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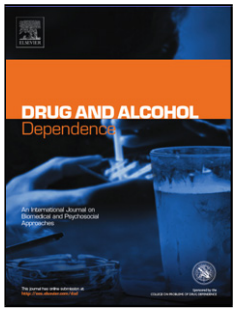

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The genetic relationship between cannabis and tobacco cigarette use in European- and African-American female twins and siblings*

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Highlights

- Heritability of cigarette and cannabis use is similar across ethnic groups.
- No ethnic differences in genetic or environmental influences on covariance.
- Shared environment more important in European-Americans.

ABSTRACT

Background: Use of cigarettes and cannabis frequently co-occurs. We examine the role of genetic and environmental influences on variation in and covariation between tobacco cigarette and cannabis use across European-American (EA) and African-American (AA) women. *Methods*: Data on lifetime cannabis and cigarette use were drawn from interviews of 956 AA and 3,557 EA young adult female twins and non-twin same sex female full siblings. Twin modeling was used to decompose variance in and covariance between cigarette and cannabis use into additive genetic, shared, special twin and non-shared environmental sources. *Results*: Cigarette use was more common in EAs (75.3%, 95% C.I. 73.8-76.7%) than AAs (64.2%, 95% C.I. 61.2-67.2%) while cannabis use was marginally more commonly reported by AAs (55.5%, 95% C.I. 52.5-58.8%) than EAs (52.4%, 95% C.I. 50.7-54.0%). Additive genetic factors were responsible for 43-66% of the variance in cigarette and cannabis use. Broad shared environmental factors (shared + special twin) played a more significant role in EA (23-29%) than AA (2-15%) women. In AA women, the influence of non-shared environment was more pronounced (42-45% vs. 11-19% in

EA women). There was strong evidence for the same familial influences underlying use of both substances (r_A=0.82-0.89; r_{C+T}=0.70-0.75). Non-shared environmental factors were also correlated but less so (r_E=0.48-0.66). No racial/ethnic differences were apparent in these sources of covariation. *Conclusion*: Heritability of cigarette and cannabis use is comparable across racial/ethnic groups. Differences in the contribution of shared and non-shared environmental influences indicate that different factors may shape substance use in EA and AA women.

KEYWORDS: Cannabis; Tobacco; Cigarette; Initiation; Twin; Heritability

1. INTRODUCTION

According to the most recent estimates from the National Survey of Drug Use and Health, 86.8% of lifetime cannabis users aged 12 and older reported a lifetime history of tobacco cigarette use while 61.7% of cigarette smokers also reported smoking cannabis during their lifetime (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014). Adolescents reporting dual use are more likely to experience problems with both drugs, including rapid escalation to more involved stages of use and difficulty quitting (Agrawal et al., 2008; Peters et al., 2012; Timberlake et al., 2007).

Contributors to the co-occurring use of cannabis and cigarettes include risk and protective influences that shape a general liability to experimentation with multiple substances (Hawkins et al., 1992) as well as influences specific to cigarette and cannabis co-use (e.g., shared route of administration; (Agrawal et al., 2012)). Both genetic and environmental influences play a role in the shared vulnerability to cannabis and cigarette use (Agrawal et al., 2010; Han et al., 1999; Young et al., 2006). One study suggested a genetic correlation as high as 0.75 (Agrawal et al., 2010) between cannabis and cigarette use while another suggested a more modest overlap of r = 0.31 (Young et al., 2006). Environmental contributions on these early stages of substance use can be further parsed into those that make members of twin and sibling pairs similar to each other (i.e., shared environment) and those that are individual-specific, with more robust evidence for the shared influences being correlated than the non-shared (Young et al., 2006). However, a study using a subset of the data from this study showed that in African American

(AA) women, the relationship between timing of onset of cigarette smoking and cannabis use was prominently attributable to overlapping individual-specific environmental factors (r = 0.95) (Sartor et al., 2009).

The strong evidence for the heritability of and the co-heritability between lifetime use of cannabis and cigarettes comes almost entirely from international research conducted in twin samples of European origin. In U.S. populations, this is particularly problematic given significant variations in the rates of cannabis and cigarette use across race/ethnicity (Garrett et al., 2011; Griesler and Kandel 1998; Keyes et al., 2015; Wallace, Jr. et al., 2003; Wu et al., 2014). Racial/ethnic differences are also particularly pronounced in females with AA adolescent girls and young adult women appearing to be less likely than their European American (EA) counterparts to use cigarettes and cannabis (Garrett et al., 2011; Keyes et al., 2015; SAMHSA, 2014; Wallace, Jr. et al., 2003). In addition, although cigarette use typically predates cannabis use in EAs, reverse gateways (cannabis before cigarettes/alcohol) are somewhat more common in AAs than EAs (Sartor et al., 2013; Vaughn et al., 2008). Notably, these variations in prevalence and sequence may relate to differing societal attitudes towards cannabis and cigarette use, the relative availability and exposure opportunity of the two drugs as well as to putative differences in biological response to anticipation and receipt of drug-related rewards. For cigarette use, we are only aware of 3 studies, including two by us in the sample under study here, that show that additive genetic factors explain similar proportions of variance (40-50%) in AAs and EAs (Sartor et al., 2009, 2015; Whitfield et al., 2007). However, in a recent study by our group (Sartor et al., 2015), the remainder of the variance in cigarette use was solely attributable to individual-specific environmental factors (44%) in AA twins while in EA twins, substantial influence of both individual-specific (10%) and shared environmental factors (34%) was noted for cigarette use. Likewise, we have previously reported that timing to cannabis use is heritable in AA female twins (0.52) and that the role of shared environment is limited (Sartor et al., 2009). However, no study to date has examined the bivariate relationship between lifetime use of cannabis and cigarettes in AA and EA twins.

In the current study, we utilize a large, general population sample of adult female twins and non-twin siblings of self-described AA (n=956) and EA (n=3557) ancestry to examine the role of additive genetic, shared environmental and individual-specific environmental influences on the covariance between lifetime cigarette and cannabis use and the extent to which the magnitude of their contribution varies across race/ethnicity.

We leveraged a sample of females who are notably understudied in addiction research. Importantly, AA females appear to be at low risk for both cannabis and cigarette involvement, relative to EA females, both during adolescence (Keyes et al., 2015; Wallace, Jr. et al., 2003) and adulthood (SAMHSA, 2014). Thus, access to related individuals of AA ancestry is a unique aspect of the present study – we are also not aware of other datasets of this magnitude with AA twins. Further, by utilizing a young adult sample, we circumvented concerns regarding lack of adequate opportunity for experimentation with cannabis (Wagner and Anthony 2002).

2. MATERIALS AND METHODS

2.1 Participants

The sample was composed of female twins who completed the fourth wave of data collection for the Missouri Adolescent Female Twin Study MOAFTS and female participants from the Missouri Family Study (MOFAM). Data on male twins were not collected in MOAFTS, although male siblings did participate in MOFAM but were not included in the present study.

2.1.1 MOAFTS . The Missouri Adolescent Female Twin Study (MOAFTS; Heath et al., 2002; Knopik et al., 2005) is a population-based longitudinal study of female twin pairs born between July 1, 1975 and June 30, 1985 in Missouri to Missouri-resident parents The sample was demographically representative of the Missouri population at the time the twins were born, with nearly 15% of twins being African-American (AA) and the remainder being of European-American (EA) descent. A baseline interview was conducted with 3,258 twins beginning in 1995 (median age=15 years). All available twins were targeted for three waves of telephone interviews (Waves 1, 4, and 5, at median ages 15, 22, and 24 years, respectively). Between 2002 and 2005, all twins from the target cohort (excluding those who had

withdrawn from the study or whose parents asked that the family not be re-contacted) were contacted for Wave 4 interviews. As all twins (N=3,787) were 18 years of age or older at the time of recruitment for Wave 4, sensitive questions regarding their illicit substance use was queried. Therefore, we limited the sample to MOAFTS participants who completed wave 4 interviews, but data from other waves (including the subsequent Wave 5, conducted from 2005 to 2008), which were available for over 95% of Wave 4 participants, were integrated as well. The Wave 4 sample consisted of 1,038 monozygotic (MZ) twin pairs, 735 dizygotic (DZ) twin pairs and 241 twins whose co-twins did not participate.

The MOAFTS protocol was approved by the Washington University School of Medicine Human Research Protections Office. All twins 18 years old or older gave informed consent prior to study participation.

2.1.2 MOFAM. MOFAM is a longitudinal family study that included high-risk and low-risk subjects and was designed to investigate the impact of paternal alcoholism on offspring outcomes in an ethnically diverse sample of youth, with oversampling of AA families (55%) to increase the statistical power to detect differences in outcomes by race/ethnicity. As detailed elsewhere (Calvert et al., 2010), between 2003 and 2009, Missouri state birth records were used to identify families with at least one child aged 13, 15, 17 or 19 years (the same age range targeted in MOAFTS) and at least one full sibling aged 13 or older. Biological mothers completed brief telephone screening interviews to determine level of familial risk for alcoholism. Families in which the mother reported that the biological father had a history of excessive drinking were classified as “high risk.” All others were classified as “low risk.” An additional group of families was selected from men identified through driving records as having 2 or more drunk-driving convictions and classified as “very high risk.” Sample enrollment occurred over 6 years. A total of 731 females (of 1,461 offspring interviewed) completed at least one interview. For the current analyses, 163 full-sibling pairs, 30 full-sibling trios, and 315 individuals with no female sibling interview data were included – 81% of these women were interviewed at least twice. Of the 511 women who were recruited in the first 3 years and were interviewed at least once, 89% had 2 or more, and 73% had 3 or more follow up

interviews. Rates are comparable across EA and AA women. These retention rates are quite good, particularly in light of the high risk nature of the families to which these women belonged.

The MOFAM study protocol was approved by the Washington University School of Medicine Human Research Protections Office and by the Ethics Board of the State Department of Health and Senior Services in accordance with regulations governing the use of vital records in research. All subjects aged 18 and older provided informed consent prior to interview, with parental consent and offspring assent obtained for those under age 18 prior to participation.

2.2 Procedure and Assessment Battery for MOAFTS and MOFAM

MOAFTS and MOFAM assessments were nearly identical by design to facilitate integration of data across studies (with adjustments for differences in ascertainment strategies). In both studies, data were collected via telephone interview by trained interviewers using a modified version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994). The SSAGA was designed to assess substance use history, psychiatric disorders, and other related psychosocial domains. Other than the wave 5 MOAFTS interview, which covered the 2 years between Wave 4 and 5 assessments, interviews queried lifetime psychiatric and psychosocial history.

Lifetime Cigarette use. Cigarette use was defined as ever having smoked one or more cigarettes. Participants who responded “Yes" to the question “Have you ever tried a cigarette?” at any wave of data collection were classified as positive for use.

Lifetime Cannabis use. Participants who responded “Yes" to the question “Have you ever used marijuana?” at any wave of data collection were classified as positive for use.

Those who reported a lifetime history of use were also asked about how old they were when they first used the substance.

2.3 Data Analysis: Twin-Sibling Modeling

Quantitative genetic analyses were used to estimate the relative contributions of genetic and environmental factors to use of cigarettes and use of cannabis, and the overlap between them. Classical

twin models were used to estimate the role of additive genetic factors (A), shared environmental factors (C; environmental influences that make twins similar to each other), and non-shared environmental factors (E; environmental influences not shared by twins, as well as error variance). Non-additive genetic influences (D) were not modeled as there was no evidence for them from inspection of the twin correlations (Neale and Cardon 1992). Correlations in DZ twin and non-twin siblings, who share their genetic material to the same extent, were compared and differences in these correlations were attributed to an additional special twin environment parameter (T; sources of twin similarity that do not relate to non-twin sibling resemblance; e.g., sharing a classroom, in-utero effects).

A bivariate model was fitted to raw categorical data from twins and siblings in the statistical software package Mx (Neale, 2004), which uses full information maximum likelihood estimation. A series of sub-models were tested to assess statistical significance of the A, C, T, and E influences and whether these influences could be equated across AA and EA subsamples. The difference between the -2 log likelihood fit of the full model and the nested sub-model, which is distributed as chi-square for the given degrees of freedom, was used to determine relative fit. All twin models were adjusted for age and study design variables (MOFAM low risk, high risk or very high risk).

3. RESULTS

3.1 Substance Use

Cigarette use was more common in EAs (75.3%) relative to AAs (64.2%) while cannabis use was marginally, but significantly, more commonly reported by the AA (55.5%) than the EA (52.4%) participants. Cigarette use (mean age at onset ~14 years) typically preceded cannabis use (mean age at onset ~17 years) in both racial/ethnic groups (see Table 1). As shown in Table 1, 50.3 and 46.4% of EA and AA participants respectively reported using both substances. While a fair proportion of women reported cigarette use alone (25.0 and 17.8% for EA and AA respectively), cannabis use in the absence of cigarette use was uncommon but more prevalent in AA (9.3%) relative to EA (2.1%) women. Reverse gateways (i.e., onset of cannabis use before the onset of cigarette use, by at least one year) were

uncommon in general, however AA women (23.5%) were more likely than EA women (5.4%) to endorse this pattern of onsets.

3.2 Twin-Sibling Models.

Twin and sibling pair correlations were lower in AA compared to EA women (Table 2). Details of the model-fitting procedure are presented in Supplementary Table 1[1]. The model-fitting indicated that there were significant familial influences on both cigarette and cannabis use in AAs; however, we could not determine the extent to which this familiality was attributable to genetic, shared environmental, and/or twin specific environmental factors (either all A parameters could be dropped or all C+T parameters could be dropped, but a model dropping A, C, and T parameters simultaneously was rejected). For EAs, there were genetic influences on both cigarette and cannabis use and either source of familial environment, C or T, could be excluded from the model, but not both.

Based on this pattern of results, for both racial/ethnic groups and substances, we proceeded with a model that allowed for A and E and combined the sources of familial environment (C+T; broad family environment) into a single parameter (Table 3). Using this model, we noted that, for each substance, while either A or C+T could be equated across racial/ethnic groups, the total extent of familial variance (A+C+T) was substantially greater in EA relative to AA women (i.e., for cigarettes: 54% in AA *vs.* 89% in EA; for cannabis: 58% in AA *vs.* 81% in EA). Consequently, the role of individual-specific environment was significantly less pronounced in EA women, particularly for cigarette use. Sensitivity analyses revealed that estimates of E for cigarette use in AA women might be 2.15 to 7.35 times greater than those for their EA counterparts (Supplemental Figure 1[2]), and that for cannabis use, the E in AA women might be 1.10 to 3.70 times greater than the EA estimate (Supplemental Figure 2[3]).

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Finally, we estimated the extent of genetic (r_A), broad familial environmental (r_{C+T}) and individual-specific environmental (r_E) correlations for both racial/ethnic groups (Table 4). We were unable to resolve the extent to which r_A or r_{C+T} contributed to the covariance between cigarette and cannabis use in AA twins. However both genetic and family environmental sources of covariance could not be simultaneously constrained to zero, indicating overlapping sources of familial influence with insufficient power to determine the source of the familial overlap. For the EA twins, both r_A and r_{C+T} were significant and substantial; confidence limits indicated the possibility of complete overlap across substances in both sources of variance. Despite racial/ethnic differences in the magnitude of E for each substance, r_E was moderate for both AAs and EAs, and could be equated in magnitude across the racial/ethnic groups.

4. DISCUSSION

To our knowledge, this is the first study to examine the role of genetic and environmental influences on cannabis use, and on covariation between cannabis use and cigarette use, separately in EA and AA women. Our study also includes the largest number of AA twins currently available for the study of substance use. We broadly replicated existing racial/ethnic trends in cannabis and cigarette use with one exception in that rates of cannabis use in our sample were comparable, if not marginally higher in AA than EA women and this difference was more pronounced in MOAFTS, which is a general population twin sample. As we relied on multiple longitudinal reports of cannabis use, it is possible that our study design allowed participants greater opportunity to admit to a potentially illicit behavior, particularly during adulthood.

We have previously reported on univariate estimates for cigarette use in the same sample (Sartor et al., 2015); that study found that while genetic influences made similar contributions in both racial/ethnic groups, EAs and AAs diverged in the extent to which environmental factors shaped their cigarette use. While the influence of familial environmental effects were quite pronounced for EA women in the univariate analysis, non-genetic sources of variance in AA women were almost entirely individual-specific in nature. The current study reveals similar racial/ethnic differences exist for cannabis use;

familial environment was somewhat important in EA twins while individual-specific environmental factors dominated in AA pairs.

The relative contribution of individual-specific environmental factors varied, both across substances and racial/ethnic groups. In EA women, factors specific to individual members of a twin pair were modest but nearly twice as prominent (and statistically different) for cannabis (19%) as for cigarette use (11%). The role of E on both substances was also considerably greater in AA (42-45%) versus EA (11-19%) women. Estimation of E arises from the deviation of the MZ twin correlation from unity (i.e., $r_{MZ} \neq 1$; (Evans et al., 2002)) and reflects person-specific factors as well as measurement error, although the latter is unlikely to be a major concern for simple binary indices of lifetime substance use in an adult population. Such differences in twin concordance across substances and ethnicities (i.e., overall: AA > EA; in EA: Cannabis > Cigarette) might be due to variations in social attitudes towards and relative availability of substances across ethnic groups, and within the EA twins, to differences in the legal status of the drugs (Boardman et al., 2010; Shanahan and Hofer 2005). For instance, while cannabis is more socially accessible in AA populations (Wallace and Muroff 2002), AA girls (but not boys) are less likely than their EA counterparts to report lifetime and recent cannabis use (Schepis et al., 2011). Another possible contributor to reduced familial and increased E variance in AA twins and siblings may be exposure to an authoritarian form of parental monitoring (Tamis-LeMonda et al., 2008), which has been shown to be more associated with reduction in substance involvement in AA than in EA youth. Interestingly, studies have shown that the relative importance of familial sources of variance is attenuated in the presence of increased parental supervision (Dick et al., 2007). An alternate explanation is reduced power associated with the notably smaller number of AA pairs (e.g., for MZ: 111 vs. 853, Table 2). Despite this limitation, confidence limits on the correlations suggest that the reduced AA r_{MZ} and r_{DZ} are meaningful.

Despite differences in the relative magnitude of E influences on variance in cannabis and cigarette use and, importantly, across racial/ethnic groups, the degree to which these factors influenced covariance between the two substances did not vary across EA and AA women. About 23-44% (Table 4)

of the individual specific environmental variance in cannabis and cigarette use was shared. Thus, while the magnitude of person-specific influences differed for each substance, the qualitative nature of those influences was similar across them.

In contrast to the variability in estimates of E on individual differences in and between cannabis and cigarette use, the role of genetic influences was comparable across substances and racial/ethnic groups. Heritability estimates (43-66%; Table 3) were similar across racial/ethnic groups and approximated reports from other studies of European twin cohorts (Madden et al., 2004; Maes et al., 2006; Pergadia et al., 2006; Verweij et al., 2010; Vink et al., 2005). Results from the bivariate model suggested that these genetic influences were highly and possibly, perfectly correlated across the substances (Table 4). Such shared genetic factors could include predisposition to a third, heritable trait, such as a general liability to disinhibited behaviors (Hicks et al., 2011) or a shared vulnerability to the use of drugs that utilize combustion/inhalation as the main route of administration (Agrawal and Lynskey 2009; van Leeuwen et al., 2011). Alternatively, genes related to cigarette use may also be linked to onset of cannabis use, such as brain-derived neurotrophic factor (*BDNF*). The *BDNF* variant rs6265 has been linked to cigarette use at $p = 1.8 \times 10^{-8}$ (Tobacco and Genetics Consortium 2010). A recent study also related this variant to cannabis use (Agrawal et al., 2015). Another study examining polygenic scores derived from a genomewide association study of tobacco smoking found these scores to predict a modest but significant proportion of variance in cannabis use as well (Vink et al., 2014).

While we could not disentangle shared and special twin environmental influences from each other, likely due to low power, there was evidence that broad shared environmental factors were more significant for EA than AA women. This observation aligns well with multiple studies showing that AA youth are less vulnerable to peer effects (Conn and Marks 2014; Mason et al., 2014; Wallace and Muroff 2002) and deviant sibling influences (Catalano et al., 1992) and that, in fact, EA women are most susceptible to peer attitudes towards substance use (Mason et al., 2014). Even though religious attendance is more common in AA youth, its protective association with substance use is more pronounced in EA

youth (Wallace and Muroff 2002). As these factors are commonly shared by twin and sibling pairs, we anticipate that they contribute to variance in EA but not AA women.

Other notable limitations of our study include the possibility of retrospective recall bias; however as the sample is relatively young, we anticipate the effects of recall bias to be minimal. Second, as our sample consists of young women, results may not extrapolate to other demographic groups. Third, the binary indices used in this study reflect initiation and there is significant variability in the extent of cigarette and cannabis use that is not captured by them (i.e., used once or twice versus daily/problem users). Thus, we are uncertain about where in the spectrum of liability these race/ethnic differences may be occurring. Fourth, we did not assess whether participants were also smoking products that combined cannabis and tobacco. While the practice of adding tobacco to cannabis joints is uncommon in the present population (and rare in the United States; Ream et al., 2008), its role should be carefully examined in international samples where the practice is common (Belanger et al., 2011) even in individuals who do not report cigarette smoking (Belanger et al., 2013; Gage et al., 2014). We also did not query participants about blunt smoking (i.e., rolling marijuana in cigar wrappers, which may contain a small, residual amount of tobacco). The practice of blunt smoking is more common in AA populations but less so in women (Fairman 2015; Timberlake 2013). Fifth, rates of cigarette and cannabis use were somewhat lower in MOFAM, which might have impacted our estimation of C+T as MOFAM was the sole source of nontwin siblings. MOFAM women were somewhat younger than MOAFTS women at their last assessment (22 *vs*. 25 years, Table 1) and may have been marginally less likely to have surpassed the full risk period for onset of cigarette and cannabis use. This age and sample effect was accounted for in all twin modeling, nonetheless combining a general population cohort of twins with a sample with overrepresentation of high-risk families may have influenced our findings.

Our study indicates that while heritable variation in cigarette and cannabis use is comparable across racial/ethnic groups, the impact of familial versus individual-specific sources of environmental

influence vary markedly across EA and AA women. Further unpacking the substance use trajectory to identify precisely when these racial/ethnic differences emerge will be critical for future studies.

Conflict of interest: AA received peer-reviewed funding and a travel honorarium from ABMRF/Foundation for Alcohol Research prior to 12/31/12. Other authors have no interests to declare.

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Table 1. Demographic and substance use characteristics of African-American and European American female twin and sibling pairs.

	African-American n=956	European-American n=3557
MOFAM participant % (n)	42.3% (N=405)	9.2% (N=326)
MOAFTS participant % (n)	57.6% (N=551)	90.8% (N=3231)
Study Design Group		
MOFAM low risk	17.6% (N=168)	2.8% (N=98)
MOFAM high risk	12.8% (N=122)	2.0% (N=70)
MOFAM very high risk	12.0% (N=115)	4.4% (N=158)
MOAFTS (general population)	57.6% (N=551)	90.8% (N=3231)
MOAFTS: Monozygotic twin (MZ),	24.6% (N=235, with 111 pairs)	50.3% (N=1790, with 853

% (n)		pairs)
MOAFTS: Dizygotic twin (DZ), % (n)	33.1% (N=316, with 143 pairs)	40.5 (N=1441, with 663 pairs)
MOFAM: Full Sibling (FS), % (n)	42.4 (N=405, with 88 pairs and 13 trios)	9.2 (N=326, with 75 pairs and 17 trios)
Mean age at first interview (SD)	18.0 (3.8)	16.8 (3.3)
MOFAM	17.8 (3.7)	17.3 (3.4)
MOAFTS	18.2 (3.9)	16.7 (3.3)
Mean age at last interview (SD)	23.5 (3.9)	24.2 (3.0)
MOFAM	21.6 (4.3)	21.5 (4.1)
MOAFTS	24.8 (2.8)	24.5 (2.7)
Ever smoked a cigarette*, %	64.2% (61.2 – 67.2)	75.3% (73.8 – 76.7)
MOFAM	59.5% (54.7 – 64.3)	66.6% (61.4 – 71.7)
MOAFTS	67.6% (63.7 – 71.6)	76.1% (74.7 – 77.6)
Mean age at cigarette use (SD)	14.6 (3.5)	14.1 (3.2)
MOFAM	14.9 (3.4)	14.2 (3.4)
MOAFTS	14.4 (3.6)	14.1 (3.2)
Ever tried cannabis*, %	55.5% (52.5 – 58.8)	52.4% (50.7 – 54.0)
MOFAM	52.8% (48.0 – 57.7)	50.6% (45.2 – 56.0)
MOAFTS	57.7% (53.6 – 61.8)	52.5% (50.8 – 54.2)
Mean age at cannabis use (SD)	16.6 (2.7)	16.7 (2.5)
MOFAM	16.0 (2.4)	16.0 (2.5)
MOAFTS	17.1 (2.7)	16.8 (2.5)
Substance Use Profile		
Neither substance*	26.5% (23.7 – 29.3) (N=253)	22.7% (21.3 – 24.0) (N=806)
Cigarettes only*	17.8% (15.4 – 20.2) (N=170)	25.0% (23.6 – 26.4) (N=889)
Cannabis only*	9.3% (7.5 – 11.2) (N=89)	2.1% (1.6 – 2.6) (N=74)
Both cigarettes and cannabis*	46.4% (43.2 – 49.6) (N=443)	50.3% (48.6 – 51.9) (N=1788)
Substance use sequence		
Cigarettes first*	61.3% (56.7 – 65.8) (N=269)	80.3% (78.4 – 82.2) (N=1418)
Both within same year	15.3% (11.9 – 18.6) (N=67)	14.3% (12.6 – 15.9) (N=252)
Cannabis first*	23.5% (19.5 – 27.4) (N=103)	5.4% (4.4 – 6.5) (N=96)
*Significantly different between EA and AA women		

Table 2. Twin-pair and sibling-pair tetrachoric correlations for cigarette and cannabis use in African-Americans and European Americans.

	r_{MZ} (MOAFTS)	r_{DZ} (MOAFTS)	r_{FS} (MOFAM)
African Americans	N=111 pairs	N=143 pairs	N=127 pairs[a]
Use of Cigarettes	0.59 (0.35 – 0.82)	0.28 (0.02 – 0.54)	0.33 (0.08 – 0.58)
Use of Cannabis	0.63 (0.42 – 0.84)	0.30 (0.06 – 0.54)	0.53 (0.28 – 0.77)
European Americans	N=853 pairs	N=663 pairs	N=126 pairs[b]
Use of Cigarettes	0.90 (0.86 – 0.93)	0.64 (0.54 – 0.73)	0.53 (0.31 – 0.75)
Use of Cannabis	0.80 (0.75 – 0.85)	0.57 (0.47 – 0.66)	0.61 (0.40 – 0.81)
NOTE: all correlations significant at $p < 0.05$ [a] includes 88 families with two siblings interviewed, and 13 families with three siblings interviewed (yielding three pairs of respondents each) [b] includes 75 families with two siblings interviewed, and 17 families with three siblings interviewed (yielding three pairs of respondents each)			

Table 3. Standardized proportions of variance [95% Confidence Intervals] attributable to additive genetic, shared environmental, and non-shared environmental influences for the final model examining the genetic and environmental contributions to the comorbidity between cigarette and cannabis use in African-American and European-American twin and sibling pairs.

	Additive Genetic	Broad Family Environment (C+T)	Non-shared Environment
African-Americans			
Use of Cigarettes	0.52 (0.00 – 0.73)	0.02 (0.00 – 0.47)	0.45* (0.27 – 0.76)
Use of Cannabis	0.43 (0.00 – 0.78)	0.15 (0.00 – 0.55)	0.42* (0.22 – 0.67)
European Americans			
Use of Cigarettes	0.66* (0.46 – 0.88)	0.23* (0.03 – 0.43)	0.11* (0.07 – 0.15)
Use of Cannabis	0.52* (0.32 – 0.72)	0.29* (0.09 – 0.45)	0.19* (0.15 – 0.25)
* Indicates variance component significant at $p < 0.05$			

Table 4. Genetic (r_A), family environmental (broad; r_C), and non-shared environmental (r_E) correlations between cigarette use and cannabis use in African-American and European American twins and sibling pairs.

	Cross-substance r_A	Cross-substance r_C	Cross-substance r_E
African-Americans	0.82 (-1.00 – 0.91)	0.75 (-1.00 – 1.00)	0.48* (0.20 – 0.79)
European Americans	0.89* (0.71 – 1.00)	0.70* (0.26 – 1.00)	0.66* (0.41 – 0.83)
Note: r_A=additive genetic correlation, r_C=family and twin-specific environmental correlation, r_E=non-			

shared environmental correlation.
* indicates $p < 0.05$