

To: **BRAIN RESEARCH**

Is low platelet MAO activity associated with antisocial behavior? Evidence from representative samples of longitudinally observed birth cohorts

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ABSTRACT

Lower platelet monoamine oxidase (MAO) activity has been associated with problem behaviors, including criminal behavior, but not all studies agree. We have examined platelet MAO activity and antisocial behavior involving police contact in a longitudinal birth cohort study. The sample included both birth cohorts (original n = 1238) of the Estonian Children Personality Behavior and Health Study. Platelet MAO activity was measured at ages 15, 18 and 25 radioenzymatically with β -phenylethylamine as the substrate. Police contacts were self-reported in an interview and drug use in a questionnaire filled in during a laboratory visit. In cross-sectional analyses, males with the record of antisocial behavior had lower platelet MAO activity. In longitudinal mixed-effect regression models, this association was found to be independent of smoking. Furthermore, including smoking in the model revealed lower platelet MAO activity also in females with past antisocial behaviour. A further exploratory regression analysis with antisocial behavior at two levels of frequency and consideration of self-reported use of illicit drugs either in a single occasion or repeatedly demonstrated some "dose-dependency" in the relationship of antisocial behavior and platelet MAO activity. Platelet MAO activity was lower in male but not female subjects with basic education level as compared to secondary and higher education, but it was not related to non-verbal intelligence. Neither was platelet MAO activity associated with socio-economic status. In conclusion, antisocial behavior as occurring in general population is associated with low platelet MAO activity that probably reflects low capacity of the serotonergic system.

Keywords:

Platelet monoamine oxidase (MAO) activity; antisocial behavior; serotonin; longitudinal; birth cohort; gender

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1. Introduction

Antisocial behavior is a behavior that differs from accepted and common behavioral norms and that in result reduces well-being of others (Frick et al., 2014). It is an umbrella term and exact definition may depend on the field or sub-field (either law, criminology, medicine, behavioral science etc). More narrowly, antisocial is a behavior when one intends to harm or disadvantage other people (Sage et al., 2006). Since aggressive behavior usually brings physical harm to others, constructs of aggressiveness have often been applied synonymously to antisocial behavior (Gretton et al., 2004, Kolla and Bortolato, 2020, van de Groep et al., 2022). However, antisocial behavior as being the opposite to law abiding is wider than just aggressive and violent behavior and can include non-aggressive rule breaking such as stealing, causing public disorder, drug use, or speeding in traffic. Precise costs of antisocial behavior to society are hard to measure. These start with the loss of life, grief and pain, but can also be explained in terms of economy. Most of relevant research has been conducted in the United States: For an example, in 2007, the crime victims in the U.S.A. suffered 15 billion USD in economic losses, and 179 billion USD were related government expenditures (McCollister et al., 2010). In Europe, one study estimated the cost of crime at £36.2 billion in the United Kingdom (Dubourg et al., 2005), another estimated it to be even higher, at £59.9 billion (Brand and Prices, 2000). More recently, £50 billion was the estimated cost of crime in England and Wales in 2015/2016 (Heeks et al., 2018). In Eastern Europe, one study estimated the cost of crime in Poland at 5.1% of GDP (Czabanski, 2009).

Aggressiveness has a moderately strong genetic component (Belfry and Kolla, 2021; Cupaioli et al., 2021) that is likely to contribute to antisocial behavior via interactions of multiple genes with environments. Of specific genes implicated in aggression, the gene (*MAOA*) encoding monoamine oxidase A (MAO-A) stands out in both animal and human studies (Brunner et al., 1993; Caspi et al., 2002; Bortolato et al., 2008), being also associated with human antisocial behavior more broadly (Kolla & Bortolato, 2020). The most consistently aggressiveness-related variant of *MAOA* has, however, no effect on MAO-A radioligand binding availability at adulthood (Fowler et al., 2007), and MAO-A inhibition does not increase aggressiveness. Nevertheless, animal studies have demonstrated increased impulsive aggressiveness in adulthood if MAO activity had been inhibited during gestation that was associated with alterations in the

serotonergic system (Whitaker-Azmitia et al., 1994; Mejia et al., 2002). Another gene, *MAOB* encodes the other of the two monoamine oxidase isoenzymes, monoamine oxidase B (MAO-B). Genes for both isoenzymes are located on the X-chromosome with 24 kb apart, but their transcription differs in many ways (Shih and Chen, 2004). While *MAOB* variants have not been consistently associated with aggressiveness, MAO-B activity as measured in platelets has stood out as a marker most consistently associated with a variety of behaviours, including several that may be related to aggression (Oreland et al., 2007). Platelet MAO activity is positively correlated with the cerebrospinal fluid (CSF) levels of 5-HIAA, the main metabolite of serotonin (Fahlke et al., 2002), suggestive of lower central 5-HT release capacity in subjects with low platelet MAO activity. This notion is supported by the finding of larger increase of the plasma prolactin levels after administration of the 5-HT releasing drug fenfluramine in subjects who have higher platelet MAO activity (Eriksson et al., 2006). In turn, low serotonergic capacity has since long been associated with impulsivity (Evenden, 1999).

Studies reporting platelet MAO activity being associated with schizophrenia (Murphy and Wyatt, 1972; Takahashi et al., 1975) or mood disorders (Georgotas et al., 1986) have been difficult to replicate if controlling for the exposure to tobacco smoke that reduces MAO activity (Fowler et al., 1996) while the active constituents of the smoke remain unknown (Sved et al., 2022). Higher prevalence of smoking in studied groups as compared to controls does however not explain several associations of platelet MAO activity with impulsive and risk-taking behaviors of different type, including Type 2 alcohol abuse (von Knorring et al., 1985; Hallman et al., 1996), bullfighting (Carrasco et al., 1999), high sensation seeking (Fowler et al., 1980), violation of traffic regulations (Eensoo et al., 2004; Luht et al., 2018), gambling (Carrasco et al., 1994; Blanco et al., 1996; suicide attempt (Jokinen et al., 2018) and bulimia (Carrasco et al., 2000). All this evidence together appears to fit well with the original proposal of Buchsbaum and colleagues (Buchsbaum et al., 1976) that platelet MAO activity is a marker of general psychiatric vulnerability, or possibly of one superspectrum of it in the modern view on the hierarchical nature of psychopathology (Watson et al., 2022). That low platelet MAO is rather non-specifically related to risk-taking behavior or recklessness was supported by the study demonstrating its association with incidence of traumatic spinal cord injury irrespective its cause (Sabre et al., 2016).

Low platelet MAO activity has also been found linked with antisocial behavior in several studies. While an early study that addressed the role of trace amines in aggression did not find any difference of male prisoners from a rather small control group (Boulton et al., 1983), Lidberg and colleagues (1985) reported lower platelet MAO activity in criminal offenders hospitalized for forensic assessment as compared to the control group of construction workers. While patients with borderline personality disorder had low platelet MAO activity, those who additionally met the criteria of antisocial personality disorder had even lower enzyme activity (Yehuda et al., 1989). Low platelet MAO activity has been found in other samples of imprisoned offenders (Garpenstrand et al., 2002) while not all studies agree (Gustavson et al., 2010). Antisocial behaviour is however an observed outcome of complex regulatory mechanisms and may involve anxiety and agitation, that in some studies have been associated with higher platelet MAO activity (Paaver et al., 2006; Nikolac Perkovic et al., 2016). An important study of Alm et al. (1994) measured platelet MAO activity in adulthood (age 38-46 years) in male subjects with record of criminal activity before age 15 and analysed the data in association with criminality registered between recruitment and the follow-up. Those former delinquent boys who had no criminality record after age 15 had platelet MAO activity similar to the control group, but of those with further criminal record, many had low platelet MAO activity. In this context, the findings that impulsive violent offenders have low levels of 5-HIAA in CSF (Linnoila et al. 1983) support the notion that low platelet MAO as a proxy for low central serotonergic capacity is reflective of a behavioral trait that involves limited self-control under the influence of factors precipitating impulsive acts.

Commonly, research on platelet MAO and antisocial behavior has been on samples of criminal offenders or individuals who had been juvenile delinquents. Most of the studies have been performed on males, relevant research on females being rare. Cederblad and colleagues (1992) studied one hundred consecutively admitted cases (43% female) at a clinic for child and youth psychiatry and if they compared the cases with behavioral disorders/drug use with the rest, platelet MAO activity was not found different in boys but was lower in girls with tendencies of antisocial behavior. The authors speculated that externalized symptoms are more strongly controlled in females, and thus in their sample the girls, the respective group had more deviant

personalities than male counterparts. Early norm-breaking behavior was associated with low platelet MAO activity in females (af Klinteberg, 1996), but this study did not find a similar difference in males. Conclusively, in law-breaching subjects platelet MAO has been found low in several studies but not in all, within a study, low platelet MAO is often found associated with antisocial behaviour in one gender but not the other, and it remains unclear whether low platelet MAO is characteristic only to the rather extreme groups selected for comparison.

In a longitudinal study of birth cohort representative samples of adolescents and young adults, we have recently found low platelet MAO activity associated with non-law-abiding behaviour in the form of experimenting with illicit drugs, but only in males (Sakala et al., 2022). The aim of the present study was to learn whether antisocial behavior in general is associated with platelet MAO activity in a population-representative sample, and to ascertain whether any such an association would be gender-specific.

2. Results

As expected, female subjects had higher platelet MAO activity compared to males at ages 15, 18 and 25 years in both birth cohorts (Table 1). At ages 18 and 25 years, male subjects with antisocial behavior with police contact had significantly lower platelet MAO activity, and a similar tendency was present already at age 15 (Table 2). According to the linear mixed-effects regression models, males with antisocial behavior with police contact had significantly lower platelet MAO activity throughout the period of observation (Table 3). While the effect of smoking was clearly present, accounting for smoking did not eliminate the association of antisocial behavior with platelet MAO activity.

A further linear mixed effects regression analysis was conducted with antisocial behavior at two levels and consideration of self-reported use of illicit drugs either in a single occasion or repeatedly. This analysis demonstrated some "dose-dependency" in the relationship of antisocial behavior and platelet MAO activity (Table 4). In males with a single police contact the platelet MAO activity was slightly higher than in the repeated police contact group, and statistical significance of the association missed the conventional level. In females with the repeated (but

not single) contact with police owing to antisocial behavior, low platelet MAO activity was also found. Additional consideration of illicit drug use revealed both similarities and differences between males and females: Females with repeated policed contact and drug use had lower platelet MAO activity, and were indeed even more different from the control group as in a respective comparison for males. In contrast, a single illicit drug use occasion together with a single police contact was not associated with low platelet MAO activity in females, but in males, this group had the largest deviation from the control.

Given these results we assessed the association of platelet MAO activity with a few measures known to be related to the expression of antisocial behavior. In male but not female subjects with basic education platelet MAO activity was lower as compared to participants with secondary or university education (Table 5) Platelet MAO activity at any age was however not related to the score of Raven SPM, a measure of intellect, the Pearson correlation coefficients being less than 0.03. Neither was platelet MAO activity different by socioeconomic status (data not shown).

Table 1. Platelet monoamine oxidase (MAO) activity in the subjects included in the presented analyses (n=917), by birth cohort and data collection wave.

	Total		Male		Female		t	df	p
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)			
Platelet MAO activity^a									
15 years, older cohort	437	9.73 (3.2)	184	9.07 (2.9)	253	10.21 (3.4)	-3.80	423.92	<0.001
15 years, younger cohort	373	10.34 (3.4)	164	9.73 (3.2)	209	10.82 (3.4)	-3.13	371	0.002
18 years, older cohort	337	10.21 (3.3)	144	9.43 (3.7)	193	10.79 (2.9)	-3.68	261.71	<0.001
18 years, younger cohort	346	11.81 (3.5)	148	10.59 (3.3)	198	12.73 (3.4)	-5.88	344	<0.001
25 years, older cohort	425	11.33 (4.2)	183	10.03 (4.1)	242	12.31 (4.0)	-5.81	423	<0.001
25 years younger cohort	404	9.79 (2.7)	177	8.77 (2.5)	227	10.60 (2.5)	-7.34	402	<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 4.3).

Table 2. Standardised platelet MAO activity^a cross-sectionally in people who had police contact, by age and gender.

		Control group (+/-SD; n)	Police contact (+/- SD; n)	t	df	p
15y platelet MAO	Male	0.123 (+/- 1.08; 209)	-0.061 (+/- 0.88; 139)	-1.67	346	0.096
	Female	0.031 (+/- 1.02; 415)	-0.090 (+/- 1.05; 47)	-0.77	460	0.442
18y platelet MAO	Male	0.135 (+/- 1.03; 183)	-0.114 (+/- 0.96; 109)	-2.05	290	0.042
	Female	0.000 (+/- 0.96; 356)	-0.021 (+/- 1.27; 35)	-0.12	389	0.904
25y platelet MAO	Male	0.133 (+/- 1.06; 218)	-0.112 (+/- 0.94; 142)	-2.23	358	0.026
	Female	-0.009 (+/- 1.03; 419)	-0.039 (+/- 0.91; 50)	-0.20	467	0.843

^aZ-scores were calculated for every study wave separately for males and females.

Table 3. Antisocial behavior with police contact and platelet MAO activity longitudinally from 15 to 25 years in the ECPBHS sample.

	MALE			FEMALE		
	Coeff.	95% CI	<i>p</i> value	Coeff.	95% CI	<i>p</i> value
Standardised platelet MAO activity						
	n=394			n=523		
Time	-0.0007	-0.0105; 0.0090	0.882	-0.0029	-0.0117; 0.0058	0.514
Police contact ¹	-0.2292	-0.4040; -0.0543	0.010	-0.0370	-0.2871; 0.2131	0.772
Standardised platelet MAO activity						
	n=394			n=522		
Time	0.0059	-0.0043; 0.0160	0.257	0.0033	-0.0053; 0.0119	0.450
Smoking	-0.1977	-0.3698; -0.0257	0.024	0.0667	-0.1773; 0.3106	0.592
Police contact ²	-0.2475	-0.3727; -0.1223	< 0.001	-0.4046	-0.5280; -0.2812	< 0.001

Estimated main effects of a linear mixed effects regression model (mean and 95% CI). Police contact classified Yes/No.

¹ Coefficient (Coeff.) can be interpreted as the mean difference in standardized platelet MAO activity between police contact(yes) and police contact(no) at each timepoint.

² Coefficient (Coeff.) can be interpreted as the mean difference in standardized platelet MAO activity between police contact(yes) and police contact(no) at each timepoint adjusted to smoking.

Table 4. Platelet MAO activity from 15 to 25 years of age according to extent of antisocial behaviour with police contact group and illicit drug use. Estimated main effects (mean and 95% CI according to linear mixed effects regression model).

	MALE			FEMALE		
	Coeff.	95% CI	<i>p</i> value	Coeff.	95% CI	<i>p</i> value
Standardised platelet MAO activity						
	n=394			n=523		
Time	-0.0007	-0.0105; 0.0090	0.882	-0.0029	-0.0117; 0.0058	0.514
Police contact	-0.2292	-0.4040; -0.0543	0.010	-0.0370	-0.2871; 0.2131	0.772
Standardised platelet MAO activity						
	n=394			n=523		
Time	-0.0008	-0.0105; 0.0090	0.880	-0.0029	-0.0117; 0.0059	0.516
One police contact	-0.1918	-0.4242; 0.0404	0.105	0.1036	-0.1753; 0.3825	0.467
Multiple police contacts	-0.2584	-0.4709; -0.0459	0.017	-0.5346	-1.0437; -0.0255	0.040
Standardised platelet MAO activity						
	n=139			n=221		
Time	0.0060	-0.0119; 0.0239	0.511	0.0002	-0.0128; 0.0132	0.973
One police contact plus a single illicit drug use	-0.8330	-1.3736; -0.2923	0.003	-0.2852	-1.2884; 0.7180	0.577
Multiple police contacts plus repeated illicit drug use	-0.5607	-0.8947; -0.2267	0.001	-0.7584	-1.3717; -0.1450	0.015

Table 5. Platelet MAO activity from 15 to 25 years of age according to education. Estimated main effects (mean and 95% CI according to linear mixed effects regression model).

	MALE			FEMALE		
	Coeff.	95% CI	<i>p</i> value	Coeff.	95% CI	<i>p</i> value
Standardized platelet MAO						
Time	-0.003	-0.012; 0.007	0.577	-0.002	-0.010; 0.007	0.622
Education (secondary) ^a	0.374	0.081; 0.668	0.012	0.020	-0.319; 0.359	0.908
Education (higher) ^a	0.390	0.105; 0.674	0.007	0.114	-0.208; 0.435	0.487

^a Coefficient (Coeff.) can be interpreted as the mean difference, in standardized platelet MAO activity between subjects with secondary education compared to basic education or higher education compared to basic education, in each time point.

3. Discussion

We report here the association of platelet MAO activity with antisocial behaviour in highly representative samples of birth cohorts that were followed longitudinally since adolescence to young adulthood, with measurement of MAO activity at three age points. Several previous studies that reported lower platelet MAO activity in subjects with different types of expression of antisocial behaviour have sampled subjects imprisoned, referred to forensic psychiatry, or others with registered criminal activity (see Introduction). One study did not establish a relationship between platelet MAO activity and recidivistic criminal behaviour within a group of subjects (age 17-76 years) referred to forensic psychiatric investigation (Gustavson et al., 2010), but in this sample also the effect of smoking on MAO activity was not detected, suggestive of some kind of sample bias. Interestingly, several nominal (but of nature one could expect) associations between platelet MAO activity and personality traits were observed even in that study, only among non-smokers. The present study suggests that at young age, low platelet MAO activity is predictive of antisocial activities of lower level of seriousness, both in males and females.

A longitudinal laboratory visit based study in a population-representative sample has limitations to the number of participants. That brings about a further natural limitation to study antisocial behaviour in its more severe forms that are not prominently represented in such a sample. Neither is antisocial behaviour likely to be expressed as a normally distributed single dimension. In order to address the question of whether platelet MAO activity has any relevance to the level of expression of antisocial behaviour, we conducted exploratory analyses stratifying by the number of police contacts and experimenting with illicit drugs. The results suggest that, in general, lower platelet MAO activity suggests higher incidence of non-law-abiding behaviour in an individual. One exception to this appears to be experimenting with illicit drugs in males. We have recently reported that the hazard ratios of a single experimenting with illicit drugs is even higher in males with low or medium as compared to high platelet MAO activity than those of repeated drug use (Sakala et al., 2022). This is reflected in the present finding that in males with one police contact and a single drug use episode, platelet MAO activity is the lowest, while in females it is repeated breach of law that is associated with low platelet MAO activity.

Because some of the illicit drugs inhibit MAO activity, the possibility of direct drug effect ought to be considered. In the present sample, most of the subjects who reported ever using amphetamine or methamphetamine (n=161), that can elicit such an effect, had done so only once in their lifetime. There were 33 users with some regularity. The probability of any subject who is not severely addicted to select to take an illicit drug within a few days before the laboratory visit that was known to involve blood sampling, also while keeping a diet diary and wearing an accelerometer that were other features of the sampling, appears as very low. According to the Mini-International Neuropsychiatric Interview conducted by a clinical psychologist at age 25 (Kiive et al., 2017), six subjects were found with lifetime amphetamine use disorder, of these just 2 with the disorder present at the time of the sampling. All this together suggests that the direct of drugs should not be thought of as a major contributory factor to the findings.

Antisocial behavior is more prevalent in males than in females (Ellis et al., 2019) and most of previous studies on antisocial behavior and platelet MAO activity have examined male samples. It has been hypothesized, however, that in females the referral to authorities represents a higher deviation from the average than in males, and this can be reflected in low platelet MAO activity (Cederblad et al., 1992). Findings of the present study are in line with their notion that in females antisocial behavior occurs at a larger deviance of the platelet MAO measure from the average. Platelet MAO activity is thought to reflect the central serotonin system, and serotonergic regulation of behaviour has important differences between genders, including its role in the regulation of aggressive behavior (Blanchard et al., 1991; Terranova et al., 2017; Paletta et al., 2022). While the bulk of research on the association of platelet MAO activity and behaviour has linked the enzyme activity to central serotonin, reflection of the contribution of other monoamine systems in platelet MAO should however also be considered a possibility, especially given the strong correlation between MAO-A and MAO-B activities in the brain at early age (Tong et al., 2013). In healthy volunteers, not only were the CSF levels of 5-HIAA in positive correlation with platelet MAO activity, but also the levels of homovanillic acid (HVA), a major metabolite of dopamine (Oreland et al., 1981). The correlation between CSF levels of HVA was also found in a sample of patients with Parkinson's disease (Mann et al., 1983). One unpublished study found a strong correlation between platelet MAO activity and CSF levels of 3-methoxy-4-hydroxyphenylglycol, the main stable metabolite of noradrenaline, in patients with self-

destructive behaviour (Lars Oreland, personal communication). Thus, preliminary evidence can be found to suggest that platelet MAO activity can also reflect the capacity of catecholamine systems, at least in subgroups of subjects.

The role of low serotonergic neurotransmission has been suggested to be specifically related to increased premature responding, and this can occur against the background of increased speed and accuracy of responding (Worbe et al., 2014). These findings were obtained using the tryptophan depletion paradigm, and suggest that serotonin has dissociable effects on different measures of impulsivity. Similar effect on premature responding has been described for serotonergic lesions in animal studies (Harrison et al., 1997). Impulsive aggressiveness in adulthood is increased if MAO activity had been inhibited during gestation (Whitaker-Azmitia et al., 1994; Mejia et al., 2002), and the MAO(-B) activity as measured in platelets is thought to reflect the prenatal gene expression state that in brain helped to shape the serotonergic system (Harro and Oreland, 2016). Of note, although at early age the levels of MAO-A and MAO-B are closely correlated, this association weakens during development (Tong et al., 2013).

The present finding provide some support to the notion that in females a higher degree antisocial behaviour is associated with low platelet MAO activity than in males (Cederblad et al., 1992). It has been recognized however that analysis in females is based on lower numbers of non-law-abiding subjects. Differences in male and female serotonin systems have been identified by a variety of approaches, and may underlie the impact of lifetime adversities (Gutknecht et al., 2015; Spies et al., 2020). A highly interesting experiment demonstrated that patterns of dendritic ramification in the rat prefrontal cortex develop during adolescence in a sex-specific manner, and that exposure to prenatal disrupted this process in males, not females (Markham et al., 2013). In contrast, the effect of prenatal stress on further dendritic ramification became evident in females by adulthood. Speculatively, the serotonin system in females may be more resilient to early stressors, but potentially vulnerable to additional psychosocial adversities at later stages such as adolescence. Specifically in female adolescents, the risk of alcohol-related problem behaviour was higher if platelet MAO activity in the lowest quartile was associated with unfavourable environment (Nilsson et al., 2008).

The present study on representative birth cohort samples provides strong support to previous reports that low platelet MAO activity is associated with antisocial behaviour, but it remains to be clarified how this comes about. One could hypothesize that low platelet MAO predisposes some individuals to socio-economic or psychosocial risk factors that are known to relate to antisocial behaviour. We have found that male, but not female subjects with the lowest level of education had lower platelet MAO activity, while MAO activity was not related to non-verbal intellectual abilities. Neither was platelet MAO activity statistically significantly associated with self-perceived socio-economic status. Because platelet MAO activity is known to be under genetic control, further studies should examine the possible role of familial aggregation, and attempt to distinguish the respective roles of genes, early family environment and life events, and to outline the developmental trajectories of more and less successful social adaptation in subjects with low platelet MAO activity.

Limitations of the study include relying on self-reports, but these were obtained under uniform laboratory conditions and as the study was longitudinal one could expect that the participants had rather high trust in confidentiality. It should also be fair to point out that no correction for multiple testing was used: Longitudinal laboratory-based studies have limits to size, and this in turn would very quickly exhaust any possibility to test hypotheses; furthermore, the appropriate level of correction is not simple to select if the variables are inter-correlated. Independent replication thus remains most desirable.

Conclusively, this longitudinal study on birth cohort representative samples strongly suggests that more common non-law-abiding behaviors are associated with low activity of platelet MAO activity in both males and females. The mediating developmental and moderating environmental factors of this association of putative lower-activity serotonergic system and low-grade antisocial behaviour deserve further investigation.

4. Method

4.1 Study design and participants

The database of the Estonian Children Personality Behaviour and Health Study (ECPBHS) was used. The participants of ECPBHS were originally recruited as the Estonian subsample of the

European Youth Heart Study (1998/1999), the rationale of the sample formation and the procedure have been described previously (Harro et al., 2001). In brief, all schools of the 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. In these schools, all children in third and ninth grades were invited to participate, and 79.1% agreed (with average age 9.6 and 15.6 years, respectively). Follow-ups have been conducted at age 15 for the younger cohort, 18 and 25 (for both cohorts) and 33 (for the older cohort) (Sakala et al., 2022). The original sample size was 1238, the number of subjects in the present analysis, with valid measures of platelet MAO activity and data on antisocial behaviour, was 917 (57% female). The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Committee on Human Research of the University of Tartu.

4.2 Antisocial behaviour with police contact

Antisocial behaviour was primarily defined as in our previous study on this sample (Schoenmacker et al., 2020). We used the item on antisocial behaviour involving police contact (e.g. warnings, arrests and/or convictions for misdemeanor or felony offenses) in the Life History of Aggression (LHA) interview (Coccaro et al., 1997) conducted by a clinical psychologist at the age of 25 (younger cohort) or 33 (older cohort). The results of this item were converted to a binary variable (out of 917 participants, 214 had antisocial behaviour involving police contact, 55 of them females). For further analysis, we stratified subjects by having a single vs. multiple police contacts (Table 6), because we had previously revealed that platelet MAO activity was lower in this sample in males with self-reported illicit drugs, even in case of a single use in lifetime (Sakala et al., 2022). Experimenting with illicit drugs is by definition an antisocial behaviour, but more often than not it does not lead to a police contact.

Table 6. Antisocial behaviour in the ECPBHS sample (n in data analysis).

	Males	Females
<i>Police contact</i>		
Control group	235	468
One contact	70	43

	Multiple contacts	89	12
<i>Police contact and drugs</i>			
	Police contact, no illicit drugs	71	212
	One police contact plus a single illicit drug use	16	3
	Multiple police contacts plus repeated illicit drug use	54	8

4.3 Platelet MAO activity

Platelet MAO activity was measured in platelet-rich plasma by a radioenzymatic method as previously described, with β -phenylethylamine as the substrate (Harro et al., 2001). On average, platelet MAO activity is different in males and females, and the raw data obtained in different study waves are not directly comparable (owing to, most importantly, specific activity of the available radiolabelled substrate). Hence platelet MAO activity levels were standardized for each data collection wave/measurement separately for males and females, and z-scores were used in all analyses.

4.4 Education, intellect and socio-economic status

After the finding that platelet MAO activity was associated with police contact, we analyzed the relationship of the enzyme activity with a few measures that are related to antisocial behaviour. Education was self-reported at age 25 and categorized as elementary, secondary (including vocational) and higher education. Raven's Standard Progressive Matrices (SPM) test (Raven, 1981), standardized on Estonian population by Lynn et al., 2002, subtests C and D were used to measure the intellectual abilities of the adolescent participants (Paaver et al., 2007). The SPM is commonly regarded as a high-quality measure of pure non-verbal reasoning ability, which is relatively independent of specific learning acquired in a particular cultural or educational context (Jensen, 1998). The test was administered without time limits. Socio-economic status was analyzed by an SES score as previously reported (Katus et al., 2020). In brief, questions about parental education level (ranging from primary and basic education to higher education), total household income (divided into income groups) and self-reported or parent-reported SES compared to peers (ranging from poor to among the wealthiest in the country) were used for participants in the age group between 15 and 18 years. For the age group

of 25 years, questions about the level of education of the subject, total household income, and self-reported SES assessment compared to peers was used. Individual SES scores were calculated by matching a numerical value for each answer option. SES scores were standardized and z-scores were used in longitudinal analysis.

4.5 Statistical analysis

Data was analysed using SPSS version 26 (IBM Corp, Armonk, NY, USA) and Stata version 14 (StataCorp LP, College Station, TX, USA). Level of significance was set at 0.05. Independent group t-test was used to test differences in platelet MAO activity (at ages 15, 18 and 25) between control and antisocial behaviour group. Linear mixed-effects regression models with random intercept and random slope were fitted to estimate the longitudinal association between antisocial behaviour and platelet MAO activity from age 15 to 25 years. Platelet MAO activity was defined as the dependent variable and antisocial behavior with police contact as the independent variable. Sampling by data waves was treated as a continuous variable. Unstructured covariance structure and restricted maximum likelihood method was used. Models were also adjusted to smoking status (Smokers/Non-smokers). Pearson correlation was used for assessment of the relationship between Raven SPM and platelet MAO activity.

CRedit authorship contribution statement

Katre Sakala: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. Urmeli Katus: Investigation, Methodology, Writing - review & editing. Evelyn Kiive: Conceptualization, Investigation, Methodology, Writing - review & editing. Toomas Veidebaum: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing. Jaanus Harro: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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