A Twin Study of Genetic Influences on Diurnal Preference and Risk for Alcohol Use Outcomes

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SCIENTIFIC INVESTIGATIONS

Objective: The population-based University of Washington Twin Registry (UWTR) was used to examine (1) genetic influences on chronobiology and (2) whether these genetic factors influence alcohol-use phenotypes.

Methods: We used a reduced Horne-Östberg Morningness-Eveningness Questionnaire (rMEQ) to survey UWTR participants for diurnal preference. Frequency and quantity of alcohol use, as well as binge drinking (6+ drinks per occasion), were assessed on a 5-point Likert scale. Both diurnal preference and alcohol use were self-reported. Twin data were analyzed by using structural equation models.

Results: The sample consisted of 2,945 participants (mean age = 36.4 years), including 1,127 same-sex and opposite-sex twin pairs and 691 individual twins. The rMEQ range was 4-25, with a mean score of 15.3 (SD 4.0). Diurnal "morning types" comprised 30.7% (N = 903) of participants, while 17.4% (N = 513) were "evening types." Regarding alcohol use, 21.2% (N = 624) reported never drinking. Among drinkers, 35.7% (N = 829) reported ≥ 3 drinks per occasion and 48.1% (N = 1,116) reported at least one instance of binge drinking. Genetic influences accounted for 37% of the variance in diurnal preference, with the remaining 63% due to non-shared environmental influences. Genetic propensities toward diurnal eveningness were significantly associated with increased alcohol quantity (β = -0.17; SE = 0.05, p < 0.001) and increased binge drinking (β = -0.19; SE = 0.04, p < 0.001), but not with frequency of alcohol use. Environmental paths between diurnal preference and alcohol use phenotypes were not significant.

Conclusions: Genetic influences on diurnal preference confer elevated risk for problematic alcohol use, including increased quantity and binge drinking. Differences in circadian rhythm may be an important and understudied pathway of risk for genetic influences on alcohol use.

Keywords: Twins, monozygotic, dizygotic, alcohol, circadian, diurnal

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Circadian rhythms are biological processes, such as the human sleep-wake cycle, with an endogenous, entrainable oscillation of roughly 24 hours. The hypothalamic suprachiasmatic nucleus is the primary circadian pacemaker, ensuring a proper duration and consistent timing of sleep. Healthy sleep arises from an effective interaction between the sleep homeostat, which increases sleep propensity as a function of prior wakefulness, and the 24-hour circadian alerting signal generated by the suprachiasmatic nucleus.[1] In practical terms, this interaction results in a wide range of circadian functioning (also known as "diurnal preference" or "chronotype"), from morning types to evening types. Morning types go to bed early and function best in the early daytime hours, whereas evening types go to bed in the early morning hours and function best at later times in the day or evening.[2] Twin and molecular genetic studies consistently show that diurnal preference is influenced by genetic factors, with heritability between 40% and 54%.[3-12]

Recent research has focused on the role of circadian rhythms in health and disease. Circadian clock disruptions, often observed in shift work disorder, are associated with numerous medical conditions, including cardiovascular disease,[13-15] cancer,[16-18] and untoward pregnancy outcomes.[19,20] It is less clear whether

BRIEF SUMMARY

Current Knowledge/Study Rationale: Preliminary evidence suggests that diurnal preference is a contributing psychological factor in a multi-causal model of alcohol consumption. The extent to which the relationship between diurnal preference and alcohol use is driven by common underlying genetic variants is unknown.

Study Impact: This study shows that genetic factors favoring evening-type diurnal preference confer increased risk of binge drinking and increased alcohol consumption. This finding suggests that biological differences in circadian rhythm may be an important pathway of risk for genetic factors that promote alcohol use.

diurnal preference alone portends specific health outcomes. Preliminary evidence suggests that evening-type diurnal preference is associated with poor diet[21] and depression[22] and has adverse effects on measures of quality of life in adolescents.[23] We previously showed an association between evening type and habitual short and long sleep duration in a twin sample.[12] Since both short and long sleep are associated with adverse health outcomes,[24-34] these findings suggest that the evening type may represent an endophenotype for poor health.

Preliminary evidence also suggests that diurnal preference influences alcohol use, such that evening types consume more

alcohol than morning types.[35-37] Alcohol consumption is associated with a single-nucleotide polymorphism in NPAS2, a gene involved in the autoregulatory transcription/translation feedback loop that drives circadian rhythmicity.[38] Evening type is also correlated with novelty-seeking, which is thought to be associated with behavior activation by low basal dopaminergic activity in the brain.[39,40] This may lead to addictive behaviors, such as alcohol abuse or dependence, in an effort to enhance dopamine levels.[41] These preliminary studies suggest that diurnal preference is a contributing psychological factor in a multi-causal model of alcohol consumption. The extent to which the relationship between diurnal preference and alcohol use is driven by common underlying genetic variants has yet to be determined. Therefore, the goals of this twin study were to (1) determine the magnitude of genetic and environmental influences on diurnal preference and (2) evaluate the extent to which genetic influences on diurnal preference confer risk for alcohol use. We hypothesized that genetic predispositions toward eveningness would be associated with more problematic alcohol use, although the dearth of previous behavioral genetic research on this topic made our hypotheses necessarily speculative.

METHODS

University of Washington Twin Registry

The University of Washington Twin Registry is a community-based sample of twins constructed with data provided by the Washington State Department of Licensing. All data collection procedures were approved by the University of Washington Institutional Review Board. The minimum age for participation is 18, and < 5% of participants are older than age 66. As of April 2013, the Registry contained more than 7,500 twin pairs. Participants' zygosity is determined by using validated self-report methods, with an accuracy ≥ 95%.[42,43] Every participant completes a recruitment survey. In 2006 and 2008, an additional health survey that included items on diurnal preference and alcohol use was mailed to more than 4,000 enrolled twins. Further details on the characteristics of Registry participants are available elsewhere.[44,45]

Our study sample consisted of 2,945 individuals, including 1,127 twin pairs (200 monozygotic [MZ] male [17.7%], 82 dizygotic [DZ] male [7.3%], 432 MZ female [38.3%], 215 DZ female [19.1%], and 198 DZ opposite-sex [17.6%]), as well as 691 individual twins who participated without their co-twins. All twin pairs were raised together. Data from incomplete twin pairs were retained because they inform the within-person correlations between diurnal preference and alcohol use. Data collection procedures were approved by the University of Washington Institutional Review Board. The sex of individual twins closely mirrored that observed in complete twin pairs.

Measures

Diurnal Preference

Diurnal preference was measured by using the reduced Morningness-Eveningness Questionnaire (rMEQ),[46] a shortened version of the Horne and Östberg Morningness-Eveningness Questionnaire.[47] The rMEQ contains 5 items that assess aspects of the morning-eveningness dimension (for example, "at what time in the evening do you feel tired and in need of sleep?"), rated on a 5-point Likert scale. Responses to each question are summed to give a total rMEQ score between 4 and 25, with higher scores indicating stronger morningness preference. We defined morning types as those with a score ≥ 18, and evening types as those with a score ≤ 11. The rMEQ has demonstrated good internal reliability and validity compared to the full Morningness-Eveningness Questionnaire.[48]

Alcohol Use Phenotypes

Aspects of alcohol use were determined by using the Registry questionnaire. Alcohol frequency was ascertained by asking, "How often do you have a drink containing alcohol?" Potential responses were never, monthly or less, 2-4 times a month, 2-3 times a week, and ≥ 4 times a week. Alcohol quantity was ascertained by asking, "How many drinks of alcohol do you have on a typical day when you are drinking?" Potential responses were 1 or 2, 3 or 4, 5 or 6, 7 to 9, and 10 or more. Binge drinking was ascertained by asking, "How often do you have 6 or more drinks on one occasion?" Potential responses were never, less than monthly, monthly, weekly, daily, or almost daily. Responses to each of the three alcohol-related questions were scored on a scale of 1 to 5.

Sociodemographics

Age, sex, and race were self-reported. Race was dichotomized into White and non-white (American Indian, Alaska Native, Native Hawaiian, Pacific Islander, Asian, black or African American, or other) categories. Education was ascertained by the question, "What is the highest level of school you have completed?" A total of 7 responses were possible, ranging from "eighth grade or less" to "graduate or professional degree." The midpoint was "some college, but no degree or certificate."

Statistical Analysis

We began by examining zygosity-specific twin pair correlations for diurnal preference and each of the 3 alcohol use phenotypes (alcohol frequency, alcohol quantity, and binge drinking). Within-trait, cross-twin correlations (e.g., the correlation between diurnal preference in Twin A and diurnal preference in Twin B) can be used to evaluate the magnitude of genetic and environmental influences on a given phenotype. Cross-trait, cross-twin correlations (e.g., the correlation between diurnal preference in Twin A and alcohol use frequency in Twin B) can be used to evaluate the contribution of genes to the association between the phenotypes.

Next, we evaluated these questions more formally by using the software program M*plus* (Muthén & Muthén, 1998-2012, Los Angeles, CA) to fit quantitative genetic models. Specifically, we fit the bivariate twin model shown in **Figure 1**. Total variance in each of the observed phenotypes (boxes labeled "Diurnal Preference" and "Alcohol Use") was decomposed into 3 latent factors: additive genetic influences (A), shared environmental influences (C, meaning common environmental influences that make siblings similar to one another), and non-shared environmental influences (E, meaning environmental influences that are unique to each twin, plus measurement

Figure 1—Structural equation model of diurnal preference and alcohol use in adult twins
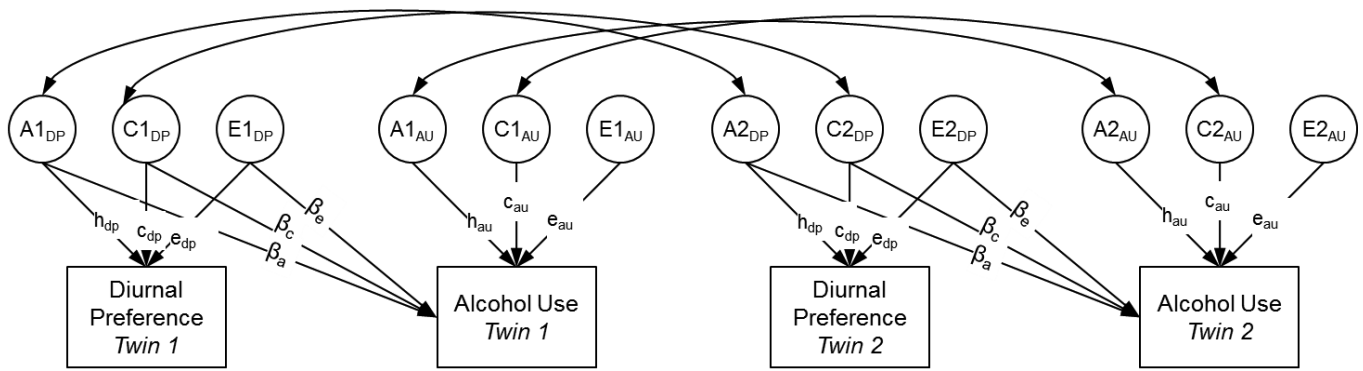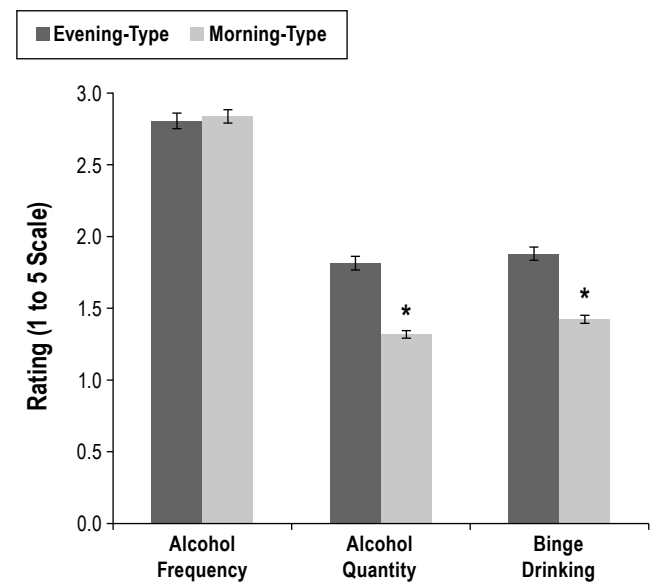

A, additive genetic variance; C, shared environmental variance; E, nonshared environmental variance. A, C, and E components standardized (mean = 0, standard deviation = 1). Correlation between A components fixed at 1.0 in monozygotic twins and 0.5 in dizygotic twins. Correlation between C components fixed to 1.0 in all twins. Correlation between E components fixed to 0 in all twins. βa, βc, and βe represent cross-paths estimating the extent to which genetic and environmental influences on diurnal preference also influence alcohol use. au, alcohol use; dp, diurnal preference.

Table 1—Sample characteristics

Demographic Characteristics	N (%)
Female	1,891 (64.2%)
White	2,607 (88.5%)
No high school degree	233 (7.9%)
≥ College degree	1,890 (64.2%)
Study Variables	**Mean (SD)**
Age (years)	36.4 (15.7)
Diurnal preference[a]	15.3 (4.02)
Alcohol use frequency[b]	2.77 (1.32)
Alcohol quantity[b]	1.49 (0.83)
Binge drinking[b]	1.59 (0.90)

MZ, monozygotic; DZ, dizygotic; SD, standard deviation. [a]The diurnal preference scale ranged from 5 to 25, with higher scores indicating more morning preference. [b]Alcohol use scales ranged from 1 to 5.

Figure 2—Alcohol use phenotypes by morning-type versus evening-type diurnal preference

Bars represent standard error around the mean. *Significant difference.

error). The ACE components for each phenotype were standardized (mean = 0, standard deviation = 1) and the paths from these components to the phenotype were estimated. The correlation between additive genetic influences (A) in the first and second member of each twin pair was fixed at 1.0 in MZ twins and 0.5 in DZ twins, consistent with genetic theory. The correlation between common environmental (C) factors was fixed at 1.0 in all pair types, whereas the correlation between unique environmental (E) factors was fixed at 0 in all pair types. Finally, alcohol use was regressed on the ACE components of diurnal preference (labeled βa, βc, βe in **Figure 1**). These cross-paths estimate the extent to which genetic and environmental influences on diurnal preference also influence alcohol use. Note that the boxes labeled "Alcohol Use" in **Figure 1** refer to each of the 3 alcohol use phenotypes, which were modeled individually. Previous authors have described the logic and parameterization of twin models in great detail.[49] All models were estimated by using full information maximum likelihood to account for missing data from incomplete twin pairs.[50] All models controlled for age, white race, and educational attainment by regressing both diurnal preference and alcohol use phenotypes on these covariates

RESULTS

Sample characteristics and descriptive statistics for all study variables are summarized in **Table 1**. Overall, the sample was composed of predominantly younger adults (mean = 36.4 years; standard deviation = 15.7; range 19-93) who were well-educated (64.2% with a college degree or higher) and predominantly white (88.5%) and female (64.2%). Morning types comprised 30.7% of participants, while evening types comprised 17.4%. Never drinking was reported by 21.2%. Among drinkers, 35.7% reported typically drinking ≥ 3 drinks, and 48.1% reported ≥ 1 occasion of binge drinking. **Figure 2** illustrates the mean levels of alcohol frequency, alcohol quantity, and binge drinking reported by morning and evening types. Morning and evening types did not significantly differ in alcohol use frequency (p = 0.66), but

Table 2—Twin correlations for diurnal preference and alcohol use phenotypes

	MZ Twin Correlations			DZ Twin Correlations			
	All	**Male**	**Female**	**All**	**Male**	**Female**	**OS**
Within-Trait Correlations							
Diurnal preference	0.50	0.57	0.46	0.30	0.27	0.18	0.44
Alcohol frequency	0.60	0.59	0.60	0.31	0.34	0.34	0.24
Alcohol quantity	0.51	0.50	0.49	0.30	0.17[ns]	0.23	0.34
Binge drinking	0.61	0.63	0.55	0.26	0.42	0.28	0.13[ns]
Cross-Trait Correlations (with Diurnal Preference)							
Alcohol frequency	0.04[ns]	0.05[ns]	0.04[ns]	-0.01[ns]	-0.04[ns]	0.02[ns]	-0.03
Alcohol quantity	-0.20	-0.28	-0.13	-0.16	-0.18[ns]	-0.05[ns]	-0.22
Binge drinking	-0.17	-0.23	-0.13	-0.17	-0.19[ns]	-0.08[ns]	-0.23

All correlations are significantly different from zero at $p < 0.05$ unless noted (ns).

Table 3—Comparisons between quantitative genetic models

Model	Fit of ACE Model (χ^2)	Fit of AE Model (χ^2)	Change in Model Fit ($\Delta\chi^2$)
Diurnal Preference → Alcohol Use Frequency	49.90 $df = 39$, $p = 0.11$	49.90 $df = 42$, $p = 0.19$	< 0.001 $df = 3$, $p = 0.99$
Diurnal Preference → Alcohol Quantity	50.69 $df = 39$, $p = 0.10$	51.03 $df = 42$, $p = 0.16$	0.34 $df = 3$, $p = 0.95$
Diurnal Preference → Binge Drinking	52.84 $df = 39$, $p = 0.07$	52.84 $df = 42$, $p = 0.12$	< 0.001 $df = 3$, $p = 0.99$

ACE = full model shown in Figure 1. AE = model in which paths from shared environmental factors (C) to phenotypes are fixed at zero.

Table 4—Results from bivariate behavioral genetic models of diurnal preference and alcohol use outcomes

Parameter	Frequency of Alcohol Use	Quantity of Alcohol Use	Binge Drinking
Genetic and Environmental Influences on Diurnal Preference			
Additive genetic (h_{dp})	0.55 (0.03)[a]	0.55 (0.03)[a]	0.55 (0.03)[a]
Non-shared environment (e_{dp})	0.72 (0.02)[a]	0.72 (0.02)[a]	0.72 (0.02)[a]
Diurnal Preference → Alcohol			
Genetic Path (β_a)	-0.06 (0.04)	-0.17 (0.05)[a]	-0.19 (0.04)[a]
Non-shared environmental path (β_e)	-0.01 (0.02)	-0.02 (0.03)	-0.01 (0.02)
Genetic and Environmental Influences Unique to Alcohol			
Additive genetic (h_{au})	0.75 (0.02)[a]	0.61 (0.03)[a]	0.72 (0.02)[a]
Non-shared environment (e_{au})	0.63 (0.02)[a]	0.73 (0.02)[a]	0.63 (0.02)[a]

Standardized parameter estimates are reported. SEs in parentheses. [a]Parameters are significantly different from zero at $p < 0.05$.

evening types consumed larger quantities ($p < 0.001$) and were more likely to report binge drinking ($p < 0.001$).

Table 2 summarizes the within-trait, cross-twin correlations for diurnal preference and alcohol use phenotypes, as well as the cross-trait, cross-twin correlations between diurnal preference and each alcohol use phenotype. Overall, the MZ correlations for each trait exceeded the DZ correlations, consistent with the presence of heritable influences on each phenotype. More specifically, descriptive heritability estimates can be calculated as $h^2 = 2*(r_{MZ} - r_{DZ})$, yielding heritabilities of 40% for diurnal preference, 58% for alcohol use frequency, 42% for alcohol quantity, and 70% for binge drinking. Similarly, the cross-trait correlations (i.e., the correlation between alcohol use in Twin A and diurnal preference in Twin B) suggest that diurnal preference is more strongly related to our measures of alcohol quantity and binge drinking than to our measures of

frequency of alcohol use. These initial descriptive results are formally assessed with the structural equation models.

Model fit comparisons for the quantitative genetic models are summarized in **Table 3**. For all alcohol use outcomes, the full "ACE" model (as illustrated in **Figure 1**) did not fit the data significantly better than a trimmed "AE" model, in which all paths from the shared environmental factors (C) to the phenotypes (c_{dp}, c_{au}, and β_c) were fixed at zero. In other words, shared environmental influences on alcohol use phenotypes, diurnal preference, and their associations were not significant. Consequently, we report standardized parameter estimates from the AE models in **Table 4**. Root mean square error of approximation (RMSEA), comparative fit index (CFI), and Tucker-Lewis Index (TLI) are alternate indices of model fit, with RMSEA values < 0.06 and CFI and TLI values > 0.95 indicating good fit.[51] The overall fit for each of the 3 AE models

was good (alcohol use frequency: RMSEA = 0.018, CFI = 0.99, TLI = 0.99; alcohol quantity: RMSEA = 0.020, CFI = 0.99, TLI = 0.99; binge drinking: RMSEA = 0.021, CFI = 0.99, TLI = 0.99).

Morning preference was significantly predicted by white race (β = 0.10, SE = 0.03, p < 0.05), higher educational attainment (β = 0.07, SE = 0.03, p < 0.05), and older age (β = 0.39, SE = 0.03, p < 0.05). Diurnal preference did not differ according to sex (males = 15.23, SD = 4.07; females = 15.28, SD = 3.94, p = 0.82). Alcohol use frequency, alcohol quantity, and binge drinking were not significantly associated with white race. Alcohol frequency was unrelated to age, but older people reported lower alcohol quantity (β = -0.01, SE = 0.002, p < 0.05) and less frequent binge drinking (β = -0.21, SE = 0.04, p < 0.05). People with higher educational attainment drank more frequently (β = 0.11, SE = 0.03, p < 0.05), but reported lower alcohol quantity per occasion (β = -0.124, SE = 0.03, p < 0.05). Educational attainment was not significantly associated with binge drinking.

After controlling for covariates, the proportion of residual variation in diurnal preference attributable to genetic influences can be calculated as the square of the genetic path (h_{dp}) divided by the sum of the squared paths ($h_{dp}^2 + e_{dp}^2$). Thus, genetic influences accounted for 37% of the variance in diurnal preference that could not be attributed to covariates, with the remaining 63% due to non-shared environmental influences. Notably, this heritability estimate is similar to that obtained in a recent study by Kuna and colleagues (41%), even though they used a different self-report instrument to assess diurnal preference.[52]

Genetic propensities toward eveningness were significantly associated with increased alcohol quantity (β_a = -0.17; SE = 0.05, p < 0.001) and increased frequency of binge drinking (β_a = -0.19; SE = 0.04, p < 0.001), but not with frequency of alcohol use. The non-shared environmental paths between diurnal preference and alcohol use phenotypes were not significant. In other words, a common set of genes influences both evening preference and elevated alcohol use, and this genetic overlap entirely accounts for the associations between diurnal preference, alcohol quantity, and binge drinking.

After accounting for variance shared with diurnal preference and with covariates, the proportions of unique variance in alcohol use frequency, alcohol quantity, and binge drinking frequency attributable to genetic influences were 59%, 41%, and 57%, respectively. The remaining variation was attributable to environmental influences unique to each twin.

DISCUSSION

We found that genetic influences on diurnal preference conferred increased risk of problematic alcohol use. Evening-type diurnal preference, alcohol quantity, and binge drinking frequency were linked by a common set of genes that entirely encompasses the association among these phenotypes. Common environmental influences were negligible, suggesting that behavior learned in early life with regard to chronotype is unrelated to familial attitudes about alcohol use—in other words, chronotype and attitudes about alcohol do not co-segregate.

Work schedules that start early in the day are most suitable for morning types. For evening types, the combination of late

bedtimes driven by the endogenous clock and early waking times dictated by social factors during the work week results in short sleep and sleep debt, for which they compensate by extending sleep duration on weekends.[53-55] This serves to reduce sleep quality and increase daytime sleepiness in evening types and drive associations between evening-type diurnal preference and untoward health outcomes, including psychological and psychosomatic disturbances.[53,56-58] We found that evening-type twins endorsed larger quantities of alcohol consumed and more frequent binge drinking than morning-type twins, a finding consistent with previous studies.[35,56,59] Alcohol consumption can represent behavioral manifestations of trouble coping with social demands,[60] such as the struggles experienced by evening types who are obliged to rise early. This social situation highlights the importance of our findings for the health of evening-type twins and suggests that evening-type diurnal preference in modern society may be innately unhealthy and lead to poor health choices.

Alcohol abuse in the US exacts over $230 billion annually in costs related to crime, lost work productivity, and healthcare, amounting to 2.7% of the US gross domestic product.[61,62] Alcohol consumption causes 3.8% of all global deaths and is responsible for 4.6% of global disability-adjusted life-years, a composite measure of total years of healthy life lost.[62] The damage to social relationships caused by alcohol abuse is harder to quantify, but no less substantial. In this context, our findings take on increased importance, as they have the potential to inform interventions to improve public and personal health. Social initiatives aimed at making work timing and other social activities more flexible for a broader range of chronotypes may reduce troublesome alcohol use. Also, elucidation of shared genetic pathways by future research may yield opportunities to develop targeted therapeutic agents that can reduce the risk of alcohol abuse in evening types.

The human circadian clock is maintained by a set of genes (CLOCK, BMAL1, PER 1, 2, and 3, CRY 1 and 2, TIM, and NPAS2) in the suprachiasmatic nucleus that control circadian rhythms, and thus diurnal preference, through a transcriptional, translational feedback loop.[63] Clock genes not only control circadian rhythms, but also rhythmically regulate nearly 10,000 mammalian genes in multiple tissues involving numerous biological processes.[64] NPAS2 is associated with average weekly alcohol intake,[38] and polymorphisms in the CLOCK, BMAL1, PER3, and TIM genes are associated with susceptibility to mood disorders such as depression,[65-68] a common risk factor for alcohol abuse.[69] Polymorphisms in the serotonin transporter gene are associated with hazardous drinking in certain environmental circumstances,[70] and this monoamine neurotransmitter is a key component of sleep/wake REM/NREM brain physiology.[71] Evening-type diurnal preference is linked with novelty seeking, a potential signal of reduced dopaminergic activity,[39,40] while dopamine promotes wakefulness and influences sleep stages.[72] These are but a few of the many potential genes and pathways that may constitute the shared genetic influences on evening-type diurnal preference and alcohol use outcomes. Future twin studies have the potential to reveal these genes and pathways by inserting polymorphisms of interest into bivariate genetic models of circadian type and alcohol use and observing the effect on the shared genetic estimates in the model.

Several issues about our study warrant discussion. Our twins were predominantly younger adult white women, and therefore our results should be applied to the general population with caution. However, this limitation is tempered by the fact our sample was derived from the community and not from a clinical population seeking healthcare, thus increasing the generalizability of our results. Subjective measures that enable the extrapolation of circadian phase, such as sleep logs, can accurately predict self-reported circadian type,[73] although direct comparisons of rMEQ scores with objective measures, such as actigraphy, are lacking. Self-reported alcohol use phenotypes are, of course, subject to biases and errors in reporting; however, there is no clear alternative to self-report for measuring alcohol use in the "real world" in humans. It would be interesting for future research to examine the relation between sleep and alcohol using ecological momentary assessment technologies,[74] which can yield data less subject to retrospective recall biases. Increased frequency of alcohol use was not associated with genetic propensity toward diurnal eveningness. This suggests that frequency of alcohol use represents a different aspect of alcohol consumption than the potentially more problematic constructs of increased quantity and binging which imply a lack of control of alcohol use. Lastly, diurnal preference was assigned based on a single measure, but it may represent a developmental state more than a trait. However, our analysis was age adjusted to account for this issue.

CONCLUSIONS

To our knowledge, this is the first study to show that genetic factors favoring evening-type diurnal preference confer increased risk of unhealthy phenotypes, namely binge drinking and increased alcohol consumption. This finding suggests that biological differences in circadian rhythm may be an important pathway of risk for genetic factors that promote alcohol use. It also provides further evidence that evening-type diurnal preference is an endophenotype of poor health. From a societal perspective, adjustment of school and work times to be more tolerant of evening-type diurnal preference may pay dividends at the public health level.

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SUBMISSION & CORRESPONDENCE INFORMATION

DISCLOSURE STATEMENT