

## ORIGINAL RESEARCH ARTICLE

# Association of allostatic load with female infertility: Findings from national health and nutrition examination survey 2017-2020

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Huiyu Chen, Ziyang Xu, Wenjun Hu and Yuhong Li\*

College of Nursing, Anhui Medical University, Hefei, Anhui, China 230032

\*For Correspondence: Email: [liyuhong@ahmu.edu.cn](mailto:liyuhong@ahmu.edu.cn); [1322043525@qq.com](mailto:1322043525@qq.com); Phone+8613855189168

### Abstract

Allostatic load (AL), which is often used to observe damage to the organism from chronic stressful stimuli, has been demonstrated to be connected to a number of harmful consequences for health. There is currently no conclusive correlation between AL and infertility. The objective of this study was to delve identify possible correlation between AL and infertility. We used data from the National Health and Nutrition Examination Survey database, from 814 women of childbearing age from the United States. We investigated the relationship between AL level and infertility using logistic regression analysis. Nine biomarkers were selected from three major systems (cardiovascular, metabolic, and immune systems) to assess AL level. Regression analysis revealed that, after controlling for the total number of deliveries, marital status, moderate work activity, and family-to-poverty income ratio, each unit increase in AL was associated with a 2.2-fold higher risk of infertility. Therefore, AL warrants greater attention as a modifiable factor related to infertility. (*Afr J Reprod Health* 2026; 30 [2]: 81-90).

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**Keywords:** allostatic load, infertility, stress, sterility

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### Résumé

La charge allostatique (CA), souvent utilisée pour observer les dommages causés à l'organisme par des stimuli stressants chroniques, s'est avérée liée à un certain nombre de conséquences néfastes pour la santé. Il n'existe actuellement aucune corrélation concluante entre l'AL et l'infertilité. L'objectif de cette étude était d'approfondir la recherche d'une corrélation possible entre l'AL et l'infertilité. Nous avons utilisé des données issues de la base de données NHANES (National Health and Nutrition Examination Survey) et avons finalement intégré 814 femmes américaines en âge de procréer. Nous avons étudié la relation entre le niveau d'AL et l'infertilité à l'aide d'une analyse de régression logistique. Neuf biomarqueurs ont été sélectionnés à partir de trois systèmes principaux (systèmes cardiovasculaire, métabolique et immunitaire) pour évaluer le niveau d'AL. L'analyse de régression a révélé qu'après avoir pris en compte le nombre total d'accouchements, la situation matrimoniale, l'activité professionnelle modérée et le ratio pauvreté/revenu familial, chaque augmentation unitaire de l'AL était associée à un risque 2,2 fois plus élevé d'infertilité. Par conséquent, l'AL mérite une plus grande attention en tant que facteur modifiable lié à l'infertilité. (*Afr J Reprod Health* 2026; 30 [2]: 81-90).

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**Mots-clés:** charge allostatique, infertilité, stress, stérilité

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### Introduction

According to the latest International Glossary of Infertility and Fertility Care, infertility is defined as a condition in which a clinical pregnancy may not occur after 12 months of regular, unprotected sex, or where a person's ability to reproduce is impaired, and includes both male and female infertility.<sup>1</sup> Available data indicate that infertility occurs in approximately 15% of couples of childbearing age worldwide.<sup>2</sup> The World Health Organization predicts that, in the 21st century, infertility will become the 3rd most intractable illness, after

tumors and cardiovascular and cerebrovascular illnesses. Infertility poses a challenge to reproductive health and has become a major public health problem worldwide.<sup>3</sup> Infertility not only causes psychological stress and emotionally drains the affected individuals but also affects the couple's relationship and can lead to health risks and financial difficulties for the family.<sup>2</sup> Hence, identifying the risk factors for infertility and establishing effective preventive and curative measures are of great significance for minimizing the adverse effects of infertility and reducing its burden on society.

Studies have reported that female fertility is influenced by several factors, including physical, lifestyle, environmental and social factors.<sup>1,4,5</sup> Among the psychosocial factors, stress is gaining increasing attention.<sup>6,7</sup> Stressors trigger synthesized physiological reactions (including neuroendocrine, metabolic, and immune reactions) that are adaptable within a short period of time, allowing the human body to react to ever-changing environments.<sup>8</sup> Nevertheless, these systems can become dysfunctional and cause damage when individuals are subjected to chronic stress stimuli for prolonged periods. Allostatic load (AL) is a comprehensive indicator of cumulative damage caused to an organism from chronic stress stimuli, and it reflects the cumulative damage caused to a number of systems, such as the cardiovascular, metabolic, immune, and neuroendocrine systems.<sup>9</sup> Allostatic load index (ALI), as an overall indicator, can measure the AL level.<sup>10</sup> Elevated AL level have been linked to cardiovascular diseases, hypertension, diabetes, and general mortality-related adverse health outcomes.<sup>11</sup>

Studies indicate that chronic and constant stress can cause menstrual disorders, anovulation, functional hypothalamic amenorrhea, and reductions in the levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and gonadotropin-releasing hormone (GnRH), resulting in low fertility or infertility.<sup>5</sup> When the neuroendocrine, immune, and cardiometabolic systems are affected (for example, due to high AL level), fertility may be damaged, and the process of pregnancy may be altered.<sup>12</sup> However, there are only a few existing studies related to AL and infertility. A study by Barrett et al.<sup>12</sup> demonstrated that AL is not associated with fertility, whereas a report by Hong et al.<sup>13</sup> indicated that AL scores are related to female fertility. As these studies are contradictory, the association between AL and infertility has not yet been clearly determined. This study, based on the National Health and Nutrition Examination Survey (NHANES) database, introduces a systems biology metric of AL for the first time in reproductive medicine research. This study aimed to reveal the link

between the physiological deterioration caused by long-term accumulated stress and reproductive dysfunction, providing critical evidence for the development of future preventive and interventional strategies targeting the reduction of AL. We hypothesized that higher AL level would correlate more significantly with infertility, meaning that women with elevated AL level would exhibit a higher risk of infertility

## Methods

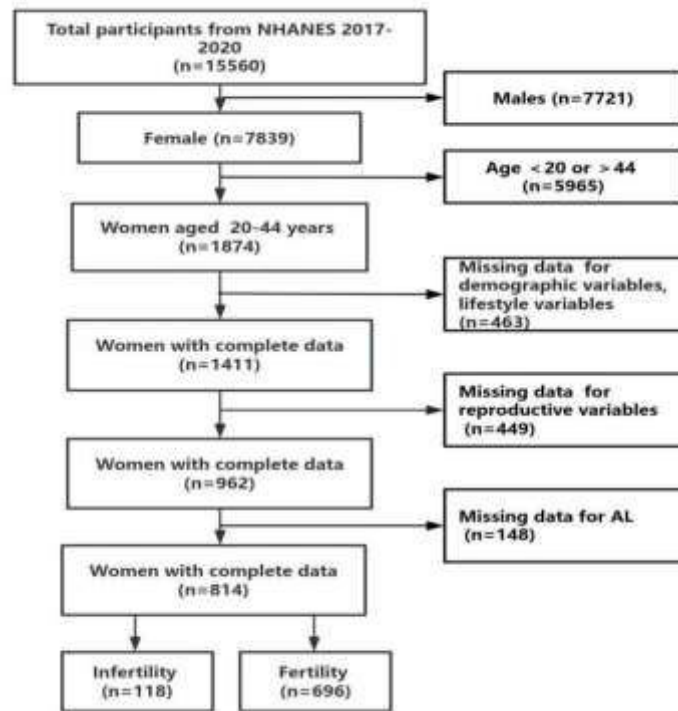
### *Participants and the screening process*

The NHANES is a research project aimed at assessing the health and nutritional status of adults and children in the United States. This study was conducted using a nationally representative sample of approximately five thousand people spread across counties in the United States, with individuals living in 15 counties were interviewed each year. The participants were compensated, and their medical findings were reported. This study is distinctive in that it integrated data from interviews and physical examinations conducted by highly trained personnel. All the information gathered during the investigation were treated with strict anonymity and confidentiality. We obtained NHANES 2017 - March 2020 survey cycle data to investigate the relationship between AL and infertility. The data source link is provided below: [https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx? Cycle=2017-2020](https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?Cycle=2017-2020). We excluded data from male participants, those outside the age range of 20 - 44 years, and those with incomplete demographic, lifestyle, reproductive variables and laboratory data. As shown in Figure 1, 814 female participants of childbearing age were finally included in this study.

### *Measures*

#### *Assessment of infertility*

This included women who had not achieved clinical pregnancy after 12 months of regular, unprotected sex, or whose ability to reproduce was impaired.<sup>1</sup>



**Figure 1:** Screening research participants' flowchart

Therefore, the criteria for identifying women with infertility in this study were based on responses to the following question from the Reproductive Health questionnaire, RHQ074, in the NHANES 2017-March 2020 survey cycle: "Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant?". Women who answered "yes" were recognized as infertile, whereas those answering "no" were considered normal.

### **Biological markers**

Based on the representativeness and universality of previously studied AL markers and completeness of the NHANES database data, as indicators, we chose commonly used biomarkers that have also been used extensively in previous NHANES studies.<sup>14</sup> In this study, nine biomarkers were selected from three systems to measure AL level.<sup>15-18</sup> Cardiovascular system indicators included total cholesterol and high-density lipoprotein (HDL) levels; metabolic system indicators included body mass index (BMI), waist-to-hip ratio, and levels of

urinary albumin, urinary creatinine, and glycohemoglobin; and immune system indicators included white blood cell count and high-sensitivity C-reactive protein level.

Professional health technicians in Mobile Examination Centers (MECs) took body measurements. BMI was expressed in kilograms per square meter and rounded to one decimal place.

Blood was collected at the MECs. Participants were instructed to fast for 9 h before blood sample collection. Detailed operating instructions for the collection, handling, and transport of specimens are available at <https://www.cdc.gov/nchs/nhanes/index.htm>.

### **ALI**

To obtain the ALI, first each biomarker was converted into a dichotomous variable based on the statistical distribution of the sample (quartiles).<sup>15</sup> The highest risk quartile was used for all biomarkers except HDL level. Values at or above the highest quartile were scored as 1 and others as 0.<sup>19</sup> Finally, the cumulative scores of all biomarkers were summed to obtain individual ALI. The greater

the ALI, the higher the prevalence of physiological disorders. The ALI in this study ranged from 0 to 8, with low ALI defined as those <3 and high ALI defined as those  $\geq 3$ .<sup>20,21</sup> Previous studies have shown that ALI > 3-4 are significantly associated with the incidence rate and mortality.<sup>22,23</sup>

### ***Assessment of covariates***

In this study, the covariates employed included several variables which may impact the association between AL and infertility, including demographic, lifestyle and reproductive health variables,<sup>24,25</sup> age (range: 20-44 years old), family-to-poverty income ratio (range: 0-5), education levels, race, marital status, history of smoking (having smoked at least 100 cigarettes in a lifetime, yes/no) and alcohol use (having consumed any kind of alcohol in the past, yes/no), vigorous work activity (yes/no), moderate work activity (yes/no), regular menstruation for the past 12 months (yes/no), age at first menstruation (range: 6-20 years), previous treatment for pelvic inflammatory/pelvic infection disease (yes/no), and total number of deliveries (range: 0-5). Educational levels were categorised as follows: less than 9th grade, 9-11th grade, high school graduate/GED or equivalent, some college or AA degree, college graduate or above. The race was classified as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian, and other races. Marital status was categorised as married or living with partner, widowed/divorced/separated, never married.

### ***Statistical analysis***

Statistical data were analyzed using SPSS 23.0 software. Participants with missing data were excluded. Continuous variables included age, age at first menstruation, family-to-poverty income ratio, and total number of deliveries. Normally distributed data were expressed as mean and standard deviation, whereas non-normally distributed data

were expressed as median (M) and interquartile range (IQR). Categorical variables were indicated using frequency and percentage. Due to the lack of theoretical and statistical procedures for integrating weights in nonparametric tests, the data were not weighted. A bivariate analysis was conducted to determine the influence of different covariates on infertility. In this study, the continuous variables had a skewed distribution and were described using M (IQR), and the Wilcoxon Mann - Whitney rank sum test was applied for between-group comparisons. Categorical variables were analyzed using the chi-squared or Fisher's exact test. The unadjusted and adjusted correlations between infertility and AL were evaluated using logistic regression models.<sup>26</sup> In the bivariate analyses, the covariates identified as associated with AL were incorporated into the logistic regression analyses. A two-sided test with  $\alpha=0.05$ ,  $P<0.05$  was considered as indicative of a statistically significant difference. The adjusted logistic regression model controlled for the total number of deliveries, marital status and moderate work activity, family-to-poverty income ratio.

### ***Ethics approval***

The project was approved by the Ethics Review Board of the National Center for Health Statistics and was based on the Declaration of Helsinki of the World Medical Association. The study participants signed informed consent forms prior to being surveyed and patient privacy was respected.

## **Results**

### ***Participants' basic characteristics***

In all 814 female participants were included in the study, including 118 women with infertility and 696 pregnant women. The basic characteristics of the participants are listed in Table 1. Of the total participants, 39.2% (n=319) had a high AL level.

**Table 1:** Basic features of included participants

Variables	Total (N=814)	Infertility (n=118)	Fertility (n=696)	$\chi^2$ /Mann-Whitney U	P
Regular menstruation for the past 12 months				0.9	0.4
Yes	730 (89.7)	103 (87.3)	627 (90.1)		
No	84 (10.3)	15 (12.7)	69 (9.9)		
Previous treatment for pelvic inflammatory/pelvic infection disease				0.2	0.6
Yes	60 (7.4)	10 (8.5)	50 (7.2)		
No	754 (92.6)	108 (91.5)	646 (92.8)		
Having consumed any kind of alcohol in the past				0.1	0.8
Yes	739 (90.8)	108 (91.5)	631 (90.7)		
No	75 (9.2)	10 (8.5)	65 (9.3)		
Having smoked at least 100 cigarettes in a lifetime				3.1	0.1
Yes	293 (36.0)	51 (43.2)	242 (34.8)		
No	521 (64.0)	67 (56.8)	454 (65.2)		
Vigorous work activity				0.3	0.6
Yes	209 (25.7)	28 (23.7)	181 (26.0)		
No	605 (74.3)	90 (76.3)	515 (74.0)		
Moderate work activity				5.3	0.02
Yes	383 (47.1)	44 (37.3)	339 (48.7)		
No	431 (52.9)	74 (62.7)	357 (51.3)		
Race				8.7	0.1
Mexican American	121 (14.9)	17 (14.4)	104 (14.9)		
Other Hispanic	84 (10.3)	12 (10.2)	72 (10.3)		
Non-Hispanic White	253 (31.1)	49 (41.5)	204 (29.3)		
Non-Hispanic Black	234 (28.7)	24 (20.3)	210 (30.2)		
Non-Hispanic Asian	69 (8.5)	10 (8.5)	59 (8.5)		
Other Races	53 (6.5)	6 (5.1)	47 (6.8)		
Marital status				7.5	0.02
Married/Living with Partner	520 (63.9)	87 (73.7)	433 (62.2)		
Widowed/Divorced/Separated	98 (12.0)	14 (11.9)	84 (12.1)		
Never married	196 (24.1)	17 (14.4)	179 (25.7)		
Education levels				0.3	1.0
Less than 9th grade	40 (4.9)	5 (4.2)	35 (5.0)		
9-11th grade	102 (12.5)	15 (12.7)	87 (12.5)		
High school graduate/GED or equivalent	173 (21.3)	24 (20.3)	149 (21.4)		
Some college or AA degree	322 (39.6)	47 (39.8)	275 (39.5)		
College graduate or above	177 (21.7)	27 (22.9)	150 (21.6)		
ALI				9.1	0.003
Low AL	495 (60.8)	57 (48.3)	438 (62.9)		
High AL	319 (39.2)	61 (51.7)	258 (37.1)		
Age at first menstruation	12 (11,13)	12 (11,13)	12 (11,13)	0.4	0.4
Total number of deliveries	2 (1,3)	2(1,3)	2 (1,3)	0.001	0.001
Family-to-poverty income ratio	1.7 (0.9, 3.1)	1.6 (0.9, 3.0)	2.1 (1.1, 3.5)	0.03	0.03
Age	35 (29, 40)	35 (29, 40)	35 (29.8, 39)	0.9	0.9

ALI: allostatic load index, AL: allostatic load

**Table 2:** Features and cutoff value of biological markers and allostatic load index

Biological markers	Range	Media (P25, P75)	Cutoff value
<b>Cardiovascular</b>			
HDL(mg/dL)	23-151	52 (44, 64)	≤44.0
total cholesterol(mg/dL)	101-343	175 (155, 199)	≥199.0
<b>Immune</b>			
high-sensitivity C-reactive protein(mg/L)	0.1-53.8	2.42 (0.9, 5.7)	≥5.7
white blood cell (1000 cells/uL)	2.8-22.8	7.30 (6.1, 8.8)	≥8.8
<b>Metabolic</b>			
BMI(kg/m <sup>2</sup> )	14.8-67	29.90 (24.4, 35.8)	≥35.8
Glycohemoglobin (%)	4.1-14.8	5.30 (5.1, 5.6)	≥5.6
Urinary albumin(mg/L)	0.3-7070	9.30 (4.6, 18)	≥18.0
Waist-to-hip ratio	0.7-1.1	0.89 (0.8, 0.9)	≥0.9
Urinary creatinine(mg/dL)	7-602	118 (66, 182.3)	≥182.3
ALI	0-8	2 (1, 3.3)	≥3

HDL:high-density lipoprot

**Supplement 1.** Distribution of fertility and infertility rates according to the ALI

ALI	Total (N=814)	Fertility (n=696)	Infertility (n=118)
0	143	125 (87.4)	18 (12.6)
1	183	156 (85.3)	27 (14.8)
2	169	157 (92.9)	12 (7.1)
3	116	96 (82.8)	20 (17.2)
4	89	70 (78.7)	19 (21.4)
5	62	51 (82.3)	11 (17.7)
6	37	30 (81.1)	7 (18.9)
7	14	10 (71.4)	4 (28.6)
8	1	1 (100.0)	0 (0.0)

ALI: allostatic load index.

**Supplement 2 :** Binary logistic regression analysis of biological markers and infertility

Biological markers	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>P</i>	<i>OR</i>	95% <i>CI</i>	
						Lower	Upper
<b>High-sensitivity C-reactive protein</b>	0.1	0.3	0.3	0.6	1.1	0.7	1.9
<b>HDL</b>	0.3	0.2	1.6	0.2	1.3	0.8	2.1
<b>Total cholesterol</b>	-0.1	0.2	0.2	0.7	0.9	0.6	1.4
<b>Urinary albumin</b>	-0.1	0.3	0.3	0.6	0.9	0.5	1.4
<b>White blood cell</b>	-0.04	0.2	0.03	0.9	1.0	0.6	1.5
<b>BMI</b>	0.5	0.2	4.1	<b>0.04*</b>	1.6	1.0	2.6
<b>Glycohemoglobin</b>	0.1	0.2	0.1	0.7	1.1	0.7	1.7
<b>Waist-to-hip ratio</b>	0.4	0.2	2.6	0.1	1.5	0.9	2.3
<b>Urinary creatinine</b>	-0.5	0.3	3.9	<b>0.05*</b>	0.6	0.3	1.0

HDL: high-density lipoprotein, BMI: body mass index, *B*: regression coefficient, *SE*: standard error, *Wald*: chi-square value, *OR*: odds ratio, 95%*CI*: 95% confidence interval.

\**P*<0.05 was statistically significant. Bold indicates statistically significant variables.

Association between AL level and infertility

**Table 3:** Allostatic load level and infertility logistic regression analysis

	Unadjusted Model			Adjusted Model		
	OR	95%CI	P	OR	95%CI	P
<b>Low AL</b>						
<b>High AL</b>	1.8	1.2, 2.7	<b>0.003</b>	2.2	1.4, 3.2	<b>0.001</b>

OR: odds ratio, 95%CI: 95% confidence interval, AL: allostatic load.

<sup>a</sup>adjusting total number of deliveries, marital status and moderate work activity, family-to-poverty income ratio.

Table 2 describes the ranges, quartiles, and cutoff values for the selected markers and ALI. The ALI ranged from 0 to 8, with a median ALI of 2.

### ***Distribution of fertility and infertility rates according to the ALI***

Based on the ALI, the participants were categorized into nine groups with ALI ranging from 0 to 8. The numbers of pregnant participants and those with infertility in each group are shown in Supplement 1.

### ***Relationship between biological markers and infertility***

We performed binary logistic regression analysis to identify the correlation between each of the nine biological biomarkers and infertility, and our findings showed that BMI and urinary creatinine level had a significant association with infertility. The higher quartiles of BMI were linked with 1.6 times higher risk of infertility, compared with the lower quartiles (See Supplement 2 for details).

### ***The link between AL level and infertility is presented in Table 3***

The results of showed an association between high AL level and infertility. High AL level was associated with infertility in the unadjusted model (odds ratio [OR]=1.8; 95% confidence interval [CI]:1.2-2.7;  $P=0.003$ ).The correlation persisted in the adjusted model after controlling for the total number of deliveries, marital status, moderate work activity, and family-to-poverty income ratio ( $OR = 2.2$ ; 95%CI:1.4-3.2;  $P = 0.001$ ), and the risk of infertility increased by 2.2 times for each unit increase in ALI

## **Discussion**

This study elucidated the correlation between AL level and female infertility. We used nine

biomarkers from three biological systems to measure AL and found the risk of infertility increased by a factor of 2.2 for each unit increase in ALI.

Previous studies on the correlation between AL and fertility reported inconsistent findings. Barrett et al.<sup>12</sup> showed that AL was related to poor pregnancy outcomes and had no association with fertility. In their study, the chances of conception, miscarriage, or live birth were not affected by AL in women undergoing fertility treatment, possibly because the participants were chosen to include those who received treatment for ovarian function; therefore, the effects of AL on ovarian dysfunction disorders were hidden during infertility treatment in that study. Hong et al.<sup>13</sup> showed that women with higher ALI tended to have lower fertility, which is consistent with our results. We illustrate the reason for this result below:

Stress is challenging for the human body, and it requires tremendous effort on the part of the organism to maintain homeostasis under stressful conditions. Previous investigations have shown that stress suppresses reproductive function and have demonstrated the interaction between stress, immune system, and female reproductive function.<sup>27</sup> Psychological interventions for may reduce anxiety and depression in women with infertility and significantly increase the odds of pregnancy.<sup>28</sup> The following mechanisms may explain the association between AL and infertility. Studies have shown that allostasis is the process by which the body of an organism maintains homeostasis in the presence of external stresses, including dynamic changes in the activity of the neuroendocrine and immune systems. Physiological reactions to stress include enhanced hypothalamic - pituitary - adrenal (HPA) axis activity, which increases the heart rate, blood pressure, and glucose production, and modifies immune system activity to ready the body for the

“fight or flight” response.<sup>29</sup> One way in which stress is commonly thought to affect reproductive function is through activation of the HPA axis.<sup>30</sup> Brain regions such as the amygdala and prefrontal cortex, recognize a stressor, trigger the release of catecholamines (epinephrine and norepinephrine) from the sympathetic-adrenal-medullary axis and glucocorticoids (cortisol or corticosterone) from the hypothalamic-pituitary-adrenal (HPA) axis, which permits the body to mobilize energy and exercise muscles, increases cardiovascular tone for energy delivery, and temporarily inhibits reproductive function.<sup>31</sup> Secondly, cortisol secretion increases in response to ongoing chronic stress.<sup>32</sup> Cortisol is a staple stress hormone released through the activation of the HPA axis and can influence human reproductive capability through immunosuppression.<sup>33</sup> Excessive cortisol may interfere with the pulsatile release of GnRH, which grips the ovulation and menstrual cycle, which is likely to result in irregular or anovulation and eventual infertility. High cortisol levels also inhibit the release of FSH and LH, thereby affecting ovarian function and reducing the likelihood of pregnancy.<sup>34</sup> Overall, prolonged psychological stress can lead to increased AL level, which influences the generation and release of hormones associated with the hypothalamic-pituitary-ovarian axis, thereby seriously affecting female reproductive function.<sup>35</sup> The body may respond to different stressors by also increasing AL level, causing variations in the body’s systems that can result in low fertility or infertility.

Based on the findings of this study, chronic stress management holds promise as a vital component of comprehensive infertility treatment plans in clinical practice. Specific measures may include providing professional psychological counseling and therapy, introducing mindfulness training and meditation courses, and promoting lifestyle medicine interventions (such as nutritional guidance, regular exercise, and sleep optimization). These approaches can directly reduce the non-steady-state stress load and improve reproductive health outcomes. At the policy level, the promotion of public health education initiatives targeting the reproductive-age population is recommended. This should involve enhancing knowledge dissemination

among young men and women regarding lifestyle, stress regulation, and reproductive health while emphasizing the importance of preconception care. Such efforts aim to raise public awareness of the detrimental effects of chronic stress on health, particularly by highlighting its potential role in the risk of infertility. This will foster early awareness and behavioral shifts toward health management in society.

## Study strengths and limitations

The sample for this study was acquired from the NHANES database and was large and representative. In addition, the NHANES database is a standardized database, in which biomarkers are collected by trained researchers in a standardized manner, reducing error bias in the main exposure variables of our study and making the results more objective and accurate. Finally, our study identified an association between AL level and female infertility, which provides a theoretical foundation for reducing the incidence of infertility in the clinical setting.

The limitation of this study is that it was a cross-sectional survey, making it difficult to delve deeper into the causal relationship between AL and infertility. Second, AL is dynamic and may influence the incidence of infertility based on an individual’s lifestyle, social stress, and coping skills. In our study, AL was assessed only once, and hence it does not reflect the overall dynamics of the participants’ attempts to conceive. Finally, due to limitations in the availability of the NHANES database, our study only included indicators of the cardiovascular, immune, and metabolic systems. Biomarkers of the neuroendocrine system (such as cortisol, dopamine, and epinephrine), which are closely related to female reproductive function, were not included.

## Conclusion

This study found an association between the body’s AL level and infertility, with high AL level increasing the risk of infertility. Therefore, AL level should receive more attention as a modifiable factor associated with infertility. In the future, measures should be taken to reduce the negative effects of stress in women.

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## Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships.

## Contribution of authors

Huiyu Chen is responsible for the overall conception of the article and the writing of the article. Ziyang Xu is responsible for data screening and processing and graphics of the article. Wenjun Hu was responsible for the material search and revision of the article. Yuhong Li was responsible for quality control, final review and proofreading of the article. All listed authors have reviewed and approved the final manuscript.

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