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RESEARCH

Interdependence Prospectively Predicts the Blood Uric Acid Level in Japan: Implications for the Metabolic Basis for Culture

Jiyoung Park[1,2] · **Shinobu Kitayama**[3]

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Abstract

Purpose Uric acid (UA), the end product of purine metabolism, serves as a potent deoxidant of the brain. UA may therefore be related to psychological activities that are culturally endorsed and normatively promoted, insofar as such activities would require high levels of cortical processing, and thus, gradually expose the brain to a greater oxidation risk. We tested this analysis in Japan, a society that values interdependence of the self with others.

Methods Middle-aged Japanese adults ($N=243$) were tested twice for the serum UA concentration, with five years in-between. Moreover, an assortment of measures assessing culturally sanctioned traits (those related to interdependence) and culturally non-sanctioned traits (those related to independence) were collected.

Results We found that the baseline levels of interdependence predicted an increase in the UA in the next five years. In contrast, there was no such effect for independence. Moreover, the effect of interdependence on the UA increase was mediated by cognitive effort in various domains (such as work, finance, and social relations), suggesting that the culturally sanctioned traits increased cognitive effort devoted to mundane everyday activities, which in turn, predicted the UA to increase over time. Notably, baseline UA levels did not affect changes in psychological traits.

Conclusion Interpreting these results in light of UA's role as a potent antioxidant for brain tissues, we propose that higher UA levels may support metabolically demanding actions aligned with culturally sanctioned practices, particularly those associated with interdependence in the Japanese context.

Keywords Uric acid · Social interdependence · Culture · Cultural evolution

Extended author information available on the last page of the article

Introduction

The brain is a mass of unsaturated fat (Bazinet & Layé, 2014). It therefore is under the constant threat of oxidation. This threat will be especially dire when the brain must function at higher levels of intensity (Wang et al., 2019). When cognitive demands increase, more oxygen is supplied to the brain (Mintun et al., 2001) and the resulting oxidation risk (Watts et al., 2018) would lead to an urgent need to deoxidize the brain (Giorgi et al., 2015). Here, we explored the possibility that the end product of purine metabolism, uric acid (UA), serves this vital function (Glantzounis et al., 2005). Specifically, we tested whether culturally sanctioned activities would longitudinally predict an increase of the UA concentration in the blood, insofar as such activities require high levels of cortical processing, and thus, gradually expose the brain to a greater oxidation risk.

Uric Acid: Functions, Correlates, and Regulation

UA is closely tied to purine, a nitrogen-containing heterocycle compound abundantly available in many foods, including those of animal origin (E. P. de Oliveira & Burini, 2012). Purine is chemically broken down to UA, which in turn can be further decomposed into allantoin. This latter step (from purine to allantoin) is caused by the enzyme uricase. Unlike UA, allantoin is highly soluble, and as a consequence, it can be excreted with urine. Interestingly, through human-line of evolution, the gene producing this enzyme has been shut down. The result was a dramatic increase of the serum UA level in the course of human evolution (Alvarez-Lario & Macarron-Vicente, 2010; Watanabe et al., 2002). Thus, in humans, once metabolized, UA tends to stay in the bloodstream (Maiuolo et al., 2016).

UA is best known as a risk factor for various health problems, including metabolic syndrome, hypertension, gout, and kidney disease (see Kuwabara et al., 2023 for review). Hence, the reason for the evolutionary change that resulted in the significant increase in the serum UA level through human evolution has been a topic of some debate, as this change must have been promoted despite the negative health effects it produces. One prominent hypothesis is motivated by the function of UA as a potent deoxidant (E. P. de Oliveira & Burini, 2012). UA is responsible for more than 50% of the antioxidant capacity in the blood (Ames et al., 1981). This analysis could apply to the brain in particular, which consumes nearly 20% of the oxygen supply to the entire system (Clarke & Sokoloff, 1999). Hence, for the brain to function at high levels, deoxidation will prove to be essential. It would therefore follow that increasing levels of cortical functioning are supported in part by the increase of UA in the circulating blood (Alvarez-Lario & Macarron-Vicente, 2010; Wang et al., 2019). Hence, the UA concentration in the blood may increase when cortical activity is intensely engaged. Altogether, it is sensible to hypothesize that through the human-line of evolution, the increase of UA concentration in the bloodstream (via the shutting down of the uricase gene) has co-evolved with an increasing demand for effective brain functioning.

Building on this analysis, we investigated whether behaviors that are culturally sanctioned and thus normatively promoted may be engaged with higher levels of motivation (Iyengar & Lepper, 1999; Na & Kitayama, 2012), resulting in an upward regulation of the UA concentration in the bloodstream.

Culture and Uric Acid

Over the last three decades, the evidence is growing that cultural norms and values vary widely across cultures (Markus & Kitayama, 1991). Particularly, the norms and values dominant in Western European countries and their diasporas, including the United States, Canada, and Australia, are based on a view of the self as independent. Although societies outside of this Western cluster of cultures are quite diverse, they share in common a more traditional view of the self as interdependent, as communal and loyal to ingroups, and thus, as embedded in and seen as an inherent part of existing social relations, such as tribes, families, workplaces, and the like. Recent evidence extends earlier work showing East Asians to be interdependent (Markus & Kitayama, 1991) to Arab regions (San Martin et al., 2018), Latin America (de Oliveira & Nisbett, 2017; Ruby et al., 2012), and minority Americans including Black Americans and Native Americans (Stephens et al., 2014).

Consistent with the hypothesis that culturally endorsed traits are linked to the UA concentration in the blood, earlier studies showed that achievement orientation, the trait which is likely to be positively endorsed regardless of culture, is a reliable correlate of the UA concentration (Brooks, 1966; Dunn, 1963; Mueller & French, 1970). Curiously, more recent studies have also identified various externalizing behaviors and traits, such as impulsivity (Sutin et al., 2014), disinhibition (Lorenzi et al., 2010), aggression (Mrug & Mrug, 2016), and extraversion (Armon, 2016), as possible correlates of UA concentration. Notably, Sutin and colleagues (2014) extended this cross-sectional evidence by showing that impulsivity at baseline predicts an increase of the serum UA level 3–5 years later among large samples of both Italians and Americans.

According to a classic scheme of value classification (Maio, 2010; Schwartz, 1992), impulsivity and other socially disengaged traits (Kitayama et al., 2006), such as anger and aggression, could be an exaggerated form of behaviors that are linked to independence (Kitayama et al., 2009), which is more motivating for Westerners (Iyengar & Lepper, 1999; Na & Kitayama, 2012). Therefore, the Sutin et al. evidence as well as other evidence linking socially disengaged traits to UA concentration is consistent with the hypothesis that a greater engagement in culturally sanctioned activities (here in this case, independence) should increase the UA concentration over time. In Western cultures, socially disengaged activities, such as those involved in the pursuit of personal desires and goals, are culturally congruous and thus they may automatically recruit various psychological resources, which may in turn engage the cortical processing more and thereby increase the need for oxygen supply to the brain.

This interpretation implies that the aforementioned evidence linking socially disengaged traits to UA concentration might not generalize to East Asian societies. In these latter societies, various traits related to interdependence may receive cultural endorsement and encouragement. These traits will then motivate culturally sanctioned behaviors (Iyengar & Lepper, 1999; Na & Kitayama, 2011), which will be pursued with greater vigor, thereby recruiting more thought and effort. Consistent with this analysis, recent research in Japan shows that avoidant personality traits, one type of socially disengaged traits (which are inversely related to interdependence), were associated with decreased levels of serum UA concentration (Hayakawa et al., 2018). Although this evidence is consistent with our prediction, the study is limited as it is cross-sectional, and moreover, it did not test positive trait markers of interdependence. Our goal was thus to extend this initial evidence by testing whether various kinds of interdependence-related traits prospectively predict an increase of the UA concentration in the blood among Japanese.

Present Study

We tested the foregoing hypothesis in two steps by using archival data from a longitudinal population-level survey conducted in Japan (Midlife in Japan, MIDJA), with two assessments that were separated by 5 years. In Analysis 1, we examined whether UA levels were related to interdependence- rather than independence-related psychological traits among Japanese adults. Notably, utilizing a longitudinal design with relevant variables measured twice, we tested cross-lag effects between UA levels and independence- and interdependence-related psychological traits. We expected that, among Japanese individuals, interdependence-related traits would prospectively predict UA levels over a 5-year period but not vice versa. In Analysis 2, we focused on one factor, cognitive effort, as a potential mediator of the longitudinal effect of interdependence on the increase in UA levels over time.

Analysis 1: Interdependence and Uric Acid Increase

In the first set of analyses, we sought to extend the Hayakawa et al. (2018) evidence in another sample of Japanese adults, recruited for the MIDJA, which involved two waves of data collection with a 5-year interval. We first tested our hypothesis that interdependence (but not independence)-related traits would predict an increase in the UA level over 5 years. To test the directionality of these associations, we further tested the reversed effects of the UA concentration on the change of interdependence-related traits over time.

Method

Participants

We used the first and second waves of the MIDJA longitudinal study. The first wave (MIDJA 1) was conducted in 2008, testing 1,027 Japanese adults randomly sampled from the Tokyo metropolitan area (522 females, M_{age} = 54.36, SD_{age} = 14.15). The second wave, MIDJA 2, was conducted five years later, testing 64.0% of the original sample (N=657; 348 females, M_{age} = 54.92, SD_{age} = 13.58). At both waves, a subsample of participants provided blood samples for biomarkers that were subsequently assayed at a medical clinic in Tokyo (MIDJA 1: N=382; 214 females, M_{age} = 55.47,

SD_{age} = 14.04, MIDJA 2: N=328; 172 females, M_{age} = 60.43, SD_{age} = 13.14). We used data from the participants who provided blood samples at both waves (N=243; 138 females, $M_{\text{age at Time 1}}$ = 56.12, $SD_{\text{age at Time 1}}$ = 13.48). All data are available at https://www.icpsr.umich.edu/web/ICPSR/studies/34969. A sensitivity power analysis we conducted using G*Power (Faul et al., 2009) showed that the current sample size provides 80% power to detect a small size effect in linear regression models (f^2=0.03; α=0.05, two-tailed).

Measures

Uric Acid Whole blood samples (sodium fluoride-anticoagulated), collected during the clinic visits at both waves, were shipped to the Showa Lab in Tokyo, Japan, within 24 h. The enzyme uricase converts UA to allantoin and hydrogen peroxide. The hydrogen peroxide product was then reacted with a chromogen by the enzyme peroxidase (POD), the process of which can be monitored photometrically. UA was estimated based on the depth of color of an oxidized chromogen (assay range: 0.05-80 mg/dL).

Psychological Traits

Interdependence-Related Psychological Dispositions.

Among the variables available at both waves of the MIDJA survey, we initially identified the following eight variables as interdependence-related—(a) agreeableness, (b) generativity, (c) positive relations with others, (d) interdependent self-construal, (e) relational interdependence, (f) support giving, (g) social obligation, and (h) behavioral adjustment. Among these variables, interdependent self-construal is the most face-valid indicator of interdependence, and yet, given the semantic relatedness of the remaining scales to interdependent self-construal, we anticipated all the eight variables to cohere into a single dimensional factor.

(a) Agreeableness was assessed with the Midlife Development Inventory (Lachman & Weaver, 1997) based on a 4-point scale (1=*not at all*, 4=*a lot*). Participants rated the extent to which each of five self-descriptive adjectives (e.g., helpful; Time 1: α=0.89, Time 2: α=0.86) described them. (b) Loyola Generativity Scale (McAdams & de St. Aubin, 1992) was used to assess generativity based on six items (e.g., You feel that other people need you; 1=*not at all*, 4=*a lot*; Time 1: α=0.89, Time 2: α=0.89). (c) Positive relations with others (7 items; e.g., People would describe me as a giving person, willing to share my time with others; Time 1: α=0.79, Time 2: α=0.75) were assessed with the psychological wellbeing scale (Ryff, 1989), using a 7-point scale (1=*strongly disagree*, 7=*strongly agree*). (d) Interdependent self-construal was assessed with the 10-item interdependence subscale of the Singelis self-construal scale (Singelis, 1994) based on a 7-point scale (1=*strongly disagree*, 7=*strongly agree*; e.g., It is important for me to maintain harmony or smooth relationships within my group; Time 1: α=0.71, Time 2: α=0.72). (e) Relational interdependence was assessed with the 10-item relational interdependent self-construal scale (Cross et al., 2000) (e.g., I usually feel a strong sense of pride when someone close to me has an important accomplishment; Time 1: α=0.76, Time 2: α=0.74), using a

7-point scale (1 = *strongly disagree*, 7 = *strongly agree*). (f) For social support giving, participants indicated the amount of social support they provided to their family (2 items), spouse (6 items), and friends (4 items), using a 4-point scale (1 = *not at all*, 4 = *a lot*) (Schuster et al., 1990) (e.g., How much can your family/spouse/friends rely on you for help if they have a serious problem?; Time 1: $\alpha = 0.85$, Time 2: $\alpha = 0.85$). (g) For social obligation, participants rated the extent to which they agreed with each statement (1 = *strongly disagree*, 7 = *strongly agree*) to assess the degree of social obligation towards public community (3 items; e.g., I feel obligated to volunteer time or money to social causes I support), family/friends (4 items; e.g., I feel obligated to contact family members on a regular basis), and members in their work (3 items; e.g., I am the one to volunteer to do unwanted tasks at work). The scores from these items were averaged to create a single index of social obligation (Gardner et al., 2001; Time 1: $\alpha = 0.74$, Time 2: $\alpha = 0.74$). (h) Finally, behavioral adjustment was assessed with five items about individuals' preparedness to adjust their behaviors to challenges or conflicts (Kitayama et al., 2018; e.g., "Once something has happened, I try to adjust myself to it because it is difficult to change it myself"; Time 1: $\alpha = 0.61$, Time 2: $\alpha = 0.54$), based on a 7 point-scale (1 = *strongly disagree*, 7 = *strongly agree*).

An exploratory factor analysis (EFA) was conducted among the Time 1 variables to test whether these variables loaded on a single factor. A principal component analysis (PCA) identified a two-factor solution, with an eigenvalue greater than 1.5, following prior work (Archer et al., 2004; Chou & Wang, 2010). All variables except for behavioral adjustment loaded on the first factor, which accounted for 39.6% of the variance. Behavioral adjustment loaded on the second factor, accounting for additional 19.2% of the variance. Since behavioral adjustment did not cohere well with the other variables, we performed the PCA again after dropping this variable, which yielded a one-factor solution, accounting for 44.5% of the variance. A confirmative factor analysis (CFA) showed that this model (after excluding behavioral adjustment) provided a good fit, $X^2(6) = 6.50$ $p = .370$, Comparative Fit Index (CFI) = 1.00, Goodness-of-Fit Index (GFI) = 0.99, Root Mean Square Error of Approximation (RMSEA) = 0.02, 90% confidence interval (CI) of RMSEA = [0.00, 0.09]. We thus used factor scores from the PCA after dropping behavioral adjustment as a composite index of interdependence-related traits at Time 1 for our main analysis.

Using the same approach, we performed a PCA on the Time 2 variables after excluding behavioral adjustment. This yielded a one-factor solution, which accounted for 44.9% of the variance. A CFA showed that this model provided a good fit to the data, $X^2(6) = 9.98$, $p = .126$, CFI = 0.99, GFI = 0.99 RMSEA = 0.06, 90% CI of RMSEA = [0.00, 0.11]. As in Time 1, factor scores from the PCA were used as interdependence-related traits at Time 2.

Independence-Related Psychological Dispositions.

The following 10 variables were initially identified as independence-related at both waves: (a) agency personality trait, (b) extraversion, (c) independent self-construal, (d) self-esteem, (e) self-sufficiency, (f) sense of control, (g) autonomy, (h) environmental mastery, (i) personal growth, and (j) self-acceptance. Although independent self-construal is the most face-valid indicator of independence among these variables, given the semantic relatedness of the remaining scales to interdependent self-construal, we anticipated all the 10 variables to cohere into a one-dimensional factor.

(a) Agency personality trait and (b) extraversion were assessed with the MIDI personality scale (Lachman & Weaver, 1997). Participants rated the extent to which 10 self-descriptive adjectives (5 items for agency; e.g., self-confident; 5 items for extraversion; e.g., outgoing) described them using a 4-point scale (1 = *not at all*, 4 = *a lot*; Time 1: $\alpha = 0.76$, Time 2: $\alpha = 0.77$ for agency and Time 1: $\alpha = 0.83$, Time 2: $\alpha = 0.83$ for extraversion). (c) Independent self-construal was assessed with the 7-item independence subscale of the Singelis scale (1994; e.g., I am comfortable with being singled out for praise or rewards; Time 1: $\alpha = 0.58$, Time 2: $\alpha = 0.61$), using a 7-point scale (1 = *strongly disagree*, 7 = *strongly agree*). (d) Rosenberg self-esteem scale (1965) was used to assess participants' self-esteem. Participants indicated their agreement with each of the seven statements (1 = *strongly disagree*, 7 = *strongly agree*; e.g., I take a positive attitude toward myself; Time 1: $\alpha = 0.73$, Time 2: $\alpha = 0.75$). (e) For self-sufficiency, participants rated their agreement (1 = *not at all*, 4 = *a lot*) with each of the two items (e.g., I don't like to ask others for help unless I have to; rs = 0.29 and 0.23 for Time 1 and Time 2 respectively, ps < 0.001). (f) Participants' sense of control was assessed with two subscales, one measuring personal mastery (4 items; e.g., What happens to me in the future mostly depends on me; Time 1: $\alpha = 0.73$, Time 2: $\alpha = 0.71$) and one measuring perceived constraints (8 items; e.g., There is little I can do to change the important things in my life; Time 1: $\alpha = 0.82$, Time 2: $\alpha = 0.84$) (Lachman & Weaver, 1998), using a 7-point scale (1 = *strongly disagree*, 7 = *strongly agree*). The ratings on the perceived constraint subscale were reverse-scored before being averaged with the ratings on the personal mastery subscale. Finally, the psychological wellbeing scale (Ryff, 1989) was used to assess (g) autonomy (7 items; e.g., I like most parts of my personality; Time 1: $\alpha = 0.70$, Time 2: $\alpha = 0.72$), (h) environmental mastery (7 items; e.g., In general, I feel I am in charge of the situation in which I live; Time 1: $\alpha = 0.73$, Time 2: $\alpha = 0.76$), (i) personal growth (7 items; e.g., For me, life has been a continuous process of learning, changing, and growth; Time 1: $\alpha = 0.71$, Time 2: $\alpha = 0.79$), and (j) self-acceptance (7 items; e.g., I judge myself by what I think is important, not by the values of what others think is important; Time 1: $\alpha = 0.83$, Time 2: $\alpha = 0.78$), based on a 7-point scale (1 = *strongly disagree*, 7 = *strongly agree*).

A PCA on the Time 1 variables identified a single factor (with an eigenvalue greater than 1.5), accounting for 46.0% of the variance. Using a cut-off score of 0.30 (Hair, 2014), we excluded one variable (i.e., self-sufficiency), which showed a low factor loading (-0.074). A CFA confirmed that the final model after variable exclusion provided a good fit to the data, $X^2(12) = 5.96$, $p = .918$, CFI = 1.00, GFI = 1.00, RMSEA = 0.00, 90% CI of RMSEA = [0.00, 0.02]. Factor scores from the PCA after dropping self-sufficiency, which accounted for 51.0% of the variance, were then used as a single index of independence-related traits at Time 1.

We conducted the same PCA on the Time 2 variables after excluding self-sufficiency. This analysis identified a single-factor solution, accounting for 52.3% of the variance. A CFA also confirmed that this model had an acceptable fit to the data, $X^2(12) = 18.73$, $p = .095$, CFI = 0.99, GFI = 0.98, RMSEA = 0.05, 90% CI of RMSEA

= [0.00, 0.09]. As in Time 1, factor scores from the PCA were employed as a composite index of independence-related traits at Time 2.

Covariates We adjusted for the effects of gender, age, body-mass-index (BMI), alcohol consumption, and smoking status at Time 1, as these variables have been shown to correlate with the UA level (Shankar et al., 2011; Sundström et al., 2005). BMI was calculated (kg/m^2) using the measurements of weight and height obtained during the clinic visit. Smoking status was indexed by two dummy-coded variables, contrasting non-smokers with former-smokers and current-smokers, respectively. The average number of alcohol drinks participants consumed per week was used as an index of alcohol consumption.

We also controlled for healthy eating since dietary factors, such as consumption of red meat, sugared beverages, and vitamin C from fruits and vegetables, are linked to the concentration of UA in the blood (Beydoun et al., 2018; Choi et al., 2005). The index of healthy eating was assessed based on six questions following the procedure from Levine et al. (2016); how often participants eat (a) beef or high fat meat, (b) fish, and (c) non-meat protein foods respectively, using a 5-point scale each (1=*never*, 2=*less than once per week*, 3=*one or two times per week*, 4=*three to four times per week*, 5=*five or more times per week*). Participants also indicated how many (d) sugared beverages they drink (1=*none*, 2=*less than one glass/day*, 3=*one to three glasses/day*, 4=*four to six glasses/day*, 5=*seven or more glasses/day*). Finally, participants indicated how many servings of (e) fruit and (f) vegetables they eat on an average day, respectively (1=*none*, 2=*less than one serving/day*, 3=*one to four servings/day*, 4=*five to nine servings/day*, 5=*10 or more servings/day*). After reverse-coding the scores of high-fat meat consumption and sugared beverages, the scores were summated to create a composite index of healthy eating.

Data Processing and Analytic Plan

Before data analysis, we inspected the raw data and winsorized a small number of outliers in the UA level and health behaviors at ± 3 standard deviations from each mean, following the standard approach in prior MIDJA-based projects (Kitayama et al., 2015, 2018; Park et al., 2024). See Table 1 for descriptive statistics for the study variables and Table 2 for inter-correlations among them at each wave.

We first examined whether interdependence-related traits at Time 1 would predict a change in UA over time (**Step 1**). To address this issue, we followed a convention in epidemiology (Castro-Schilo & Grimm, 2018; Glymour et al., 2005) and computed a change score of UA by subtracting the Time 1 variable from the Time 2 variable, such that higher numbers indicate a greater increase in UA over the 5-year period, and then regressed this score on interdependence-related traits. Second, we tested the reversed effects of the UA concentration on the change of interdependence-related traits over time by regressing a change score in interdependence (Time 2 – Time 1) on UA at Time 1 (**Step 2**). For both analyses, we also tested the bidirectional associations between independence-related traits and the UA concentration.

Table 1 Descriptive statistics for study variables at both waves of MIDJA

Variable	Time 1			Time 2		
	N	M	SD	*N*	M	SD
Demographic & health variables						
Gender (% female)	138	56.8%		138	56.8%	
Age	243	56.12	13.48	243	60.44	13.47
Educational attainment	241	4.59	2.03	242	4.62	2.08
Smoking status (% yes)						
Never-smoker	117	48.1%		*214	*88.1%	
Former-smoker	56	23.0%				
Current-smoker	50	20.6%		29	11.9%	
Missing	20	8.2%		0	0.0%	
Alcohol consumption	241	7.19	9.96	238	5.95	8.00
Body-mass-index (BMI)	243	22.75	3.08	243	22.84	3.10
Healthy eating	239	20.74	2.54	235	20.51	2.51
Uric acid (UA)	243	5.36	1.38	241	5.35	1.36
Interdependence-related traits						
Agreeableness	242	2.71	0.65	243	2.68	0.60
Generativity	243	12.28	3.85	240	12.24	3.82
Positive relations with others	243	34.00	6.00	238	34.09	5.09
Interdependent self-construal	243	4.77	0.64	239	4.83	0.62
Relational interdependence	236	4.87	0.66	232	4.86	0.64
Support giving	243	2.62	0.45	243	2.25	0.38
Social obligation	237	5.03	0.69	235	4.93	0.70
Independence-related traits						
Agency personality trait	242	1.90	0.58	243	1.90	0.58
Extraversion	242	2.49	0.68	243	2.51	0.65
Independent self-construal	240	4.73	0.67	240	4.73	0.67
Self-esteem	242	31.57	6.09	243	31.93	5.95
Sense of control	242	4.72	0.85	242	4.67	0.84
Autonomy	243	30.84	5.54	239	31.41	5.21
Environmental mastery	243	32.18	5.63	238	32.41	5.37
Personal growth	243	34.35	5.46	238	33.96	5.72
Self-acceptance	243	31.50	6.20	238	31.46	5.41
Cognitive effort						
Life overall	242	6.41	2.14	243	6.37	2.23
Health	243	6.48	2.08	243	6.65	2.21
Work situation	176	7.13	2.12	162	7.18	2.06
Financial situation	243	6.68	2.19	240	6.64	2.27
Close relationships	181	6.92	2.22	179	6.99	1.80
Relationships with children	182	6.92	2.44	184	7.03	2.34

Note. UA, BMI, alcohol consumption and healthy eating were winsorized at ± 3 standard deviations from each mean. Education attainment was assessed on an 8-point scale (1 = *8th grade*, *junior high school graduate*, 8 = *graduate school*). *The question item about formal-smoker was dropped from the MIDJA 2 survey, and thus, only the contrast between current-smoker and the rest two groups (former- and never-smoker groups combined) was computed for Time 2

Table 2 Inter-correlations among key study variables at each wave

	Time 1 variables	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
1.	Gender	−0.07	−0.39***	−0.40***	−0.29***	−0.34***	0.20**	$0.12^{\dagger}$	0.05	0.16	−0.57***
2.	Age	--	0.19**	−0.05	0.13*	−0.16*	0.25***	0.06	−0.01	0.07	0.05
3.	Body-mass-index		--	0.13*	$0.12^{\dagger}$	0.18**	−0.09	0.06	0.07	−0.14	0.40**
4.	Alcohol consumption			--	0.10	0.31***	−0.10	−0.02	0.02	0.04	0.36***
5.	Former smoker				--	−0.28***	$0.11^{\dagger}$	−0.01	−0.01	−0.14	0.14*
6.	Current smoker					--	−0.26***	−0.02	−0.00	$-0.16^{\dagger}$	0.24***
7.	Healthy eating						--	0.19**	0.10	0.30**	$-0.11^{\dagger}$
8.	Interdependence							--	0.61***	0.43***	0.03
9.	Independence								--	0.38***	0.07
10.	Cognitive effort									--	−0.10
11.	Uric acid										--
	Time 2 variables	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
1.	Gender	−0.07	−0.37***	−0.41***	--	0.32***	0.14*	0.08	0.08	0.28**	−0.60***
2.	Age	--	0.13*	−0.14*	--	0.13*	0.19**	0.05	0.03	−0.13	0.08
3.	Body-mass-index		--	$0.13^{\dagger}$	--	$-0.12^{\dagger}$	−0.09	0.02	0.02	−0.16	0.38***
4.	Alcohol consumption			--	--	−0.29***	−0.05	−0.03	0.01	−0.12	0.33***
5.	Former smoker				--	--	--	--	--	--	--
6.	Current smoker					--	0.21**	−0.02	0.01	0.05	−0.20**
7.	Healthy eating						--	0.26***	0.15*	0.24*	−0.06
8.	Interdependence							--	0.59***	0.55***	$0.13^{\dagger}$
9.	Independence								--	0.43***	0.04
10.	Cognitive effort									--	−0.08
11.	Uric acid										--

Note. The question item about formal-smoker was dropped from the MIDJA 2 survey, and thus, only the contrast between current-smoker and the rest two groups (former- and never-smoker groups combined) was computed for Time 2. $^{\dagger}p<.10$, $^{*}p<.05$, $^{**}p<.01$, $^{***}p<.001$

The larger study protocol was approved by the University of Wisconsin-Madison Institutional Review Board (IRB); the current study was exempt from an IRB review because we used publicly available, de-identifiable data. The analysis was not pre-registered.

Results

Step 1. Does Interdependence Predict an Increase in UA over Time?

To test whether interdependence-related traits at Time 1 predict an increase of UA over time, we regressed an increase of the UA concentration from Time 1 to Time 2 on the composite index of interdependence-related traits as well as covariates from Time 1. Males showed a greater increase in UA over time than females and those without any history of cigarette smoking showed a greater increase in their UA level compared to former-smokers (see Table 3-A for statistics). Notably, this analysis also yielded a significant effect of interdependence-related traits, $b = 0.144$, 95% confidence interval (CI) [0.029, 0.260], $t(219) = 2.47$, $p = .014$, demonstrating that interdependence at Time 1 significantly predicted an increase in UA over time (see Fig. 1-A).[1,2]

We further tested each measure of interdependence-related traits as a single predictor of the UA change score. Among the seven facets of interdependence we tested, interdependent self-construal had a significant longitudinal effect on UA, $b = 0.231$, 95% CI [0.053, 0.409], $t(226) = 2.55$, $p = .011$. All the remaining traits showed similar effects, although none of them achieved statistical significance when tested separately, ts < 1.91, ps > 0.057 (see Table S1-A for statistics).

Of importance, there was no significant effect of the composite index of independence-related traits at Time 1 on the UA change score, $b = 0.043$, 95% CI [-0.071, 0.157], $t(223) = 0.75$, $p = .456$ (see Table 3-B for full statistics and Table S1-B for statistics from individual variables constituting the measure of independence-related traits). Moreover, when the effect of independence-related traits was simultaneously estimated, interdependence-related traits still significantly predicted an increase in UA over time, $b = 0.177$, 95% CI [0.032, 0.323], $t(216) = 2.40$, $p = .017$.

[1] An alternative way of testing the current analysis is to use the UA level at Time 2 as an outcome variable while partialling out the effect of UA at Time 1. Although commonly used, this analysis is vulnerable to biases when there is an assortment of variables that influence the UA levels at both time points (Castro-Schilo & Grimm, 2018). Hence, its results must be interpreted with caution. Nevertheless, when we used this analytic approach, interdependence-related traits at Time 1 significantly predicted UA at Time 2 while controlling for UA at Time 1, $b = 0.202$, 95% CI [0.095, 0.309], $t(218) = 3.74$, $p < .001$.

[2] In Hayakawa et al. (2018), the negative association between the UA level and social withdrawal was evident among Japanese males (but not among females). However, there was no such evidence of gender differences in our data. The prospective effect of interdependence on the UA increase was not moderated by gender, $b = 0.024$, 95% CI [-0.213, 0.261], $t(218) = 0.20$, $p = .841$. In addition, given the wide age range of our sample (31–80), we tested if age moderated our result and it did not, $b = 0.002$, 95% CI [-0.007, 0.010], $t(218) = 0.37$, $p = .708$.

Table 3 Regression coefficients in predicting UA increase as a function of (A) interdependence-related traits and (B) independence-related traits at Time 1

A. Predictor variables at Time 1	**UA increase**		
	b	**95% CI**	**t-test**
Gender	-0.381	[-0.679, -0.084]	-2.53*
Age	0.002	[-0.007, 0.011]	0.37
Body-mass-index	-0.039	[-0.080, 0.002]	-1.87†
Alcohol consumption	-0.007	[-0.019, 0.006]	-1.06
Former smoker	-0.327	[-0.632, -0.021]	-2.11*
Current smoker	-0.198	[-0.532, 0.136]	-1.17
Healthy eating	-0.014	[-0.063, 0.035]	-0.58
Interdependence-related traits	0.144	[0.029, 0.260]	2.47*
B. Predictor variables at Time 1	**UA increase**		
	b	**95% CI**	**t-test**
Gender	-0.369	[-0.671, -0.068]	-2.42*
Age	0.001	[-0.008, 0.011]	0.32
Body-mass-index	-0.035	[-0.077, 0.006]	-1.67†
Alcohol consumption	-0.008	[-0.020, 0.005]	-1.17
Former smoker	-0.311	[-0.622, 0.000]	-1.97*
Current smoker	-0.202	[-0.540, 0.136]	-1.18
Healthy eating	-0.005	[-0.054, 0.043]	-0.22
Independence-related traits	0.043	[-0.071, 0.157]	0.75

Note. *N*s = 228 and 232 for (A) and (B), respectively. CI = confidence interval of unstandardized regression coefficient. †$p < .10$, *$p < .05$

Step 2. Does UA Predict an Increase in Interdependence?

Next, we tested the reverse cross-lag effect, with UA at baseline predicting a change in interdependence over time. Specifically, we regressed the interdependence change score (Time 2 – Time 1) on the UA level at Time 1 with the same set of covariates as additional predictors. There was no longitudinal effect of UA at Time 1 on interdependence over time, $b = 0.002$, 95% CI [-0.080, 0.085], $t(198) = 0.06$, $p = .955$ (see Table 4-A for full statistics). When each variable constituting the composite index of interdependence-related traits was tested separately, none of the change scores of these variables was significantly predicted by UA at Time 1, $ts < |-1.94|$, $ps > 0.053$.

Finally, when we tested whether UA at Time 1 predicts an increase in independence-related traits over time, there was no such longitudinal effect, $b = -0.043$, 95% CI [-0.112, 0.026], $t(218) = -1.23$, $p = .220$ (See Table 4-B for full statistics). The results did not differ when each facet of independence-related traits was tested separately, $ts < |-1.36|$, $ps > 0.175$.

Summary

In Analysis 1, we extended a prior study showing that the UA blood concentration is positively associated with social engagement in Japanese (Hayakawa et al., 2018) and found a directional effect of interdependence on an increase of the UA blood concentration over a 5-year period in another independent sample of Japanese. In our data, this effect was observed equally regardless of participant gender and age (see

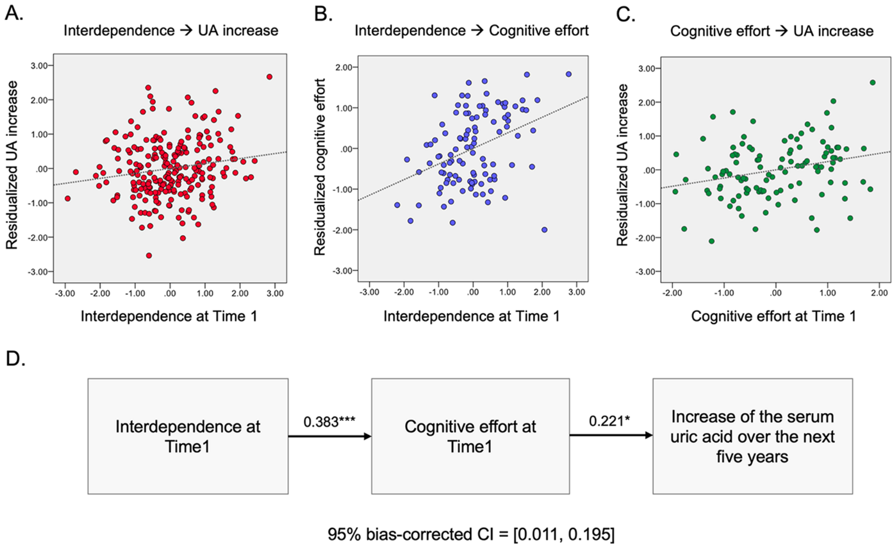

Fig. 1 Linking Interdependence at Time 1, Cognitive Effort at Time 1, and the Increase of UA over the Next Five Years (Time 2 – Time 1). *Note.* (**A**) Interdependence at Time 1 predicts the UA increase over time. (**B**) Interdependence at Time 1 predicts cognitive effort at Time 1. (**C**) Cognitive effort at Time 1 predicts the UA increase over time. (**D**) The effect of interdependence at Time 1 on the UA increase is mediated by cognitive effort at Time 1. Residualized scores indicate the scores after partialling out the effects of gender, age, BMI, alcohol consumption, smoking status, and healthy eating at Time 1. $*p<.05$, $***p<.001$

Footnote 2). Moreover, the pattern was consistent across multiple measures of social interdependence. Of note, the reverse cross-lag effect of UA leading to an increase in social interdependence was negligible. Lastly, comparable effects of independence were also negligible. Our results starkly contrast with the cumulative evidence in Western samples that the blood concentration of UA is associated with various externalizing traits—extreme or unhinged forms of the self's independence. Importantly, a recent study did show that this effect is also directional, with an extreme degree of independence (impulsivity) predicting an increase in the UA concentration in blood over a three to five years period (Sutin et al., 2014). Altogether, the available evidence is consistent with the hypothesis that culturally congruous behavioral dispositions (independence in Western cultures and interdependence in East Asian cultures) predict an increase in the UA concentration in the bloodstream longitudinally.

Analysis 2: A Mediating Role of Cognitive Effort

Our working hypothesis is based on a putative function of UA to deoxidize the brain, thereby enabling higher-level cognitive functioning (E. P. de Oliveira & Burini, 2012). It holds that engagement in culture involves strategic planning, execution of culturally appropriate actions, coordination of actions with others, and the like. Consequently, cultural engagement is supposedly highly effortful cognitively. Hence, indi-

Table 4 Regression coefficients in predicting increases in (A) interdependence-related traits and (B) independence-related traits as a function of uric acid (UA) at Time 1

A. Predictor variables at Time 1	**Interdependence increase**		
	b	**95% CI**	**t-test**
Gender	-0.187	[-0.445, 0.072]	-1.43
Age	-0.005	[-0.013, 0.002]	-1.37
Body-mass-index	-0.010	[-0.044, 0.024]	-0.56
Alcohol consumption	-0.002	[-0.012, 0.008]	-0.36
Former smoker	-0.162	[-0.407, 0.083]	-1.30
Current smoker	-0.197	[-0.462, 0.069]	-1.46
Healthy eating	0.017	[-0.022, 0.056]	0.85
Uric acid	0.002	[-0.080, 0.085]	0.06
B. Predictor variables at Time 1	**Independence increase**		
	b	**95% CI**	**t-test**
Gender	0.092	[-0.122, 0.306]	0.85
Age	0.003	[-0.004, 0.009]	0.81
Body-mass-index	0.009	[-0.020, 0.037]	0.60
Alcohol consumption	0.000	[-0.009, 0.008]	-0.06
Former smoker	0.159	[-0.049, 0.367]	1.51
Current smoker	0.058	[-0.167, 0.282]	0.51
Healthy eating	-0.001	[-0.033, 0.032]	-0.04
Uric acid	-0.043	[-0.112, 0.026]	-1.23

Note. *N*s = 207 and 227 for (A) and (B), respectively. CI = confidence interval of unstandardized regression coefficient

viduals more intensely engaged in their cultural contexts may experience an increase in UA concentration over time due to the metabolic demands of cultural engagement. Various interdependent psychological dispositions are required to fully engage in Japanese culture, which is organized by interdependent views of the self. Thus, the finding that interdependent psychological dispositions at one time point predicts an increase in UA concentration in bloodstream over a 5-year period among Japanese is consistent with this hypothesis. Our analysis implies, however, that this effect may be more directly explained by cognitive effort in various life domains. Those high in interdependence may be expected to expend more cognitive effort, which may in turn, explain why they show an increased UA level over a 5-year period.

Method

Cognitive Effort

We used the same dataset, which included measures that tapped on cognitive effort. These measures assessed the degree to which individuals extended effort and thought in six domains of life, including (a) life overall, (b) health, (c) work situation, (d) financial situation, (e) close relationships such as marriage, and (f) relationships with children. Participants indicated how much thought and effort they put into each domain of their life using a 11-point scale (e.g., Using a 0 to 10 scale where 0 means “no thought or effort” and 10 means “very much thought and effort,” how much thought and effort do you put into your work situation these days?). Two PCAs identified a one-factor solution for both Time 1 and Time 2 variables, accounting for 36.5% and 45.0% of the variances, respectively. CFAs also confirmed that the single-factor model provided an acceptable fit to the data both at Time 1, $X^2(8)=8.38$, $p=.397$, CFI = 0.99, GFI=0.98, RMSEA=0.02, 90% CI of RMSEA = [0.00, 0.12], and at Time 2, $X^2(8)=8.07$, $p=.426$, CFI = 1.00, GFI=0.97, RMSEA=0.01, 90% CI of RMSEA = [0.00, 0.12]. We used the factor scores from the PCAs as a composite index of cognitive effort at Time 1 and Time 2. We used the same set of covariates from Analysis 1.

Analytic Plan

We first tested whether there was any association between interdependence (or independence) and cognitive effort at both time points (**Step 1**). We then tested whether cognitive effort would prospectively predict an increase of the in-blood UA concentration (**Step 2**). Third, we tested whether the impact of interdependence on the UA increase over time would be mediated by cognitive effort (**Step 3**).

Table 5 Regression coefficients in predicting cognitive effort as a function of interdependence-related traits and independence-related traits at (A) Time 1 and (B) Time 2, respectively

A. Predictor variables at Time 1	**Cognitive effort**		
	b	**95% CI**	**t-test**
Gender	-0.285	[-0.774, 0.205]	-1.16
Age	0.001	[-0.017, 0.018]	0.07
Body-mass-index	-0.017	[-0.078, 0.043]	-0.57
Alcohol consumption	0.005	[-0.013, 0.024]	0.57
Former smoker	-0.585	[-1.060, -0.110]	-2.45*
Current smoker	-0.549	[-1.057, -0.041]	-2.14*
Healthy eating	0.098	[0.017, 0.179]	2.40*
Interdependence-related traits	0.283	[0.058, 0.507]	2.50*
Independence-related traits	0.181	[-0.031, 0.393]	1.70†
B. Predictor variables at Time 2	**Cognitive effort**		
	b	**95% CI**	**t-test**
Gender	0.175	[-0.242, 0.593]	0.84
Age	0.002	[-0.014, 0.018]	0.24
Body-mass-index	-0.014	[-0.069, 0.041]	-0.51
Alcohol consumption	-0.012	[-0.034, 0.010]	-1.08
Current smoker	-0.064	[-0.612, 0.483]	-0.23
Healthy eating	0.070	[-0.015, 0.156]	1.64
Interdependence-related traits	0.363	[0.124, 0.602]	3.02**
Independence-related traits	0.244	[0.031, 0.457]	2.28*

Note. *N*s = 104 and 89 for (A) and (B), respectively. CI = confidence interval of unstandardized regression coefficient. †$p<.10$, *$p<.05$, **$p<.01$

Table 6 Regression coefficients in predicting (A) UA increase as a function of cognitive effort at Time 1 and (B) the increase in cognitive effort as a function of UA at Time 1

A. Predictor variables at Time 1	**UA increase**		
	b	**95% CI**	**t-test**
Gender	0.031	[-0.432, 0.493]	0.13
Age	0.007	[-0.009, 0.023]	0.82
Body-mass-index	-0.014	[-0.072, 0.045]	-0.46
Alcohol consumption	0.001	[-0.017, 0.019]	0.11
Former smoker	0.089	[-0.374, 0.552]	0.38
Current smoker	0.017	[-0.473, 0.507]	0.07
Healthy eating	-0.060	[-0.137, 0.017]	-1.55
Cognitive effort	0.243	[0.068, 0.417]	2.76**
B. Predictor variables at Time 1	**Cognitive effort increase**		
	b	**95% CI**	**t-test**
Gender	0.156	[-0.370, 0.682]	0.59
Age	-0.010	[-0.027, 0.007]	-1.21
Body-mass-index	0.016	[-0.044, 0.076]	0.52
Alcohol consumption	-0.001	[-0.020, 0.019]	-0.08
Former smoker	-0.189	[-0.680, 0.301]	-0.77
Current smoker	-0.011	[-0.560, 0.538]	-0.04
Healthy eating	-0.005	[-0.078, 0.068]	-0.13
Uric acid	0.071	[-0.067, 0.210]	1.03

Note. *N*s = 110 and 90 for (A) and (B), respectively. CI = confidence interval of unstandardized regression coefficient. ***p* < .01

Results

Step 1. The Association between Cognitive Effort and Interdependence

In Step 1, we examined whether interdependence-related traits at Time 1 would concurrently predict cognitive effort. As predicted and also shown in Fig. 1-B, this effect was statistically significant after controlling for the covariates (see Table 5), $b = 0.383$, 95% CI [0.195, 0.571], $t(96) = 4.05$, $p < .001$. This relationship remained significant when independence-related traits were additionally controlled, $b = 0.283$, 95% CI [0.058, 0.507], $t(94) = 2.50$, $p = .014$ (see Table S2-A for full statistics). In this latter analysis, the effect of independence was not significant, $b = 0.181$, 95% CI [-0.031, 0.393], $t(94) = 1.70$, $p = .093$.

When the same regression was performed at Time 2, the effect of interdependence proved significant as predicted, $b = 0.536$, 95% CI [0.339, 0.733], $t(82) = 5.41$, $p < .001$. This pattern of result was replicated when independence-related traits were additionally controlled, $b = 0.363$, 95% CI [0.124, 0.602], $t(80) = 3.02$, $p = .003$. In this analysis, there was some effect of independence that attained statistical significance, $b = 0.244$, 95% CI [0.031, 0.457], $t(80) = 2.28$, $p = .025$ (see Table S2-B for full statistics). This effect, however, was substantially weaker than the effect of interdependence.

Step 2. Cognitive Effort as a Predictor of the UA Increase

We then tested whether cognitive effort at Time 1 had a longitudinal effect on UA. The UA change score was regressed on cognitive effort as well as covariates at Time 1. As shown in Table 6-A and also shown in Fig. 1-C, cognitive effort at Time 1 predicted a significant increase in UA over time, $b=0.243$, 95% CI [0.068, 0.417], $t(101)=2.76$, $p=.007$. When we tested the residuals in the Time 2 UA level after controlling for the Time 1 UA level, the result was no different. Cognitive effort at Time 1 significantly predicted the residualized Time 2 UA level, $b=0.258$, 95% CI [0.089, 0.427], $t(100)=3.02$, $p=.003$.

When each variable constituting the composite index of cognitive effort was tested as a separate predictor of the UA change score, there was a significant effect of cognitive effort made in the domain of close relationships, $b=0.076$, 95% CI [0.016, 0.136], $t(168)=2.49$, $p=.014$. None of the remaining items had a significant effect, but the patterns were in the expected direction in all cases except for one variable (see Table S1-C). Of importance, the effect of cognitive effort on UA increase was directional. The UA concentration at Time 1 did not predict changes in cognitive effort over time, $b=0.071$, 95% CI [-0.067, 0.210], $t(81)=1.03$, $p=.308$ (see Table 6-B for full statistics).

Step 3. Mediation Analysis

Finally, we conducted a combined analysis to test whether the longitudinal effect of interdependence on the UA level may be mediated by cognitive effort. We tested this mediation model using the Hayes' PROCESS Model 4, in which the link from interdependence at Time 1 to UA increase was hypothesized to be mediated by cognitive effort at Time 1, after partialling out the effects of covariates from Time 1. As noted above and also shown in Fig. 1-B and C, interdependence at Time 1 was positively associated with cognitive effort at Time 1, $b=0.383$, 95% CI [0.195, 0.571], $t(96)=4.05$, $p<.001$. Cognitive effort at Time 1, in turn, predicted a significant increase in UA over time, $b=0.221$, 95% CI [0.033, 0.410], $t(95)=2.33$, $p=.022$. In contrast, the effect of interdependence at Time 1 on UA increase became weak, $b=0.194$, 95% CI [0.005, 0.383], $t(95)=2.03$, $p=.045$, when its effect was simultaneously estimated with the effect of cognitive effort at Time 1. As implied by these patterns, the mediating path was statistically significant, 95% bootstrapping bias-corrected CI = [0.011, 0.195] (see Fig. 1-D). Of note, the result was no different when independence-related traits were additionally controlled for.

Summary

Analysis 2 shows that one important reason why interdependent psychological traits prospectively increase the in-blood UA concentration in Japanese is because these traits are associated with cognitive effort in various domains, such as health, work, home, and finance. We showed that cognitive effort reliably mediated the impact of interdependent traits on the longitudinal UA increase in the Japanese sample. These findings are consistent with the prior evidence that UA serves as a potent antioxidant in the brain and thus can compensate for the metabolic cost resulting from the increased cognitive effort (Glantzounis et al., 2005).

Discussion

Revisiting the Hypotheses

Our study set forth with two primary hypotheses: the first posited that traits related to interdependence in the Japanese context would predict an increase in blood UA levels over a period of five years, but not vice versa (Analysis 1); the second proposed that cognitive effort would account for the longitudinal impact of interdependence-related traits on the UA increase (Analysis 2). Our findings lend robust support to both hypotheses, revealing that interdependence is indeed associated with an increase in UA levels in the Japanese population, and moreover, this effect was mediated by cognitive effort in various life domains, such as work, finance, and social relations.

Psychological Correlates of Uric Acid: The Culture Connection

Research on UA has traditionally been limited to medical domains, often overlooking its potential role in the realm of psychology. Our current study contributes to this gap by revealing differing patterns of UA concentration related to psychological traits in Western and Japanese adults. In particular, we found that in Japan, traits related to interdependence are associated with an increase in UA levels, a finding mediated by cognitive effort across different life domains, a contrast to Western trends that link independent traits like impulsivity with increased UA (Sutin et al., 2014).

To provide context, we rely on a broader understanding of culture as a set of patterned behaviors and interactions (Adams & Markus, 2004; Kitayama & Salvador, 2024). Building on Bourdieu's (1977) idea of culture as a "game," we may posit that individuals must expend cognitive effort to succeed in their specific cultural settings. This is particularly true for those who aim to excel within their cultural norms, whether those norms prioritize independence (as in Western cultures) or interdependence (as observed in our Japanese study group). This increased cognitive effort—encompassing planning, strategizing, and executing actions—may in turn, lead to elevated UA levels in the bloodstream. The elevation is significant as UA plays a role in brain deoxidization, supporting optimal cognitive function (E. P. de Oliveira & Burini, 2012). Incidentally, our hypothesis offers a potential explanation for earlier findings linking higher UA levels with intelligence and social status (Brooks, 1966; Dunn, 1963; Mueller & French, 1970). Altogether, our data open the door to the idea that culture can be metabolically adaptive. By this, we mean that the cognitive demands of participating successfully in one's culture might affect biological markers like UA, which in turn, can be related to broader social and cognitive outcomes.

Evolutionary Considerations

While the specific mechanisms that increase UA levels in response to heightened cognitive effort are not yet fully understood, it is important to note that the kidneys play a crucial role in regulating UA concentrations (Alvarez-Lario & Macarron-Vicente, 2010). The kidneys filter circulating blood, during which UA is temporarily extracted. However, because UA is not fully water-soluble, a large portion is reabsorbed back into the bloodstream rather than being excreted in the urine. Additionally, extra UA may be secreted into the bloodstream, and these processes are all tightly controlled by gene transcription. The involvement of kidneys suggests a plausible, yet hypothetical, feedforward mechanism that could elevate UA levels in response to anticipated cognitive demands. Furthermore, by closely examining this tightly regulated network of processes, one may begin to see why the upregulation of UA by cultural engagement is also strictly limited with a certain upper-bound.

How about the biological evolution of UA regulation? Evidence suggests that serum UA levels have dramatically increased during primate evolution (Alvarez-Lario & Macarron-Vicente, 2010; Watanabe et al., 2002). This is thought to have occurred due to the suppression of a gene responsible for an enzyme that breaks down purines. The increase in UA is considered advantageous due to its antioxidant capacity, which accounts for over 50% of the antioxidant ability in blood (Ames et al., 1981). This is particularly crucial for the brain, which consumes about 20% of the body's oxygen supply (Clarke & Sokoloff, 1999). Thus, one could hypothesize that elevated levels of UA support increased cortical functioning (Alvarez-Lario & Macarron-Vicente, 2010; Wang et al., 2019). This evolutionary perspective further highlights how our contemporary cultural practices may be deeply rooted in physiological mechanisms that offered adaptive advantages in the past.

Insofar as there is substantial stability in interdependence ($r = .79$ over the five years in our sample), one might wonder why the level of UA concentration in the blood does not go up infinitely for those high in interdependence. However, it must be recognized that the level of UA in the bloodstream is tightly regulated by multiple mechanisms. Hence, for every increase of UA by interdependence, there may be feedback loops that keep the fluctuation of UA within a limited range. Moreover, as one becomes more interdependent, there may be increased levels of motivation, which will contribute to the increase of UA. At the same time, however, under such conditions, there may also be increased automaticity in carrying out interdependent behaviors (Kitayama & Yu, 2020). This increased automaticity may make interdependent behaviors cognitively less effortful, which could limit the increase of UA in the bloodstream.

Limitations and Conclusion

Our study has limitations. First, the relationship between independence-related traits and UA in Western populations needs further empirical validation. Second, we controlled for a variety of potential confounding variables, such as demographic and health-related variables, and yet, UA levels may be regulated by various other lifestyle factors, such as exercise (Green & Fraser, 1988), medications (Jamil et al., 2024), and sleep (Shi et al., 2019). Future research must test the robustness of our finding after including a more extensive set of covariates. On the other hand, however, it is possible that these lifestyle factors, such as diet and sleep, might serve as proximal mechanisms linking increased cultural engagement with UA elevation. For example, interdependent Japanese may engage in social eating and drinking more, resulting in a greater intake of high purine, fat, sugar, and alcohol, all of which can increase UA levels (Ekpenyong & Daniel, 2015). Social activities, such as social drinking, may also cause sleep disturbances (Holding et al., 2020), thereby elevating UA levels (Shi et al., 2019). Fourth, future studies should employ behavioral markers to gauge cognitive effort or other types of mental effort outside the cognitive domain more broadly. Behavioral markers are critical because they provide direct, observable evidence of the cognitive processes at play, allowing for a more precise understanding of how cultural engagement influences physiological outcomes like UA levels. Without these markers, it is challenging to determine whether the cognitive effort inferred from self-report measures or other indirect indicators accurately reflects the mental and physical exertion involved in cultural participation. Lastly, the social regulation of gene transcription, as it pertains to UA, remains an underexplored topic (Cole, 2014).

Despite these limitations, our work provides initial evidence for the potentially adaptive function of UA, shedding light on why this compound has been preserved through human evolution despite its association with various medical conditions, such as metabolic syndrome, hypertension, gout, and kidney disease. We propose that the UA's role in deoxidizing cortical processes is so critical that it has been maintained, even at the cost of increasing various health risks. In all likelihood, the UA's role in facilitating higher-order cortical functions makes it a crucial component in human evolution, particularly over the past 50,000 years of cultural evolution. Through further investigation into the phylogeny, ontogeny, mechanisms, and adaptive functions of UA, we may deepen our understanding of human evolution as a uniquely cultural species (Henrich, 2017; Kitayama & Uskul, 2011; Richerson & Boyd, 2005).

Our findings offer important practical and policy implications, especially given that blood UA levels have traditionally been examined mainly through a medical lens. In Japan, where cultural values emphasize interdependence, elevated UA levels may result from an excessive commitment to these values, possibly leading to health issues. For instance, social obligations and a propensity for overwork could elevate UA levels, thereby increasing the risk of associated medical conditions. In such cases, interventions could focus on moderating extreme adherence to group norms to manage UA-related health risks. In Western contexts, where elevated UA levels are linked to traits like impulsivity, targeted interventions could aim to modify such traits. Notably, this cultural insight can enrich cross-cultural medical practices. Healthcare providers could consider a patient's cultural background when assessing UA-related health risks, such as gout or kidney disease. Overall, our study paves the way for a more holistic approach to public health by integrating the cultural factors that influence biochemical variables like UA.

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Data Availability All data are available at https://www.icpsr.umich.edu/web/ICPSR/studies/34969.

Declarations

Competing Interests The authors declare no competing interests.

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Authors and Affiliations

Jiyoung Park[1,2] · Shinobu Kitayama[3]

✉ Jiyoung Park
j-park@kaist.ac.kr

✉ Shinobu Kitayama
kitayama@umich.edu

1 School of Digital Humanities and Computational Social Sciences, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea

2 Center for Contemplative Science, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea

3 Department of Psychology, University of Michigan, Ann Arbor, USA