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The second to fourth digit (2D:4D) ratios, smoking, and problem drinking in a young adult university student sample

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ABSTRACT

Background: Relative length of second finger to fourth finger (2D:4D ratio) has been shown to be a putative indirect marker of the amount of*in utero* testosterone levels. 2D:4D ratios are claimed to be inversely associated with prenatal testosterone levels.

Objective: We aimed to investigate whether 2D:4D ratios are independently associated with smoking and problem drinking in young adults.

Methods: We recruited a convenience sample of 661 university students and used the CAGE questionnaire to identify problem drinking. Smokers were assessed with the Fagerström Test for Nicotine Dependence (FTND). Impulsivity was measured with the Barratt Impulsiveness Scale. Results: 2D:4D ratios were lower in students who were problem drinkers than in those who were non-drinkers or non-problematic drinkers ($t = -2.07$, $p = .039$ for right hand; $t = -2.02$, $p = .044$ for left hand). 2D:4D ratios were comparable between regular smoker students and non-smoker or irregular smoker students. Problem drinking or regular smoking were not independently associated with 2D:4D ratios in regression analyses. However, 2D:4D ratios on both hands associated negatively with CAGE scores (95% CI: −6.24 to −.64, $p = .016$ for right hand; 95% CI: −6.68 to −.41, $p = .027$ for left hand) and positively with FTND scores (95% CI: 1.58–27.06, $p = .028$ for right hand; 95% CI: 5.06–29.03, $p = .006$ for left hand) independently of the effects of age, sex, and impulsivity.

Conclusion: Prenatal testosterone levels, as indirectly assessed by 2D:4D ratios, are independently associated with the severity of alcohol abuse and nicotine dependence when other factors such as sex, age, and impulsivity are considered.

1. Introduction

It was observed decades ago that the ratio between the length of the 2nd (the “index” finger) and 4th (the “ring” finger) digit (2D:4D) is determined as early as the second trimester of fetal life (Garn, Burdi, Babler, & Stinson, 1975) and becomes stable across the lifespan (Manning, Trivers, Thornhill, & Singh, 2000). 2D:4D ratio is putatively associated with prenatal testosterone levels (Lutchmaya, Baron-Cohen, Raggatt, Knickmeyer, & Manning, 2004) and is a sexually dimorphic trait, with males tending to have lower values then females (Malas, Dogan, Evcil, & Desdicioglu, 2006). Pathologically elevated levels of prenatal testosterone, as commonly seen in congenital adrenal hyperplasia, have been shown to cause lower 2D:4D ratios in females (Okten, Kalyoncu, & Yariş, 2002) which strongly supports the view that 2D:4D ratios are associated with testosterone levels *in utero*.

Prenatal testosterone levels are not only associated with lower 2D:4D ratios but also with masculinization of the fetal brain (Williams et al., 2000). As a consequence, typical masculine traits such as aggression (Dogan, Barut, Konuk, & Bilge, 2008), competitiveness (Manning & Taylor, 2001), dominance (Manning & Fink, 2008), and unfaithfulness (DeLecce, Polheber, & Matchock, 2014) are shown to be inversely correlated with 2D:4D ratios. Variations in 2D:4D ratios have also been detected in many psychiatric disorders. For example, patients with attention-deficit/hyperactivity disorder (Stevenson et al., 2007) and autism (Manning, Baron-Cohen, Wheelwright, & Sanders, 2001) have exhibited smaller ratios, whereas those with schizophrenia (Collinson et al., 2010) had higher values when compared with non-affected individuals.

Current scientific evidence on the association of 2D:4D ratios and addictive disorders is small. To our knowledge, there are six published

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studies investigating the association of 2D:4D ratios and alcohol or nicotine abuse. Most of those studies have demonstrated low 2D:4D ratios in alcohol abuse (Han, Bae, Lee, Won, & Kim, 2016; Kornhuber et al., 2011; Lenz et al., 2017; Lenz, Bouna-Pyrrou, Mühle, & Kornhuber, 2018; Manning & Fink, 2011) and high 2D:4D ratios in nicotine abuse (Borkowska & Pawlowski, 2013; Manning & Fink, 2011). Only one study (Lenz et al., 2017), however, used validated instruments to assess the severity of drinking or smoking. Moreover, only one study (Manning & Fink, 2011) applied regression analyses using relevant independent variables such as sex or age to determine whether 2D:4D ratios are independently associated with alcohol or nicotine dependence.

Higher levels of impulsivity is associated with substance use disorders (von Diemen, Bassani, Fuchs, Szobot, & Pechansky, 2008) and smaller 2D:4D ratios (Hanoch, Gummerum, & Rolison, 2012). A study in patients with heroin use disorder showed that 2D:4D ratios were not significant independent predictors of heroin use disorder when impulsivity was considered in regression analysis (Canan et al., 2018). Previous studies have not examined the role of impulsivity in the relationship between 2D:4D ratios and alcohol or nicotine dependence.

We aimed to examine the relationship between problem drinking and smoking and 2D:4D ratios among university students using validated instruments to measure smoking and drinking severity. We also aimed to examine whether that possible relationship is affected by impulsivity or other relevant variables such as age and sex.

2. Materials and methods

2.1. Ethical clearance

The study was approved by the Committee for the Protection of Human Subjects of the Akdeniz University School of Medicine Institutional Review Board before the initiation of the study. Signed consent was obtained from all participants.

2.2. Participants

This was a cross-sectional study. The target population was undergraduate students at the main campus of a large public university located on the southern Turkey. This study is a part of a broader research effort aimed at the examination of addictive disorders and their relations to various factors among undergraduate students. The sample was conveniently selected from several faculties (medicine, fine arts, law, management, engineering, nursing, agriculture, and dentistry) where the researchers had contact persons for easy data collection. Participants were recruited through classes, personal contact, fliers, and a student volunteer subject pool. No exclusion criteria were applied. Individuals were not offered any compensation for their participation. A convenience sample of 694 students were recruited. After excluding students with incomplete data, the final analyzed sample consisted of 661 students.

2.3. Measures

2.3.1. 2D:4D ratios

Finger lengths were measured using a digital Vernier caliper (accurate to 0.01 mm). Participants were instructed to place their hands on the table with their palms facing up and to extend their fingers as much as possible. As described by Verster and de Haan (2011), measurement landmarks were the ventrally located proximal-most (boundary) metacarpophalangeal flexion crease that divides the finger from the palm region and the fingertip, excluding possibly protruding fingernail. For each subject, two consecutive measurements were performed by two different observers. Each measurement was averaged to obtain a final value. The reliability of the two measurements was calculated for each finger separately for the right and left hand using the two-way random intra-class correlation coefficient (ICC). The reliability of the two raters was high for both the right hand (2D: ICC = 0.993; 4D: ICC = 0.994) and the left hand (2D: ICC = 0.991; 4D: ICC = 0.990).

2.3.2. Problem drinking

Frequency of alcohol use over the past six months was assessed using a Likert response format (0 = never, 1 = three times a month or less, 2 = once a week, 3 = a few times each week, 4 = every day). Alcohol users were also assessed with the CAGE questionnaire (Ewing, 1984). The acronym “CAGE” stands for the following: Cutting down, Annoyance due to criticism, Guilty feeling, and Eye-openers. The questions were dichotomous: (0) “no” and (1) “yes”. The score on the CAGE scale was established by summing the answers of the four questions. We defined problem drinking as at least two reported problems on the CAGE questionnaire in combination with an alcohol consumption of at least a few times each week. This resulted in a dichotomous variable: (1) “non-problem drinkers” and (2) “problem drinkers” (Sebena, El Ansari, Stock, Orosova, & Mikolajczyk, 2012).

2.3.3. Smoking

Students were asked how often they smoked cigarettes over the past six months (0 = never, 1 = irregularly/not daily, 2 = regularly/daily). Smokers would also answer Fagerström Test for Nicotine Dependence (FTND), a widely used instrument to assess severity of smoking (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). The FTND includes 6 items and the total score can range from 0 to 10, with higher scores indicating higher levels of nicotine dependence.

2.3.4. Impulsivity

The Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, & Barratt, 1995) is a 30-item self-administered questionnaire. The BIS-11 is a valid and reliable instrument, and one of the most often used tools to assess impulsivity. The BIS-11 items use a 4-point Likert scale and item values range from 1 = rarely/never to 4 = almost always. The Turkish version of the BIS-11 was found to be reliable among healthy students and patients with psychiatric disorders (Cronbach’s α coefficient: .78 and .81, respectively) (Gulec et al., 2008).

2.4. Statistical analysis

We used SPSS for statistical analyses and set statistical significance at $p < 0.05$. Student's t-tests were utilized to assess between-group differences with respect to continuous variables. The $\chi 2$ test was used to compare proportions between the groups. The correlation of 2D:4D ratios with participants' CAGE and FTND scores were analyzed using Pearson correlation test. To determine which variables might predict regular smoking, FTND score, problem drinking, or CAGE score we performed multiple linear regression analyses entering demographic variables (age and sex), impulsivity (BIS-11 score), problem drinking (in models predicting regular smoking and FTND score), regular smoking (in models predicting problem drinking and CAGE score), and 2D:4D ratios.

3. Results

The sample consisted of 374 females (56.6%) and 287 males (43.4%). The mean age of participants was 20.8 years (range, 17–27 years). The prevalence of non-problem and problem drinking in the total sample were 30.9% and 8.2%, respectively. A majority of the participants (61.0%) denied drinking during the previous 6 months. The prevalence of regular (daily) smoking and occasional smoking were 15.7% and 10.3%, respectively. Nearly three quarters of the students reported not smoking six months prior to study entry.

Table 1 provides demographic characteristics, BIS-11 and CAGE scores, and 2D:4D ratios for both smoking status groups. Regular smokers were significantly older, had a significantly lower proportion

Table 1
Sample characteristics by smoking status.

	Non-smoking / irregular smoking (n = 557)	Regular smoking (n = 104)	t / χ^2	p
Age, mean (SD)	20.7 (2.1)	21.3 (2.4)	2.43	**.015**
Female, % (n)	61.9 (345)	27.9 (29)	41.37	< **.001**
Problem drinker, % (n)	4.5 (25)	27.9 (29)	63.94	< **.001**
BIS-11 score, mean (SD)	57.6 (12.1)	63.9 (14.1)	4.76	< **.001**
CAGE score, mean (SD)*	.5 (.9)	1.0 (1.0)	4.08	< **.001**
Right 2D:4D, mean (SD)	1.003 (.053)	.997 (.035)	−1.05	.292
Left 2D:4D, mean (SD)	.994 (.037)	.991 (.035)	−.78	.436

The bold p values are significant.
*Only drinkers (39%, n = 258).
BIS-11: Barratt Impulsiveness Scale, version 11.

Table 2
Sample characteristics by drinking status.

	Non-drinking/ non-problem drinking (n = 607)	Problem drinking (n = 54)	t / χ^2	p
Age, mean (SD)	20.8 (2.1)	21.0 (2.7)	.79	.433
Female, % (n)	58.8 (357)	31.5 (17)	15.08	< **.001**
Regular smoker, % (n)	12.3 (75)	53.7 (29)	63.94	< **.001**
BIS-11 score, mean (SD)	58.2 (12.2)	62.8 (16.1)	2.58	**.010**
FTND score, mean (SD)*	3.6 (2.2)	4.9 (2.3)	2.52	**.013**
Right 2D:4D, mean (SD)	1.003 (.052)	.989 (.034)	−2.07	**.039**
Left 2D:4D, mean (SD)	.995 (.037)	.984 (.035)	−2.02	**.044**

The bold p values are significant.
*Only smokers (26%, n = 172).
BIS-11: Barratt Impulsiveness Scale, version 11; FTND: Fagerström Test for Nicotine Dependence.

of females, had a significantly higher proportion of problem drinkers, and had significantly higher BIS-11 and CAGE scores when compared to the combined group of non-smokers and irregular smokers. 2D:4D measurements for right and left hands did not differ between smoking status groups.

As shown in Table 2, at the bivariate level, problem drinkers had a significantly lower proportion of females, had a significantly higher proportion of regular smokers, had significantly higher BIS-11 and FTND scores, and exhibited lower 2D:4D ratios on both hands when compared to the combined group of non-drinkers and non-problematic drinkers.

Pearson`s correlation analysis revealed that 2D:4D ratios on the left hand were positively associated with FTND scores (n = 172, r = .263, p = .007). The correlation between FTND scores and 2D:4D ratios on the right hand fell somewhat short of significance (n = 172, r = .174, p = .077). CAGE scores correlated negatively with 2D:4D ratios on the right hand (n = 258, r=-.167, p = .007) and on the left hand (n = 258, r=-.154, p = .014).

Four multiple linear regression models were constructed to predict regular smoking and FTND score (dependent variables, one per model) from a list of independent variables including demographic characteristics (age and sex), problem drinking, BIS-11 score, and right or left 2D:4D ratios (Table 3). Regular smoking was positively associated with problem drinking, male sex, and BIS-11 score, independently of the effects of one another (Table 3, Models 1 and 2). 2D:4D ratios were not independently associated with regular smoking. Since only smokers completed the FTND, multiple linear regression to predict FTND score was constructed for the data of smokers only (n = 172). FTND score was positively and independently associated with problem drinking, BIS-11 score, and right 2D:4D ratios. Model 4 in Table 3 revealed that FTND score was positively associated with BIS-11 score and left 2D:4D ratios independently of the effects of one another; problem drinking fell just short of significance.

Table 4 presents results of multiple linear regression models predicting problem drinking and CAGE scores from the same independent variables with the substitution of regular smoking for problem drinking. Models 1 and 2 revealed that problem drinking was positively and independently associated with regular smoking. Since only drinkers completed the CAGE, multiple linear regression to predict CAGE score was constructed for the data of drinkers only (n = 258). CAGE score associated positively with regular smoking and negatively with age and 2D:4D ratios on both hands independently of the effects of one another (Table 3, Models 3 and 4).

4. Discussion

In this study, we found that 2D:4D ratios were lower in university students who were problem drinkers than in those who were non-drinkers or non-problematic drinkers. 2D:4D ratios were comparable between regular smoker students and non-smoker or irregular smoker students. Regression analyses showed that problem drinking or regular smoking were not independently associated with 2D:4D ratios. However, severity of drinking associated negatively and severity of nicotine dependence associated positively with 2D:4D ratios on both hands independently of the effects of age, sex, and impulsivity.

Lower 2D:4D ratios in problem drinkers found in this study is a relatively consistent finding across previous studies. Two studies collecting data via Internet surveys concluded that 2D:4D ratios on both hands were inversely associated with higher alcohol intake (Manning & Fink, 2011) and binge drinking (Lenz et al., 2018). Similar findings were demonstrated in inpatients with alcohol use disorder, such that patients had smaller 2D:4D ratios on both hands compared to healthy controls (Han et al., 2016; Kornhuber et al., 2011; Lenz et al., 2017). In addition, Lenz et al. (2017) showed that 2D:4D ratios correlated negatively with the severity of alcohol withdrawal (measured with Clinical Institute Withdrawal Assessment for Alcohol revised scale) and positively with the intensity of nicotine dependence (measured with FTND) in 200 early-abstinent alcohol dependent patients. Although our sample was a non-clinical one, our findings corroborate those of Lenz et al. (2017), indicating that 2D:4D ratios are associated with the

Table 3
Multiple regression models predicting regular smoking or FTND score (dependent variables respectively, one per model).

Regular smoking (n = 661)							FTND score (n = 172)						
Model 1 (R^2 = .116)							**Model 3** (R^2 = .161)						
Independent variables	**df**	**β**	**SE**	**t**	**p**	**95% CI**	*Independent variables*	**df**	**β**	**SE**	**t**	**p**	**95% CI**
Age	1	.01	.01	1.59	.113	−.01, .02	Age	1	.13	.09	1.43	.155	−.05, .31
Sex	1	.14	.03	5.26	< **.001**	.09, .19	Sex	1	.46	.50	.92	.923	−.53, 1.46
Problem drinking	1	.35	.05	7.31	< **.001**	.26, .45	Problem drinking	1	1.09	.49	2.25	**.027**	.13, 2.05
BIS-11 score	1	.01	.01	4.10	< **.001**	.01, .01	BIS-11 score	1	.03	.02	2.01	**.048**	.01, .06
Right 2D:4D	1	.06	.26	.15	.828	−.45, .57	Right 2D:4D	1	14.32	6.42	2.23	**.028**	1.58, 27.06
Model 2 (R^2 = .163)							**Model 4** (R^2 = .185)						
Independent variables	**df**	**β**	**SE**	**t**	**p**	**95% CI**	*Independent variables*	**df**	**β**	**SE**	**t**	**p**	**95% CI**
Age	1	.01	.01	1.57	.116	−.01, .02	Age	1	.15	.09	1.63	.106	−.03, .32
Sex	1	.14	.03	5.28	< **.001**	.09, .20	Sex	1	.19	.47	.92	.688	−.75, 1.13
Problem drinking	1	.35	.05	7.31	< **.001**	.26, .45	Problem drinking	1	.93	.48	1.95	.054	−.02, 1.87
BIS-11 score	1	.01	.01	4.11	< **.001**	.01, .01	BIS-11 score	1	.03	.02	2.14	**.035**	.01, .06
Left 2D:4D	1	.12	.36	.33	.738	−.58, .82	Left 2D:4D	1	17.05	6.42	2.82	**.006**	5.06, 29.03

The bold p values are significant.
BIS-11: Barratt Impulsiveness Scale, version 11; FTND: Fagerström Test for Nicotine Dependence.

severity of nicotine dependence and problem drinking. In addition to previous reports, our results suggest that these associations are independent of sex, age, and impulsivity.

Similar to our study, Manning and Fink (2011) constructed multiple linear regression models to predict alcohol intake and nicotine intake. They found that sex, age, education, alcohol intake (independent variable predicting nicotine intake), nicotine intake (independent variable predicting alcohol intake), and 2D:4D ratios on both hands independently predicted alcohol and nicotine intake. Our regression models, including impulsivity as an independent variable among others, showed that male sex, problem drinking, and impulsivity were independently associated with regular smoking, but 2D:4D ratios were not. The only independent variable positively associated with problem drinking was found to be regular smoking. The severity of nicotine dependence, as measured by FTND, was independently and positively associated with 2D:4D ratios on both hands. Problem drinking severity, as measured by CAGE, was also independently but negatively associated with 2D:4D ratios. Our findings indicate that the relationships between 2D:4D ratios and alcohol or nicotine use problems are complex and can be affected by several factors including impulsivity.

We compared the 2D:4D ratios of the students with and without regular smoking and found no difference. This finding contrasts with previous studies (Borkowska & Pawlowski, 2013; Manning & Fink, 2011) showing higher 2D:4D ratios in individuals with nicotine use. Of note, Borkowska and Pawlowski (2013) found positive association between left 2D:4D ratios and smoking only among females. These differences across studies may indicate a genetic variation in the relationship between prenatal testosterone exposure and smoking. Interestingly, we found that 2D:4D ratios on both hands were independent predictors of the severity of nicotine dependence although they did not predict regular smoking status. By focusing on individuals with smoking and measuring the intensity of nicotine dependence, the relationship of 2D:4D and smoking should be investigated carefully to draw more robust conclusions.

Positive association between 2D:4D ratios and nicotine dependence (Borkowska & Pawlowski, 2013; Lenz et al., 2017; Manning & Fink, 2011) in contrast to the negative association between 2D:4D ratios and other addictive disorders such as alcohol use disorder (Han et al., 2016; Kornhuber et al., 2011; Lenz et al., 2017, 2018; Manning & Fink, 2011), heroin use disorder (Canan et al., 2018; Cicek et al., 2017), and problematic Internet use (Canan et al., 2017; Kim, Roh, Lee, Canan, & Potenza, 2018) is of interest. The present data support the opposite relationship of 2D:4D ratios, nicotine dependence, and problem drinking. Higher prenatal testosterone levels might lead to more severe alcohol use problems, whereas exposure to lower levels of testosterone *in utero* might cause worse nicotine dependence in adulthood via unknown mechanisms.

Although we recruited a relatively large sample size and performed two consecutive measurements of 2D:4D ratios conducted by two independent observers, several limitations should be noted. First, the sample was recruited conveniently rather than randomly, thus cannot accurately represent the entire university population. Second, the sample was drawn from a single university, thus limiting the results` generalizability to universities of similar background and geographic

Table 4
Multiple regression models predicting problem drinking or CAGE score (dependent variables respectively, one per model).

Problem drinking (n = 661)							CAGE score (n = 258)						
Model 1 (R^2 = .328)							**Model 3** (R^2 = .340)						
Independent variables	**df**	**β**	**SE**	**t**	**p**	**95% CI**	*Independent variables*	**df**	**β**	**SE**	**t**	**p**	**95% CI**
Age	1	−.01	.01	−.19	.849	−.01, .01	Age	1	−.06	.03	−2.24	**.026**	−.11, -.01
Sex	1	.04	.02	1.85	.064	−.01, .08	Sex	1	.14	.12	1.19	.235	−.09, .38
Regular smoking	1	.21	.03	7.31	< **.001**	.16, .27	Regular smoking	1	.44	.13	3.30	**.001**	.18, .70
BIS-11 score	1	.01	.01	1.14	.253	−.01, .01	BIS-11 score	1	.01	.01	1.84	.066	−.01, 02
Right 2D:4D	1	−.32	.20	−1.58	.114	−.71, .08	Right 2D:4D	1	−3.44	1.42	−2.42	**.016**	−6.24, -.64
Model 2 (R^2 = .329)							**Model 4** (R^2 = .336)						
Independent variables	**df**	**β**	**SE**	**t**	**p**	**95% CI**	*Independent variables*	**df**	**β**	**SE**	**t**	**p**	**95% CI**
Age	1	−.01	.01	−.14	.888	−.01, .01	Age	1	−.05	.03	−2.09	**.038**	−.11, -.01
Sex	1	.04	.02	1.92	.055	−.01, .08	Sex	1	.18	.12	1.52	.129	−.05, .41
Regular smoking	1	.21	.03	7.31	< **.001**	.16, .27	Regular smoking	1	.45	.13	3.39	**.001**	.19, .71
BIS-11 score	1	.01	.01	1.08	.280	−.01, .01	BIS-11 score	1	.01	.01	1.59	.113	−.01, 02
Left 2D:4D	1	−.46	.28	−1.66	.098	−.99, .08	Left 2D:4D	1	−3.55	1.60	−2.23	**.027**	−6.68, -.41

The bold p values are significant.
BIS-11: Barratt Impulsiveness Scale, version 11.

region. Also, study participants may not be representative of the general population. Third, although using a digital Vernier caliper to measure 2D:4D is an acceptable method, simultaneously scanning participants` hands would offer an opportunity to conduct reliability analyses. Fourth, the number of participants with regular smoking and problem drinking were small, which may lead to less reliable statistical results. Fifth, we assessed smoking and problem drinking by use of a standardized self-report instrument rather than by a full diagnostic interview.

4.1. Conclusion

With the present work, we demonstrated that students with problem drinking had more masculinized (lower) 2D:4D ratios when compared with non-affected students. It should be noted that the relationship between 2D:4D ratios and problem drinking was no longer classifiable as one of mutual independence when multiple linear regression analysis was performed using smoking, age, sex, and impulsivity as independent factors. However, 2D:4D ratios independently associated with the severity of problem drinking (negatively) and of nicotine dependence (positively). Prenatal testosterone levels, as indirectly assessed by 2D:4D ratios, do not predict problem drinking or nicotine dependence, but they predict the severity of these conditions.

To better understand the association between 2D:4D ratios and substance-related and addictive disorders, future studies should examine larger, preferably community-based, cohorts using full diagnostic criteria and symptom severity measures. Whenever populations are studied, it is crucial to control for potentially confounding factors such as demographics and other psychopathology, including impulsivity, which are shown to be associated with 2D:4D ratios. Since cross-sectional studies do not provide evidence for temporal or causal associations, future research should re-examine the findings of this study using prospective methodological designs. If the findings of this study could be replicated in larger populations, measurement of 2D:4D ratios before young adulthood could assist in future public health interventions limiting the risk of smoking and problem drinking.

Ethical statement

The study was approved by the Committee for the Protection of Human Subjects of the Akdeniz University School of Medicine Institutional Review Board before the initiation of the study. Signed consent was obtained from all participants.

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