Lower digit ratio (2D:4D) in alcohol dependence: Confirmation and exploratory analysis in a population-based study of young men

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Abstract
Moderately sized, case-control studies have related alcohol dependence in middle-aged in-patients to lower second-to-fourth finger length ratio (2D:4D), a proxy for prenatal hyperandrogenization. As primary aim, we here intended to confirm that lower 2D:4D is also associated with Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV/–5 alcohol dependence and alcohol use disorder in a large population-based cohort of young males. Exploratory aims included underlying mechanisms. We analyzed self-reported data on 2D:4D, DSM-IV/–5 criteria, anticipated subjective responses to alcohol, and willingness to purchase alcoholic drinks from 4989 Swiss men of the Cohort Study on Substance Use Risk Factors (C-SURF). The mean of right-hand 2D:4D and left-hand 2D:4D was lower in men with DSM-IV alcohol dependence than in those without (0.975 vs 0.981, P = .035) and lower in men with moderate to severe (0.974) than in those with mild (0.982, P = .001) or no (0.981, P = .003) DSM-5 alcohol use disorder. Moreover, mean 2D:4D was lower in those reporting recent use of health services due to substance use problems (0.968 vs 0.981, P = .046). Lower mean 2D:4D correlated with a stronger anticipation to feel high following alcohol consumption (total cohort: \( \rho = -0.033, P = .026 \)) and with a willingness to purchase more higher-priced alcoholic drinks (DSM-IV alcohol dependence subgroup: \( \rho_{\min} = -0.162, P = .002 \)). This is the first population-based study on young males to demonstrate lower 2D:4D in DSM-IV alcohol dependence, DSM-5 alcohol use disorder, and the related use of health care services. We also provide novel insight into cognitive-behavioral mechanisms. These results should help to establish more effective preventive and therapeutic strategies targeting 2D:4D and prenatal androgen exposure.
1 | INTRODUCTION

Alcohol dependence and alcohol use disorder are among the most prevalent and burdening psychiatric disorders worldwide. They are subject to a distinct gender dimorphism. In 2016, alcohol was responsible for more deaths in men than in women (2.3 vs 0.7 million), and more men than women (237 vs 46 million) were affected by alcohol use disorder worldwide. In line with genetic evidence, this suggests that sex hormone activity is involved in alcohol dependence.

Hyperandrogenization during prenatal and early postnatal life programs behavioral masculinization and permanently affects neural architecture. It has been speculated that early androgen effects also contribute to greater male phenotypic variability and increased environmental susceptibility.

A growing body of evidence from animal and human studies indicates that increased prenatal androgen exposure predisposes to develop alcohol dependence in adulthood in a sex-specific manner. In male mice, prenatal androgen receptor inhibition by flutamide decreases alcohol intake during adulthood and, in female mice, prenatal androgen receptor activation by dihydrotestosterone increases adult alcohol intake. Prenatal exposure to excess testosterone increases the number of tyrosine hydroxylase-immunoreactive cells in the ventral tegmental area of adult ewes. Higher amniotic testosterone predicts increased behavioral approach tendencies in 8- to 11-year-old children by influencing brain regions (caudate, putamen, nucleus accumbens) to be more responsive to positive compared with negatively valenced cues. These studies suggest that prenatal androgen program the fetal brain’s reward system, which is relevant to addictive behavior later in life.

In humans, it is hardly feasible to directly investigate the role of prenatal androgen exposure in alcohol dependence due to ethical constraints and the long time period between the intrauterine window and adulthood. Biomarkers of prenatal androgen exposure have been established. The most widely studied proxy is the second-to-fourth finger length ratio (2D:4D). Lower 2D:4D is indicative of higher prenatal androgen exposure for a critical review, see previous studies. To date, three case-control studies have investigated the relationship between 2D:4D and alcohol dependence. These have consistently reported lower 2D:4D in male alcohol-dependent in-patients compared with male control subjects. The findings indicate that higher prenatal androgen exposure predisposes males to develop a dependence on alcohol in adulthood. The prenatal androgen activity model of alcohol dependence has been supported by observations of weaker transient evoked otoacoustic emissions and a higher incidence of late pubertal onset, both also proxies for increased prenatal androgen exposure, in male alcohol-dependent in-patients relative to control subjects. As for females, the data remain controversial because one study supports the effect and the only other failed to find evidence thereof.

Three studies have been published on the relationship between 2D:4D and alcohol dependence in humans, yet these are subject to several limitations: (a) Their sample sizes are limited to less than 500 participants in each of these investigations. (b) The alcohol-dependent in-patients were compared with control subjects from the general population. The use of different target populations to recruit participants likely induced bias. Lower 2D:4D has been related to lower educational attainment, and a lower educational level is a characteristic of alcohol dependence. Because the groups in these three available studies have not been balanced for educational attainment, a relevant bias cannot be ruled out. (c) All three cohorts were, on average, middle-aged (Kornhuber et al; median age 46 years; Han et al; mean age 51 years; Lenz et al; median age 48 years). Therefore, the results cannot easily be applied to individuals of younger age. However, this is an important goal because, relative to other age groups, the risk for alcohol dependence is particularly high during early adulthood. (d) It remains unclear whether 2D:4D is associated with alcohol dependence and/or alcohol use disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, DSM-5) because two of the available studies primarily employed the 10th edition of the International Classification of Diseases (ICD-10) to classify alcohol dependence, and the third study used the Korean version of the alcohol dependence scale. (e) The cognitive-behavioral mechanisms underlying the association between 2D:4D and alcohol dependence remain unexplored.

1.1 | Aims of the study

We conducted this study to address the above-reported limitations. The primary aim was to confirm that lower 2D:4D is related to DSM-IV alcohol dependence and DSM-5 alcohol use disorder by analyzing the data from a large, population-based cohort of young males. To provide novel and mechanistic insight into the association between 2D:4D and alcohol dependence, the exploratory aims were to investigate associations of 2D:4D with DSM-IV alcohol abuse, single DSM-IV/5 criteria, use of health services due to substance use problems, anticipated subjective responses to standard alcoholic drinks, and willingness to purchase standard alcoholic drinks across a range of prices.

2 | MATERIALS AND METHODS

2.1 | Study sample

We analyzed data from the third survey wave of the Cohort Study on Substance Use Risk Factors (C-SURF; www.c-surf.ch). This longitudinal investigation conducted in Switzerland is directed by the Centre hospitalier universitaire vaudois (CHUV) in Lausanne and the University

KEYWORDS
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of Zurich. During the consent period from 2010 to 2011, 13,237 young males who attended their mandatory recruitment for the Swiss army were invited to participate in C-SURF. Of these, 7556 gave written informed consent and 5987 participated in the first wave. The first survey wave took place between September 2010 and March 2012, the second between March 2012 and January 2014, and the third between April 2016 and March 2018 (see www.c-surf.ch/img/questionnaires_pdf/q3_follow_up2_en.pdf for the English Questionnaire 3). In total, 5516 males participated in the third survey wave.

The participants reported separately for each criterion whether, over the preceding 12 months, they fulfilled the criteria for DSM-IV alcohol dependence, DSM-5 alcohol use disorder, and DSM-IV alcohol abuse (Questionnaire 3 ID: D14-16). Participants who answered “no” to the filter question “IN THE PAST 12 MONTHS, have you drunk AT LEAST ONE standard drink with alcohol (not counting when you just had a sip to give it a try)?” (Questionnaire 3 ID: D3) were coded as no in terms of the DSM-IV alcohol dependence, DSM-5 alcohol use disorder, and DSM-IV alcohol abuse criteria. Participants who fulfilled up to two of the DSM-IV alcohol dependence criteria were assigned to the “DSM-IV nonalcohol dependence subgroup,” and those fulfilling at least three to the “DSM-IV alcohol dependence subgroup.” The participants who fulfilled zero or one of the DSM-5 alcohol use disorder criteria were grouped into the “DSM-5 nonalcohol use disorder subgroup,” those who fulfilled two to three criteria into the “DSM-5 mild alcohol use disorder subgroup,” and those who fulfilled at least four criteria into the “DSM-5 moderate/severe alcohol use disorder subgroup.” The DSM-5 moderate and severe alcohol use disorder subgroups were combined to ensure a sufficient sample size. Respondents who fulfilled none of the DSM-IV alcohol abuse criteria were assigned to the “DSM-IV nonalcohol abuse subgroup,” those fulfilling at least one to the “DSM-IV alcohol abuse subgroup.”

Nine individuals were excluded from the statistical analyses due to missing values or eliminations resulting from quality control of R2D:4D and L2D:4D, resulting in a total cohort of 4989 study subjects and M2D:4D, R2D:4D, and L2D:4D subcohorts of 4770, 4869, and 4890 individuals.

Data were analyzed using IBM SPSS Statistics Version 24 for Windows (SPSS Inc., Chicago, IL, USA) and Graph Pad Prism 5 (Graph Pad Software Inc., San Diego, CA, USA). As calculated using the custom tables function in SPSS, continuous data are presented as the median and interquartile range and nominal data as frequencies and odds ratio (OR). For missing data points, the corresponding study subjects were included in the specific analyses, and the number of individuals included in these analyses is reported. We used the Mann–Whitney U and Kruskal–Wallis tests to compare independent groups. The $\chi^2$ test was employed to evaluate the differences in the frequency of the nominal variables. Correlations were calculated using Spearman’s method. For two-sided tests, $P < .05$ was considered to be statistically significant.

The main analyses were conducted after exclusion of finger lengths under 10 mm or over 100 mm and 2D:4D values outside of the 2.5 and 97.5 percentiles. Because the remaining reports of very short and very long finger lengths provide uncertainty and are subject to a high error risk, we tested the major findings for robustness. The

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2.2 Behavioral phenotyping

An adapted version of the drug effects questionnaire was used to quantify the participants’ anticipation of how they would feel immediately after consuming five standard alcoholic drinks containing approximately 10 g of alcohol each. They were asked about their expectation to feel any effect from the substance, to feel high, to like the effects, to dislike the effects, and to want more alcohol on an 11-point scale from 0 (not at all), over 5 (moderately), to 10 (extremely) (Questionnaire 3 ID: D13). Moreover, an adapted version of the simulated alcohol purchase task was conducted to quantify the participants’ willingness to pay for standard alcoholic drinks across a broad price range. They were asked “How many standard drinks with alcohol would you have if … Drinks are free? Every drink costs 50 cents? Every drink costs 1/2/3/4/6/8/10/15/20 Swiss francs?” (Questionnaire 3 ID: D12).
significant findings related to the primary predictor M2D:4D were recalcuated after exclusion of finger lengths under 10 mm or over 100 mm, absolute right-hand and left-hand second and fourth finger lengths outside of the 2.5 and 97.5 percentiles, and 2D:4D values outside of the 2.5 and 97.5 percentiles (supporting information).

3 | RESULTS

3.1 | Sociodemographic characteristics

The DSM-IV alcohol dependence subgroup did not significantly differ from the DSM-IV nonalcohol dependence subgroup with regard to age, body height, body weight, body mass index, level of education, or whether the participants were gainfully employed (Table 1). DSM-IV alcohol dependence was significantly associated with more standard alcoholic drinks per drinking day and higher smoking prevalence (OR 2.8). Both subgroups differed significantly in how they covered their living expenses and in their civil status. Individuals in the DSM-IV alcohol dependence subgroup were significantly more likely to be eliminated from the M2D:4D (OR 1.9) and the R2D:4D (OR 2.2) subcohorts but not from the L2D:4D sub-cohort (for the total cohort, see Table 1; for descriptive statistics of 2D:4D and details of M2D:4D, R2D:4D, and L2D:4D subcohorts, see Tables S1 and S2).

3.2 | Primary aim - confirmatory analysis: 2D:4D, DSM-IV alcohol dependence, and DSM-5 alcohol use disorder

M2D:4D (primary indicator) and L2D:4D were significantly lower in the DSM-IV alcohol dependence subgroup compared with the DSM-IV nonalcohol dependence subgroup (Figure 1A and 1C). The DSM-5 moderate/severe alcohol use disorder was associated with significantly lower M2D:4D (primary indicator), R2D:4D, and L2D:4D than the DSM-5 mild or nonalcohol use disorder (Figure 1A-C). 2D:4Dr-I was not significantly related to DSM-IV alcohol dependence or DSM-5 alcohol use disorder (Figure 1D).

3.3 | Exploratory aims: 2D:4D, DSM-IV alcohol abuse, DSM-IV/-5 items, and use of health services

2D:4D did not significantly differ between the DSM-IV alcohol abuse subgroup and the DSM-IV nonalcohol abuse subgroup (for details, see Table S3). The number of fulfilled DSM-IV alcohol dependence criteria, DSM-5 alcohol use disorder criteria, or DSM-IV alcohol abuse criteria did not significantly correlate with M2D:4D, R2D:4D, L2D:4D, or 2D:4Dr-I (for details, see Table S4). We explored associations between 2D:4D and the single criteria for DSM-IV alcohol dependence, DSM-5 alcohol use disorder, and DSM-IV alcohol abuse. These analyses revealed significantly lower M2D:4D and L2D:4D in participants who stated that, during the past 12 months, their drinking had caused them to miss a class, work, or to fail to look after their family more than once (M2D:4D 0.976 [0.953-1.000] vs 0.981 [0.955-1.000]; L2D:4D 0.975 [0.949-1.000] vs 0.986 [0.950-1.000]) and that they experienced such a strong desire or urge to drink that they could not help but do so (M2D:4D 0.974 [0.953-1.000] vs 0.981 [0.955-1.000]; L2D:4D 0.974 [0.939-1.000] vs 0.986 [0.950-1.000]; for details, see Table S5).

We found lower M2D:4D in study subjects with at least one visit in emergency departments, ambulatory care, or a special clinic due to problems with substance use during the past 12 months compared with those without (Mann-Whitney U test; M2D:4D, 0.968 [0.939-1.000] vs 0.981 [0.955-1.000], n = 36 vs 4730, U = 68,740, P = .046, R2D:4D, n = 39 vs 4826, U = 83,806, P = .237, L2D:4D, n = 39 vs 4847, U = 78,920, P = .074, 2D:4Dr-I, n = 36 vs 4730, U = 74,940, P = .209).

3.4 | Exploratory aims: 2D:4D and anticipated subjective responses to 5 standard alcoholic drinks

Lower 2D:4D correlated significantly with greater anticipation of feeling high following consumption of five standard alcoholic drinks in the total cohort and the DSM-IV nonalcohol dependence subgroup and with greater anticipation to dislike the effects of five standard alcoholic drinks in the DSM-IV nonalcohol dependence subgroup (Table 2). 2D:4D did not significantly correlate with the anticipated subjective responses in the alcohol dependence subgroup (Table S6).

3.5 | Exploratory aims: 2D:4D and simulated alcohol purchase task

For higher-priced standard alcoholic drinks (ie, at least six Swiss francs each), lower 2D:4D correlated significantly with the willingness to purchase more standard alcoholic drinks in the DSM-IV alcohol dependence subgroup (Table 3). 2D:4D did not significantly correlate with the number of standard alcoholic drinks when these cost less than six Swiss francs each. There were also no convincing associations between 2D:4D and willingness to purchase standard alcoholic drinks in the total cohort or the DSM-IV nonalcohol dependence subgroup, despite the larger sample size (Table S7).

3.6 | Positive control: 2D:4D, body mass index, body height, body weight, and age

We aimed to confirm previously reported correlations of 2D:4D with body mass index and age as positive controls. In this study, lower M2D:4D correlated significantly with taller body height and lower R2D:4D with lower body mass index and younger age (Table 4).

4 | DISCUSSION

4.1 | 2D:4D and group comparisons

In line with the primary aim, this population-based study confirmed lower 2D:4D in young males diagnosed with alcohol dependence according to DSM-IV compared with their nonalcohol-dependent
|                                | Alcohol Dependence Subgroup | Nonalcohol Dependence Subgroup | \( \chi^2 \) or \( U \) | \( P \) |
|--------------------------------|-----------------------------|--------------------------------|-------------------|------|
| \( N \)                        | 381                         | 4608                           |                   |      |
| Males (%)                      | 100                         | 100                            |                   |      |
| Age (years)                    | 25.0 (24.5-26.0)            | 25.0 (24.5-26.0)               | 834,703           | .107 |
| Body height (m)                | 1.80 (1.75-1.84)            | 1.80 (1.75-1.84)               | 868,614           | .759 |
| Body weight (kg)               | 75 (70-84)                  | 75 (70-84)                     | 854,429           | .413 |
| Body mass index (kg/m\(^2\))  | 23.5 (22.2-25.5)            | 23.5 (21.8-25.5)               | 855,495           | .441 |
| Gainfully employed (%)         | 76.4                        | 79.8                           | 2.6               | .108 |
| Level of education (%)         |                             |                                |                   |      |
| Secondary education            | 3.9                         | 2.9                            |                   |      |
| Basic vocational education     | 0.5                         | 1.3                            |                   |      |
| Secondary vocational/technical education | 33.3                | 34.5                           |                   |      |
| Community college              | 5.5                         | 4.2                            |                   |      |
| Vocational high school         | 13.4                        | 11.0                           |                   |      |
| High School                    | 13.1                        | 11.6                           |                   |      |
| Bachelor (University)          | 21.3                        | 23.6                           |                   |      |
| Master (University)            | 5.5                         | 6.2                            |                   |      |
| Other                          | 3.4                         | 4.7                            |                   |      |
| Covers living expenses by (%)  |                             |                                | 6                 | 7.2  |
| Himself                        | 52.5                        | 59.1                           |                   |      |
| His parents and other sources  | 11.5                        | 11.1                           |                   |      |
| Himself and external financial support | 36.0                        | 29.7                           |                   |      |
| Civil status (%)               |                             |                                | 8                 | 17.6 |
| Single                         | 90.3                        | 82.3                           |                   |      |
| Married                        | 2.4                         | 5.5                            |                   |      |
| Divorced                       | 0.3                         | 0.1                            |                   |      |
| Not married, not separated, not divorced but living together with my partner (e.g., in registered partnership) | 7.1                        | 11.9                           |                   |      |
| Married but separated          | 0.0                         | 0.2                            |                   |      |
| Widow                          | 0.0                         | 0.1                            |                   |      |
| Number of standard alcoholic drinks per drinking day | 5 (3-8)                   | 3 (2-4)                        | 514,391           | <.001 |
| 12-month smoking history (%)   | 64.8                        | 39.3                           | 1                 | 94.7 |
| Availability of valid 2D:4D (n) |                             |                                |                   |      |
| M2D:4D and 2D:4Dr-I            | 352                         | 29                             | 4418              | 190  |
| R2D:4D                         | 363                         | 18                             | 4506              | 102  |
| L2D:4D                         | 370                         | 11                             | 4520              | 88   |

Note. This table shows absolute and relative frequencies and medians with interquartile ranges of the total cohort of young Swiss males. For Questionnaire 3 IDs see supporting information. \( P < .05 \) in bold print.

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; 2D:4D, second-to-fourth finger length ratio; M2D:4D, mean of R2D:4D and L2D:4D; R2D:4D, right-hand 2D:4D; L2D:4D, left-hand 2D:4D; 2D:4Dr-I, difference between R2D:4D and L2D:4D; M, absolute number of missing data points.

\( a \) Mann-Whitney \( U \) test

\( b \) \( \chi^2 \)-test
counterparts, which is consistent with previous studies on middle-aged male alcohol-dependent in-patients.\textsuperscript{16-18} 2D:4D was also lower in individuals with at least one visit in emergency departments, ambulatory care, or a special clinic due to problems with substance use during the past 12 months than in those without. These results suggest that prenatal hyperandrogenization predisposes males to develop alcohol dependence in adulthood and necessitates the related use of health care services.

The present investigation complements previous work in several aspects, such as cohort characteristics, the use of DSM-IV/-5 criteria, and the investigation of cognitive-behavioral mechanisms. With nearly 5000 participants, the cohort analyzed here is by far the largest in the area of 2D:4D in alcohol dependence. This cohort can be considered as representative of the national Swiss population of young males because of the specific C-SURF recruitment process, which used the mandatory military recruitment system in Switzerland. The results show that the observed effects are relevant, not only to the clinical setting, but also at the population level. This study is the first to find that lower 2D:4D associates with alcohol dependence in a cohort balanced for educational attainment (the DSM-IV alcohol dependence and nonalcohol dependence subgroups did not significantly differ in their educational level). In contrast to the other available studies in the field on middle-aged cohorts,\textsuperscript{16-18} the C-SURF cohort is comprised exclusively of young males. The results presented here confirm that the association between 2D:4D and alcohol dependence is already established as early as during the third decade of life. The fact that males are at particular risk for alcohol dependence during early adulthood\textsuperscript{21} highlights the importance of this investigation. Whereas previous studies primarily used ICD-10 criteria and the alcohol dependence scale,\textsuperscript{16-18} here we employed the DSM-IV alcohol dependence criteria, the DSM-5 alcohol use disorder criteria, and the DSM-IV alcohol abuse criteria. Despite the large sample size, 2D:4D did not significantly differ between participants with DSM-IV alcohol abuse and those without or between participants with the DSM-5 mild alcohol use disorder and those without the DSM-5 alcohol use disorder. In contrast, we found lower 2D:4D in participants with DSM-IV alcohol dependence than in those without and lower 2D:4D in participants with the DSM-5 moderate to severe alcohol use disorder than in those with the DSM-5 mild alcohol use disorder or without the DSM-5 alcohol use disorder. In summary, 2D:4D appears to be associated with the complex trait of alcohol dependence but not with alcohol abuse or mild alcohol use disorder. This agrees with the results of a recent meta-analysis showing lowered 2D:4D in subjects diagnosed with alcohol dependence according to established diagnostic criteria, but not in those classified by other parameters of alcohol use.\textsuperscript{23} We found only a few minor associations between single DSM-IV/-5 items and 2D:4D, suggesting that 2D:4D influences alcohol dependence via a complex interaction between multiple behavioral traits rather than a single trait.

\subsection*{4.2 Mechanistic investigation}

The present study provides the first evidence that to feel high following alcohol consumption, to dislike the effects of alcohol, and to be
Abbreviations: 2D:4D, second-to-fourth finger length ratio; M2D:4D, mean of R2D:4D and L2D:4D; R2D:4D, right-hand 2D:4D; L2D:4D, left-hand 2D:4D; 2D:4Dr-l, difference between R2D:4D and L2D:4D.

### TABLE 3

Spearman correlations: 2D:4D and willingness to purchase standard alcoholic drinks of different prices in the alcohol dependence subgroup.

| Price (Swiss francs) | M2D:4D | R2D:4D | L2D:4D | 2D:4Dr-l |
|----------------------|--------|--------|--------|----------|
|                      | N  | p     | N  | p     | N  | p     | N  | p     |
| Alcohol dependence subgroup (≥3 fulfilled DSM-IV criteria) |
| 0                    | 352 | -0.060 | 0.263 | 363 | -0.009 | 0.860 | 370 | -0.072 | 0.165 | 352 | 0.034 | 0.521 |
| 0.5                  | 351 | -0.067 | 0.213 | 361 | -0.016 | 0.766 | 369 | -0.067 | 0.202 | 351 | 0.017 | 0.752 |
| 1                    | 351 | -0.087 | 0.103 | 361 | -0.036 | 0.490 | 369 | -0.077 | 0.141 | 351 | 0.010 | 0.846 |
| 2                    | 350 | -0.089 | 0.098 | 360 | -0.048 | 0.363 | 368 | -0.072 | 0.165 | 350 | 0.012 | 0.817 |
| 3                    | 350 | -0.076 | 0.158 | 360 | -0.045 | 0.391 | 368 | -0.050 | 0.341 | 350 | 0.004 | 0.946 |
| 4                    | 350 | -0.099 | 0.065 | 360 | -0.073 | 0.167 | 368 | -0.058 | 0.270 | 350 | -0.003 | 0.949 |
| 6                    | 350 | -0.125 | 0.020 | 361 | -0.116 | 0.027 | 368 | -0.067 | 0.198 | 350 | -0.018 | 0.731 |
| 8                    | 350 | -0.162 | 0.002 | 361 | -0.161 | 0.002 | 368 | -0.090 | 0.083 | 350 | -0.055 | 0.303 |
| 10                   | 350 | -0.138 | 0.010 | 361 | -0.152 | 0.004 | 368 | -0.068 | 0.195 | 350 | -0.068 | 0.207 |
| 15                   | 348 | -0.097 | 0.069 | 359 | -0.128 | 0.015 | 366 | -0.026 | 0.615 | 348 | -0.098 | 0.069 |
| 20                   | 348 | -0.091 | 0.089 | 359 | -0.133 | 0.011 | 366 | -0.023 | 0.662 | 348 | -0.085 | 0.113 |

Note. P < .05 in bold print.

Abbreviations: 2D:4D, second-to-fourth finger length ratio; M2D:4D, mean of R2D:4D and L2D:4D; R2D:4D, right-hand 2D:4D; L2D:4D, left-hand 2D:4D; 2D:4Dr-l, difference between R2D:4D and L2D:4D.

Willing to purchase more alcoholic drinks might represent mechanisms underlying the consistently reported lower 2D:4D in alcohol-dependent individuals. These cognitive-behavioral traits are involved in the development and maintenance of alcohol dependence.

In the total cohort and the DSM-IV nonalcohol dependence subgroup, lower 2D:4D correlated with greater anticipation of feeling high following alcohol consumption. Thus, individuals with lower 2D:4D might be more likely to instrumentalize alcohol consumption, which may influence the risk of developing alcohol dependence. It has been shown that the μ-opioid receptor alpha (OPRM1) interacts with prenatal androgen exposure to influence adult alcohol drinking. Moreover, OPRM1 inhibition using naltrexone decreases feelings of euphoria, which underlies the medication’s clinical effect of reducing relapse risk. In light of these investigations, the present study’s
findings of a correlation between lower 2D:4D and greater anticipation of feeling high further support the theory that prenatal exposure to excess androgen organizes the cerebral opioid system in a way that influences addictive alcohol consumption behavior later in life.

Lower 2D:4D correlated with greater anticipation of disliking the effect of alcohol. This association reached significance only in the DSM-IV nonalcohol dependence subgroup, suggesting that prenatal hyperandrogenization (2D:4D as a proxy) might exert a protective effect against alcohol dependence under certain conditions. We conclude that 2D:4D interacts with genetic and environmental factors to influence cognitive-behavioral traits that cause or maintain alcohol dependence.

Participants with lower 2D:4D were willing to purchase more higher-priced standard alcoholic drinks and this correlation was only detected in the DSM-IV alcohol dependence subgroup. Hence, in alcohol-dependent males, lower 2D:4D might contribute to the maintenance of alcohol dependence via lower inhibition of investing money in higher-priced standard alcoholic drinks.

The associations described above between 2D:4D and cognitive-behavioral traits are supported by results from previous studies in nonalcohol-dependent samples. Higher prenatal testosterone predicts stronger behavioral approach tendencies and more mesolimbic activity in response to positive valence cues\(^\text{12}\) and lower L2D:4D relates to neural sensitivity, as measured by the P2a event-related potential component to the delivery of motivational stimuli.\(^\text{36}\)

Moreover, lower R2D:4D correlated with lower age. This observation replicates a similar correlation from another sample of older subjects with a broader age distribution.\(^\text{29}\) It is unlikely that these correlations are due to changes in 2D:4D with growing age because it is assumed that 2D:4D develops during the early intrauterine window with only minor alterations thereafter.\(^\text{14,38-40}\) There is evidence for an alternate explanation. A recent national-level study revealed a positive correlation between male 2D:4D and life expectancy (after normalization to the national mean of males and females), which suggests that lower 2D:4D is associated with lower life expectancy.\(^\text{31}\) Lower 2D:4D relates to a number of causes of deaths relevant to young males such as aggression-related injuries\(^\text{42}\) and suicide.\(^\text{43,44}\) Thus, the positive correlation between 2D:4D and age observed here might support a reduced life expectancy in individuals with lower 2D:4D.

### 4.4 Additional strengths and limitations

The 7.6% prevalence of DSM-IV alcohol dependence observed in this study cohort of young males is consistent with other population-based estimates (4.6% to 6.1% for males and females combined, aged 21-29 years, Germany\(^\text{21}\); 6.1% for males, all age groups combined, Europe\(^\text{3}\)). Moreover, the R2D:4D and L2D:4D medians of 0.985 and 0.986 in this investigation agree with the median R2D:4D and L2D:4D values of 0.988 and 0.987 in a previous study using a similar self-measurement method\(^\text{29}\) and with the means from the British Broadcasting Corporation (BBC) Internet study of 0.984 and 0.985.\(^\text{45}\) These consistencies confirm the validity and the reliability of our measures and support that the analyzed cohort can be considered as representative of the population. Moreover, the DSM-IV alcohol dependence and nonalcohol dependence subgroups were well-balanced in terms of many sociodemographic characteristics. We also replicated previous findings as positive controls. The sensitivity analysis not only confirmed the robustness of the major findings but also showed higher effect sizes (see supporting information).

Taken as a whole, the observed effect sizes are small, which might be explained by several underlying factors. Addictive behaviors are caused by a complex interaction between bio-psycho-social factors. Previous case-control studies investigated alcohol-dependent inpatients, whereas this study classified individuals from a population...
of young men as alcohol-dependent regardless of whether they were in treatment or not. Most likely, this resulted in less affected alcohol dependence and alcohol use disorder groups compared with previous investigations. Moreover, no direct clinical interviews have been conducted that may have reduced the diagnostic precision, although the prevalence estimate of alcohol dependence is in the expected range. Self-measured 2D:4D is said to reach only 46% of the reliability conferred by expert-measured 2D:4D. Furthermore, we did not assess finger deformation in this project, which has reduced precision. Moreover, we acknowledge that the use of 2D:4D as a proxy for prenatal androgen exposure has been criticized for not being a good indicator for individual differences in prenatal androgen exposure. The experimental evidence used to support the validity of 2D:4D as a biomarker of prenatal androgen exposure has not been replicated consistently. Beyond the a priori-defined group comparisons, we conducted many exploratory statistical tests. We did not correct for multiple hypothesis testing, which might have entailed false-positive findings. Thus, future research is needed to confirm these novel results.

4.5 | Perspective

This study’s finding of lower 2D:4D in alcohol-dependent individuals in a population-based cohort informs the generation of more effective preventive strategies targeting the development of 2D:4D. There is some evidence from animal and human studies that maternal stress, smoking, and alcohol consumption during pregnancy are related to lower 2D:4D in the offspring. Currently, a prospective, controlled, and investigator-blinded study is being conducted that examines how a stress-reducing mindfulness-based intervention carried out by pregnant women affects their children’s 2D:4D. Moreover, the novel mechanistic findings reported here might encourage future research using 2D:4D as a biomarker and help to establish effective preventive and therapeutic strategies.

5 | CONCLUSIONS

To the best of our knowledge, this study is the first to establish in a population-based cohort of young males that lower 2D:4D relates to DSM-IV alcohol dependence, DSM-5 alcohol use disorder, and the use of health care services due to problems with substance use and that the anticipation of feeling high following alcohol consumption and the willingness to purchase higher-priced standard alcoholic drinks represent underlying cognitive-behavioral mechanisms. These observations support the model that prenatal androgen exposure increases the risk of alcohol dependence in adulthood and provide a basis for establishing novel preventive and therapeutic strategies.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTION

Conceived and designed the experiments: BL and JK. Analyzed the data and wrote the paper: BL. Performed the experiments: GG, MMK, SM, SF, and JS. Commented on the manuscript and provided intellectual input: CM, GG, and JK. All authors have critically reviewed the content and approved the final version submitted for publication.

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SUPPORTING INFORMATION

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

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