allergic rhinitis (*N* = 4254)**	**Nonallergic rhinitis (*N* = 351)**
Yes	11,327 (24.5%)	10,272 (24.7%)	972 (22.8%)	83 (23.6%)
p	—	—	0.008[a]	0.696
Asthma, *n* (%)				
No	41,465 (89.7%)	38,708 (93.0%)	2505 (58.9%)	252 (71.8%)
Yes	4740 (10.3%)	2892 (7.0%)	1749 (41.1%)	99 (28.2%)
p	—	—	< 0.001[a]	< 0.001[a]
GERD, *n* (%)				
No	41,472 (89.8%)	38,513 (92.6%)	2738 (64.4%)	221 (63.0%)
Yes	4733 (10.2%)	3087 (7.4%)	1516 (35.6%)	130 (37.0%)
p	—	—	< 0.001[a]	< 0.001[a]

Abbreviations: GED, general educational development; SD, standard deviation; USD, US Dollars.
a$p < 0.05$. *p* values were calculated using chi-square or *t*-test as appropriate, comparing each group to the cohort without rhinitis.
[b]Values only consider contraceptives initiated prior to rhinitis diagnosis in participants with rhinitis.
[c]Values hidden in accordance with AoURP policy requiring values less than 20 to be obscured to protect participant privacy.

terms of odds of AR. These associations persisted after sensitivity analyses removing hormonal contraceptives listed as estrogen-only in the AoURP data and removing participants taking hormonal contraceptives with low systemic absorption (Supporting Informations).

Our findings contribute to the paucity of literature supporting a hormonal role in the pathogenesis of allergic and inflammatory conditions such as AR [9–11, 17, 26]. However, given our results illustrating no difference between POCs and ECCs, progesterone may have a larger role in nasal inflammation than suggested in prior studies, which have primarily focused on estrogen [27–29] due to the presence of estrogen-α and estrogen-β receptors in the nasal mucosa [30, 31]. There does exist some evidence supporting a pathophysiological foundation for our findings. One study has suggested that progesterone may play a role in cytokine production in asthma [7], while studies in a murine model found that progesterone contributed to eosinophilic airway inflammation [8] and induction of eosinophil degranulation in combination with estrogen [6]. However, the lack of progesterone receptors in the nasal mucosa complicates this association mechanistically [31]. Our findings support these prior studies from a clinical perspective, warranting additional investigation into the proinflammatory role of progesterone in the nasal mucosa and the complex and possibly mutualistic relationship between estrogen and progesterone in modulating nasal inflammation. To our knowledge, no other studies have investigated the clinical role of progesterone in rhinitis or nasal inflammation.

Establishing an association between systemic hormonal contraceptives and rhinitis has significant implications in the clinical management of this condition. For example, women may be encouraged to consider the risk of rhinitis exacerbation prior to starting systemic hormonal contraceptives, and women with rhinitis already on contraceptives may need to weigh their risks and benefits. Additionally, clinicians may have a higher vigilance for rhinitis symptoms in adult women taking systemic hormonal contraceptives.

Our study has several limitations. The cross-sectional design of our study precludes establishing causation. Although the medication list in AoURP included precise initiation dates, stop dates were often inaccurate or omitted, making it difficult to determine the length of exposure to systemic hormonal contraceptives prior to rhinitis diagnosis. Socioeconomic variables such as income, education, and insurance status in the AoURP data set were self-reported by participants, potentially introducing bias. Additionally, since NAR encompasses a diverse range of pathologies, our findings may not be applicable to all forms of NAR. Lastly, although systemic hormonal contraceptives should only include drugs that are progestin-only or combination progestin and estrogen, some estrogen-only drugs were classified as systemic hormonal contraceptives within AoURP. As such, we grouped these drugs with ECCs in our data set; however, sensitivity analyses excluding these indicated minimal impact on our study outcomes.

In conclusion, our study found a significant association of both ECC and POC use with AR, but not with NAR. Moreover, there was no difference between ECCs and POCs in terms of the odds of AR. This study provides more credence to the role of sex hormones in the manifestations of allergic and inflammatory conditions. Further research should investigate the association of hormonal contraceptives and rhinitis longitudinally to establish causation and continue to explore the mechanisms underlying this effect. In particular, more studies are needed to characterize the impact of progesterone on rhinitis and the mechanisms underlying the inflammatory-modulating roles of female sex hormones in the nasal mucosa.

TABLE 2 | Adjusted associations between systemic hormonal contraceptive use and rhinitis, with participants without rhinitis as the reference group.

	Allergic rhinitis ($N = 45,854$)	Nonallergic rhinitis ($N = 41,951$)
Hormonal contraceptives for systemic use		
No	Ref	Ref
Yes	**1.32 (1.20–1.44)**	1.20 (0.90–1.56)
Age	**1.03 (1.03–1.04)**	**1.04 (1.02–1.06)**
Race/Ethnicity		
Non-Hispanic White	Ref	Ref
Non-Hispanic Black	**0.80 (0.72–0.89)**	0.83 (0.59–1.17)
Hispanic	**0.79 (0.71–0.86)**	0.80 (0.59–1.07)
Other	**0.82 (0.72–0.93)**	0.81 (0.53–1.20)
Annual income (USD)		
Less than 10,000	Ref	Ref
10,000–25,000	1.14 (0.99–1.29)	0.94 (0.60–1.47)
25,000–35,000	1.05 (0.91–1.21)	1.20 (0.76–1.88)
35,000–50,000	1.09 (0.95–1.26)	**1.57 (1.01–2.42)**
50,000–75,000	1.08 (0.93–1.25)	1.33 (0.84–2.12)
75,000–150,000	0.99 (0.85–1.14)	1.33 (0.85–2.11)
More than 150,000	**0.79 (0.66–0.94)**	1.29 (0.76–2.19)
Education		
Less than high school	Ref	Ref
High school or GED	**1.30 (1.06–1.61)**	1.58 (0.77–3.67)
Some college	**1.54 (1.26–1.88)**	**2.33 (1.18–5.29)**
Advanced degree	**1.49 (1.20–1.86)**	2.00 (0.96–4.71)
Health insurance		
None	Ref	Ref
Medicare/medicaid	**1.53 (1.27–1.86)**	1.37 (0.79–2.59)
Private/employer	**1.94 (1.60–2.38)**	1.34 (0.77–2.55)
Other	**1.48 (1.16–1.90)**	0.92 (0.41–2.05)
Smoking history		
No	Ref	Ref
Yes	**0.73 (0.67–0.80)**	0.79 (0.60–1.03)
Asthma		
No	Ref	Ref
Yes	**6.84 (6.32–7.40)**	**3.21 (2.46–4.16)**
GERD		
No	Ref	Ref
Yes	**4.02 (3.70–4.36)**	**4.98 (3.88–6.37)**

Note: $p < 0.05$. Values represent OR (95% CI). Bold values represent $p < 0.05$.
Abbreviations: GED, general educational development; USD, US Dollars.

TABLE 3 | Adjusted associations between progestin-only or estrogen-containing systemic hormonal contraceptives and rhinitis, with participants without systemic hormonal contraceptive use as the reference group.

	Allergic rhinitis ($N = 45,854$)	Nonallergic rhinitis ($N = 41,951$)
Hormonal contraceptive		
None	Ref	Ref
Progestin only	**1.29 (1.12–1.48)**	1.04 (0.66–1.57)
Estrogen-containing	**1.35 (1.21–1.51)**	1.33 (0.95–1.81)
Age	**1.03 (1.03–1.04)**	**1.04 (1.02–1.06)**
Race/Ethnicity		
Non-Hispanic White	Ref	Ref
Non-Hispanic Black	**0.80 (0.72–0.89)**	0.85 (0.60–1.18)
Hispanic	**0.78 (0.71–0.86)**	0.80 (0.59–1.07)
Other	**0.82 (0.72–0.93)**	0.82 (0.53–1.21)
Annual income		
Less than 10,000	Ref	Ref
10,000–25,000	1.14 (1.00–1.30)	0.94 (0.60–1.46)
25,000–35,000	1.06 (0.92–1.22)	1.18 (0.75–1.85)
35,000–50,000	1.10 (0.96–1.28)	1.51 (0.97–2.35)
50,000–75,000	1.09 (0.94–1.27)	1.28 (0.81–2.04)
75,000–150,000	1.00 (0.86–1.15)	1.28 (0.81–2.02)
More than 150,000	**0.80 (0.67–0.95)**	1.24 (0.73–2.10)
Education		
Less than high school	Ref	Ref
High school or GED	**1.31 (1.07–1.61)**	1.58 (0.77–3.66)
Some college	**1.54 (1.27–1.89)**	**2.29 (1.16–5.20)**
Advanced degree	**1.50 (1.21–1.87)**	1.94 (0.93–4.59)
Health insurance, *n* (%)		
None	Ref	Ref
Medicare/medicaid	**1.55 (1.28–1.88)**	1.32 (0.76–2.50)
Private/employer	**1.92 (1.58–2.34)**	1.38 (0.76–2.50)
Other	**1.47 (1.15–1.87)**	1.01 (0.46–2.22)
Smoking history		
No	Ref	Ref
Yes	**0.73 (0.67–0.80)**	0.80 (0.61–1.05)
Asthma		
No	Ref	Ref
Yes	**6.83 (6.31–7.39)**	**3.22 (2.46–4.17)**
GERD		
No	Ref	Ref
Yes	**4.01 (3.69–4.35)**	**5.00 (3.90–6.39)**

Note: $p < 0.05$. Values represent OR (95% CI). Bold values represent $p < 0.05$.
Abbreviations: GED, general educational development; USD, US Dollars.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

This study used data from the All of Us Research Program's Controlled Tier Dataset v7, available to authorized users on the Researcher Workbench.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.