Pre-pandemic leukocyte count is associated with severity of post-acute sequelae of SARS-CoV-2 infection among older women in the Women's Health Initiative

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Abstract

Objective: Although dysregulated inflammation has been postulated as a biological mechanism associated with post-acute sequelae of severe acute respiratory coronavirus 2 (SARS-CoV-2) infection (PASC) and shown to be a correlate and an outcome of PASC, it is unclear whether inflammatory markers can prospectively predict PASC risk. We examined the association of leukocyte count and high-sensitivity C-reactive protein (hsCRP) concentrations, measured ~25 years prior to the coronavirus disease 2019 (COVID-19) pandemic, with PASC, PASC severity, and PASC-associated cognitive outcomes at follow-up among postmenopausal women.

Methods: Using biomarker data from blood specimens collected during pre-pandemic enrollment (1993–1998) and data on 1,237 Women's Health Initiative participants who completed a COVID-19 survey between June 2021 and February 2022, we constructed multivariable regression models that controlled for pertinent characteristics. PASC status was defined according to established World Health Organization criteria.

Results: Controlling for baseline characteristics, $\log_e$-transformed leukocyte count ($\beta = 0.27$; 95% confidence interval, 0.07–0.47, $P = 0.009$) and leukocyte count ≥5.5 × 1,000 cells/μL ($\beta = 0.13$; 95% confidence interval, 0.02–0.23; $P = 0.02$) were positively associated with PASC severity, defined as the sum of PASC symptoms, but not associated with overall PASC occurrence or PASC-related cognitive outcomes. Concentration of hsCRP, available on only ~27% of participants, was not associated with any of the PASC outcomes, controlling for the same covariates.

Conclusions: Leukocyte count, a widely available clinical marker of systemic inflammation, is an independent predictor of PASC severity in postmenopausal women. Heightened inflammation preceding SARS-CoV-2 infection may contribute to PASC development. Limited statistical power to assess hsCRP role warrants further study.

Key Words: Inflammation, Long coronavirus disease 2019, Post-acute sequelae of SARS-CoV-2 infection, Women.

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Millions of people in the United States and worldwide suffer from post-acute sequelae of severe acute respiratory coronavirus 2 (SARS-CoV-2) infection (PASC),[1] defined by a Delphi consensus as "a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis."[2,3] PASC has become an

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increasingly important public health issue, resulting in an increased number of individuals with sustained debilitating outcomes, including cognitive impairment and chronic fatigue syndrome, and detrimental long-term effects on the healthcare system.[4] Despite the enormous individual and societal burden of PASC, our understanding and approach to estimating risks associated with PASC remains in its infancy.

Patients suffering from PASC often present with multiple symptoms, which reflects their severity level and burden.[5] In PASC, brain fog, that is, cognitive impairment, is one of the most common symptoms, second only to fatigue, occurring in about 70% of patients.[6–8] A recent study showed that 86% of participants who reported brain fog or cognitive impairment had reduced work ability,[8] severely and adversely impacting their quality of life.[9] Furthermore, older adults have an excess risk of persistent and new sequelae after a SARS-CoV-2 infection,[10] and the prevalence of PASC is reported to be up to four times higher among women.[11] Therefore, it is important to investigate potential mechanisms and risk factors as well as symptomatology of PASC in older women.

The pathogenesis of PASC, however, remains unclear. Although primarily a respiratory disease, the sustained effects of COVID-19 on many organ systems are hypothesized to be via the biological pathway of eliciting a cytokine storm.[12,13] Studies have shown excessive immune response to COVID-19 infection,[14,15] characterized by elevated proinflammatory markers following diagnosis, which is also postulated to contribute to PASC.[16] A prominent marker of inflammation, high-sensitivity C-reactive protein (hsCRP), is predictive of PASC-related complications and prognosis,[17,18] although shown to be elevated to abnormal levels only in about 8% of PASC cases.[19] Mechanistically, SARS-CoV-2 could enter the brain via the olfactory system, activating microglia to release proinflammatory molecules, leading to neuroinflammation and its accompanying functional impact such as brain fog and cognitive impairment.[19] Neuroinflammation could also be accompanied by systemic inflammation with an increased leukocyte count in the blood. Clinical studies have found that older adults who had COVID-19 with a higher leukocyte count had worse prognosis, indicating that they were more likely to develop a critical illness and had higher rates of intensive care unit (ICU) admission and mortality. Conversely, conflicting evidence is found in another study showing that patients with COVID-19 had a lower leukocyte count compared to uninfected individuals. Despite these postulated biological mechanisms for dysregulated inflammation underlying PASC, it is unclear whether routinely used clinical inflammatory markers measured preinfection can be used to predict the risk of developing PASC and related outcomes.

The role played by acute COVID-19 symptom severity in PASC development remains inconclusive.[5,20] Therefore, uncovering preexisting risk factors indicated by routinely measured clinical biomarkers prior to SARS-CoV-2 infection would be of high utility in identifying high-risk groups and developing PASC prevention strategies. As women have been shown to have a higher risk of developing PASC compared to men,[20] rich longitudinal data afforded by studies such as the Women's Health Initiative (WHI) could offer valuable insights. Several previous reports based on the WHI observational study have shown the utility of routinely used clinical proinflammatory markers, including leukocyte count and hsCRP, in predicting future adverse health outcomes many years later, such as type 2 diabetes,[21] multiple cancer types,[22] various cardiovascular events, and mortality.[23] Thus, in this study of a secondary analysis of the WHI data, we examined whether leukocyte count and/or hsCRP concentration measured among midlife and older postmenopausal women pre-COVID-19 pandemic was associated prospectively with PASC outcomes, specifically PASC (primary), PASC severity (secondary), and PASC-associated cognitive outcomes (exploratory), at follow-up approximately 25 years later among postmenopausal women.

METHODS

Database

Baseline Women's Health Initiative clinical trials and observational study (1993–1998)

The WHI collected baseline data, between 1993 and 1998, among 161,808 postmenopausal women, who were enrolled at 40 geographically diverse clinical centers (24 states and the District of Columbia) in the United States.[24] Postmenopausal women, 50 to 79 years of age, completed a WHI baseline assessment including demographics, anthropometric and clinical characteristics, medical history, and medication use. They also underwent blood draws for biomarker measurements.

WHI COVID-19 survey 2 (June 2021–February 2022)

Two COVID-19 surveys were conducted using self-administered questionnaires among WHI participants. Although both surveys included items on COVID-19 testing and results, only Survey 2 (completed between June 2021 and February 2022) included items on 16 PASC-related symptoms, namely, brain fog, memory problems, difficulty thinking or concentrating, fever, cough, headache, chest pain/tightness, fast heartbeat/heart pounding, muscle pain, joint pain, fatigue, shortness of breath/difficulties breathing, loss of smell, loss of taste, sleep disturbance, and general malaise. Specifically, if the survey respondents reported at least one positive COVID-19 test, they were asked to report whether they experienced these symptoms after a COVID-19 diagnosis and to report the duration of these symptoms as follows: <2 weeks, 2 weeks to <8 weeks, 8 weeks to <6 months, and ≥6 months.

Study variables

Independent variables

Venous blood samples were collected at the WHI baseline visit, on site, in the morning, and after a 12-hour tobacco-free fast by certified staff at multiple clinical sites.[23] These samples were collected in a tube containing the anticoagulant, EDTA, and then analyzed at local laboratories within the WHI clinical centers. Approximately 160,000 participants (nearly all participants) had available leukocyte count (1,000 cells/μL), and nearly 78,000 participants had hsCRP concentration (mg/L) at the WHI baseline visit (1993–1998) measured separately in several ancillary studies.

Dependent variables

Data elements used to define primary, secondary, and exploratory PASC outcomes were derived from the WHI COVID-19 Survey 2, which was completed between June 2021 and February 2022, as described in Table 1. Briefly, PASC outcomes were defined only among participants who reported a positive COVID-19 test result. The primary outcome, PASC, was operationalized as a binary (yes/no) variable based on self-report of ≥1 COVID-19 symptoms for ≥8 weeks as defined by the World Health Organization and the Centers for Disease Control and Prevention.[2] Sixteen items, each pertaining to ≥8 weeks of a self-reported COVID-19 symptom, were coded as 0 for "no" and 1 for "yes," and these items were summed to create a PASC severity score that ranged between 0 and 16. Subsequently, two secondary outcomes were defined among a subset of participants who reported a positive COVID-19 test result and screened positive for PASC, namely, a binary PASC severity and a continuous PASC severity outcome. The binary PASC severity outcome (yes/no) was defined based on the presence of at least two PASC symptoms, whereas the continuous PASC severity outcome was defined as the summation of PASC symptoms, ranging between 1 and 16. Lastly, three exploratory PASC outcomes with a focus on cognitive symptoms, that is, "memory problems," "confusion or difficulty thinking or concentrating," and "brain fog," were defined as binary (yes/no) variables among participants who reported a positive COVID-19 test result.

Covariates

Potential confounders for the hypothesized role of inflammation in PASC outcomes from the WHI baseline were defined as follows: age (years), race (White vs other [American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islanders, Black, and more than one race]), ethnicity (Hispanic vs non-Hispanic), education (some college/college/higher level vs less than high school/high school), body mass index (BMI) (kg/m^2), smoking status (ever vs never), alcohol consumption (nondrinker, former drinker, <1 drink/mo, <1 drink/wk, 1 to <7 drinks/wk), medical history of cardiometabolic diseases (yes/no) (diabetes, hypertension, hypercholesterolemia, transient ischemic attack, stroke, myocardial infarction, cardiac arrest, heart failure, cardiac catheterizations, heart or coronary bypass surgery, angioplasty of the coronary arteries, carotid endarterectomy or carotid angioplasty, atrial fibrillation, aortic aneurysm),[23] history of cancer (yes/no) (brain, breast, bone, bladder, cervical, colorectal, endometrial, Hodgkin's lymphoma, ovarian, liver, lung, lymphoma, skin, thyroid, or other),[22] history of rheumatoid arthritis (yes/no), physical activity[25] (MET units) measured by the International Physical Activity Questionnaire, and hormone therapy use (yes/no) as well as COVID-19-specific variables, including COVID-19 vaccination status (yes/no),[26] COVID-19-specific therapies (yes/no), and COVID-19 severity, that is, ICU admission (yes/no) and hospitalization (yes/no). Multivariable regression models included a priori confounders (age, race, ethnicity, BMI, smoking status, histories of cardiometabolic disease, cancer, and rheumatoid arthritis) previously found to be associated with chronic diseases and inflammatory markers in WHI studies,[22,23] as well as covariates that were found to differ between PASC and non-PASC participants at $\alpha = 0.25$. Accordingly, three multivariate regression models were constructed for each hypothesized relationship. Model I was a partially adjusted model that controlled for baseline age, race, and ethnicity. Model II was a fully adjusted model that additionally controlled for BMI, smoking status, hormone therapy use, as well as histories of cardiometabolic disease, cancer, and rheumatoid arthritis at baseline. Model III was a sensitivity analysis that additionally controlled for COVID-19-specific variables, including vaccination, therapies, ICU admission, and hospitalization at follow-up. Covariates were entered into Models I, II, and III based on *a priori* conceptualizations.

Statistical analysis

All statistical analyses were performed using Stata version 18 (StataCorp, College Station, TX). Summary statistics (eg, mean, standard deviation, minimum, maximum) were calculated, and frequency distributions were examined to determine if statistical assumptions were violated, while assessing the nature of any missing data. After assessing their distribution, leukocyte count and hsCRP concentration were $\log_e$-transformed prior to being added to regression models. WHI participants with extreme values for leukocyte count <2.5 × 1,000 cells/μL or >15 × 1,000 cells/μL as well as those with hsCRP ≥25 mg/L were excluded from analyses, as previously described.[22] Measures of association (β) with their 95% confidence intervals (CI) were reported for each independent variable within multivariable regression models. We constructed three separate multivariable regression models. First, binary logistic and Poisson regression models were constructed to assess the relationship of each $\log_e$-transformed biomarker (ie, leukocyte count, hsCRP) assessed at the WHI baseline visit with each primary, secondary, or exploratory PASC outcome, controlling for covariates. Second, the same analyses were conducted whereby the two $\log_e$-transformed biomarkers (ie, leukocyte count, hsCRP) assessed at WHI baseline visit and covariates were entered simultaneously in regression models of these PASC outcomes. Third, sensitivity analyses were performed whereby leukocyte count and hsCRP concentration were defined as dichotomous variables and entered separately in regression models for predictors of PASC outcomes, controlling for covariates. The leukocyte count was dichotomized according to the median level in our sample (≥5.5 × 1,000 cells/μL vs <5.5 × 1,000 cells/μL whereas hsCRP concentration was dichotomized based on a clinical cutoff point indicating high risk for cardiovascular disease (≥3 mg/L vs <3 mg/L).[27] To address missing data on items pertaining to PASC symptoms, proration was applied whereby the mean values were imputed for participants with missing data on <8 out of 16 items. After restricting the study sample to WHI participants with no extreme values on inflammatory markers as previously described,[22] multiple imputations with chained equations (20 imputations and 10 iterations) were applied for missing data on PASC outcomes, inflammatory markers, and covariates, using linear and binary logistic regression models, as appropriate. A total of 37,289 (23.0%) women of 161,808 WHI participants completed the COVID-19 Survey 2 between June 2021 and February 2022. Of these, 1,237 (3.3%) reported at least 1 positive test for COVID-19. The final analytic sample

TABLE 1. Definition of post-acute sequelae of SARS-CoV-2 infection (PASC) outcomes

Subset	Outcomes
COVID-19 positive subset: Only participants who have reported a positive test result for COVID-19 (answered "yes" to Question 9 of COVID-19 Survey 2 [Have you been tested for COVID-19?] and answered "yes" to Question 9.4 of COVID-19 Survey 2 [Did any of these tests come back positive for a COVID-19 infection?]) were included in the analysis for this outcome measure.	***Primary outcome: PASC (yes (1), no (0)):*** The "yes" and "no" groups were defined among participants who answered "yes" to Question 9 of COVID-19 Survey 2 [Have you been tested for COVID-19?] and answered "yes" to Question 9.4 [Did any of these tests come back positive for a COVID-19 infection?] of COVID-19 Survey 2. PASC was operationalized as participants with a positive COVID-19 test who reported experiencing ≥1 symptom 8 wk and beyond (answering "yes" to either the response category "8 wk to <6 mo" or "6 mo or more for ≥1 symptom"), as per World Health Organization and Centers for Disease Control and Prevention PASC definition.[2]
PASC subset: Apart from reporting previously testing positive for COVID-19 (answered "yes" to Question 9 of COVID-19 Survey 2 [Have you been tested for COVID-19?] and answered "yes" to Question 9.4 of COVID-19 Survey 2 [Did any of these tests come back positive for a COVID-19 infection?]), only participants fulfilling the additional criterion of having a self-reported PASC as defined above in the primary outcome were included.	***Secondary outcomes:*** ***1. PASC Severity (yes, no):*** Severe cases of PASC were defined in the presence of multiple COVID-19 associated symptoms (≥ 2 of 16) from the list in Question 9.5, among participants with self-reported PASC. ***2. PASC Severity (sum):*** Based on Question 9.5 of COVID-19 Survey 2, PASC severity was operationalized as a count outcome, derived from the summation of 16 symptoms included in the list, among participants with self-reported PASC. Participants who responded "yes" and "no" to either the response category "8 wk to <6 mo" or "6 mo or more for ≥1 symptom" were coded as 1 and 0, respectively. Hence, the range of the total score will be 1–16.
PASC subset: Only participants who have reported a positive test result for COVID-19 (answered "yes" to Question 9 of COVID-19 Survey 2 [Have you been tested for COVID-19?] and answered "yes" to Question 9.4 of COVID-19 Survey 2 [Did any of these tests come back positive for a COVID-19 infection?]) were included in the analysis for this outcome measure.	***Exploratory outcomes:*** ***Three PASC cognition-related individual symptoms (yes (1), no (0)):*** Three cognition-related individual symptoms (ie, memory problems, confusion or difficulty thinking or concentrating, and brain fog) as individual symptom outcome measures. Participants with a positive COVID-19 test who responded "yes" and "no" to either the response category "8 wk to <6 mo" or "6 mo or more for ≥1 symptom."

Source: Form 191–COVID-19 Survey 2 (whi.org).

COVID-19, coronavirus disease 2019; PASC, post-acute sequelae of SARS-CoV-2 infection; SARS-CoV-2, severe acute respiratory coronavirus 2.

after multiple imputation consisted of a maximum of 1,237 WHI participants for analyses excluding hsCRP concentration and a maximum of 332 of 1,237 WHI participants (~27%) for analyses including hsCRP concentration (Fig. 1). Two-sided statistical tests were examined at $\alpha = 0.05$, with P values between 0.05 and 0.1 considered as having borderline statistical significance. Taking familywise Bonferroni correction for multiple comparisons whereby three models (Models I, II, and III) were applied for each hypothesized relationship, statistical significance was evaluated at $\alpha = 0.02$, with P values between 0.02 and 0.03 considered as having borderline statistical significance.

RESULTS

The prevalence rates were 35.6% (95% CI, 32.8%-38.3%) for 1 or more PASC symptoms, 12.7% (95% CI, 10.8%-14.6%) for "memory problems," 11.1% (95% CI, 9.3%-12.9%) for "confusion or difficulty thinking or concentrating," and 11.6% (95% CI, 9.7%-13.4%) for "brain fog." We also estimated that the prevalence rate for experiencing two or more PASC symptoms was 74.8% (95% CI, 70.7%-79.0%). Also, the mean number of PASC symptoms was 3.70, with 95% CI ranging between 3.44 and 3.97 symptoms.

Table 2 describes the characteristics of WHI participants in the overall study sample, including demographic, socioeconomic, lifestyle, and health characteristics assessed at the WHI baseline visit, and COVID-19-specific characteristics based on the COVID-19 Survey 2. Women who self-reported PASC symptoms were significantly younger and more likely to be ever-smokers and to be taking menopausal hormone therapy at the WHI baseline visit. They were also more likely to have been vaccinated for COVID-19, to have received COVID-19-specific therapies, and/or to have experienced severe COVID-19, as indicated by COVID-19-specific hospitalizations and ICU admissions, than their non-PASC counterparts.

The relationships of $\log_e$-transformed leukocyte count and hsCRP concentration examined separately at the WHI baseline visit with PASC outcomes in multivariable regression models are presented in Table 3. Log_e-transformed hsCRP concentration was not associated with any of the PASC outcomes. In contrast, $\log_e$-transformed leukocyte count was associated with the number of PASC symptoms but not with other primary, secondary, or exploratory PASC outcomes. Specifically, a positive relationship was observed between $\log_e$-transformed leukocyte count at the WHI baseline visit and the sum of PASC symptoms at the COVID-19 Survey 2 visit, in Poisson regression models that adjusted for baseline and/or follow-up covariates (Model I: $\beta = 0.36$; 95% CI, 0.17-0.56; $P < 0.0001$; Model II: $\beta = 0.27$; 95% CI, 0.07-0.47; $P = 0.009$; Model III: $\beta = 0.20$; 95% CI, 0.002-0.40; $P = 0.047$). As shown in Table 4, leukocyte count ≥5.5 × 1,000 cells/μL at the WHI baseline visit and the sum of PASC symptoms at the COVID-19

Survey 2 visit were positively related in Model I (β = 0.17; 95% CI, 0.07-0.27; P = 0.001), Model II (β = 0.13; 95% CI, 0.02-0.23; P = 0.02), and Model III (β = 0.13; 95% CI, 0.03-0.23; P = 0.01). As shown in Table 5, hsCRP concentration ≥3 mg/L was significantly associated with the sum of PASC symptoms in Model I (β = 0.22; 95% CI, 0.02-0.43; P = 0.03), but not in Models II and III.

Further sensitivity analyses displayed in Supplemental Tables 1-3 (http://links.lww.com/MENO/B336) whereby $\log_e$-transformed leukocyte count and $\log_e$-transformed hsCRP concentration were entered simultaneously into multivariable regression models for the PASC primary, secondary, and exploratory outcomes in a subset of 332 participants revealed that $\log_e$-transformed leukocyte count at baseline was no longer associated with the sum of PASC symptoms at the COVID-19 Survey 2 visit, in multivariable regression models that controlled for $\log_e$-transformed hsCRP and covariates in Models I-III. Also, $\log_e$-transformed leukocyte count was not associated with other PASC outcomes, in multivariable regression models that also controlled for $\log_e$-transformed hsCRP concentration. Finally, $\log_e$-transformed hsCRP concentration was not significantly associated with any of the PASC outcomes in multivariable regression models that also controlled for $\log_e$-transformed leukocyte count.

DISCUSSION

In this study, we examined two routinely used clinical immune parameters (leukocyte count and hsCRP concentration) collected pre-pandemic, from approximately 25 years prior to the assessment of PASC outcomes among older women, and found that a higher leukocyte count was associated with self-reported PASC severity, even after controlling for pertinent confounders and correcting for multiple testing. The study also revealed that hsCRP concentration was not associated with any of the examined PASC outcomes, controlling for the same confounders. Our finding that higher level of leukocyte count was prospectively and independently associated with more PASC symptoms suggests that midlife and older women who experience severe PASC may be more likely to have had chronic low-grade inflammation prior to the acute COVID-19 event pre-pandemic. These findings are consistent with evidence showing that elevated inflammatory markers during or after COVID-19 infection are associated with subsequent PASC severity and PASC-associated symptoms.[28,29] It is worth noting that, unlike previous studies which had examined inflammatory markers *after* patients had contracted COVID-19 or experienced PASC symptoms, our study is the first to examine the association of inflammatory markers assessed *before* SARS-CoV2 infection as predictors of PASC and PASC severity. Furthermore, of the several potential immunological mechanisms proposed for PASC, our findings of an association between a clinical marker of baseline inflammation (even when assessed many years pre-pandemic) and PASC symptoms may lend support to the hypothesis of inflammatory dysregulation underlying PASC.[30] We also recognize that other PASC mechanisms may exist, including the potential roles of persistent viral antigen and immune activation after infection resolution,[30] but these are beyond the scope of this investigation.

Previous findings from WHI investigations have also highlighted the association between leukocyte count and incidence of other health outcomes several years later. For example, a previous study from the WHI report found a higher leukocyte count at baseline was predictive of increased risks for future cardiovascular events and all-cause mortality in postmenopausal women.[23] Another WHI study found a high baseline leukocyte count was positively associated with coronary heart disease mortality risk, although its association with cancer mortality risk was weaker.[31] Lastly, another WHI study showed that postmenopausal women with higher leukocyte count had higher risk of invasive breast, colorectal, endometrial, and lung cancers, as well as higher risk of mortality attributable to several cancers.[23] Similar to our models, all models controlled for pertinent covariates, thus establishing the independent associations of leukocyte count with multiple health outcomes and highlighting its predictive utility.

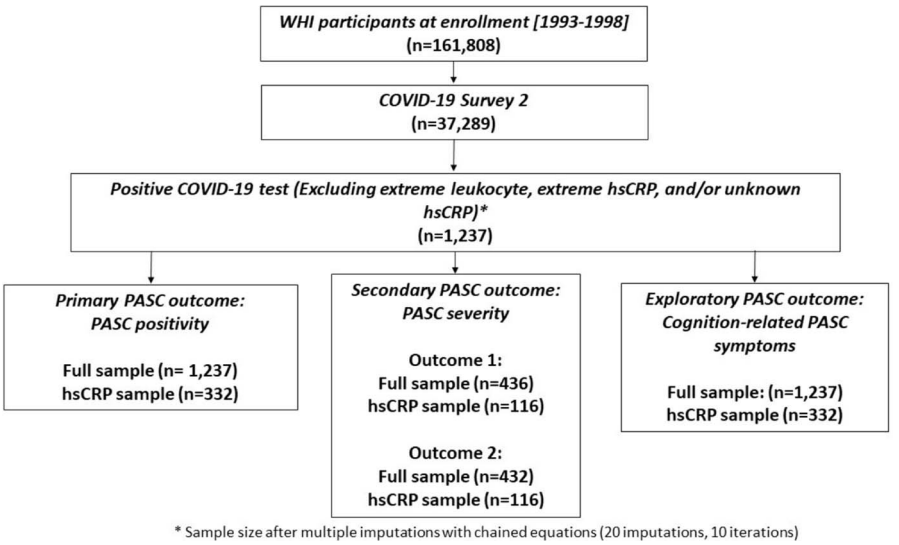

FIG. 1. Study flowchart. COVID-19, coronavirus disease 2019; hsCRP, high-sensitivity C-reactive protein; PASC, post-acute sequelae of SARS-CoV-2 infection; SARS-CoV-2, severe acute respiratory coronavirus 2; WHI, Women's Health Initiative.

TABLE 2. Descriptive statistics of the baseline characteristics categorized by PASC status (n = 1,237)[a]

	Total	Without PASC	With PASC	*P*
		WHI Baseline		
Age (years)				0.04
Mean (SE)	58.84 (0.16)	59.09 (0.21)	58.38 (0.27)	
Race (%)				0.18
White	92.17	92.96	90.73	
Other[b]	7.83	7.04	9.27	
Ethnicity (%)				0.84
Hispanic	3.65	3.72	3.50	
Non-Hispanic	96.35	96.27	96.50	
Education (%)				0.36
Less than high school/high school	27.66	28.54	26.05	
Some college/completed college or higher level	72.34	71.46	73.94	
Body mass index (kg/m^2)				0.17
Mean (SE)	27.82 (0.15)	27.66 (0.19)	28.09 (0.26)	
Smoking status (%)				0.06
Never smoker	53.22	55.21	49.63	
Ever smoker	46.77	44.79	50.37	
Alcohol consumption (%)				0.44
Nondrinker	11.11	11.80	9.86	
Former drinker	14.54	13.44	16.55	
<1 drink/mo	11.19	11.14	11.28	
<1 drink/wk	24.52	25.86	22.08	
1 to <7 drinks/wk	27.69	27.25	28.47	
7+ drinks/wk	10.94	10.50	11.75	
Medical history of cardiometabolic diseases (%)				0.84
Yes	39.21	38.99	39.58	
No	60.79	61.00	60.41	
Medical history of cancers (%)				0.89
Yes	15.20	15.29	15.02	
No	84.80	84.70	84.97	
Medical history of rheumatoid arthritis (%)				0.91
Yes	3.72	3.76	3.63	
No	96.28	96.23	96.36	
Physical activity (in MET unit)				0.59
Mean (SE)	12.67 (0.38)	12.82 (0.49)	12.39 (0.60)	
Hormone therapy use (%)				0.03[c]
Yes	72.44	70.28	76.34	
No	27.55	29.71	23.65	
		COVID-19 Survey 2		
COVID-19 vaccination status (%)				0.003[d]
Yes	90.19	88.28	93.67	
No	9.81	11.72	6.32	
COVID-19-specific medication or treatment (%)				0.083
Yes	95.23	94.37	96.78	
No	4.77	5.63	3.22	
COVID-19 severity (ICU admission) (%)				
Yes	4.04	2.82	6.26	0.005[d]
No	95.96	97.18	93.74	
COVID-19 severity (hospitalization) (%)				<0.0001[e]
Yes	18.76	14.54	26.38	
No	81.24	85.46	73.62	

COVID-19, coronavirus disease 2019; PASC, post-acute sequelae of SARS-CoV-2 infection; SARS-CoV-2, severe acute respiratory coronavirus 2; SE, standard error; WHI, Women's Health Initiative.

Medical history of cardiometabolic diseases is defined as the presence/absence of diabetes, hypertension, hypercholesterolemia, transient ischemic attack, stroke, myocardial infarction, cardiac arrest, heart failure, cardiac catheterizations, heart or coronary bypass, angioplasty of the coronary arteries, carotid endarterectomy or carotid angioplasty, atrial fibrillation, and/or aortic aneurysm; medical history of cancers is defined as the presence/absence of brain, breast, bone, bladder, cervical, colorectal, endometrial, Hodgkin's lymphoma, ovarian, liver, lung, lymphoma, skin, thyroid, and/or other cancer types.

[a]Statistical analyses were performed after imputations with chained equations were applied. *P* values are based on chi-square and independent samples *t* tests.

[b]American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islanders, Black, and more than one race.

[c]Indicates $P < 0.05$.

[d]Indicates $P < 0.01$.

[e]Indicates $P < 0.001$.

One of several hypotheses for PASC and associated symptoms is that the chronic inflammation causes wear and tear in the body, and that the acute inflammatory response induced by COVID-19 infection may overwhelm the body's immune response and damage tissues, thus causing the debilitating symptoms. It is noteworthy, however, that there was no statistically significant relationship between baseline hsCRP concentration and PASC outcomes 25 years later, even among those with hsCRP concentrations at baseline above the clinical cutoff point of 3 mg/L signifying elevated cardiovascular disease risk, after controlling for covariates. Our null findings pertaining to hsCRP are consistent with findings from a recent study showing that C-reactive protein was not related to concurrent fatigue or neuropsychiatric symptoms in patients with PASC[29] and another study on the lack of association between trajectories in inflammatory markers and PASC-associated cognitive symptoms among patients hospitalized for COVID-19.[32] These studies, however, measured hsCRP during or after the acute COVID-19 infection. The reasons behind a lack of associations observed between hsCRP and PASC remain unclear, but we cannot rule out the possibility of insufficient statistical power due to the smaller sample of WHI participants with available hsCRP versus leukocyte count measurements.

Our findings should be interpreted with caution, considering several limitations. First, we examined only two biomarkers at one time point many years before the reported PASC outcomes, and associations may be stronger with more recent and repeated pre-COVID-19 measurements. Second, a positive test result for COVID-19 was based on self-report, and many PASC symptoms are not exclusive to COVID-19,

TABLE 3. Associations of each inflammatory biomarker (leukocyte count or hsCRP concentration) measured at WHI baseline visit with each PASC outcome measured at COVID-19 survey follow-up time[a]

	β (95% CI), *P*		
	Model I	**Model II**	**Model III**
	Log_e-transformed leukocyte count (1,000 cells/μL)		
Self-reported PASC (n = 1,237)			
Log_e (leukocyte count)	0.06 (−0.41 to 0.52), *P* = 0.82	−0.08 (−0.56 to 0.40), *P* = 0.75	−0.11 (−0.59 to 0.38), *P* = 0.67
PASC Severity (binary) (n = 436)			
Log_e (leukocyte count)	0.08 (−0.78 to 0.95), *P* = 0.85	−0.19 (−1.08 to 0.69), *P* = 0.67	−0.21 (−1.13 to 0.70), *P* = 0.64
PASC Severity (sum of PASC symptom counts) (n = 432)			
Log_e (leukocyte count)	0.36 (0.17 to 0.56), *P* < 0.0001[b,c]	0.27 (0.07 to 0.47), *P* = 0.009[b,c]	0.20 (0.002 to 0.40), *P* = 0.047[b]
Memory problems (n = 1,237)			
Log_e (leukocyte count)	0.14 (−0.54 to 0.82), *P* = 0.69	0.07 (−0.63 to 0.77), *P* = 0.84	0.03 (−0.69 to 0.75), *P* = 0.94
Confusion or difficulty thinking or concentrating (n = 1,237)			
Log_e (leukocyte count)	0.04 (−0.67 to 0.75), *P* = 0.91	−0.10 (−0.86 to 0.65), *P* = 0.79	−0.19 (−0.97 to 0.58), *P* = 0.62
Brain fog (n = 1,237)			
Log_e (leukocyte count)	0.41 (−0.27 to 1.08), *P* = 0.24	0.32 (−0.38 to 1.02), *P* = 0.37	0.26 (−0.46 to 0.98), *P* = 0.48
	Log_e-transformed hsCRP concentration (mg/L)		
Self-reported PASC (n = 332)			
Log_e (hsCRP concentration)	−0.04 (−0.24 to 0.17), *P* = 0.73	−0.09 (−0.32 to 0.14), *P* = 0.45	−0.13 (−0.36 to 0.11), *P* = 0.30
PASC Severity (binary) (n = 116)			
Log_e (hsCRP concentration)	0.07 (−0.33 to 0.46), *P* = 0.74	−0.19 (−0.64 to 0.26), *P* = 0.41	−0.24 (−0.72 to 0.24), *P* = 0.33
PASC Severity (sum of PASC symptom counts) (n = 116)			
Log_e (hsCRP concentration)	0.05 (−0.04 to 0.14), *P* = 0.30	−0.06 (−0.16 to 0.04), *P* = 0.27	−0.09 (−0.20 to 0.01), *P* = 0.08
Memory problems (n = 332)			
Log_e (hsCRP concentration)	0.04 (−0.27 to 0.34), *P* = 0.82	−0.03 (−0.36 to 0.31), *P* = 0.87	−0.08 (−0.43 to 0.27), *P* = 0.67
Confusion or difficulty thinking or concentrating (n = 332)			
Log_e (hsCRP concentration)	0.07 (−0.27 to 0.40), *P* = 0.69	−0.05 (−0.42 to 0.32), *P* = 0.79	−0.19 (−0.59 to 0.20), *P* = 0.34
Brain fog (n = 332)			
Log_e (hsCRP concentration)	−0.01 (−0.32 to 0.29), *P* = 0.93	−0.11 (−0.46 to 0.24), *P* = 0.53	−0.14 (−0.51 to 0.22), *P* = 0.43

β, slope; CI, confidence interval; COVID-19, coronavirus disease 2019; hsCRP, high-sensitivity C-reactive protein; ICU, intensive care unit; PASC, post-acute sequelae of SARS-CoV-2 infection; SARS-CoV-2, severe acute respiratory coronavirus 2; WHI, Women's Health Initiative.

[a]Statistical analyses were performed after imputations with chained equations were applied. Multivariable binary logistic and Poisson regression models were constructed for log_e-transformed leukocyte count or log_e-transformed hsCRP concentration at WHI baseline as predictors of primary, secondary, and exploratory PASC outcomes, controlling for pertinent confounders. Models I were controlled for baseline age (years), race (White vs other [American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islanders, Black, and more than one race]), and ethnicity (Hispanic vs non-Hispanic). Models II were controlled for all variables in Models I + smoking status (ever/never), body mass index (kg/m^2), cardiometabolic disease (yes/no), cancer (yes/no), rheumatoid arthritis (yes/no), and hormone therapy (yes/no), at baseline. Models III were controlled for all variables in Models II + COVID-19 vaccination (yes/no), COVID-19 therapies (yes/no), COVID-19 ICU admission (yes/no), and COVID-19 hospitalization (yes/no) at follow-up.

[b]Indicates *P* < 0.05 (before familywise Bonferroni correction).

[c]Indicates *P* < 0.02 (after familywise Bonferroni correction).

TABLE 4. Relationships of leukocyte count measured at WHI baseline and defined as a categorical variable (≥5.5 × 1,000 cells/μL vs <5.5 × 1,000 cells/μL) with PASC outcomes measured at COVID-19 survey follow-up time[a]

	β (95% CI), *P*		
	Model I	**Model II**	**Model III**
Self-reported PASC (n = 1,237)			
Leukocyte count ≥5.5 × 1,000 cells/μL	0.08 (−0.16 to 0.32), *P* = 0.50	0.03 (−0.22 to 0.28), *P* = 0.83	0.02 (−0.24 to 0.27), *P* = 0.89
PASC Severity (binary) (n = 436)			
Leukocyte count ≥5.5 × 1,000 cells/μL	0.22 (−0.24 to 0.68), *P* = 0.36	0.13 (−0.34 to 0.60), *P* = 0.59	0.09 (−0.39 to 0.58), *P* = 0.69
PASC Severity (sum of PASC symptom counts) (n = 432)			
Leukocyte count ≥5.5 × 1,000 cells/μL	0.17 (0.07 to 0.27), *P* = 0.001[b,c]	0.13 (0.02 to 0.23), *P* = 0.02[b,c]	0.13 (0.03 to 0.23), *P* = 0.01[b,c]
Memory problems (n = 1,237)			
Leukocyte count ≥5.5 × 1,000 cells/μL	0.05 (−0.30 to 0.40), *P* = 0.77	0.03 (−0.33 to 0.39), *P* = 0.89	0.03 (−0.34 to 0.40), *P* = 0.88
Confusion or difficulty thinking or concentrating (n = 1,237)			
Leukocyte count ≥5.5 × 1,000 cells/μL	−0.03 (−0.39 to 0.34), *P* = 0.88	−0.09 (−0.47 to 0.29), *P* = 0.64	−0.11 (−0.50 to 0.28), *P* = 0.59
Brain fog (n = 1,237)			
Leukocyte count ≥5.5 × 1,000 cells/μL	0.22 (−0.14 to 0.58), *P* = 0.24	0.18 (−0.18 to 0.56), *P* = 0.33	0.19 (−0.19 to 0.57), *P* = 0.34

β, slope; CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; PASC, post-acute sequelae of SARS-CoV-2 infection; SARS-CoV-2, severe acute respiratory coronavirus 2; WHI, Women's Health Initiative.

[a]Statistical analyses were performed after imputations with chained equations were applied. Multivariable binary logistic and Poisson regression models for leukocyte count ≥5.5 × 1,000 cells/μL at WHI baseline as predictors of primary, secondary, and exploratory PASC outcomes, controlling for pertinent confounders. Models I were controlled for baseline age (years), race (White vs other [American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islanders, Black, and more than one race]), and ethnicity (Hispanic vs non-Hispanic). Models II were controlled for all variables in Models I + smoking status (ever/never), body mass index (kg/m^2), cardiometabolic disease (yes/no), cancer (yes/no), rheumatoid arthritis (yes/no), and hormone therapy (yes/no), at baseline. Models III were controlled for all variables in Models II + COVID-19 vaccination (yes/no), COVID-19 therapies (yes/no), COVID-19 ICU admission (yes/no), and COVID-19 hospitalization (yes/no) at follow-up.

[b]Indicates $P < 0.05$ (before familywise Bonferroni correction).

[c]Indicates $P < 0.02$ (after familywise Bonferroni correction).

TABLE 5. Relationships of hsCRP concentration measured at WHI baseline and defined as a categorical variable (≥3 mg/L vs <3 mg/L) with PASC outcomes measured at COVID-19 survey follow-up time[a]

	β (95% CI)		
	Model I	**Model II**	**Model III**
Self-reported PASC (n = 332)			
hsCRP concentration ≥3 mg/L	−0.03 (−0.49 to 0.43), *P* = 0.89	−0.12 (−0.64 to 0.38), *P* = 0.62	−0.15 (−0.68 to 0.37), *P* = 0.56
PASC Severity (binary) (n = 116)			
hsCRP concentration ≥3 mg/L	0.44 (−0.43 to 1.31), *P* = 0.32	−0.02 (−1.02 to 0.98), *P* = 0.96	−0.02 (−1.07 to 1.04), *P* = 0.97
PASC Severity (sum of PASC symptom counts) (n = 116)			
hsCRP concentration ≥3 mg/L	0.22 (0.02 to 0.43), *P* = 0.03[b]	0.006 (−0.22 to 0.24), *P* = 0.96	0.007 (−0.22 to 0.24), *P* = 0.95
Memory problems (n = 332)			
hsCRP concentration ≥3 mg/L	0.41 (−0.24 to 1.07), *P* = 0.22	0.31 (−0.41 to 1.03), *P* = 0.40	0.24 (−0.50 to 0.99), *P* = 0.52
Confusion or difficulty thinking or concentrating (n = 332)			
hsCRP concentration ≥3 mg/L	0.36 (−0.37 to 1.10), *P* = 0.33	0.16 (−0.65 to 0.97), *P* = 0.70	0.006 (−0.87 to 0.88), *P* = 0.99
Brain fog (n = 332)			
hsCRP concentration ≥3 mg/L	0.40 (−0.29 to 1.09), *P* = 0.26	0.24 (−0.51 to 1.01), *P* = 0.52	−0.21 (−0.56 to 0.99), *P* = 0.59

β, slope; CI, confidence interval; COVID-19, coronavirus disease 2019; hsCRP, high-sensitivity C-reactive protein; ICU, intensive care unit; PASC, post-acute sequelae of SARS-CoV-2 infection; SARS-CoV-2, severe acute respiratory coronavirus 2; WHI, Women's Health Initiative.

[a]Statistical analyses were performed after imputations with chained equations were applied. Multivariable binary logistic and Poisson regression models for hsCRP ≥3 mg/L at WHI baseline as predictors of primary, secondary, and exploratory PASC outcomes, controlling for pertinent confounders. Models I were controlled for baseline age (years), race (White vs other [American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islanders, Black, and more than one race]), and ethnicity (Hispanic vs non-Hispanic). Models II were controlled for all variables in Models I + smoking status (ever/never), body mass index (kg/m^2), cardiometabolic disease (yes/no), cancer (yes/no), rheumatoid arthritis (yes/no), and hormone therapy (yes/no), at baseline. Models III were controlled for all variables in Models II + COVID-19 vaccination (yes/no), COVID-19 therapies (yes/no), COVID-19 ICU admission (yes/no), and COVID-19 hospitalization (yes/no) at follow-up.

[b]Indicates $P < 0.05$ (before familywise Bonferroni correction).

[c]Indicates $P < 0.02$ (after familywise Bonferroni correction).

and it is uncertain if the reported symptoms are attributed solely to PASC. However, it is worth noting that there are no currently available tests specific to PASC symptoms as a singular condition given its heterogeneous and multiorgan presentations. Third, despite the large initial sample of 161,808 WHI participants, a subset who completed the WHI COVID-19 Survey 2 and confirmed SARS-CoV-2 infection consisted of a much smaller sample of 1,237 WHI participants. The sample size further diminished when restricted to participants with PASC symptoms, resulting in reduced statistical power to detect significant associations between inflammatory biomarkers and secondary PASC outcomes, particularly for hsCRP, which may explain its null findings. Finally, though our multivariate regression models included many pertinent covariates previously shown to confound hypothesized relationships, an inherent limitation of observational studies is that we may not have been able to fully control for all confounders, and there remains the possibility of residual confounding.

Several strengths of our study also warrant consideration. The extant PASC literature includes findings of immune markers mostly obtained from blood samples collected at hospital admission and during acute infection or recovery, *after* the onset of COVID-19 infection, thereby offering mechanistic insight through the examination of immunological reactions. Our study adds to the literature by examining baseline biomarker predictors assessed *prior to* COVID-19 and PASC, as far back as ~25 years. Although representing a smaller subset of the WHI, this study included a relatively large sample size, especially of older women, whose prevalence of PASC is reported to be up to four times higher than men.[11] In addition, we examined a comprehensive panel of PASC outcome measures, including PASC status, PASC severity, and PASC-associated cognitive symptoms.

CONCLUSIONS

Our findings suggest that leukocyte count, a well-standardized, stable, widely available, and inexpensive clinical marker of inflammation, is an independent predictor of future PASC severity in postmenopausal women. Our study extends the evidence that low-grade inflammation is not only a *correlate or an outcome* of PASC severity, but also *precedes* the acute COVID-19 infection leading to this debilitating outcome, further supporting a role of inflammation in the etiology of PASC. Studies with repeated measures of inflammatory biomarkers over a span of pre-pandemic years and with larger sample sizes will be helpful to replicate our findings.

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