

Weighted Family History Density of Substance Use: Influence on Participant Substance Use Onset, Duration, and Escalation

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Purpose: This study investigates how weighted family history density (WFHD) influences the intergenerational transmission of substance use disorders (SUDs), focusing on onset, escalation, and duration of substance use. Substance preference concordance and sex-specific links between affected family members and participants were also assessed.

Methods: A cross-sectional analysis of the National Epidemiological Survey on Alcohol and Related Conditions III (NESARC-III) included 36,309 adults. WFHD was defined as drug or alcohol problems among first- and second-degree relatives. Linear regression models assessed the relationships between WFHD, age at onset, and duration of substance use, adjusting for sociodemographic factors. The escalation period to peak alcohol use was plotted by WFHD level, and correlation analyses examined the role of affected family members in shaping participant substance preferences and sex-stratified SUD diagnoses.

Results: Each unit increase in WFHD was linked to a minimum 0.53-year earlier onset [$\beta = -0.53$, $SE = 0.02$] and 0.48-year longer duration ($\beta = 0.48$, $SE = 0.03$) of substance use. WFHD increased the adjusted odds of onset before age 18 by 27% and duration exceeding half of one's age by 19%. Adjusted odds for durations exceeding 5 and 10 years rose by 26% and 21%, respectively. Higher WFHD was linked to faster escalation to peak use. Substance preferences showed significant concordance within families. Males were most strongly associated with paternal use, while females were more closely linked to maternal use.

Conclusion: Higher WFHD is strongly associated with earlier initiation, faster escalation to peak use, prolonged duration of substance use, and patterns of substance preference concordance, highlighting the importance of including family history assessments in substance use prevention and intervention strategies. Future research should use longitudinal studies to establish causal relationships and explore interactions between WFHD and other risk factors, such as environmental stressors, epigenetic changes, or genetic markers.

Plain Language Summary:

Why This Study Was Done: People with family members who have experienced alcohol or drug problems are at a higher risk of developing substance use problems themselves. This study measures that risk using Weighted Family History Density (WFHD), which considers how many close and extended family members have struggled with substance use.

What the Study Found: Using data from over 36,000 adults in the National Epidemiological Survey on Alcohol and Related Conditions-III (NESARC-III), we explored whether higher WFHD is linked to earlier onset, longer duration, and faster escalation to peak substance use. We also examined whether familial substance use patterns differed by sex and whether people's substance choices aligned with those of their family members.

What the Results Mean: Our results show that higher WFHD is associated with earlier substance use, longer duration, and faster escalation to peak use. Substance preferences often matched those of their family members. Correlation analyses showed that males with substance use disorders had stronger correlations with affected fathers, while females had stronger correlations with affected mothers.

Why This Is Important: These results highlight the importance of considering family history in substance use prevention and treatment. Identifying individuals at high familial risk could aid in developing early interventions to delay or reduce substance use and inform and help connect those at risk with treatment resources before their condition escalates. Future studies should explore the

biological and environmental mechanisms behind these patterns to develop more effective prevention strategies.

Keywords: substance use disorder, addiction, predisposition, genetic, environment, inheritance

Introduction

Substance use disorders (SUDs) pose significant public health concerns, affecting millions worldwide and imposing substantial individual, societal, and economic burdens. Defined by physiological, behavioral, and cognitive symptoms resulting from ongoing substance use despite substance-related problems, distress, and/or impairment,¹ SUDs impacted 16.5% of Americans aged 12+ (46.3 million individuals) in 2021.² SUDs contribute extensively to the global disease burden, with 28.2% of nonelderly United States (US) adults experiencing alcohol or drug use disorders in their lifetime.³ The annual economic impact exceeds \$400 billion,⁴ highlighting the urgent need to identify risk factors for effective prevention and intervention.

While genetics, environment, and social factors contribute to SUD vulnerability (Figure 1),^{5–9} family history (FH), which refers to the presence of SUDs in an individual’s biological relatives, is a potent risk factor, with positive FH individuals exhibiting a two- to eight-fold higher risk of developing a SUD themselves.¹⁰ The influence of familial SUDs is striking: individuals with alcoholism in second/third-degree relatives have a 45% increased risk for alcohol dependence, rising to 86% with alcoholism in first-degree relatives, and 167% if both categories are affected.¹¹ Similar patterns have been observed for other SUDs.^{8,12,13}

The heightened risk is well-documented,^{9,14–17} with the impact varying based on participant sex, race/ethnicity, and the density of familial SUDs,¹⁸ as well as by specific substance types.^{14,19} Children of high family history density (FHD) backgrounds (4+ first- and second-degree relatives) exhibit an earlier onset of regular drinking,²⁰ are more likely to develop substance abuse/dependence, and tend to do so at an earlier age¹⁷ compared to children of low-FHD backgrounds. These trends extend to other substances, like cannabis, where higher FHD predicts greater consumption and prolonged use.²¹ Moreover, greater FHD has been linked to a faster escalation to peak use—highlighting its potential as an early indicator of heightened risk.²²

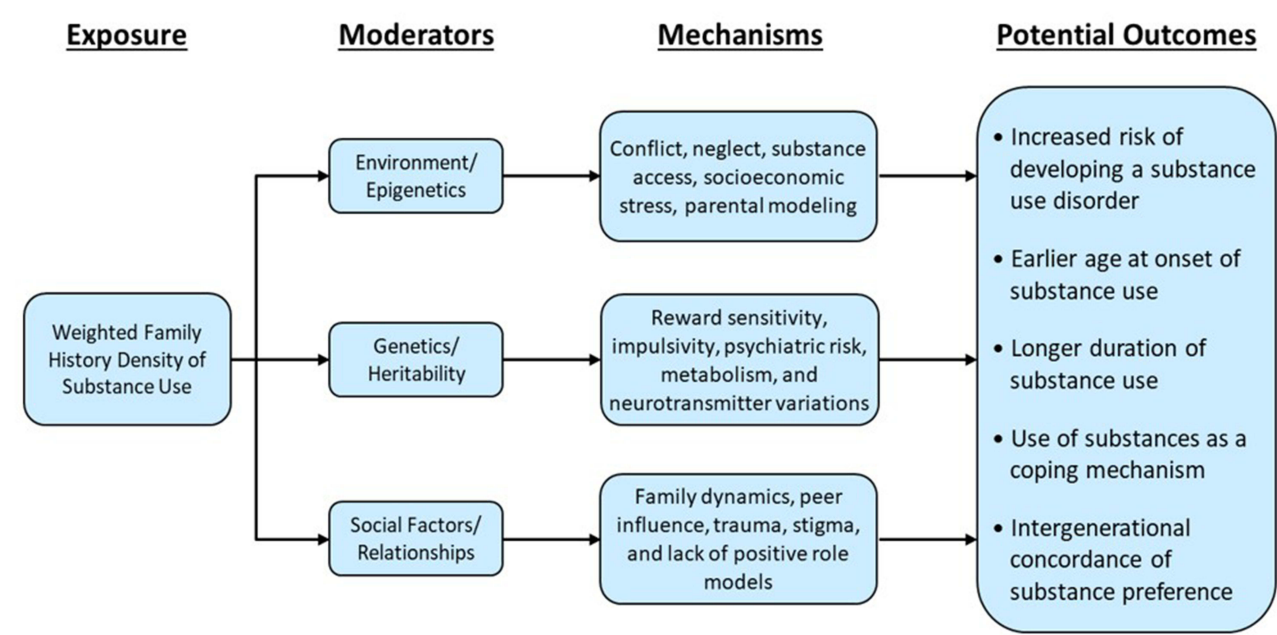


Figure 1 Influence of WFHD on substance use risk factors and outcomes.

Beyond general risk elevation, the familial transmission of SUDs may follow substance-specific pathways. Relatives of individuals with specific SUDs, such as opioid use disorder, are more likely to develop the same disorder, indicating specificity in inheritance.¹⁹ Hill et al²³ demonstrated this substance-specific pattern by showing that alcoholism and opiate abuse each clustered significantly within families but transmitted independently from each other. Even when individuals had both disorders, their relatives' substance use patterns aligned with whichever disorder developed first in the proband, supporting the notion that different substances may involve distinct familial pathways.

Meller et al²⁴ further supported this pattern of substance-specific familial clustering, reporting that alcoholism and opiate addiction tended to aggregate independently within families, with concordance most apparent among same-substance-using male siblings. Notably, the presence of both disorders in a proband did not correspond to increased cross-substance transmission in relatives, reinforcing the conclusion that the familial transmission of alcoholism and opiate addiction reflects largely distinct pathways. These findings directly inform our examination of generational transmission of substance preferences, where we expect family alcohol use problems (AUPs) to be more strongly associated with participant alcohol use disorder (AUD) than drug use disorder (DUD), while family drug use problems (DUPs) will show stronger associations with participant DUD than AUD.

Despite these insights, much of this research is outdated, focusing on specific substances, primarily white male participants, and immediate family members, while relying on simplistic “positive/negative” FH measures. Critically, traditional binary measures fail to distinguish between minimal family history, such as having a single distant uncle affected, and extensive family history, exemplified by having both parents, all siblings, all grandparents, and multiple maternal and paternal aunts and uncles affected. By employing weighted family history density (WFHD), our approach captures these significant differences in familial risk exposure with greater precision. This study addresses these limitations by leveraging the National Epidemiological Survey on Alcohol and Related Conditions-III (NESARC-III) dataset, a large, nationally representative sample enabling a more in-depth analysis of familial influences on SUDs. We move beyond dichotomous measures by employing measures of WFHD, which has proven more robust in both sexes, enhancing diagnostic accuracy over simpler FH classifications.¹⁸

Building on prior research, we examine the impact of WFHD of substance use problems (SUPs) on three key outcomes: age at first use, escalation to peak use, and duration of use, across substances like alcohol, nicotine, and drugs. While age at onset has been commonly examined in familial risk studies, our inclusion of escalation and duration represents a more detailed approach to substance use trajectories, capturing clinically meaningful patterns of progression and chronicity that have received less attention in large-scale epidemiological research. We anticipate that higher WFHD will be associated with an earlier onset, a shorter escalation period, and a longer duration of use, including onset before age 18 and durations exceeding half of one's current age, less than 5 years, and more than 10 years.

We also investigate sex differences in familial transmission patterns, expecting correlations between affected family members and participants to vary by sex. Although meta-analytic findings by Verhulst et al¹⁶ indicate that the overall magnitude of genetic influences on AUD is similar across sexes, other studies suggest sex-specific transmission effects. For instance, a Swedish national study on the transmission of alcohol use disorder across three generations found that familial risk is substantially stronger in same-sex pairs compared to opposite-sex pairs.²⁵ Similarly, Prescott et al²⁶ reported that same-sex twins exhibit considerably higher concordance for AUD than opposite-sex twins, suggesting that genetic and environmental liabilities are more consistently shared within each sex. Together, these findings imply that while both sexes possess a significant genetic risk for AUD, the manner in which this risk is transmitted within families differs by sex, supporting our hypothesis that familial correlations will vary accordingly.

Methods

Study Design and Population

At the time of study conception, NESARC-III was the most comprehensive dataset available for investigating familial patterns of substance use, offering an unmatched breadth and depth of family history variables—including parents, siblings, aunts, uncles, and grandparents. The survey includes a nationally representative sample of 36,309 noninstitutionalized adult civilians in the US, including those in select group quarters. Data for this cross-sectional analysis were

collected between April 2012 and June 2013.²⁷ NESARC-III applied random sampling, selecting counties or county groups (primary), Census-defined blocks (secondary), and households (tertiary).²⁷ To enhance representation, the study prioritized selecting two respondents from households with ≥ 4 minority individuals and oversampled Hispanic, Black, and Asian participants. Imputation addressed missing or inconsistent data for variables like age, marital status, and income, with adjustments needed for $<1\%$ of cases during weighting.²⁸ The final sample included 36,309 individuals, achieving an overall response rate of 60.1%, comparable to other recent US national surveys.²⁷

Ethics Approval and Data Access

This study involved secondary analysis of de-identified, limited-access data from the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), accessed through a Data Use Agreement with the National Institute on Alcohol Abuse and Alcoholism (NIAAA). All participants in the original NESARC-III study provided informed consent under protocols approved by NIAAA.

The data were handled per federal human subjects and privacy protections, including the Privacy Act of 1974 (5 U.S.C. §552a), the Health Insurance Portability and Accountability Act of 1996 (HIPAA) or equivalent privacy regulations, 45 C.F.R. Part 46, 21 C.F.R. Parts 50 and 56, and FDA Good Clinical Practice Guidelines (ICH E6, 62 FR 25692). Protections were further supported by a Certificate of Confidentiality issued by the NIH per 42 U.S.C. 241(d) of the Public Health Service Act.

Data were maintained securely with access limited to approved research personnel, and no attempts were made to identify individual participants. The University of Kentucky Institutional Review Board reviewed this project and determined that it was exempt from further review (IRB Protocol #94948), based on the use of fully de-identified, secondary data. All analyses complied with the confidentiality and security terms outlined in the NIAAA Data Use Agreement.

Primary Exposure of Interest: WFHD of SUPs

Self-reported FH of SUPs, operationalized as WFHD, was derived from survey questions assessing SUPs among first- and second-degree relatives. In this study, first-degree relatives are defined as biological parents and siblings, while second-degree relatives are defined as biological grandparents, aunts, and uncles. Family members who were under 10 years old or who passed away before reaching age 10, as well as participants' children and adoptive parents, were excluded; however, family members over 10 years old were included even if deceased at the time of the interview. For siblings, aunts, and uncles, the survey also quantified the number of affected relatives for a more accurate assessment of WFHD.

The survey inquired about lifetime SUPs for each family member, with separate sets of questions for drug- and alcohol-related problems. Although the survey did not assess formal SUD diagnoses or the specific drugs used, the questions provided clear definitions of what constituted a “problem” with drugs or alcohol by referencing clinical criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), such as physical or emotional difficulties, relationship conflicts, work or school problems, driving under the influence, and significant time spent using or recovering from substances.^{29,30}

In contrast, NESARC-III participants were diagnosed with SUDs based on the Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5),³¹ a structured, computer-assisted interview administered by trained lay interviewers. The AUDADIS-5 systematically assessed alcohol and drug use behaviors and experiences across multiple timeframes (past-year, prior-to-past-year, and lifetime), using built-in skip patterns and DSM-5-based criteria. For the present study, we used the lifetime SUD diagnosis variable, which indicates whether a participant met the diagnostic criteria—defined as endorsing two or more symptoms within a single 12-month period—at any point in their life. Diagnostic variables in the NESARC-III dataset were generated using validated scoring algorithms developed by the NESARC-III team,³² mapped individual item responses to DSM-5 criteria and are publicly documented to support transparency and reproducibility. Thus, participant diagnoses in the current study reflect formal, criteria-based determinations aligned with DSM-5 standards.

WFHD was calculated using a method inspired by Zucker, Ellis and Fitzgerald's³³ family expression of alcoholism formula. Due to limitations of the NESARC-III dataset, adjustments for affected-to-total family ratios were not possible. Instead, WFHD was calculated by assigning weights of 0.5 to affected first-degree relatives and 0.25 to affected second-degree relatives, yielding values from 0 to 18.25. This method reflects genetic proximity and its influence on familial substance use patterns.

$$\text{Total Weighted FHD} = (\sum \text{1st degree relatives with SUP} \times 0.5) + (\sum \text{2nd degree relatives with SUP} \times 0.25)$$

Where Substance Use Problems include both Drug Use and Alcohol Use Problems.

Primary Outcomes of Interest: Age at Onset and Duration of Substance Use

Our primary outcomes were (1) age at onset and (2) duration of substance use. Age at onset was calculated via self-reported responses to questions regarding participants' age at first use of any substance, including sedatives/tranquilizers, painkillers, cannabis, cocaine/crack, stimulants, club drugs, hallucinogens, inhalants/solvents, heroin, other drugs, cigarettes, cigars, pipes, snuff/chewing tobacco, e-cigarettes, and alcohol.

The duration of substance use was calculated in two steps. First, the age at most recent use was identified using variables measuring time since last use across substance categories. The time scale varied: alcohol was measured in days or months, nicotine in hours, and other drugs in days. The total duration of any substance use was then calculated by subtracting the earliest age at onset from the age at the most recent substance use.

Separate analyses were conducted for alcohol, nicotine, and other drugs. Three sets of models were run: (1) WFHD of any substance use problems (SUPs) predicting age at onset and duration of alcohol, drug, and nicotine use; (2) WFHD of alcohol use problems (AUPs) predicting these same outcomes; and (3) WFHD of drug use problems (DUPs) predicting these outcomes. Each outcome—alcohol, drug, and nicotine age at onset and duration—was modeled separately.

While NESARC-III also included questions about the age at which problematic use became more regular, we focused on age at first use because it reflects the earliest point of exposure—an important marker of risk. Numerous studies have demonstrated that early initiation is associated with increased vulnerability to substance use problems and the later development of substance use disorders, regardless of whether use continued immediately thereafter.^{34–36}

To further explore whether these associations differed among individuals with and without a history of SUD, we re-ran all models restricting the sample to participants with a lifetime SUD diagnosis. Additionally, we tested interactions between WFHD and lifetime SUD status to formally assess whether associations between WFHD and substance use outcomes differed based on whether a participant had ever met criteria for a SUD ($n = 15,104$).

Secondary Analyses of Interest: Escalation of Substance Use, Correlation Between Affected Family Members and Participants, and Concordance of Substance Preferences

To assess whether higher WFHD correlates with a shorter escalation period to peak alcohol use, we calculated an “escalation period” variable, defined as the number of years between age at first alcohol use and the age participants reported as the start of their heaviest drinking period. We then examined correlations between participants' DSM-5 diagnosed SUDs and SUPs among parents, siblings, and extended relatives to identify which affected family members had the strongest associations with affected participants, while also considering potential sex-specific patterns in familial SUD transmission. Lastly, we investigated how participants' preferences for alcohol and drugs aligned with those of their family members, identifying familial trends in substance choice to provide insights into how substance use behaviors may be influenced or inherited.

Statistical Analysis

To explore the relationship between WFHD and various sociodemographic and health characteristics, we categorized participants into tertiles based on their WFHD scores, with an additional “none” group for those without a FH of SUPs. We analyzed these groups on a range of sociodemographic variables and displayed the total sample size, group sizes, and

the percentage distribution of each characteristic within each group (Table 1). Specifically, we compared sex, age, race/ethnicity, sexual orientation, religious affiliation, educational attainment, income, rurality, and Census region across the WFHD groups to identify significant patterns associated with differing levels of familial SUPs. We conducted Chi-square tests to compare distributions of categorical variables across WFHD tertiles, ANOVA tests for normally distributed continuous variables, and Kruskal–Wallis tests for continuous variables that were not normally distributed.

Linear regression models examined relationships between WFHD, age at onset, and duration of substance use, controlling for potential confounding variables. Logistic regression tested WFHD's relationship with dichotomous outcomes, including early onset (<18 years) and long-term use (>5 years, >10 years, over half of current age). A Kaplan–Meier survival analysis assessed escalation periods (time from first alcohol use to peak use). WFHD categories (None, Tertiles 1–3) were compared using survival curves and Log rank tests to evaluate whether higher WFHD predicted shorter escalation periods.

Pearson correlations (r) between affected family members and participants, stratified by participant sex, were examined to identify potential sex-specific or intergenerational patterns in SUD inheritance. Logistic regression analyses assessed the association between WFHD of alcohol and drug use problems and the likelihood of AUD and DUD development in participants. Separate models were used to assess the impact of alcohol-related WFHD on AUDs and DUDs and drug-related WFHD on AUDs and DUDs.

In additional analyses, we repeated all regression models among the subset of participants with a lifetime substance use disorder diagnosis to test whether the strength or direction of associations differed in this high-risk group. These models mirrored the structure of the primary analyses and included unadjusted and fully adjusted versions. We then conducted formal interaction analyses to test whether the relationships between WFHD and each outcome (onset and duration) significantly differed between individuals with and without a lifetime SUD diagnosis. Interaction terms between WFHD and lifetime SUD status were added to each model, and interaction p -values were evaluated for significance. Finally, we conducted logistic regression models using both the full sample and the SUD-only subset for all dichotomized outcomes (eg, onset before age 18, duration longer than 5 or 10 years, and duration exceeding half of current age) and compared odds ratios across four tiers of model adjustment (unadjusted, adjusted for demographics, adjusted for socioeconomic status, and adjusted for geography). This allowed us to assess whether restricting to individuals with a SUD history meaningfully altered model estimates or improved prediction of key substance use outcomes.

Two-tailed p -values < 0.05 were considered statistically significant. All analyses were conducted using R Studio Version 4.3.1 and were weighted to account for the complex survey design and probability of non-response in NESARC-III. While this analysis offers insights into familial patterns and substance use, it was not pre-registered and should be considered exploratory.

Results

Description of Study Participants

Table 1 compares the sociodemographic and health characteristics of NESARC-III participants across different categories of WFHD, showing significant differences across all variables ($p < 0.001$). Males constituted 43.7% of the total sample, with male representation decreasing as WFHD increased. Younger individuals (18–29) were more prevalent in higher WFHD tertiles. Racial/ethnic distribution indicated a higher proportion of non-Hispanic Whites in lower WFHD categories, while higher tertiles contained more Hispanic participants. Sexual orientation, religion, education, income, rurality, and census region also varied significantly across WFHD categories, with higher WFHD tertiles generally associated with lower income and educational levels, and more urban residence.

Impact of WFHD of SUPs on Age at Onset and Duration of Substance Use Across Alcohol and Drug Use

Table 2 presents regression results examining the association between WFHD and the onset and duration of substance use, revealing consistent and significant associations. In unadjusted models, each unit increase in WFHD was linked to an earlier

Table 1 Descriptive Statistics Comparing NESARC-III Participant Sociodemographic and Health Characteristics Between WFHD Categories

Characteristic	Total Sample (n = 36,309)	WFHD None (0) (n = 11,349)	WFHD Tertile 1 (0.01–0.75) (n = 7528)	WFHD Tertile 2 (0.76–1.75) (n = 9228)	WFHD Tertile 3 (>1.75) (n = 8204)	p value ^a
Sex						
Male	15,862 (43.7%)	5252 (46.3%)	3479 (46.2%)	3919 (42.5%)	3212 (39.2%)	<0.0001
Female	20,447 (56.3%)	6097 (53.7%)	4049 (53.8%)	5309 (57.5%)	4992 (60.8%)	
Age, years						
18–29	8888 (24.5%)	2716 (23.9%)	1849 (24.6%)	2198 (23.8%)	2125 (25.9%)	<0.0001
30–39	6815 (18.8%)	1911 (16.8%)	1343 (17.8%)	1774 (19.2%)	1787 (21.8%)	
40–49	6575 (18.1%)	1902 (16.8%)	1317 (17.5%)	1734 (18.8%)	1622 (19.8%)	
50–59	6197 (17.1%)	1825 (16.1%)	1253 (16.6%)	1655 (18.0%)	1464 (17.8%)	
60–69	4302 (11.8%)	1440 (12.7%)	985 (13.1%)	1100 (11.9%)	777 (9.5%)	
70–90+	3532 (9.7%)	1555 (13.7%)	781 (10.4%)	767 (8.3%)	429 (5.2%)	
Race/Ethnicity						
White (non-Hispanic)	19,194 (52.9%)	5521 (48.7%)	4214 (56.0%)	5260 (57.0%)	4199 (51.2%)	<0.0001
Black (non-Hispanic)	7766 (21.4%)	2466 (21.7%)	1475 (19.6%)	1924 (20.9%)	1901 (23.2%)	
American Indian/Alaska Native	511 (1.3%)	88 (0.8%)	85 (1.1%)	127 (1.4%)	211 (2.6%)	
Asian/Native Hawaiian/Pacific Islander	1801 (5.0%)	1069 (9.4%)	337 (4.5%)	271 (2.9%)	124 (1.4%)	
Hispanic (any race)	7037 (19.4%)	2205 (19.4%)	1417 (18.8%)	1646 (17.8%)	1769 (21.6%)	
Sexual Orientation						
Heterosexual	34,644 (95.4%)	10,927 (96.3%)	7223 (95.9%)	8791 (95.3%)	7703 (93.9%)	<0.0001
Gay/Lesbian/Bisexual	1152 (3.2%)	228 (2.0%)	219 (2.9%)	323 (3.5%)	382 (4.7%)	
Not Sure/Unknown	513 (1.4%)	194 (1.7%)	86 (1.1%)	114 (1.2%)	119 (1.5%)	
Religious Affiliation						
Religious	32,585 (89.7%)	10,244 (90.3%)	6749 (89.7%)	8247 (89.4%)	7345 (89.5%)	<0.0001
No religious affiliation/Agnostic/Atheist	3230 (8.9%)	886 (7.8%)	687 (9.1%)	872 (9.4%)	785 (9.6%)	
Unknown	494 (1.4%)	219 (1.9%)	92 (1.2%)	109 (1.2%)	74 (0.9%)	
Educational Attainment						
Less than high school	5490 (15.1%)	1793 (15.8%)	1002 (13.3%)	1280 (13.9%)	1415 (17.3%)	<0.0001
Completed high school or GED	9799 (27.0%)	3067 (27.0%)	1919 (25.5%)	2440 (26.4%)	2373 (28.9%)	
Some college or technical school	12105 (33.3%)	3393 (29.9%)	2523 (33.5%)	3218 (34.9%)	2971 (36.2%)	
Bachelor's degree or higher	8915 (24.6%)	3096 (27.3%)	2084 (27.7%)	2290 (24.8%)	1445 (17.6%)	
Annual Personal Income						
< \$30,000	22,544 (62.1%)	7016 (61.8%)	4432 (58.9%)	5606 (60.7%)	5490 (66.9%)	<0.0000
\$30,000–\$49,999	7010 (19.3%)	2118 (18.7%)	1500 (19.9%)	1853 (20.1%)	1539 (18.8%)	
\$50,000–\$99,999	5197 (14.3%)	1662 (14.6%)	1200 (15.9%)	1376 (14.9%)	959 (11.7%)	
\$100,000+	1558 (4.3%)	553 (4.9%)	396 (5.3%)	393 (4.3%)	216 (2.6%)	
Rurality						
Urban	30,193 (83.2%)	9571 (84.3%)	6215 (82.6%)	7625 (82.6%)	6782 (82.7%)	0.0006
Rural	6116 (16.8%)	1778 (15.7%)	1313 (17.4%)	1603 (17.4%)	1422 (17.3%)	
Census Region						
Northeast	5180 (14.3%)	1787 (15.7%)	1063 (14.1%)	1293 (13.9%)	1037 (12.6%)	<0.0001
Midwest	7566 (20.8%)	2322 (20.5%)	1618 (21.5%)	1934 (21.0%)	1692 (20.6%)	
South	14,532 (40.0%)	4490 (39.6%)	3038 (40.4%)	3742 (40.6%)	3262 (39.8%)	
West	9031 (24.9%)	2750 (24.2%)	1809 (24.0%)	2259 (24.5%)	2213 (27.0%)	

Notes: ^ap-values were determined using Chi-square tests for categorical variables and ANOVA or Kruskal–Wallis tests for continuous variables, as appropriate. The first level within each characteristic served as the reference group. Percentages shown are calculated within each tertile (“% per column”), and small corrections were applied to ensure that values add up to 100%.

Abbreviations: SUD, substance use disorder; FH, family history; WFHD, weighted family history density; AUD, alcohol use disorder; DUD, drug use disorder; SUP, substance use problem; AUP, alcohol use problem; DUP, drug use problem; OR, odds ratio; CI, confidence interval.

Table 2 Impact of WFHD on Substance Use Onset and Duration: Unadjusted and Adjusted Regression Models

WFHD Variable	Unadjusted Models ^{a, b, d, f}	Adjusted Models ^{c, e, g}
	β (SE) [95% CI]	β (SE) [95% CI]
All SUP on Age at Onset		
Intercept	18.27 (0.04) [18.19, 18.35] ^{a***}	10.52 (0.26) [10.01, 11.03] ^{***}
WFHD – All SUP	–0.54 (0.02) [–0.59, –0.50] ^{***}	–0.53 (0.02) [–0.57, –0.49] ^{***}
DUP on Age at Onset		
Intercept	17.92 (0.04) [17.85, 17.99] ^{a***}	10.15 (0.26) [9.64, 10.65] ^{***}
WFHD – DUP	–0.68 (0.04) [–0.75, –0.61] ^{***}	–0.61 (0.04) [–0.68, –0.54] ^{***}
AUP on Age at Onset		
Intercept	18.23 (0.04) [18.15, 18.31] ^{a***}	10.36 (0.26) [9.86, 10.87] ^{***}
WFHD – AUP	–0.82 (0.03) [–0.89, –0.76] ^{***}	–0.84 (0.03) [–0.91, –0.78] ^{***}
All SUP on Duration		
Intercept	–13.59 (0.14) [–13.87, –13.31] ^{b***}	–7.18 (0.39) [–7.95, –6.41] ^{***}
WFHD – All SUP	0.48 (0.03) [0.42, 0.54] ^{***}	0.55 (0.03) [0.48, 0.61] ^{***}
DUP on Duration		
Intercept	–13.24 (0.14) [–13.52, –12.96] ^{b***}	–6.81 (0.39) [–7.57, –6.05] ^{***}
WFHD – DUP	0.52 (0.05) [0.42, 0.63] ^{***}	0.59 (0.05) [0.49, 0.70] ^{***}
AUP on Duration		
Intercept	–13.45 (0.14) [–13.73, –13.17] ^{b***}	–7.05 (0.39) [–7.81, –6.28] ^{***}
WFHD – AUP	0.79 (0.05) [0.69, 0.89] ^{***}	0.90 (0.05) [0.80, 1.00] ^{***}

Notes: *** $p < 0.001$. ^aUnadjusted Age at Onset Model Predictors: WFHD [DUP, AUP, or All SUP—both AUP and DUP]

^bUnadjusted Duration Model Predictors: WFHD, Age. ^cAdjusted Predictors: WFHD, Sex, Age, Race/Ethnicity, Sexual Orientation, Religious Affiliation, Educational Attainment, Annual Personal Income, Rurality, Census Region Model Fit Statistics: ^dOnset Models - Unadjusted: All SUP ($R^2 = 0.020$, $F(1, 32,333) = 663.310$), DUP ($R^2 = 0.011$, $F(1, 32,532) = 349.221$), AUP ($R^2 = 0.017$, $F(1, 32,333) = 571.617$). ^eOnset Models - Adjusted: All SUP ($R^2 = 0.088$, $F(10, 32,324) = 312.005$), DUP ($R^2 = 0.077$, $F(10, 32,523) = 273.067$), AUP ($R^2 = 0.087$, $F(10, 32,324) = 309.686$). ^fDuration Models - Unadjusted: All SUP ($R^2 = 0.746$, $F(2, 32,088) = 47,177.805$), DUP ($R^2 = 0.745$, $F(2, 32,285) = 47,271.839$), AUP ($R^2 = 0.746$, $F(2, 32,088) = 47,190.580$). ^gDuration Models - Adjusted: All SUP ($R^2 = 0.756$, $F(10, 32,080) = 9929.021$), DUP ($R^2 = 0.755$, $F(10, 32,277) = 9929.699$), AUP ($R^2 = 0.756$, $F(10, 32,080) = 9933.138$).

Abbreviations: WFHD, weighted family history density; SUP, substance use problem; AUP, alcohol use problem; DUP, drug use problem; CI, confidence interval.

onset of substance use by 0.54 to 0.82 years ($p < 0.001$), with the strongest effect for those with a FH of AUPs ($\beta = -0.82$, 95% CI: $-0.89, -0.76$). Similarly, WFHD was associated with a longer duration of substance use, extending it by 0.48 to 0.79 years ($p < 0.001$), with FH of AUPs again showing the strongest association ($\beta = 0.79$, 95% CI: $0.69, 0.89$). These effects remained robust after adjusting for confounds, with each unit increase in WFHD continuing to predict an earlier onset by 0.53 to 0.84 years and a longer duration by 0.55 to 0.90 years, particularly for AUDs (onset: $\beta = -0.84$, 95% CI: $-0.91, -0.78$; duration: $\beta = 0.90$, 95% CI: $0.80, 1.00$). The adjusted models demonstrated improved explanatory power, particularly for age of onset ($R^2 = 0.077$ to 0.088) and duration ($R^2 = 0.755$ to 0.756), highlighting the strong predictive influence of WFHD on both the initiation and persistence of substance use across different substance types.

Detailed Analysis of the Associations Between WFHD and Age at Onset and Duration Across Adjusted Models

Table 3 displays the impact of WFHD on substance use onset and duration, demonstrating consistent associations across various levels of model adjustment. For onset before age 18, each one-unit increase in WFHD corresponded to a 26% increase in odds in the unadjusted model (OR = 1.26, 95% CI: $1.24-1.28$, $p < 0.001$), rising to 27% in the fully adjusted model (OR = 1.27, 95% CI: $1.25-1.29$, $p < 0.001$), with model fit improving from a McFadden's R^2 of 0.019 to 0.059.

Table 3 Effect of WFHD on Substance Use Onset and Duration: Odds Ratios and Model Fit Statistics by Sequentially Adjusted Models

Outcome	Model	OR (95% CI)
Age at Onset: Before Age 18	Unadjusted ^a	1.26 (1.24–1.28)***
Age at Onset: Before Age 18	Demographics ^c	1.28 (1.26–1.31)***
Age at Onset: Before Age 18	Socioeconomics ^d	1.27 (1.25–1.29)***
Age at Onset: Before Age 18	Geographics ^e	1.27 (1.22–1.29)***
Duration: > ½ of Current Age	Unadjusted ^b	1.17 (1.15–1.19)***
Duration: > ½ of Current Age	Demographics ^c	1.18 (1.16–1.21)***
Duration: > ½ of Current Age	Socioeconomics ^d	1.19 (1.17–1.21)***
Duration: > ½ of Current Age	Geographics ^e	1.19 (1.17–1.21)***
Duration: > 5 years	Unadjusted ^b	1.22 (1.18–1.26)***
Duration: > 5 years	Demographics ^c	1.24 (1.20–1.27)***
Duration: > 5 years	Socioeconomics ^d	1.26 (1.22–1.30)***
Duration: > 5 years	Geographics ^e	1.26 (1.22–1.30)***
Duration: > 10 years	Unadjusted ^b	1.18 (1.15–1.21)***
Duration: > 10 years	Demographics ^c	1.19 (1.17–1.22)***
Duration: > 10 years	Socioeconomics ^d	1.20 (1.18–1.23)***
Duration: > 10 years	Geographics ^e	1.21 (1.18–1.23)***

Notes: *** $p < 0.001$ Age at onset: Before age 18: $n = 32,358$ All other outcomes: $n = 32,112$. ^aUnadjusted Model Predictors: WFHD. ^bUnadjusted Model Predictors: Model A plus Age. ^cDemographics Predictors: (Constant), Model B plus Race/Ethnicity, Sexual Orientation, and Religious Affiliation. ^dSocioeconomics Predictors: (Constant), Model C plus Educational Attainment and Annual Personal Income. ^eGeographics Predictors: (Constant), WFHD, Model D plus Rurality and Census Region.

Abbreviations: WFHD, weighted family history density; OR, odds ratio.

For substance use duration exceeding half of one's current age, a one-unit increase in WFHD raised the odds by 17% in the unadjusted model (OR = 1.17, 95% CI: 1.15–1.19, $p < 0.001$), reaching 19% in the fully adjusted model (OR = 1.19, 95% CI: 1.17–1.21, $p < 0.001$), with R^2 improving from 0.27 to 0.288. For substance use lasting over five years, the odds increased by 22% in the unadjusted model (OR = 1.22, 95% CI: 1.18–1.26, $p < 0.001$), and up to 26% in the fully adjusted model (OR = 1.26, 95% CI: 1.22–1.30, $p < 0.001$) for each unit increase in WFHD, with R^2 improving from 0.267 to 0.293. For duration exceeding ten years, a one-unit increase in WFHD raised the odds by 18% in the unadjusted model (OR = 1.18, 95% CI: 1.15–1.21, $p < 0.001$), and by 21% in the fully adjusted model (OR = 1.21, 95% CI: 1.18–1.24, $p < 0.001$), with an enhanced model fit from $R^2 = 0.387$ to $R^2 = 0.402$, explaining about 40% of the variance in substance use duration. Results remained consistent when analyses were restricted to participants with a lifetime SUD diagnosis, with nearly identical effect sizes and significance levels across models and only two of 18 interaction terms reaching significance, underscoring the robustness of WFHD as a predictor of earlier onset and longer substance use duration regardless of clinical history ([Supplemental Tables 1 and 2](#)).

Impact of WFHD Type on Age at Onset and Duration of Substance Use Across Substance Types

Increases in WFHD of SUPs were linked to earlier onset and longer duration of alcohol, drug, and nicotine use. As shown in [Table 4](#) Model 1 (overall SUPs), higher WFHD predicted significantly earlier onset (by 0.30–0.47 years) and longer duration (by 0.31–0.73 years) across all substances ($p < 0.001$). [Table 5](#) Model 2 (alcohol use problems) showed the strongest effect on drug use (onset: –0.79 years; duration: +1.06 years), whereas [Table 6](#) Model 3 (drug use problems) most strongly predicted drug use outcomes (onset: –0.54 years; duration: +1.01 years). These findings suggest that WFHD of alcohol use problems had a broader cross-substance impact—particularly on drug use—while WFHD of drug use problems demonstrated greater substance specificity. Notably, this initial analysis included all participants with

Table 4 Model 1: Adjusted Analysis of WFHD of All Substance Use Problems Predicting Participant Age of Onset and Duration of Alcohol, Drug, and Nicotine Use

Outcome	Estimate	Std. Error	t value
Participant Alcohol Age at Onset	−0.4003***	0.0208	−19.269
Participant Drug Age at Onset	−0.4727***	0.0386	−12.242
Participant Nicotine Age at Onset	−0.2991***	0.0253	−11.825
Participant Alcohol Duration	0.3086***	0.0326	9.481
Participant Drug Duration	0.7323***	0.0586	12.496
Participant Nicotine Duration	0.4535***	0.0566	8.015

Notes: *** $p < 0.001$. Adjusted Predictors: WFHD of all substance use problems, Sex, Age, Race/Ethnicity, Sexual Orientation, Religious Affiliation, Educational Attainment, Annual Personal Income, Rurality, Census Region Model Fit Statistics: Alcohol Age at Onset ($R^2 = 0.0771$, $F(10, 31,510) = 263.1$) Drug Age at Onset ($R^2 = 0.1779$, $F(10, 12,738) = 275.7$) Nicotine Age at Onset ($R^2 = 0.0420$, $F(10, 15,776) = 69.13$) Alcohol Duration ($R^2 = 0.721$, $F(10, 31,087) = 8035$) Drug Duration ($R^2 = 0.2693$, $F(10, 11,403) = 420.3$) Nicotine Duration ($R^2 = 0.445$, $F(10, 15,747) = 1262$).

Abbreviation: WFHD, weighted family history density.

Table 5 Model 2: Adjusted Analysis of WFHD of Alcohol Use Problems Predicting Participant Age of Onset and Duration of Alcohol, Drug, and Nicotine Use

Outcome	Estimate	Std. Error	t value
Participant Alcohol Age at Onset	−0.6843***	0.0336	−20.381
Participant Drug Age at Onset	−0.7906***	0.0652	−12.128
Participant Nicotine Age at Onset	−0.4966***	0.0404	−12.296
Participant Alcohol Duration	0.5071***	0.0526	9.639
Participant Drug Duration	1.0648***	0.0992	10.732
Participant Nicotine Duration	0.9508***	0.0902	10.537

Notes: *** $p < 0.001$. Adjusted Predictors: WFHD of all SUP, Sex, Age, Race/Ethnicity, Sexual Orientation, Religious Affiliation, Educational Attainment, Annual Personal Income, Rurality, Census Region Model Fit Statistics: Alcohol Age at Onset ($R^2 = 0.0783$, $F(10, 31,510) = 267.8$) Drug Age at Onset ($R^2 = 0.1777$, $F(10, 12,738) = 275.3$) Nicotine Age at Onset ($R^2 = 0.0427$, $F(10, 15,776) = 70.31$) Alcohol Duration ($R^2 = 0.7211$, $F(10, 31,087) = 8036$) Drug Duration ($R^2 = 0.2667$, $F(10, 11,403) = 414.7$) Nicotine Duration ($R^2 = 0.4466$, $F(10, 15,747) = 1271$).

Abbreviation: WFHD, weighted family history density.

available family history data—not only participants with SUDs—emphasizing the predictive value of familial SUPs across the full sample. However, this unexpected cross-substance association persisted even when restricting the sample to individuals with a lifetime SUD diagnosis ([Supplemental Table 3](#), Models 1–3). Sample sizes for each model varied slightly depending on outcome availability and inclusion criteria, as detailed in [Table 7](#).

Analysis of Alcohol Use Escalation

The Kaplan-Meier survival analysis ([Figure 2](#)) suggested that participants with higher WFHD of AUPs tended to reach peak alcohol use more quickly compared to those with lower WFHD. This observation highlights the potential influence of familial AUPs on the trajectory of participant alcohol consumption, with greater WFHD contributing to faster escalation to peak use.

Table 6 Model 3: Adjusted Analysis of WFHD of Drug Use Problems Predicting Participant Age of Onset and Duration of Alcohol, Drug, and Nicotine Use

Outcome	Estimate	Std. Error	t value
Participant Alcohol Age at Onset	−0.4053***	0.0357	−11.355
Participant Drug Age at Onset	−0.5437***	0.0648	−8.393
Participant Nicotine Age at Onset	−0.3085***	0.0437	−7.061
Participant Alcohol Duration	0.3333***	0.0558	5.973
Participant Drug Duration	1.0139***	0.0986	10.279
Participant Nicotine Duration	0.2331***	0.0976	2.388

Notes: *** $p < 0.001$. Adjusted Predictors: WFHD of all SUP, Sex, Age, Race/Ethnicity, Sexual Orientation, Religious Affiliation, Educational Attainment, Annual Personal Income, Rurality, Census Region Model Fit Statistics: Alcohol Age at Onset ($R^2 = 0.0697$, $F(10, 31,707) = 237.6$) Drug Age at Onset ($R^2 = 0.1720$, $F(10, 12,828) = 266.5$) Nicotine Age at Onset ($R^2 = 0.0363$, $F(10, 15,886) = 59.85$) Alcohol Duration ($R^2 = 0.7209$, $F(10, 31,282) = 8078$) Drug Duration ($R^2 = 0.2661$, $F(10, 11,489) = 416.6$) Nicotine Duration ($R^2 = 0.443$, $F(10, 15,857) = 1261$).

Abbreviation: WFHD, weighted family history density.

Table 7 Participant Sample Sizes per Analysis

Test	Number of Participants
Total number of participants	36,309
WFHD Drug predicting DUD, AUD, SUD	36,309
WFHD Alcohol predicting DUD, AUD, SUD	36,309
Age of Onset (continuous)	32,335
Onset Before Age 18	32,358
Longest Duration of Use (continuous)	32,091
Duration > 1/2 of Current Age, 5 years, 10 years	32,112

Notes: Adjusted Predictors: WFHD of all AUP, Sex, Age, Race/Ethnicity, Sexual Orientation, Religious Affiliation, Educational Attainment, Annual Personal Income, Rurality, Census Region Model Fit Statistics: Alcohol Age at Onset ($R^2 = 0.0697$, $F(10, 31,707) = 237.6$) Drug Age at Onset ($R^2 = 0.1720$, $F(10, 12,828) = 266.5$) Nicotine Age at Onset ($R^2 = 0.0363$, $F(10, 15,886) = 59.85$) Alcohol Duration ($R^2 = 0.7209$, $F(10, 31,282) = 8078$) Drug Duration ($R^2 = 0.2661$, $F(10, 11,489) = 416.6$) Nicotine Duration ($R^2 = 0.443$, $F(10, 15,857) = 1261$).

Abbreviations: SUD, substance use disorder (all types listed below); WFHD, weighted family history density; AUD, alcohol use disorder; DUD, drug substance use disorders related to sedatives, cannabis, opioids, cocaine, stimulants, hallucinogens, inhalants/solvents, club drugs, heroin, or tobacco; other SUD, any substance use disorder other than AUD.

Differential Impact of WFHD on Alcohol and Drug Use Disorders

For alcohol-related WFHD, each unit increase corresponded to a 56.8% increase in the odds of AUD diagnosis (OR = 1.568, 95% CI: 1.530–1.607) and a 56.4% increase in the odds of DUD diagnosis (OR = 1.564, CI: 1.526–1.603). Similarly, for drug-related WFHD, each unit increase was associated with a 41.8% increase in the odds of DUD (OR = 1.418, CI: 1.383–1.455) and a 39.5% increase in the odds of AUD (OR = 1.395, CI: 1.360–1.430).

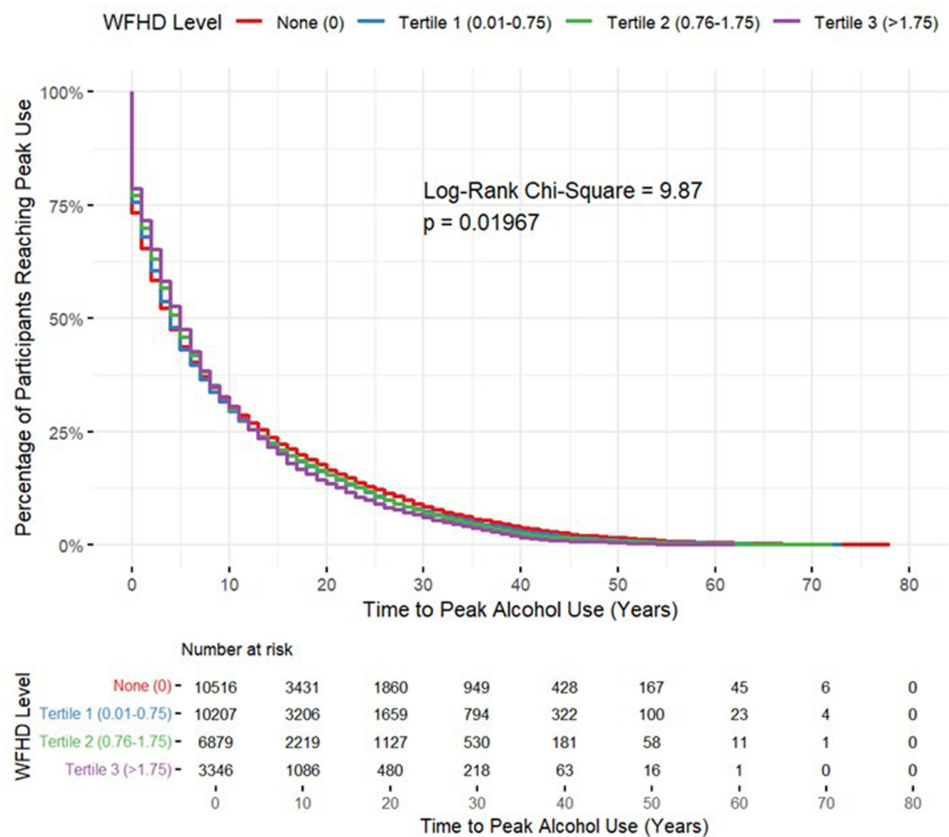


Figure 2 Kaplan-Meier survival probability of peak alcohol use by WFHD level of AUP.

Sex-Specific Patterns of Inheritance

A heatmap analysis revealed sex-specific correlations between SUP prevalence in family members and SUDs in male and female participants (Figure 3). For males, the strongest correlations were linked to fathers ($r = 0.195$), followed by maternal grandfathers ($r = 0.155$), and mothers ($r = 0.147$), suggesting a greater paternal role in SUD predisposition. Conversely, for females, the correlations with mothers ($r = 0.203$) and fathers ($r = 0.201$) were nearly identical, indicating similar maternal and paternal influences. However, the mother-daughter correlation ($r = 0.203$) was notably stronger than the mother-son correlation ($r = 0.147$), highlighting a more substantial maternal impact on female participants.

Discussion

Our study highlights the strong association between WFHD and substance use behaviors, influencing when individuals start using substances, how quickly they escalate to peak use, and how long they continue. Higher WFHD was associated with earlier onset and longer duration of substance use across alcohol, drug, and nicotine outcomes, even after adjusting for demographic, socioeconomic, and geographic characteristics. In addition, individuals with higher WFHD of alcohol use problems experienced shorter periods from first use to peak use, reflecting a faster progression of substance use among those with elevated familial risk. We also observed concordance in substance preferences within families, indicating that specific substance use patterns are often replicated across generations. Finally, distinct male and female inheritance patterns emerged, suggesting the need for sex-specific prevention and treatment approaches.

These associations remained robust in models restricted to individuals with a lifetime history of SUDs, with nearly identical effect sizes and directions of association, emphasizing the clinical relevance of these patterns among affected populations. All main findings—across onset and duration of alcohol, drug, and nicotine use—remained significant in the SUD-only models, with results consistent with those observed in the full sample. Interaction models further indicated that associations between WFHD and substance use outcomes were largely similar across participants with and without

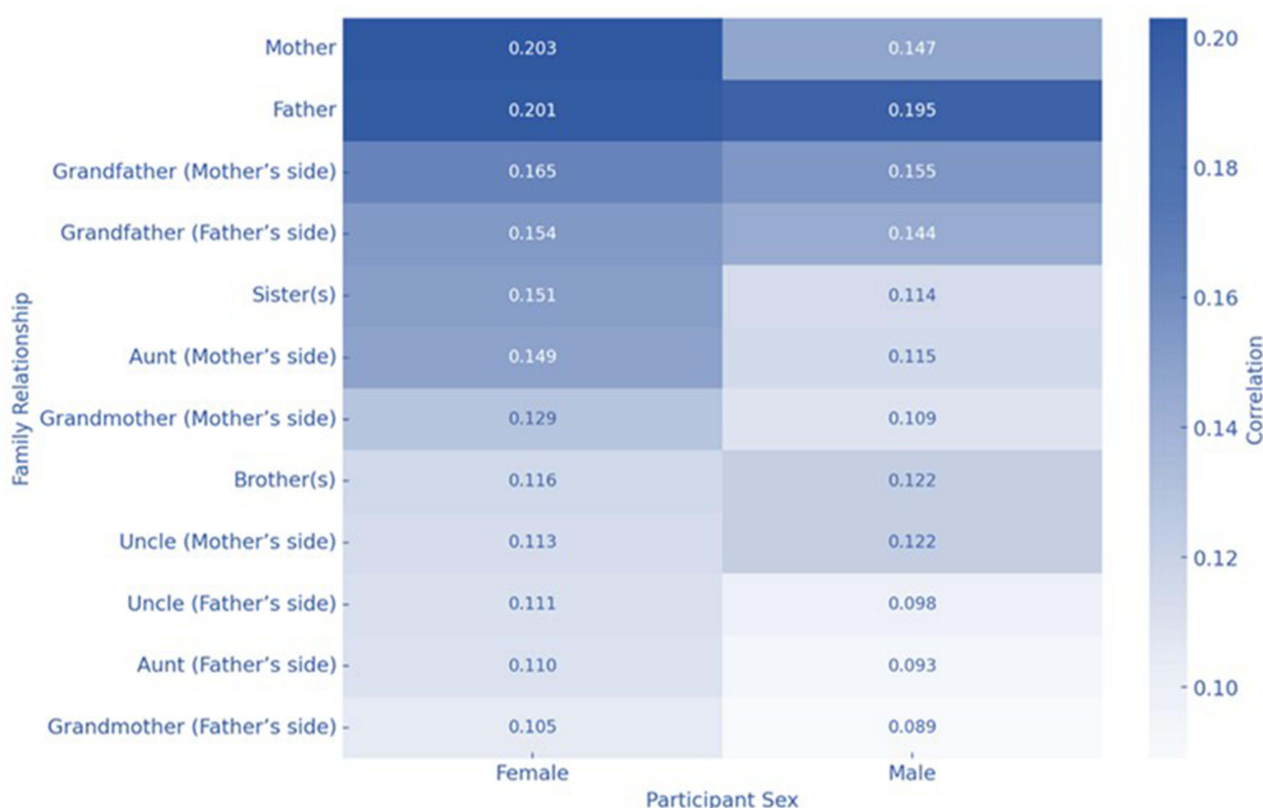


Figure 3 Heatmap of sex-specific correlations between affected family AUPs and participant SUDs.

Note: Pearson's r was used to compute correlation coefficients.

SUDs, with only two of eighteen interaction terms reaching statistical significance. This consistency supports the inclusion of all participants in our primary analyses. Models examining alcohol-specific and drug-specific WFHD revealed the same patterns, with alcohol-related WFHD predicting broader, cross-substance effects and drug-related history showing greater substance specificity. This consistency supports the inclusion of all participants in our primary analyses and emphasizes the value of assessing WFHD not only for early identification of risk but also for understanding severity, chronicity, and progression among those already experiencing substance use problems.

These results are consistent with a robust body of evidence identifying family history as a central factor in the development and progression of substance use problems.^{9,12,13,16–21,37} For example, Hill and Yuan²⁰ reported that adolescents from high-density alcohol-affected families initiated regular drinking at significantly younger ages than those from low-density families, while Hill et al¹⁷ found that children with elevated familial alcohol risk exhibited both earlier onset and higher risk of developing substance abuse problems. Similarly, Dawson et al¹¹ demonstrated a dose-response effect, showing that risk for alcohol dependence increased in proportion to the number of affected first- and second-degree relatives. Our findings extend this work by using a continuous, WFHD measure to predict not only onset but also escalation and duration, with associations persisting across substances even after adjusting for socio-demographic and geographic factors.

Further supporting familial specificity, our findings reveal that WFHD of AUPs more strongly predicted AUD than DUD, while WFHD of DUPs more strongly predicted DUD than AUD. This observation aligns with Bierut et al,¹⁴ who reported that siblings of alcohol-dependent individuals were more likely to develop alcohol dependence, while siblings of cannabis- and cocaine-dependent individuals were at higher risk for those specific dependencies. Similarly, Merikangas et al¹⁹ and Tyringsson et al³⁷ identified strong familial concordance for opioid, cannabis, alcohol, and stimulant use disorders, reinforcing the idea of substance-specific inheritance.

Despite this substance-specific diagnostic concordance, we observed that WFHD of AUPs was unexpectedly associated with earlier onset and longer duration of drug use compared to alcohol use. This finding suggests that familial AUPs represent a broader, transdiagnostic risk factor, potentially due to shared genetic and environmental vulnerabilities, cross-substance escalation, and social influences, with familial traits such as impulsivity, sensation seeking, or altered stress responses potentially heightening susceptibility to earlier onset and prolonged drug use even when the primary SUD risk remains alcohol-specific. These associations remained when the analysis was restricted to individuals with a lifetime history of SUD, with nearly identical direction and magnitude of effects, reinforcing the robustness and clinical relevance of these subtype-specific patterns. Taken together, the results suggest that WFHD is not only a meaningful marker of individual risk—but one that consistently shapes substance use trajectories across both general and affected populations. Supporting this, Grucza et al³⁸ observed significant associations between familial alcoholism risk and obesity, particularly among women, suggesting that familial AUDs may confer a transdiagnostic vulnerability—potentially through shared neurobehavioral pathways such as reward processing dysregulation and heightened impulsivity—with sex-specific biological or environmental factors amplifying this risk in women. Mennella et al³⁹ similarly reported heightened sweet preferences in children with a family history of alcoholism, further supporting the concept of shared reward-processing pathways underlying broader susceptibilities.

Neuroimaging research by Lees et al⁴⁰ also offers valuable insights into sex-specific neurobiological mechanisms underlying this broader vulnerability. They observed that children with a parental history of AUD exhibited sex-specific neural differences during response inhibition tasks; notably, all youth with paternal AUD history showed increased activation in the medial orbital frontal cortex during successful inhibition, while only female youth with maternal AUD history displayed heightened neural activation in the cerebellum during failed inhibition. These neural findings indicate distinct sex-specific neurodevelopmental vulnerabilities affecting cognitive control and impulse regulation, potentially explaining why familial AUP risk broadly influences susceptibility to drug use behaviors beyond alcohol alone, particularly regarding early onset and prolonged duration among women with affected mothers.

This interpretation aligns with our observed sex-specific patterns: Males showed stronger correlations with paternal substance use, whereas females exhibited stronger correlations than males with nearly all affected family members—especially with affected mothers (Figure 3). Christensen and Bilenberg⁴¹ noted that daughters are often more affected by parental alcoholism than sons, possibly due to greater emotional involvement and engagement with family matters.^{37,42} Dawson et al¹¹ also found that women with multiple alcoholic relatives were significantly more likely than men to begin drinking before age 15, with elevated risk persisting into adulthood compared to men.

McGue et al⁴³ provide further insight into these sex-specific familial pathways, showing that early alcohol use is highly heritable in boys—primarily due to genetic liability for disinhibitory psychopathology—whereas in girls, early alcohol use is more strongly linked to shared environmental influences, particularly maternal drinking. Together, these findings suggest that while familial alcohol problems may confer substance-specific risk, their broader and more diffuse impact—particularly among women—may reflect environmentally mediated pathways that extend beyond alcohol use, underscoring the need for prevention efforts that account for both the substance type and the sex-specific nature of familial transmission.

Limitations

Our study contributes strong evidence that WFHD consistently influences substance use behaviors, influencing when individuals start using substances, how quickly they escalate to peak use, and how long they continue. We observed concordance in substance preferences within families, indicating that specific substance use patterns are often replicated across generations. Distinct male and female inheritance patterns further suggest the need for sex-specific prevention and treatment approaches.

While our study boasts a large sample size and comprehensive control of potential confounds, its cross-sectional design limits causal inferences. Additionally, reliance on self-reported survey data may introduce recall and social desirability biases, potentially affecting the accuracy of WFHD variables and reported substance use behaviors. These concerns may be especially relevant given the wide age range of the sample—approximately 20% of whom were aged 60 or older—raising the possibility that older participants may have less reliable recall or reduced contact with affected relatives. Conversely,

individuals in the highest WFHD tertile were disproportionately younger (about 50% under age 40), which may reflect greater proximity to living, substance-affected relatives or enhanced recall, potentially introducing bias.

Although our findings strongly suggest that greater WFHD influences earlier onset, longer duration, and faster escalation to peak substance use, the retrospective design requires cautious interpretation of these associations. The absence of clinical severity and comorbidity data in our current analytic models also limits our ability to fully characterize these familial risk pathways. While the NESARC-III dataset includes DSM-5-based severity gradings and information on psychiatric comorbidities, our analytic focus was limited to lifetime SUD status to maintain consistency across substance categories and avoid overcomplicating model interpretations. Future research could build on these findings by examining how familial risk interacts with disorder severity, comorbidity, and diagnostic timing. Longitudinal data could also address these limitations by tracking substance use behaviors over time to establish causation and reduce recall bias. Investigating how WFHD interacts with environmental stressors, epigenetic changes, and genetic markers could further clarify substance use etiology.

Conclusion

Recognizing the importance of FH and inheritance patterns is essential as we refine approaches to substance use prevention and treatment. Incorporating FH assessments into prevention strategies can enable early identification of individuals with a high familial burden of SUDs, facilitating targeted efforts to delay onset, reduce duration, and address rapid escalation of substance use. Moreover, sustained interventions are critical, not only to address initiation, continuation, and escalation of substance use, but also to equip individuals in recovery with the skills to navigate relationships with family members who are actively using substances. Future causal longitudinal studies should extend these findings across diverse populations, examining genetic predispositions, environmental factors, and interactions by substance type and participant sex. By considering familial patterns and integrating broader variables, we can create more personalized prevention and treatment strategies, ultimately advancing public health and clinical solutions for managing SUDs.

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References

1. Substance use disorder. American Psychological Association. Available from: <https://dictionary.apa.org/substance-use-disorder>. Accessed September 4, 2024.
2. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: results from the 2021 National Survey on Drug Use and Health. HHS Publication No. PEP22-07-01-005, NSDUH Series H-57. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2022. Available from: <https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report>. Accessed September 4, 2024.
3. Wu L-T. Substance abuse and rehabilitation: responding to the global burden of diseases attributable to substance abuse. *Subst Abuse Rehabil*. 2010;2010(1):5–11. doi:10.2147/SAR.S14898
4. U.S. Department of Justice, National Drug Intelligence Center. *National Drug Threat Assessment*; 2011.
5. Hines LA, Morley KI, Mackie C, Lynskey M. Genetic and environmental interplay in adolescent substance use disorders. *Curr Addict Rep*. 2015;2(2):122–129. doi:10.1007/s40429-015-0049-8
6. Pinto E, Reggers J, Gorwood P, et al. The TaqI A DRD2 polymorphism in type II alcohol dependence: a marker of age at onset or of a familial disease? *Alcohol*. 2009;43(4):271–275. doi:10.1016/j.alcohol.2009.02.006
7. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood: a convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci*. 2006;256(3):174–186. doi:10.1007/s00406-005-0624-4
8. Nepl TK, Diggs ON, Cleveland MJ. The intergenerational transmission of harsh parenting, substance use, and emotional distress: impact on the third-generation child. *Psychol Addict Behav*. 2020;34(8):852–863. doi:10.1037/adb0000551
9. Hamad AF, Roos LL, Bolton JM, Wall-Wieler E. Familial associations in adolescent substance use disorder: a population-based cohort study. *Addiction*. 2022;117(10):2720–2729. doi:10.1111/add.15981
10. Merikangas KR, McClair VL. Epidemiology of substance use disorders. *Hum Genet*. 2012;131(6):779–789. doi:10.1007/s00439-012-1168-0
11. Dawson DA, Harford TC, Grant BF. Family history as a predictor of alcohol dependence. *Alcohol Clin Exp Res*. 1992;16(3):572–575. doi:10.1111/j.1530-0277.1992.tb01419.x

12. Chassin L, Curran P, Hussong A, Colder C. The relation of parent alcoholism to adolescent substance use: a longitudinal follow-up study. *J Abnorm Psychol.* 1996;105(1):70–80. doi:10.1037/0021-843X.105.1.70
13. Chassin L, Pitts SC, DeLucia C, Todd M. A longitudinal study of children of alcoholics: predicting young adult substance use disorders, anxiety, and depression. *J Abnorm Psychol.* 1999;108(1):106–119. doi:10.1037/0021-843X.108.1.106
14. Bierut LJ, Dinwiddie SH, Begleiter H, et al. Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the collaborative study on the genetics of alcoholism. *Arch Gen Psychiatry.* 1998;55(11):982–988. doi:10.1001/archpsyc.55.11.982
15. Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse: cross-fostering analysis of adopted men. *Arch Gen Psychiatry.* 1981;38(8):861–868. doi:10.1001/archpsyc.1981.01780330019001
16. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychol Med.* 2015;45(5):1061–1072. doi:10.1017/S0033291714002165
17. Hill SY, Shen S, Lowers L, Locke J. Factors predicting the onset of adolescent drinking in families at high risk for developing alcoholism. *Biol Psychiatry.* 2000;48(4):265–275. doi:10.1016/S0006-3223(00)00841-6
18. Pandey G, Seay MJ, Meyers JL, et al. Density and dichotomous family history measures of alcohol use disorder as predictors of behavioral and neural phenotypes: a comparative study across gender and race/ethnicity. *Alcohol Clin Exp Res.* 2020;44(3):697–710. doi:10.1111/acer.14280
19. Merikangas KR, Stolar M, Stevens DE, et al. Familial transmission of substance use disorders. *Arch Gen Psychiatry.* 1998;55(11):973–979. doi:10.1001/archpsyc.55.11.973
20. Hill SY, Yuan H. Familial density of alcoholism and onset of adolescent drinking. *J Studies on Alcohol.* 1999;60(1):7–17. doi:10.15288/jsa.1999.60.7
21. Khoddam R, Worley M, Browne KC, Doran N, Brown SA. Family history density predicts long-term substance use outcomes in an adolescent treatment sample. *Drug Alcohol Depend.* 2015;147:235–242. doi:10.1016/j.drugalcdep.2014.11.009
22. Hussong A, Bauer D, Chassin L. Telescoped trajectories from alcohol initiation to disorder in children of alcoholic parents. *J Abnorm Psychol.* 2008;117(1):63–78. doi:10.1037/0021-843X.117.1.63
23. Hill SY, Cloninger CR, Aye FR. Independent familial transmission of alcoholism and opiate abuse. *Alcohol Clin Exp Res.* 1977;1(4):335–342. doi:10.1111/j.1530-0277.1977.tb05790.x
24. Meller WH, Rinehart R, Cadoret RJ, Troughton E. Specific familial transmission in substance abuse. *Int J Addict.* 1988;23(10):1029–1039. doi:10.3109/10826088809056183
25. Kendler KS, Ohlsson H, Sundquist J, Sundquist K. Transmission of alcohol use disorder across three generations: a Swedish national study. *Psychol Med.* 2018;48(1):33–42. doi:10.1017/S0033291717000794
26. Prescott CA, Aggen SH, Kendler KS. Sex differences in the sources of genetic liability to alcohol abuse and dependence in a population-based sample of U.S. twins. *Alcohol Clin Exp Res.* 1999;23(7):1136–1144. doi:10.1111/j.1530-0277.1999.tb04270.x
27. Grant BF, Goldstein RB, Smith SM, et al. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5): reliability of substance use and psychiatric disorder modules in a general population sample. *Drug Alcohol Depend.* 2015;148:27–33. doi:10.1016/j.drugalcdep.2014.11.026
28. Grant BF, Amsbary M, Chu A, et al. *Source and Accuracy Statement: National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III)*. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism; 2014.
29. Chen CM, Slater ME, Castle IJP, Grant BF. Alcohol use and alcohol use disorders in the United States: main findings from the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III). NIH Publication No. 16-AA-8020. National Institute on Alcohol Abuse and Alcoholism; 2016.
30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th. American Psychiatric Association; 2013.
31. Grant BF, Goldstein RB, Chou SP, et al. *The Alcohol Use Disorder and Associated Disabilities Interview Schedule—Diagnostic and Statistical Manual of Mental Disorders, Version (AUDADIS-5)*. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism; 2011.
32. McDowell Y, Sher KJ. The alcohol use disorder and associated disabilities interview schedule—diagnostic and statistical manual of mental disorders—fifth edition version. Available from: https://www.phenxtoolkit.org/toolkit_content/supplemental_info/atos/additional_info/NESARC_III_Manual.pdf. Accessed April 25, 2025.
33. Zucker RA, Ellis DA, Fitzgerald HE. Developmental evidence for at least two alcoholisms. I. Biopsychosocial variation among pathways into symptomatic difficulty. *Ann N Y Acad Sci.* 1994;708(1):134–146. doi:10.1111/j.1749-6632.1994.tb24706.x
34. Hu MC, Davies M, Kandel DB. Epidemiology and correlates of daily smoking and nicotine dependence among young adults in the United States. *Am J Public Health.* 2006;96(2):299–308. doi:10.2105/AJPH.2004.057232
35. Lynskey MT, Heath AC, Bucholz KK, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA.* 2003;289(4):427–433. doi:10.1001/jama.289.4.427
36. Dawson DA, Goldstein RB, Chou SP, Ruan WJ, Grant BF. Age at first drink and the first incidence of adult-onset DSM-IV alcohol use disorders. *Alcohol Clin Exp Res.* 2008;32(12):2149–2160. doi:10.1111/j.1530-0277.2008.00806.x
37. Tyrfinngsson T, Thorgeirsson TE, Geller F, et al. Addictions and their familiarity in Iceland. *Ann N Y Acad Sci.* 2010;1187(1):208–217. doi:10.1111/j.1749-6632.2009.05151.x
38. Gruzza RA, Krueger RF, Racette SB, Norberg KE, Hipp PR, Bierut LJ. The emerging link between alcoholism risk and obesity in the United States. *Arch Gen Psychiatry.* 2010;67(12):1301–1308. doi:10.1001/archgenpsychiatry.2010.155
39. Mennella JA, Pepino MY, Lehmann-Castor SM, Yourshaw LM. Sweet preferences and analgesia during childhood: effects of family history of alcoholism and depression. *Addiction.* 2010;105(4):666–675. doi:10.1111/j.1360-0443.2009.02865.x
40. Lees B, Aguinaldo L, Squeglia LM, et al. Parental family history of alcohol use disorder and neural correlates of response inhibition in children from the Adolescent Brain Cognitive Development (ABCD) study. *Alcohol Clin Exp Res.* 2020;44(6):1234–1244. doi:10.1111/acer.14343
41. Christensen HB, Bilenberg N. Behavioural and emotional problems in children of alcoholic mothers and fathers. *Eur Child Adolesc Psychiatry.* 2000;9(3):219–226. doi:10.1007/s007870070046
42. Dawson DA. The link between family history and early onset alcoholism: earlier initiation of drinking or more rapid development of dependence? *J Stud Alcohol.* 2000;61(5):637–646. doi:10.15288/jsa.2000.61.637
43. McGue M, Iacono WG, Legrand LN, Elkins I. Origins and consequences of age at first drink. II. Familial risk and heritability. *Alcohol Clin Exp Res.* 2001;25(8):1166–1173. doi:10.1111/j.1530-0277.2001.tb02331.x

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