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Predictors of Increases in Alcohol Problems and Alcohol Use Disorders in Offspring in the San Diego Prospective Study

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Background: The 35-year-long San Diego Prospective Study documented 2-fold increases in alcohol problems and alcohol use disorders (AUDs) in young-adult drinking offspring compared to rates in their fathers, the original probands. The current analyses use the same interviews and questionnaires at about the same age in members of the 2 generations to explore multiple potential contributors to the generational differences in adverse alcohol outcomes.

Methods: Using data from recent offspring interviews, multiple cross-generation differences in characteristics potentially related to alcohol problems were evaluated in 3 steps: first through direct comparisons *across* probands and offspring at about age 30; second by backward linear regression analyses of predictors of alcohol problems *within* each generation; and finally third through R-based bootstrapped linear regressions of differences in alcohol problems in randomly matched probands and offspring.

Results: The analyses across the analytical approaches revealed 3 consistent predictors of higher alcohol problems in the second generation. These included the following: (i) a more robust relationship to alcohol problems for offspring with a low level of response to alcohol; (ii) higher offspring values for alcohol expectancies; and (iii) higher offspring impulsivity.

Conclusions: The availability of data across generations offered a unique perspective for studying characteristics that may have contributed to a general finding in the literature of substantial increases in alcohol problems and AUDs in recent generations. If replicated, these results could suggest approaches to be used by parents, healthcare workers, insurance companies, and industry in their efforts to mitigate the increasing rates of alcohol problems in younger generations.

Key Words: Alcohol, Prevalence, Level of Response, Impulsivity, San Diego Prospective Study.

LEVELS OF PER capita alcohol consumption, alcohol problems, and alcohol use disorders (AUDs) fluctuate over time. These changes are best documented through epidemiologic studies of representative samples of the general population. However, while ideal for estimating rates of AUDs across a country, these large-scale studies of tens of thousands of subjects are usually limited to low frequencies of re-evaluations, difficulty following multiple members of the same families from multiple generations over time, and limitations in the depth of details that can be covered. The strengths of large national surveys are exemplified by the National Epidemiological Surveys on Alcohol and Related Conditions (NESARC) that reported that lifetime histories of AUDs increased stepwise from 20.5% for men born between 1934 and 1943 to 33.1% for the male cohort born between 1964 and 1973, with rates for women increasing from 11.2% in the earlier cohort to 21.2% in the more recent birth group (Grucza et al., 2008). More recently, as reported by Grant and colleagues (2017), between about 2001 and 2013 the 12-month prevalence for DSM-IV defined AUDs (American Psychiatric Association, 2000) increased by 49.4% (from 8.5% to 12.2%) overall, including increases of 34.7% in men and 83.7% in women. Similar recent AUD increases have been reported in most other studies, along with a narrowing of the male/female ratio for alcohol diagnoses (Livingston et al., 2018; Slade et al., 2016; Stanesby et al., 2018).

In-depth study of the multiple biological, environmental, and attitudinal characteristics that might have contributed to changes in alcohol problems and AUDs in recent decades (e.g., Kendler et al., 2018; Reilly et al., 2017; Schuckit et al., 2017) is challenging to do in these larger investigations because the additional questionnaires required to evaluate these phenomena are time-consuming and difficult to add to an already full interview schedule. Data from smaller sample-based longitudinal studies structured to gather data across multiple domains and multiple generations of the same families might be able to better address such a wide range of potential contributors to changes in rates of alcohol problems. One

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example is our San Diego Prospective Study (SDPS) protocol that followed original 20-year-old subjects (probands who at baseline were drinkers but did not at the time fulfill AUD criteria) and their offspring with repeated evaluations over 35 years. The results of the most recent evaluation demonstrated that drinking 18-year old and older offspring of the original probands demonstrated higher rates of alcohol problems and AUDs than their fathers, increases that are similar to those reported in NESARC and other national surveys (Schuckit et al., 2019). That increase in adverse alcohol outcomes in the SDPS offspring along with the fact that the same interview and questionnaires were used in both generations offers an opportunity to look for differences across generations that might have contributed to the increase in alcohol problems in the offspring.

To prepare for the analyses presented below, we searched the literature for potential correlates of rates of alcohol problems across cohorts. First, regarding *demography*, in most studies SES related to alcohol problems, although the direction on the link varied across investigations (e.g., Caldwell et al., 2008; Crum et al., 2006; Davis and Slutske, 2018; Huerta and Borgonovi, 2010; Maggs et al., 2008; Swendsen et al., 2009). Also, individuals with European American (EA) and/or Hispanic backgrounds generally had higher rates of AUDs compared to African American and Asian individuals (Cook and Caetano, 2014; Greenfield et al., 2017; Pedersen and McCarthy, 2009). Sex differences generally indicated females demonstrated higher proportions of abstainers, lower drinking quantities per occasion, and a need for fewer drinks for effects, the latter reflecting lower body water and slower alcohol metabolism compared to male drinkers (Becker and Chartoff, 2019; Salvatore et al., 2017). Therefore, SES, sex, and ethnicity should be considered in analyses evaluating rates of alcohol-related problems across generations.

Consideration was also given to another domain represented by several *genetically influenced risk factors*, some of which require studies like the SDPS that evaluated subjects in multiple generations. In addition to a family history (FH) of AUDs, the risk factors evaluated in cross-sectional and cohort studies include higher impulsivity or sensation seeking (Kendler et al., 2018; Pears et al., 2007; Schuckit et al., 2017; Sher et al., 1999). Other genetically influenced risk factors for alcohol-related problems include a low level of response (low LR) to alcohol that can be measured through alcohol challenges or by a retrospective questionnaire (Quinn and Fromme, 2011; Ray et al., 2010; Schuckit, 2018; Viken et al., 2003) and a higher level of alcohol-related stimulation usually seen at rising blood alcohol concentrations (BACs; King et al., 2016; Roche et al., 2014). Recent work supported relationships of a low LR to higher rates of alcohol problems in a younger generation (Schuckit et al., 2019) but did not evaluate additional characteristics, including mediators of the impact of LR on alcohol problems, to establish the combination of variables that contribute to the higher rates of problems in younger generations (Schuckit et al., 2017, 2019).

A third group of variables historically evaluated cross-sectionally and in prospective cohort studies includes *potential mediators* of the impact of predisposing risk factors on drinking behaviors. In our own work, these mediators have included the influence of heavier drinking peers, positive expectations of the effects of alcohol, and using alcohol to cope with stress, as discussed in more detail elsewhere (Borsari and Carey, 2001; Henry et al., 2005; Patrick et al., 2010; Rose, 1999; Schuckit et al., 2004, 2017).

Several *additional potential differences* across generations that might contribute to higher alcohol-related problems in different generations include the use of tobacco and illicit drugs (Borges et al., 2015; Hingson et al., 2008; Terry-McElrath et al., 2013; Weinberger et al., 2015), levels of religious identity (Button et al., 2010; Grigsby et al., 2016; Koopmans et al., 1999; Timberlake et al., 2007), and being married and having children, each of which could affect the impact of risk factors for alcohol-related problems (Barr et al., 2017; Kendler et al., 2016; Staff et al., 2010; Waldron et al., 2011).

The current analyses take advantage of the longitudinal nature of the SDPS that gathers extensive data related to multiple domains of predictors across generations of the same families to search for differences across generations that might have contributed to the higher rates of alcohol problems in the younger cohort. Hypothesis 1 is that even after controlling for generational differences in demography (education, race/ethnicity, age, and sex), the higher number of alcohol problems in the offspring will relate to generational differences in a low LR and impulsivity/sensation seeking, and/or in mediators of their effects (e.g., Drinking to Cope, peer maximum drinks, aspects of alcohol expectancies, and smoking/illicit drug use). Hypothesis 2 is that similar correlates of the higher rate of alcohol problems in the offspring generation will be seen within males and females. Although we expect the sexes to differ on characteristics that typically distinguish between men and women (e.g., women are likely to need fewer drinks for effects and to have fewer alcohol problems), our prior work indicated that within males and females similar characteristics predicted alcohol problems (Eng et al., 2005; Schuckit et al., 2011).

MATERIALS AND METHODS

Selection and Initial Evaluation of Original SDPS Probands

The 35-year longitudinal SDPS, a project where each stage of the work was approved by the University of California, San Diego (UCSD), Human Research Protections Committee, began in 1978 with the recruitment of the original subjects (probands; Schuckit and Gold, 1988). Each year between 1978 and 1988 questionnaires was randomly distributed to UCSD students to recruit 18- to 25-year-old drinking men who consumed alcohol but had never met criteria for alcohol dependence (e.g., Schuckit and Gold, 1988; Schuckit et al., 2019). Individuals with lifetime histories of schizophrenia, bipolar disorder, or dependence on alcohol or illicit drugs were excluded, and appropriate probands were initially

evaluated for LR using oral alcohol challenges where peak BAC averaged 60 mg/dl at 60 minutes (e.g., Ehlers et al., 1999; Schuckit and Gold, 1988).

Follow-ups, Offspring Enrollment, and Testing

Probands were followed with personal interviews about every 5 years regarding changes in demography, substance use and problems, and major psychiatric disorders using questions derived from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) instrument (validity, retest reliabilities, and cross-interviewer reliabilities of 0.7 to 0.8; Bucholz et al., 1994; Hesselbrock et al., 1999). The same SSAGA-based interviews and the same questionnaires described below were administered to drinking offspring age 18+, with the current analyses focusing on offspring interviews obtained between 2014 and 2019. FH of AUDs for probands used the FH method and FH for offspring came from personal interviews of their fathers (i.e., our probands) and mothers. Proband follow-up interviews that had been completed when they were aged 30 to 35 (93% follow-up) are key to the current analyses, as are recent offspring follow-up interviews when these sons and daughters were about age 30.

During evaluations, probands and offspring gave information on their LR to alcohol using the SRE, which is the sole LR measure used in both generations. The SRE records the standard drinks (~10 g of ethanol) required for up to 4 effects actually experienced during a drinking period (first feeling an effect, feeling as if speech was beginning to slur, perceiving being unsteady on your feet, and unwanted falling asleep). Several scores are generated from this instrument including values for the first 5 times of ad lib drinking (SRE-5), the period of heaviest drinking, the recent 3 months drinking, and the average across all 3 periods (SRE-T; Schuckit, 2018; Schuckit et al., 1997). Because SRE-5 and SRE-T correlations are >0.82, only SRE-5 values are used here. SRE scores correlate positively and significantly with recent drinking quantities in individuals as young as age 12 and adults in their 40s and 60s, and predict future heavy drinking and alcohol problems in both younger and older drinkers (Daeppen et al., 2000; Schuckit et al., 2008, 2011, 2018), and individuals demonstrate similar SRE values for over 5 years (Schuckit and Smith, 2013). The SRE-5 Cronbach α is >0.90 for this and most prior evaluations, retest reliabilities are 0.8, and SRE scores correlate with the alcohol challenges in predicting future heavy drinking at about 0.60 (Ray et al., 2010; Schuckit et al., 1997).

Additional Proband and Drinking Offspring Data

Beginning with the 15-year follow-up of SDPS families, protocols included environmental and attitudinal characteristics that partially mediate effects of a low LR and/or higher impulsivity on heavy drinking and alcohol problems (Schuckit et al., 2004, 2011, 2017). These mediators included the following: (i) a person's perception of the maximum standard drinks consumed in close peers using a short version of the Important People and Activities Scale, which is scored from zero (abstainer) to 4 (>10 drinks) with retest reliabilities >0.85 and current alpha 0.76 for offspring and 0.57 for probands (Longabaugh et al., 1993); (ii) the usual effects a person expects from alcohol as measured by the Social Behavior (e.g., alcohol makes parties more fun) and Increased Arousal (e.g., alcohol helps people stand up to others) subscales of the Alcohol Expectancy Questionnaires (AEQ). These are graded on a 5-point scale with current sample Social Behavior Cronbach alphas >0.91 for both offspring and probands, and values for Arousal of 0.69 and 0.76 (Brown et al., 1987; Goldman, 2002); and (iii) the Drinking to Cope scale that records how respondents actually used alcohol to decrease negative emotions, boredom, or to feel more confident, with scores of 1 (almost never) to 4 (almost always), and current Cronbach alpha >0.87 for both age groups (Carver et al., 1989; Cooper et al., 1995).

Data Analyses

The analyses included all probands participating in their 10- to 15-year follow-up (96.9%) and offspring who between 2014 and 2019 were age 18+ and reported having experience with alcohol. Among the 243 estimated relevant offspring, 212 (87.2%) were interviewed, including 29 families with only 1 relevant offspring, 59 with 2 offspring, and 19 with 3 or more, creating a design effect of 1.66 (2.0 would indicate a potential meaningful effect of individuals per family [Muthen and Satorra, 1995]). We chose to include all offspring in analyses to maximize statistical power and because the key Table 3 uses R where each randomly selected proband was compared to randomly selected offspring in relevant regression analyses, a process repeated through 1,000 bootstrapped iterations, thus minimizing the impact of cluster effects within families. Results were also re-analyzed with 1 offspring per family. A related issue is our decision to not limit the sample to 107 proband/offspring pairs but to maximize power and better control for characteristics related to lower alcohol problem risks such as raising children, which by definition apply to all probands but an as yet unknown proportion of offspring (e.g., Staff et al., 2010; Waldron et al., 2011). Not controlling for characteristics that might contribute to raising children by using only probands and their own offspring pairs might have artificially minimized the relative number of alcohol problems in probands compared to offspring. However, we also re-analyze data using proband/offspring pairs.

Among the 651 individuals in these analyses, results were evaluated separately at about age 30 for 439 original probands and 212 drinking offspring (including 115 males). In this approach, probands and offspring from these families received the same SSAGA interview, SRE, and measures of environmental/attitudinal characteristics at about age 30 (i.e., about 25 years apart). Note that the FH of the probands used the FH method and relied solely on the proband's report, while offspring FH came directly from SSAGA-based interviews with each parent.

The search for differences between probands and offspring that might have contributed to higher alcohol problems in the second generation began in Table 1 with a simple comparison of characteristics of members of the 2 generations using ANOVA for means/standard deviations (SD) for continuous variables and chi-square (χ^2) for categorical data. In the second approach in Table 2, intergenerational differences from Table 1 were entered into 4 separate backward elimination linear regression analyses for probands, combined male and female offspring, males alone, and for females alone using the dependent variable (DV) of lifetime alcohol problems. Number of problems was used rather than presence/absence of lifetime AUDs to take advantage of the wider range of scores for the continuous outcome measure. In these analyses, maximum likelihood procedures were used to address missing data, and skew was mitigated with square root, logarithmic, and inverse-reflected transformations where needed.

In the third approach, the DV for regression analyses in Table 3 was the *difference* in the number of alcohol problems across probands and offspring when each group was about age 30. That difference across generations was generated through aggregating 1,000 bootstraps, without replacement, in R (R Core Team, 2013) by subtracting the probands' number of DSM-IV alcohol problems from the those reported by offspring (Schuckit et al., 2019). Here, subsets of the sample were created by using the sample_n function within the dplyr package in R (Wickham et al., 2018), which randomly selected an equal number of observations of probands and offspring. The cases were paired and a difference score for number of alcohol problems was calculated. Linear modeling and stepwise

Table 1. Comparisons of Proband Characteristics at Age 30 With the Same Characteristics in Male and Female Offspring at Age 28

Variables	1 All Probands (N = 439) [mean (SD), %]	2 All Offspring (N = 212) [mean (SD), %]	3 Proband versus Offspring Statistics [F-test, χ^2]	4 Male Offspring (N = 115) [mean (SD), %]	5 Proband versus Male Statistics [F-test, χ^2]	6 Female Offspring (N = 97) [mean (SD), %]	7 Proband versus Female Statistics [F-test, χ^2]
Demography							
Age	31.3 (2.89)	27.9 (5.04)	86.51***	27.6 (5.09)	88.60***	28.1 (5.00)	50.67***
European American %	98.4	94.8	6.87**	93.9	7.47**	95.9	2.53
Ever married %	63.6	36.3	42.78***	32.2	36.62***	41.2	16.42***
Any religion %	54.4	41.5	9.56**	35.7	12.87***	48.5	1.14
Education (years)	17.3 (2.20)	15.6 (2.37)	79.20***	15.2 (2.50)	76.71***	16.1 (2.13)	24.21***
Alcohol							
Family history AUD %	55.6	45.3	6.08*	43.5	5.36*	47.4	2.13
SRE-5	3.4 (1.55)	3.0 (1.35)	8.24**	3.3 (1.39)	0.01	2.6 (1.20)	21.20***
SRE-T	4.4 (1.71)	3.8 (1.70)	15.29***	4.4 (1.86)	0.03	3.3 (1.23)	42.04***
Maximum drinks	9.7 (5.20)	8.4 (4.22)	8.35**	9.8 (4.57)	0.17	6.8 (3.02)	27.41***
Number of 11 DSM items	1.6 (1.98)	2.7 (2.75)	14.88***	3.2 (2.91)	23.09***	2.1 (2.41)	1.12
Ever AUD %	31.0	55.1	36.60***	63.5	40.97***	46.4	8.44**
Drugs							
Use tobacco %	13.0	22.6	9.86**	25.2	10.40***	19.6	2.85
Use CB %	81.8	67.9	15.62***	72.2	5.21*	62.9	16.72***
Use drugs other than CB %	58.1	32.5	37.30***	40.9	10.89***	22.7	39.88***
SUD CB %	9.8	22.2	18.38***	28.7	27.50***	14.4	1.80
SUD drugs other than CB %	9.6	5.2	3.67*	7.8	0.33	2.1	5.94*
Personality							
Zuckerman total	20.0 (5.50)	19.2 (6.37)	2.99	20.0 (6.38)	0.02	18.3 (6.28)	7.60**
Zuckerman disinhibition	4.2 (2.32)	3.9 (2.56)	2.14	4.2 (2.54)	0.08	3.7 (2.57)	4.42*
Karolinska impulsivity	20.0 (2.86)	20.8 (3.38)	10.35***	21.4 (3.22)	21.89***	20.1 (3.43)	0.13
Potential mediators							
Drink to cope	1.5 (0.46)	1.4 (0.88)	7.07**	1.4 (0.91)	6.06*	1.4 (0.85)	4.38*
Peer\maximum drinks	1.6 (0.87)	1.5 (1.25)	15.24***	1.5 (1.22)	12.22***	1.5 (1.01)	8.47**
AEQ changes in social behavior subscale	3.0 (0.82)	3.2 (0.72)	9.35**	3.2 (0.73)	6.38*	3.2 (0.70)	4.60*
AEQ increased arousal subscale	2.7 (0.60)	2.8 (0.57)	10.57***	2.8 (0.57)	7.74**	2.8 (0.50)	4.73*

AEQ, Alcohol Expectancy Questionnaire; AUD, alcohol use disorder; CB, cannabis; DSM, Diagnostic and Statistical Manual; (SD), standard deviation; SRE-5, Self-Report of the Effects of Alcohol during the first 5 times of drinking; SRE-T, Total Self-Report of the Effects of Alcohol including during the first 5 times of drinking, recent 3 months of drinking, and during the time of heaviest drinking; SUD, substance use disorder.

*$p < 0.05$, **$p < 0.01$; ***$p < 0.001$.

backward regressions were done using the subset of observations within R. The mean-adjusted R^2 from all 1,000 bootstraps was calculated using the fisherz and fisherz2r functions in the psych package (Revelle, 2018) and the mean function within R. Standardized Beta weights were generated using the lm.beta function (Fletcher, 2012). The mean p-values from all 1,000 bootstraps were calculated with the meanp function from the metap package (Dewey, 2019). In these analyses, in the absence of generally accepted guidelines for the optimal number of bootstrapped regression analyses to which a variable must have entered significantly, we used an approach similar to that invoked in 1 step of latent class analyses, and evaluated the clinical implications and internal consistency of results when a priori values of 100, 200, and 300 iterations marked the cutoff for inclusion of a variable in Table 3. Requiring inclusion in only 100 of the 1,000 iterations in Table 3 resulted in all variables from Table 2 contributing significantly and requiring 300 iterations entered for Table 3 resulted in only 2 items entering (SRE-5 and using drugs other than cannabis). Thus, we required variables needed to have added significantly to 200 iterations to be included in Table 3.

RESULTS

Subject Characteristics and Comparisons Across Subgroups

Table 1 presents an overview of the characteristics of the 651 SDPS participants involved in the current analyses. These include 439 male probands in data column 1, all of whom had experience with alcohol when recruited, and 212 combined male and female drinking offspring in data column 2. As shown in the table, at about age 30 the probands were predominantly well-educated, married, EA drinkers who endorsed having experienced an average of 1.6 DSM-IV criterion items in their lifetime and a lifetime rate of AUDs of 31% at that stage of the study. The combined male and female drinking offspring, at an average age of 28, were also relatively well educated and primarily of EA heritage, endorsed an average of 2.7 DSM-IV AUD criterion items, and 55% had ever fulfilled criteria for an AUD.

Table 2. Linear Regression Equations [Backward Elimination] Predicting Number of Alcohol Problems Separately within Probands, All Offspring, and Male and Female Offspring (Standardized Betas)

Variables	Probands (N = 439)	All offspring (N = 212)	Male offspring (N = 115)	Female offspring (N = 97)
Demography				
Age				
European American				
Ever married	−0.15***			
Any religion				
Education (years)				
Alcohol				
Family history AUD	0.08*	0.12*		0.19*
SRE-5	0.10*	0.40***	0.56***	0.32***
Drugs				
Use tobacco	0.11**			
Use CB				
Use drugs other than CB	0.17***	0.26***	0.22**	0.24**
SUD CB				
SUD drugs other than CB	0.17***			
Personality				
Karolinska impulsivity		0.14**	0.15*	
Potential mediators				
Drink to cope	0.26***			
Peer maximum drinks	0.15***		0.18*	
AEQ changes in social behavior subscale		0.20***		0.30***
AEQ increased arousal subscale				
R^2	0.35***	0.45***	0.48***	0.39***

AEQ, Alcohol Expectancy Questionnaire; AUD, alcohol use disorder; CB, cannabis; SRE-5, Self-Report of the Effects of Alcohol during the first 5 times of drinking; SUD, substance use disorder; Empty cells, not significant.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 3. One Thousand Bootstrapped Linear Regression Equations [Backward Elimination] Predicting Differences in Number of Alcohol Problems between Offspring and Probands[a]

	All offspring N = 106		Male offspring N = 57		Female offspring N = 48	
Variables	#	β	#	β	#	β
Demography (NA)						
Alcohol						
Family history AUD	182	0.22*	124	0.24*	234	0.32*
SRE-5	959	0.34**	863	0.41**	435	0.40*
Drugs						
Use drugs other than CB	428	0.28*	197	0.32*	292	0.40*
Personality						
Karolinska impulsivity	212	0.20*	144	0.26*	199	0.28*
Potential mediators						
Peer maximum drinks	209	0.20*	145	0.21*	194	0.31*
AEQ changes in social behavior subscale	277	0.28*	143	0.30*	277	0.43*
Average R^2	0.29		0.35		0.35	

Variable inclusion in the table requires # ≥200 in at least 1 of the 3 analyses.
β = Averaged Standardized Beta.
AEQ, Alcohol Expectancy Questionnaire; AUD, alcohol use disorder; CB, cannabis; SRE-5, Self-Report of the Effects of Alcohol during the first 5 times of drinking.
[a]# = # of 1,000 bootstraps where the variable remained in the model.
*$p < 0.05$; **$p < 0.01$.

Relevant to Hypothesis 1, the current analyses were prompted by that higher rate of alcohol-related problems and AUDs in the younger generation shown in Table 1. Comparisons of probands and the combined group of all offspring also revealed that, despite the higher number of alcohol problems and proportion with AUDs for offspring, the combined male and female offspring were less likely than probands to have a parent with an AUD, required fewer drinks for effects on the SRE-5 and SRE-T, and reported lower maximum drinks per occasion. Additional differences across the older and younger generations regarding characteristics that might relate to differences in drinking problems and AUDs included offspring demonstrating lower values for some drug-related items, but higher values for smoking and substance use disorders related to cannabis. In addition, while probands had higher values for Drinking to Cope and perceived peer maximum drinks, offspring had higher values for impulsivity and both alcohol expectancy AEQ subscales.

Recognizing the male/female differences in alcohol use and problems discussed in the Introduction, and to help interpret results when all probands are male, the remaining columns in Table 1 present data for male and female offspring separately. Relevant to Hypothesis 2, compared to female offspring male offspring reported more alcohol problems, $F = 7.05$, $p < 0.001$, and higher proportions had ever met criteria for AUDs ($\chi^2 = 6.22$, $p < 0.02$). Additional sex differences relevant to analyses in Tables 2 and 3 include higher scores for male offspring compared to female for SRE-5, $F = 15.16$, $p < 0.001$, SRE-T, $F = 23.69$, $p < 0.001$, impulsivity, $F = 9.10$, $p < 0.01$, and a substance use disorder for cannabis ($\chi^2 = 6.20$, $p < 0.02$). The pattern of differences between probands and male offspring was similar to those for the full sample of offspring except for the greater similarity across generations for maximum drinks and SRE scores.

Most probands versus *female offspring* findings were consistent with results for proband versus combined male and female offspring, but female offspring impulsivity values were not significantly higher than those for probands.

Summarizing some key results from Table 1, direct comparisons *across* probands and offspring identified several characteristics that might have contributed to higher alcohol problems in offspring. These included higher alcohol expectancies in both male and female offspring compared to probands and higher impulsivity in male offspring. The similarity of impulsivity for female offspring and the all-male proband group is also worth noting in light of the expected higher impulsivity in males noted in the Introduction.

Prediction of Numbers of Alcohol Problems Within Generations

The next step in the search for items that might have contributed to higher rates of alcohol problems in offspring evaluated whether variables that differed *across* proband and offspring generations in Table 1 related differently to the number of lifetime DSM-IV alcohol problems *within* each group, as shown in Table 2. The number of alcohol problems endorsed was selected as the DV in Table 2 because that outcome had a wider range of scores than the presence versus absence of an AUD and might be a more sensitive measure of alcohol impairment. In regression equations with R^2 values between 0.35 and 0.48, the potential predictors included all relevant items from Table 1 except for variables that greatly overlapped with the outcome (e.g., maximum drinks) or with another predictor (i.e., we selected SRE-5 over SRE-T). In Table 2, the Beta weight for SRE-5 was significantly higher in offspring than in proband equations (e.g., for probands vs. male offspring, $z = 3.84$, $p < 0.001$), indicating that even though probands needed a higher number of drinks for effects overall in Table 1, a higher SRE-5 score was more robustly related to higher numbers of alcohol problems for offspring than for probands. While not shown in the table, when SRE-T was substituted for the closely correlated SRE-5 in the regression analysis, the result regarding the performance of SRE was similar to that shown in Table 2. Two additional variables of interest in Table 2 were Social Behavior expectancies and impulsivity, each of which contributed significantly to regression analyses predicting alcohol problems in the all offspring group but not in probands. Although several items were significant for probands but not offspring, a higher value for a mediator of the effects of LR or impulsivity in probands compared to offspring would be unlikely to have enhanced alcohol problem risk in the younger generation (i.e., tobacco use, a substance use disorder on a drug other than cannabis and Drinking to Cope). One item, having never been married, might have contributed to the problem risk for probands but not offspring as a reflection of the higher rate of marriage in the third decade of life in probands compared to offspring.

Predictors of Differences in Alcohol Problems Between Generations

Table 3 analyses more directly evaluate predictors of the *difference* in numbers of alcohol problems between probands and offspring through regression analyses where the DV was the difference score. That outcome was measured by subtracting the number of alcohol problems endorsed by a proband from the number of alcohol problems reported by an offspring in 1,000 bootstrapped backward elimination linear regression equations. For example, in the first data column of Table 3, the first of 1,000 regression analyses began by randomly selecting 106 probands and matching each selected proband with a randomly selected offspring. Within each of the 1,000 regression analyses, once a proband and an offspring had been used, they were deleted (not replaced) from the pool in run 1 of 1,000. The matched pairs in run 1 were then used for a regression analysis that determined which of the predictors were significant along with associated Beta weights within the regression analysis. Subsequently, for run 2 of 1,000 (998 runs to go) all probands and offspring were returned to the pool, a new group of 106 random probands were selected, these were each randomly matched with an offspring, a new regression analysis was run with these new 106 pairs, and so on 1,000 times. Then, predictors that significantly contributed to at least 200 of the 1,000 runs for combined offspring, and/or male and/or female offspring were used to create Table 3. In Table 3, data are first presented regarding the number of bootstraps of proband/offspring differences where the variable added significantly to the regression equation, followed by the average standardized Beta weight for that variable across the 1,000 regression analysis. Additionally regarding sex, hierarchical linear regression analyses were run for the combined offspring analyses in both Tables 2 and 3, entering the 2 main effects followed by an interaction term, and no interaction with sex was significant.

The data in Table 3 demonstrate that all 3 of the offspring variables highlighted as potentially relevant to the higher number of alcohol problems in offspring in Tables 1 and 2 (SRE, impulsivity, and alcohol expectancy subscale scores) significantly contributed to the regression analyses in equations that accounted for averages of 29 to 35% of the variance explained (R^2). The highest Beta weight across all offspring, males only and females only, and the highest average number of significant contributions to the 1,000 regression analyses as a predictor of a higher number of alcohol problems in offspring compared to probands was seen for SRE-5. Tied for second highest average Beta weights and having the second highest number of regression analyses with significant contributions was the AEQ Social Behavior score, while lower average Beta weights and numbers of regressions entered were seen for impulsivity.

An additional iteration of Table 3 was carried out where the analyses were reevaluated when only 1 offspring was selected per family (the oldest drinking son or daughter). Here, using 53 offspring the predictors that contributed

significantly to the regression analyses were almost identical to those listed in Table 3, with $R^2 = 0.35$. The only difference was that the expectancy score that entered was Arousal, rather than Social Behavior. Note that those 2 expectancy values correlated at 0.72, and if the analysis was rerun without Arousal, Social Behavior became significant and the R^2 remained 0.35. A second iteration of Table 3 used the R approach for 107 father/offspring pairs, again limiting the analyses to 1 offspring per family. Once again, the results were almost identical to Table 3, with the only exceptions being FH (note that FH differences across father/offspring pairs are difficult to interpret), and the addition of a significant value for having a cannabis use disorder.

Other offspring characteristic that added significantly to the prediction of the higher number of alcohol problems in offspring included the proportion of offspring who had used illicit drugs other than cannabis, and for the iteration of Table 3 that limited analyses to father–offspring pairs, a cannabis use disorder diagnosis. The first of these predictors was significantly higher in probands in Table 1 (the opposite of what might have been considered as a predictor of higher alcohol problems in offspring), but Beta weights were similar for probands and offspring for this variable in Table 2. Other items in Table 3 that evidenced less-consistent hints of potential contributions to generational differences in offspring alcohol problems in Tables 1 and 2 but contributed to Table 3 included a FH of AUDs and perceived peer maximum drinks. Results for male and female offspring separately in data columns 2 and 3 of Table 3 were generally similar to the combined group of offspring regarding variables related to higher alcohol problems in the younger generation.

While not shown in the table, the data in Table 3 were also re-analyzed in logistic regression analyses using the presence or absence of a lifetime DSM-IV AUD as the DV. The results for the all offspring group were similar to those shown in Table 3 with all the same alcohol, drug, personality, and potential mediators entering 200 or more of the bootstrapped regression equations. Here, 1 additional variable predicted AUDs, a history of a substance use disorder diagnosis for drugs other than cannabis. Also similar to Table 3, among the most robust predictors of the difference in proportions with AUDs in probands versus offspring were the SRE-5 (OR = 1.63), Social Behavior expectancies (OR = 1.60), and impulsivity (OR = 1.40), along with using drugs other than cannabis (OR = 1.55), perceived peer maximum drinks (OR = 1.43), and an AUD FH (OR = 1.40). Separate analyses for males and females for the dichotomous presence or absence of AUDs could not be carried out because of problems with separation in logistic regressions for several variables within the relatively smaller sex-based groups.

DISCUSSION

The number of alcohol problems and rates of AUDs was almost 2-fold higher in the second generation of SDPS families compared to original probands. Reasons for the increase in alcohol-related problems in younger generations in recent decades in the literature (e.g., Grant et al., 2017) and in this study are likely to reflect changes in many different characteristics over the 20 to 25 years between generations. The current analyses were limited to the measures that had been used in both proband and offspring generations, and it is likely that these are only a few of the many characteristics described in the Introduction that might have contributed to the generational differences in numbers of alcohol problems. Our current search for factors that might have contributed to the enhanced rates of problems in SDPS offspring included the following: (i) comparisons of characteristics *across* proband and offspring groups (Table 1); (ii) comparisons of variables related to the number of alcohol problems *within* probands and *within* offspring (Table 2); and (iii) direct evaluations of characteristics related to generational *differences* in the number of alcohol problems reported by probands and offspring (Table 3).

Focusing on patterns across all 3 steps in these analyses, the current results highlighted potential roles in the higher rates of alcohol problems in offspring for 3 variables. The first was the more robust relationship to alcohol problems in offspring by the need for more drinks for effects on the SRE (i.e., a lower LR per drink; Schuckit, 2018). Although SRE values were not higher in offspring compared to probands in Table 1, regression analyses in Table 2 revealed significantly higher Beta weights for SRE-5 in predicting alcohol problems for offspring. In addition, in Table 3 Beta weights for SRE-5 were among the highest of any variable regarding its contribution to the different numbers of alcohol problems across probands and offspring. Potential reasons why a low LR might have a more robust relationship to alcohol problems in the offspring are discussed in a recent paper (Schuckit et al., 2019) and immediately below.

Because SRE values in probands and offspring were similar in Table 1, but the relationships of SRE to alcohol problems were more robust in the younger generation in Tables 2 and 3, those differences in problems across tables might reflect the effect of a second variable, alcohol expectancies. In past research by our group, AEQ subscales mediated the effect of LR on drinking behaviors (e.g., Schuckit et al., 2009, 2011). Higher values for alcohol expectancies relating to beliefs that drinking makes parties more fun and allows people to better stand up for themselves are characteristics that might facilitate higher alcohol intake in people who have few effects at low alcohol doses but who can become very intoxicated at high BACs (Brown et al., 1987; Schuckit, 2018). In the current analyses, higher scores for AEQ subscales were seen for offspring in Tables 1 and 2 and in Table 3 contributed robustly to the higher number of alcohol problems in offspring. The high correlation between expectancy measures of Social Behavior and Arousal makes it difficult to tell which of these values is more important as a mediator of the impact of a low LR of drinking problems.

Regarding the third notable variable, impulsivity, the relationship to alcohol problems for this propensity to make

spur-of-the-moment decisions without adequate consideration of consequences is well documented in the literature (e.g., Dick et al., 2013; Moeller et al., 2001; Reilly et al., 2017; Sher et al., 1999, 2005). In Table 1, the full group of 212 offspring and the male offspring group had significantly higher impulsivity scores than probands. The fact that males often score higher on impulsivity than females (Weafer and deWit, 2014; Weinstein and Dannon, 2015) might indicate that even the slightly higher scores for this variable in female offspring compared to probands might be meaningful. Further indications of the potential importance of impulsivity to the higher rate of alcohol problems in offspring, especially for males, come from Table 2, where impulsivity contributed significantly to regression analyses predicting alcohol problems within the all offspring group and in male offspring but was not significant for probands. Furthermore, impulsivity added significantly to the prediction of the generational difference in alcohol problems in Table 3. Thus, differences across generations for this characteristic might have contributed to the higher number of alcohol problems in offspring both directly and through relationships with additional characteristics such as alcohol expectancies (Dick et al., 2013; Kaiser et al., 2016; Meyers et al., 2014; Salvatore et al., 2015; Wardell et al., 2015). Several issues might have contributed to the modestly, but significantly, higher impulsivity scores in the offspring. First, it is possible that maternal families or the mother's practices during pregnancy (e.g., smoking and diet) might have contributed to the modest, but significantly higher impulsivity in the offspring (Brook et al., 2006; Hibbeln et al., 2017). Second, the drinking itself in the offspring generation, perhaps reflecting cross-generational differences in environment and attitudes, might have contributed to higher impulsivity scores (Chao et al., 2017).

Looking at the pattern of results across all 3 tables, consistent with Hypothesis 2, male and female offspring had many similarities in these analyses. Differences across the sexes might be inferred in Table 2 for the AEQ subscale scores, but values were similar across the sexes in Tables 1 and 3. Also, as might be expected from the literature, although impulsivity scores were significantly higher for males in Table 1 and impulsivity added significantly to the regression analyses within males but not females in Table 2, in Table 3 there were no notable differences for males and females regarding relationships of impulsivity to the male/female differences in alcohol problems. Overall, our interpretation is that most variables performed similarly across the sexes in these analyses.

Finally, it is important to highlight several caveats. First, the data gave cross-sectional snapshots of probands and offspring at about the same age, and future prospective testing of these results is needed. Second, the SRE was developed and used in probands when they were about age 30 at a time when the possible effects of higher stimulation at rising BACs had not been as well established as an AUD risk factor, and, thus, stimulation questions were not included in the SRE and could not be used in the current analyses. In addition, SRE values change moderately over time, and while the scores on this measure relate significantly to drinking practices and problems in a wide range of age groups, it is likely that correlations diminish moderately with longer periods of time that elapse after the earliest drinking experiences. Third, for reasons explained in additional papers (Schuckit and Gold, 1988) the original probands recruited in the decade following 1978 are males, and although female spouses were evaluated for SRE values, cost constraints did not allow for recording most of the characteristics in Table 1 in those women. Therefore, we cannot control for the impact of the mother on alcohol problems in the offspring, although prior work indicated that only 9% of the spouses had a lifetime AUD and only 20% had an AUD parent (Schuckit et al., 2002). Fourth, to take advantage of the wider range of scores inherent in the number of DSM-IV AUD items, that continuous variable, rather than a dichotomous DV of the presence of an AUD, was the focus of the analyses, although similar findings were recorded when AUD was tested as the primary outcome. Fifth, there are potential biases in our decision to use all probands and all offspring in these analyses and to not limit data to proband/offspring pairs, although similar results were observed when analyses were limited to 1 offspring per family or when only probands and their own offspring were used. Sixth, the decision to require in Table 3 that a predictor of generational differences in alcohol problems had to contribute significantly to 200 bootstrapped equations was made using an approach similar to a step in latent class analyses and there are no established guidelines for this decision. Finally, the analyses were limited to variables that had been measured in both generations and there are many additional variables, such as social norms (Lewis et al., 2015) that could not be used.

In conclusion, despite these caveats, the current analyses offer preliminary data regarding variables that might have contributed to the higher numbers of alcohol problems in recent generations, including a greater impact of a low LR to alcohol, higher impulsivity, and more positive alcohol expectancies.

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CONFLICT OF INTEREST

No author for this paper has a conflict of interest regarding the contents of the paper.

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