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Low cholesterol levels in children predict impulsivity in young adulthood

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Running Head: Childhood lipid levels and adulthood impulsivity

Abstract

Objective: Severe behavioural issues such as impulsive action and suicide have since long been associated with low levels of cholesterol. While it is known that cholesterol plays a role in neural development and hence low levels of serum lipids could have long-term effects on behaviour, there are no longitudinal studies showing association of serum lipids levels with impulsivity. We aimed to examine the prognostic properties of serum lipid levels during childhood and adolescence on measures of impulsivity during early adulthood in a representative birth cohort sample. *Methods:* We have investigated whether serum lipid levels measured at 9, 15, 18 and 25 years of age have an association with impulsivity in 25 years old young adults. This analysis was based on data of the birth cohort representative samples of the Estonian Children Personality Behaviour and Health Study (original n=1238). Impulsivity was self-reported with the Adaptive and Maladaptive Impulsivity Scale. *Results:* Total and LDL cholesterol measured in 9, 15 and 18 years old boys predicted Disinhibition and Thoughtlessness in 25 years old young adults. High scores of Disinhibition were associated with low total and LDL cholesterol levels in males but, while less consistently, with high total and LDL cholesterol levels in females. Cross-sectional analysis did not result in systematic outcomes. *Conclusions:* Serum lipid levels could have an impact on development of maladaptive impulsivity starting from an early age. This effect of cholesterol continues throughout adolescence into young adulthood.

Keywords:

Cholesterol; Impulsivity; Children; Young adults; Sex

Significant Outcomes

• In males, impulsivity in adulthood is predicted by low cholesterol levels already in childhood

• Association between cholesterol and impulsivity in males is specific to maladaptive aspects of impulsivity

• The association between cholesterol and impulsivity is different in males and females of the same birth cohort

Limitations

Impulsivity was self-reported.

Introduction

Low serum lipid levels have repeatedly been linked to several psychopathologies, including violent criminal behaviour (Repo-Tiihonen *et al.*, 2002), aggression towards others and self (Sahebzamani *et al.*, 2013), and suicide (Daray *et al.*, 2018). Impulsivity, being an essential feature of disruptive behaviour disorders (Dougherty *et al.*, 1999), excessive risk taking (Eensoo *et al.*, 2018; Tokko *et al.*, 2019) and pathologically aggressive (Barratt *et al.*, 1999) or suicidal behaviour (Corruble *et al.,* 1999), is one of the key elements of maladaptive behaviours associated with low cholesterol levels (Troisi, 2011). However, results of some studies have been in conflict with the assumption that cholesterol levels and impulsivity, aggressiveness or suicidality could be correlated in a general and linear manner (Corruble *et al.*, 1999; Troisi, 2011; Tomson-Johanson and Harro, 2018).

Meta-analyses conducted in adults or elderly population support the link between low levels of serum lipids and suicidality (Muldoon *et al*., 1990; Wu *et al.*, 2015). In the same time studies conducted in paediatric and adolescent psychiatric patients remain conflicting, and are very scarce. In a study of 66 patients ranging from 8 to 18 years consecutively admitted to a psychiatric inpatient unit following attempted suicide, levels of cholesterol were found to be significantly lower in attempted suicide patients than in inpatients who had not attempted suicide. Control subjects were paired with case subjects according to psychiatric diagnosis, age and gender (Plana *et al.*, 2010). In contrast, in a similar study of 152 adolescent psychiatric inpatients ranging from 12 to 21 years it was found that serum cholesterol levels were significantly higher in both male and female suicidal adolescent patients than in non-suicidal adolescents. Yet, within the suicidal group, but not in the total inpatient group, serum cholesterol correlated negatively with the degree of suicidal behaviour. No correlation

between serum cholesterol levels and impulsivity was detected (Apter *et al.*, 1999). Nevertheless, age of the onset of the potential impact of cholesterol on behaviour may be of key importance.

Cholesterol is an essential structural component for cellular membrane and myelin. By forming microdomains with phospholipids, membrane rafts have been proposed to play active roles in a wide range of physiological processes, including signal transduction, protein sorting, cellular entry of viruses/toxins and apoptosis (Simons and Vaz, 2005). Both lack and also surplus of cholesterol can have negative effects. It is well established that neuronal cells regulate their cholesterol content by a feedback mechanism that balances biosynthesis, import, and excretion (Zhang and Liu, 2015). While the main sources of cellular cholesterol involve uptake from cholesterol-rich low-density lipoprotein (LDL) cholesterol or its de novo synthesis from acetyl-CoA, excessive cholesterol can be eliminated in the presence of high-density lipoprotein (HDL) cholesterol that acts as a lipid acceptor (Matsuda et al., 2013).

According to the classic theory of Engelberg (1992) lowered serum cholesterol concentration may contribute to a decrease in brain serotonergic neurotransmission via altered microviscosity, resulting in poorer suppression of aggression towards self and others. Cholesterol metabolism has a long-term effect on synaptogenesis, dendrite differentiation and axonal growth, thus being crucial for synaptic plasticity (Goritz *et al.*, 2005). Cholesterol is also an essential component for neuronal physiology that is needed for synaptic growth and plays a crucial role during developmental stages (Mauch *et al.*, 2001).

Owing to the role cholesterol plays in neurodevelopment, children should be especially susceptible towards negative effects of low serum lipids. Yet while the association of serum lipid levels with various forms of aggression and impulsivity has been studied in adults in cross-sectional studies (Repo-Tiihonen *et al.*, 2002; Pozzi *et al.*, 2003; Vevera *et al.*, 2003),

cohort samples (Svensson *et al.*, 2017), psychiatric patients (Bartoli *et al.*, 2017) and criminals (Hillbrand *et al.*, 2000), in children such studies remain scarce. To our knowledge there has been no investigation on whether serum lipid levels in childhood or adolescence would be associated with aggression or impulsivity in later life.

Aims of the study

The aims of the present study were to investigate the prognostic properties of serum lipid levels in childhood and adolescence on measures of impulsivity in early adulthood in a population-representative sample.

Material and methods

Sample

This study was carried out on the Estonian sample of the European Youth Heart Study (1998/1999), which was subsequently incorporated into the longitudinal Estonian Children Personality Behaviour and Health Study (ECPBHS). The European Youth Heart Study sample of the ECPBHS consists of two birth cohorts. The rationale and procedure of sample formation, and further data collection waves have been described elsewhere in detail (Harro *et al.*, 2001; Tomson *et al.*, 2011; Roy *et al.*, 2018). In brief, all schools of Tartu County, Estonia, that agreed to participate (54 of the total of 56) were included into the sampling using the probability proportional to the number of students of the respective age groups in the school, and 25 schools were selected. ECPBHS is highly representative of the birth cohorts of a local population, as 79% of subjects of the randomized regional sample participated in the original data collection. All the subjects are of European descent. The total number of

subjects, for whom all data used in this paper were available, was 1160, 93.7% of the original sample. Schematic overview of the follow-up of the two cohorts is presented in Figure 1. This study was approved by the Ethics Review Committee on Human Research of the University of Tartu, and written informed consent was obtained from all the participants, and in case of minors, also from their parents.

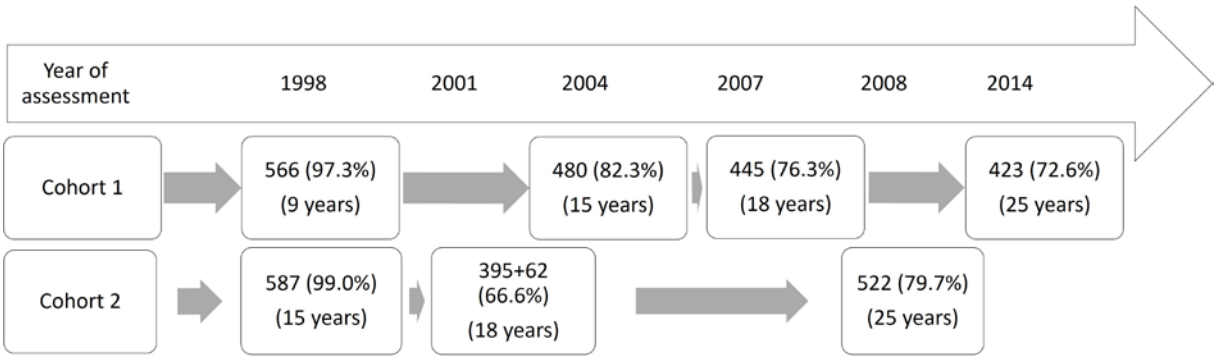

Figure 1. Schematic overview of the follow-up of the two cohorts. Number of subjects with complete data on lipid levels and impulsivity available, percentage of original sample in brackets (in Cohort 2 at age 18 years 62 new subjects were involved and percentage at age 25 years indicates the proportion of original sample plus later included subjects).

Behavioural measures

Different facets of impulsivity (Fast decision making, Excitement seeking, Disinhibition, Thoughtlessness) were self-reported at 15, 18 and 25 years of age in both cohorts using the Adaptive and Maladaptive Impulsivity Scale (AMIS; (Laas *et al*., 2010)). AMIS is an instrument for the measurement of distinct aspects of impulsivity developed on the basis of the concept of Dickman (1990) of functional and dysfunctional impulsivity. The subscales Fast decision making and Excitement seeking form Adaptive impulsivity, and Disinhibition and Thoughtlessness form Maladaptive impulsivity. There are statistically significant, but weak correlations between the subscales of Adaptive and Maladaptive impulsivity (r=0.1-0.3) while the subscales within Adaptive and Maladaptive impulsivity are closely related (r=0.52 and 0.65, respectively; Laas *et al*., 2010). Both major aspects of impulsivity indicate openness to action with less forethought than risk-free, but high Maladaptive impulsivity has high harm risk while Adaptive impulsivity supports success by agility. Previously, AMIS has been applied in a series of studies on risk-taking behaviour and impulsivity-related candidate genes studies, and found to have good predictive validity (e.g., Eensoo *et al.*, 2004; Paaver *et al*., 2006; Laas *et al*., 2015a; Laas *et al*. 2015b; Laas *et al.*, 2017; Luht *et al.*, 2019). Impulsivity data were available for 481 subjects at age 15 (Cohort 1 only, 260 females), 899 subjects at age 18 (509 females) and 935 subjects at age 25 (539 females).

At age 25, the Mini-International Neuropsychiatric Interview (MINI.5.0.0), (Sheehan *et al.*, 1998) Estonian version (Shlik *et al.*, 1999) was used to screen for current and lifetime psychiatric disorders. Diagnostic assessment was carried out by experienced clinical psychologists.

At the age of 18 maltreatment was assessed using the Tartu Family Relationships Scale, a self-reported scale that assesses relationships in the family and is composed for Estonian Children Personality, Behaviour and Health Study. Maltreatments scale comprises of 17 Likert scale questions about misprize within the family and about emotional and physical abuse (Paaver *et al.*, 2008; Kiive *et al.*, 2010).

Blood lipid measurements

Fasting basal cholesterol (total cholesterol (TC), low density lipoprotein (LDL) and high density lipoprotein (HDL), as well as triglyceride (TRG) levels were measured by conventional techniques in the Central Laboratory of the Tartu University Hospital, and presented in mmol/l. The procedure was same for both cohorts throughout the study. LDL data of the sampling in 1998 were calculated based on the Friedewald formula (Winocour *et al.*, 1989). In the follow-up studies all serum lipid levels, including LDL cholesterol, were measured directly from the serum.

Smoking status and use of alcohol, narcotic substances and medications

Smoking status was assessed at the age of 25 years with the question whether participants had smoked in the last month resulting in a two-point scale.

The subjects reported at the age of 25 whether they had consumed in the last year a certain type of alcohol at least once a month. Subjects were divided into low, medium and high alcohol use groups.

Illicit substance use was assessed at the age of 25 years with the question of whether participants had ever tried an illicit substance, resulting in a two-point scale.

Subjects reported use of blood pressure medications and hormonal contraceptives for women at the age of 25. None of the subjects reported usage of lipid lowering drugs.

Statistical analysis

The effects of sex and age on serum lipid levels were studied using two-way analysis of variance (ANOVA) with Tukey post-hoc test. To determine the predictive effects of serum lipid levels (triglycerides, HHL, LDL and total cholesterol) at 9, 15 and 18 years of age on impulsivity traits at 25 years of age, one-way analysis of covariance (ANCOVA) was performed. The effects of serum lipid levels at each age group were tested separately; also for both sexes different models were constructed. In each analysis an impulsivity measure (Fast decision making, Excitement seeking, Disinhibition or Thoughtlessness) was set as dependent variable, serum lipid level measured at specific time point as independent variable and cohort, psychiatric disorders, medications, alcohol and illicit substance use, smoking and maltreatment as covariates. Outlier analysis was conducted to meet the ANCOVA assumption of normal distribution Pearson correlation analysis was used to illustrate the strength of association of serum lipids with impulsivity measures and to investigate the relationship of impulsivity and serum lipid levels cross-sectionally at specific age. To omit any cohort effect both impulsivity and serum lipid levels were transformed into z-scores within both cohorts. Serum lipid levels in males and females are innately different. To omit any sex effect on the link between serum lipid levels and impulsivity males and females were analysed separately. The level of significance was set at $p<0.05$. Statistical analyses were carried out using SPSS version 23 (IBM corp, 2015)t.

Results

Description of the sample

Sample characteristics, mean total, HDL, LDL cholesterol and triglyceride levels in males and females at ages 9, 15, 18 and 25 are presented in Table 1. Sex had a significant effect on total, HDL and LDL cholesterol ($F(1,2833)=79.9$, 201.8, and 14.9, respectively; $p<0.001$). Females mostly had significantly higher levels of lipids than males but there were a few exceptions.

Table 1. Characteristics of the analyzed sample and an overview of the total, HDL and LDL cholesterol and triglyceride levels in different age groups.

Age	**9**	**15**	**18**	**25**
Sample size (n)	566	1067	902	945
Number of females (%)	296 (52.3)	587 (55.0)	510 (56.5)	539 (57.0)
TC in males	4.36 ± 0.72	3.84 ± 0.66*#	3.97 ± 0.69*#	4.42 ± 0.80
TC in females	4.50 ± 0.76	4.27 ± 0.70#	4.34 ± 0.83#	4.56 ± 0.82
HDL in males	1.50 ± 0.30#	1.35 ± 0.28*#	1.36 ± 0.28*	1.31 ± 0.33*
HDL in females	1.43 ± 0.27#	1.50 ± 0.31#	1.61 ± 0.34#	1.69 ± 0.40
LDL in males	2.54 ± 0.60*#	2.22 ± 0.56*#	2.33 ± 0.62*#	2.78 ± 0.73*
LDL in females	2.71 ± 0.67	2.50 ± 0.62#	2.48 ± 0.69	2.59 ± 0.75
TRG in males	0.68 ± 0.27#	0.76 ± 0.37#	0.87 ± 0.48#	1.09 ± 0.61*
TRG in females	0.77 ± 0.27#	0.83 ± 0.36#	0.81 ± 0.41#	0.94 ± 0.45

Values are given in mmol/L and expressed as mean ± SD. Total cholesterol (TC), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG). *$p < 0.05$, males *vs.* females. #$p<0.01$, difference with serum lipid level at 25 years.

Data of both birth cohorts were available starting from the age of 15 years. For that age serum lipid levels were compared with the recommended values of National Cholesterol Education

Program (NCEP) Expert Panel on Cholesterol Levels in Children (1992). In the total sample, 72% of the participants had acceptable TC levels (<4.4 mmol/l), 22% had borderline high levels (4.4–5.2 mmol/l), and 6% had high levels (>5.2 mmol/l). In case of LDL cholesterol, 81% of the participants had acceptable levels (<2.8 mmol/l), 13% had borderline high levels (2.8–3.4 mmol/l) and 6% had high levels (>3.4 mmol/l). 80% of the participants had acceptable triglyceride levels (<1.0 mmol/l), 14% had borderline high levels (1.0-1.5 mmol/l) and 6% had high levels (>1.5 mmol/l). 8% of the participants had low HDL cholesterol levels (<1.0 mmol/l), 8% had borderline low levels (1.0-1.2 mmol/l) and 84% had acceptable HDL cholesterol levels (>1.2 mmol/l).

The total cholesterol values of our sample at 9 years of age are in the same range with other studies. In a Norwegian study where blood samples of 1340 children were available at the age of 9 years girls had the median total cholesterol values of 4.4 mmol/l and boys 4.2 mmol/l (Strand et al., 2018). In a Dutch study of 8071 children the median value for 9 year old boys was 4.1 mmol/l and for girls 4.2 mmol/l (Balder et al., 2018). In a study where 23 cohorts of children from Europe and United States (total 22,479 observations) were pooled mean reference values of total cholesterol in girls were 4.4 mmol/l and in boys 4.25 mmol/l (Stavnsbo et al., 2018). As expected, intra-individually the cholesterol levels correlated; detailed information on this is provided in Supplementary Table 1.

Longitudinal analyses

In males, according to ANCOVA models, impulsivity measures at 25 years were predicted by serum lipid levels as early as at the age of 9 years (Table 2). Both total cholesterol and LDL at 9, 15 and 18 years predicted Disinhibition and Thoughtlessness, both components of Maladaptive Impulsivity at 25 years. As to the facets of adaptive impulsivity, Excitement

seeking at 25 years was predicted only by total cholesterol at 15 years. Fast decision making at 25 years was predicted by HDL cholesterol at 15 years.

Correlation analyses without covariates were similar to the results with ANCOVA (Table 3). In most cases where serum lipid levels had predicted impulsivity measures at 25 years the correlation also reached statistical significance.

Significant correlations between serum lipid levels and impulsivity measures in males were negative, while in females these correlations were positive. While correlation was borderline significant between Disinhibition measured at 25 years and total and LDL cholesterol at 15 years in females, it was not significant in ANCOVA model and thus can be attributed to the effect of covariates.

Adjusted R^2 was above 0.2 for models where Disinhibition was predicted by total, HDL or LDL cholesterol measured at 9, 15 or 18 years. Surprisingly, this was the case for both men and women. In men, also Thoughtlessness predicted by total or LDL cholesterol measured at 9 years had an adjusted R^2 value over 0.2.

Table 2. Results of ANCOVA predicting impulsivity measures at 25 years of age based on serum lipid levels separately at 9, 15 and 18 years of age by gender. Covariates included cohort, psychiatric disorders, medications, alcohol and illicit substance use, smoking and maltreatment. Regression coefficients b presenting the effect size and direction and p-values are presented.

MALES									
		Disinhibition		Thoughtlessness		Excitement seeking		Fast decision making	
		b	p	b	p	b	p	b	p
9 years	TC	-1.88	<**0.001**	-2.05	<**0.01**	-0.01	0.99	0.33	0.63
	HDL	-3.92	<**0.01**	-3.96	**0.01**	0.81	0.58	0.54	0.75
	LDL	-1.74	<**0.01**	-2.13	<**0.01**	-0.09	0.89	0.28	0.73
	TRG	-1.60	0.299	-0.63	0.75	-0.46	0.79	1.98	0.33
15 years	TC	-1.43	<**0.001**	-1.39	<**0.01**	1.03	**0.04**	1.02	0.04
	HDL	-2.53	0.10	-1.58	0.21	1.54	0.20	3.05	**0.01**
	LDL	-1.51	<**0.01**	-1.60	**0.01**	0.81	0.19	0.38	0.49
	TRG	0.39	0.59	0.14	0.87	0.40	0.66	0.84	0.36

18 years	TC	-1.15	**<0.01**	-1.04	**0.04**	0.91	0.07	0.73	0.14
	HDL	-2.59	**<0.01**	-1.85	0.12	2.97	0.01	1.72	0.13
	LDL	-0.81	0.07	-0.95	**0.01**	0.60	0.28	0.57	0.30
	TRG	0.83	0.12	0.70	0.29	-0.89	0.17	-0.27	0.67

FEMALES

		Disinhibition		Thoughtlessness		Excitement seeking		Fast decision making	
		b	p	b	p	b	p	b	p
9 years	TC	0.15	0.81	-0.23	0.73	0.38	0.60	-0.87	0.24
	HDL	-0.01	1.00	1.23	0.50	1.31	0.49	-0.39	0.84
	LDL	0.37	0.61	-0.52	0.54	0.25	0.77	-1.06	0.24
	TRG	0.47	0.78	0.06	0.98	1.55	0.43	0.54	0.79
15 years	TC	-0.20	0.62	-0.43	0.34	-0.07	0.88	-0.52	0.27
	HDL	-0.98	0.29	-0.60	0.54	1.08	0.31	0.25	0.81
	LDL	-0.37	0.39	-0.63	0.22	-0.66	0.24	-0.95	0.08

	TRG	0.02	0.98	-0.04	0.96	0.01	0.99	-0.33	0.72
18 years	TC	-0.04	0.89	0.20	0.61	0.13	0.77	-0.08	0.84
	HDL	-0.33	0.66	-0.46	0.59	1.79	0.07	0.83	0.37
	LDL	-0.17	0.67	-0.13	0.78	-0.26	0.62	-0.41	0.40
	TRG	0.03	0.97	1.10	0.13	-0.63	0.44	-0.10	0.89

Total cholesterol (TC), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG). P-value marked in bold while significant at $p<0.05$.

Table 3. Correlations between serum lipids at 9, 15, and 18 years, and impulsivity measures at 25 years, separately in males and females.

		MALES				FEMALES			
		Disinhi-bition	Thought-lessness	Excitement seeking	Fast decision making	Disinhi-bition	Thought-lessness	Excitement seeking	Fast decision making
9 years	TC	**-0.21**	-0.14	-0.02	-0.01	0.12	0.01	0.04	0.01
	HDL	-0.06	-0.03	0.07	0.12	0.13	0.09	0.01	-0.03
	LDL	**-0.20**	-0.12	-0.03	-0.05	0.07	-0.03	0.04	0.03
	TRG	-0.08	-0.14	**-0.15**	-0.08	0.07	0.01	-0.03	-0.03
15 years	TC	**-0.18**	**-0.12**	0.03	0.01	**0.10**	0.02	0.00	-0.07
	HDL	-0.10	-0.07	0.00	0.10	0.03	0.01	0.05	0.00
	LDL	**-0.16**	-0.09	0.01	-0.04	**0.11**	0.02	-0.01	-0.06
	TRG	-0.02	-0.03	0.00	0.04	0.04	0.04	0.01	0.01
18 years	TC	**-0.13**	**-0.12**	0.09	0.06	0.01	0.03	-0.01	-0.01
	HDL	-0.08	-0.02	**0.14**	0.08	0.02	0.02	0.08	0.07

LDL	**-0.13**	**-0.13**	0.07	0.03	0.03	0.02	0.00	-0.03
TRG	0.11	0.05	-0.02	0.01	0.00	0.04	-0.01	0.07

Correlations of total cholesterol (TC), HDL cholesterol (HDL), LDL cholesterol (LDL) and triglycerides (TRG) with the impulsivity measures are in bold while significant at $p<0.05$.

Cross-sectional correlation analyses

When impulsivity and serum lipid levels were examined cross-sectionally at age 15, 18 or 25, a few statistically significant correlations emerged (Table 4) but these were not very systematic. Perhaps most interesting was the finding of negative correlations between total and LDL cholesterol and both facets of adaptive impulsivity in females at age 15. Nevertheless, these correlations completely disappeared after puberty. In males, cross-sectional negative correlations of total cholesterol and LDL with maladaptive impulsivity emerged by age 25 but only with the Thoughtlessness facet (Table 4).

Table 4. Correlations between serum lipid levels at 15, 18 and 25 years and impulsivity measures at the same respective age, separately in males and females.

		MALES				FEMALES			
		Disinhi-bition	Thought-lessness	Excitement seeking	Fast decision making	Disinhi-bition	Thought-lessness	Excitement seeking	Fast decision making
15 years	TC	-0.04	-0.03	-0.04	-0.10	0.06	-0.08	**-0.12**	**-0.15**
	HDL	0.11	0.09	0.02	0.06	0.07	0.03	0.03	-0.02
	LDL	-0.07	-0.07	-0.03	-0.13	0.03	-0.11	**-0.13**	**-0.14**
	TRG	-0.05	0.01	-0.06	-0.08	0.08	0.05	-0.07	-0.10
18 years	TC	-0.02	0.01	-0.01	0.04	0.06	0.03	0.01	-0.03
	HDL	**-0.16**	-0.01	**0.13**	0.07	0.02	0.05	0.08	-0.05
	LDL	0.01	-0.04	-0.03	0.02	0.03	-0.04	-0.03	-0.02
	TRG	0.08	**0.13**	-0.08	0.01	0.08	0.05	0.03	0.01
25 years	TC	-0.08	**-0.12**	0.05	0.05	0.05	-0.06	-0.08	0.01

HDL	-0.04	-0.02	0.10	0.05	0.01	-0.08	-0.01	0.02
LDL	-0.06	**-0.11**	0.03	0.06	0.04	-0.02	-0.09	-0.02
TRG	-0.01	-0.04	-0.03	-0.03	0.01	-0.02	-0.07	0.02

Total cholesterol (TC), HDL cholesterol (HDL), LDL cholesterol (LDL) and triglycerides (TRG) correlations with impulsivity measures are in bold while significant at $p \leq 0.05$.

Discussion

We have found that, in males, impulsivity self-reported at 25 years of age was predicted by total and LDL cholesterol levels measured as early as at the age of 9 years. Indeed, correlations between cholesterol levels and impulsivity were higher at younger age and became lower as the subjects matured, while remaining statistically significant throughout adolescence. This suggests that the oft-observed association between cholesterol levels and impulsive behaviour becomes established at early age and may if anything rather weaken under the influence of the variety of lifetime factors affecting blood lipid levels as well as impulse control regulation. Hence the inconsistency between studies with regard to cross-sectional correlations may reflect the variability of confounding factors between samples.

While cognitive styles involving fast decision making and excitement seeking are weakly related to disinhibition and thoughtlessness at a higher order level (Laas *et al.,* 2010), association of only Maladaptive Impulsivity with cholesterol levels suggests that the impact of cholesterol is specifically on those neurodevelopmental mechanisms that are responsible for the dysfunctional aspects of impulsivity. While serum lipid levels have been historically associated with impulsivity, several authors have drawn attention to the heterogeneity between sexes in that matter (Tomson *et al.,* 2016; Eriksen *et al.,* 2017). Considerable number of studies that had both sexes represented has found the association between cholesterol and impulsivity only in males (Muldoon *et al.,* 1990; Lindberg *et al.,* 1992; Golier *et al.,* 1995; Wu *et al.,* 2015). The studies where association has been found also in females remain rather conflicting. For example, the study by Svensson *et al.* (2017) found, by analysing 16 341 men and 28 905 women aged 40–69 from the Japan Public Health Centre-based Prospective Study followed from 1990 to 2012, that suicide mortality was associated with high serum total

cholesterol in women. There was no association between total cholesterol levels, or lipid fractions, and suicide in men. Similarly in the study by Siegman *et al*. (2002) the impulsive anger-out significantly predicted high total and LDL cholesterol and triglyceride levels, but only in physically unfit women. In accordance, in our study Disinhibition in 25 year old women was correlated with high levels of total and LDL cholesterol in 15 year old girls.

The gender differences may relate to the central serotonergic function, one of the possible mediators of serum lipid levels and impulsivity (Steegmans *et al*., 1996; Terao *et al*., 2000; Vevera *et al*., 2003; Luht *et al*., 2019). Serotonin pathways function as a behavioural restraint system that inhibits impulsive behaviour (Miyazaki *et al*., 2012). A number of studies have suggested major differences between males and females in a variety of measures of the serotonergic system as well as in their functional associations (e.g., Nishizawa *et al*., 1997; Jovanovic *et al*., 2008; Soloff *et al*., 2014; Kotting *et al*., 2013; Walderhaug *et al*., 2010; (Walderhaug *et al*., 2007). Similarly, studies on gene-environment interactions with genes with major impact on serotonin function and on platelet MAO that reflects capacity of the central serotonergic system (Harro and Oreland, 2016) consistently support the notion that the role of serotonin system in behavioural regulation is not identical in males and females.

Cholesterol may influence the conformation and function of membrane-bound proteins and receptors by reducing neuronal membrane fluidity and increasing mechanical strength of the membranes. Mechanisms underlying the association between cholesterol and serotonin activity have not yet become clear, however, it has been suggested that both high and low cholesterol levels may lead to lower serotoninergic activity (Papakostas *et al*., 2004). The rigidity of cholesterol-enriched membrane can alter or disrupt the function of lipid rafts (Björk *et al*., 2010) where a variety of neurotransmitter receptors operate (Bruses *et al*., 2001; Sooksawate and Simmonds, 2001; Suzuki *et al*., 2001). Low serum lipid levels have been

found to influence the conformation and function of membrane-bound proteins and receptors (Ohvo-Rekila *et al*., 2002), and amongst others to modulate the affinity of serotonin receptor agonists and serotonin transporter activity (Pucadyil and Chattopadhyay, 2004; Sjoegren *et al*., 2006; Scanlon *et al*., 2001). Other factors that could influence serum lipid and impulsivity association include age, nutritional status, substance (including alcohol) abuse, medication and lifestyle. Epidemiological studies relating impulsivity and serum lipids are limited by the fact that adults commonly have clinically problematic serum lipid levels. High total cholesterol levels can be result of negative lifestyle choices that subjects have been exposed to for decades, and potentially have been managed with statins over a long period of time (Asellus *et al.*, 2014; Naiberg *et al.*, 2016; Bartoli *et al.*, 2017). One of the strengths of the current study is inclusion of children starting from age of 9 years into the longitudinal design, who because of their young age have been exposed to possible confounding factors to a lesser extent. Several factors like demographics, biochemical factors and adverse childhood experiences have been shown to have an effect on the relationship of cholesterol and impulsivity (Bartoli *et al*., 2017; Kraav *et al*, 2019). By adding several covariates like presence of psychiatric disorders, medications, alcohol and narcotic substance use, smoking and maltreatment to our statistic model we have however eliminated their possible effect on the relationship of serum lipid levels and impulsivity in this age range. Also, the birth cohort representative design of the study decreases the bias caused by the confounding factors on the association of impulsivity and serum lipid levels. Nevertheless, confounding factors demand careful consideration in the future research.

Literature is inconsistent with regard to which lipid fractions could be the best predictors of psychopathologies associated with impulsivity. Low total serum cholesterol as well as low HDL cholesterol has been shown to predict violent behaviour during the follow-up in patients released after treatment at a psychiatric ward (Roaldset *et al.*, 2011; Eriksen *et al.*, 2017). In

patients with schizophrenia (Mensi *et al.*, 2016) and major depressive episode ((Messaoud *et al.*, 2017) low levels of total cholesterol have been proposed as surrogate markers for impulsivity and suicidality. In schizophrenic patients LDL cholesterol levels have been recommended as a potential marker (Kavoor *et al.*, 2017). The results of the current study are in agreement with works showing that LDL and total cholesterol, rather than HDL cholesterol, are predictive of impulsivity, but this could vary within specific patient groups.

In the current study Disinhibition and Thoughtlessness in males was predicted by total and LDL cholesterol, but not by triglycerides level. The interaction of serum lipid levels and impulsivity may have behavioural background. Triglycerides have been used in previous literature to control for the nutritional intake effect on the association of cholesterol and impulsivity (Kaplan *et al.*, 1997). Previous research has shown, that considerable number of patients with higher BMI, triglycerides, and cholesterol may have maladaptive nutritional behaviours such as binge eating. An association between binge eating and suicide attempts and suicidal ideation has been described in the literature (Favaro and Santonastaso, 1997). Our study suggests that cholesterol levels are predicting impulsivity independently of triglycerides, and thus it can be hypothesized that nutritional intake has not played a role in the interaction of impulsivity and serum lipid levels as a confounding factor.

In contrast to the longitudinal analysis, the cross-sectional analyses did not result in a coherent outcome. This is not surprising: While there are many studies showing an association between low serum lipids and problematic behaviour including impulsivity, other studies failed to find such an association. For example the results of the Coronary Artery Risk Development in Young Adults study conducted in 4240 young adults aged 23 to 35 showed that while persons in the lowest 10% of plasma total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were compared with the other

participants in each race/sex group, using standardized measures of hostility, anger suppression, depressive symptoms, and anxiety low cholesterol levels were not related to any of the psychological measures in any race or sex group (Markovitz *et al.*, 1997). Similarly, Fowkes *et al*. (1992) failed to show association between aggression and low serum lipids in a random sample of 1592 men and women aged between 55 and 74 years. A possible explanation to these inconsistencies is that low serum lipid levels have an effect on behavioural measures only during a specific period, and not throughout life. In addition, cross-sectional relationships may be inconsistent simply because the impulsive behaviour is a developmental outcome of interaction of past cholesterol levels and accumulating experiences. Cross-sectionally measured serum lipid levels may not adequately represent the effect lipids have on behavioural measurements. Cholesterol is an essential component of the cell membranes and is crucial especially during the sensitive time of neurodevelopment. Our results that highlight importance the childhood serum lipid levels have on impulsivity in adulthood rather than impulsivity measured cross-sectionally are in line with neurodevelopmental studies highlighting the role of cholesterol during childhood and early adolescence. During that period the development of prefrontal cortex, part of the brain highly involved in the control of impulsivity, takes place (Casey *et al.*, 2008; Steinberg, 2008). During childhood and early adolescence the prefrontal cortex and parietal lobes begin a period of prolonged pruning of neuronal axons resulting in thinning of cortical grey matter. It is hypothesised that pruning in the prefrontal cortex represents the growth of frontal control over impulsive behaviour (Romer, 2012). While most cross-sectional analysis find association between low serum lipid levels and high impulsivity in males, our results indicate that it can be helpful to measure cholesterol levels already during childhood, the time when neurodevelopmental processes pave the road to future impulsivity.

Cholesterol metabolism is much more active in the first two decades of human life (Björkhem *et al.*, 1998) when external stressful events, such as interpersonal violence, are hypothesised to have larger developmental consequences for a young individual. This has been shown in a study of 81 adult suicide attempters with age ranging between 18 and 68 years where only in patients with serum cholesterol below median (median 4.9 mmol/l), the correlation between exposure to violence as a child and used adult violence was significant ($r=0.52$, $p=0.002$), while in patients with serum cholesterol above the median, the correlation between exposure to violence as a child and expressed violent behaviour as an adult was not significant ($r=0.25$, $p=0.2$) (Naiberg *et al.*, 2016).

In conclusion, low total and LDL cholesterol levels predict high impulsivity in adult males already starting from early childhood and do so continuously throughout adolescence. Since cholesterol levels have a great impact on development of impulsivity starting from early age and continuing throughout adolescence they should be monitored also in psychiatry and early on.

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Conflicts of interest. None**.**

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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