Sinonasal Cytokines as Biomarkers of Gulf War Veteran Exposures: *A VAGLAHS population investigation*

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Introduction

Gulf War Illness (GWI) affects roughly one third of the 700,000 U.S. personnel who served in the 1990–1991 Persian Gulf War. Nasal congestion is the single most common symptom, reported by 47% of Veterans with GWI — yet the sinonasal immune environment of Gulf War Veterans (GWVs) has never been characterized.

Deployment exposures (burn pit emissions, oil well fire particulate, pesticides, nerve agents) are linked to neuroinflammation and systemic immune dysregulation. Whether that reaches the sinonasal mucosa is unknown.

We compared symptom burden, radiographic severity, inflammatory endotype, and 38-plex sinonasal cytokine profiles in GWVs and non-Gulf War Veterans (NGWs), with and without chronic rhinosinusitis (CRS).

Methods

Design. Cross-sectional study of Veterans prospectively enrolled at VA Greater Los Angeles between 2022 and 2025 under an IRB-approved protocol. Exposure history was ascertained by structured interview.

Diagnosis. CRS per EPOS 2020 and ICAR-RS 2021: two or more cardinal sinonasal symptoms for ≥ 12 weeks with endoscopic or CT confirmation; polyp status on endoscopy.

Assessments. Lund-Mackay CT score (0–24) and the 22-item Sinonasal Outcome Test.

Cytokines. Middle meatal secretions collected on Leukosorb filter paper, centrifuged, and stored at −80° C, then quantified on a 38-plex Luminex immunoassay spanning Type 2 mediators, regulatory and innate cytokines, chemokines, and growth factors.

Endotype. Type 2 defined as IL-4, IL-5, or IL-13 above the Stevens 90th-percentile threshold derived from group-specific non-CRS controls.

Analysis. Chi-squared and Wilcoxon rank-sum for baseline comparisons. Cytokines modelled by log-link GLM with robust standard errors; endotype by Firth penalized logistic regression, adjusted for age, collection year, race/ethnicity, and allergic rhinitis.

Results

Patient characteristics

Analytic cohort · VAGLAHS 2022–2025
n = 88

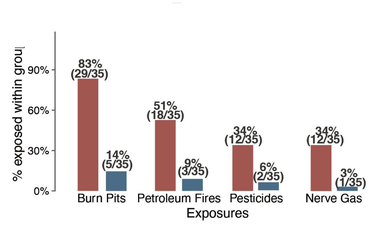
Gulf War Veterans n = 40		Non-Gulf War Veterans n = 48	
CRS (GWI)	No CRS	CRS	No CRS
19	21	18	30

Eighty-eight Veterans had complete demographic data. Thirty-seven met criteria for CRS and carried the endotype and cytokine analyses.

Characteristic	GWV N = 40	NGW N = 48	p
Age, years, mean (±SD)	58 (±6)	53 (±14)	**0.001**
Sex			
Male	38 (95%)	41 (85%)	—
Race / Ethnicity			**0.2**
White	16 (40%)	22 (46%)	
Black	9 (22%)	11 (23%)	
Asian	4 (10%)	1 (2%)	
Hispanic / Latino	7 (18%)	10 (25%)	
Other	4 (8.9%)	2 (4.1%)	
LA County resident	17 (42%)	20 (41%)	0.9
Comorbidities			
Allergic rhinitis	13 (32%)	11 (23%)	0.3
Asthma	6 (19%)	4 (13%)	0.4
Hypertension	15 (42%)	11 (30%)	0.2
Diabetes	6 (17%)	5 (13%)	0.6
Sinonasal diagnosis			
CRS diagnosis	19 (48%)	18 (38%)	0.3
Nasal polyps (CRSwNP)	11 (28%)	6 (13%)	0.11
Deployment (n = 35 per group)			
Deployed	29 (83%)	20 (57%)	0.08
Southwest Asia	29 (100%)	15 (75%)	
Europe / East Asia	0 (0%)	5 (25%)	

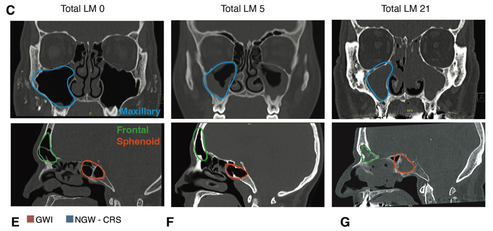
GWV, Gulf War Veteran; NGW, non-Gulf War Veteran; CRS, chronic rhinosinusitis. Chi-squared and Wilcoxon rank-sum. Polyps were present in 11 of 19 GWVs and 6 of 18 NGWs with CRS.

Deployment exposures



Gulf War Veterans reported far higher exposure to burn pit emissions (83% vs 14%), petroleum fires (51% vs 9%), pesticides (34% vs 6%), and nerve agents (34% vs 3%). Branch of service was comparable, so the gap reflects where and when Veterans deployed rather than who they were.

Radiographic severity



Coronal (top) and sagittal (bottom) sinus CT at total Lund-Mackay 0, 5, and 21. Maxillary (blue), frontal (green), sphenoid (orange).

Lund-Mackay CT score
9.0 vs 6.8
GWI vs NGW-CRS · p = 0.044

Opacification was more extensive in GWI patients across the sphenoid, posterior ethmoid, and maxillary sinuses. The 2.2-point gap is real but modest, on the order of one additional partially opacified sinus.

Symptom burden

SNOT-22 total score
43.9 vs 26.0
GWI vs NGW-CRS · 17.9-point gap

Symptoms diverged far more than imaging: 17.9 points on SNOT-22 against 2.2 on Lund-Mackay. GWI patients scored higher on every nasal and otologic item examined, including runny nose, sneezing, ear fullness, and ear pain. Symptom burden outruns what the CT explains, pointing to neuroimmune amplification rather than structural disease alone.

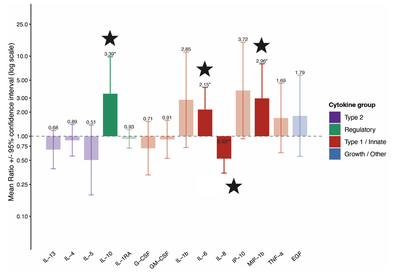
Type 2 endotype

Type 2 endotype among CRS patients
43% vs 22%
GWI vs NGW-CRS · p = 0.03

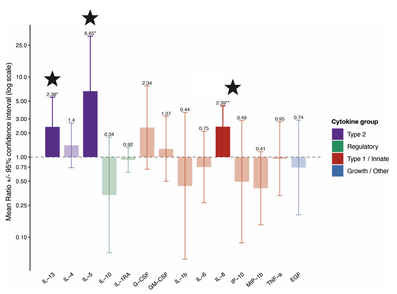
GWV vs NGW	Log OR (95% CI)	p
Model 1 — race / ethnicity	1.59 (0.12, 3.93)	**0.03**
Model 2 — + LA County	1.70 (0.02, 4.08)	**0.04**
Model 3 — + age, allergic rhinitis	1.54 (0.12, 3.85)	**0.034**

Firth penalized regression, CRS patients only. Gulf War Veteran status nearly doubled the odds of a Type 2 endotype, and the effect held across all three adjusted models, so the Th2 skew is not explained by age, residence, or allergic rhinitis.

Sinonasal cytokine profile



GWV versus NGW, independent of CRS. IL-10, IL-6, and MIP-1b were elevated and IL-8 reduced. Mucosal dysregulation is therefore present in Veterans with no sinus disease at all, suggesting exposure primes the airway before CRS develops.



GWI versus NGW-CRS. The Type 2 mediators IL-5 and IL-13 were elevated, matching the endotype classification above. The innate marker IL-8 rose as well, raising the possibility of a mixed Th2 and neutrophilic endotype.

References

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Discussion and Conclusions

- GWVs with CRS show a Th2-predominant sinonasal endotype: IL-5 and IL-13 elevated, twice the rate of Type 2 classification, and higher nasal polyp burden.
- Immune dysregulation precedes CRS. GWVs without sinus disease had elevated IL-10, IL-6, and MIP-1b with reduced IL-8, consistent with exposure-primed mucosa.
- Symptom burden outpaced radiographic disease, pointing to neuroimmune amplification beyond structural sinonasal pathology.
- GWVs with CRS may be a biologically distinct population suited to anti-Type 2 biologics such as dupilumab.

Limitations and Future Directions

- Cross-sectional design precludes causal inference; exposures were ascertained retrospectively and are subject to recall bias.
- The CRS subgroup is small, the cohort is exclusively male, and cytokines cytokines reflect a single timepoint.
- Many NGW controls were also deployed, likely narrowing the true contrast in toxicant exposure between groups.
- Longitudinal sampling and comparison against non-deployed civilians are needed to link cumulative exposure to Th2 polarization.