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Age moderates non-genetic influences on the initiation of cannabis use: a twin-sibling study in Dutch adolescents and young adults

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ABSTRACT

Aims To examine the heritability of cannabis initiation, the influence of a possible twin-specific environment and the influence of age on the effects of genes and environment in Dutch adolescents and young adults. **Design** Genetic structural equation modelling was used to partition the variance in the liability to cannabis initiation into genetic and environmental components. **Setting** All participants were registered with the Netherlands Twin Register. **Participants** A total of 6208 twins (age 13–20) and 1545 siblings (age 11–25) from 3503 families participated in this study. **Measurements** Self-reported cannabis use was assessed prospectively with the Dutch Health Behavior Questionnaire. **Findings** At the median age of the sample (16.5), genetic factors explained 40% of the individual differences in liability to cannabis initiation. Twins resembled each other more than non-twin siblings, which could not be attributed to the age difference between non-twin siblings. Environmental influences increased with age. This increase applied to environmental factors shared by twins (47% of the variance), environmental factors shared by twins and siblings (24%) and environmental factors unique to an individual (13%). **Conclusion** The heritability of the liability for cannabis initiation is higher in adolescents than in young adults due to a larger contribution of environmental factors in young adults. This is due mainly to environmental factors only shared by twins and those shared by all offspring growing up in the same family, but the contribution of environmental factors specific to individuals is also larger in young adults.

Keywords Adolescents, cannabis initiation, heritability, substance, twin study.

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INTRODUCTION

Twin studies have demonstrated that genetic factors influence the liability to cannabis initiation, with heritability estimates ranging from modest (13%) to high (72%) in American samples of adolescents and young adults [1–5]. A Finnish twin study (mean age 17.5) conducted by Huizink *et al.* [6] reported a heritability of 32% for initiation to cannabis and other illicit drugs. In a Dutch sample of adult twins, heritability was estimated at 44% [7]. A recent meta-analysis of adolescent and adult studies of cannabis use initiation across the globe reported heritability estimates of 48% for males and 40% for females [8]. In most twin studies the heritability was not estimated dependent on age, although the age range of the sample was often wide, and most twin studies did not include siblings of twins.

Twin studies partition individual differences in a trait into parts due to (i) genetic and (ii) environmental differences between individuals. Adding non-twin siblings to the classical twin design permits testing whether estimates from twin studies generalize to non-twins. Environmental influences that are shared by all siblings within a family can then be distinguished from those that are shared only by twins (i.e. by siblings who are of the same age).

We are aware of only three twin studies of cannabis phenotypes that included non-twin siblings. Kendler *et al.* [9] studied cannabis use in a sample of twins and siblings aged 25–74 years and did not find evidence for a twin-specific environment. Young *et al.* [10] analysed data on repeated use of cannabis of twins and siblings aged 12–18 years and found no significant twin-specific environmental effect, although there was a trend for dizygotic twins to resemble each other more than non-twin siblings. The only study to analyse data from twins as well as siblings on cannabis initiation was conducted by Rhee *et al.* [1]. Data from 1364 twins and 760 siblings aged 12–19 years were analysed; no influence of a twin-specific environment emerged, although there was a trend for dizygotic same sex twins to resemble each other more than same sex non-twin siblings.

The relative importance of genetic and environmental factors on individual differences in cannabis initiation may vary from puberty into young adulthood. For other substance use measures, such as smoking behaviour and alcohol use, the importance of genetic factors increases while that of shared environmental factors decreases from adolescence to young adulthood [11–15]. Only one study [13] investigated the changing role of genes and environment with age for cannabis phenotypes. This study found that the heritability of cannabis use increased from adolescent to early adulthood.

In the present study we investigate the moderating effect of age on the additive genetic and environmental variance in the liability for cannabis initiation in a large sample of Dutch adolescent and young adult twins and their non-twin siblings. By adding siblings of twins to the classical twin design we investigate whether the influence of shared environmental factors on individual differences in cannabis initiation is larger in twins than in non-twin siblings.

METHODS

Participants

Participants were registered at birth with the Netherlands Twin Registry [16]. During childhood, information on emotional and behavioural problems was collected through parental and teacher reports. When the twin pair reached the age of 13 years parents were asked for informed consent to contact the adolescent twins and their non-twin siblings (aged 12 years and older) directly. Next, adolescent twins and siblings were invited to complete a questionnaire at age 14, 16 and 18 years [17].

Data were collected between 2004 and 2008. Some individuals completed the questionnaire twice, but data from the most recent survey in which both twins completed a questionnaire were included. When there was no survey in which both twins participated we selected the most recent data for an individual. If siblings participated more than once, the data were selected from the age of the sibling that was closest to the age of the twins. The total sample for analysis consisted of 6208 twins and 1545 siblings from 3503 families. There were 995 monozygotic male (MZM) twins (469 complete twin pairs), 848 dizygotic male (DZM) twins (390 complete twin pairs), 1444 monozygotic female (MZF) twins (778 complete twin pairs), 1039 dizygotic female (DZF) twins (480 complete twin pairs), 871 male and 1011 female twins from dizygotic opposite sex (DOS) twin pairs (809 complete twin pairs), 678 brothers of twins and 867 sisters of twins. At most, one brother and one sister per family were included in the analyses; the data of remaining siblings were excluded ($n = 76$). An overview of the sample configuration is shown in Table 1. The twins' mean age was 16.23 years [range 13–20, standard deviation (SD) = 1.5]; that of siblings 17.6 years (range 11–25, SD = 2.8). The mean age difference between

Table 1 Family configuration in the sample according to zygosity and number of additional non-twin siblings.

		No siblings	*Brother*	*Sister*	*Brother and sister*	*Total*
MZM	Twin pair	251	97	115	6	469
	Single twin	39	8	10	0	57
DZM	Twin pair	207	78	99	6	390
	Single twin	49	4	13	2	68
MZF	Twin pair	375	149	149	5	678
	Single twin	61	9	16	2	88
DZF	Twin pair	271	88	112	9	480
	Single twin	62	6	11	0	79
DOS	Twin pair	479	139	180	11	809
	Single twin	211	22	30	1	264
No twins		–	31	85	5	121
Total		2005	631	820	47	*3503*

MZM: monozygotic male; DZM: dizygotic male; MZF: monozygotic female; DZF: dizygotic female; DOS: dizygotic opposite sex.

twins and their brothers was 0.95 (SD = 2.99). The mean age difference between twins and their sisters was 1.32 (SD = 2.94). Most siblings were slightly older than the twin (69% of the sisters and 64% of the brothers).

Same-sex twin pairs' zygosity was determined by DNA analysis ($n = 1136$); blood group polymorphisms ($n = 409$); or questionnaire items from the previously collected parental reports ($n = 2781$). Agreement between the two methods of zygosity assignment was 93% [18].

Measures

In the Dutch Health Behavior Questionnaire (DHBQ), subjects were asked whether they ever used cannabis and, if so, how many times. Responses were recoded into the variable 'initiated cannabis' with two possible categories: 0, when a subject never used cannabis; and 1, when a subject had ever used cannabis.

Twin-family studies

Twin-family studies make use of the different degree of genetic relatedness between twins and non-twin family members to estimate the relative contribution of genes and environment to individual differences (variance) in a trait. MZ twins are genetically (almost) identical while DZ twins and non-twin siblings share on average 50% of their segregating genes [19]. The correlations within twin pairs and twin-sib pairs provide a first impression of the relative contribution of genes and environment to variation in a trait. When MZ twins resemble each other more than DZ twins, genetic effects (A) are implied. When the DZ correlation is more than half the MZ correlation, there is also evidence for environmental effects shared by offspring from the same family (C). Differences within MZ twin pairs are due to unique environmental effects, which includes measurement error (E). Unique environmental factors also contribute to differences within DZ and sibling pairs. However, in these pairs genetic factors also contribute to phenotypic differences. Environmental influences shared by twins but not siblings are suggested when DZ twins correlation exceeds that of non-twin siblings [20].

Genetic modelling

Genetic structural equation modelling was carried out in Mx [20] by fitting liability models to dichotomous data. In this approach, a normal distributed liability (with standard Z-scores as unit of measurement) underlying the categorical variable is assumed. Liability is the sum of the effects of many genetic and environmental factors. In the case of a dichotomous trait such as cannabis initiation, the liability distribution has one threshold which divides the sample into 'unaffected' and 'affected' individuals. The proportion of the distribution above the threshold reflects the prevalence. Resemblance between relatives for this underlying liability distribution can be assessed with tetrachoric correlations.

We started with fitting a saturated model in which all thresholds and all tetrachoric correlations were estimated. Thresholds were estimated separately for twins and non-twin brothers and sisters, and were adjusted for possible age effects (for males and females separately) by including the regression of age (standardized with zero mean and unit variance) on cannabis initiation in the model. Thus the threshold (T) consists of an intercept independent of age (X) plus the effect of age, for example: $T_{mzm} = X_{mzm} + \beta_{age\_males} \times$ age for MZM twins and $T_{mzf} = X_{mzf} + \beta_{age\_females} \times$ age for MZF twins, where X is the value of the threshold when age = 0. Consequently, X may be the same for twins and siblings, although the actual prevalence could be higher in siblings as a result of their older age. Five twin correlations (one for each sex by zygosity group) and three sibling correlations (male–male, female–female and male–female sibling pairs) were estimated.

We tested for: (i) differences in the age effect on the thresholds (i.e. prevalence) between men and women; and (ii) the significance of the effect of age. Next we tested for differences in thresholds between zygosity groups, twins and siblings and males and females. Finally, we tested for differences in correlations between DZ twins and non-twin siblings and for quantitative and qualitative sex differences. Quantitative sex differences in the heritability are suggested if the same-sex twin and sibling correlations are significantly different for men and women. Qualitative sex differences are implied if the DZ opposite-sex twin correlation is not predicted from the correlations in same-sex twin pairs. These differences refer to the fact that different genes may be expressed in men and women.

In a genetic model (Fig. 1), the influence of A and E on the liability to cannabis initiation was estimated by the parameters (factor loadings) a and e. The latent additive genetic factors correlate perfectly in MZ twins, and 0.5 in DZ twins and non-twin siblings. The correlations between the environmental factors are estimated for twins and siblings separately (r_{Etwin} and r_{Esib}). If r_{Etwin} and r_{Esib} are significant, this indicates that environmental factors that influence cannabis initiation are correlated in twins and siblings from the same family. This parameterization is an alternative to estimating the importance of common environment (C) in twins and siblings and allows for the environment shared by twins to be more similar than that shared by siblings.

The environmental correlation between siblings was modelled as a function of their age difference: $r_{Esib} + \beta_{rEsib} \times age\text{-}diff$. Here r_{Esib} represents the environmental correlation between siblings independent of the

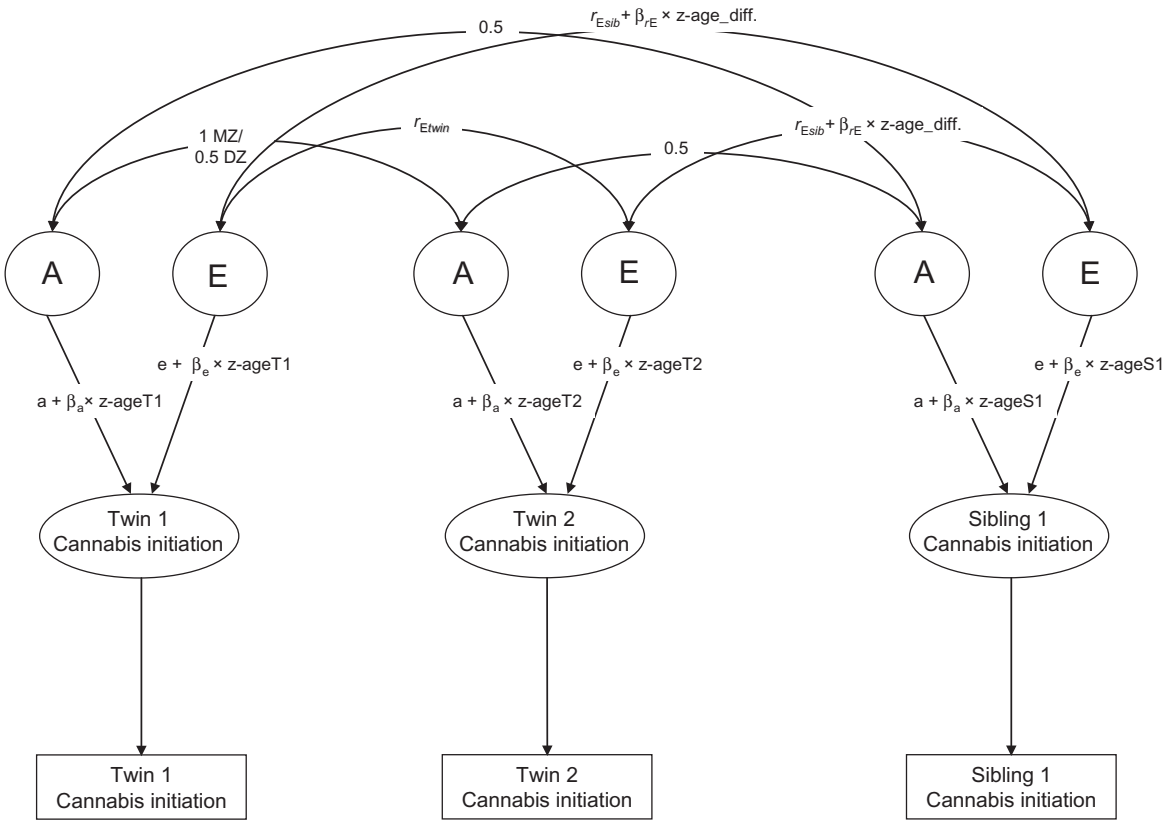

Figure 1 Genetic model for cannabis initiation with age included as a moderator. T1 = twin one, T2 = twin two, S1 = sibling one, A = additive genetic variance, a = factor loading of A, E = environmental variance, e = factor loading of E, r_{Etwin} = environmental correlation between twin 1 and twin 2, r_{Esib} = environmental correlation between non-twin siblings

age difference between the siblings. If β_{rEsib} is significantly different from zero, an interaction between the environmental influences that are shared between siblings and the age difference between siblings is present. The significance of greater sharing of environmental influences by twins within a family is evaluated by testing whether constraining r_{Etwin} and r_{Esib} to be equal results in a significant deterioration in model fit.

The effect of age on the genetic and environmental (E + C) factors was modelled by including age as a moderator on the path from latent factors A and E. The unmoderated estimates of A and E represent those that are observed at the median (age) of the sample. To ensure identification of the model, the total variance is constrained to unity when the moderator equals zero ($a^2 + e^2 = 1$). The moderation of age is represented as $a + \beta_a \times age_{t1}$ for the path from A to the phenotype of twin 1 (see Fig. 1). Here, a represents the effect of A independent from age. If β_a is significantly different from zero, an interaction between A and age is present. In the same way, an interaction effect between age and E is tested by constraining β_e to equal zero.

The relative contribution of A to the liability for cannabis initiation can be calculated for both twins and siblings as the genetic variance divided by the total variance: $(a + \beta a \times age)^2/((a + \beta a \times age)^2 + (e + \beta e \times age)^2)$. The relative influence of C and E should be calculated separately for twins and siblings if their environmental correlations differ (i.e. $re_{twins} \neq re_{siblings}$). For twins, C is calculated as $(e + \beta e \times age)^2 \times re_{twins}/((a + \beta a \times age)^2 + (e + \beta e \times age)^2)$ and E as $((e + \beta e \times age)^2 \times (1 - re_{twins}))/((a + \beta a \times age)^2 + (e + \beta e \times age)^2)$. For siblings, C is calculated as $(e + \beta e \times age)^2 \times re_{siblings}/((a + \beta a \times age)^2 + (e + \beta e \times age)^2)$ and E as $((e + \beta e \times age)^2 \times (1 - re_{siblings}))/((a + \beta a \times age)^2 + (e + \beta e \times age)^2)$. Statistical significance of the contribution of C to individual differences in the liability for cannabis initiation was tested by constraining re_{twins} and $re_{siblings}$ to equal zero. Statistical significance of a^2 was assessed by testing whether it could be fixed at zero without a significant deterioration in the model fit. As in the saturated model, thresholds in the genetic modelling were adjusted for possible age effects by including the regression of age on cannabis initiation in the threshold model.

The raw data full information maximum likelihood approach in Mx was used to fit different models to the data. Testing of submodels was performed by means of likelihood-ratio tests, by subtracting the minus two times

the log-likelihood (−2LL) for the more general model from the −2LL for the more restricted model. This yields a statistic that, under certain regularity conditions, is distributed as χ^2 with degrees of freedom (d.f.) equal to the difference in the number of parameters in the two models. If the χ^2 test yields a *P*-value higher than 0.01, the constrained model is deemed not significantly worse than the previous model and is kept as the most parsimonious model to which the next model will be compared.

RESULTS

The upper part of Table 2 shows the prevalence rates for male and female twins and siblings from three different age categories. The lower part gives the heritability estimates from analyses using only the twin data, to give a first impression of the change in heritability with age. As can be seen, the additive genetic influence decreases and the common environmental influence increases with age.

Results of tests based on the saturated model fitted to the twin–sibling sample are shown in Table 3. The estimates of the parameters are shown in Table 4. The effect of age on the threshold was equal for men and women (model 1). There was a significant negative effect of age ($\beta_{age} = -0.47$) on the threshold. This indicates that the threshold moves to the left end of the distribution with increasing age, corresponding to a higher prevalence in older participants (model 2). There was no significant effect of zygosity on the prevalence (model 3). The prevalence does not differ between twins and siblings, but men

Table 2 Prevalence rates for ever use of cannabis for male and female twins and siblings in three age categories and the heritability estimates based on the three age groups of twins.

	Twins aged 13–15	*Twins aged 16–17*	*Twins aged 18–20*	*Siblings aged 11–15*	*Siblings aged 16–17*	*Siblings aged 18–25*
Descriptive						
Prevalence males (*n* males)	4.0% (1076)	18.2% (1163)	33.7% (475)	1.3% (159)	15.0% (187)	41.3% (332)
Prevalence females (*n* females)	2.3% (1235)	13.4% (1489)	23.9% (770)	1.8% (169)	15.0% (214)	30.2% (484)
Twin correlations						
MZ twins	0.702	0.739	0.815			
DZ twins	0.625	0.568	0.721			
Genetic analyses						
% variance explained by A	41%	25%	15%			
% variance explained by C	48%	60%	72%			
% variance explained by E	11%	15%	13%			

A: additive genetic variance; C: environmental variance shared between all siblings within a family; E: unique environmental variance. MZ: monozygotic; DZ: dizygotic.

Table 3 Model fit results for the saturated model of cannabis initiation.

	−2 LL	*d.f.*	*versus*	*Δd.f.*	χ^2	*P*
Saturated model						
0. Full saturated model	5328.405	7735				
1. β_{age} threshold males = β_{age} threshold females	5329.211	7736	0	1	0.806	0.367
2. Significance of β_{age}	5879.819	7737	1	1	550.6	<0.001
3. Threshold MZM = DZM and threshold MZF = DZF	5330.809	7738	1	2	1.599	0.450
4. Threshold MZM = DZM = DOSm and threshold MZF = DZF = DOSf	5333.109	7740	3	2	2.301	0.317
5. Threshold MZM = DZM = DOSm = brothers and threshold MZF = DZF = DOSf = sisters	5338.682	7742	4	2	5.577	0.062
6. Threshold males = threshold females	5360.330	7743	5	1	21.646	<0.001
7. rDZM = rBB & rDZF = rSS and rDOS = rBS	5353.111	7745	5	3	14.425	0.002
8. rMZM = rMZF and rDZM = rDZF and rBB = rSS	5348.055	7745	5	3	9.373	0.025
9. rMZM = rMZF and rDZM = rDZF = DOS and rBB = rSS = rBS	5348.443	7747	8	2	0.388	0.824

−2LL: −2 log-likelihood; d.f.: degrees of freedom; *P*: *P*-value; MZM: monozygotic male twins; DZM: dizygotic male twins; MZF: monozygotic female twins; DZF: dizygotic female twins; DOS: dizygotic opposite sex twins; DOSm: male twin from dizygotic opposite sex twin pair; DOSf: female twin from dizygotic opposite sex twin pair; *r*: correlation; BB: non-twin brother–brother pair; SS: non-twin sister–sister pair; BS: non-twin brother–sister pair.

Table 4 Thresholds, prevalences and tetrachoric correlations of having initiated cannabis use (99% confidence intervals).

Saturated (full) model	*Thresholds*	*Prevalence*
MZM twins	1.117 (1.00–1.28)	13.2%
DZM twins	1.013 (0.86–1.17)	15.6%
MZF twins	1.218 (1.07–1.37)	11.2%
DZF twins	1.185 (1.03–1.34)	11.8%
Male twins from DOS twin pairs	0.962 (0.83–1.10)	16.8%
Female twins from DOS twin pairs	1.176 (1.04–1.32)	11.9%
Brothers	1.149 (0.99–1.31)	12.5%
Sisters	1.303 (1.16–1.45)	9.6%
Reduced (best) model		
Males	1.045 (0.97–1.12)	14.8%
Females	1.218 (1.14–1.29)	11.2%
Age regression coefficient	–0.469 (–0.52–0.42)	
Saturated (full) model	Correlations	
MZM twin pairs	0.804 (0.64–0.91)	
DZM twin pairs	0.537 (0.29–0.73)	
MZF twin pairs	0.907 (0.82–0.96)	
DZF twin pairs	0.668 (0.46–0.82)	
DOS twin pairs	0.639 (0.47–0.77)	
Male sibling pairs	0.257 (0.01–0.48)	
Female sibling pairs	0.519 (0.30–0.69)	
Sibling pairs of opposite sex	0.429 (0.29–0.53)	
Reduced (best)model		
All MZ twin pairs	**0.868 (0.79–0.92)**	
All DZ twin pairs	**0.620 (0.51–0.72)**	
All sibling pairs	**0.415 (0.30–0.52)**	

MZM: monozygotic male; DZM: dizygotic male; MZF: monozygotic female; DZF: dizygotic female; DOS: dizygotic opposite sex; MZ: monozygotic; DZ: dizygotic. The bottom three rows collapse across categories above. Correlations from best fitting model are printed in bold.

have a significantly higher prevalence than do women (models 4–6). The DZ twin correlation was significantly higher than the sibling correlation (model 7). There were no quantitative (model 8) or qualitative (model 9) sex differences, indicating that the heritability is the same for males and females and that the same genes are expressed in both sexes.

Table 4 gives the correlations from the full and the most parsimonious model. The lower sibling correlation than DZ twin correlation suggests a specific twin environment which influences liability to cannabis initiation, or possibly an interaction between age and either genetic or environmental factors. We therefore fitted a genetic model in which the environmental correlation was estimated separately for twins and siblings and in which the environmental correlation between siblings was a function of the age difference between the siblings (r_{Etwin} and $r_{Esib} + \beta_{rE} \times$ age difference).

Results of the genetic model fitting are presented in the left part of Table 5. First, a full genetic model, including age as a moderator on A and E, was fitted to the data. The environmental correlation was estimated separately for twins and siblings ($r_{Etwin} = 0.74$ and $r_{Esib} = 0.32$ in the full model). Sharing of environmental influences between non-twin siblings was modelled as a function of the siblings' age difference ($\beta_{rE} = 0.04$ in the full model). Dropping this effect of age difference from the model (model 1) did not cause a significant deterioration in model fit ($\chi^2_{(1)} = 0.122$, $P = 0.727$). Constraining the environmental correlation for twins and siblings to be equal (model 2) resulted in a significant deterioration in model fit ($\chi^2_{(1)} = 10.891$, $P = 0.001$). The significance of environmental influences shared between siblings within a family was tested by constraining both environmental correlations to equal zero (model 3). This also led to a significant deterioration in model fit ($\chi^2_{(2)} = 15.172$, $P < 0.001$). Thus, shared family environment influences cannabis initiation, but to a larger extent in twins than in non-twin siblings. Models 4 and 5 show that β_a is not significantly different from zero ($\chi^2_{(1)} = 4.556$, $P = 0.033$), but that β_e was significantly different from zero ($\chi^2_{(1)} = 29.081$, $P < 0.001$). The environmental variance thus increases as a function of age. The final test (model 6) shows that A contributes significantly to variance in the liability to cannabis initiation ($\chi^2_{(1)} = 74.881$, $P < 0.001$). The right section of Table 5 gives the parameter estimates of all fitted models. Figure 2 gives a graphical representation of the unstandardized and standardized estimates of A, C and E for twins and siblings, which can be calculated using the parameters estimates given in Table 5 and the equations shown in the caption of Fig. 2.

At the median age of the sample (16.5 years) individual differences in the liability for cannabis initiation are 40% A, 47% C and 13% E in twins, and 40% A, 24% C and 36% E in non-twin siblings. The significant positive moderation effect of age on E ($\beta_e = 0.36$) indicates that the influence of the environment increases with age. Moreover, this effect becomes more important in the oldest age group (18–20 years), as is evident from the results presented in Table 2. Consequently, the heritability is lower in young adults then in adolescents.

DISCUSSION

Regular cannabis use is associated with a whole range of negative outcomes, including physical and psychological problems [21–23] and increased risk for the subsequent use of hard drugs [21]. The increased risk for hard drug use is also seen in the Netherlands, where the use of cannabis is illegal but tolerated. The data included in the present study were collected between 2004 and 2008. At the end of 2005, the Netherlands had 729 officially tolerated cannabis outlets (called 'coffee shops')

Table 5 Genetic model fit results and parameter estimates of the model shown in Fig. 1.

	–2 LL	*df*	*versus*	*Δdf*	χ^2	*P*	*βa*	*a*	*βe*	*e*	βr_{Esib}	r_{Etwin}	r_{Esib}
0. Full ACE model	5272.833	7744	–	–	–	–	0.14	0.72	0.26	0.69	0.04	0.74	0.32
1. Test significance of the difference in age between non-twin siblings on the environmental correlation ($\beta r_{Esib} = 0$).	5272.955	7745	0	1	0.122	0.727	0.13	0.72	0.26	0.69	0	0.74	0.37
2. Test significance environmental influences specific to twins ($r_{Etwin} = r_{Esib}$).	5283.854	7746	1	1	10.899	0.001	0.25	0.85	0.12	0.52	0	0.53	0.53
3. Test significance of shared environmental influences ($r_{Etwin} = r_{Esib} = 0$).	5288.127	7747	1	2	15.172	<0.001	0.27	0.94	0.07	0.34	0	0	0
4. Test significance of age moderation on A ($\beta_a = 0$).	5277.501	7746	1	1	4.546	0.033	0	0.63	0.36	0.78	0	0.76	0.40
5. Test significance of age moderation on E ($\beta_e = 0$).	5348.442	7747	4	1	29.081	<0.001	0	0.70	0	0.71	0	0.74	0.33
6. Test significance of A (A = 0).	5302.620	7747	4	1	74.881	<0.001	0	0	0.27	1	0	0.73	0.42

A: additive genetic variance; C: environmental variance shared between all siblings within a family; E: unique environmental variance (ACE).

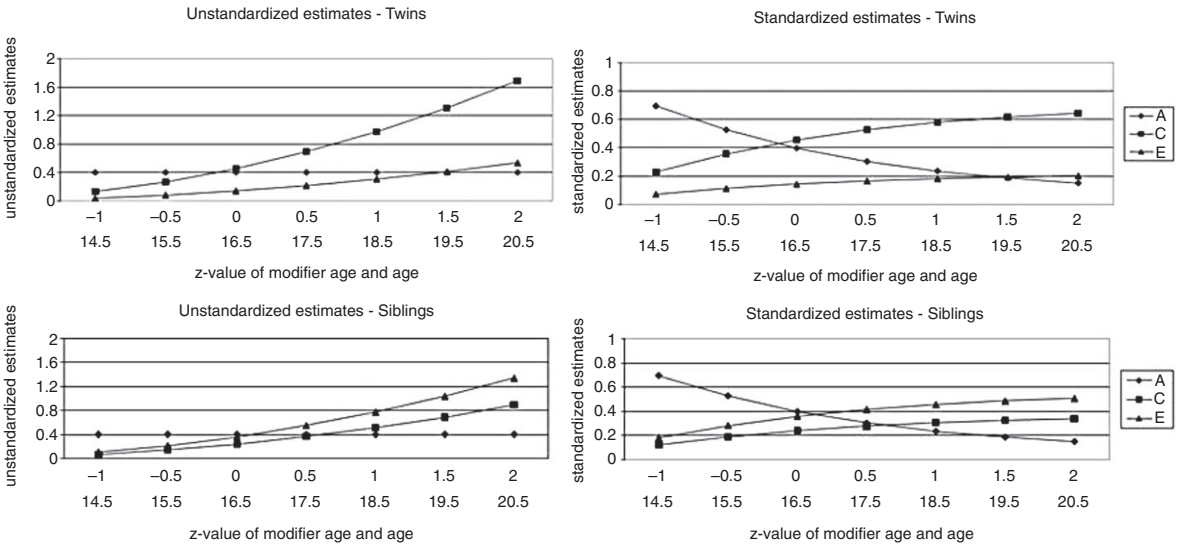

Figure 2 Graphical representation of the estimates from the best fitting model to explain variance in cannabis initiation in twins and siblings. A = additive genetic variance, C = shared environmental variance, E = unique environmental variance. Standardized estimates twins: $A = (a + \beta a^*age)^2/((a + \beta a^*age)^2 + (e + \beta e^*age)^2)$; C *twins* $= (e + \beta e^*age)^2 \times re_{twins}/((a + \beta a^*age)^2 + (e + \beta e^*age)^2)$; E *twins* $= ((e + \beta e^*age)^2 \times 1 - re_{twins})/((a + \beta a^*age)^2 + (e + \beta e^*age)^2)$. Standardized estimates siblings: $A = (a + \beta a^*age)^2/((a + \beta a^*age)^2 + (e + \beta e^*age)^2)$; C *siblings* $= (e + \beta e^*age)^2 \times re_{siblings}/((a + \beta a^*age)^2 + (e + \beta e^*age)^2)$; E *siblings* $= ((e + \beta e^*age)^2 \times 1 - re_{siblings})/((a + \beta a^*age)^2 + (e + \beta e^*age)^2)$. Unstandardized estimates twins: $A = (a + \beta a^*age)^2$; C *twins* $= (e + \beta e^*age)^2 \times re_{twins}$; E *twins* $= ((e + \beta e^*age)^2 \times 1 - re_{twins})$. Unstandardized estimates siblings: $A = (a + \beta a^*age)^2$; C siblings $= (e + \beta e^*age)^2 \times re_{siblings}$; E siblings $= ((e + \beta e^*age)^2 - ((e + \beta e^*age)^2 \times re_{siblings}))$

(http://www.wodc.nl/images/1462b_fulltext_tcm44-75372.pdf). The prevalence of cannabis initiation in the Netherlands is substantially lower than in countries such as the United States or Australia [8,24]. Young adults from New Zealand and the United States report the highest rates of cannabis use across the globe (27% and 20% at the age of 15 and 62% and 54% at the age of 21, respectively). In the Netherlands, 7% of young adults report having used cannabis by the age of 15 and 35% by the age of 21 [24]. In line with findings from populations around the globe [24], the prevalence of cannabis initiation in the present study was higher in men and in 18–25-year-olds than in women and younger participants.

Many published twin studies report the heritability of cannabis initiation in adolescents and adults. The present study contributes to the available literature by testing for the influence of a specific twin environment and for the influence of age by genetic and environmental variance components. To this end, cross-sectional data from 7753 Dutch twins and siblings were analysed. Data were collected prospectively overcoming the issue of retrospective recall bias.

There were moderate genetic influences on cannabis initiation at the median age of the sample (at age 16.5, A = 40%). Previous studies using adolescent samples conducted in the United States and the United Kingdom report heritability estimates ranging from 13 to 72%, with the majority reporting an estimate between 20 and 40% [1–5,25,26]. It is sometimes argued that a liberal cannabis use policy may lead to a lower relative influence of environmental factors as a result of the availability of cannabis. However, additive genetic and shared environmental influences found in the present study are similar to estimates found in studies using samples from other countries. This is the first study to investigate the moderation of age on additive genetic and environmental influences. Age moderation on the genetic factor was not significantly different from zero. For the environmental factor, a significant positive moderation effect was identified. The influence of the environment thus increases from ages 11 to 25, while that of genetic factors remains constant, so the heritability decreases. We did not find evidence for a different heritability estimates or different genes being expressed in men and women. This is in line with most other studies [3–5]. Only Rhee *et al.* [1] found a lower heritability estimate in female than male adolescents, but the magnitude of the difference is difficult to interpret, as the confidence intervals around the estimates were very wide. Also, equating the parameter estimates for males and females did not result in significant worsening of model fit based on the χ^2 difference test, but the authors chose the heterogeneity model to be the best-fitting model based on Akaike's information criterion.

The only study of cannabis initiation in adolescents that also incorporated non-twin siblings did not find significant environmental influences specific to twins [1]. However, the correlation structure showed that twins resemble each other more than non-twin siblings. In the present study DZ twins resemble each other significantly more than siblings ($r_{twins} = 0.62$ versus $r_{siblings} = 0.42$). Due most probably to the larger sample size than the study by Rhee *et al.* ($n = 2124$ versus $n = 7753$), we obtained evidence for environmental influences that are shared only by twins. An alternative explanation for twins to resemble each other more (i.e. an interaction between the age difference between siblings and environmental influences) was not supported.

To summarize, our findings suggest that both genetic factors and shared environmental factors explain familial resemblance in cannabis initiation. Twins share more familial environment than non-twin siblings. The influence of environmental factors to the liability for cannabis initiation increases and the relative influence of genetic factors decreases from early adolescence to young adulthood.

Declarations of interest

None.

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