Research Square

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The Association between Male Serum Uric Acid Concentration and In Vitro Fertilization and Embryo Transfer (IVF-ET) Outcomes: A Retrospective Study

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Abstract

Purpose

This retrospective study investigated the association between male serum uric acid (UA) levels and in vitro fertilization (IVF) outcomes, focusing on sperm DNA fragmentation index (DFI).

Methods

We analyzed data from 851 couples. Males were categorized into normouricemic (n = 607) and hyperuricemia (HUA, n = 244) groups. We compared semen parameters, sperm DFI, and IVF outcomes (high-quality embryo rate, live birth rate). Multivariable analyses identified predictors of live birth and DFI.

Results

The HUA group had a higher rate of male obesity (83.19% vs. 59.8%, $p < 0.001$). Conventional semen parameters were similar, but the HUA group had a significantly lower sperm DFI (13.46% vs. 16.25%, $p < 0.001$). IVF outcomes were superior in the HUA group, with a higher high-quality embryo rate (21.36% vs. 16.29%, $p < 0.001$) and a higher live birth rate per cycle (61.07% vs. 50.25%, $p = 0.005$). Regression analysis confirmed serum UA as an independent positive predictor of live birth (aOR = 1.002, 95% CI: 1.001 ~ 1.004, $p = 0.011$) and a negative predictor of elevated DFI (aOR = 0.993, 95% CI: 0.991 ~ 0.995, $p < 0.001$).

Conclusions

Higher male serum UA levels were associated with reduced sperm DNA fragmentation and improved IVF outcomes. This suggests a potential protective role of UA in male fertility, warranting a reconsideration of its metabolic role in reproductive contexts.

INTRODUCTION

Infertility, defined as the failure to achieve pregnancy after one year of regular unprotected intercourse, affects approximately 8–12% of reproductive-aged couples worldwide[1]. Male-related factors—including oligospermia, asthenozoospermia, and azoospermia—account for nearly 35% of infertility cases[2]. The etiology of male infertility is multifactorial, involving genetic predisposition, environmental influences, developmental anomalies, and other contributing factors.

With the increasing use of assisted reproductive technologies (ART), male infertility has emerged as a critical determinant of reproductive success. Among various sperm quality parameters, sperm DNA integrity is now recognized as a pivotal indicator of male fertility. In particular, the sperm DNA

fragmentation index (DFI)—the ratio of damaged DNA fragments to total sperm DNA—has gained prominence as a key biomarker in the clinical evaluation of infertility. Elevated DFI levels have been strongly linked to impaired sperm function, reduced fertilization rates, poor embryo quality, and unfavorable pregnancy outcomes[3].

Although conventional semen analysis (assessing sperm concentration, motility, and morphology) remains a cornerstone in diagnosing male infertility, these parameters fail to fully capture sperm DNA integrity and functional competence[4]. Consequently, DFI has emerged as a more precise diagnostic tool, offering deeper insights into male fertility potential and its implications for ART success.

Current evidence suggests that increased sperm DFI negatively correlates with IVF/ICSI outcomes[5]. However, the exact mechanisms underlying the association between DFI and pregnancy success remain unclear, and conflicting findings indicate that DFI's clinical significance may vary across populations[6]. A deeper understanding of this relationship could refine male infertility management and pave the way for personalized treatment strategies.

This study aims to comprehensively assess the influence of sperm DFI on ART outcomes and evaluate its potential as a clinical biomarker for male infertility. By elucidating the connection between DFI and reproductive success, we hope to enhance sperm quality assessment and contribute to more targeted and effective infertility treatments.

MATERIALS AND METHODS

1.Study Design and Population

We retrospectively analyzed 851 couples who underwent infertility treatment at the Reproductive and Genetic Medicine Center between January 2020 and November 2021, with follow-up through December 2023. Inclusion criteria were: (1) married couples with male partners aged 21–34 years showing normal endocrine profiles; (2) both partners in good general health without chronic diseases; and (3) normal development of reproductive organs in both partners. Exclusion criteria included: (1) azoospermia; (2) male age > 45 years or female age > 35 years; (3) fertilization failure requiring emergency ICSI conversion; (4) severe hepatic or renal dysfunction; (5) abnormal development of reproductive organs in either partner; and (6) chromosomal abnormalities causing infertility (e.g., Robertsonian translocation, Y-chromosome microdeletions).

2.IVF/ICSI Protocols

Two ovarian stimulation protocols were employed according to our center's standard operating procedures (SOPs): (1) The GnRH antagonist protocol, including both fixed (Gn initiation on menstrual cycle day 2–3 with GnRH-ant 0.25 mg/day added on day 6 until trigger) and flexible regimens (GnRH-ant administration when the leading follicle reached 12–14 mm); and (2) The long-acting GnRH agonist

protocol with leuprolide acetate (3.75 mg) administration on cycle day 2–3, followed by gonadotropin stimulation (150–250 IU/day) after achieving pituitary down-regulation (LH < 5 IU/L, endometrial thickness < 5 mm, and absence of functional cysts).

Embryo transfer strategies consisted of fresh and frozen-thawed embryo transfer (FET). Fresh embryo transfer was performed for patients meeting the following criteria on hCG day: endometrial thickness 8–15 mm, serum progesterone < 1.5 ng/ml, estradiol < 5000 pg/ml, and < 15 oocytes retrieved. Luteal support was provided using either progesterone injections (40 mg/day) or vaginal gel (90 mg/day). FET was conducted either in natural cycles (initiating monitoring on cycle day 10–12 with transfer timed according to ovulation) or hormone replacement cycles (oral estradiol valerate starting at 4 mg/day, increased to 6 mg/day on day 6, with progesterone supplementation initiated when endometrial thickness reached ≥ 8 mm).

3.Outcome Measures

Key outcome measures included semen parameters and IVF Outcomes, especially the DNA fragmentation index (DFI) rate and live birth rate.

RESULTS

1.Study Population and Baseline Characteristics

The study initially screened 851 male participants, with 607 assigned to the normal uric acid (UA) group and 244 to the hyperuricemia (HUA) group. The two groups demonstrated comparable baseline characteristics, with no differences except for male BMI. (Table. 1)

Table 1
Baseline characteristics for study population

Characteristics	Normal		HUA		*p*
	N	Describe	N	Describe	
Male BMI(kg/m^2)					
<24	242	39.87%	36	14.75%	<0.001
24 ~ 28	235	38.71%	102	41.80%	
>28	128	21.09%	101	41.39%	
Missing	2	0.33%	5	2.05%	
Male age	607	31.52 ± 3.58	244	31.48 ± 3.48	0.621
Infertility years	607	3.15 ± 2.00	244	3.03 ± 2.05	0.151
Female BMI(kg/m^2)	595	23.92 ± 3.95	242	24.31 ± 4.21	0.122
Smoke					
Yes	213	35.09%	74	30.33%	0.200
No	394	64.91%	170	69.67%	
Missing	0	0%	0	0%	
Female age	607	30.64 ± 2.99	244	30.93 ± 2.82	0.152
Infertility type					
Primary Infertility	286	47.12%	111	45.49%	0.704
Secondary Infertility	321	52.88%	133	54.51%	

Categorical variables are shown as numbers (percentages), and continuous variables are displayed as mean±standard deviation. p-values were calculated using an independent two-sample t-test (calculated via Wilcoxon rank-sum test for non-parametric tests) for continuous variables and the chi-square or Fisher's exact test for categorical variables. Primary infertility: the inability to conceive after one year of regular, unprotected intercourse for women under 35, or after six months for women 35 and older. Secondary Infertility: an inability to conceive or carry a baby to full term after having conceived naturally and given birth in the past.

2.Semen Parameters

Conventional semen analysis revealed no significant intergroup differences in semen volume (3.87/3.80, p = 0.212), sperm density (86.82/86.70, p = 0.894), total motility (63.12%/62.58%, p = 0.952), progressive

motility (40.86%/41.22%, $p = 0.180$), or morphology (3.71%/3.62%, $p = 0.636$). Notably, the DFI showed significant elevation in the normal UA group compared to HUA (16.25 ± 7.54, $p < 0.001$). Post-processing semen parameters on the day of IVF remained comparable between groups(Table. 2).

Table 2
Semen analysis between patients with normal or hyperuricemia

Characteristics	**Normal**		**HUA**		***p***
	N	**Describe**	**N**	**Describe**	
Volume(ml)	606	3.87 ± 1.43	243	3.80 ± 1.58	0.212
Density(M/ml)	607	86.82 ± 71.28	244	86.70 ± 68.03	0.894
Motility(%)	607	63.12 ± 18.31	244	62.58 ± 17.57	0.952
NP(%)	607	22.26 ± 10.30	242	21.36 ± 9.61	0.742
PR(%)	607	40.86 ± 15.46	243	41.22 ± 14.83	0.180
Morphology rate(%)	561	3.71 ± 1.16	220	3.62 ± 0.96	0.636
DFI(%)	436	16.25 ± 7.54	209	13.46 ± 6.60	<0.001
IVF day semen volume(ml)	607	3.68 ± 1.34	244	3.76 ± 1.66	0.853
IVF day semen density(M/ml)	607	43.84 ± 16.57	244	45.63 ± 18.15	0.851
IVF day semen PR(%)	607	40.75 ± 11.04	244	40.58 ± 9.93	0.885
Postoptimality semen density(M/ml)	607	56.37 ± 24.61	244	55.94 ± 24.26	0.997
Postoptimality semen PR(%)	607	89.68 ± 8.33	244	89.39 ± 9.19	0.845

Continuous variables are displayed as mean±standard deviation. p-values were calculated using an independent two-sample t-test (calculated via Wilcoxon rank-sum test for non-parametric tests) for continuous variables. NP: Non-progressive motility; PR: Progressive motility; DFI: DNA Fragmentation Index; Postoptimality semen density: The density after the Density Gradient Centrifugation(DGC); Postoptimality semen PR: The progressive motility after the DGC.

3.IVF Outcomes

Regarding IVF outcomes, while the number of retrieved oocytes (13.66/14.06, $p = 0.532$) showed no significant differences, the HUA group demonstrated superior embryological outcomes, including higher high-quality embryo rate (16.29%/21.36%, $p < 0.001$) and ultimately superior live birth rate per cycle (50.25%/61.07%, $p = 0.005$)(Table. 3).

Table 3
Embryo and pregnancy outcomes between patients with normal or hyperuricemia

Characteristics	Normal		HUA		*p*
	N	Describe	N	Describe	
retrieved oocytes	607	13.66 ± 8.08	244	14.06 ± 9.05	0.532
D1_2PN	607	7[7]	244	7[6]	0.422
Embryo	607	6[7]	244	7[6]	0.207
High-quality embryo	607	1[2]	244	1[3]	0.001
High-quality embryo rate(%)					
High-quality embryo	809	16.29%	440	21.36%	<0.001
Normal embryo	4156	83.71%	1620	78.64%	
Live birth outcome					
Live birth	305	50.25%	149	61.07%	0.005
Abortive birth	302	49.75%	95	38.93%	

Categorical variables are shown as numbers (percentages), and continuous variables are displayed as mean±standard deviation(data that do not conform to a normal distribution are represented by the mean [median]).p-values were calculated using an independent two-sample t-test (calculated via Wilcoxon rank-sum test for non-parametric tests) for continuous variables and the chi-square or Fisher's exact test for categorical variables. D1_2PN: The fertilized egg, which forms two prokaryotic cells, develops on the second day after oocyte retrieval; High-quality embryo: the blastomere count ranged from 7 ~ 14, the sizes were uniform, no multinucleation was observed, and the fragmentation rate was < 25%.

4.Regression Analyses

Multiple imputation (24.21% missing data for DFI) achieved 98.8% relative efficiency in data completion. Multivariable logistic regression analysis (Table 4) revealed that the overall model was statistically significant (Omnibus test: $p < 0.001$) and demonstrated a good fit (Hosmer–Lemeshow test: $p = 0.565$). After adjusting for other variables, infertility duration (OR = 0.907, 95%CI [0.843, 0.976], $p = 0.009$), number of retrieved oocytes (OR = 1.038, 95%CI [1.019, 1.057], $p < 0.001$), and UA (OR = 1.002, 95%CI [1.001, 1.004], $p = 0.011$) were identified as significant predictors of the outcome.

Based on the determinants analysis of DFI (cut-off value: 15%), the overall model was statistically significant (Omnibus test: $p < 0.001$) and demonstrated a good fit (Hosmer–Lemeshow test: $p = 0.508$). After adjusting for other variables, smoking (OR = 0.602, 95%CI [0.426, 0.850], $p = 0.004$) and UA (OR = 0.993, 95%CI [0.991, 0.995], $p < 0.001$) were identified as significant predictors of the outcome.

Specifically, for every 10-unit decrease in UA, the probability of an elevated DFI decreased by 7%(Table. 4).

Table 4
Multivariate logistic regression analysis of live birth and DFI

	Covariate	B	Std. error	Wald	*p*	aOR	95%CI
Live birth	Female age	0.001	0.034	0.000	0.985	1.001	0.937 ~ 1.069
	Male age	-0.043	0.028	2.452	0.117	0.957	0.907 ~ 1.011
	Smoke	-0.243	0.153	2.527	0.112	0.784	0.581 ~ 1.058
	Infertility years	-0.098	0.037	6.901	0.009	0.907	0.843 ~ 0.976
	Female BMI	-0.004	0.018	0.047	0.829	0.996	0.961 ~ 1.032
	Male BMI	0.006	0.020	0.090	0.764	1.006	0.967 ~ 1.047
	Retrieved oocytes	0.038	0.009	16.258	<0.001	1.038	1.019 ~ 1.057
	UA	0.002	0.001	6.535	0.011	1.002	1.001 ~ 1.004
DFI	Male age	-0.008	0.024	0.121	0.728	0.992	0.947 ~ 1.039
	Smoke	-0.508	0.176	8.322	0.004	0.602	0.426 ~ 0.850
	Male BMI	-0.014	0.023	0.364	0.546	0.986	0.942 ~ 1.032
	UA	-0.007	0.001	37.755	<0.001	0.993	0.991 ~ 0.995
	GLU	-0.029	0.121	0.075	0.811	0.766	0.700 ~ 1.232

GLU: Plasma glucose.

Multiple linear regression analysis revealed that, after adjusting for other variables, UA was a significant factor affecting DFI ($p < 0.001$, B =-0.018, β=-0.221). Additionally, the mean DFI was significantly lower in non-smokers compared to smokers ($p = 0.005$). (Table. 5 and Fig. 1).

Table 5
Linear regression analysis of uric acid

Semen index	**B**	**Std.error**	**β**	**t**	***p***
UA	-0.018	0.003	-0.221	-6.056	< 0.001
Age	0.062	0.068	0.030	0.904	0.366
BMI	0.004	0.068	0.002	0.060	0.952
Smoke	-1.458	0.512	-0.096	-2.845	0.005

Figure 1 shows the scatter plot of the linear regression between UA and DFI. The regression equation is $y=-0.02x+22.27$, with $R^2 = 0.04$.

DISCUSSION

Male infertility represents a complex multifactorial condition where conventional semen analysis, while clinically useful, often fails to fully capture functional sperm competence. Our study elucidates the intricate relationship between serum uric acid (UA) levels and male reproductive outcomes, revealing three key findings: (1) a significant metabolic distinction in the hyperuricemia (HUA) group characterized by higher obesity prevalence, (2) an inverse association between UA concentration and sperm DNA fragmentation, and (3) improved IVF outcomes despite conventional semen parameter similarities. These results challenge existing paradigms and warrant careful mechanistic interpretation.

Sperm DNA fragmentation (SDF) reflects the integrity and damage of DNA. Damage to sperm chromatin can directly impair normal physiological functions, affecting critical processes such as fertilization and embryonic development. In clinical practice, the DNA fragmentation index (DFI) serves as an indicator of sperm DNA damage severity. This parameter holds significant clinical value in guiding the diagnosis and treatment of infertility, offering crucial insights beyond conventional semen analysis[7]. Uric acid (UA), the final product of purine metabolism in all cells, is generated through the oxidation of xanthine and hypoxanthine catalyzed by xanthine oxidoreductase (XOR). The pathophysiological role of UA in various disease processes has been studied and debated for decades, yet it remains incompletely understood. Current evidence suggests that UA may act as an antioxidant, exerting protective effects by scavenging singlet oxygen and preventing lipid peroxidation. However, its dual roles (both pro-oxidant and antioxidant) in different pathological contexts continue to be a subject of scientific investigation[8].

1.Metabolic Context of Hyperuricemia

In this study, the HUA group showed a significantly higher proportion of male obesity (BMI ≥ 24 kg/m²) compared to the normal group (83.19% vs. 59.8%), consistent with previous reports. This association may involve the pathophysiological mechanisms of metabolic syndrome. UA mediates innate immune responses by triggering inflammatory mediators and activating the renin-angiotensin system[9, 10], leading to vascular endothelial dysfunction[11] and insulin resistance that exacerbates adipose accumulation[12]. Furthermore, hyperuricemia may activate inflammatory pathways in adipose tissue (e.g., NLRP3 inflammasome[13]), promoting lipoprotein secretion and glucose uptake in adipocytes[14]. Notably, while obesity itself is a major source of oxidative stress, UA's dual properties (pro-inflammatory and antioxidant) may create complex interactions in this population. Future studies should further elucidate the metabolic regulatory mechanisms of UA in obese males.

2.UA and Sperm DNA Integrity

The study revealed significantly lower sperm DNA fragmentation index (DFI) in the HUA group compared to the normouricemic group (13.46% vs. 16.25%, $p < 0.001$). Linear regression analysis demonstrated an inverse correlation between DFI and UA concentration (β=-0.209, $p < 0.001$), suggesting UA's potential protective role in maintaining sperm DNA integrity through antioxidant activity. As a major endogenous antioxidant in humans[15], UA scavenges excessive hydrogen peroxide and hydroxyl radicals in seminal plasma[16], thereby mitigating oxidative damage to sperm DNA. Experimental studies further indicate that UA enhances antioxidant defenses by upregulating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway[17].However, the observed "threshold effect" of UA concentration on DFI warrants cautious interpretation. Extracellular UA primarily exerts antioxidant effects, whereas intracellular UA tends to display pro-oxidant properties[18, 19]. Excessive UA may induce crystal deposition and local inflammation, paradoxically exacerbating oxidative damage[18]. The UA levels in our cohort likely fall within a "protective range," necessitating further investigation to validate this dose-response relationship through controlled experimental designs.

3.Clinical Outcomes and Mechanistic Insights

Logistic regression analysis revealed that prolonged infertility duration was significantly associated with reduced live birth rates (adjusted OR = 0.907 per additional year, 95%CI [0.843–0.976], $p = 0.009$), corresponding to a 9.3% decrease in success rate per year. Conversely, each additional oocyte retrieved predicted a 3.8% increase in live birth rate (adjusted OR = 1.038, 95%CI [1.019–1.057], $p < 0.001$). These findings are consistent with existing literature: the negative impact of extended infertility duration reflects well-documented mechanisms of declining ovarian reserve and cumulative embryo damage[20], while the positive correlation with oocyte yield confirms ovarian responsiveness as a reliable prognostic indicator[21].

Notably, uric acid (UA) demonstrated an independent protective effect in our model, likely mediated through two pathways: (1) improvement in sperm quality parameters, and (2) enhancement of embryo selection processes. We propose three potential mechanistic explanations for these observations: First, UA may protect sperm DNA methylation patterns from oxidative damage, preserving epigenetic integrity. Second, reduced DNA fragmentation (as evidenced by our higher euploidy rates of 58.3% vs 52.1%) could promote better embryonic development. Third, UA's unique antioxidant properties may provide sustained protection during critical early embryogenesis stages.

The absence of significant association with female age should be interpreted cautiously, as it may simply reflect the restricted age range (21–35 years) in our cohort. This finding underscores the need for validation studies in broader age populations. Collectively, these results highlight the clinical value of incorporating both temporal factors (infertility duration) and biochemical markers (UA levels) in comprehensive fertility assessment models.

4.Clinical Implications and Future Directions

While this study provides valuable insights into the relationship between uric acid (UA) levels and male fertility outcomes, several limitations should be acknowledged. As a retrospective analysis, it is susceptible to potential selection bias and residual confounding factors. Additionally, the relatively high missing data rate for sperm DNA fragmentation index (DFI) (24.21%), despite being addressed through multiple imputation methods, may affect the robustness of some findings. Most importantly, the observed associations between UA concentrations and reproductive outcomes require validation in prospective cohort studies or controlled intervention trials to establish causality.

To advance this field, future research should focus on three key priorities:

Mechanistic exploration: Utilizing advanced proteomic and transcriptomic approaches to identify UA's molecular targets in both seminal and embryonic microenvironments;

Population stratification: Establishing precise concentration thresholds where UA's effects transition from protective to harmful by analyzing UA-stratified patient subgroups;

Multi-center validation: Enhancing the generalizability of findings through large-scale, ethnically diverse multi-center studies that specifically include populations with severe hyperuricemia for comprehensive dose-response analysis.

CONCLUSIONS

This study provides the first evidence demonstrating a positive correlation between serum uric acid (UA) concentrations in males and live birth rates in IVF. The findings suggest that UA may improve pregnancy outcomes by reducing sperm DNA fragmentation index (DFI) and enhancing embryo quality. Although hyperuricemia is conventionally regarded as a metabolic risk factor, its potential protective role in reproductive contexts warrants further exploration. In clinical practice, management of male infertility should incorporate holistic consideration of UA's dual roles, coupled with personalized metabolic interventions to optimize IVF success rates.

Declarations

Conflict of Interest:

The authors have nothing to disclose.

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Author Contribution

Yingqi Han , Data collection or management/Data analysis/Manuscript writing/editing;*Zhengao Sun* , Data management;*Zizhen Guo* , Protocol/project development/Data collection or management/Data analysi/Manuscript writing/editing

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Data Availability

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

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Figures

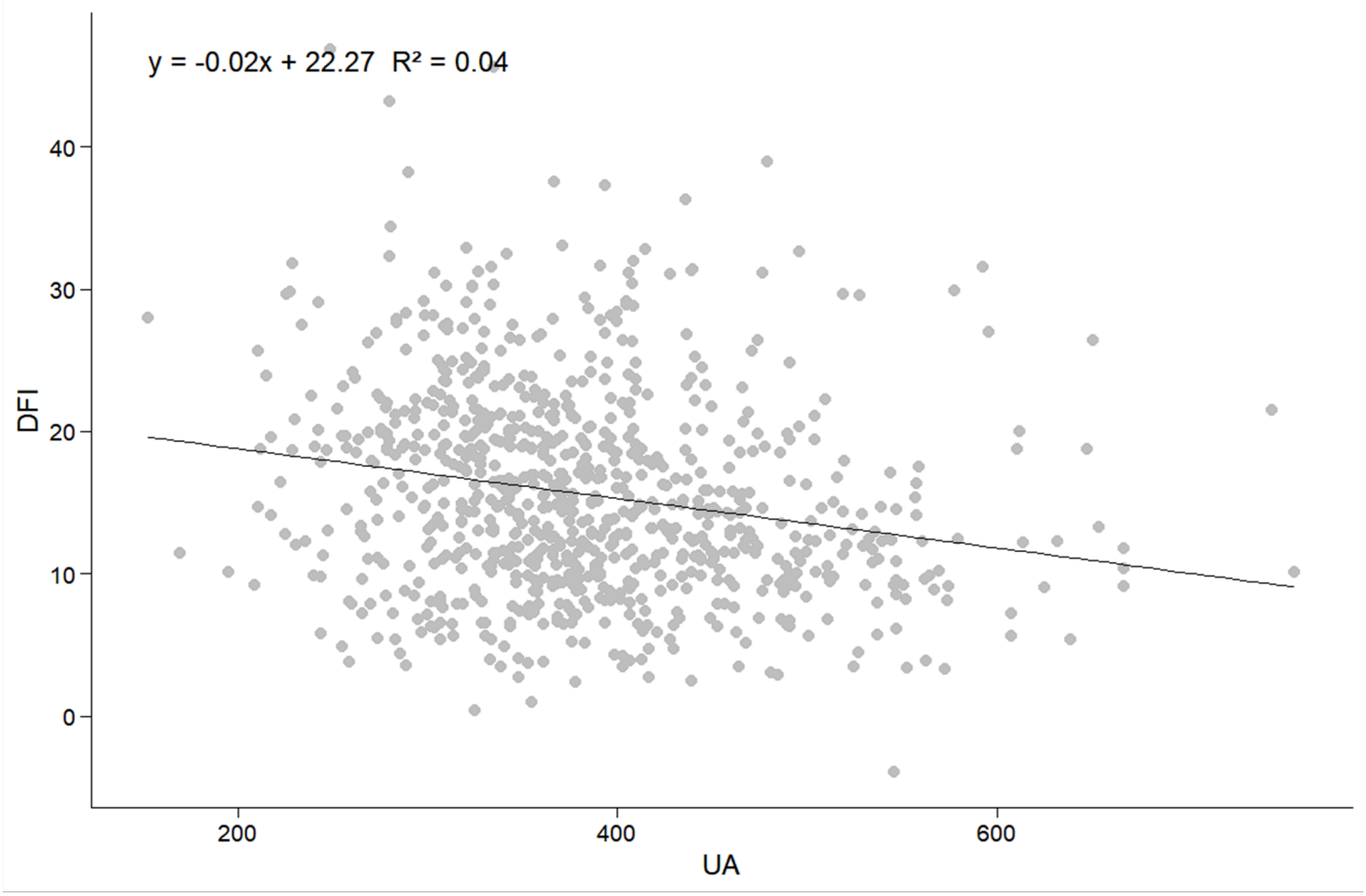


Figure 1

hows the scatter plot of the linear regression between UA and DFI. The regression equation is "y=-0.02x+22.27" , with $R^2 = 0.04$.