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ORIGINAL RESEARCH ARTICLE

Female fecundability is associated with pre-pregnancy allostatic load: Analysis of a Chinese cohort

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Abstract

Introduction: Allostatic load (AL) is a practical index that reflects multi-system physiological changes which occur in response to chronic psychosocial stress. This study investigated the association between female pre-pregnancy allostatic load and time to pregnancy.

Material and methods: We enrolled 444 women who met the inclusion criteria and were attempting to achieve pregnancy. Their allostatic load scores at baseline were evaluated by nine indicators (systolic blood pressure, diastolic blood pressure, fasting plasma glucose, plasma cortisol, noradrenaline, interleukin-6, hypersensitive C-reactive protein, high density lipoprotein cholesterol and body mass index). The participants were followed up and their pregnancy outcome ascertained 1 year later; we then calculated time-to-pregnancy. Cox models were used to estimate fecundability ratios and their 95% confidence intervals (95% CI) for different allostatic load scores.

Results: The median allostatic load score was 1 with a range of 0–6. The females were divided into four groups according to allostatic load score: group A (allostatic load = 0, 150/444, 33.8%), group B (allostatic load = 1–2, 156/444, 35.1%), group C (allostatic load = 3–4, 100/444, 22.5%) and group D (allostatic load = 5–6, 38/444, 8.6%). The cumulative pregnancy rate over 12 months for the four groups (A–D) was 55.4%, 44.5%, 50.9% and 26.9%, respectively (log-rank test, $p = 0.042$). After adjusting for potential confounding factors, group D showed a 59% reduction of fecundability compared with group A (fecundability ratio = 0.41, 95% CI 0.21–0.83).

Conclusions: Women with a higher allostatic load score may have lower fecundability. Our findings suggest that the assessment of allostatic load during pre-conception consultation would be highly prudent.

KEYWORDS
allostatic load, cohort study, fecundability, infertility, psychosocial stress, time to pregnancy

Abbreviations: AL, allostatic load; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IL-6, interleukin-6; NA, noradrenaline; SBP, systolic blood pressure; TTP, time to pregnancy.

1 | INTRODUCTION

The reduction of human fecundability not only makes individuals infertile, it also creates social aging problems. Female fecundability is a complicated topic that can be influenced in many ways, including physical factors and psychological factors.[1] Previous studies tended to focus on the impact of chronic diseases, such as hypertension,[2] diabetes[3] and obesity.[4] However, mental factors, including psychological pressure, anxiety and depression, could also potentially exert impact on female fecundability.[5] The current evidence supports that the infertility may cause stress in many ways,[6] but it is unclear whether the stress causes infertility, or what is the interactions between stress and human fecundability.[7] A precise cause–effect relation is still difficult to demonstrate due to conflicting results and the lack of objective measures/instruments of evaluation.[5] There is inevitably subjective bias when some scales are used to evaluate the stress. Thus, some scholars proposed the concept of allostatic load (AL) to reflect multisystem physiological changes in response to chronic psychosocial stress.[8]

In general, the AL index is regarded as a marker of cumulative biological risk and represents the functions of the neuroendocrine, immune, metabolic and cardiovascular systems.[9] As an objective, quantitative and appreciable index, the AL has been widely studied and has been associated with coronary heart disease,[10] cancer-specific mortality[11] and type 2 diabetes.[12] Previous studies found that among infertile women undergoing ovarian stimulation, a higher AL at baseline was not associated with conception, spontaneous abortion or live birth, but was significantly associated with an increased odds of preeclampsia and preterm birth.[13] Gauri et al.[14] also found that the higher anxiety scale scores were negatively associated with clinical pregnancy after in vitro fertilization. However, it is not known whether these findings apply to all health women planning pregnancies.

We speculate that the women with a higher AL score, which means they have a higher chronic psychosocial stress, would have a lower fecundability and would spend more time achieving pregnancy. Given this hypothesis, the infertility-based case–control study is not a suitable design because we could not tell whether the women's high AL score comes from knowing their infertility diagnosis and getting assisted reproductive therapy, or from original daily life style stress. Thus, prospective pregnancy-planning cohort study is necessary to verify this association. At present, preconception counseling pays more attention to reducing the incidence of adverse pregnancy outcomes;[15] however, we believe that pre-conception interventions targeting chronic psychosocial stress can also improve female fecundability and shorten the time to pregnancy (TTP) if the causality between higher AL and reduced fecundability is confirmed. This will have important public health value. Therefore, in the present study, we preliminarily investigated the potential association between baseline AL score and the time to pregnancy in a Chinese pregnancy-planning cohort.

Key message

Women with a higher allostatic load score, which suggests a higher chronic psychosocial stress, may have a lower fecundability.

2 | MATERIAL AND METHODS

2.1 | Study population

We recruited all couples who took part in the National Free Pre-conception Check-up Project (NFPCP) in the Maternal and Child Center of Gulou district in Nanjing city from June 13, 2018 to May 30, 2020. The original design, organization and implementation of the NFPCP was described previously.[16] The original purpose of this project was to reduce the risk of birth defects, and therefore we set strict criteria for this research. Inclusion criteria were as follows: (1) according to the legal age for marriage in China, the female needed to be older than 20 years, and the male older than 22 years, and only legally married couples could apply for this project; (2) couples who reported that they were ready to become pregnant. Exclusion criteria were as follows: (1) females who were already pregnant when taking part in the project, because their fecundability could not be assessed by the TTP; (2) either partner had been diagnosed with a medical condition unsuitable for pregnancy, including infertility diagnosis, uterine malformation, testicular loss or *Treponema pallidum* infection, because we only focused on the common pregnancy-planning couples and tried to control the influence of these confounding factors on TTP; (3) women who refused to allow the collection of blood samples, because the AL score could not be assessed without it; and (4) women who left the cohort without any effective TTP, as these couples might simply be looking for a free checkup rather than actually trying to get pregnant. Figure 1 shows the details about study population selection.

2.2 | The collection of baseline characteristics and covariates

All participants were asked to complete a uniform questionnaire with the help of health workers. This questionnaire was developed by the committee of experts of NFPCP from 2010. The data have been widely mined for scientific exploration.[2,17] We acquired the birthdays of each couple so that we could calculate the ages and age difference between couples. All women self-reported a range of data, including educational level, occupation, pregnancy history, number of children, menstruation situation, and drinking and smoking habits. Educational level was summarized as a dichotomous variable: "high school and below" and

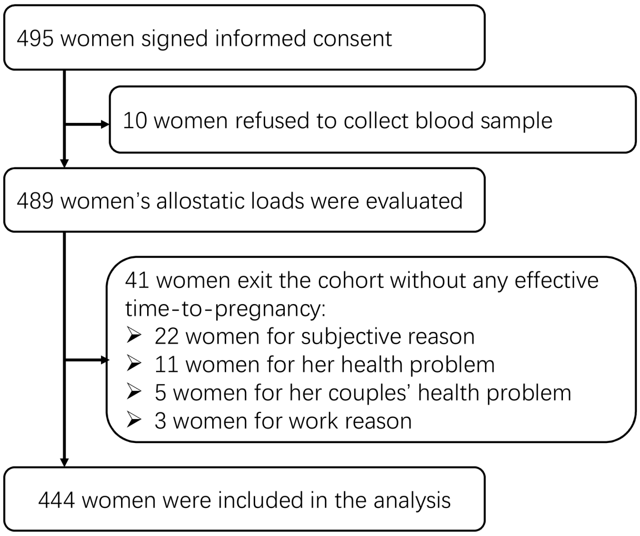

FIGURE 1 Flow chart showing the study population.

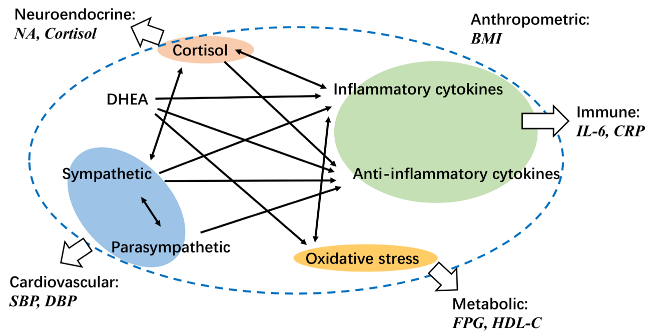

FIGURE 2 The non-linear network of mediators of allostasis involved in the stress response and the associations between indices which the study selected. Arrows indicate that each system regulates the others. BMI, body mass index; NA, noradrenaline; DHEA, dehydroepiandrosterone; interleukin-6, IL-6; CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol.

"higher education and above." Occupation classification included worker, office clerk and others. Pregnancy history was defined as ever having had a clinically confirmed pregnancy through ultrasonography or urine pregnancy test, whether delivered or not. The number of children who need to be raised in their family were recorded, whether a biological child or not. A regular menstrual cycle was defined as a cycle length of 21–35 days.[18] Alcohol intake was defined as participants who drank at least once a week, regardless of the amount of alcohol consumed (Yes or never [No]). Smoking was defined as smoking at least one cigarette per day for at least 1 year. All of the women reported they did not smoke. This information was potentially associated with female fecundability [19]and were therefore selected as confounding factors in our study.

2.3 | AL evaluation

Although different studies included different biomarkers for AL calculation, most of them covered five physiological dimensions.[8] According to Juster's conclusions,[8] we took full account of the indices which exist in the NFPCP project, and the most frequent indices used in the existing studies; we finally selected nine indicators from the five dimensions, the hypothesis pattern being shown in Figure 2 (adapted from Juster[8]). The anthropometric index was body mass index (BMI), which was calculated using the formula: BMI (kg/m^2) = weight (kg)/ height^2 (m). Cardiovascular indices systolic blood pressure (SBP) and diastolic blood pressure (DBP); these were measured using an electronic sphygmomanometer (Yuwell Co., YE670A) after the women had rested for 10 minutes. Fasting blood samples were collected from each female for the measurement of fasting plasma glucose (FPG) levels; this is a metabolic index. In addition, we used enzyme-linked immunosorbent assays (BioSwamp Life Science Lab, Wuhan, China) to determine the plasma levels of cortisol and noradrenaline (NA) (neuroendocrine indices), interleukin-6 (IL-6), hypersensitive C-reactive protein (CRP) (inflammation indices) and high-density lipoprotein cholesterol (HDL-C) (metabolic index). The kits were used in accordance with the manufacturer's instructions (www.bio-swamp.com). In brief, the color change for the specific antibody–antigen–enzyme antibody complex was measured spectrophotometrically at a wavelength of 450 nm. A standard curve was created using the optical densities in different standard concentrations (Table S1). Then the sample concentration could be calculated through the standard curve.

According to AL-related theory, an organism must vary parameters of its internal milieu and match them appropriately to environmental demands, only when the adaptive responses to challenge lie chronically outside of normal operating ranges, wear and tear on regulatory systems occurs and AL accumulates.[9] Therefore, we do not need a very 'sensitive' indicator to reflect the minor changes of our body system, which are thought to be repaired because of homeostasis regulation. Referring to Seeman's standard,[9] the membership in the upper/lower quartile represents a quantitative way of classifying those exposed to more extreme levels of system activity relative to the rest of the population. Thus, in our study, individuals were classified into quartiles based on the distribution of scores in the baseline cohort, except for SBP, DBP and FPG; these were classified as normal and abnormal according to the clinical standard. The thresholds for SBP, DBP and FPG were 140 mm Hg, 90 mm Hg and 6.1 mmol/L, respectively. AL was measured by summing the number of parameters for which the subject fell into the highest risk quartile (all parameters except HDL-C cholesterol, for which membership in the highest quartile corresponds to the highest risk).[9] In fact, this is the traditional count-based formulation and is the most often used.[8,13,20,21]

2.4 | Outcome assessment

All the participants were followed up by telephone every 3 months until 1 year later; whether they were pregnant and their last menstrual periods (LMP) were recorded. The TTP was calculated as the interval between the date of participation in the study and the date of the LMP obtained at follow-up (if pregnant within 1 year) or last follow-up date (if not pregnant), and the TTP was measured as the number of months or menstrual cycles.

2.5 | Statistical analyses

The continuous variables were described as mean ± standard deviation (normal distribution) or median with interquartile range (IQR, non-normal distribution). All the participants were divided into four groups according to the AL scores (AL = 0, AL = 1–2, AL = 3–4, AL = 5–6). Comparison among groups was assessed by variance analysis (normal distribution) or Kruskal–Wallis test (non-normal distribution). The Chi-square test was used to test differences in frequency distribution among groups. The Kaplan–Meier method was used to estimate cumulative pregnancy rates for different groups. Cox models were used to estimate fecundability ratios and their 95% confidence intervals (95% CI) for different AL scores, after adjusting for potential confounding factors. Nevertheless, many important confounders were not measured in our study design, such as semen quality and sexual frequency. To estimate the effect of the potential unmeasured confounders, we calculated the E-value for the fecundability ratio, which denoted the degree to which one or more non-observed confounders would need to increase the risk of exposure and outcome to account fully for the observed associations.[22] A two-sided p-value ≤0.05 was deemed statistically significant.

2.6 | Ethics statement

The study was approved by the Ethics Committee of Zhongda Hospital (Reference: 2018ZDSYLL116-P01) on May 31, 2018. All participants signed an informed consent form.

3 | RESULTS

3.1 | Baseline characteristics of participants

In total, 444 women were included in this study. The mean age of the women was 29.21 years; on average, their male partners were 1.49 years older. For most of the women, this was their first attempt at pregnancy (77.6%, 336/444). There were significant differences between the women who were included or excluded ($n = 51$) with regard to any of the characteristics ($p > 0.05$, see Table S2); This means that the exclusions were random.

Table 1 shows the AL-related indices at baseline. The median BMI was 20.69 kg/m^2 and the prevalence of overweight/obesity was 9.0% (40/444). The median SBP and DBP were 105 and 70 mm Hg, respectively; only one woman fulfilled the criteria for hypertension. The median fasting blood glucose was 4.80 mmol/L; five women (1.1%) had a fasting blood glucose of more than 6.1 mmol/L. According to the AL formula, the AL score ranged from 0 to 6 and the median score was 1. The women were divided in to four groups according to the AL score: A (AL = 0, 150/444, 33.8%), B (AL = 12, 156/444, 35.1%), C (AL = 3–4, 100/444, 22.5%) and D (AL = 5–6, 38/444, 8.6%). Many baseline characteristics between the four groups were statistically different (Table 2). Interestingly, AL score increased with age (means for A–D group, 28.39 vs. 29.60 vs. 29.00 vs. 31.38 years old, $p < 0.001$). Women with a higher AL had a higher likelihood of having more than one child (group D vs A, 26.3% vs. 4.7%).

3.2 | The fecundability of different AL groups

According to the Kaplan–Meier plot (Figure 3), the cumulative pregnancy rates over 12 months for the four groups (A–D) were 55.4%, 44.5%, 50.9% and 26.9%, respectively (log-rank test, $p = 0.042$). After adjusting for potential confounding factors, group D showed a 59% reduction of fecundability compared with group A (Model 4: F fecundability ratio = 0.41, 95% CI 0.21–0.83). Although groups B

TABLE 1 AL-related indices at baseline

Dimensionality	Indices	Median	P25-P75	Mean ± *SD*
Anthropometric	BMI, kg/m^2	20.7	19.1–22.3	21.5 ± 6.8
Cardiovascular	SBP, mmHg	105.0	99.0–112.0	106.9 ± 10.2
	DBP, mmHg	70.0	65.0–74.0	70.0 ± 7.5
Neuroendocrine	Cortisol, μg/dl	12.5	7.0–32.2	21.4 ± 18.6
	NA, nmol/L	1.3	0.7–3.5	2.2 ± 1.8
Inflammation	IL-6, pg/ml	119.5	65.7–377.2	256.0 ± 255.3
	hs-CRP, mg/dl	0.6	0.4–1.8	1.2 ± 1.0
Metabolic	HDL-C, md/dl	54.6	28.9–149.5	93.6 ± 81.6
	FBG, mmol/L	4.8	4.6–5.0	4.8 ± 0.9
AL score		1	0–4	1.8 ± 1.8

Abbreviations: CRP, C-reactive protein; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IL, interleukin.

TABLE 2 Baseline characteristics among different groups according to AL grouping

	0 n = 150	1–2 n = 156	3–4 n = 100	5–6 n = 38	p
Age, year, mean (*SD*)	28.39 (2.88)	29.60 (4.32)	29.00 (3.45)	31.38 (5.51)	<0.001
The difference between couples, year, mean (*SD*)	1.41 (2.80)	1.91 (3.21)	1.16 (2.96)	1.74 (3.08)	0.224
Educational level, *n* (%)					0.033
High school and below	14 (9.3)	27 (17.3)	7 (7.0)	7 (18.4)	
Higher education and above	136 (90.7)	129 (82.7)	93 (93.0)	31 (81.6)	
Occupation, *n* (%)					0.035
Worker	2 (1.3)	2 (1.3)	1 (1.0)	1 (2.6)	
Office clerk	114 (76.0)	95 (60.9)	78 (78.0)	29 (76.3)	
Other	34 (22.7)	59 (37.8)	21 (21.0)	8 (21.1)	
Pregnancy history, *n* (%)					0.002
No	125 (85.0)	102 (67.5)	82 (82.8)	27 (75.0)	
Yes	22 (15.0)	49 (32.5)	17 (17.2)	9 (25.0)	
Number of children, *n* (%)					<0.001
0	143 (95.3)	133 (85.3)	95 (95.0)	28 (73.7)	
1	7 (4.7)	23 (14.7)	5 (5.0)	10 (26.3)	
Regular menstruation, *n* (%)					0.082
No	21 (14.0)	130 (83.3)	85 (85.0)	31 (81.6)	
Yes	129 (86.0)	145 (92.9)	98 (98.0)	33 (86.8)	
Alcohol drinking, *n* (%)					0.082
No	137 (91.3)	145 (92.9)	98 (98.0)	33 (86.8)	
Occasionally	13 (8.7)	11 (7.1)	2 (2.0)	5 (13.2)	

Abbreviation: *SD*, standard deviation.

and C also showed reduced trends for fecundability, these differences were not statistically different when compared with group A ($p > 0.05$). Whether the TTP was in a month or in a menstrual cycle, the results were robust (models 2 and 4 in Table 3). The *E*-value for group D was 4.31 (Figure S1); this indicated that the observed odds ratio of 0.41 could be explained away by an unmeasured confounder that was associated with both the AL and female fecundability by an odds ratio of 4.31-fold. Figure 4 shows that female fecundability decreased with AL and that there was a linear dose–response relation (non-linear trend test, $p = 0.89$).

4 | DISCUSSION

This cohort study clearly demonstrated the negative correlation between female AL score and fecundability. This means that women who have a higher level of psychosocial stress would spend more time achieving pregnancy. To our knowledge, this is the first study to report this association among general pregnancy-attempting women from a cohort design. Our results will help to provide scientific evidence to improve the pre-pregnancy health of women by developing appropriate management strategies.

Previous studies always focused on the mental status of infertile women, especially for those who were receiving assisted reproductive treatment.[23] In fact, mental or physical stress might potentially affect human fecundability,[7] although this effect needs to be verified via a study featuring an appropriate cohort design. In addition, it is very challenging to estimate mental or physical stress. Moderate levels of tension associated with attempting pregnancy might encourage couples to learn some information about pregnancy, thus increasing the rate of pregnancy. However, excessive levels of tension might play the opposite role; this is a complex problem. Traditional questionnaires or scales have unavoidable subjective measurement bias. Regardless of the source of stress, subtle changes may occur in body function and then impact fecundability. Thus, the AL score is an ideal method for reflecting multi-system physiological changes. The same stressor may have different effects on different individuals; this is because the hypothalamic–pituitary–adrenal axis in stress-sensitive individuals is highly responsive to even small increases in serotonin.[24] Thus, assessing the effects of stress is more important than assessing the stress itself. Similar to other studies, our AL score combined information from five physiological dimensions, anthropometric, cardiovascular, metabolic, neuroendocrine and immune indices.[8] This index has been used to determine the risk factors of coronary heart disease,[10] cancer-specific mortality[11] and type 2 diabetes.[12] However, this study is the first to use AL scores with regard to TTP.

Several mechanisms may explain the association between AL and TTP. Initial evidence showed that stress might influence the function of the hypothalamic–pituitary–adrenal axis and then exert influence on the endocrine system and ovulation.[25] Salivary α-amylase, an established biomarker for the hypothalamic–pituitary–adrenal axis, has been found to be associated with infertility.[26] Secondly, glucocorticoid secretion in response to stress contributes to the well-characterized suppression of the HPG axis[27]; this would determine the decline in female fecundability. Thirdly, life stressors and personality factors would lead to a low sexual desire; this could also reduce pregnancy rate.[28]

Our present study does not allow us to determine how AL impacts female fecundability; further research is now needed to identify these mechanisms. Although there are many advantages related to AL assessment, there are still some limitations to our study that need to be considered. We used a widely accepted calculation formula based on quartiles; this is convenient and accurate.[9] However, there are also other methods that we could have used, such as the average *z*-score method; this method was used in some studies and yielded comparable results.[29] Furthermore, previous studies used a range of different indices to estimate the AL,[8,11] thus limiting the comparability of the findings from different studies. In addition, our

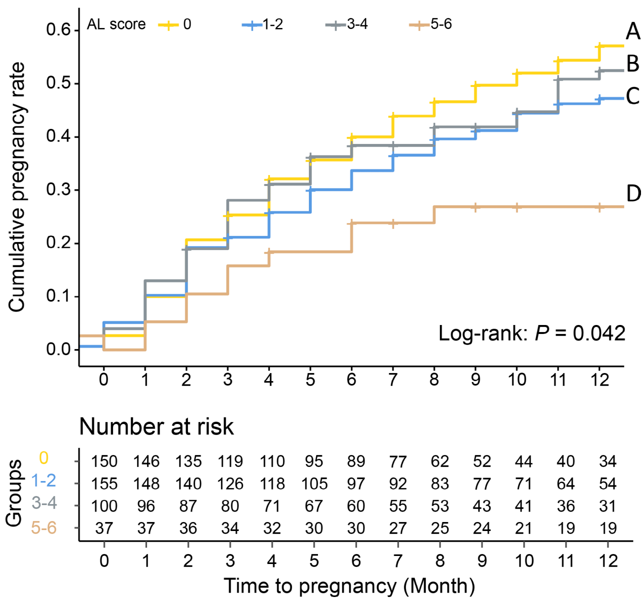

FIGURE 3 Kaplan–Meier plots for cumulative pregnancy rate among different allostatic load statuses.

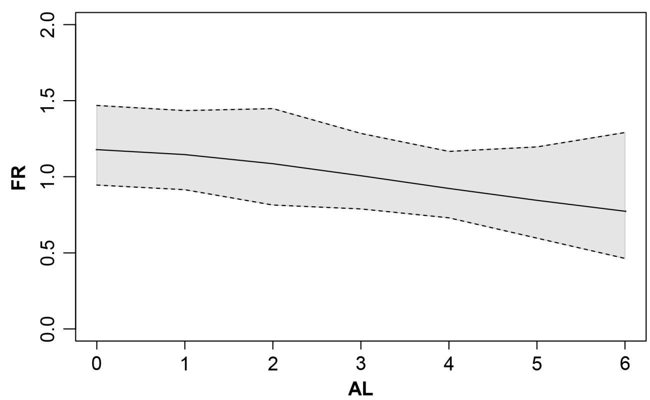

FIGURE 4 Cubic spline for allostatic load (AL) score and fecundability. The model was adjusted for female age, the difference between couples, educational level, occupation, pregnancy history, the number of children in the family, menstrual regularity, and drinking habits.

TABLE 3 Fecundability ratios for different AL statuses

AL groups	Crude FR (95% CI)	Model 1 FR (95% CI)	Model 2 FR (95% CI)	Model 3 FR (95% CI)	Model 4 FR (95% CI)
A: 0	Ref	Ref	Ref	Ref	Ref
B: 1–2	0.82 [0.59, 1.12]	0.90 [0.65, 1.24]	0.87 [0.62, 1.21]	0.88 [0.63, 1.21]	0.85 [0.61, 1.18]
C: 3–4	0.89 [0.62, 1.27]	0.91 [0.64, 1.31]	0.93 [0.65, 1.34]	0.91 [0.64, 1.30]	0.93 [0.65, 1.34]
D: 5–6	**0.40 [0.21, 0.78]**	**0.47 [0.24, 0.92]**	**0.41 [0.20, 0.82]**	**0.48 [0.25, 0.93]**	**0.41 [0.21, 0.83]**

Note: Models 1 and 3 were adjusted for female age and differences between couples. Models 2 and 4 were adjusted for female age, differences between couples, educational level, occupation, pregnancy history, the number of children in the family, menstrual regularity and drinking habits. Models 1 and 2 were based on time to pregnancy in months. Models 3 and 4 were based on time to pregnancy in cycles.

AL scores were only evaluated once; this does not reflect the dynamic change in the process of attempting pregnancy.

The crucial limitation of our study was the potential unmeasured confounding effect. Many potential factors associated with female fecundability were not collected, such as the pelvic pathology status of the female partner, the semen quality of the male partner and a couple's sexual frequency. Additionally, details about sleep, diet and socioeconomic status would potentially impact the AL score, but we did not collect them. To assess the possible effect, we estimated the *E*-value for the highest AL group. The result indicated that if the unmeasured confounder was associated with both the AL and female fecundability by an odds ratio of more than 4.31, our observed odds ratio of 0.41 could be explained away.[22] We believe this is a small probability event, because we had adjusted many covariates in current model. This is only a compensating estimation method—further research should address this limitation from the original study design. Finally, our findings should be interpreted with caution because all participants were Chinese women from one city. In addition, according to project's aim, only legally married couples could participate the project and thus selection bias was inevitable. The universality of the findings should be further confirmed.

5 | CONCLUSION

Women with a higher AL score may have lower fecundability. The assessment of AL during pre-conception consultation seems to be necessary and important.

AUTHOR CONTRIBUTIONS

HX and WB conceived and designed the research. HX and YJ analyzed data. HX drafted the manuscript. ZF and WW edited and revised the manuscript. DX and YH carried out the data collection work. All the author approved the final version of manuscript.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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