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A Twin Study of Genetic Heritage and Environmental Influences on Tobacco Susceptibility and Initiation on Early Age

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ABSTRACT

Purpose: Tobacco product susceptibility is defined as the interest a person has to start smoking. Tobacco product initiation refers to whether a person has ever used tobacco products. We aim to understand and explain how genetic and environmental factors affect tobacco products' susceptibility and initiation in children. **Methods:** The classical twin model estimates three sources of variance: additive genetic (A), shared environmental (C), and unique environments (E). Each source of variance is latent and is calculated from the similarity in the correlations of twin pairs on a phenotype. The magnitude of difference in the correlation of a particular phenotype by zygosity is used to attribute additive genetic or shared environmental sources of variance. Data for this study were obtained from The Adolescent Brain Cognitive Development (ABCD) study. **Results/Findings:** A total of 884 twin pairs with study variables data were included in the present analyses. We estimate how much the variation in a phenotype is due to additive genetic effects (A), the common environment (C), and the unique, random environment (E) by SAS software. Tobacco products' susceptibility is primarily influenced by environmental factors, especially one's unique factors (C^2=37%, p<.0001 vs. E^2=63%, p<.0001). In comparison, the variance associated with tobacco products' initiation was close between common and unique environmental factors (C^2=32%, p=0.02 vs. E^2=29%, p=0.02). **Conclusion:** This study suggests that environmental factors, incredibly unique environments, impact tobacco product susceptibility, and there is an additive genetic liability combined with environmental factors that can explain tobacco product initiation at an early age. This result advocates intervention strategies focusing on the unique environment to decrease children's smoking susceptibility and calls for more studies on the genetic components of smoking initiation.

CHAPTER 1: INTRODUCTION

Our study is the first to analyze the genetic and environmental influences on children's interest and usage of tobacco products' using Adolescent Brain and Cognitive Development (ABCD) data, which has a large sample size and a diverse population in the country. We aim to understand and explain to what extent additive genetic and environmental factors affect the susceptibility to tobacco product use and tobacco product ever use.

CHAPTER 2 – BACKGROUND

Tobacco use is the leading cause of preventable disease and death in the United States. Most tobacco use begins during youth and young adulthood. Around 90 percent of adult cigarette smokers in the U.S. first tried cigarettes by age 18, and 98 percent first tried cigarettes by age 26. According to National Youth Tobacco Survey, 2011-2018, the percentage of current tobacco product users showed a notable resurgence since the reversal of its downtrend in 2018. To be noticed, the upsurge in tobacco product use was mainly correlated with electronic cigarette (e-cigarettes) use.

In 2014, e-cigarettes surpassed cigarettes as the most-used tobacco product among adolescents in the United States. Since then, more teens have been using e-cigarettes and other non-cigarette tobacco products [1-4]. In 2020, 19.6% of high school and 4.7% of middle school students reported using e-cigarettes in the past 30 days [2]. During the COVID pandemic, 37.9% of e-cigarette users among youth and young adults reported increasing e-cigarette use [5]. Although the long-term health effects of e-cigarettes are still being investigated, a growing number of studies have also documented lung injury [6, 7], mental health problems [8], and brain development [9, 10]

associated with e-cigarettes in adolescents. Longitudinal studies [11-14] have also shown that adolescents who try e-cigarettes are at greater risk of starting to use other substances, such as combustible tobacco and marijuana, and becoming regular users of these substances than adolescents who do not use e-cigarettes.

Both environments and genes affect smoking behavior. Some common environmental factors are peer pressure, smoking attractiveness, and tobacco use by family members. Behavioral genetic analysis can help conduct targeted public health programs dealing with e-cigarettes and tobacco threats. Previous behavioral genetics studies[15-17] of e-cigarette use in youth and young adults suggest that environmental factors in the family play a dominant role in e-cigarette use initiation, consistent with findings in tobacco. Previous studies of the heritability of tobacco use in youth and young adults using behavioral genetic designs have shown that additional genetic and environmental effects contribute uniquely to lifetime tobacco use and current tobacco use.
However, limited statistical power and relatively older age (young adults) impeded the generalizability to the teen population.

The Adolescent Brain and Cognitive Development (ABCD) Study followed over 10,000 9–10 -year-old adolescents with susceptibility to use tobacco products (including e-cigarettes, cigarettes, cigars, smokeless tobacco, hookah, pipe, and nicotine replacement therapy (NRT)), among many other constructs [18]. ABCD Study includes 1,800 monozygotic and dizygotic twin pairs, intending to explore the genetic and behavioral contributions to various health outcomes [19]. ABCD data enables us to conduct behavioral genetic analysis on a large and diverse population at an early age.

CHAPTER 3 – DATA AND METHODS

Data for this study were obtained from The Adolescent Brain Cognitive Development (ABCD) study [18]. ABCD is the most extensive study in the United States on brain development and child health. 11,880 children aged 9 and 10 were enrolled at baseline at 21 study sites in the United States. Wave 1 participants were recruited through a probability sample of schools selected for sex at birth, race/ethnicity, socioeconomic status, and urbanicity to maintain the sample demographics following the American Community Survey 3rd and 4th-grade enrollment statistics at each site. This study has collected neurocognition, physical and mental health data, social and emotional functions, and culture and environment data. Study procedures were approved by the UC San Diego Central Institutional Review Board (IRB) and each local institutional IRB. A total of 884 twin pairs with data on the study variables were included in the present analyses.

Measures

Zygosity

Saliva and blood were collected to determine whether participants were monozygotic (MZ) or dizygotic (DZ) twins through genotyping [20]. For those twins whose zygosity information was missing, researchers rated the zygosity according to their physical characteristics and similarity. The parameters included facial appearance, complexion, hair color, hair texture, hair curliness, hair pattern, amount of hair, ear appearance, hair darkness, hair type, and eye color [21].

Tobacco products ever use, and susceptibility to tobacco products use.

Participants were first asked whether they had heard of tobacco products, such as cigarettes, smokeless tobacco, cigars, hookah, and electronic or e-cigarettes. Those who reported "Yes" were

further asked whether they have ever tried any tobacco products in their life (i.e., e-cigarette, cigarette, cigar, smokeless tobacco, hookah, pipe, and nicotine replacement therapy (NRT)). Those who reported "Yes" were classified as "ever tobacco users."

Those who reported "No" were classified as "never tobacco users" and were asked, "Have you ever been curious about using a tobacco product such as cigarettes, e-cigarettes, hookah, or cigars?" with response options of "Very curious," "Somewhat curious," "A little curious," and "Not at all curious." They were also asked, "Do you think you will try a tobacco product soon?" and "If one of your best friends were to offer you a tobacco product, would you try it?" with response options "Definitely yes," "Probably yes," "Probably not," and "Definitely not." Those who reported "Not at all curious" and "Definitely not" to all three susceptibility questions were classified as "not susceptible to tobacco use."

Statistical Methods

Twin studies estimate heritability using phenotype data from twins. The aim is to quantify the roles of genetic and environmental causes of variation in phenotypes or disease susceptibility. In this study, tobacco products' ever-use status ("ever tobacco users" or "never tobacco users") and susceptibility to tobacco product use status ("susceptible" or "not susceptible") are the binary phenotypes we are interested in. For observed phenotype data measured from MZ and DZ twins, the variance of this phenotype can be explained by variance components due to additive genetic effects (A), the shared environment (C), and the unique environment (E). Additive genetic effects encompass the impacts of multiple genes that have minor effects. Environmental effects are segregated into two categories: shared and unique. Shared environmental effects denote non-

genetic influences that twins in a family have in common, including the family's socioeconomic status or the parents' conduct. Unique environmental effects signify sources of variation specific to each individual, such as a twin experiencing an accident. It is a classic twin model called the ACE model. It is assumed that MZ twins share 100% of genes, while DZ twins share, on average, 50%. If a phenotype is heritable, the phenotype will have a higher correlation in MZ twins than DZ twins. Moreover, the excess similarity between MZ twins over DZ twins shows the level of genetic contribution. This model is shown in Figure 1 as a path diagram.

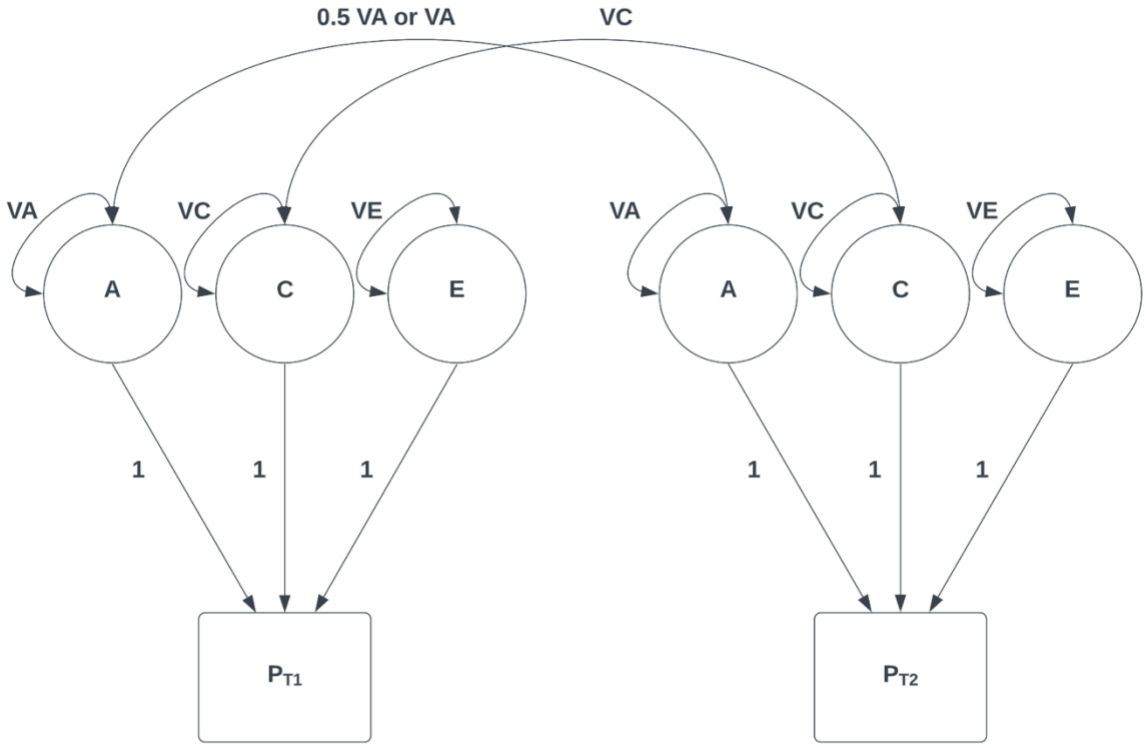

Figure 1: ACE Genetic Model for Twin Data

Path model for additive genetic (A), shared environment (C), and specific environment (E) effects on phenotypes (P) of pairs of twins (T1 and T2). Each source of variance is latent. The path between the latent A factors is VA for MZ twins and 0.5VA for DZ twins.

First, we used a correlation test (Cor) to estimate variance components additive genetic (A), shared environment (C), and specific environment (E) effects. There could be three situations [15]: 1) when the MZ correlation is twice as significant as the DZ correlation, the variance is due to additive genetic factors; 2) when the MZ correlation is close to the DZ correlation, the variance is due to shared environmental factors (C), and 3) when the DZ correlation is less than twice the MZ correlation, variance is due to both additive genetic (A) and shared environment factors (C). According to the path-tracing rule,

$$Cor_{MZ} = VA + VC;$$

$$Cor_{DZ} = 0.5 * VA + VC$$

Moreover, we can calculate variance components A, C, and E from the following equations:

$$VA = 2 *(Cor_{MZ}-Cor_{DZ});$$

$$VC = Cor_{MZ} – A$$

Then, we ran the ACE analysis using the probit model to get stringent results. The assumption for ACE model is that both MZ and DZ twins are sampled from same population [22], which means equal means/variances in Twin 1 vs. Twin 2 and equal means/variances in MZ and DZ twins. Other assumptions include random mating [23] and absence of gene-environment interactions[24]. A binary response Y and p covariates, denoted by X, are available for each twin. In this study, covariates are sex and race. The model includes covariate effects, additive genetic effects (A), the common environment (C), and the unique environment (E) effects and can be expressed as:

$$Probit\big(\Pr\big(Y_{ij} = 1\big)\big) = a_{ij} + c_i + \varepsilon_{ij}$$

Where probit(.) is the inverse function of the cumulative standard normal distribution, i is the

index for n_1 MZ and n_2 DZ twin pairs, and j (1 or 2) is the index for one of the twins in a pair. a, c, ε measure additive genetic effects (A), the common environment (C), and the unique, random environment (E) on the i^{th} twin pair. We assume that a, c, ε are independently normally distributed with mean 0 and variance A, C and E, respectively. A^2 indicates the proportion of variance due to additive genes, C^2 indicates the proportion of variance due to shared environmental sources, and E^2 indicates the proportion of variance due to the unique environment. For example:

$$A^2 = \frac{A}{A + C + E} * 100\%$$

Structural equation modeling (SEM) uses the maximum likelihood method to partition the variance of the phenotype into these three components. We used SAS software to calculate the correlation and fit the model.

CHAPTER 4 – RESULTS

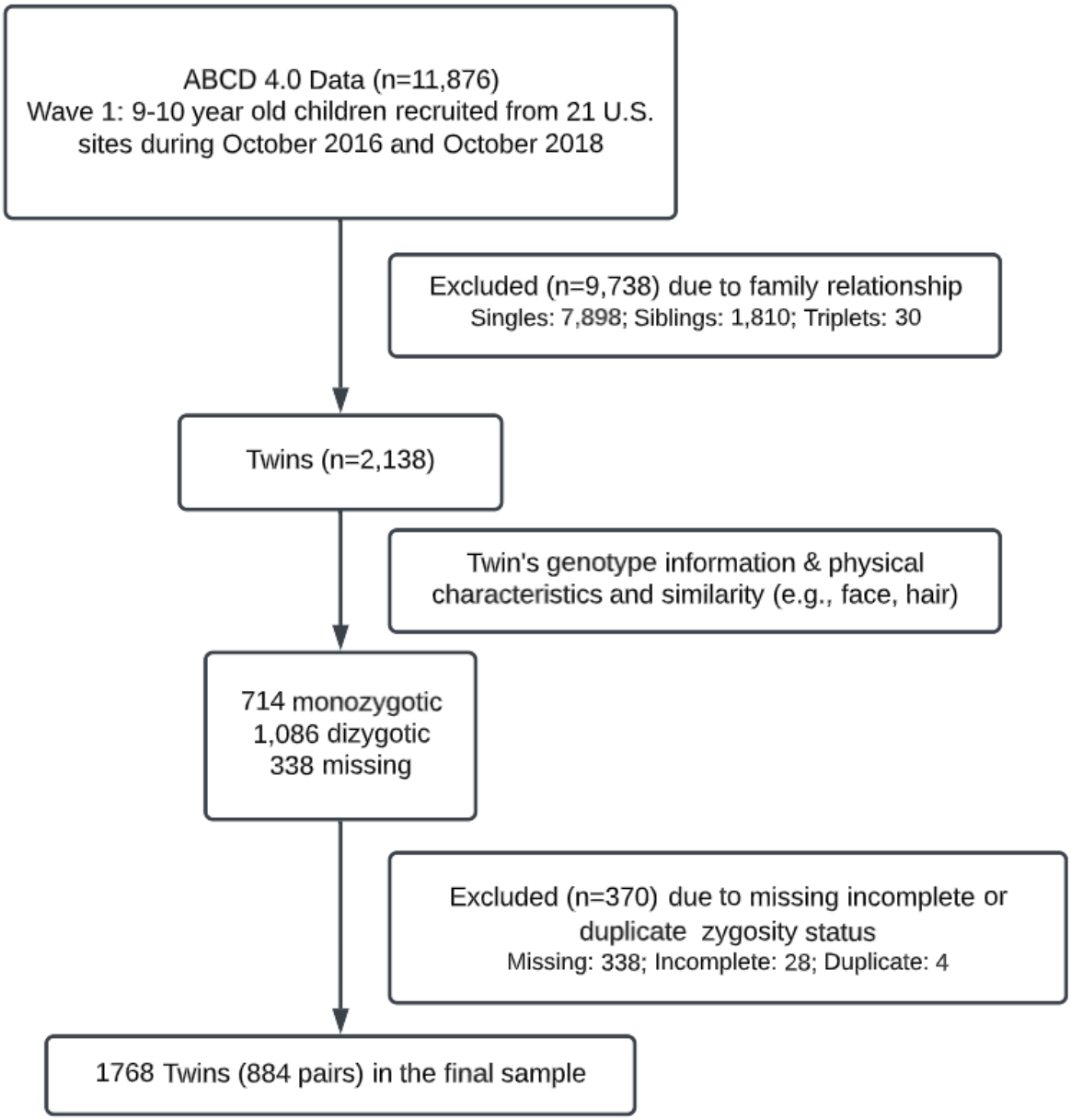

Figure 2. Flowchart of Participants Included in the Twin Study Analysis

From October 2016 to October 2018, 11,876 children were recruited from 21 U.S. sites for this study. Of this number, 9,738 individuals were excluded due to not being twins (singles, siblings, or triplets). In contrast, 338 were excluded because they lacked physical characteristics and

similarity, which made it impossible to determine their zygosity status (monozygosity or dizygosity). Additionally, 28 were excluded due to incomplete twin pairs, and 4 had duplicate information, resulting in their removal from the study. Finally, 1,768 individuals, 884 twin pairs, were included in the analysis. A diagram outlining the process of identifying eligible twins from the original sample is provided in Figure 1.

	Dizygosity (DZ) (N=1068)	**Monozygosity (MZ) (N=700)**	**Overall (N=1768)**
Age			
Mean (SD)	9.55 (0.502)	9.62 (0.486)	9.58 (0.497)
Median [Min, Max]	10.0 [9.00, 11.0]	10.0 [9.00, 10.0]	10.0 [9.00, 11.0]
Gender			
Male	535 (50.1%)	368 (52.6%)	903 (51.1%)
Female	533 (49.9%)	332 (47.4%)	865 (48.9%)
Race			
White	694 (65.0%)	461 (65.9%)	1155 (65.3%)
Black	158 (14.8%)	88 (12.6%)	246 (13.9%)
Hispanics	118 (11.0%)	74 (10.6%)	192 (10.9%)
Other	97 (9.1%)	77 (11.0%)	174 (9.8%)
Missing	1 (0.1%)	0 (0%)	1 (0.1%)
Tobacco Susceptibility			
No	744 (69.7%)	512 (73.1%)	1256 (71.0%)
Yes	169 (15.8%)	108 (15.4%)	277 (15.7%)
Missing	155 (14.5%)	80 (11.4%)	235 (13.3%)
Tobacco Initiation			
No	1054 (98.7%)	691 (98.7%)	1745 (98.7%)
Yes	14 (1.3%)	9 (1.3%)	23 (1.3%)

Table 1. Participants Characteristics

Table 1 provides a summary of the study characteristics. The study included 1768 individuals, with 1068 individuals in the dizygosity twin group and 700 individuals in the monozygotic twin group. The average age of dizygosity twins was 9.55±0.50 years, while that of monozygotic twins was 9.62±0.49 years. The percentage of male participants was similar in both groups but slightly higher than in females (DZ: 50.1% vs. 49.9%; MZ: 52.6% vs. 47.4%). Most participants were White (DZ: 65%; MZ: 65.9%). In the dizygosity group, 774 out of 1068 individuals were identified as not susceptible to tobacco, while 512 out of 700 were in the monozygotic group. There was a total of 235 missing values for tobacco susceptibility status. In the dizygosity group, 1054 out of 1068 individuals were identified as having no tobacco susceptibility, while 691 out of 700 were in the monozygotic group.

	Tobacco Susceptibility	**Tobacco Initiation**
Prevalence (% yes)		
All individuals	18.07	1.30
Dizygotic individuals	18.51	1.31
Monozygotic individuals	17.42	1.29
Pearson Correlation (p-value)		
Dizygotic Twins	0.21 (p<0.001)	0.13 (p=0.002)
Monozygotic Twins	0.19 (p=0.002)	0.44 (p<0.001)

Table 2. Pearson Correlation Results

There were similar prevalence rates of tobacco susceptibility between the dizygotic twin group (18.51%) and the monozygotic group (17.42%), with Pearson correlation results indicating a similar association between the two groups (0.21 vs. 0.19). It indicates the variance of tobacco susceptibility is due to environmental factors. As for tobacco initiation, the prevalence of individuals who had already initiated tobacco use was 1.31% in the dizygotic twin group and 1.29% in the monozygotic group. However, the Pearson correlation results suggested a stronger association between tobacco initiation in the monozygotic group, which was more than two times higher than the dizygosity group. It shows the variance is due to both additive genetic (A) and shared environment factors (C).

ACE model		
	Tobacco Susceptibility	**Tobacco Initiation**
BIC	1448.0	252.7
A^2	0	0.39 (0.07 to 0.70) P=0.02
C^2	0.37 (0.24 to 0.51) P<.0001	0.32 (0.04 to 0.59) P=0.02
E^2	0.63 (0.49 to 0.76) P<.0001	0.29 (0.05 to 0.54) P=0.02
Post-hoc Analysis - CE model		
	Tobacco Susceptibility	
BIC	1444.2	
C^2	0.37 (0.24 to 0.51)	

	P=0.56	
E^2	0.63 (0.49 to 0.76) P<.0001	

Table 2. ACE and post-hoc Analysis Results

A^2 indicates the proportion of variance due to additive genes,
C^2 indicates the proportion of variance due to shared environmental sources,
and E^2 indicates the proportion of variance due to the unique environment.

We tested the fit of all three sources: A (Heritability from Additive Genes), C (Common Environment), and E (Unique Environment). For tobacco susceptibility, the contribution of A was found to be negligible, and thus dropping A from the model was more appropriate. Subsequently, we conducted post-hoc analysis using CE model to test the fit of two sources: C (Common Environment) and E (Unique Environment). Results showed that a unique environment could explain 63% (49%-76%) of the variance in tobacco susceptibility.

For tobacco initiation, both genetics and environment play a role and additive genes are the largest source of variance (A^2=39%, p=0.02). ACE model showed 39% (7%-70%) of the variance could be explained by heritability from additive genes, 32% (4%-59%) of the variance be explained by common environment, 29% (5%-54%) of the variance be explained by unique environment.

CHAPTER 5 – DISCUSSION

The use of tobacco products during childhood and adolescence can lead to significant health issues among young individuals, such as an increased risk of heart disease, chronic lung disease, and even nicotine addiction. Therefore, understanding the determinants of tobacco product use behavior will help us find the best intervention for designing effective interventions to reduce such usage and associated risks. This study aims to understand and explain how additive genetic and environmental factors affect susceptibility to tobacco product use and lifetime use.

According to the analysis results, in teens aged 9-11, the variance of tobacco product initiation can be explained by heritability from additive genes, common environment, and unique environment. Although the prevalence of tobacco product initiation is only 1.30%, 18.07% of participants were susceptible to tobacco products. An increase in tobacco product use is expected if no intervention is conducted. And the unique environment best explains the variance of susceptibility to using tobacco products.

This research has several limitations that should be considered. Firstly, tobacco products are an umbrella term; no details about each product are available in the original data. According to the definition in the ABCD study survey, tobacco products include cigarettes, smokeless tobacco, cigars, hookah, and electronic or e-cigarettes. Each tobacco product may have different characteristics. For example, a previous study showed that shared environment plays a more significant role in e-cigarette use than additive genes. However, in this study, we cannot identify the behavior genetics information for each of the product. Secondly, the prevalence of tobacco initiation is not constant and may change as age increases. Whether the change in prevalence will

result in different ACE analysis result, need further investigation. Because of that, one should be cautious when generalizing the results to different age groups.

Despite these limitations, this new evidence on the behavioral genetics of tobacco product use among teens is consistent with prior evidence for smoking behavior [25]. And our study is the first one using the large, diverse, 9-11 year old children population in the US. It provides evidence of preventive efforts focusing on the genetics impact on tobacco initiation and the social environment for tobacco susceptibility.

By understanding the genetic inheritability of tobacco initiation, we assume that identifying genetically high-risk populations and spending more resources to support them will be beneficial for children. And potentially, by understanding more genetics details in the future, drug companies will have incentives to design effective smoking cessation medications for high-risk population [26]. Genetics research and programs in other diseases have already developed. Alcohol use disorder (AUD) is also a moderate heritable phenotype [27], influenced by multiple genes. To identify these specific genes, the Collaborative Studies on Genetics of Alcoholism (COGA) has been funded since 1989. It improved our understanding of how genes affect AUD, which will help in the development and enhancement of prevention and treatment strategies. It will be beneficial if similar programs could be initiated for children's tobacco initiation.

As for tobacco susceptibility, interventions in social environments, especially unique environments, are warranted. Environmental influences are classified as the common environment that makes the twins more similar and unique environments that contribute to differences between the twins. Thus,

personalized counseling could be a way to decrease tobacco susceptibility.

In summary, this study suggests that environmental factors, incredibly unique environments, impact tobacco product susceptibility, and there is an additive genetic liability combined with environmental factors that can explain tobacco product initiation at an early age. Evidence-based intervention strategies are needed to prevent tobacco use at a young age. This result advocates intervention strategies focusing on the unique environment to decrease children's smoking susceptibility and calls for more studies on the genetic components of smoking initiation.

APPLICATION OF PUBLIC HEALTH COMPETENCIES

Foundational competency:

- Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software as appropriate

Concentration competencies:

- Apply appropriate statistical methods for estimation and inference using a software package for data management, statistical analyses, and data presentation.
- Develop written and oral presentations based on statistical findings for both public health professionals and lay audiences.

Explanation:

This project used the open-access result data from Adolescent Brain Cognitive Development (ABCD) study. We ran a secondary analysis using those quantitative data. The primary purpose is to estimate the extent of additive genetic and environmental factors using a Twin model via SAS software. The preliminary analysis results have been presented in the 2nd annual Midwest Public Health Innovation and Research Expo (PHIRE). Final analysis results will be shared in the Capstone final presentation and report in 2023.

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BIOGRAPHY:

Yadi Liu is a fourth year PharmD and MPH student focusing on biostatistics at the University of Nebraska Medical Center. She received a bachelor's degree in pharmacy from China Pharmaceutical University in Nanjing, China. She is a research assistant at the University of Nebraska Medical Center College of Public Health and a pharmacist intern at Nebraska Medicine. Her interests include twin study, health promotion, and practice areas where pharmacy and public health intersect.