To: **Psychopharmacology**

Association between platelet MAO activity and lifetime drug use in a longitudinal birth cohort study

Katre Sakala[1,2,3], Kairi Kasearu[4], Urmeli Katus[2], Toomas Veidebaum[1], Jaanus Harro[3,5]

[1]Department of Chronic Diseases, National Institute for Health Development, Hiiu 42, 11619 Tallinn, Estonia

[2]Department of Family Medicine and Public Health, Faculty of Medicine, University of Tartu, Ravila 19, 50411 Tartu, Estonia

[3]School of Natural Sciences and Health, Tallinn University, Narva Road 29, 10120 Tallinn

[4]Department of Social Studies, Faculty of Social Sciences, University of Tartu, Lossi 36, 51003 Tartu, Estonia

[5]Chair of Neuropsychopharmacology, Institute of Chemistry, University of Tartu, Ravila 14, 50411, Tartu, Estonia

Corresponding author:

Jaanus Harro, M.D, Ph.D., Chair of Neuropsychopharmacology, Institute of Chemistry, University of Tartu, Ravila 14A, 50411 Tartu, Estonia

Telephone: +372 737 6657; E-mail: jaanus.harro@ut.ee.

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ABSTRACT

Rationale: Platelet monoamine oxidase (MAO) activity, a marker of central serotonergic capacity, has been associated with a variety of problem behaviours. However, studies on platelet MAO activity and addictive drugs has not been consistently linked with addiction or found to predict illicit substance use initiation or frequency.

Objectives: Platelet MAO activity and illicit drug use was examined in a longitudinal birth cohort study.

Methods: The sample included both birth cohorts (original n = 1238) of the Estonian Children Personality Behaviour and Health Study. Longitudinal association from age 15 to 25 years between platelet MAO activity and lifetime drug use was analyzed by mixed-effects regression models. Differences at ages 15, 18 and 25 were analyzed by t-test. Cox proportional hazard regression analysis was used to assess the association between platelet MAO activity and the age of drug use initiation.

Results: Male subjects who reported at least one drug use event had lower platelet MAO activity compared to nonusers, both in cross-sectional and longitudinal analysis. Males with low platelet MAO activity had started to use drugs at a younger age. Moreover, in male subjects who had experimented with illicit drugs only once in lifetime, low platelet MAO activity was also associated with higher risk at a younger age. In females, platelet MAO activity was not associated with drug use.

Conclusion: In males, low platelet MAO activity is associated with drug abuse primarily owing to risk taking at early age.

Keywords Platelet monoamine oxidase (MAO) activity; lifetime drug use; longitudinal birth cohort study; survival analysis; gender

1. INTRODUCTION

Incidence of alcohol and drug use disorder has increased within the last couple of decades. Substance use and abuse has led to a rise in unintentional injuries, suicides, a variety of other diseases (Degenhardt et al. 2018) and premature deaths (Roth et al. 2018). Having a substance use disorder does not only affect health condition but presents a much broader burden for society. Drug addiction is characterized by poorly managed motivated behaviour comprising an uncontrollable drive to seek drugs while the value of non-drug-related incentives is reduced (Nieuwenhuys et al. 2008). The factors related to drug abuse are manifold but have both inheritable and environmental components. Many studies have demonstrated a link between genetic vulnerability and substance use disorders (Carpentier et al. 2013; Saraceno et al. 2009; Ujike et al. 2009; Yuferov et al. 2010). While a variety of candidate gene and genome wide association studies have addressed the link between genes and drug use (Han et al. 2012; Sherva et al. 2016), specific genetic factors underlying substance use remain largely unknown. This may be related to the multitude of psychological and behavioural factors underlying drug use (Volkow and Baler 2014). Owing to this complexity, the neurobiology behind drug use is poorly understood; in particular, the pathway from drug use initiation to dependency remains unclear (Volkow et al. 2019).

Indeed, whatever the exact mechanism of genetic vulnerability (Cloninger et al. 1981; Hart, Kranzler 2015; Oreland et al. 2018) or contribution of environmental factors (Enoch 2012; Kendler et al. 2012) in addiction, one will first need to try drugs before habitual use and addiction can develop. Furthermore, it has been demonstrated that an early-onset of substance use is a risk factor for later higher substance use and substance use disorder (Huizink et al. 2010;

Rhee et al. 2003). The reason why certain people but not others initiate drug use is thus of paramount importance but has remained unresolved. Some studies have noted that environmental exposure to drugs, that is, e.g., easy availability and peer pressure, is a key element (Odgers et al. 2008; Volkow et al. 2019). Others have focused on personality traits (Terracciano et al. 2008) or genetic factors (e.g., Minică et al. 2018).

At the systems level, drug use has most consistently been associated with a reduced functioning of the dopamine and/or serotonin system (Groenman et al. 2016; Kirby et al. 2011; Volkow et al. 2009). In humans, low serotonergic function can be assumed on the basis of low levels of 5-HIAA, the main stable metabolite, in the CSF. Levels of 5-HIAA, in turn, are strongly correlated with the activity of monoamine oxidase (MAO) in platelets, both in rhesus monkeys (Fahlke et al. 2002) as well as in humans (Oreland et al. 1981). Prolactin response to the administration of fenfluramine, a serotonin-releasing drug, is significantly correlated with platelet MAO activity (Eriksson et al. 2006), further suggesting that platelet MAO activity reflects central 5-HT release potential, possibly owing to common regulatory mechanisms that shaped the development of serotonergic system during fetal stage (Harro and Oreland 2016). Platelet MAO activity was first proposed a marker of general psychiatric vulnerability (Buchsbaum et al. 1976), but subsequently several associations between platelet MAO activity and psychopathology (such as schizophrenia) were explained by the inhibitory effect of tobacco smoking on MAO (Fowler et al. 1996). More recent work has however supported the link of platelet MAO activity, irrespective of smoking, specifically with impulsive traits (Oreland et al. 2007), excessive risk-taking (Carrasco et al. 1999; Fowler et al. 1980, Luht et al. 2018), drunk driving (Eensoo et al. 2004), alcohol abuse (Fowler et al. 1996; von Knorring and Oreland 1996; Nilsson et al. 2008;

Wiberg et al. 1977), proneness to accidents (Harro and Oreland 2016), and antisocial behaviour (Carrasco et al. 1994; Stalenheim 2004; Oreland et al. 2007).

Given that low platelet MAO activity, presumably reflecting lower capacity of serotonergic neurotransmission, has been rather consistently associated with risk-taking, impulsive, and antisocial behaviour, it is surprising that any consistent association with alcohol or illicit drug use appears not to have been shown. Thus, alcohol use and dependence has been studied in association with platelet MAO activity but with contradictory results (Anthenelli et al. 1998; Whitfield et al. 2000; Snell et al., 2002; Oreland et al. 2007; Pivac et al. 2005; Nedic Erjavec et al. 2014) even in the large studies, and for use of illicit drugs that should even more strongly rely on excessive risk-taking than alcohol use, the relatively small studies on diagnosed heroin and psychostimulant addicts (von Knorring et al. 1987; Mukasa et al. 1990; Faraj et al. 1994; Macedo et al. 1995) have not yielded in a coherent outcome either. To address the question of whether low platelet MAO activity is associated with drug use, we have therefore taken advantage of the unique longitudinal database of the Estonian Children Personality Behaviour and Health Study (ECPBHS) that is highly representative of local birth cohorts and includes platelet MAO activity measured at different ages.

2. MATERIAL AND METHODS

2.1. Study sample

This study was carried out on the Estonian subsample of the European Youth Heart Study (1998/1999), which was later incorporated into the longitudinal ECPBHS. ECPBHS consists of two birth cohorts that have participated in four study waves. The study procedure, sample

formation, and data collection has been described in detail elsewhere (Luht et al. 2018; Joost et al. 2019). All schools of Tartu County, Estonia, that agreed to participate (54 of the total of 56) were included into the sampling and 25 schools were selected based on the probability proportional to school size. At recruitment the children were at either third (younger cohort, average age 9.6 years, 52.3% female) or ninth (older cohort, average age 15.6 years, 56.2% female) grade. ECPBHS is highly representative of two birth cohorts of a local population, as 79.1% of subjects of the randomized regional sample participated in the original data collection. All the subjects are of European descent. Follow-up studies for the younger birth cohort have been taken place in ages 15 years (n = 483), 18 years (n = 454) and 25 years (n = 441) and for the older birth cohort in ages 18 years (n = 417 + additional 62), 25 years (n = 541) and 33 years (n = 504). Data collection occurred during a visit to the laboratory. The original size of the sample was 1238; the number of subjects with valid platelet MAO activity and drug use data for the present analysis was 1046 (55% female). Drug use status is given in Table 1. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu and conducted in accordance with the Declaration of Helsinki.

2.2. Platelet MAO activity

Platelet MAO activity was measured in platelet-rich plasma by a radioenzymatic method as previously described (Harro et al. 2004). Due to a gender difference in platelet MAO activity, and to account for variance in the laboratory methods (most importantly, specific activity of the available radiolabelled substrate) in different study waves, we analysed data of males and females separately, and platelet MAO activity levels were standardized and z-scores were used in longitudinal analysis as well as in cross-sectional analysis at ages 15, 18 and 25 years.

Table 1. Illicit drug use in the ECPBHS sample (n).

	Female	Male	Total
Total [a]	580	466	1046
Nonusers	241	107	348
Users	339	359	698
one-time users	101	87	188
more than once users	199	218	417
level of drug experience not known	39	54	93
only cannabis users	98	122	220

[a] Only subjects with valid drug use information and platelet MAO activity data are included.

For Cox proportional hazard regression analysis, a new categorical variable "Lifetime platelet MAO activity" was constructed, where study participants were divided into three subgroups: low MAO activity (lower 25th percentile), medium MAO activity, high MAO activity (upper 25th percentile). For example, if a subject was in a low subgroup in every study wave, they were allocated into a "low MAO activity" group. If during the study waves a subject belonged to different MAO activity groups, an average was used. Subjects who had data from only one study wave (n=154) were excluded from this analysis. Platelet MAO activity of excluded subjects did not differ significantly from the included subjects.

2.3. Substance use

Initiation of drug use

Variable "Initiation of drug use" was constructed based on the question "Have you ever tried illegal drugs?" at ages 15, 18, 25 and 33 (older cohort) years. Subjects were categorized into two groups: 1) nonusers (n=348; 69% female), if they had answered "No" in all the study waves; 2) if the subject had answered "Yes" in at least one study wave, he/she was categorized as "user"

(n=698; 49% female). Data of 192 participants were categorized as missing, because they had provided no drug use information or had reported no drug use in earlier study wave but did not participate in the last study wave.

Age of initiation

Subjects were asked to report the age (in years) when they first tried illicit drugs at each study wave. If a subject had left the corresponding question unanswered at age 15 years, but participated in the follow-up study, data from the follow-up was used. If the responses differed between study waves, the first reported age was used.

Lifetime drug use

An additional variable "Lifetime drug use" was created to estimate the platelet MAO effect on drug use frequency. Subjects were asked to answer the question: "How often have you used the following drugs (list of 18 drugs)". Thus, we divided subjects with drug use experience into three groups: 1) nonusers (n=348); 2) had used drugs only once (n=188; 54% female) and those who had used drugs from adolescence to adulthood more often (n=417; 48% female) (Table 2). 285 participants' data were categorized as missing, because they had no drug use information or had incomplete data regarding frequency of drug use.

First, to test the association between platelet MAO and initiation of drug use, one-time users and frequent users were analysed together, while combining all drug categories. Secondly, to test the association between platelet MAO activity and intensity of drug use, subgroup analyses were performed by differentiating nonusers, one-time users and frequent users.

Table 2. Platelet monoamine oxidase (MAO) activity in the ECPBHS sample by birth cohort and age (n=1046).

	Total		Male		Female			
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**t**	**df**	***p***
Platelet MAO activity [a]									
15 years, older cohort	496	9.59 (3.1)	218	8.95 (2.9)	278	10.23 (3.3)	-4.49	489.84	**<0.001**
15 years, younger cohort	411	10.29 (3.4)	184	9.63 (3.2)	227	10.83 (3.4)	-3.68	409	**<0.001**
18 years, older cohort	378	10.26 (3.4)	165	9.44 (3.5)	213	10.90 (3.1)	-4.29	376	**<0.001**
18 years, younger cohort	381	11.62 (3.5)	165	10.40 (3.4)	216	12.56 (3.3)	-6.22	379	**<0.001**
25 years, older cohort	466	11.22 (4.1)	203	9.87 (4.0)	263	12.26 (3.9)	-6.53	464	**<0.001**
25 years younger cohort	407	9.8 (2.7)	179	8.76 (2.5)	228	10.62 (2.5)	-7.43	405	**<0.001**

[a] Comparison of male and female subjects within the same data collection wave. Direct comparison between data collection waves is not feasible (see 2.2).

Cannabis use

Cannabis belonged to illicit substances. However, since cannabis is the most commonly used drug (European Monitoring Centre for Drugs and Drug Addiction 2020) and belongs to a somewhat grey zone in public attitude, we also analysed separately the association between platelet MAO activity and cannabis use. Here subjects were included who had only tried or used cannabis in their lifetime, but no other drugs (n=220; 45% female).

Tobacco smoking

At each study wave, participants reported whether and how frequently they smoke, and how many cigarettes they had consumed within the last week. Subjects who smoked less frequently

than daily were grouped together for comparison with regular smokers, and subjects who consumed ≤10 cigarettes per day were compared to those who smoked more.

2.4. Statistical analysis

Data were analysed using SPSS version 26 (IBM Corp, Armonk, New York, USA) and Stata version 14 (StataCorp LP, College Station, Texas, USA). Level of significance was set at 0.05. No adjustment for multiple comparisons was made in the reported p-values, since several measures are inter-related.

Differences in platelet MAO activity between nonusers and users at ages 15, 18 and 25 years were assessed by t-test. Linear mixed-effects regression models with random intercept and random slope were fitted to estimate the longitudinal association between initiation of drug use and platelet MAO activity from age 15 to 25 years. Platelet MAO activity was defined as the dependent variable and initiation of drug use as the independent variable. Time was treated as a continuous variable. Unstructured covariance structure and restricted maximum likelihood method was used. As an additional exploratory analysis, the models were also adjusted for smoking status (binary variable; no/yes).

Cox proportional hazard regression analyses was used to test the association between platelet MAO activity category and the self-reported age of first time drug use. The curve differences of MAO activity groups were assessed by using the log-rank test. Cox models were used to assess hazard ratios (HRs) with 95% confidence intervals (CIs). Separate analysis was conducted for

drug use and non-use and for the subgroup of one-time users compared to nonusers. In an additional regression model the effect of smoking at age 15 on drug use was assessed.

3. RESULTS

3.1. Platelet MAO activity in drug users and nonusers

In all study waves, females had higher platelet MAO activity than males (Table 2). According to linear mixed-effects regression models male drug users had significantly lower platelet MAO activity throughout the period of observation (Table 3). When considering drug use experience, both one-time users and repeated drug users had significantly lower platelet MAO activity from 15 to 25 years of age, as compared to nonusers. This effect remained similar when the models were adjusted for smoking (Supplementary Table 1).

Table 3. Platelet MAO activity in 15 to 25 years old drug users and nonusers: Estimated main effects (mean and 95% CI) in male and female subjects of the ECPBHS sample.

	MALE			FEMALE		
	Coeff.	95% CI	p value	Coeff.	95% CI	p value
standardised platelet MAO activity						
time	-0.002	-0.011; 0.007	0.660	-0.003	-0.012; 0.005	0.451
drug users [a]	-0.411	-0.594; -0.229	**< 0.001**	-0.042	-0.190; 0.105	0.573
standardised platelet MAO activity						
time	-0.002	-0.011; 0.008	0.733	-0.004	-0.012; 0.005	0.394
one-time users [b]	-0.359	-0.604; -0.114	**0.004**	-0.024	-0.232; 0.184	0.822
recurrent drug users [c]	-0.413	-0.613; -0.213	**< 0.001**	-0.085	-0.253; 0.082	0.318

[a] Coefficient (Coeff.) can be interpreted as the mean difference in standardized platelet MAO activity between nonusers and users at each timepoint.
[b] Coefficient (Coeff.) can be interpreted as the mean difference in standardized platelet MAO activity between nonusers and one-time users at each timepoint.
[c] Coefficient (Coeff.) can be interpreted as the mean difference in standardized platelet MAO activity between nonusers and recurrent users at each timepoint.

In comparison of platelet MAO activity at different age points, males who had used drugs at least once by age 25 (younger cohort) or by age 33 (older cohort), had lower platelet MAO activity at age 15, 18 and 25 (Table 4) compared to nonusers. Again, in females, no difference was observed.

Table 4. Standardised platelet MAO activity [a] in drug users and nonusers by age and gender.

		Drug users (n)	Nonusers (n)	t	df	*p*
15 years	Male	-0.085 (310)	0.347 (94)	-3.19	126.34	**0.002**
	Female	0.047 (291)	0.010 (216)	0.41	505	0.683
18 years	Male	-0.095 (247)	0.310 (86)	-3.29	331	**<0.001**
	Female	-0.023 (259)	0.012 (172)	-0.36	418.91	0.731
25 years	Male	-0.088 (283)	0.289 (102)	-2.92	147.51	**0.004**
	Female	-0.045 (275)	0.032 (217)	-0.84	490	0.401

[a] Z-scores were calculated for every study wave separately for males and females.

Because platelet MAO activity has a complex relationship with tobacco smoking (see Discussion), we compared the association between platelet MAO activity and drug use in regular (daily) smokers and irregular smokers, as well as in subjects who smoked ≤10 cigarettes per day or more. Data in Table 5 reveal that among males who did not smoke daily platelet MAO activity was also lower in illicit drug users. Findings were very similar if subjects who smoked more than 10 cigarettes per day were excluded (data not shown).

To learn whether the association between platelet MAO activity is related to drug use initiation or habit, one-time users and repeated drug users were separately compared to nonusers. At all age points, nonusers had higher platelet MAO activity compared to both one-time users (Table 6) and repeated drug users (Table 7).

Table 5. Standardised platelet MAO activity [a] in drug users and nonusers by age and sex in non-smokers and irregular (not daily) smokers.

		Drug users (n)	Nonusers (n)	t	df	*p*
15 years	Male	-0.035 (265)	0.380 (91)	-2.96	128,08	**0.004**
	Female	0.089 (267)	0.006 (206)	0.88	471	0.378
18 years	Male	-0.005 (165)	0.415 (67)	-3.07	230	**0.002**
	Female	0.105 (204)	0.076 (152)	0.27	354	0.785
25 years	Male	-0.088 (283)	0.289 (102)	-2.92	147.51	**0.004**
	Female	-0.045 (275)	0.032 (217)	-0.84	490	0.401

[a] Z-scores were calculated for every study wave separately for males and females.

Table 6. Standardised platelet MAO activity [a] in one-time drug users and nonusers by age and gender.

		One-time users (n)	Nonusers (n)	t	df	*p*
15 years	Male	-0.065 (74)	0.347 (94)	2.41	166	**0.017**
	Female	0.020 (84)	0.010 (216)	-0.08	298	0.939
18 years	Male	-0.005 (64)	0.310 (86)	1.86	148	0.065
	Female	0.009 (76)	0.012 (172)	0.03	246	0.980
25 years	Male	-0.068 (80)	0.289 (102)	2.20	180	**0.029**
	Female	0.056 (88)	0.032 (217)	-0.18	303	0.857

[a] Z-scores were calculated for every study wave separately for males and females.

Table 7. Standardised platelet MAO activity [a] in frequent drug users and nonusers by age and gender.

		Repeated use (n)	Nonusers (n)	t	df	*p*
15 years	Male	-0.060 (190)	0.347 (94)	3.15	282	**0.002**
	Female	0.035 (176)	0.010 (216)	-0.24	390	0.812
18 years	Male	-0.126 (150)	0.310 (86)	3.29	234	**<0.001**
	Female	-0.092 (154)	0.012 (172)	-0.95	291.1	0.342
25 years	Male	-0.074 (183)	0.289 (102)	2.85	283	**0.005**
	Female	-0.115 (166)	0.032 (217)	1.39	381	0.165

[a] Z-scores were calculated for every study wave separately for males and females.

Table 8. Standardised platelet MAO activity [a] in exclusively cannabis users and drug nonusers by age and gender.

		Cannabis users (n)	Nonusers (n)	t	df	*p*
15 years	Male	-0.078 (112)	0.347 (94)	-2.85	204	**0.005**
	Female	-0.067 (81)	0.010 (216)	0.42	295	0.672
18 years	Male	-0.012 (98)	0.310 (86)	-2.13	182	**0.035**
	Female	0.011 (74)	0.012 (172)	-0.01	244	0.996
25 years	Male	-0.033 (122)	0.289 (102)	-2.25	222	**0.025**
	Female	-0.051 (85)	0.032 (217)	-0.62	300	0.538

[a] Z-scores were calculated for every study wave separately for males and females.

The most frequently used drug in our sample was cannabis, and the public attitude toward cannabis is more tolerant compared to other substances. Therefore the association between platelet MAO activity and cannabis use was separately analysed. In male exclusively cannabis users, platelet MAO activity was also significantly lower at all ages (Table 8).

3.2. Platelet MAO activity in prediction of the risk of initiation and repeated drug use

A log rank test was run to determine if there were differences in the survival distribution (not using the drugs) related to platelet MAO activity. The survival distributions for low, medium and high platelet MAO activity groups differed significantly in males ($\chi^2(2) = 12.2$, $p<0.01$) but not in females ($\chi^2(2) = 0.66$, $p=0.72$). The hazard of drug use by platelet MAO activity category was assessed with Cox regression models for survival analysis of first drug experience. During the adolescence and young adulthood, the hazard to use drugs increased in males who had lower platelet MAO activity compared to males who had higher platelet MAO activity (HR = 1.84; 95%CI = 1.28-2.64). Also, males who had medium platelet MAO activity had higher hazard to

use drugs than males who had higher platelet MAO activity (HR = 1.48; 95%CI = 1.11-1.97) (Figure 1).

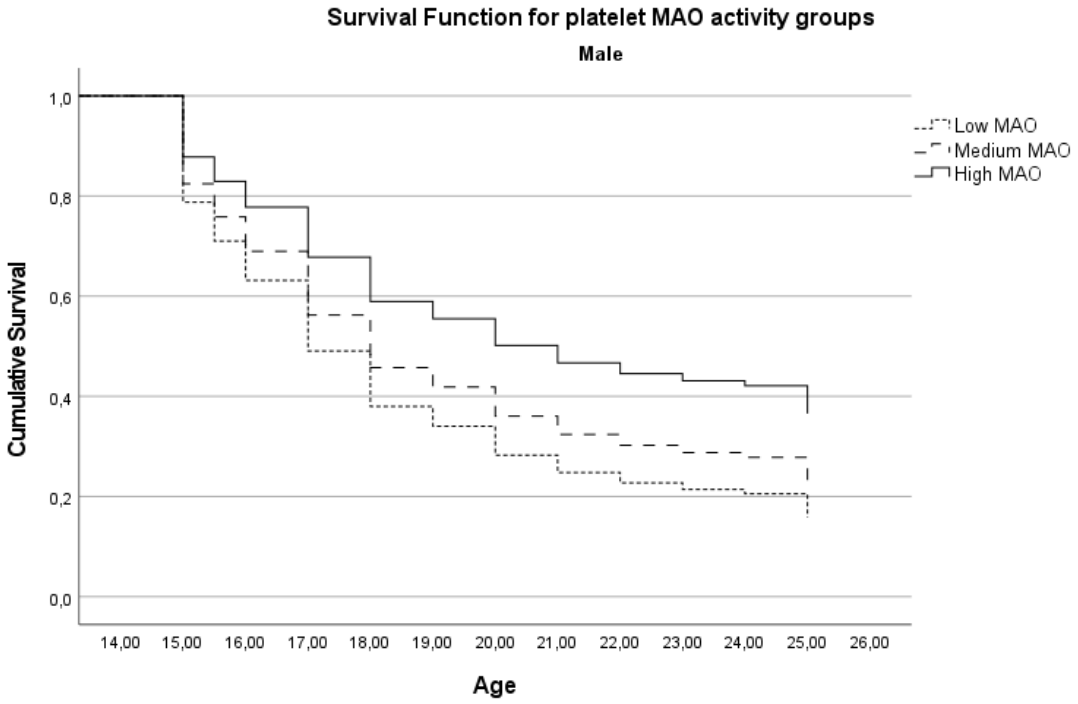

Figure 1. Survival curves for the first time drug use with low, medium and high platelet MAO activity groups in male subjects of the ECPBHS sample in the age period of 15 to 25 years (all subjects, n=422).

Higher risk with lower platelet MAO activity was also found if the comparison with nonusers was restricted to one-time drug users. According to the log rank test, a difference in the survival distribution in males ($\chi^2(2) = 8.44$, $p=0.015$), but not in females ($\chi^2(2) = 0.48$, $p=0.79$) among the subsample of one-time drug users was present. The hazard ratio for first-time drug use for males with low platelet MAO activity was HR = 2.44 (95%CI = 1.19-5.01) and for medium platelet MAO activity was HR = 2.04 (95%CI = 1.17-3.55) (Figure 2).

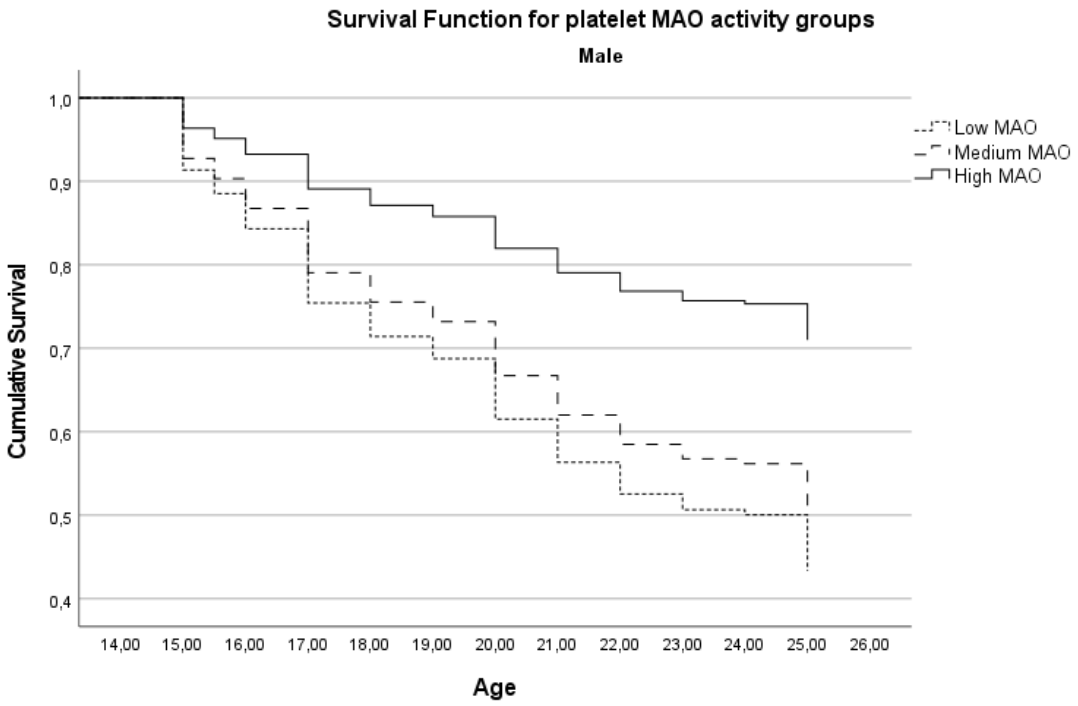

Figure 2. Survival curves for the first-time drug use with low, medium and high platelet MAO groups in male subjects of the ECPBHS sample in the age period of 15 to 25 years (one-time users and nonusers, n=190).

4. DISCUSSION

We have shown an association between platelet MAO activity and experience of illicit drug use, with gender differences. While male one-time or repeated drug users had lower platelet MAO activity compared to nonusers, no such a relationship was observed among female participants. Male subjects, with low platelet MAO activity, initiated drug use at an earlier age.

Central MAO enzymatic activity has a major impact on behavioural regulation (Bortolato and Shih 2011), but possibly the best replicable association of an MAO activity measure is between platelet MAO activity and risk-taking behaviours (Harro and Oreland 2016). Regarding substance use, several studies have found an association of platelet MAO activity with alcohol

abuse but some of these show opposite results (Oreland et al. 2007; Pivac et al. 2005; Nedic Erjavec et al. 2014), and even the largest studies do not agree, having reported no association independent of the smoking effect (Anthenelli et al. 1998; Whitfield et al. 2000) or lower in alcohol dependence even among non-smokers (Snell et al. 2002). A variety of factors may account for these discrepancies in literature, one of these being the possible association of platelet MAO activity only with the Type II alcoholism that is less common, occurs predominantly in males, and is characterized by early onset and poor behavioural adjustment (von Knorring and Oreland 1985). After the original sampling of the present cohorts, we had not detected any association of platelet MAO activity with drug use in the data of the first study wave (Merenäkk et al. 2003), but by then the participants had been too young to experiment with illicit drugs to any significant extent. Otherwise literature is surprisingly scarce on platelet MAO activity and illicit substances. To our knowledge this is the first study to analyse the association between platelet MAO activity and illicit drug use initiation and does so longitudinally throughout adolescence and young adulthood. Platelet MAO activity, measured already at age 15, was lower in subjects who became experimenters with illicit substances. This finding supports the notion that low platelet MAO activity is associated with excessive risk-taking. Importantly, platelet MAO activity predicted experimenting with illicit drugs but not any further whether the subject continued with drug use. This is compatible with platelet MAO activity not been shown associated with addictive disorders, as control subjects may well have included those who had some drug experience. Experimenting with drugs appears rather a correlate of risk-taking behaviour in general population. One could speculate that once the curiosity satisfied, some low platelet MAO subjects have no increased desire for the drug experience.

Tobacco smoking can cause a reduction of MAO activity (Fowler et al. 2015). Nonetheless, the association between risk-taking behaviours and low platelet MAO activity has been shown to occur in non-smoking human subjects (Eensoo et al. 2004) and has been described in rhesus monkeys (Fahlke et al. 2002). Correction for smoking has confirmed that association of impulsive behaviour with low platelet MAO activity has a tobacco-independent component (Snell et al. 2002; Harro and Oreland 2016), but the relationship between smoking, risk-taking and platelet MAO activity is complex as longitudinal studies have shown that both low and high platelet MAO subjects are more likely to start smoking as adolescents (Harro et al. 2004). Nevertheless, the effect of tobacco smoking on MAO is dose-dependent and no significant effect has been observed in large samples unless ≤10 cigarettes are consumed daily (Whitfield et al. 2000; Eensoo et al. 2004). Therefore we examined separately subjects who had low levels of smoking. Low platelet MAO was again predictive of illicit drug experience.

Association between platelet MAO activity and drug use was present only in males. Some previous studies have found platelet MAO activity associated with behavioural measures only in males (e.g., Jokinen et al. 2018; Oreland et al. 2007), others have been conducted in males-only samples (e.g., Carrasco et al. 1999; Eensoo et al. 2004). However, low platelet MAO activity was also found in girls with oppositional defiant disorder (Malmberg et al. 2008), in the small female subsample of a study of accident proneness (Harro and Oreland 2016) and associated with risk-taking in traffic in female (but not male) adolescents (Luht et al. 2018). The latter study was indeed on the same birth cohort representative sample as the study described here. Thus, low platelet MAO activity is associated with behaviours commonly referred to as risk-taking, but with different expressions in males and females. This may be related to the overall higher

expression of risk-taking behaviours in males and different following of cultural norms between genders, but requires further analysis. It is however of interest that the well-described gene-environment interaction between the *MAOA* VNTR and early life adversity in shaping antisocial behaviour (Caspi et al. 2002) is different, and rather with opposite effect, in males and females (Byrd and Manuck 2014). For the *MAOA* VNTR, a moderating role of sex on neural activation patterns associated with the gene-environment interactive effects has been described, and increase in the activity of amygdala was associated with measures of aggression in low-activity MAOA alleles in males but with the high activity alleles in females (Holz et al. 2016). Such finding suggest a different neural organization of aggressiveness in males and females. It should be noted that genes encoding both monoamine oxidases are located on the X chromosome, and the activities of MAO-A and MAO-B are very highly correlated at infant age, the correlation declining thereafter (Tong et al. 2013). It remains to be clarified which intermediate phenotypes could explain the different behavioural expressions in males and females with low platelet MAO activity.

By which mechanism platelet MAO activity is associated with risk-taking behaviour remains to be explained. The positive relationship between indirect measures of serotonin release and platelet MAO activity (Fahlke et al. 2002; Eriksson et al. 2006; Oreland et al. 1981) suggests that low platelet MAO reflects lower capacity of the central serotonergic system for neurotransmitter release, possibly owing to the early, prenatal genetic effect on MAO-B activity on the development of the brain (Harro and Oreland 2016). In experimental animal studies, partial inhibition of MAO activity during brain development promotes aggressiveness in adulthood (Mejia et al. 2002) and persistently reduces serotonin transporter binding in cortical and raphe

areas (Burke et al. 2018). It is thus conceivable that low MAO activity during development contributes to reduced serotonergic innervation, but this remains to be demonstrated. Importantly, experimental studies suggest that both low and high levels of serotonin availability during the perinatal period can similarly lead to deviant social behaviour (for review, see Shah et al. 2018). This can explain why higher platelet MAO levels have been reported in juvenile correctional facilities (Podobnik et al. 2020) and, within the same sample as in the present study, both low and high platelet MAO activity were found in adolescent smokers (Harro et al. 2004). In another large sample, both low and high platelet MAO activity were found in male with traffic law violators, but in a different manner: low MAO activity in drunk drivers and high MAO activity in speed limit exceeders (see Harro and Oreland 2016). That the latter was particularly true for drivers who did recognize speeding as a risk suggests that low platelet MAO subjects may simply underestimate risks while high MAO subjects make risky decisions under perceived peer pressure, but this hypothesis remains to be properly addressed.

As a limitation of this study, illicit drug use was self-reported. However, data were mostly collected in uniform laboratory conditions and the participants could be confident of anonymity of their records. The time between drug use initiation and blood sampling for platelet MAO activity is individually variable. However, given the low levels of drug use in this birth cohort sample, direct effect on platelet MAO activity is very unlikely. Indeed, the association between low platelet MAO activity and drug experience was present in subjects who reported a single use in lifetime. Another aspect to consider lies in the characteristics of the sample: It is highly representative of a regional birth cohort, that is a strength but may limit generalization of the results. Estonia underwent a remarkably rapid societal change after regaining independence in

1991. When the present data collection started, illicit drug use was much less common among schoolchildren than a decade later. According to the ESPAD Reports illicit drug use was the lowest among Estonian schoolchildren compared to other European countries in years 1995 and 1999, but it reached to European average by year 2003 (Hibell et al. 2012). It can thus not be excluded that this strong association between platelet MAO activity and illicit drug use is particularly characteristic to a society in transformation. Nevertheless, this would not invalidate the findings but suggests a further research direction.

5. CONCLUSION

Conclusively, platelet MAO activity, a putative marker of central serotonergic capacity and risk-taking behaviour, was found consistently associated with illicit drug use in males in a longitudinal study on birth cohort representative samples. This association was common to experimenting with either 'hard drugs' or cannabis, but rather related to just experimenting than to repeated use or addiction. Male subjects with lower platelet MAO activity were more likely to try an illicit substance and made their drug use debut at an earlier age.

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