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Article

Association between allostatic load and prevalent breast cancer: findings from the national health and nutrition examination survey

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Abstract: Background: Breast cancer is a multifactorial disease influenced by genetic, hormonal, and lifestyle-related factors. Identifying modifiable factors associated with breast cancer may provide insights into disease prevention. However, the association between allostatic load and prevalent breast cancer remains unclear. This study evaluated the relationship between allostatic load and prevalent breast cancer. Methods: This cross-sectional study used data from the National Health and Nutrition Examination Survey (NHANES) 2005–2010. An allostatic load scoring system was established based on eight biomarkers. Survey-weighted logistic regression models were applied to assess the association between allostatic load and prevalent breast cancer with sequential adjustment for potential confounders. Restricted cubic spline and subgroup analyses were conducted to evaluate dose-response relationships and potential effect modifications. Results: Among 5892 women included in the analysis, 178 had prevalent breast cancer. Participants with higher allostatic load showed a higher prevalence of breast cancer. In the fully adjusted model, each one-unit increase in allostatic load score was associated with increased odds of prevalent breast cancer (OR = 1.17, 95% CI: 1.05–1.30, P = 0.006). Conclusions: Higher allostatic load was significantly associated with prevalent breast cancer among women. Allostatic load may serve as a potential biomarker reflecting physiological stress burden related to breast cancer, although further prospective studies are needed for validation.

Keywords: breast cancer; allostatic load; NHANES; chronic stress; cross-sectional study

1. Introduction

As the most commonly diagnosed malignancy in females, breast cancer continues to be the major cause of cancer mortality. Approximately 2.3 million new cases were diagnosed worldwide, constituting nearly one-quarter of all cancers affecting women in 2020 [1]. Breast cancer is a multifactorial disease influenced by genetic susceptibility, hormonal regulation, environmental exposures, and lifestyle-related factors [2]. Beyond age, genetics, and reproductive history, everal additional factors have been associated with prevalent breast cancer, including being overweight or obese, insufficient physical activity, and habits like drinking alcohol and using tobacco [3,4]. Thus, identifying potentially modifiable factors associated with breast cancer is of great importance.

Over the past decade, researchers have increasingly utilized allostatic load (AL), defined as the cumulative physiological burden resulting from chronic

exposure to stressors and the repeated adaptation of multiple physiological systems. AL reflects the "wear and tear" that accumulates across cardiovascular, metabolic, immune, neuroendocrine, and other physiological systems during chronic stress. Despite the absence of a universally accepted scoring method, biomarker-based AL indices have been widely used in epidemiological studies to quantify cumulative physiological dysregulation [5,6]. Evidence from these investigations indicates that allostatic load provides a useful framework for understanding the association between prolonged exposure to chronic stressors and the pathophysiology of diseases such as cardiovascular disorders, diabetes, and various forms of cancer [7–9]. Regarding breast cancer, a number of investigations have examined the potential association between allostatic load and adverse clinical outcomes [10–15]. For instance, high allostatic load has been associated with less favorable tumor differentiation and increased tumor dimensions [13–15]. This condition also tied to decreased functional outcomes and poorer quality of life, specifically for Black females with breast cancer [15]. After adjusting for demographic and behavioral variables, a history of breast cancer showed no link to allostatic load in White women, whereas a strong positive association was observed in Black women [16]. A previous investigation reported that increased allostatic load was linked to a higher overall cancer risk in women [17]. This association remained significant after adjustment for established breast cancer-related factors. Hence, allostatic load might represent a potential biomarker reflecting physiological stress burden associated with breast cancer [18].

However, the biological mechanisms linking chronic stress, allostatic load, and breast cancer remain incompletely understood. Persistent stress exposure may be associated with neuroendocrine dysregulation, chronic inflammation, and impaired immune surveillance, which may contribute to a physiological environment involved in carcinogenesis [19–21]. Chronic inflammatory responses can further disrupt immune homeostasis and may be involved in the establishment of a tumor-supportive microenvironment, partly through immunosuppressive neutrophil polarization and microbiome-mediated regulation of inflammatory pathways [22,23]. Collectively, these findings provide a biologically plausible explanation for the observed association between cumulative stress burden and breast cancer.

However, to date, few studies have examined the association between allostatic load and prevalent breast cancer using nationally representative NHANES data. Consequently, findings here may not be consistent with those obtained in large, population-based cohorts, the UK Biobank. Further studies are warranted to more clearly elucidate this association.

Consequently, this research sought to clarify this relationship using data from NHANES database. It was posited that women with higher AL scores would be associated with a higher prevalence of breast cancer among women.

2. Materials and methods

2.1. Study population

This was a cross-sectional study based on data from the National Health and Nutrition Examination Survey (NHANES). Data for analysis were obtained from NHANES, which employs a combination of household interviews and standardized physical exams to monitor both health and nutrition for US adult and pediatric populations. Conducted biennially since 1999, each survey is implemented in a single cycle. Ethical clearance for the study was granted by the Research Ethics Committees of the National Center for Health Statistics and the Centers for Disease Control and Prevention. Participants or their legal proxies, chosen via a sophisticated multistage

probability sampling scheme, all provided written informed consent for this study.

This investigation sourced its data from NHANES survey cycles conducted spanning 2005 to 2010. The initial cohort comprised 28,610 individuals, from whom comprehensive data were collected on race, cancer history, medical background, lifestyle factors, and other relevant variables. However, 22,176 individuals were excluded due to missing data on cancer-related questionnaires, systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated hemoglobin (HbA1c), serum creatinine, albumin and triglycerides, C-reactive protein, total cholesterol, and body mass index (BMI). The exclusion was primarily due to missing information required for AL calculation and covariate adjustment rather than outcome-based selection. Additionally, 542 participants with missing multivariate data including age, race, PIR, cotinine, alcohol consumption, hypertension, diabetes, depression, lymphocyte count, segmented neutrophils, eosinophils, basophils, monocytes, and mean platelet volume were removed. Final analytical samples included 5,892 eligible participants (**Figure 1**).

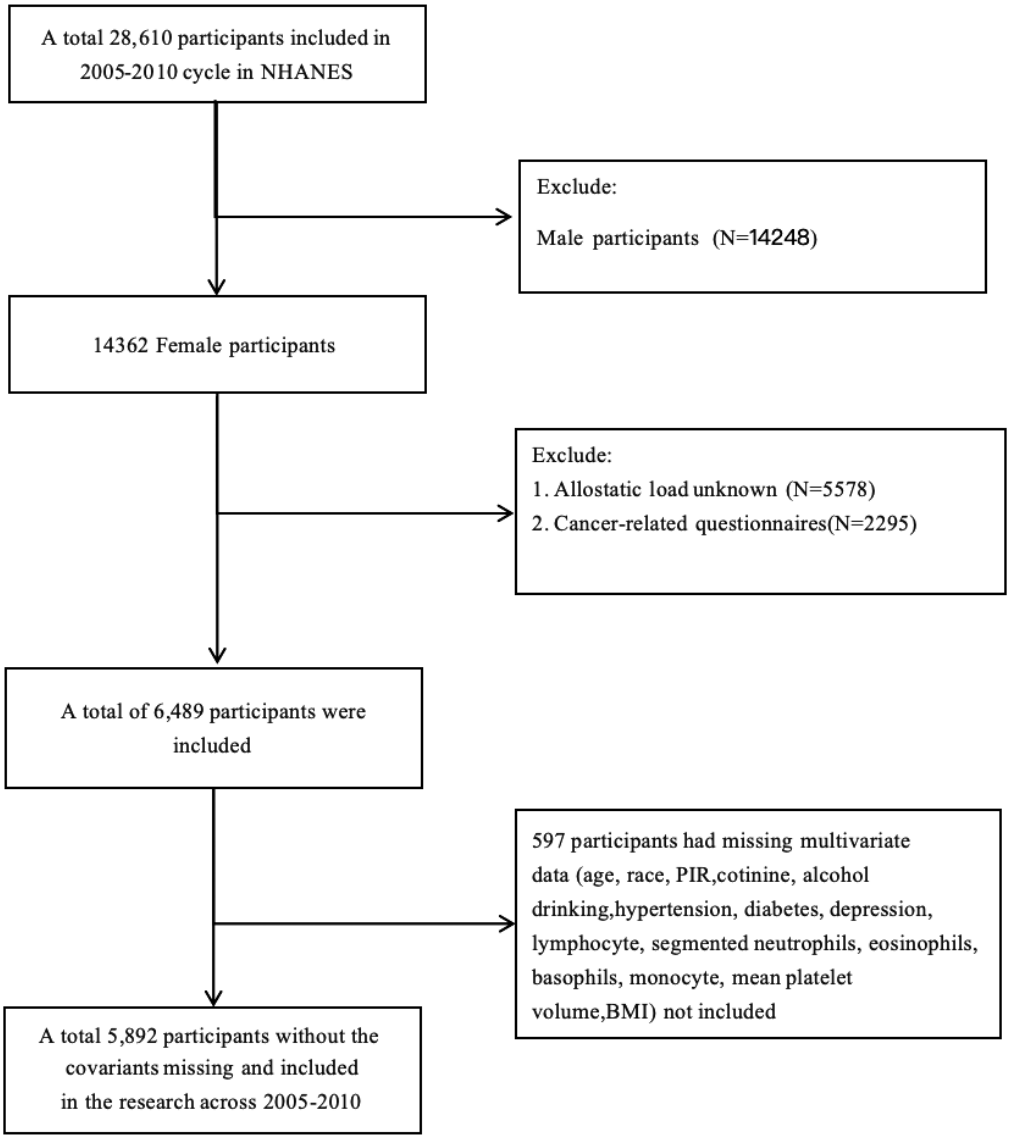

Figure 1. Flow chart depicting the processes of participant selection. The analysis encompassed data from NHANES survey cycles conducted in 2005–2010. The initial pool consisted of 28,610 individuals; however, 22,176 individuals were excluded due to missing information on cancer-related questionnaires. Additionally, 542 participants with missing multivariate data were excluded leaving 5,892 eligible participants eligible for subsequent analyses.

2.2. Assessment of breast cancer

Breast cancer status was determined through self-reported data from the Medical Conditions Questionnaire. Those being surveyed were queried "Have you been told by a clinician or any other healthcare professionals that you got a cancer or any form of malignancy?" Those participants who gave a "yes" answer would be questioned, "What type of cancer?" Patients with breast cancer were regarded as those respondents who only reported having breast cancer (primary and single tumor). Individuals who either gave "no" answer, had additional cancer histories, or had breast cancer alongside other malignancies were classified as non-breast cancer patients [24].

2.3. Allostatic load score construction

Allostatic load refers to a multidimensional concept that integrates biomarkers from a variety of physiological systems, encompassing neuroendocrine, metabolic, immune, and cardiovascular domains. Although no universally standardized set of biomarkers exists for its quantification [25], the present study adopted the biomarker-based AL scoring approach proposed by Geronimus et al. and subsequently summarized by Duong et al., which has been widely applied in NHANES-based epidemiological studies [25,26]. Eight biomarkers were selected to construct the AL score, including C-reactive protein (CRP), systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated hemoglobin (HbA1c), serum triglycerides, total cholesterol, serum creatinine, and serum albumin. Following previously published AL calculation methods [25,26], participants were assigned a score of 1 when a biomarker reached the predefined high-risk threshold and 0 otherwise. Specifically, high-risk status was defined as values above the 75th percentile for CRP, SBP, DBP, HbA1c, serum triglycerides, total cholesterol, and serum creatinine, whereas serum albumin values below the 25th percentile were considered indicative of physiological dysregulation. The individual component scores were summed to generate the total AL score, ranging from 0 to 8, with higher scores indicating greater cumulative physiological dysregulation.

Based on previous epidemiological studies [26], participants were categorized into low and high AL groups using an AL score cutoff of 3, with scores ≥ 3 defined as high allostatic load and scores < 3 defined as low allostatic load.

2.4. Covariates information

According to previous studies [27,28], we selected covariates associated with breast cancer prevalence in our study. Covariates had as components age, race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or other race), BMI, poverty-to-income ratio (PIR) (< 1.30, 1.30–3.50, and > 3.50), alcohol drinking indication (yes or no), serum cotinine (< 0.05 ng/ml, 0.05–2.99 ng/ml, ≥ 3 ng/ml), hypertension (yes or no), diabetes (yes or no), depression (yes or no), count of lymphocytes indicated, count of segmented neutrophils indicated, count of eosinophils indicated, count of basophils indicated, count of monocytes indicated, and mean platelet volume. Alcohol intake was classified based on consumption of at least 12 alcoholic drinks annually or not drinking any [29]. The definition of hypertension includes the following criteria: (a) being notified that hypertension is diagnosed; (b) self-reporting taking antihypertensive medications; (c) or having higher biological parameters (average SBP ≥ 130 mmHg or DBP ≥ 80 mmHg) [30]. The condition of diabetes is characterized by the treatment or the medical diagnosis of abnormally high blood sugar (hyperglycemia), or HbA1c $\geq 6.5\%$, or in situations where two-hour

blood glucose ≥ 200 mg/dl, or fasting plasma glucose ≥ 126 mg/dL [8]. Depression was identified with the help of the Patient Health Questionnaire (PHQ-9), with a binary threshold of ≥ 10 to signify depressive symptoms [9].

2.5. Statistical analysis

Initially, the distribution difference of each covariate was compared between those with prevalent breast cancer and the entire study cohort. An allostatic load score was subsequently calculated based on eight selected factors, and its distribution was similarly contrasted across these groups. Because NHANES employs a complicated, multistage probability sampling strategy to select a representative sample, all analyses incorporated sample weights, clustering, and stratification to generate estimates representative of the U.S. population. Baseline characteristics of participants were described according to their breast cancer status. Variables following a normal distribution are presented as mean ± standard deviation (SD), whereas those with a non-normal distribution are reported as median and interquartile range [M (Q1, Q3)]. Between-group comparisons utilized t-tests for normally distributed data and Kruskal-Wallis H tests for non-parametric distributions. Categorical variables were expressed as frequency counts and percentages [n (%)], with comparisons performed using chi-square (χ^2) or Fisher's exact tests depending on the situation.

In order to prevent multicollinearity, variance inflation factor (VIF) was computed for all predictors. All covariates included in this study had VIF values under 10, implying that there was no severe multicollinearity.

To evaluate the association of allostatic load with prevalent breast cancer, we employed a 'survey' package to perform multivariate logistic regression analyses. The analysis included three models: Model 1 (crude, without adjustments), Model 2 (adjusted for age, race, and poverty-income ratio), and Model 3 (comprehensively adjusted), which additionally accounted for factors such as pentamidine, alcohol exposure, hypertension, diabetes, depression, lymphocytes, segmented neutrophils, eosinophils, basophils, monocytes, and mean platelet volume. In sensitivity analyses, we additionally adjusted for physical activity and sleep disorders (Model 4), and further adjusted for marital status and education level (Model 5) to test the robustness of the findings. The functional form of the relationship was explored using restricted cubic splines. In the presence of a non-linear relationship, threshold effect analysis was conducted using two-piecewise logistic regression models. Subgroup analyses were further conducted to assess heterogeneity and potential interactions across specific populations, including age (≤ 65, > 65), PIR (< 1.30, 1.3–3.5, > 3.5), pentamidine (< 0.05 ng/ml, 0.05–2.99 ng/ml, ≥ 3 ng/ml), alcohol consumption (yes/no), diabetes (yes/no), hypertension (yes/no), and depression (yes/no). Finally, a mediation analysis was conducted to evaluate BMI as a potential mediator in the association between allostatic load and breast cancer. Using the R "mediation" package, we estimated the indirect, direct, and total effects in the association between allostatic load and breast cancer through BMI. The mediation effect of BMI was quantified as the ratio of the indirect effect over total effect. A non-parametric bootstrap procedure was applied based on a total of 1,000 resamples to determine the 95% confidence interval (CI) for this mediation proportion.

To evaluate potential selection bias due to missing data, baseline characteristics were compared between included and excluded participants among women aged ≥ 20 years. Differences between groups were assessed using appropriate statistical tests.

Finally, a sequence of sensitivity analyses were performed: (1) The main analysis was repeated using a dataset free of potential biases. (2) Individuals who

were diagnosed additional types of cancer were excluded from the control group, and the main analysis was repeated to assess any bias related to these individuals. (3) Additional confounding factors, including education level, marital status, physical activity, and sleep disorders, were incorporated into revised logistic regression models allowed for an exploration of possible connection between allostatic load and breast cancer.

Statistical analyses were carried out using R software (version 4.4.1), with *P*-values less than 0.05 applied to determine statistical significance.

3. Results and discussion

3.1. Baseline characteristics of the study population

Final analysis comprised 5,892 female participants, including 178 participants with prevalent breast cancer. The distribution of key demographic and clinical characteristics for these cases, along with total study cohort, is summarized in **Table 1**. Compared with the general participant pool, breast cancer cases demonstrated a higher prevalence of older age (56.16% vs. 15.07%, $P < 0.01$), White race (85.57% vs. 71.61%, $P < 0.01$), history of smoking (67.87% vs. 54.01%, $P < 0.01$), diabetes (19.84% vs. 10.92%, $P < 0.01$) and hypertension (64.11% vs. 42.64%, $P < 0.01$). They also had lower lymphocyte counts (1.7 vs. 2.1 × 10^9/L, $P < 0.01$), higher SBP (125 vs. 116 mmHg, $P < 0.01$), HbA1c (5.6% vs. 5.4%, $P < 0.01$), total cholesterol (202 vs. 196 mg/dL, $P < 0.05$), triglycerides (141 vs. 112 mg/dL, $P < 0.01$), creatinine (0.82 vs. 0.77 mg/dL, $P < 0.01$), and allostatic load scores (3 vs. 2, $P < 0.01$). No evidence of significant differences were found for PIR, BMI, alcohol consumption, depression, segmented neutrophils, eosinophils, basophils, monocytes, mean platelet volume, DBP, or C-reactive protein albumin.

Table 1. Differences for the baseline characteristics in terms of studying variables by breast cancer.

Characteristic	Overall	Non-breast cancer	Breast cancer	*P*-value
Age				< 0.001
≤ 65	4,744 (84.93%)	4,678 (86.16%)	66 (43.84%)	
> 65	1,148 (15.07%)	1,036 (13.84%)	112 (56.16%)	
Race				0.002
Mexican American	1,133 (7.528%)	1,117 (7.680%)	16 (2.440%)	
Other Hispanic	499 (4.253%)	493 (4.344%)	6 (1.205%)	
Non-Hispanic White	2,873 (71.61%)	2,751 (71.19%)	122 (85.57%)	
Non-Hispanic Black	1,137 (11.10%)	1,108 (11.21%)	29 (7.228%)	
Other race	250 (5.514%)	245 (5.572%)	5 (3.553%)	
PIR				0.500
≤ 1.3	1,851 (20.37%)	1,807 (20.51%)	44 (15.96%)	
> 3.5	1,784 (42.86%)	1,725 (42.75%)	59 (46.51%)	
1.3–3.5	2,257 (36.77%)	2,182 (36.75%)	75 (37.54%)	
Body mass index (kg/m^2)	27.18 (23.39, 32.64)	27.16 (23.41, 32.63)	27.61 (22.71, 33.16)	0.900

Continuation Table:

Characteristic	Overall	Non-breast cancer	Breast cancer	*P*-value
Cotinine, serum (ng/mL)				0.003
< 0.05 ng/ml	3,149 (54.01%)	3,035 (53.60%)	114 (67.87%)	
≥ 3 ng/ml	1,295 (22.37%)	1,267 (22.58%)	28 (15.40%)	
0.05–2.99 ng/ml	1,448 (23.61%)	1,412 (23.82%)	36 (16.73%)	
Alcohol drinking				0.200
No	2,308 (32.14%)	2,236 (31.95%)	72 (38.60%)	
Yes	3,584 (67.86%)	3,478 (68.05%)	106 (61.40%)	
Diabetes				< 0.001
No	5,017 (89.08%)	4,881 (89.35%)	136 (80.16%)	
Yes	875 (10.92%)	833 (10.65%)	42 (19.84%)	
Hypertension				< 0.001
No	3,165 (57.36%)	3,112 (58.00%)	53 (35.89%)	
Yes	2,727 (42.64%)	2,602 (42.00%)	125 (64.11%)	
Depression				0.068
No	5,286 (91.64%)	5,123 (91.54%)	163 (94.78%)	
Yes	606 (8.36%)	591 (8.458%)	15 (5.217%)	
Lymphocyte number (1000 cells/uL)	2.10 (1.70, 2.50)	2.10 (1.70, 2.50)	1.70 (1.40, 2.30)	< 0.001
Segmented neutrophils number (1000 cell/uL)	4.10 (3.20, 5.20)	4.10 (3.20, 5.20)	4.10 (3.00, 5.10)	0.800
Eosinophils number (1000 cells/uL)	0.20 (0.10, 0.20)	0.20 (0.10, 0.20)	0.20 (0.10, 0.20)	0.300
Basophils number (1000 cells/uL)	0.00 (0.00, 0.10)	0.00 (0.00, 0.10)	0.00 (0.00, 0.10)	0.600
Monocyte number (1000 cells/uL)	0.50 (0.40, 0.60)	0.50 (0.40, 0.60)	0.50 (0.40, 0.70)	0.300
Mean platelet volume (fL)	7.90 (7.30, 8.40)	7.90 (7.40, 8.40)	7.70 (7.10, 8.40)	0.200
DBP (mmHg)	69.33 (62.00, 76.00)	69.33 (62.00, 76.00)	68.67 (60.67, 74.00)	0.200
SBP (mmHg)	116.00 (106.67, 128.00)	116.00 (106.67, 128.00)	125.00 (115.33, 136.00)	< 0.001
HbA1c (%)	5.40 (5.10, 5.70)	5.40 (5.10, 5.70)	5.60 (5.40, 5.90)	< 0.001
Total cholesterol (mg/dL)	196.00 (171.00, 225.00)	196.00 (171.00, 224.00)	202.00 (179.00, 234.00)	0.037
C-reactive protein (mg/dL)	0.22 (0.08, 0.51)	0.22 (0.08, 0.51)	0.23 (0.09, 0.52)	0.800

Continuation Table:

Characteristic	Overall	Non-breast cancer	Breast cancer	*P*-value
Triglycerides (mg/dL)	112.00 (75.00, 168.00)	111.00 (75.00, 167.00)	141.00 (90.00, 205.00)	< 0.001
Creatinine (mg/dL)	0.77 (0.68, 0.87)	0.76 (0.68, 0.86)	0.82 (0.72, 0.92)	< 0.001
Albumin (g/dL)	4.20 (4.00, 4.40)	4.20 (4.00, 4.40)	4.20 (3.90, 4.40)	0.700
AL	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	3.00 (2.00, 4.00)	< 0.001

Table 2 shows the distribution of scores of allostatic load in the entire study population as well as in breast cancer cases. The allostatic load spanned from 0 to 8. Approximately 21.84% of the study population, the largest proportion among all levels, were women whose allostatic load was equal to 1. Generally speaking, the distribution of allostatic load showed a downward trend from 1 to 8, and merely around 9% of females had an allostatic load equal to or higher than 5. The distribution of allostatic load scores differed significantly when comparing overall study population to breast cancer cases ($P < 0.01$). Specifically, participants with breast cancer had lower proportions of allostatic load scores of 0 and 1 and a higher likelihood of having allostatic load points of 2 or upwards. When analyzed as a continuous variable, average AL scores for breast cancer patients were 2.96, substantially exceeding the average (2.22) in overall study population ($P < 0.01$). Furthermore, for the purpose of further streamlining the data, a dichotomized variable named allostatic load category was created. This variable consists of two groups: one is the low allostatic load group with scores ranging from 0 to 2, and the other is the high allostatic load group with scores ranging from 3 to 8. Allostatic load categories differed markedly between breast cancer cases and study population ($P < 0.01$). A higher proportion of participants with breast cancer were classified into the high allostatic load group compared with other participants (63.49% vs. 40.49%, $P < 0.01$).

Table 2. Distribution of allostatic load (AL) scores and AL score categories in all cohorts and breast cancer cases.

Characteristic	Overall	Non-breast cancer	Breast cancer	*P*-value
	N = 5892	N = 5714	N = 178	
AL				< 0.001
0	818 (15.98%)	815 (16.42%)	3 (1.296%)	
1	1,154 (21.84%)	1,136 (22.14%)	18 (11.74%)	
2	1,238 (21.69%)	1,199 (21.64%)	39 (23.47%)	
3	1,218 (19.23%)	1,163 (18.92%)	55 (29.54%)	
4	837 (12.42%)	797 (12.07%)	40 (24.12%)	
5	404 (5.901%)	389 (5.888%)	15 (6.317%)	
6	178 (2.259%)	170 (2.222%)	8 (3.507%)	
7	41 (0.621%)	41 (0.640%)	0 (0%)	
8	4 (0.060%)	4 (0.062%)	0 (0%)	

Continuation Table:

Characteristic	Overall	Non-breast cancer	Breast cancer	*P*-value
	N = 5892	N = 5714	N = 178	
AL category				< 0.001
< 3	3,210 (59.51%)	3,150 (60.20%)	60 (36.51%)	
≥ 3	2,682 (40.49%)	2,564 (39.80%)	118 (63.49%)	
AL continuous	2.20 (1.60)	2.18 (1.61)	2.96 (1.28)	< 0.001

Next, relationship between allostatic load and breast cancer was examined (**Table 3**). When allostatic load was analyzed as a continuous variable, each one-point increase in AL score was significantly associated with higher odds of prevalent breast cancer in the unadjusted model (OR = 1.32, 95% CI: 1.23–1.42, $P < 0.001$). This association remained significant after adjustment for potential confounders, with ORs of 1.16 (95% CI: 1.04–1.29, $P = 0.007$) in Model 2 and 1.17 (95% CI: 1.05–1.30, $P = 0.006$) in Model 3.

Table 3. Relationship between allostatic load and prevalent breast cancer.

Participants	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Allostatic load classify	1.32 (1.23, 1.42)	< 0.001	1.16 (1.04, 1.29)	0.007	1.17 (1.05, 1.30)	0.006
< 3	ref.		ref.		ref.	
≥ 3	2.63 (1.70, 4.07)	< 0.001	1.71 (1.02, 2.86)	0.042	1.71 (1.03, 2.85)	0.041

Note: Model 1: No adjustment; Model 2: Adjusted for age, race, PIR; Model 3: Adjusted for age, race, PIR, cotinine, alcohol drinking, hypertension, diabetes, depression, lymphocyte, segmented neutrophils, eosinophils, basophils, monocyte, mean platelet volume.

Restricted cubic spline analysis revealed a significant nonlinear association between allostatic load and breast cancer (P for nonlinearity < 0.001), with an inflection point at an AL score of 2 (**Figure 2**).

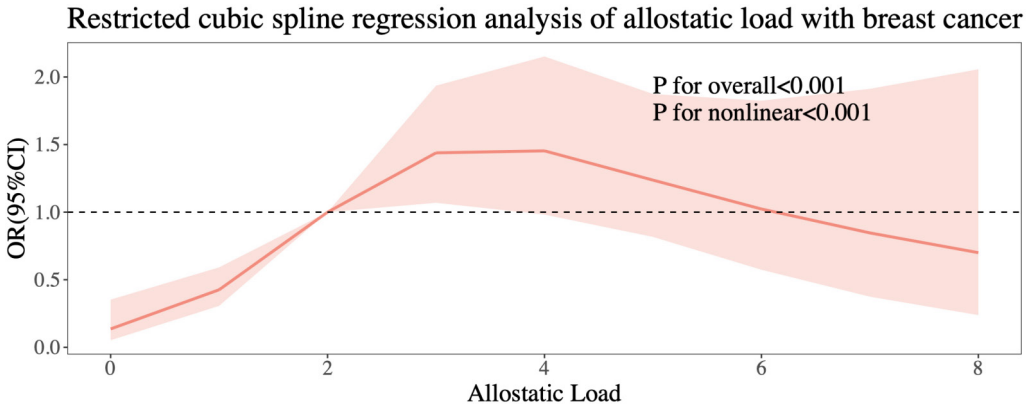

Figure 2. Restricted cubic spline regression analysis of allostatic load with breast cancer. The restricted cubic spline regression results indicated that the association between allostatic load and breast cancer was not linear (nonlinear $P < 0.001$), with the inflection point at 2.

Further, a two-piecewise logistic regression model was constructed to evaluate the threshold effect of allostatic load on breast cancer. The resultsshowed a nonlinear association between AL and prevalent breast cancer. When AL score was ≤ 2, each one-unit increase in AL was associated with higher odds of prevalent breast cancer (OR = 2.36, 95% CI: 1.52–3.66, $P < 0.001$). However, when AL score exceeded 2, no significant association was observed (OR = 0.99, 95% CI: 0.85–1.14, $P = 0.800$) (**Table 4**).

Table 4. Threshold effect analysis of allostatic load on breast cancer using a two-piecewise logistic regression model.

Participants	Adjusted OR (95% CI)	*P*-value
Allostatic load	1.17 (1.05, 1.30)	0.006
cutoff		
≤ 2	2.36 (1.52, 3.66)	< 0.001
> 2	0.99 (0.85, 1.14)	0.800
Log-likelihood ratio	< 0.001	

Note: Adjusted for age, race, PIR, cotinine, alcohol drinking, hypertension, diabetes, depression, lymphocyte, segmented neutrophils, eosinophils, basophils, monocyte, mean platelet volume.

3.2. Subgroup analysis

To further evaluate the robustness and potential heterogeneity of the association between allostatic load (AL) and breast cancer, subgroup analyses were performed across predefined populations (**Table 5)**. A significant positive association between AL and prevalent breast cancer was observed among participants aged ≤ 65 years (OR = 1.32, 95% CI: 1.10–1.59, $P = 0.005$) and those without diabetes (OR = 1.43, 95% CI: 1.16–1.77, $P = 0.002$). Similar positive associations were also observed in Mexican Americans, Non-Hispanic Whites, participants with PIR > 3.5, serum cotinine < 0.05 ng/mL, alcohol consumers, participants without hypertension, and those without depression (**Table 5**). Interaction analyses showed that diabetes significantly modified the association between AL and breast cancer (P for interaction = 0.013), whereas no significant interactions were observed for age, race, PIR, serum cotinine level, alcohol consumption, hypertension, or depression (all P for interaction > 0.05).

Table 5. Stratified analysis evaluating association between allostatic load and breast cancer.

Participants	OR (95% CI)	*P*-value	*P* for interaction
Age			0.163
≤ 65	1.32 (1.10, 1.59)	0.005	
> 65	1.03 (0.88, 1.20)	0.700	
Race			0.674
Mexican American	1.82 (1.22, 2.71)	0.005	
Other Hispanic	1.61 (0.92, 2.81)	0.089	
Non-Hispanic White	1.17 (1.04, 1.32)	0.012	
Non-Hispanic Black	0.80 (0.52, 1.21)	0.300	

Continuation Table:

Participants	OR (95% CI)	*P*-value	*P* for interaction
Other race	1.80 (0.80, 4.04)	0.140	
PIR			0.664
≤ 1.3	1.00 (0.81, 1.24)	> 0.900	
1.3–3.5	1.12 (0.90, 1.39)	0.300	
> 3.5	1.33 (1.09, 1.61)	0.006	
Cotinine, serum (ng/mL)			0.999
< 0.05 ng/ml	1.21 (1.06, 1.39)	0.007	
≥ 3 ng/ml	0.99 (0.86, 1.15)	> 0.900	
0.05–2.99 ng/ml	1.17 (0.82, 1.67)	0.400	
Alcohol drinking			0.929
No	1.15 (0.94, 1.42)	0.200	
Yes	1.16 (1.00, 1.34)	0.048	
Hypertension			0.854
No	1.16 (1.01, 1.33)	0.043	
Yes	1.13 (0.89, 1.44)	0.300	
Diabetes			0.013
No	1.43 (1.16, 1.77)	0.002	
Yes	1.03 (0.92, 1.17)	0.600	
Depression			0.285
No	1.19 (1.06, 1.33)	0.004	
Yes	0.82 (0.49, 1.38)	0.400	

Note: Adjusted for age, race, PIR, cotinine, alcohol drinking, hypertension, diabetes, depression, lymphocyte, segmented neutrophils, eosinophils, basophils, monocyte, mean platelet volume.

To assess potential selection bias resulting from missing data, baseline characteristics were compared between included and excluded participants among women aged ≥ 20 years (**Supplementary Table 1**). Compared with excluded participants, included participants were significantly different in age, race, serum cotinine level, depression status, eosinophil count, basophil count, monocyte count, and mean platelet volume (all $P < 0.05$). No significant differences were observed for poverty-income ratio, hypertension, diabetes, alcohol consumption, or most other examined variables.

3.3 Sensitivity analysis

We repeated the main analysis process using unweighted data, and obtained consistent results (**Table 6**). Subsequently, after excluding individuals with additional malignancies from control, we repeated the main analysis process for the participants to investigate any potential biases related to these individuals. The association between allostatic load and prevalent breast cancer remained statistically significant

(**Table 7**). As a sensitivity analysis, AL was categorized into tertiles (T1–T3). Higher AL tertiles were associated with increased odds of prevalent breast cancer compared with the lowest tertile (T1), and the results remained consistent with the primary analysis (**Table 8**). Finally, after adjusting for additional confounding factors (education level, marital status, physical activity, sleep disorders, etc.), we re-built the logistic regression model and analyzed relationship between allostatic load and breast cancer. We found that these associations did not undergo substantial changes (**Table 9**).

Table 6. Relationship between allostatic load and breast cancer (unweighted).

Participants	Model 1		Model 2		Model 3	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Allostatic load	1.28 (1.17, 1.39)	< 0.001	1.12 (1.01, 1.24)	0.025	1.12 (1.00, 1.26)	0.049
classify						
< 3	ref.		ref.		ref.	
≥ 3	2.42 (1.77, 3.33)	< 0.001	1.54 (1.11, 2.16)	0.011	1.51 (1.04, 2.19)	0.030

Note: Model 1: No adjustment; Model 2: Adjusted for age, race, PIR; Model 3: Adjusted for age, race, PIR, cotinine, alcohol drinking, hypertension, diabetes, depression, lymphocyte, segmented neutrophils, eosinophils, basophils, monocyte, mean platelet volume.

Table 7. Association between allostatic load and prevalent breast cancer after excluding participants with other malignancies.

Participants	Model 1		Model 2		Model 3	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Allostatic load	1.32 (1.23, 1.43)	< 0.001	1.16 (1.04, 1.29)	0.007	1.17 (1.05, 1.30)	0.005
classify						
< 3	ref.		ref.		ref.	
≥ 3	2.63 (1.70, 4.07)	< 0.001	1.71 (1.02, 2.86)	0.042	1.71 (1.03, 2.85)	0.041

Note: Model 1: No adjustment; Model 2: Adjusted for age, race, PIR; Model 3: Adjusted for age, race, PIR, cotinine, alcohol drinking, hypertension, diabetes, depression, lymphocyte, segmented neutrophils, eosinophils, basophils, monocyte, mean platelet volume.

Table 8. Relationship between allostatic load and breast cancer.

Participants	Model 1		Model 2		Model 3		
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	
Allostatic load	1.32(1.23, 1.43)	< 0.001	1.16 (1.04, 1.29)	0.007	1.17 (1.05, 1.30)	0.005	
classify							
T1	ref.		ref.		ref.		
T2	10.2 (3.07, 33.8)	< 0.001	6.83 (1.94, 24.1)	0.004	6.89 (1.97, 24.2	)	0.004
T3	20.2 (5.84, 69.9)	< 0.001	9.88 (2.53, 38.6)	0.002	10.4 (2.69, 40.1)	0.001	

Note: Model 1: Non-adjusted; Model 2: Adjusted for age, race, PIR; Model 3: Adjusted for age, race, PIR,cotinine, alcohol drinking, hypertension, diabetes, depression, lymphocyte, segmented neutrophils, eosinophils, basophils, monocyte, mean platelet volume; OR: adjusted odds ratio; CI: confidence interval.

Table 9. Relationship between allostatic load and breast cancer after adjusting for additional confounding factors.

Participants	OR (95% CI)	*P*-value
Model 3	1.12 (1.00, 1.26)	0.049
Model 4	1.16 (1.02, 1.32)	0.028
Model 5	1.15 (1.03, 1.29)	0.014

Note: Model 3: Adjusted for age, race, PIR, cotinine, alcohol drinking, hypertension, diabetes, depression, lymphocyte, segmented neutrophils, eosinophils, basophils, monocyte, mean platelet volume; Model 4: Physical activity and sleep disorders were adjusted on the basis of Model 2; Model 5: Marital Status and education Level were adjusted on the basis of Model 2.

4. Discussion

Elevated prevalence or burden of many chronic diseases has been linked to chronic stress. However, the extent to which chronic stress is associated with cancer remains unclear. To address this question, the present analysis utilized NHANES data to evaluate how allostatic load, a physiological indicator of chronic stress accumulation, correlate with prevalent breast cancer. Previous epidemiological studies investigating the relationship between psychological stress and breast cancer have yielded inconsistent findings, with some studies reporting positive associations while others finding no significant relationship [31–34].

In contrast to earlier investigations that relied on self-reported instruments to assess stressors ranging from daily hassles to social pressures [35], the present research employed allostatic load as a composite physiological measure. Since allostatic load can reflect cumulative physiological dysregulation associated with chronic stress exposure and account for individual variation in biological responses, it is deemed appropriate to serve as a suitable biomarker for examining the relationship between chronic stress and chronic diseases. Nevertheless, research on the specific connection between allostatic load and prevalent breast cancer remains limited. Only limited prior research, such as the SWAN study and analyses of the UK Biobank, has proposed that elevated allostatic load scores correlate with higher odds of both overall cancer and breast cancer [17]. Previous epidemiological studies have provided partially consistent but not entirely concordant evidence. The SWAN study reported that high allostatic load was associated with a higher prevalence of cancer among postmenopausal women, although the association with breast cancer was limited by the relatively small number of cases [36]. Similarly, analyses from the UK Biobank suggested that elevated allostatic load was independently associated with higher odds of breast cancer after adjustment for conventional breast cancer-related factors [18]. However, previous studies have mainly focused on specific populations, and differences in study design, participant characteristics, biomarker composition, and adjustment strategies may contribute to variations in observed associations. Our findings based on a nationally representative NHANES cohort provide additional epidemiological evidence supporting the potential relationship between cumulative physiological stress burden and prevalent breast cancer.

The analysis included 5,892 women ultimately, among whom 178 prevalent breast cancer cases were identified. The distribution of allostatic load scores was examined across entire study population as well as within the group of breast cancer females. Individuals with high allostatic load scores showed higher odds of prevalent breast cancer compared with those with lower scores. When analyzed as a

continuous measure, each one-unit increment in allostatic load was associated with higher odds of prevalent breast cancer (OR = 1.17, 95% CI: 1.05–1.30). Subsequent modeling involved two progressively adjusted statistical models, with the positive association between allostatic load and prevalent breast cancer remained statistically significant across all specifications. Subgroup analyses yielded consistent results among participants aged ≤ 6 5 years, Mexican American, Non-Hispanic White, PIR > 3.5, cotinine < 0.05 ng/ml, alcohol consumers, individuals without hypertension, without diabetes, and with depression. Notably, diabetes significantly modified the association between allostatic load and prevalent breast cancer (*P* for interaction = 0.013). This finding may be partly explained by the shared metabolic dysfunction and inflammatory pathways between diabetes and allostatic load, which may influence the observed association between cumulative physiological stress burden and breast cancer. However, the underlying mechanisms remain unclear and warrant further investigation. Restricted cubic spline (RCS) analyses indicated that when allostatic load was ≤ 2, it was positively associated with prevalent breast cancer, whereas no statistically significant association was observed when allostatic load was > 2. These findings are consistent with prior studies using other data sources. For example, analyses from the UK Biobank reported that higher allostatic load was associated with increased odds of breast cancer after adjustment for conventional breast cancer-related factors [18]. Regarding racial variations, breast cancer history showed no correlation with allostatic load in White women, but a statistically significant positive relationship was documented among Black women [16].

Biological mechanisms may partially explain the observed association between allostatic load and prevalent breast cancer. Sustained stress exposure may be associated with prolonged activation of the sympathetic nervous system, accompanied by increased circulating concentrations of stress hormones such as glucocorticoids, epinephrine, and norepinephrine [37,38]. Overproduction of these hormones may affect the regulation of tumor-related genes such as *BRCA1* and *p53*, potentially contributing to DNA damage accumulation and tumor-related biological processes [39–41]. In addition, stress hormones can interfere with multiple physiological systems including cardiovascular, metabolic, immune, as well as neuroendocrine pathways through complex mechanisms, thereby potentially enhancing tumor growth, invasion, and metastasis [42–44]. Specifically, glucocorticoids can inhibit the complete maturation process of dendritic cells, which play a vital role in initiating antitumor adaptive immunity [45]. Chronic exposure to glucocorticoids has also been associated with visceral fat accumulation and insulin resistance [46]. Moreover, through adrenergic receptors, epinephrine and norepinephrine can stimulate the proliferation, migration, and invasion of breast cancer cells [47].

Allostatic load was composed of DBP, SBP, glycated hemoglobin (HbA1c), serum triglycerides, creatinine and albumin, total cholesterol, and C-reactive protein. Multiple covariates were evaluated for their potential confounding effects, encompassing demographic characteristics including age, race (Mexican American, other Hispanic, non-Hispanic black or white, etc.), along with PIR, BMI, serum cotinine, alcohol consumption, hypertension, diabetes, depression, lymphocyte count, segmented neutrophil count, eosinophil count, basophil count, monocyte count, and mean platelet volume. Collectively, these variables may modify connections of allostatic load and prevalent breast cancer, potentially affecting the observed outcome. In logistic regression analyses, there was a consistent association revealed between allostatic load and prevalent breast cancer across both the univariate (Model

1) and multivariate analyses (Models 2–3), suggesting that the association between allostatic load and prevalent breast cancer remained independent of these measured covariates. A similar association was observed through a SWAN study, where notable link between allostatic load and the association with overall cancer remained after adjusting for healthy behaviors and socioeconomic variables [17]. While the precise biological mechanisms underlying this association remain unclear, our findings suggest that chronic stress-related physiological dysregulation may be associated with prevalent breast cancer beyond the associations observed with several measured conventional factors. The interpretation is reinforced by the stability of the allostatic load-breast cancer relationship observed across nearly all covariate subgroups. A notable finding is that in subgroups including individuals aged ≤ 65 years, Mexican American, Non-Hispanic White, PIR > 3.5, cotinine < 0.05 ng/ml, alcohol consumers, those without hypertension, without diabetes, and with depression, significant differences in allostatic load scores were detected between breast cancer cases and the overall cohort. This pattern contrasts with earlier work by Parente et al., which reported that breast cancer history was not associated with elevated allostatic load in White women but showed a significant positive correlation among Black women [16]. Collectively, these findings suggest that allostatic load may serve as a potential biomarker for evaluating physiological stress burden in breast cancer-related research. For example, allostatic load could be used to evaluate effects of stress-reduction interventions, like mindfulness-based programs, among populations with elevated physiological stress burden and cancer survivors. To confirm these findings, further studies with larger sample sizes are warranted.

Allostatic load may represent a potential biomarker for identifying individuals with increased physiological vulnerability related to chronic stress and could complement existing approaches for evaluating breast cancer-related physiological characteristics. Incorporating AL evaluation into future clinical assessment strategies may help identify individuals with elevated physiological stress burden who may benefit from targeted supportive interventions, including stress management and lifestyle modification programs. However, before AL can be implemented in routine clinical practice, further prospective studies are required to establish standardized assessment criteria, validate its clinical relevance, and determine whether AL-guided interventions can improve breast cancer-related outcomes.

This study has several limitations. One is the limited number of research subjects. To further verify our new findings, additional research with large sample sizes is required. Second is the limited data on breast cancer subtypes in the National Health and Nutrition Examination Survey, which restricted this research to account for breast tumor heterogeneity. Given that breast cancer subtypes have distinct biological behaviors and etiologies, the association between allostatic load and breast cancer may differ across tumor subtypes. Further investigations are required to clarify the underlying relationships and to determine whether the observed association varies according to tumor subtypes.Third, potential selection bias due to missing data cannot be completely excluded. Although baseline characteristics between included and excluded participants were compared (**Supplementary Table 1**), some differences were observed. The use of NHANES sampling weights, multivariable adjustment, and sensitivity analyses may have partially mitigated the potential impact of this bias. Finally, although multiple potential confounders were adjusted for, residual confounding cannot be completely excluded. Several important breast cancer-related factors, including family history, reproductive history, menopausal status, hormone

therapy history, and BRCA mutation status, were unavailable in NHANES or could not be fully adjusted for. In addition, breast cancer diagnosis was based on self-reported information, which may introduce potential recall or misclassification bias. Future studies incorporating more comprehensive clinical and genetic information are needed to further validate the association between allostatic load and breast cancer.

5. Conclusion

Chronic stress has been associated with a greater burden of various chronic diseases; however, its relationship with breast cancer remains incompletely understood. Using data from the NHANES, this study investigated the association between allostatic load, a composite indicator of cumulative physiological stress burden, and breast cancer prevalence among women. High allostatic load was significantly associated with increased odds of breast cancer. These findings suggest that allostatic load may represent a potential candidate biomarker for identifying individuals with greater physiological stress burden and may provide insights into the relationship between physiological stress and breast cancer. However, further prospective studies are required to determine its clinical relevance and applicability.

Supplementary materials: Supplementary Table 1. Comparison of baseline characteristics between included and excluded participants among women aged ≥ 20 years.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary Table 1. Comparison of baseline characteristics between included and excluded participants among women aged ≥ 20 years.Values are presented as n (%) for categorical variables and median (interquartile range) for continuous variables. *P* values were calculated using the chi-square test or Wilcoxon rank-sum test, as appropriate. Missing data were not included in percentage calculations, and the number of participants may vary across variables due to missing data.

Variable	Level	Included	Excluded	*P*-value
Age	≤ 65	4744 (80.5)	19150 (75.5)	< 0.001
	> 65	1148 (19.5)	6202 (24.5)	
Race	Mexican American	1133 (19.2)	3916 (15.4)	< 0.001
	Other Hispanic	499 (8.5)	2114 (8.3)	
	Non-Hispanic White	2873 (48.8)	11681 (46.1)	
	Non-Hispanic Black	1137 (19.3)	5044 (19.9)	
	Other Race	250 (4.2)	2597 (10.2)	
PIR	≤ 1.3	1851 (31.4)	8203 (32.4)	0.369
	> 3.5	1784 (30.3)	7606 (30)	
	1.3–3.5	2257 (38.3)	9543 (37.6)	
Cotinine, serum (ng/mL)	< 0.05 ng/ml	3149 (53.4)	10534 (55.4)	0.0111
	≥ 3 ng/ml	1295 (22)	3875 (20.4)	
	0.05–2.99 ng/ml	1448 (24.6)	4593 (24.2)	
Hypertension	No	3152 (53.5)	13198 (52.1)	0.0533
	Yes	2740 (46.5)	12139 (47.9)	
ALQ	No	2308 (39.2)	7138 (39.1)	0.896
	Yes	3584 (60.8)	11134 (60.9)	
Diabetes	No	5017 (85.1)	21653 (85.4)	0.588
	Yes	875 (14.9)	3691 (14.6)	
Depression	No	5286 (89.7)	11028 (87.9)	< 0.001
	Yes	606 (10.3)	1516 (12.1)	
Lymphocyte number (1000 cells/uL)		2.100 (1.700, 2.600)	2.100 (1.700, 2.600)	0.0732
Segmented neutrophils num (1000 cell/uL)		4.100 (3.100, 5.300)	4.100 (3.100, 5.300)	0.963
Eosinophils number (1000 cells/uL)		0.200 (0.100, 0.200)	0.100 (0.100, 0.200)	0.00168
Basophils number (1000 cells/uL)		0.000 (0.000, 0.100)	0.000 (0.000, 0.100)	< 0.001
Monocyte number (1000 cells/uL)		0.500 (0.400, 0.600)	0.500 (0.400, 0.600)	< 0.001
Mean platelet volume (fL)		7.900 (7.400, 8.400)	8.200 (7.600, 8.900)	< 0.001