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Impulsivity, serum lipids and serotonin-related functional gene variants

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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, further referred to by respective Roman numerals, and some unpublished analyses.

I. Katrin Tomson, Liis Merenäkk, Helle-Mai Loit, Jarek Mäestu, Jaanus Harro. The relationship between serotonin transporter gene promoter polymorphism and serum lipid levels at young age in a longitudinal population-representative study. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2011; 35:1857–1862.

II. Katrin Tomson, Mariliis Vaht, Kariina Laas, Toomas Veidebaum, Jaanus Harro. Effect of a human serotonin 5-HT2A receptor gene polymorphism on impulsivity: Dependence on cholesterol levels. Journal of Affective Disorders 2016; 206:23–30.

III. Katrin Tomson-Johanson, Jaanus Harro. Low cholesterol, impulsivity and violence revisited. Current Opinion in Endocrinology, Diabetes and Obesity 2018; 25:103–107.

IV. Katrin Tomson-Johanson, Tanel Kaart, Raul-Allan Kiivet, Toomas Veidebaum, Jaanus Harro. Low cholesterol levels in children predict impulsivity in young adulthood. Acta Neuropsychiatrica 2020; 32:196–205.

Contribution of the author
For all the papers, the author of the dissertation formulated research hypotheses, conducted the data analysis, wrote the first draft of the manuscript and was responsible for the final form.

ABBREVIATIONS

5-HT	5-hydroxytryptamine; serotonin
5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter gene-linked polymorphic region
AMIS	Adaptive and Maladaptive Impulsivity Scale
BIS-11	Barratt Impulsiveness Scale
BMI	body mass index
CHL	total cholesterol
ECPBHS	Estonian Children Personality, Behaviour, and Health Study
EPSTB	Estonian Psychobiological Study of Traffic Behaviour
HDL	high density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methyl-glutaryl coenzyme A
HTR2A	5-hydroxytryptamine 2A receptor gene
L	long
LDL	low density lipoprotein cholesterol
L/L	long/long
MAO	monoamine oxidase
PCR	polymerase chain reaction
S	short
S/L	short/long
S/S	short/short
SLC6A4	human serotonin transporter gene
SLE	stressful life events
SNP	single nucleotide polymorphism
TRG	triglyceride
TPH	tryptophan hydroxylase

1. INTRODUCTION

Impulsivity is a key feature in several psychological disorders like disruptive behaviour disorders, substance use disorder, personality disorders, bipolar disorder, and pathologically aggressive or suicidal behaviour, and plays a prominent role in the diagnosis of various other forms of psychopathology. Yet, impulsivity also has a functional aspect. Dickman (1990) has differentiated functional and dysfunctional impulsivity, which both lead to fast and error-prone action but are different in essence. Functionally impulsive individuals make quick decisions according to the situation, gaining from rapid action; dysfunctionally impulsive people, on the other hand, act with little forethought in a non-reflective manner, despite negative consequences.

Serum lipid levels are biological factors that scientist have historically associated with impulsive behaviour. Although studies have shown an association of serum cholesterol with impulsivity and violence, it must be remembered that serum cholesterol itself has no direct effect on these behaviours. Mechanisms underlying the association between cholesterol and impulsive behaviour have not yet become clear. However, it has been suggested that both high and low cholesterol levels may lead to behavioural changes through lower serotoninergic activity. Previous studies have highlighted that the correlation of cholesterol levels with impulsivity, aggressiveness, risk behaviour, or suicide is not a linear one, and confounding factors should be considered.

To meet the aim of the current thesis and elucidate the association between impulsivity, genetic markers of the serotonergic system, and serum lipid levels from childhood through young adolescence, we have used the data from the Estonian Children Personality, Behaviour, and Health Study (ECPBHS), a longitudinal, highly representative birth cohort study.

2. REVIEW OF LITERATURE

2.1. Aspects of impulsivity, with focus on dysfunctional vs. functional impulsivity

Impulsivity is an essential feature of disruptive behaviour disorders (Dougherty et al., 1999), substance use disorder (Allen et al., 1998; Brady et al., 1998), personality disorders (Mulder et al., 1999), bipolar disorder (Swann et al., 2001), pathologically aggressive (Barratt et al., 1999) or suicidal behaviour (Corruble et al., 1999), and plays a prominent role in the diagnosis of various other forms of psychopathology. From a behavioural perspective, impulsivity includes a wide variety of actions that are immature, dangerous, inappropriate to the situation and done without consideration, which usually bring about unwanted consequences (Bakhshani, 2014).

Although there are many ways to define impulsivity, it is generally considered as acting without forethought and adequate processing of information (Barratt, 1994). A person that is described as impulsive is someone who thinks little of the consequences his/her actions might bring and thus takes unwarranted risks. According to DSM-5, impulsivity is defined in terms of an aspect of disinhibition and considered as an immediate reaction to stimuli, an unplanned reaction on the spur of the moment or with no regard for its consequences, problem in programming or adhering to programs, sense of urgency and self-harming behaviour in the time of emotional turmoil (American Psychiatric Association, 2022). This clinical conceptualization only includes negative and pathological aspects of impulsivity and does not distinguish between impulsivity and aggression.

Although there is a full variety of classifications of impulsivity facets (e.g., Cognitive vs. Behavioural Impulsivity, Motor vs. Non-Motor Impulsivity, Reward vs. Punishment Sensitivity, Bari & Robbins, 2013; Carver & White, 1994; Logan et al., 1997, respectively), these mostly refer to impulsivity as a maladaptive trait. Yet, impulsivity also has a functional aspect. For example, when the experimental task is very simple, highly impulsive style and rapid style in responding has little cost in errors (Brunas-Wagstaff et al., 1995). When the time available for making a decision is extremely brief, people with high impulsivity are more accurate than people with low impulsivity (Dickman & Meyer, 1988).

Dickman (1990) has proposed two different traits of impulsivity - functional and dysfunctional impulsivity, which both lead to fast and error-prone action but are different in essence. One that results in rapid inaccurate performance in situations where this is optimal and the other that results in rapid, inaccurate performance in situations where this is nonoptimal: “At this point, it would seem that the best way to characterize functional impulsivity is to say that it represents the tendency to engage in rapid, error-prone information processing (i.e., to act with a relatively little forethought) when such a strategy is rendered optimal by the individual’s other personality traits. Dysfunctional impulsivity appears to represent the tendency to engage in rapid, error-prone information processing because

of an inability to use a slower, more methodical approach under certain circumstances. It was suggested earlier that it might be stressful circumstances that interfere with ability of subjects high in dysfunctional impulsivity to engage in slow, accurate information processing; however, this is a possibility that must be confirmed by future research." (Dickman, 1990). Functionally impulsive individuals make quick decisions according to a situation, gaining from rapid action, dysfunctionally impulsive people on the other hand act with a little forethought in a non-reflective manner, despite negative consequences. Dickman (1990) further found that the two types of impulsive personality performed differently on a cognitive figure matching task. Whereas functional impulsivity was related to the speed of information processing, dysfunctionally impulsive people were not distinguished by a rapid information processing style.

When analysing Dickman's conceptualisation of functional and dysfunctional impulsivity as separate impulsive personality dimensions, Brunas-Wagstaff et al. (1997) found, that it is possible to apply this distinction to children as well as to adults. They re-wrote the items of the Dickman impulsivity inventory making it suitable for children. The study sample consisted of children aged 8–16. Regardless of the age of participants, there were no significant correlations between functional and dysfunctional impulsivity. The results were fully in line with Dickman's results in adults showing that the subscales of functional and dysfunctional impulsivity are not in correlation starting from a young age. Based on the results of the study the authors concluded that the findings support Dickman's conceptualisation of functional and dysfunctional impulsivity as separate impulsive personality dimensions and suggest that it is possible to apply this distinction to children as well as to adults.

There are several self-report tests to measure impulsivity, but none of them are flawless; it may not be clear which aspects of impulsivity they are addressing, how these aspects are inter-correlated and which scales measure similar constructs. The Barratt Impulsiveness Scale (BIS-11) is one of the most widely used self-report measures of impulsivity (Patton et al., 1995). BIS-11 questionnaire consists of 30 items measuring aspects of impulsivity like attentional, motor, and non-planning impulsiveness and is used across different age groups and populations. Although Barratt´s scale is frequently used and has been confirmed to be reliable, it primarily focuses on three primary features of impulsivity, and thus possibly does not exhaustively reflect on the whole multidimensional nature of impulsivity, perhaps disregarding specific aspects, especially the positive ones. Moreover, it depends on self-reporting data making it susceptible to biases such as social desirability or faulty self-perception (Kapitány-Fövény et al., 2020; Stanford et al., 2009). The Behavioural Inhibition/Activation Scales (BIS/BAS) are primarily designed to measure sensitivity to punishment (BIS) and reward (BAS), respectively, but the scales also capture aspects of impulsivity, particularly in response to incentives. Similarly to BIS-11, also these scales are applicable across different age groups. The biggest drawback of the BIS/BAS scale is that since they focus on sensitivity towards rewards and punishments, they do not exclusively measure impulsivity. Instead, they are designed to assess larger

dimensions related to behavioural inhibition and activation. Being a self-report test, they rely solely on the reporter and thus can be biased (Carver & White, 1994). The UPPS-P Impulsive Behaviour Scale assesses five specific aspects of impulsivity: urgency, lack of preparation, lack of persistence, sensation seeking, and positive urgency. It is efficient in evaluating impulsivity in adults but not in children. Similarly to the BIS-11, the UPPS-P relies on self-report and is susceptible to the risk of potentially overlooking important aspects of the construct. Although the UPPS-P is popular in research settings, it has not been translated as extensively as the BIS-11 and is less commonly available in clinical settings (Whiteside & Lynam, 2001). The Eysenck Impulsiveness Questionnaire (EIQ), a self-report measure developed by Eysenck and Eysenck (Eysenck & Eysenck, 1977), includes items related to impulsivity, venturesomeness, and empathy. The questionnaire aims to assess impulsivity as a personality trait measuring individual differences in impulsive behaviour and decision-making tendencies.

Examination of various definitions of impulsivity highlights the difficulties faced when attempting to measure the construct. To tackle that problem Miller et al. (2004) examined the component structure of impulsivity by conducting a Principal Components Analysis of 12 subscales from four widely used self-report measures of impulsivity; the Dickman Impulsivity Inventory, the Eysenck Impulsiveness Questionnaire, the Barratt Impulsiveness Scale and Carver and White's BIS/BAS scales. Analysis of the relationship between the subscales revealed that both the Dickman and the Eysenck scales share a similar two-component structure, while Dysfunctional impulsivity correlates with Eysenck's Impulsiveness and Functional impulsivity with Venturesomeness. This provides further evidence that the impulsivity measures of Dickman and Eysenck measure the same components of impulsivity. While the results of the study suggest a third dimension next to the Dickman's and Eysenck's two-dimensional model, the authors highlight that the third dimension, the Reward Responsiveness/Drive subscale, may indeed measure some facet outside the impulsivity construct. This latter argument supports a two-component model of impulsivity (e.g. Buss & Plomin, 1975; Dickman, 1990; Eysenck & Zuckerman, 1978; Hoptman et al., 2002; Parker et al., 1993).

It has been known for many years from animal studies that the prefrontal cortex plays an important role in inhibitory control over behaviour. For example, selective lesions of the rat medial prefrontal cortex impair simple measures of behavioural inhibition, including novelty and stimulant-induced locomotor activity (Dalley, 1999; Jaskiw et al., 1990; Whishaw et al., 1992), as well as responding in extinction (Morgan et al., 1993; Quirk et al., 2006). Also, the striatum, with its high connectivity with the prefrontal cortex, contributes to several forms of impulsive behaviour. The prominent roles of the medial and lateral striatum in the 5-choice serial reaction time task performance have been shown with lesions of the medial striatum resembling those targeting medial cortical structures (Christakou et al., 2001; Dalley et al., 2008).

Previous studies done in human subjects have consistently found the prefrontal cortical deficit associated with impulsive types of violent and criminal

behaviour (Brower & Price, 2001). Within the prefrontal cortex, functional or structural deficits in the orbitofrontal region have been implicated in impulsive aggression and violence in schizophrenia (Joyal et al., 2004; Naudts & Hodgins, 2006). The orbitofrontal cortex, if damaged, is known to result in disinhibition and antisocial behaviour (Bechara et al., 1997; Bechara et al., 2000; Damasio, 1995; Schoenbaum et al., 2006; Wallis, 2007). Kumari et al. (2009) found an association between high dysfunctional impulsivity scores and lower orbitofrontal grey matter volume, suggesting that impulsivity may be an important mediating factor in the commonly found association between prefrontal cortex reductions and violent and antisocial behaviour. From all prefrontal cortex subregions studied, impulsiveness scores correlated significantly negatively only with the orbitofrontal cortex grey matter volumes suggesting regional specificity. In other studies, it has been ventromedial prefrontal cortex that has been recognized as the brain region critically involved in cognitive impulsivity that is characterized by the inability to compare immediate consequences and the future of events with each other, and consequently, the inability to delay satisfaction (Bakhshani, 2014).

2.2. Serum lipids

High levels of cholesterol, and especially low-density lipoprotein cholesterol (LDL), have been shown to raise the risk of heart disease and stroke. The high-density lipoprotein (HDL) cholesterol, sometimes called "good" cholesterol, plays a pivotal role in the prevention of cardiovascular diseases due to its distinct roles within the lipid metabolism pathway (Rader & Hovingh, 2014). The HDL cholesterol has antioxidant and antithrombotic properties, which collectively contribute to its atheroprotective effects, but most importantly presence of HDL cholesterol helps to eliminate excess cholesterol from peripheral tissues and transport it back to the liver for excretion through reverse cholesterol transport. The process involves multiple steps that lead to the overall transfer of cholesterol from peripheral tissues to the liver through the plasma compartment (Bruce et al., 1998). Reverse cholesterol transport plays an important role in alleviating the risk of atherosclerosis and cardiovascular disorders by facilitating the elimination of excess cholesterol from peripheral tissues and promoting its excretion from the body. Whilst the levels of cholesterol should be maintained under a certain limit for the prevention of cardiovascular disease, it is also important to note that a low level of cholesterol is a risk factor for impulsivity and death by suicide (Troisi, 2009).

Cholesterol is an essential structural component for cellular membranes 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 & Vaz, 2005). Both lack and surplus of cholesterol can have negative effects. A connection of serum to central nervous system cholesterol has

not been established, since central nervous system cholesterol is not transported from peripheral sources but synthesized in the brain (Björkhem et al., 2004; Jurevics & Morell, 1995). Neuronal cells regulate their cholesterol content by a feedback mechanism that balances biosynthesis, import, and excretion (J. Zhang & Liu, 2015). While the main sources of cellular cholesterol involve uptake from cholesterol-rich LDL cholesterol or its de novo synthesis from acetyl-CoA, excessive cholesterol can be eliminated in the presence of HDL cholesterol that acts as a lipid acceptor (Matsuda et al., 2013). Cholesterol is also an essential component of neuronal physiology that is needed for synaptic growth and plays a crucial role during developmental stages (Mauch et al., 2001).

2.2.1. Serum lipids and impulsivity

Cholesterol levels have been associated with psychiatric and behavioural disorders while it is generally accepted that people with lower levels of cholesterol are at a higher risk (Jokinen et al., 2010). However, several studies have suggested that the relationship between cholesterol and psychological variables may be non-linear. For example, suicide risk has been found the highest in patients within the lowest cholesterol quartile (Golier et al., 1995; Lindberg, et al., 1992). Using a similar cut-off point, Troisi (2011) found a highly significant difference in attentional impulsivity between participants with total cholesterol levels lower than 4.3 mmol/l and the rest of the sample, with low cholesterol associated with high impulsivity. However, across the entire range of cholesterol (2.8–7.6 mmol/l) only a weak linear correlation was found. In the study of Pozzi et al. (2003), conducted in a sample of 2051 healthy men with a mean age of 23 years, the significant inverse association between total and HDL cholesterol with impulsivity rested completely on subjects in the lowest tenth of total cholesterol (≤3.7 mmol/l).

While most of the studies have found a negative correlation between cholesterol levels and impulsivity, it is not universal. In a study of 30 healthy participants with mean age of 45 years, after adjusting for several relevant covariates including sex, BMI and reported life stress, high levels of total cholesterol were significantly positively associated with a higher behavioural impulsivity (Gendle et al., 2011). A study conducted in the Korean population revealed that not only high but also low total and LDL cholesterol levels predicted an increased incidence of suicidal ideation in the elderly population (Kim et al., 2014). Additionally, a Finnish study of 448 depressed elderly participants found higher total and LDL cholesterol levels in subjects with suicidal behaviour (Koponen et al., 2015). Another earlier Finnish study found that high cholesterol levels are associated with the level of violence in suicidal behaviour (Tanskanen et al., 2000). However, meta-analyses conducted in adults or elderly populations support the link between low levels of serum lipids and suicidality (Arnedo et al., 2015; Hawton et al., 2013). A more recent meta-analysis (Wu et al., 2015) screened 65 studies on suicides and cholesterol fractions. It concluded that it is the low total and LDL cholesterol as well as triglyceride levels that predict suicidality within patient groups. When compared with the healthy controls the suicidal patients had

significantly lower total, HDL and LDL cholesterol levels. While impulsivity and suicidality are not completely overlapping traits, maladaptive impulsivity may occasionally lead to self-destructive behaviour.

The majority of studies done on impulsivity and serum lipid levels have been conducted in clinical samples. 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 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 (New et al., 1999). However, the results of some studies have conflicted 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). For example no association of cholesterol with measures of impulsiveness and aggression was found children hospitalized in psychiatric departments (Rao et al., 1991).

It is conceivable that cholesterol levels play a role in impulsiveness only in specific pathophysiologies. Patients with schizophrenia are four times as likely to be engaged in violent acts (Lewis et al., 2009). Violence toward self and others can be explained through heightened impulsivity levels. Suicide accounts for a substantial proportion of excess mortality in patients with schizophrenia (Anthes, 2014), with increased lethality, violence, intent to die and multiple attempts (Volavka & Citrome, 2008). Total cholesterol is significantly lower in those schizophrenic patients who have made a suicide attempt compared with those without suicide attempts (Mensi et al., 2016). In a study by Kavoor et al. (2017) conducted in a patient group of 60 patients with schizophrenia who were drug-free for at least 4 weeks, total cholesterol, LDL and triglyceride levels had a significant negative correlation with impulsivity, as measured by the Impulsivity Rating Scale. Total cholesterol and LDL levels also showed a significant negative correlation with the Beck Scale for Suicide Ideation. Antipsychotic drugs variously influence lipid levels in schizophrenia (Meyer & Koro, 2004), and therefore, drug status could be an important confounder. Hence, this study strongly supports the notion that lower total cholesterol, HDL and LDL levels may increase the propensity towards acting impulsively and indulging in self-harming/suicidal behaviours in patients with schizophrenia.

Historically, studies have indicated that low plasma cholesterol level was significantly related to depression in elderly men (Morgan et al., 1993) and men with low cholesterol levels had a higher risk of depression (Steegmans et al., 1996) and suicide risk (De Berardis et al., 2012; Engelberg, 1992). In a Finnish study with over 29 000 men, it was shown that low levels of total cholesterol were associated with major depressive disorder and death from suicide (Partonen et al., 1999). However, a recent cross-sectional study using the National Health and Nutrition Examination Survey (NHANES) found no association between low serum lipid levels and increased risk of depression (Zhang et al., 2022). Although

age, body mass index, sex, smoking, alcohol use, health status, and exposure to statins and antipsychotics were considered potential confounders in the NHANES study the sample formation, including ethnicity, dietary preferences and other lifestyle choices may have played a role in mediating the effect of serum lipids and depression. The importance of regional differences has been highlighted also by a large-scale study of 4949 participants conducted in the Korean population where there was a significant association between the high level of HDL cholesterol and depression in adult men, but not in women (Oh & Kim, 2017).

Depression is one of the risk factors for suicide and the most common psychiatric disorder in people who die by suicide (Hawton et al., 2013). Most suicides (about 60%) occur in the context of depressive disorders (Barraclough et al., 1974; Carlson et al., 1991; Hagnell & Rorsman, 1979). Personality traits associated with low cholesterol, like impulsivity and aggression are also associated with vulnerability to suicidal behaviour (Mann, 2003). Thus, patients with depression and low cholesterol levels have a heightened risk for suicide. For example, (Messaoud et al., 2017) carried out a study in 162 patients with major depressive disorder. The mean plasma level of cholesterol was significantly lower among the suicide attempters than in the non-suicidal depressive group (3.47 ± 0.95 vs 4.15 ± 0.75 mmol/l) or the control group (4.27 ± 1.01 mmol/l). In a similar study conducted in 149 major depressive disorder patients admitted to an emergency room following a suicide attempt significant differences in total serum cholesterol levels were observed between the suicide patients and non-suicide depression patients and between violent suicide patients and non-violent suicide patients with total cholesterol level being significantly lower among the suicidal depressive group compared to the depressive or normal control group. The effect persisted when age, sex, BMI and total serum protein levels were controlled (Kim & Myint, 2004).

Another factor that appears to need consideration is the presence of anhedonia: Loas et al. (2016) explored the relationships between anhedonia, alexithymia, impulsivity, suicidal ideation, recent suicide attempt, C-reactive protein and serum lipid profile in 122 patients with depression or anxiety disorders. Consummatory anhedonia was significantly associated with low levels of total and HDL cholesterol whereas anticipatory and state anhedonia were significantly associated with suicidal ideations. Alexithymia was associated with low-serum total cholesterol and low LDL levels. Both low attentional impulsivity and high level of suicidal ideation were independent predictors of low levels of HDL.

However, studies conducted in paediatric and adolescent psychiatric patients remain conflicting. 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 sex (Plana et al., 2010). 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). The age of the study subjects may be of key importance when interpreting the studies. The effects of high or low serum lipid levels can emerge over time and may need a contribution of other factors.

2.2.2. Cholesterol fractions

Studies on impulsivity and cholesterol levels have mainly focused on total cholesterol. From the few studies addressing the cholesterol fractions, it appears that low HDL cholesterol levels can be linked with aggression, impulsivity and also depression and low LDL levels with suicide and self-harm.

For example, the study by Pozzi et al. (2003) assessed separately LDL and HDL cholesterol levels and found that the lipid fractions related to impulse control in healthy subjects were the total and HDL cholesterol. In an Italian community-based sample, impulsivity-related traits measured by the NEO-PI-R were associated with lower HDL cholesterol and higher triglycerides. Also, a study of patients who exhibited aggression and problems in impulse control found only the HDL cholesterol levels to be significantly lower. The total and LDL cholesterol were also lower in these patients, but the differences did not reach the conventional level of significance (Buydens-Branchey et al., 2000).

Studies on the association between cholesterol and depression mostly suggest that a low level of the HDL type of cholesterol is a risk factor (Dimopoulos et al., 2007; Kim et al., 2011; Lehto et al., 2008). Other studies have found total cholesterol and LDL cholesterol levels to be significantly lower in the group of patients who had experienced failed attempts of suicide or exhibited other self-injurious behaviour compared to non-suicidal psychiatric patients and normal controls (Agargun et al., 2004; Garland et al., 2007; Lee & Kim, 2003).

While different cholesterol fractions seem to be related to different aspects of mental health, no study has tried to differentiate between the effect of LDL, HDL or total cholesterol on behavioural aspects and thus the data remains too scarce to make any conclusions.

2.2.3. Biological mechanisms of how low serum lipids influence behaviour through serotonin

Although numerous studies have shown an association of cholesterol with impulsivity and violence, it must be remembered that serum cholesterol cannot directly affect behaviours. Mechanisms underlying the association between cholesterol and impulsive behaviour have not yet become clear; however, it has been suggested that both high and low cholesterol levels may lead to behavioural changes through lower serotoninergic activity.

Based on studies done in macaques on a cholesterol-restricted diet, Kaplan et al. (1997) proposed the cholesterol–serotonin hypothesis of aggression, ac-

cording to which low levels of cholesterol lead to aggression through an altered serotonergic system. A decrease in serum cholesterol may induce a relative increase in brain cell membrane fluidity, which increases presynaptic serotonin reuptake and decreases postsynaptic serotonin function (Diebold et al., 1998).

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 (Hawton et al., 1993). It has been shown that reduced cholesterol levels result in lower cell-membrane fluidity, which leads to lower uptake of serotonin (5-hydroxytryptamine; 5-HT) and a decrease in the number of serotonin receptors (Engelberg, 1992). Low serum lipid levels have been found to influence the conformation and function of membrane-bound proteins and receptors (Ohvo-Rekilä et al., 2002). Amongst others, low serum lipid levels reduce the binding affinity of a serotonin 5-HT1A and 5-HT7 receptor agonists (Pucadyil & Chattopadhyay, 2004; Sjoegren et al., 2006) and modulate serotonin transporter activity (Scanlon et al., 2001).

On the other hand, mechanisms have been proposed to explain how high cholesterol levels could also lead to low serotonergic function. Studies on hypercholesterolemic patients show lower serotonergic action through blunted serotonin-mediated vasodilation in forearm arteries and lower platelet serotonin concentrations than in controls (Smith & Betteridge, 1997; Stroes et al., 1997). Another study by Herrera-Marquez et al. (2011) has shown that adolescents with metabolic syndrome have a lower brain serotonin tone than healthy controls. The serotonergic brain activity was assessed through decrease of free fraction of L-tryptophan in plasma and increase of the response of intensity-dependent auditory-evoked potentials. High densities of cholesterol, in the lipid rafts, are found at the postsynaptic membrane, in the vicinity of various neurotransmitter receptor clusters. Altered membrane properties can affect membrane-bound receptors (Borroni et al., 2016). The lipid rafts are specialised micro-domains within the cellular membrane and contain twice the amount of cholesterol than found in the surrounding bilayer (Björk et al., 2010). They compartmentalise cellular processes and serve as assembly and sorting platforms for signalling complexes (Becher et al., 2001). Cholesterol may influence the conformation and function of membrane-bound proteins and receptors by reducing neuronal membrane fluidity and increasing the mechanical strength of the membranes. The rigidity of cholesterol-enriched membrane may, in turn, alter or disrupt the function of lipid rafts (Ohvo-Rekila et al., 2002) and it is known that a variety of neurotransmitter receptors operate using the lipid rafts (Brusés et al., 2001; Sooksawate & Simmonds, 2001; Suzuki et al., 2001).

Cholesterol can influence serotonergic function also indirectly by binding tightly to transmembrane ion channels, enzymes and receptors (Haines, 2001). Also, experimental and computational evidence supports that view and has pointed to lipids influencing receptor oligomerization not only directly, by physically interacting with the receptor and participating in membrane formation, but also indirectly, by altering the intensive properties of the membrane

(Ramírez-Anguita et al., 2018). Experimentally decreasing the cholesterol content of cell membranes has been shown to reduce the binding affinity of a serotonin 5-HT1A and 5-HT7 receptor agonists as well as to alter the G-protein coupling of the receptor (Pucadyil & Chattopadhyay, 2004; Scanlon et al., 2001; Sjögren et al., 2006).

Statins or 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors are hypocholesterolemic drugs with proven effectiveness in primary and secondary coronary heart disease prevention. If the reduction of cholesterol levels were causally related to destructive behaviour, then statin therapy should be a major psychiatric risk factor. This, however, appears not to be the case: the most recent meta-analysis on statin usage does not suggest any increase in violent death (Tuccori et al., 2014). However, it has been demonstrated in animal experiment (Vevera et al., 2016) that 4 weeks of administration of simvastatin to rats reduced cholesterol levels in the brain as well as membrane microviscosity as measured in erythrocytes. Interestingly, chronic simvastatin treatment also increased the time spent in the open arms of the elevated plus-maze and the number of entrances to the closed arms. Such an atypical profile of behaviour in this prototypic anxiety test is well corresponding to the notion that reduction of serotonergic activity leads to impulsivity-driven behaviour in the plus-maze (Harro, 2018).

2.2.4. Role of cholesterol in neurodevelopment

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 of neuronal physiology that is needed for synaptic growth and plays a crucial role during developmental stages (Mauch et al., 2001).

Neurodevelopmental studies highlight the role of cholesterol during childhood and early adolescence. During that period the development of the 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, 2010).

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 ages 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).

2.3. Serotonergic system

The serotonin system is a complex network based on neurons that produce and use the neurotransmitter serotonin (5-HT). Serotonin is a neurotransmitter that is involved in many physiological processes underlying learning and memory, social behaviour, mood, reproduction, pain perception, circadian rhythm, thermoregulation, food intake and sleep (Lesch, 2007; Olivier et al., 2011).

Serotonin has various effects on different neural circuits in the brain. For example, in the prefrontal cortex, serotonin has been shown to modulate cognitive processes such as attention, decision making, and memory (Iigaya et al., 2018). In the amygdala, a brain region involved in emotional processing, serotonin has been shown to regulate anxiety and fear responses (Yamamoto et al., 2014). In the hypothalamus, serotonin plays a role in appetite regulation and the regulation of body temperature (Haleem & Mahmood, 2021).

The serotonin system originates in the brainstem located at the base of the brain. The brainstem plays an important role in regulating basic life-sustaining functions, such as heart rate, breathing, and digestion (Castle et al., 2005). The raphe nuclei of the brainstem divide into rostral and caudal groupings (Celada et al., 2013).

The rostral group contains the majority of serotonergic neuron bodies of the brain. The rostral raphe nuclei are clusters of neurons that extend from the brainstem to the upper part of the brain and release serotonin with both paracrine and autocrine effects, as well as synaptic connections. While the raphe nuclei are primarily composed of serotonergic neurons, there are also non-serotonergic neurons present within these nuclei. These non-serotonergic neurons release different neurotransmitters, contributing to the overall functionality of the raphe nuclei. The rostral raphe nuclei are in turn divided into two main groups: the dorsal raphe nuclei and the median raphe nuclei. The dorsal raphe nucleus extends from midline to the periaqueductal grey, and it is located between the oculomotor nucleus and the mid-pons. The median raphe is a neural structure that spans from the posterior border of the superior cerebellar peduncles to the motor nucleus of the ventral horn. Afferents for the dorsal raphe and median raphe come from the limbic system. The efferents of the rostral group project via two pathways: the medial forebrain bundle connects the hypothalamus, amygdala, hippocampus, and medial cortex, while the internal capsule links the lateral cortex (Azzalini et al., 2019; Walker & Tadi, 2023).

The raphe magnus, located midway in the pons at the level of the nucleus of VII, is situated within the caudal group of the raphe nuclei. The periaqueductal grey, hypothalamic nuclei, and amygdala provide catecholaminergic innervation to these nuclei. The caudal group of the spinal cord is connected to the dorsal,

intermediate, and ventral horns through two parallel pathways (Walker & Tadi, 2023).

Tryptophan is an amino acid that is essential for the production of serotonin. It is an essential amino acid that cannot be synthesized by the body and must be obtained from the diet. It is found in a variety of foods, including eggs, seafood, turkey, and salami. The conversion of tryptophan to serotonin occurs in two steps. First, tryptophan is converted to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase (TPH). This step is the rate-limiting step in the production of serotonin. Once 5-HTP is formed, it is then converted to serotonin by the enzyme aromatic L-amino acid decarboxylase (Bakshi & Tadi, 2020). Adequate levels of tryptophan are necessary for the proper functioning of the serotonin system. Low levels of tryptophan have been associated with depression and other mood disorders (Davidson et al., 2022). It has been shown that patients with tryptophan hydroxylase 2 gene polymorphism that results in low tryptophan levels have a weaker response to treatment of depression with selective serotonin reuptake inhibitors (SSRI-s) (Kulikov et al., 2018).

Serotonin exerts its effects on post-synaptic cells via neurotransmitter-binding receptors. There are fourteen subtypes of 5-HT receptors and majority of them are G-protein-coupled receptors, the exception being 5-HT3, which is a ligand-gated cation channel and are involved in neurotransmission in the central and peripheral nervous systems (Hoyer & Schoeffter, 1991).

The 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, and 5-HT1F receptors are generally involved in inhibitory neurotransmission and 5-HT4, 5-HT6, and 5-HT7 receptors are linked to excitatory neurotransmission. The 5-HT2A, 5-HT2B, and 5-HT2C receptors are associated with various physiological processes, including mood regulation, appetite control, and vascular function (Chagraoui et al., 2016; Nagatomo et al., 2004; Nebigil et al., 2001).

In the synapse, the action of serotonin is terminated primarily by the membrane-bound serotonin transporter (5-HTT) molecules located on the presynaptic neuron, which regulate the synaptic serotonin levels by re-uptake. Blocking some of the serotonin re-uptake, and hence, increasing the synaptic serotonin levels, is the action mechanism for the most commonly used antidepressants, SSRIs (Hyttel, 1993).

2.3.1. Serotonin and impulsivity

The pivotal role of brain serotonin in impulse control has emerged from many experimental and clinical studies that have demonstrated an association between lower serotonin transmission and high impulsivity (Brown et al., 1979; Carver & Miller, 2006; Harro & Oreland, 2016; Linnoila et al., 1983; Paaver et al., 2007). Experimental data have further supported this concept by altering impulsive performance with serotonergic manipulations (Dalley & Roiser, 2012; Murphy et al., 2003; Nomura et al., 2006; Roy et al., 1988; Walderhaug et al., 2002). More insights have emerged from the effects of selective 5-HT agonists and anta-

gonists, which, respectively, exert inhibitory and excitatory effects on impulsivity in rats (Dalley & Roiser, 2012).

Most studies suggest impulsivity is related to lower serotonergic capacity (Harro & Oreland, 2016). Highly impulsive subjects have diminished cortical metabolic response to pharmacological challenge with the serotonin releasing drug fenfluramine (Siever et al., 1999; Soloff et al., 1999). Diminished serotonergic regulation in prefrontal areas, especially the orbital and medial prefrontal cortex might decrease response inhibition, increase impulsivity and aggression, and increase the risk of suicidal behaviour (Soloff et al., 2007).

2.3.2. Genes encoding the serotonin transporter and receptors

Coding for proteins involved in the synthesis, transport, and degradation of serotonin involves a number of genes. Many studies have implicated genetic variability in these genes in modulating susceptibility to traits and conditions like impulsivity, depression, anxiety, aggression, and dependence (Albert & Benkelfat, 2013). Yet the relation between these traits and the genetic variability has not always been consistent and has displayed interactions with confounding circumstances, e.g. the environmental factors.

One of the most well-known serotonin related genes is the serotonin transporter gene (*SLC6A4*), which encodes for a protein that is responsible for transporting serotonin from the synaptic cleft back into the presynaptic neuron. This gene has been implicated in several psychiatric disorders, including depression, anxiety, and obsessive-compulsive disorder. In particular, a common variation in the *SLC6A4* gene known as the serotonin transporter-linked polymorphic region (5-HTTLPR) has been extensively studied. Individuals with the short allele of this gene are more likely to develop depression or anxiety in response to stress compared to those with the long allele (Caspi et al., 2003).

From the 14 serotonin receptors the most studied serotonin receptor gene is the serotonin receptor gene *HTR1A*. 5-HT1A is the most abundantly expressed 5-HT receptor subtype in the mammalian brain (Guan et al., 2016). Variations in this gene have been linked to several psychiatric disorders, including major depression, bipolar disorder, and schizophrenia (López-Figueroa et al., 2004). A study by Shoval et al. (2014) found that two other serotonin receptors, *HTR1B* and *HTR1E* had expression levels that exhibit a sharp transition in the prefrontal cortex in adolescence, highlighting the genes as major candidate genes involved in pathway maturation processes. A study by Hakulinen et al. (2013) investigated the role of the *HTR1B* rs6296 genotype in the development of aggressive behaviour and hostility over a lifespan, finding that childhood aggressive behaviour predicts adulthood hostility and that the *HTR1B* SNP rs6296 is associated with childhood aggression but not adulthood anger or hostility, suggesting a potential role of the serotonin system in the regulation of hostility, anger, and aggressive behaviour, as well as in the development of these behavioural patterns.

The serotonin receptor gene *HTR2A* also encodes for a receptor that is involved in serotonergic transmission. Variations in this gene have been associated

with various psychiatric disorders, including depression, anxiety, and bipolar disorder (Serretti et al., 2007). The -1438A/G polymorphism of the *HTR2A* gene was associated with susceptibility to schizophrenia (Gu et al., 2013). Other variations in this gene have been linked to an increased risk of bipolar disorder and depression (Tan et al., 2014). Activation of the 5-HT2A receptor is key to how psychedelics exert their actions - both therapeutic and hallucinogenic (Kim et al., 2020). The *HTR2A* rs6313 polymorphism has been shown to moderately alter some effects of 3,4-methylenedioxymethamphetamine (MDMA) in healthy subjects (Vizeli et al., 2019).

An important role for serotonin in regulating energy balance involves its control of gut motility. Through serotonin receptor transduction in enteric neurons, serotonin controls and induces muscular peristaltic action in the digestive tract. Through 5-HTR3 receptor it influences the activation and inhibition of submucosal and myenteric neurons that are involved in intestinal peristalsis, secretion, and sensation (Yabut et al., 2019; Shaijb and Khan, 2015). Variations in this gene have been linked to irritable bowel syndrome (IBS) and other gastrointestinal disorders. Since the *HTR3A* gene is expressed in the central nervous system, particularly in regions associated with mood regulation, anxiety, and cognition its genetic variations do also have an effect on occurrence of psychiatric and behavioural disorders. While all serotonin receptors have an important role in regulation of mood and gastrointestinal function, activation of 5-HT4 receptors has been linked to improvements in cognitive function. These receptors play a role in synaptic plasticity, which is essential for learning and memory processes (Hu et al., 2020). Several studies have implicated *HTR5A* in the control of circadian rhythms, mood and cognitive function and in genetic associations with bipolar disorder and major depression (Guan et al., 2016; Yosifova et al., 2009). The rs1800883 polymorphism in the *HTR5A* gene has been shown to be significantly associated with schizophrenia. Moreover, the SNP significantly interacted with executive function when processing the perseverative error of Wisconsin Card Sorting Test in patients (Guan et al., 2016). The 5-HT6 receptors are specifically targeted for therapeutic purposes by various antidepressants, such as mianserin (Hirst et al., 2000) and second-generation antipsychotics like olanzapine (Bymaster et al., 2002). The 5-HT6 receptors are expressed in the frontal cortex, hippocampus, amygdala, and striatum and are primarily found on gamma-amino butyric acid (GABA)-ergic neurons. The activation of these receptors indirectly modulates several neurotransmitters, including serotonin, acetylcholine, glutamate, and dopamine (Chalmers & Watson, 1991; Fone, 2008; Fukuo et al., 2010; King et al., 2008). Animal and pharmacological research indicates a potential association between the 5-HT6 receptor gene and the etiology of mood disorders (Kulkarni & Dhir, 2009; Wesołowska et al., 2006). However, studies based on Japanese population show that this effect may not be present in specific populations (Fukuo et al., 2010). Earlier research has indicated significance of *HTR7* in shaping behavioural phenotypes. Namely, a study by Roberts et al. (2004) demonstrating that 5-HTR7 knockout mice show impaired contextual fear conditioning, indicating the receptor's function in contextual hippocampal-

dependent learning. In addition, study by Wesołowska et al. (2006) presented that the behaviour of the knockout mice resulted in an antidepressant-like phenotype, suggesting the gene was important to antidepressant action. Genome-wide association studies (GWAS) have suggested a relationship between *HTR7* genetic polymorphisms and schizophrenia (Mowry et al., 2000). The results of a recent study provided novel pharmacogenomic evidence to support the role of *HTR7* in association with antidepressant response (Wei et al., 2020).

Aside from these serotonin receptor genes, several other genes play a role in regulating serotonin signalling. For example, the tryptophan hydroxylase gene (*TPH1*) codes for the enzyme that peripherally converts tryptophan into 5-hydroxytryptophan (5-HTP). Variants in this gene have been linked to psychiatric disorders, such as bipolar disorder and schizophrenia. At the periphery *TPH1* has a modulatory role in physiological processes, such as the cardiovascular function (Côté et al., 2003) and digestive system disorders (Grasberger et al., 2013). The *TPH2* gene codes for an enzyme that is primarily involved in the production of serotonin in the brain. Variations in this gene have been associated with various psychiatric disorders, including depression, anxiety, and bipolar disorder. The *MAOA*, monoamine oxidase A gene codes for an enzyme that breaks down serotonin and other neurotransmitters. Variations in this gene have been associated with aggressive behaviour and impulsive traits (Brunner, 1996; Meyer-Lindenberg et al., 2006).

2.3.2.1. Serotonin transporter gene

5-HTT is the primary target of the SSRIs that are the first line treatment for patients who suffer from depression and most anxiety disorders (Bystritsky et al., 2001). Taking also into consideration the data on in vivo and post-mortem studies of 5-HTT in patients (Gaspar & Lillesaar, 2012), there is strong evidence that serotonin is implicated in the neuropathology underlying depression and anxiety (Ogilvie et al., 1996), both having a strong genetic component. There is a biallelic polymorphism (5-HTTLPR) in the 5′ promoter region of the human serotonin transporter gene (*SLC6A4*) located on chromosome 17q11.1-q12 with short (S) and long (L) alleles. This is a highly common polymorphism consisting of a 44-base pair insertion/deletion of a repetitive sequence (Lesch et al., 1996). Having one or two copies of the S allele of this polymorphism is associated with significantly lower 5-HTT binding in the brain (Little et al., 1997), lower mRNA expression and transcriptional activity (Heils et al., 1996), as well as a 40% decrease in 5-HT re-uptake in blood platelets (Greenberg et al., 1999). The carriers of the S allele tend to have increased anxiety related temperamental traits (Lesch et al., 1996), which are related to an increased risk for depression. Nevertheless, not all studies have detected this association (Fergusson et al., 2011).

Single nucleotide polymorphisms have been detected within the promoter region of the *SLC6A4* gene, including an A→G substitution rs25531 (Nakamura et al., 2000). That polymorphism is located at nucleotide 6 within the first of two extra 22-bp repeats that characterise the L allele. The Lg allele, which is the L

allele with the A→G substitution, creates a binding site for the AP2 transcription factor, suppressing the transcription activity similar to the S allele carriers of the biallelic 5-HTTLPR polymorphism (Hu et al., 2006). A PET study investigating 5-HTT binding potentials as an index of 5-HTT density showed that compared to others, the La/La genotype had the highest 5-HTT binding potential in the putamen (Praschak-Rieder et al., 2007). However, it was shown that both, S/S, Lg/S as well as Lg/Lg genotypes can be associated with childhood aggression (Beitchman et al., 2006).

Carriers of the low-functioning variant of 5HTTLPR are particularly vulnerable to stressful life events (Caspi et al., 2003). This was also found in a study based on the ECPBHS sample: a study by Zareei et al. (2022) found that the impact of family relations on the frequency of drinking alcohol was statistically significant only among the S allele carriers. The participants with the LL-genotype were less malleable by the environment. According to the recent review of 54 articles by López-Echeverri et al. (2023), the short allele of the 5-HTTLPR polymorphism was found to be the most reported risk factor related to the development of depression and its severity. The polymorphism in the *SLC6A4* gene significantly influences the vulnerability of individuals to the depressive effects caused by stressful events. Individuals with the SS homozygous genotype have a higher level of sensitivity to the impact of lived events.

Indeed, a higher prevalence of the S allele of the 5-HTTLPR polymorphism has been reported in impulsive suicide attempters (Baca-García et al., 2005; Gonda et al., 2011). Although multiple meta-analyses provide significant evidence for the involvement of the S allele in suicidality (Anguelova et al., 2003; Li & He, 2007), there are additional studies that have reported contradictory findings (Lin & Tsai, 2004). A study by Gonda et al. (2011) highlighted that when distinguishing between various forms of suicidality among the samples, the clarity and specificity of suicidality becomes more distinct. When examining different types of suicidal behaviour separately, the meta-analyses indicate that the S allele of the serotonin transporter gene is strongly linked to violent completed suicide (Bondy et al., 2000), violent suicide attempts (Bayle et al., 2003; Bellivier et al., 2000; Courtet et al., 2001), and repeated suicide attempts (Courtet et al., 2004). The presence of the S allele is associated with an increased likelihood of violent aggressiveness or an intense drive towards committing suicide. This is also seen in individuals with the S allele who demonstrate a propensity toward employing more injurious and potentially fatal methodologies in their suicide attempts (Wasserman et al., 2007). In live with these results it has been shown that the occurrence of the S allele is not higher in a group of non-violent individuals who had attempted suicide (Courtet et al., 2003). Additionally, the S allele is not linked to suicidal ideation (Wang et al., 2009).

A study by Akkermann et al. (2010) investigated the impact of the 5-HTTLPR genotype on binge eating behaviour. Although the 5-HTTLPR genotype alone did not predict eating disorder symptoms in the general population after being controlled for impulsivity and anxiety, women prone to binge eating with the S/S genotype exhibited heightened state anxiety and impulsivity. The 5-HTTLPR

genotype may have moderated the course of binge eating in the way that S/S genotype increased the risk for symptom severity and affective instability (Akkermann et al., 2010). Moreover, in a review of seven different studies on eating disorders, adverse life events were found to moderate the association between 5-HTTLPR and binge eating, particularly among S allele carrying adolescent girls. A stronger effect was observed when in addition to traumatic life events both sexual and physical abuse was considered. This interaction highlights the potential role of childhood stressors in heightening vulnerability to serotonergic dysregulation, ultimately leading to disturbed eating behaviours in individuals predisposed to eating disorders (Rozenblat et al., 2017).

Similar results were observed in risk taking traffic behaviour studied in the Estonian Children Personality, Behaviour, and Health Study at the ages of 15 and 18 years, where male carriers of the 5-HTTLPR S allele were more likely to exhibit high-risk traffic behaviour at ages 15 and 18. Notably, Maladaptive Impulsivity and risky behaviours, such as smoking and alcohol use, were also predictors of belonging to the high-risk group (Luht et al., 2018). Contrastingly, in another traffic behaviour study conducted in Estonia on a sample recruited at traffic schools with a mean age of 23 years, the Estonian Psychobiological Study of Traffic Behaviour (EPSTB), Eensoo et al. (2018) found that L allele carriers of the 5-HTTLPR polymorphism had significantly higher odds of speeding offences and traffic accidents. Interestingly, statistically significant intervention effects were observed in L/L homozygotes following brief intervention in traffic schools, emphasizing the potential for targeted interventions to improve traffic safety. Moreover, Tokko et al. (2022) conducted a subsequent study in the EPSTB sub-sample looking into mediating and moderating factors. While 5-HTTLPR polymorphism was not directly associated with speeding or driving while impaired by alcohol, the S allele carriers had lower alcohol use disorder scores if they were not junk food eaters, and vice versa, L/L homozygosity was associated with driving while impaired by alcohol via higher alcohol use disorder scores. These findings highlight the complex interplay between genetic variation, lifestyle factors, and risky traffic behaviour and clarify why studies that fail to include these variables also fail to show an effect of the 5-HTTLPR polymorphism.

The linkage between serotonin transport and cholesterol became evident in a study showing that depletion of cholesterol in human embryonic cell culture results in a 5-HTT activity decrease (Scanlon et al., 2001). Previously it has been found in the large Vienna Trans-Danube Aging study, with 566 participants aged 75.7 ± 0.45 years, that the L allele of the 5-HTTLPR polymorphism is an independent risk factor for higher mean fasting LDL cholesterol levels (Fischer et al., 2006). Yet, a study by Sookoian et al. (2007) found that it was the anxiety related S allele that was a risk factor for overweight independently of sex, age, and hypertension.

2.3.2.2. Serotonin 5-HT2A receptor gene

In humans, several polymorphic variants have been described in the gene of *HTR2A*, among them the -1438A/G polymorphism in the promoter region, rs6311 (Chen et al., 1992). The individuals carrying the A allele of the -1438A/G polymorphism have a higher promoter activity and expression of the receptor gene than the G/G homozygotes, and may yield a larger number of 5-HT2A receptors (Myers et al., 2007; Parsons et al., 2004). The A allele of the 5-HT2A receptor gene has been shown to correspond to higher transcriptional activity in the reporter gene assay in cell cultures and to be associated with increased 5-HT2A receptor binding (Parsons et al., 2004; Turecki et al., 1999). It is conceivable that higher levels of 5-HT2A receptors are associated with lower presynaptic serotonergic output, and, in turn, impulsivity. Indeed, post-mortem studies in suicide victims have demonstrated an increase in the number of post-synaptic 5-HT2A binding sites in the prefrontal cortex (Pandey et al., 2002).

Several studies have demonstrated associations between the *HTR2A* -1438A/G polymorphism and mental disorders that are characterized by impulsive behaviour (Nishiguchi et al., 2001; Nomura & Nomura, 2006a; Ricca et al., 2004). For example, the A allele was reported to be associated with impulsive traits in alcohol-dependent patients (Preuss et al., 2001) and with susceptibility to anorexia nervosa (Collier et al., 1997). It was also found that patients carrying the A allele who suffered either from anorexia nervosa or bulimia nervosa exhibited greater overall severity of the corresponding eating disorder (Nomura & Nomura, 2006; Ricca et al., 2004). In a meta-analysis, obsessive compulsive disorder (OCD) was significantly associated with the A allele of rs6311 (Taylor, 2016). In a more recent meta-analysis, *HTR2A* gene variants G-1438 A were associated with obsessive-compulsive disorder but after stratification for sex age of onset the association only remained significant for females and those with early-onset OCD (Mattina et al., 2020).

2.4. Moderating the association of cholesterol with impulsivity

Several factors play a role in moderating the association of cholesterol with impulsivity. Recent literature has shown that a number of factors like demographics and comorbid disorders need to be taken into account and that discrepancies between studies may be explained by various factors that have not been considered (Apter et al., 1999; Eriksen et al., 2017). Sex is of a special importance since males seems to be of greater risk of low cholesterol levels leading to impulsivity, violence and possibly suicide, and the nature of the association between cholesterol, neurotransmission and impulsivity may be in part different in males and females. Factors like age of the study population is of importance and warrant further investigation. Among other things, ethnic disparities in the

sample, which mix genetic variants, cultural traditions, and environmental factors, may be the cause of discrepancies between study results.

2.4.1. Age

Maturation of neurobiological systems involved in impulse control and reward sensitivity occurs throughout adolescence, and parallel increases in risky behaviour across this period (e.g., (Blakemore & Robbins, 2012; Romer, 2017; Steinberg, 2008).

Due to the role cholesterol plays in neurodevelopment, children should be especially susceptible to low serum lipids' negative effects. Yet while the association of serum lipid levels with various forms of aggression and impulsivity has been studied in adults in cross-sectional studies (Pozzi et al., 2003; Repo-Tiihonen et al., 2002; Vevera et al., 2003), general population cohort samples (Svensson et al., 2017), psychiatric patients (Bartoli et al., 2017) and criminals (Hillbrand et al., 2000), in children such studies remain scarce.

There are no studies that have focused on the interaction of the serotoninergic system and lipid metabolism in children, and only a few have examined adolescents (Herrera-Marquez et al., 2011; Sookoian et al., 2007). The study of Sookoian et al. (2007) was conducted in two young groups: a cross-sectional, high school student population of an Argentinian rural town and a group of outpatients from a Children's County Hospital. The first sample consisted of 172 adolescents with self-reported European ancestry aged 16 ± 2 years. No significant difference between the S allele carriers and non-carriers of the 5-HTTLPR polymorphism was found in cholesterol levels, but the S allele was associated with overweight. The S allele carriers were almost twice as likely to be overweight than subjects homozygous for the L allele. In the sample of outpatients, no association between 5-HTTLPR polymorphism and overweight was found. Though the samples were of Caucasian descent, social differences in lifestyle and diet may account for the discrepant findings of Sookoian et al. (2007) study.

Even if the qualities of impulsivity and suicidality do not entirely coincide, maladaptive impulsivity can result in self-destructive behaviour. It has long been suggested that younger and older suicides may represent different populations (Conwell et al., 1998; Heikkinen et al., 1995; McGirr, 2011; Robins et al., 1991) and it remains to be better understood whether suicide is the same phenomenon across the life cycle, or whether it is characterized by a different meaning and set of risk factors when it occurs in youth or older age (McGirr et al., 2008). A previous study by Rich et al. (1986) which compared a sample of suicides dichotomized as a function of age, revealed that the importance of impulsive aggression was greater among younger suicides. Even among adolescent suicides, younger suicides appear to have lower levels of intent (Brent et al., 1999), and such successful suicides are believed to be accompanied by higher levels of impulsivity. Analyses done by McGirr et al. (2008) indicate an inverse relationship between impulsive aggression and the age at which individuals die by suicide. Impulsive aggression may, as has been previously suggested, predispose indivi-

duals to the development of psychopathology strongly associated with suicide, yet in addition, their results suggest that impulsive aggression is itself associated with suicide earlier in life.

2.4.2. Sex

While serum lipid levels association with impulsivity is generally acknowledged, several authors have drawn attention to the heterogeneity between sexes in that matter (Derefinko et al., 2014).

Several studies on cholesterol and impulsivity or aggression levels have included only men (Buydens-Branchey et al., 2000; Conklin & Stanford, 2008; Pozzi et al., 2003; Roy et al., 2001; Troisi & D'Argenio, 2006) and a considerable number of studies with both sexes represented have found the association between cholesterol and impulsivity only in men (Eriksen et al., 2017; Golier et al., 1995; Lindberg, et al., 1992). The studies where the 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.

Sex was addressed as an important factor in cholesterol and impulsivity association in patients arriving at the psychiatric emergency unit was explicitly (Eriksen et al., 2017). In univariate analysis, low HDL was associated with violence during the hospital stay for the whole sample, but this association was dependent on the male sex, involuntary admission and presence of psychosis. In men but not in women, levels of HDL were significantly inversely associated with violence within the first 3 months after discharge from the hospital.

The sex difference in depression rates is significant, with women having a prevalence of depressive disorders than men (Kuehner, 2017). This difference is evident in different income countries but sex differences do not exist across all race-ethnic groups (Kessler, 2003; Yancu, 2011). The disparity in depression rates across sexes becomes apparent throughout adolescence and persists until old age (Angold & Worthman, 1993), although the sex gap in adulthood is less pronounced compared to earlier age groups (Kiely et al., 2019; Patten et al., 2016). However, there was no sex difference in recurrence, remission, or chronicity of depression. Also, women were more likely to exhibit symptoms like increased appetite, hypersomnia, and somatic symptoms, and may have comorbidities with anxiety disorders and post-traumatic stress disorder (Zhao et al., 2020).

The sex differences may relate to the central serotonergic function, one of the possible mediators of serum lipid levels and impulsivity (Luht et al., 2019; Steegmans et al., 1996; Terao et al., 2000; Vevera et al., 2003). Serotonin pathways

function as a behavioural restraint system that inhibits impulsive behaviour (Miyazaki et al., 2012). The mean rate of serotonin synthesis in the brain measured by PET scan was found to be 52% higher in males than in females (Nishizawa et al., 1997). Compared to men, women had significantly higher 5-HT1A receptors and lower serotonin transporter binding potential in a wide array of cortical and subcortical brain regions (Jovanovic et al., 2008). In patients with borderline personality disorder, the 5-HT2A receptor binding was greater in females than in males, and only in female patients predicted impulsivity and aggression (Soloff et al., 2014). Acute tryptophan depletion has led to increased aggressive response in young boys (age 9–15 years) with attention deficit hyperactivity disorder, but not in girls (Kötting et al., 2013). Similarly, a study of healthy males and females aged 20–33 has shown that acute tryptophan depletion that was achieved by administering a tryptophan-deficient amino acid mixture increased impulsivity in males, and decreased impulsivity in females (Walderhaug et al., 2010). A study by the same group has specified, that during acute tryptophan depletion, women reported mood reduction and showed a cautious response style, which is commonly associated with depression while men showed an impulsive response style and did not report mood reduction (Walderhaug et al., 2007). Similarly, studies on gene-environment interactions with genes with a major impact on serotonin function and on platelet MAO that reflects the capacity of the central serotonergic system (Harro & Oreland, 2016) consistently support the notion that the role of the serotonin system in behavioural regulation is not identical in males and females. The sex-specific properties of the serotonergic system are also expected to affect the interaction of serum lipid levels and behavioural measures.

Further, it is known that sex differences exist in lipid levels as well as in depression prevalence, and thus sex stratification may have an impact on results (LaRosa, 1992). A study has found a significant interaction effect of 5-HTTLPR and LDL cholesterol in elderly men on the risk of depression, with low LDL and the S allele together increasing the risk, but no significant association between this polymorphism and lipid levels (Ancelin et al., 2010).

Evolutionary history has significantly influenced human physiology, with adaptations influenced by gender roles. These adaptations, while possibly not directly relevant to current environmental conditions, can influence behaviour and psychiatric vulnerability. The sex specific association of low cholesterol and low central nervous system serotonergic activity has been given an evolutionary perspective by (Erickson, 1997) who proposed that lowered serum cholesterol may function as an internal signal of threatened starvation, adaptively increasing aggressive behaviour through effects on serotonergic activity. The results of a much later study highlight, that the link between low cholesterol and low serotonergic activity is present only in males, predisposing them for violent and risky behaviours. Investigating serum total cholesterol and central nervous system levels of the main serotonin metabolite 5-HIAA in medication free male and female subjects for whom diagnostic lumbar puncture was performed (Markianos

et al., 2010) found, that the association of low cholesterol with low serotonergic activity is present only in males, and not in females.

Conclusively, while many differences between males and females can be explained by sex hormones, it is also possible that sex-specific differences in serotonergic agonism may play a role (Moses et al., 2000).

2.5. Rationale of the current studies

Despite the abundance of studies on the association between impulsivity, serum lipid levels, and the serotonergic system in specific populations, some aspects remain unclear. These associations are known to be modulated by factors like age, sex, and environment. Previous studies have shown that the associations found in the general population may not always hold true for older individuals. Similarly, straight application of findings from the general population to children is not feasible, yet there are very few studies conducted on either children or adolescents. The longitudinal approach could clarify how the association between impulsivity, serotonergic system, and serum lipid levels changes across different stages of an individual's lifespan. Most studies on impulsivity, violence, aggression, and suicide either exclusively involve male participants or show a significant bias towards them. Sex hormones play a significant role in psychological disorders; therefore, examining the associations between impulsivity and serum lipid levels separately in males and females provides a valuable overview of sex differences. Accounting for environmental factors is challenging, but it is not possible to overlook the fact that children raised in high-stress environments face a higher risk of experiencing various physical and mental health issues during their adult years than their peers raised in low-stress environments.

A possible biological mechanism for how low serum lipids influences behaviour is the decrease in brain serotonergic neurotransmission. The polymorphisms of the serotonin transporter gene and the serotonin receptors can significantly influence an individual's susceptibility to mood and anxiety disorders, emotional regulation, and general reaction to stress. Low serotonergic turnover, similar to low cholesterol, could also lead to higher impulsivity. However, the data on the possible role of serotonin transporter and receptor polymorphisms in the association of impulsivity and serum lipid levels, especially in a longitudinal sample starting from childhood to adulthood, is scarce, if not non-existent.

3. AIMS OF THE STUDY

This thesis aimed to elucidate the association of impulsivity with genetic markers of the serotonin system and serum lipid levels during childhood and young adolescence in highly representative birth cohort samples.

The specific aims were formulated as follows:

1. To critically analyse the available evidence on the association of serum lipid levels and impulsivity (Paper III);
2. To study whether serum lipid levels are correlated with impulsivity or risk behaviour cross-sectionally starting from childhood and continuing to adolescence (Paper IV, unpublished data);
3. To study whether impulsivity is correlated with risk behaviour or suicide tendency cross-sectionally starting from childhood and continuing to adolescence (unpublished data);
4. To study whether serum lipid levels measured during childhood or adolescence are predicting impulsivity in later life (Paper IV);
5. To study whether serum lipid levels correlate with impulsivity cross-sectionally or predict impulsivity differently in low of high stress environments (unpublished data);
6. To characterize the association of the 5-HTTLPR and *HTR2A* -1438A/G polymorphisms, and serum lipid levels in children and adolescents in a longitudinal, population-representative sample (Paper I, unpublished data);
7. To determine a possible role of 5-HTTLPR and *HTR2A* -1438A/G polymorphisms in the association of impulsivity and serum lipid levels (Paper II, unpublished data).

4. MATERIALS AND METHODS

4.1. Subjects

The sample on which the analyses in this thesis are based is the Estonian sample of the population representative European Youth Heart Study, that was conducted in Estonia in 1998/1999 with extended socioeconomic and an additional psychobiological module, and subsequently incorporated into the longitudinal Estonian Children Personality, Behaviour, and Health Study (ECPBHS). All schools of Tartu County, Estonia, which 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. In 1998/99, all children from grades 3 (younger cohort) and 9 (older cohort) were invited to participate and written informed consent was received from 79% of the invited subjects and their parents. The total number of subjects in this sampling was 1176, including 593 in the younger cohort and 583 in the older cohort. All participants were of European descent. Adolescents and their parents gave their informed consent in all study waves. Permission for the studies was obtained from the Committee of Ethics of the University of Tartu, Estonia.

In the follow-ups of the younger cohort 83% (n= 483; 222 males and 261 females; mean age 15.3 ± 0.3 years), 78% (n= 453; 201 males and 252 females; mean age 18.0 ± 0.3 years) and 76% (n=441 195 males and 246 females; mean age 25.0 ± 0.3 years) of the original cohort were recruited. Of the older cohort 81% (n=479; 206 males and 273 females; mean age 18.0 ± 0.3 years) and 91% (n=541; 230 males and 311 females; mean age 25.0 ± 0.3 years) of the original cohort were recruited. In 2001, 62 additional subjects (mean age 18.4 ± 0.9) were recruited and pooled to the older cohort. A schematic overview of the follow-ups of the two cohorts is given in Figure 1.

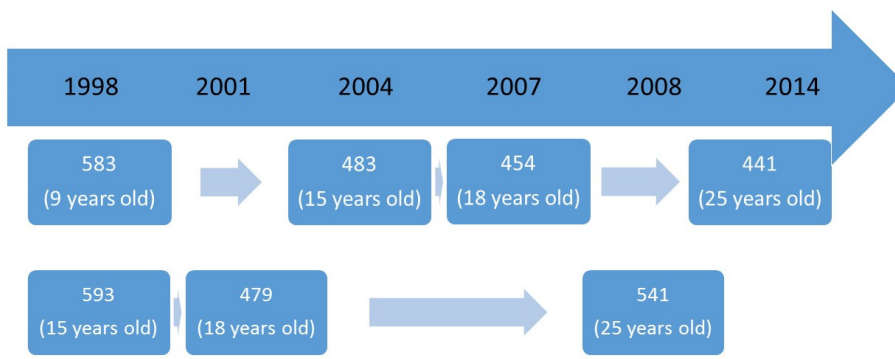

Figure 1. Schematic overview of the study waves of the two cohorts.

4.2. Questionnaires

4.2.1. Adaptive and Maladaptive Impulsivity Scale (AMIS)

Different facets of impulsivity were self-reported using the Adaptive and Maladaptive Impulsivity Scale (AMIS) (Laas et al., 2010). AMIS is an impulsivity questionnaire developed on the basis of the concept of functional and dysfunctional impulsivity proposed and elaborated by Dickman (1990), drawing on both Dickman impulsivity inventory (Dickman, 1990) and the five-factor personality model (Costa & McCrae, 2010). Two of the four subscales are based on the Dickman Impulsivity Inventory measuring functional ("Fast Decision Making" in AMIS) and dysfunctional impulsivity ("Thoughtlessness" in AMIS). Two other subscales are based on impulsivity related subscales of NEO-PI, Impulse Control ("Disinhibition" in AMIS) subscale under the domain of Neuroticism and Excitement Seeking ("Excitement Seeking" in AMIS) subscale under the domain of Extraversion. Fast decision making and Excitement seeking were summed up to obtain a measure termed Adaptive Impulsivity, while Disinhibition and Thoughtlessness formed Maladaptive Impulsivity.

4.2.2. Risk behaviour

A variety of risk behaviours was assessed with questionnaires that are described in sections below. Overview of different risky behaviours and number of subjects in risk behaviour analysis is in the Table 1. All risk behaviour data is present at the age of 15 years only for the younger cohort. Data of traffic behaviour was not collected for the older cohort at the age of 18 years and therefore, only data from one cohort is available for analysis. Data of sexual behaviour was not collected for the younger cohort at the age of 25 years and thus analysis can only be conducted using data from a single cohort. If one or more items were reported missing in the questionnaire, the subject was excluded from data analysis.

Table 1. Number of subjects in risk behaviour analysis for whom all data were available.

		Traffic behaviour	Alcohol	Tobacco	Drugs	Sexual behaviour
MALES	15 years	222	191	214	219	211
	18 years	201	382	385	382	368
	25 years	386	414	357	417	225
FEMALES	15 years	261	240	256	252	257
	18 years	252	499	499	508	497
	25 years	521	545	434	550	306

4.2.2.1. Traffic behaviour

Subjects reported their traffic behaviour during the past year in a self-administered questionnaire. The items were selected to enable a comparison with previous epidemiological health studies in Estonia and neighbouring countries. To the following four items: (1) "Frequency of using a seat belt in the front seat," (2) "Frequency of using a seat belt in the back seat," (3) "Frequency of using a reflector while moving on streets and roads in darkness," and (4) "Frequency of bicycle racing or motorbike racing with cars in traffic," participants responded on a five-point scale ranging from "1" – "Always" to "5" – "Never." To reduce skewness, the five-point scale was dichotomized. Answer "Always" was given a value of "0", all other answers were given a value of "1". Responses to the question on racing were scored with "Never" resulting in value "0", all other answers a value of "1".

In addition, a question about "Riding with a drunk driver" was included. Subjects responded with "1" – "No," "2" – "Do not know for sure whether they had" or "3" – "Yes." Answer "Yes" was given a value of "1", all other answers were given value of "0". To reduce the number of comparisons, all five items were included in a traffic risk score. To ensure normal distribution of the traffic risk score, subjects were divided into low, medium and high traffic risk groups (scores 0–1; 2–3; 4–5, respectively).

4.2.2.2. Alcohol use

Alcohol use was self-reported during the visit to the laboratory. The subjects reported at the age of 15, 18 and 25 in all waves whether they had consumed a certain type of alcohol at least once a month. The list of alcoholic beverages included beer, other alcoholic beverages with low alcohol content, wine or champagne, strong alcohol, and other unspecified alcoholic drinks. Participants responded with "1" - "Yes" or "0" - "No". Responses for all alcoholic beverages were summed as a total score of alcohol consumption. To ensure normal distribution of the alcohol use scores, subjects were divided into low, medium and high alcohol use groups (scores 0–1; 2–3; 4–5, respectively).

4.2.2.3. Tobacco use

Tobacco use was self-reported at the age of 15, 18 and 25 in all waves. Smoking habits were assessed with the question of whether participants had smoked in the last month resulting in a two-point scale.

4.2.2.4. Narcotic and psychoactive drug use

Illicit narcotic and psychoactive drug use was self-reported at the age of 15, 18 and 25 in all waves. The drug use was assessed with the question whether participants had ever tried a narcotic or psychoactive substance resulting in a two-point scale.

4.2.2.5. Sexual behaviour

Subjects reported their sexual behaviour in a self-administered questionnaire containing three items. To two items: “Have you ever had sexual intercourse with a stranger” and “Did you use birth control during your first intercourse” were given “Yes” – “1” or “No” – “0” answers. The third item “How many sexual partners have you had during lifetime” was given a value of 0 if the number of sexual partners was below median or median and 1 if the number of sexual partners was above median of the measured study wave. To ensure normal distribution of the sexual behaviour score, subjects were divided into low and high sexual behaviour groups (scores 0 and 1–3, respectively).

4.2.3. Suicide ideation and risk

Both younger and older cohort were asked at 18 years a dichotomous question about suicide ideation and having attempted suicide. Recent and lifetime suicide risk were assessed at 25 years as part of the psychiatric assessment based on DSM-IV that was carried out by experienced clinical psychologists using the Mini-International Neuropsychiatric Interview (M.I.N.I.5.0.0) (Sheehan et al., 1998; Estonian version: Shlik et al., 1999; Laas et al., 2014).

4.2.4. Stressful life events

History of stressful life events were recorded at 15 years of age in both cohorts. The list of adverse life events varied between the cohorts consisting of 29 stressful experiences in the younger cohort and of 21 stressful experiences in the older cohort. The events recorded included parental health and socioeconomic status, living conditions, heath of the subject, physical or emotional abuse and severe concerns. History of stressful life events was self-reported. The events were recorded as dichotomous variables (present or not present) and were then counted to form the number of experienced stressful life events. Subjects were divided into low and high stressful life events exposure groups by median split (Reif et al., 2011) in the two cohorts separately, data was then merged.

4.3. Physical measurements

4.3.1. Lipid levels

Fasting basal cholesterol (total, LDL and HDL) and triglyceride levels were measured by conventional techniques. In the 1998 year sample LDL levels were calculated based on the Friedewald formula (Winocour et al., 1989). In follow-up studies all serum lipid levels, including LDL cholesterol were measured directly from the serum. Original values were transformed into z-scores ($ZX = (X - MX) / SDX$) expressing deviance from the mean (M) of each cohort ex-

pressed in standard deviation (SD) of the whole sample. We also used the Friedewald formula for the follow-up samples to yield LDL data, but this did not change the reported results.

4.3.2. BMI

Height and weight were measured in light clothing by standardized procedures. Body mass index (BMI) was calculated using the formula BMI = kg/m2.

4.3.3. Pubertal status

Pubertal status of children was assessed by trained observers of the same sex visually in a private room using Tanner's stages (Tanner, 1953) of breast development for girls, testicle development for boys and pubic hair development for both sexes.

4.3.4. Genotyping

4.3.4.1. 5-HTTLPR

Genotyping was done in two stages. First all subjects were genotyped for the 5-HTTLPR polymorphism, then SNP rs25531 (A→G). The alleles at the 5-HTTLPR locus were amplified from genomic DNA using PCR as in previous studies (Anchordoquy et al., 2003). The polymorphic region was amplified using the primers 5-HTTLPR-F: 5′-6FAM-ATG CCA GCA CCT AAC CCC TAA TGT-3′ and 5-HTTLPR-R: 5′-GGA CCG CAA GGT GGG CGG GA-3′. PCR reaction components and final concentration were as follows: 1 x of 5x HotFirepol BLEND with BSA 2.5 mM MgCl2 (Solis Biodyne); 5% of DMSO; 1 x of 10x Solution S (Solis Biodyne); 380 µM each of the forward and reverse primers; 10–50 ng of template DNA. The amplification was conducted in a total volume of 20 µl. The touchdown PCR cycles were used as by Anchordoquy et al. (2003). The electrophoresis was made on ABI PRISM 3130XL genetic analyser and the components used were: 1 µl PCR product, 10 µl Hi-Di formamide, 0.25 µl Liz 500 size standard. Genotypes were generated using ABI Gene-Mapper V 4.0 software. Genotype frequencies were in Hardy–Weinberg equilibrium. The distribution of genotype was as follows: 43.9% L/L, 42.8% S/L and 13.3 % S/S.

For genotyping of SNP rs25531 (La/Lg) the MspI restriction analysis was conducted in a total volume of 10 µl (2 µl of PCR product and 8 µl of restriction master mix). The reaction components and final concentrations of the restriction master mix were as follows: 1 x Buffer Tango; 4 units of MspI restriction enzyme (Fermentas). Samples were then incubated on 37 °C for 3 h and on 65 °C for 20 min. MspI digest electrophoresis was conducted using ABI PRISM 3130XL genetic analyser and the components used were: 1 µl digest product; 10 µl Hi-Di formamide; 0.25 µl LIZ 500 size standard. The distribution of genotypes was as follows: 38.2% S/La, 13.3% S/S, 5.7% S/Lg, 32.8% La/La, 9,6% La/Lg, 0.3% Lg/Lg. When genotype was analysed as triallelic following sets of contrast were

used: one contrasting L/L genotype with other groups (the effect of being S allele carrier), second contrasting the L/L and S/L genotype with S/S genotype (the effect of being L allele carrier) and third contrasting S/S, Lg/S and Lg/Lg genotype to La/La, La/Lg and La/S genotypes (the effect of being La allele carrier).

3.3.4.2. *HTR2A*

DNA was extracted from whole blood samples using Qiagen QIAamp Mini kit. Genotyping of the -1438A/G (rs6311) polymorphism was performed as previously described (Maksimov et al., 2015) using the TaqMan® Pre-Designed SNP Genotyping Assay on the Applied Biosystems ViiA™ 7 Real-Time PCR. The distribution of genotype was as follows: 42.4 % G/G, 45,4 G/A, 12,2 A/A.

4.4. Statistical analysis

Missing values were taken into account by assuming that they are missing at random ("direct likelihood" approach). All data were tested for assumptions of normality and independence. Outlier analysis was conducted to meet the assumption of normal distribution. Serum lipid levels in males and females are innately different. To omit any sex effect males and females were analysed separately. Data from the two cohorts were transformed into z-scores and combined according to age groups. Genotypes (*HTR2A,* biallelic and triallelic 5-HTTLPR) were grouped based on their allelic variances. All genotype frequencies were found to be consistent with the Hardy-Weinberg equilibrium. Cohort, sex, calorie intake, physical activity, BMI, pubertal stage, psychiatric disorders, medications, alcohol and illicit substance use, smoking and maltreatment were all investigated for possible interaction effects.

Differences between groups regarding continuous variables were analysed with analysis of variance (ANOVA) with Tukey's post hoc multiple comparison procedures where necessary (Paper I, II and IV, unpublished data). Linear mixed effects models were used for testing interactions between serum lipid levels and serotonin transporter gene linked promoter region (5-HTTLPR) polymorphism in our sample using three time points (Paper I). General liner models (GLM) were performed (Paper II) to determine the interaction effects of genotype, sex, and cholesterol levels on impulsivity traits. The associations between continuous variables were tested by regression analysis (Paper II, unpublished data). To determine the predictive effects of stressful life events at 15 and 18 years on predicting impulsivity measures at 25 years one-way analysis of covariance (ANCOVA) was performed (unpublished data). Similarly, ANCOVA was used to determine the predictive effects of serum lipid levels at three different ages (9, 15 and 18) on impulsivity traits at 25 years of age (Paper IV, unpublished data for separate analysis in subjects with high or low stressful life events). Pearson correlation analysis was used to illustrate the strength of association of serum lipids with impulsivity measures and to investigate the interactions of impulsivity and serum

lipid levels cross-sectionally at specific age (Paper IV). Binary logistic regression analyses were used for predicting suicide ideation by serum lipid levels or BMI in 18 and 25 year old subjects (unpublished data). Multinomial and binary logistic regression were utilized to study the effects of serum lipid levels and BMI on different facets of risk behaviour (unpublished data). The level of significance was set at $p < 0.05$, and where appropriate, Bonferroni correction was used. Data were analysed using SPSS (version 23.0 SPSS, Chicago, IL), Statistica (version 7.0 StatSoft, Tulsa OK, USA), and R freeware version 2.10.1.

5. RESULTS AND DISCUSSION

5.1. The ECPBHS sample

5.1.1. Serum lipid levels

Data of both birth cohorts were available at the ages of 15, 18 and 25 years. An overview of the serum lipid levels at ages from 9 to 25 years, separately in males and females, is presented in Table 2. The CHL values of our sample at 9 years of age are in the same range as other studies. For example, in a large scale Norwegian study where blood samples of 1340 children were available at the age of 9 years, girls had the median CHL 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 girls was 4.2 mmol/l and for boys of the same age it was 4.1 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, the mean reference values of CHL in girls were 4.4 mmol/l and in boys 4.3 mmol/l (Stavnsbo et al., 2018). The values for serum lipid levels in our sample are in the same range with other large studies and thus the results based on the serum lipid values are extrapolatable.

Serum lipids of subjects were compared with the recommended reference values of the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children at ages 9, 15 and 18 and with recommendations of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (2002) when the cohort had reached adulthood at 25 years (Lipsy, 2003).

BMI, triglycerides, LDL and total cholesterol were positively correlated at all ages. HDL cholesterol was negatively correlated with triglycerides and BMI and positively correlated with total cholesterol levels (Table 3). There was a strong correlation between LDL and total cholesterol and it remained so throughout all age groups ($r=0.93$; 0.91; 0.90 and 0.87 respectively, $p<0.001$). There was a significant correlation between BMI and triglycerides already at the age of 9 years ($r=0.09$, $p<0.05$) that only grew stronger throughout years ($r=0.14$ $r=0.09$, $p<0.24$; $r=0.09$, $p<0.05$ and $r=0.35$, $p<0.05$, respectively) indicating, that there is a strong association between food intake and body mass index. The opposite was evident between the correlation of BMI and cholesterol. While it was significant at young age of 9 and the teenagerhood at 15 ($r=0.14$, $p<0.05$ and $r=0.07$, $p<0.05$), by the time subjects reached 18 years of age the correlation was no longer present (Table 4). The correlation between BMI and total cholesterol varies over the course of an individual's lifetime. When examining inconsistencies in cholesterol-focused studies, it is crucial to take into account the impact of time and age on this change.

Table 2. Body mass index (BMI) and blood lipid levels in the ECPBHS sample from 9 to 25 years of age.

Age	**9**	**15**	**18**	**25**
Sample size (n)	567	1067	873	982
Number and % of females	297 (52.4)	587 (55.0)	493 (56.5)	561 (57.0)
MALES				
BMI	16.66 ± 1.88	20.38 ± 2.74	22.53 ± 3.20	24.96 ± 3.69
CHL	4.36 ± 0.05	3.85 ± 0.70	3.95 ± 0.72	4.43 ± 0.85
HDL	1.51 ± 0.30	1.35 ± 0.28	1.36 ± 0.28	1.31 ± 0.33
LDL	2.54 ± 0.60	2.24 ± 0.61	2.33 ± 0.62	2.79 ± 0.80
TRG	0.69 ± 0.02	0.77 ± 0.47	0.88 ± 0.51	1.14 ± 0.83
FEMALES				
BMI	16.45 ± 2.29	20.62 ± 3.60	21.79 ± 3.38	22.93 ± 4.39
CHL	4.52 ± 0.79	4.27 ± 0.73	4.35 ± 7.50	4.58 ± 0.85
HDL	1.45 ± 0.29	1.5 ± 0.62	1.62 ± 3.97	1.69 ± 0.41
LDL	2.73 ± 0.71	2.5 ± 0.62	2.49 ± 5.05	2.6 ± 0.77
TRG	0.77 ± 0.28	0.84 ± 0.42	0.84 ± 1.34	0.95 ± 0.47

Body mass index (BMI) in kg/m^2. Total cholesterol (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG) in mmol/L. All values are expressed as mean ± SD. Only the data of younger cohort were available at 9 years of age.

Table 3. Blood lipid levels in the ECPBHS sample from 9 to 25 years of age: correspondence to reference values.

Age	**9**			**15**			**18**			**25**		
	Acceptable	Borderline High	High	Acceptable	Borderline High	High	Acceptable	Borderline High	High	Acceptable	Borderline High	High
CHL	47.6%	37.2%	15.2%	72%	22%	6%	63.3%	27.8%	8.9%	84%	11%	5%
	<4.4	4.4–5.2	>5.2	<4.4	4.4–5.2	>5.2	<4.4	4.4–5.2	>5.2	<5.2	5.2–6.0	>6.0)
LDL	64.9%	22.6%	12.5%	81%	13%	6%	73.7%	17.9%	8.4%	50%	47%	3%
	<2.8	2.8–3.4	>3.4	<2.8	2.8–3.4	>3.4	<2.8	2.8–3.4	>3.4	<2.6	2.6–4.1	>4.1
TRG	77.2%	12.2%	10.6%	80%	14%	6%	70.0%	22.0%	8.0%	91%	5%	4%
	<0.9	0.9–1.1	>1.1	<1.0	1.0–1.5	>1.5	<1.0	1.0–1.5	>1.5	<1.7	1.7–2.3	>2.3
	Acceptable	Borderline Low	Low	Acceptable	Borderline Low	Low	Acceptable	Borderline Low	Low	Acceptable		Low
HDL	76.9%	22.3%	2.8%	84%	8%	8%	82.4%	13.3%	4.3%	89%		11%
	>1.2	1.0–1.2	<1.0	>1.2	1.0–1.2	<1.0	>1.2	1.0–1.2	<1.0	>1.0		<1.0

All recommended values are given in mmol/l. Total cholesterol (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG).

Table 4. Correlations between serum lipid levels and BMI at the ages of 9, 15, 18 and 25 years.

	BMI 9 y.	CHL 9 y.	HDL 9 y.	LDL 9 y.	TRG 9 y.
BMI 9 y.	■	**0.14***	-0.01	**0.15***	**0.09***
CHL 9 y.	**0.14***	■	**0.40***	**0.93****	**0.21***
HDL 9 y.	-0.01	**0.40***	■	0.07	**-0.31***
LDL 9 y.	**0.15***	**0.93****	**0.07***	■	**0.18***
TRG 9 y.	**0.09***	**0.21***	**-0.31***	**0.18***	■
	BMI 15 y.	CHL 15 y.	HDL 15 y.	LDL 15 y.	TRG 15 y.
BMI 15 y.	■	**0.07***	**-0.21***	**0.13***	**0.14***
CHL 15 y.	**0.07***	■	**0.37***	**0.91****	**0.30***
HDL 15 y.	**-0.21***	**0.37***	■	0.05	**-0.27***
LDL 15 y.	**0.13***	**0.91****	0.05	■	**0.27***
TRG 15 y.	**0.14***	**0.30***	**-0.27***	**0.27***	■
	BMI 18 y.	CHL 18 y.	HDL 18 y.	LDL 18 y.	TRG 18 y.
BMI 18 y.	■	0.06	**-0.17***	**0.15***	**0.24***
CHL 18 y.	0.06	■	**0.28***	**0.90****	**0.19***
HDL 18 y.	**-0.17***	**0.28***	■	-0.03	**-0.07***
LDL 18 y.	**0.15***	**0.90****	-0.03	■	**0.17***
TRG 18 y.	**0.24***	**0.19***	**-0.07***	**0.17***	■
	BMI 25 y.	CHL 25 y.	HDL 25 y.	LDL 25 y.	TRG 25 y.
BMI 25 y.	■	**0.15***	**-0.41***	**0.28***	**0.35***
CHL 25 y.	**0.15***	■	**0.22***	**0.87****	**0.37***
HDL 25 y.	**-0.41***	**0.22***	■	**-0.18***	**-0.30***
LDL 25 y.	**0.28***	**0.87****	**-0.18***	■	**0.26***
TRG 25 y.	**0.35***	**0.37***	**-0.30***	**0.26***	■

Body mass index (BMI), total cholesterol (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG). Correlations marked in bold and * are significant at $p < 0.05$. Correlations marked in bold and ** are significant at $p < 0.01$

5.1.2. Impulsivity

In all ages was there a positive correlation between the subscales of Maladaptive and the subscales of Adaptive Impulsivity. Namely, the subscales of Maladaptive Impulsivity, Disinhibition and Thoughtlessness had a positive correlation at the ages of 15, 18 and 25 ($r=0.58$, $p<0.001$; $r=0.44$, $p<0.001$, $r=0.60$, $p<0.001$, respectively). Adaptive Impulsivity subscales Excitement seeking and Fast decision making were also positively correlated in 15, 18 and 25 year olds ($r=0.54$, $p<0.001$, $r=0.45$, $p<0.001$ and $r=0.58$, $p<0.001$, respectively). No statistically significant correlation existed between the main impulsivity factors, Adaptive and Maladaptive Impulsivity at any age.

Similar analysis has been conducted on the database of the Estonian Psychobiological Study of Traffic Behaviour that includes male Caucasian subjects in age range of 15–70 years who drive a vehicle (Laas et al., 2010). The subscales of Maladaptive Impulsivity were correlated at Pearson $r=0.65$, $p<0.001$, and the subscales of Adaptive Impulsivity were correlated at Pearson $r=0.52$, $p<0.001$,

respectively. Within the Adaptive or Maladaptive Impulsivity construct the two subscales had a strong correlation, but across the constructs their subscales of impulsivity correlated only at a weak level.

The differentiation between adaptive and maladaptive impulsivities in our study is in accordance with idea about distinct subtypes of impulsivity (Dickman, 2000; Evenden, 1999; Lynam & Miller, 2004). The AMIS constructs have been derived from the concept of functional and dysfunctional impulsivity (Dickman, 1990) that distinguishes decision-making at the spur of the moment by the success of outcome. Our longitudinal study has revealed that components of adaptive and maladaptive impulsivity are related from adolescence to young adulthood within the main factor, while the main factors with their respective components stand separate throughout development.

5.2. Impulsivity including risk behaviour, and serum lipid levels

5.2.1. Cross-sectional analysis of serum lipids and impulsivity (Paper IV)

When impulsivity and serum lipid levels were examined cross-sectionally at age 15, 18 or 25, a few statistically significant correlations emerged (Table 5) but these were not very systematic. Perhaps most fascinating was the finding of negative correlations between total and LDL cholesterol and both facets of Adaptive Impulsivity in females at age 15. However, these correlations ceased to exist entirely following the onset of puberty. By the age of 25, there were negative correlations between total cholesterol and LDL levels and Maladaptive Impulsivity in males. However, these correlations were only observed with the Thoughtlessness facet, as shown in Table 5.

The cross-sectional analysis yielded an inconclusive result, which is to be expected. Although numerous studies have demonstrated a correlation between low serum lipids and problematic behaviour, such as impulsivity, it is worth noting that certain 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 23–35 showed that while persons in the lowest 10% of plasma CHL, LDL cholesterol, HDL cholesterol, and TRG levels were compared with the other participants in each race/sex group, using standardised 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 the 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, not throughout the life. Furthermore, it is important to note that cross-sectional associations may exhibit

inconsistency since impulsive behaviour is a result of the developmental interplay between previous cholesterol levels and the accumulation of experiences. Serum lipid levels assessed at a single point in time may not accurately reflect the impact of lipids on behavioural assessments.

Table 5. 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	CHL	-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	CHL	-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	CHL	-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 (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL) and triglycerides (TRG) correlations with impulsivity measures in bold while significant at $p<0.05$.

5.2.2. Cholesterol as predictor of impulsivity (Paper IV)

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 6). Disinhibition and Thoughtlessness, which are both components of Maladaptive Impulsivity, measured at 25 years, were predicted by LDL and total cholesterol levels at 9, 15, and 18 years. Regarding the aspects of Adaptive Impulsivity, the level of Excitement Seeking at the age of 25 was solely predicted by total cholesterol at the age of 15. HDL cholesterol levels at 15 years were found to be a predictor of Fast Decision-making at 25 years. The association between only Maladaptive Impulsivity and cholesterol levels indicates that cholesterol selectively affects the neurodevelopmental mechanisms responsible for the dysfunctional aspects of impulsivity.

Correlation analyses without covariates were similar to the results with ANCOVA. In most cases where serum lipid levels 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 (data not shown). Previously, several authors have drawn attention to the differences between sexes

(Eriksen et al., 2017), mostly reporting the association between cholesterol and impulsivity only in males (Golier et al., 1995; Lindberg et al., 1992; Muldoon et al., 1990; Wu et al., 2015).

One of the strengths of the current analysis is the inclusion of children starting from the 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 adverse childhood experiences, demographics, and biochemical factors 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 such as 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 between 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.

In the current analysis, Disinhibition and Thoughtlessness in males were predicted by total and LDL cholesterol but not by TRG level. The interaction of serum lipid levels and impulsivity may have behavioural background. TRGs 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 body mass index, TRGs 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 & Santonastaso, 1997). Our analysis suggests that cholesterol levels are predicting impulsivity independently of TRGs, and thus it can be hypothesised that nutritional intake has not played a role in the interaction of impulsivity and serum lipid levels as a confounding factor.

Our results that highlight the importance the childhood serum lipid levels have on impulsivity in adulthood are in line with the neurodevelopmental studies on the role of cholesterol during childhood and early adolescence. While most cross-sectional analyses find an association between low serum lipid levels and high impulsivity in adult 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.

Table 6. 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 sex. 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	b	p
9 years	CHL	-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	CHL	-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	CHL	-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	b	p
9 years	CHL	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	CHL	-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	CHL	-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 (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG). P-values marked in bold are significant at $p<0.05$.

5.2.3. Suicide ideation, cholesterol and impulsivity

There were in total 390 men and 610 women who were asked about suicidal thoughts either at the age of 18, 25 or both ages. One hundred and five men had suicide ideation and 12 had attempted suicide by the age of 18 years. By the age of 25 years 17 men had a lifetime risk of suicide according to M.I.N.I., and 3 had recent risk of suicide. There were 209 women with suicide ideation and 36 women who had attempted suicide by the age of 18 years. By the age of 25 years 37 women had a M.I.N.I. lifetime risk of suicide and 11 had recent risk of suicide. There was 27% of 18 year old men and 34% of 18 year old women reported having had thought at least once about attempting suicide. Although this number may appear very high, similar reports have been shown in Estonian children, adolescents, and adults before (Rooväli et al., 2018). Similarly, the Health Behaviour in School-aged Children' Study, with a sample of 5707 students aged 11-, 13- and 15-years, the authors reported that approximately 40% of schoolchildren reported depressive feelings and/or suicidal ideation (Samm et al., 2010). As a limitation, they bring out that, similarly to our study, their analysis was based on a single question in a self-report. Interestingly, in this study suicide ideation was the highest in the 11 year old group and declined with age (23.8%; 11.4% and 13.5%, respectively). According to the authors, suicide ideation measured in children may reflect on aspects of their relationships, rather than on a suicidal process. That might also be the case at a tender age of 18 years.

Low lipid levels have been associated with suicide and suicide ideation. We have examined whether attempted suicide or suicidal ideation at 18 years and suicidal risk at 25 years are associated with serum lipids or BMI. Logistic regression analysis revealed that serum lipid levels or BMI did not have an effect on suicide attempts or suicide ideation in 18 year old males or females and had no effect on suicide risk in 25 year old females. In 25 year old males high total and LDL cholesterol and triglyceride levels (OR=3, p=0.02, OR=4.37, p=0.01, OR=3.67, p=0.01, respectively) and low HDL cholesterol levels (OR=0.28, p=0.04) were associated with recent suicide risk, but not with lifetime suicide risk. Additional independent samples t-test analysis confirmed that 25 year old men with high recent suicide risk also had high total and LDL cholesterol and triglycerides levels ($F(1, 398)=6.66$, $p=0.01$, $F(1, 398)=7.85$, $p=0.005$, $F(1, 387)=12.88$, $p<0.005$, respectively) and low HDL cholesterol levels ($F(1, 399)=3.8$, $p=0.05$).

Table 7. Means for serum lipid levels in recent suicide risk group and no recent suicide risk group in 25 year old males.

	Risk		No risk		
	Mean	SD	Mean	SD	p (t-test)
CHL	5.50	1.31	4.41	0.78	**0.011**
HDL	0.97	0.31	1.31	0.32	**0.048**
LDL	3.82	0.78	2.76	0.71	**0.005**
TRG	1.92	0.16	1.02	0.44	**0.005**

Total cholesterol (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG). The number of subjects in the risk group was 3 and no risk group was 402 for CHL, LDL and HDL and 391 for TRG.

Our results are in apparent contradiction with the sizeable literature on the relationship between suicide and low cholesterol. The most recent meta-analysis demonstrated a robust effect across 65 studies (comprising upward of 500,000 participants), showing that suicidal patients have lower total cholesterol levels than non-suicidal controls and that lower total cholesterol was associated with a 112% higher risk of suicidality (Wu et al., 2015). The subgroup analysis of the meta-analysis highlighted that the association between lower serum lipid levels and suicidality was stronger in participants younger than 40 years when compared to older participants. A study conducted in Korean population found that low cholesterol levels predicted suicide among female suicide attempters, but not among men (Park et al., 2024).

However, not all previous literature shows association between low cholesterol and suicidality. Quite in contrast, Fiedorowicz & Coryell (2007) reported that when analysing only younger patients, the patients made more suicide attempts when the cholesterol levels were high and not low. In this context it should be noted that in our sample low cholesterol levels at early age predicted impulsivity, while suicide is considered a reflection of low impulse control. Obviously, the relationship between cholesterol levels, impulsivity and suicide is not linear. While the association of early cholesterol levels and impulsivity were based on data across the whole range of both measures, suicide-related measures were positive only in a small number of participants.

Indeed, several studies suggest that suicide completers have higher levels of impulsivity and aggressive behaviours (Brent et al., 1994, 1996, 2002), an association that seems to be independent from psychopathology (Dumais et al., 2005). Nevertheless, suicide is a complex behaviour that is probably the result of the interaction of several different factors and is unlikely to be in a simple causal relationship with impulsivity that is a strongly hereditary trait (McGirr et al., 2008).

In our sample, both Maladaptive Impulsivity traits Disinhibition and Thoughtlessness were high in persons who had suicide ideation or attempted suicide at 18

or had been rated to have high suicide lifetime risk at 25. To analyse relationship between impulsivity and suicide subjects were divided onto two groups- those who have had any suicide ideation, attempts or risk for them and those who have not. Men with suicide ideation and having had attempted suicide at 18 years had high levels of Disinhibition and Thoughtlessness at respective age ($F(1, 382)=11.92$, $p<0.001$; $F(1, 383)=6.11$, $p=0.01$ and $F(1, 382)=9,27$, $p=0.002$; $F(1, 383)=4.81$, $p=0.03$, respectively). Men with a lifetime suicide risk at 25 years had also high levels of Disinhibition and Thoughtlessness ($F(1, 383)=8.00$, $p=0.005$; $F(1, 383)=7.15$, $p=0.007$, respectively). Women with suicide ideation at 18 years had high levels of both Disinhibition and Thoughtlessness ($F(1, 502)=15.44$, $p<0.001$; $F(1, 500)=13.08$, $p<0.001$, respectively). Women with a lifetime suicide risk at 25 years and having had attempted suicide at 18 years had high levels of Thoughtlessness at respective ages ($F(1, 504)=7.64$, $p=0.006$, $F(1, 498)=5.06$, $p=0.02$, respectively), but not Disinhibition. It should however be acknowledged that the associations with suicide ideation are derived from a much smaller number of subjects than the association between impulsivity and cholesterol levels that refer to a strongly birth cohort representative sample. It thus appears that suicide ideation is most likely in subjects with a mismatch with the general association of cholesterol with impulsivity.

5.2.4. Risk behaviour and impulsivity

Previous studies have shown that youth who engage in early risk taking, such as illicit drug use and risky sexual behaviour, exhibit also higher levels of impulsive behaviour (Arnett, 1992). Our analysis indicated that risk behaviour is correlated with different facets of impulsivity, according to age and sex (Table 8). In males, most risk behaviours were correlated with Adaptive Impulsivity and only to some extent in the youngest years with Maladaptive Impulsivity. In women however risk behaviour correlated more with Maladaptive Impulsivity though all ages. The correlations between risk behaviour and impulsivity were altered throughout time. While in 15 and 18 year old women risk behaviour was correlated with Excitement seeking, the same trend was present only in 18 year old men. While the correlation was strongest in both men and women at the age of 18, by the time of 25 years, the correlation disappeared in both men and women.

Table 8. Correlation of risk behaviour and impulsivity at the age of 15, 18, and 25 years.

		MALES					FEMALES				
		Traffic behaviour	Alcohol	Tobacco	Drugs	Sexual behaviour	Traffic behaviour	Alcohol	Tobacco	Drugs	Sexual behaviour
15	Disinhibition	0.15	0.09	**0.19**	**0.21**	0.14	0.11	**0.13**	0.07	-0.01	-0.03
	Thoughtlessness	**0.22**	0.06	0.05	0.15	0.03	**0.16**	**0.14**	**0.14**	0.06	0.08
	Excitement seeking	0.05	**0.19**	0.12	0.12	0.08	**0.32**	**0.16**	0.07	**0.16**	**0.20**
	Fast decision making	0.06	0.03	**0.21**	**0.20**	**0.16**	**0.23**	0.04	0.04	0.04	0.09
18	Disinhibition	**0.17**	0.03	0.13	-0.09	0.06	**0.15**	**0.15**	**0.22**	**-0.25**	0.18
	Thoughtlessness	**0.29**	0.08	0.05	-0.13	0.07	**0.18**	**0.14**	**0.16**	**-0.20**	**0.25**
	Excitement seeking	**0.20**	**0.21**	**0.16**	**-0.20**	**0.20**	**0.30**	**0.18**	0.12	**-0.20**	0.12
	Fast decision making	0.08	**0.19**	**0.17**	**-0.23**	**0.30**	0.11	0.03	-0.04	-0.04	0.06
25	Disinhibition	0.04	0.05	0.14	0.12	0.10	0.11	**0.14**	0.06	**0.20**	**0.14**
	Thoughtlessness	0.09	-0.02	0.09	0.07	0.05	0.05	0.10	**0.17**	0.09	**0.16**
	Excitement seeking	**0.21**	-0.00	0.09	**0.16**	**0.26**	0.09	0.06	**0.16**	0.11	**0.17**
	Fast decision making	0.13	0.06	**0.20**	0.12	**0.28**	-0.00	0.01	0.09	0.02	0.10

Pearson correlation coefficient r. Correlations marked in bold are significant at $p < 0.05$

Previous studies conducted in longitudinal Estonian Psychobiological Study of Traffic Behaviour have shown that risky behaviour in traffic can be associated with both maladaptive and adaptive features of impulsivity. While drunk driving was associated only with Maladaptive types of impulsivity, exceeding speed limits was associated primarily with Adaptive Impulsivity traits such as Fast Decision Making and Excitement Seeking and, to a lesser degree, with Thoughtlessness (Paaver et al., 2006). The high level of Disinhibition in drunk drivers was also confirmed by Tokko et al. (2022). Similar trend of differentiation was seen when high scores of Maladaptive Impulsivity predicted drunk driving and high scores of Adaptive Impulsivity predicted exceeding speed limit and active traffic accidents (Tokko et al., 2019). In the current analysis, risky traffic behaviour measures were accommodated for under-aged subjects and thus did not focus on drunk driving or speeding. Our analysis indicated that while risky traffic behaviour at 15 and 18 years was correlated with maladaptive trait Thoughtlessness, at the ages of 18 and 25 it was correlated with adaptive trait Excitement seeking. The main conclusion of the analysis is that risky traffic behaviour is correlated with impulsivity, but the type of impulsivity changes, possibly owing to the change of traffic behaviours one is primarily engaged with, and also the experiences gained.

Previous research has consistently demonstrated a relationship between impulsivity and alcohol consumption (Merchán-Clavellino et al., 2020), narcotics (James & Taylor, 2007), and tobacco use (Kelly et al., 2019) in young people, showing that greater impulsivity is associated with higher consumption of alcohol, tobacco, and narcotics. In our analysis, alcohol consumption was correlated with Excitement seeking at the teenage years while the association disappeared in young adulthood. Tobacco consumption was correlated with Fast Decision Making in men and with Thoughtlessness in women. When compared with other risky behaviours, in the case of narcotics use, the importance of age is the most noticeable. There was no overall consistency in association between narcotics use and impulsivity. However, only at the age of 18, narcotics use was negatively correlated with all aspects of impulsivity in both sexes, as opposed to all other risky behaviours being positively correlated with impulsivity measures. While subjects with low impulsivity engaged generally in low risky behaviour, at the age of 18, in both men and women, low impulsivity was correlated with higher use of narcotic substances. This highlights that engagement in a certain risky behaviour can have a fundamentally different reasoning and origin based on the age of the subject. Risky sexual behaviour has been well documented to have an association with impulsivity across sex, age, and race (Dir et al., 2014). Interestingly, impulsivity traits associated with risky sexual behaviour in men are only the traits of Adaptive Impulsivity. In women, the association was more complex. While similarly to men, there was an association between risky sexual behaviour and excitement seeking, there was also a correlation with the Maladaptive Impulsivity traits, but only at the ages of 18 and 25. Compared to other risky behaviours, sexual behaviour exhibited a significantly lower change between different age groups. At the age of 15, in both sexes, sexual behaviour is corre-

lated with Adaptive Impulsivity traits. While in men the correlation remains throughout youth up until adulthood, women see a shift after puberty that continues into adulthood. A study conducted only in men (Derefinko et al., 2014) indicated that sensation seeking and behavioural risk-taking predicted a high number of sexual partners. The results of the same study showed that young men who were impulsive in the context of negative emotions were less likely to use condoms, suggesting that distinct traits of impulsivity are associated with particular aspects of risky sexual behaviour. To summarise, impulsivity is associated with risky behaviour. Yet every type of risky behaviour is associated with a specific measure of impulsivity and there is no universal link between these two measures. Association between impulsivity and risky behaviour is also dependent on age and sex.

5.2.5. Risk behaviour and cholesterol

The effects of serum lipid levels on risk behaviour were assessed by the means of multinomial and binominal logistic regression separately in males and females at 15, 18 and 25 years. Low levels of cholesterol have been historically associated with high impulsivity and suicidal tendencies. However, our analysis has failed to show such a straightforward association. Aligned with these results there was also no straightforward effect of serum lipid levels on risk behaviour. The highest odds ratio in the analysis was low total and LDL cholesterol leading to high risk taking in traffic in 15 year old girls. However, this effect was borderline significant at the age of 18 and disappeared by the age of 25 years.

In 18 years old males sexual behaviour was influenced by total cholesterol levels, males with high cholesterol levels having higher odds of being in the sexual behaviour risk group. In 18 year old females high triglyceride levels were associated with high risk in sexual behaviour and high total cholesterol levels associated with high tobacco use. In 25 year old females low HDL cholesterol levels were related with high tobacco use.

In 15 year old females both low total and low LDL cholesterol levels were linked with high risk taking in traffic. In 25 year old females low LDL cholesterol levels were associated with more frequent alcohol use. In males, high triglycerides levels at 18 years and lower LDL levels at 25 years were linked with higher risk taking in traffic at the respective age. (Table 9; Table 10).

Table 9. Multinomial logistic regression showing effect of serum lipid levels and BMI on traffic behaviour and alcohol use.

MALES						FEMALES			
		Traffic behaviour		Alcohol		Traffic behaviour		Alcohol	
15 years		OR	CI	OR	CI	OR	CI	OR	CI
BMI	Low risk vs high risk	1.01	0.89, 1.14	0.80	0.65, 0.99	1.03	0.92, 1.15	1.01	0.91, 1.13
	Medium risk vs high risk	1.00	0.90, 1.11	0.98	0.88, 1.10	1.00	0.91, 1.10	1.00	0.92, 1.09
CHL	Low risk vs high risk	1.02	0.57, 1.81	1.08	0.54, 2.18	**3.35****	1.79, 6.25	1.34	0.78, 2.31
	Medium risk vs high risk	0.99	0.62, 1.58	0.99	0.59, 1.65	**2.30****	1.35, 3.90	0.98	0.64, 1.49
HDL	Low risk vs high risk	0.34	0.09, 1.25	0.82	0.18, 3.75	2.72	0.82, 9.03	0.77	0.23, 2.60
	Medium risk vs high risk	0.64	0.23, 1.83	1.64	0.54, 4.98	2.29	0.85, 6.18	1.00	0.41, 2.46
LDL	Low risk vs high risk	1.27	0.65, 2.49	0.87	0.39, 1.93	**3.10****	1.58, 6.11	1.41	0.76, 2.59
	Medium risk vs high risk	1.15	0.67, 1.98	0.71	0.40, 1.28	**2.09***	1.18, 3.70	0.86	0.54, 1.39
TRG	Low risk vs high risk	1.23	0.48, 3.14	1.64	0.68, 3.96	1.43	0.51, 3.97	1.47	0.50, 4,32
	Medium risk vs high risk	1.59	0.76, 3.35	1.10	0.52, 2.33	1.26	0.53, 3.01	1.80	0.79, 4.06
18 years									
BMI	Low risk vs high risk	0.93	0.82, 1.06	1.29	0.88, 1.91	0.92	0.82, 1.04	1.09	0.76, 1.57
	Medium risk vs high risk	1.01	0.92, 1.10	1.11	0.90, 1.38	0.91	0.81, 1.01	1.07	0.88, 1.29
CHL	Low risk vs high risk	0.91	0.48, 1.74	0.73	0.47, 1.12	1.18	0.68, 2.07	1.25	0.86, 1.81
	Medium risk vs high risk	0.92	0.57, 1.51	0.97	0.78, 1.21	1.27	0.75, 2.16	0.88	0.72, 1.07
HDL	Low risk vs high risk	1.08	0.25, 4.72	0.79	0.51, 1.21	0.98	0.26, 3.66	0.97	0.65, 1.44
	Medium risk vs high risk	0.97	0.31, 3.03	0.81	0.65, 1.02	0.94	0.27, 3.26	1.03	0.85, 1.26
LDL	Low risk vs high risk	0.99	0.50, 1.95	0.80	0.53, 1.23	1.18	0.59, 2.35	1.27	0.88, 1.84
	Medium risk vs high risk	1.05	0.63, 1.76	1.05	0.85, 1.31	1.30	0.67, 2.50	0.88	0.73, 1.07
TRG	Low risk vs high risk	**0.28***	0.10, 0.80	0.90	0.58, 1.38	0.62	0.18, 2.13	0.70	0.46, 1.07
	Medium risk vs high risk	0.54	0.27, 1.05	0.97	0.78, 1.21	0.69	0.22, 2.17	0.79	0.66, 0.96

MALES							FEMALES					
		Traffic behaviour			Alcohol		Traffic behaviour			Alcohol		
25 years		OR	CI		OR	CI	OR	CI		OR	CI	
BMI	Low risk vs high risk	0.67	0.45,	0.99	1.11	0.66, 1.85	0.93	0.48,	1.83	0.97	0.73,	1.30
	Medium risk vs high risk	0.71	0.49,	1.04	1.14	0.89, 1.45	0.70	0.35,	1.38	1.02	0.85,	1.21
CHL	Low risk vs high risk	1.50	1.00,	2.26	0.84	0.53, 1.36	0.68	0.33,	1.41	1.26	0.93,	1.69
	Medium risk vs high risk	1.46	0.98,	2.18	0.88	0.70, 1.11	0.71	0.34,	1.48	1.24	1.02,	1.50
HDL	Low risk vs high risk	1.08	0.73,	1.58	0.75	0.47, 1.21	0.65	0.30,	1.42	0.93	0.69,	1.26
	Medium risk vs high risk	1.39	0.95,	2.03	0.85	0.68, 1.07	0.70	0.32,	1.53	0.90	0.75,	1.08
LDL	Low risk vs high risk	**1.66***	1.11,	2.48	1.00	0.64, 1.58	0.79	0.37,	1.67	**1.41***	1.04,	1.90
	Medium risk vs high risk	**1.50***	1.01,	2.23	0.87	0.69, 1.09	0.81	0.38,	1.72	**1.32****	1.09,	1.61
TRG	Low risk vs high risk	0.92	0.64,	1.32	1.05	0.66, 1.66	1.02	0.45,	2.29	1.01	0.74,	1.39
	Medium risk vs high risk	0.73	0.51,	1.04	1.08	0.86, 1.36	0.98	0.44,	2.23	1.16	0.96,	1.40

Odds ratios (OR) with 95% confidence intervals (CI). Body mass index (BMI), total cholesterol (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG).

The numbers of subjects was as follows: 221 (15 year old males for serum lipid level and traffic interaction), 190 (15 year old males for serum lipid level and alcohol interaction), 201 (18 year old males for serum lipid level and traffic interaction), 382 (18 year old males for serum lipid level and alcohol use interaction), 386 (25 year old males for serum lipid level and traffic interaction), 414 (25 year old males for serum lipid level and alcohol interaction); 261 (15 year old females for serum lipid level and traffic interaction), 240 (15 year old females for serum lipid level and alcohol interaction), 252 (18 year old females for serum lipid level and traffic interaction), 499 (18 year old females for serum lipid level and alcohol use interaction), 521 (25 year old females for serum lipid level and traffic interaction), 545 (25 year old females for serum lipid level and alcohol interaction).

Odds ratios marked in bold and * are significant at $p<0.05$ and odds ratios marked in bold and ** are significant at $p<0.005$.

Table 10. Logistic regression showing the effect of serum lipid levels and BMI on use of tobacco and narcotics as well as on sexual behaviour.

	MALES									FEMALES								
	Tobacco			Drugs			Sexual behaviour			Tobacco			Drugs			Sexual behaviour		
	OR	CI		OR	CI		OR	CI		OR	CI		OR	CI		OR	CI	
15 years																		
BMI	1.05	0.95,	1.14	1.09	0.99,	1.20	1.03	0.90,	1.15	1.04	0.96,	1.13	1.05	0.95,	1.15	1.07	0.98,	1.16
CHL	1.20	0.73,	1.67	1.12	0.63,	1.61	1.07	0.51,	1.64	0.75	0.30,	1.19	0.68	0.14,	1.22	0.74	0.27,	1.21
HDL	0.77	-0.26,	1.80	1.21	0.12,	2.30	0.89	-0.37,	2.15	0.73	-0.19,	1.65	0.53	-0.57,	1.63	1.20	0.24,	2.16
LDL	1.21	0.67,	1.76	1.29	0.73,	1.86	1.36	0.70,	2.02	0.84	0.34,	1.33	0.70	0.10,	1.30	0.69	0.16,	1.22
TRG	0.95	0.26,	1.64	0.72	-0.09,	1.52	1.16	0.34,	1.98	0.93	0.13,	1.72	0.54	-0.53,	1.62	0.54	-0.42,	1.49
18 years																		
BMI	1.04	0.83,	1.24	0.91	0.70,	1.12	1.21	1.00,	1.41	1.04	0.86,	1.22	1.10	0.92,	1.27	1.03	0.85,	1.20
CHL	1.10	0.89,	1.31	0.97	0.76,	1.18	**1.37****	1.16,	1.59	**1.24***	1.05,	1.43	1.14	0.96,	1.32	1.10	0.92,	1.28
HDL	1.18	0.97,	1.39	1.17	0.96,	1.38	1.12	0.91,	1.33	0.98	0.79,	1.17	0.99	0.81,	1.16	1.02	0.84,	1.20
LDL	0.93	0.72,	1.14	0.92	0.71,	1.13	1.21	1.00,	1.42	0.96	0.77,	1.15	1.12	0.94,	1.30	1.00	0.82,	1.18
TRG	1.14	0.93,	1.35	0.96	0.74,	1.17	1.24	1.03,	1.46	1.02	0.83,	1.22	1.09	0.91,	1.27	**1.45****	1.26,	1.64
25 years																		
BMI	0.95	0.71,	1.18	1.12	0.90,	1.34	1.23	0.87,	1.58	1.17	0.98,	1.37	1.09	0.92,	1.25	1.04	0.98,	1.10
CHL	1.04	0.82,	1.27	1.10	0.90,	1.30	0.92	0.61,	1.22	0.90	0.70,	1.11	1.02	0.85,	1.19	0.87	0.58,	1.16
HDL	0.97	0.75,	1.19	0.96	0.76,	1.16	1.08	0.78,	1.38	**0.80***	0.60,	1.00	0.96	0.79,	1.13	1.05	0.36,	1.73
LDL	0.97	0.75,	1.19	1.15	0.95,	1.35	0.89	0.59,	1.19	0.95	0.75,	1.16	1.07	0.89,	1.24	0.83	0.52,	1.14
TRG	1.20	0.97,	1.42	1.17	0.97,	1.38	0.99	0.69,	1.30	1.11	0.92,	1.31	0.93	0.77,	1.09	0.97	0.39,	1.56

Odds ratios (OR) with 95% confidence intervals (CI). Body mass index (BMI), total cholesterol (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG).

The numbers of subjects was as follows: 214 (15 year old males for serum lipid level and tobacco use interaction), 219 (15 year old males for serum lipid level and narcotics use interaction), 211 (15 year old males for serum lipid levels and sexual behaviour interaction), 383 (18 year old males for serum lipid levels and tobacco use interaction), 203 (18 year old males for serum lipid level and narcotics interaction), 386 (18 year old males for serum lipid level and sexual behaviour interaction), 357 (25 year old males for serum lipid level and tobacco use interaction), 417 (25 year old males for serum lipid level and narcotics use interaction), 225 (25 year old males for serum lipid levels and sexual behaviour interaction); 256 (15 year old females for serum lipid level and tobacco use interaction), 252 (15 year old females for serum lipid level and narcotics use interaction), 257 (15 year old females for serum lipid levels and sexual behaviour interaction), 499 (18 year old females for serum lipid levels and tobacco use interaction), 508 (18 year old females for serum lipid level and narcotics interaction), 497 (18 year old females for serum lipid level and sexual behaviour interaction), 434 (25 year old females for serum lipid level and tobacco use interaction), 550 (25 year old females for serum lipid level and narcotics use interaction), 306 (25 year old females for serum lipid levels and sexual behaviour interaction).

Odds ratios marked in bold and * are significant at $p<0.05$ and odds ratios marked in bold and ** are significant at $p<0.005$.

5.3. Impulsivity, cholesterol and genotype

The genes of the serotonergic system have been previously shown to have an effect on impulsivity levels. The distribution of genotypes of two genes of the serotonergic system, *HTT* and *HTR2A* of the sample is presented in Table 11.

Table 11. Genotype distribution in sample

	HTT									*HTR2A*		
	5-HTTLPR					rs25531				rs6311		
	L/L	S/L	S/S	S/La	Lg/La	S/S	Lg/S	La/La	Lg/Lg	A/A	G/G	A/G
n	542	528	164	472	119	164	70	405	4	151	523	560
%	43.92	42.79	13.29	38.25	9.64	13.29	5.67	32.82	0.32	12.24	42.38	45.38

5.3.1. Impulsivity, and *HTR2A* and *HTT* genes (Paper II)

The A allele of the 5-HT2A receptor gene has been shown to correspond to higher transcriptional activity in the reporter gene assay in cell cultures and to be associated with increased 5-HT2A receptor binding (Parsons et al., 2004; Turecki et al., 1999).

Although only speculatively related to the present findings, it is conceivable that higher levels of 5-HT2A receptors are associated with lower presynaptic serotonergic output, and, in turn, maladaptive impulsivity. Indeed, Van Heeringen et al. (2003) showed the involvement of the brain serotonergic system in suicidal behaviour by means of a SPECT 5-HT2A receptor study using a highly selective ligand (Audenaert et al., 2001). When compared to normal controls, patients with a recent history of suicide attempts showed a significant decrease in 5-HT2A binding index in the prefrontal cortex, the decrease being significantly more marked among patients who used violent methods to attempt suicide than among those who attempted suicide by means of self-poisoning.

In the present analysis we found that the A/A genotype of the *HTR2A* –1438A/G polymorphism expresses significantly higher Maladaptive, but not Adaptive Impulsivity. The *HTR2A* genotype had statistically significant main effects on Disinhibition, Thoughtlessness, and Maladaptive Impulsivity: The A/A homozygotes had higher expression of these impulsivity traits ($F(2, 503)=5.20$, $p=0.006$; $F(2, 503)=5.79$, $p=0.003$; $F(2, 503)=6.30$, $p=0.002$ respectively; Figure 2).

An interaction effect between sex and genotype on Disinhibition ($F(2, 503)=3.64$, $p=0.03$), Thoughtlessness ($F(2, 503)=3.67$, $p=0.03$) and Maladaptive Impulsivity ($F(2, 503)=3.84$, $p=0.02$) was also detected. The lowest impulsivity scores were found in male A/G heterozygotes and female G/G homozygotes, and these groups were significantly different from the female A/A homozygotes who had the highest scores. The effect on Disinhibition was found only in women and not in men, while in case of Thoughtlessness the effect was clearer in men. This finding supports the notion described earlier, that serotonergic function is innately different in men and women (Cosgrove et al., 2007).

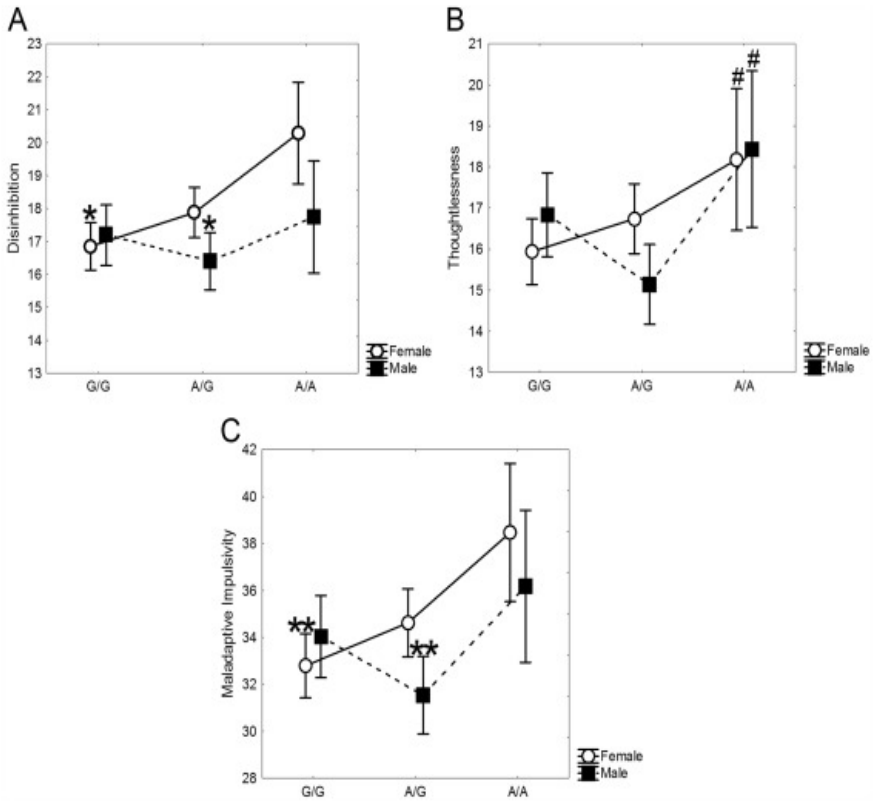

Figure 2. A–C. Association of the *HTR2A* genotype with impulsivity traits in males and females. Disinhibition (A) and Thoughtlessness (B) Are subscales of Maladaptive Inhibition (C). All Data Are expressed as Mean ± SEM. A. *p<0.05 different from females with A/A genotype. B. #p<0.01 different from males with A/G genotype. C. **p<0.01 different from females with A/A genotype.

There was no main effect of 5-HTTLPR polymorphism on impulsivity in either males or females. Similar results have been published earlier by Paaver et al. (2008) when using the AMIS scale and by da Cunha-Bang et al. (2023) when impulsivity was measured using the Barratt Scale of Impulsivity. There were no significant differences observed between those carrying the S allele (SL/SS) and those with the LL genotype in terms of their overall cognitive capacity and performance on the Barratt scale. The second marker of the capacity of the central serotonergic system investigated in this study was platelet MAO. Although there was no significant association between MAO activity or 5-HTTLPR polymorphism and the BIS-11 total score, a significant interaction effect was observed. This means that individuals with low MAO activity and carrying the S allele had higher scores in self-reported impulsiveness compared to individuals with low MAO activity and LL genotype. A notable inverse relationship was observed between MAO activity and impulsiveness in individuals carrying the S

allele of 5-HTTLPR, whereas no such link was found in individuals with the LL genotype. The impact of the 5-HTTLPR genotype on impulsivity is influenced by platelet MAO activity and there is a possible confounding effect also with other markers of the serotonergic system. It should be noted that both, 5-HTTLPR polymorphism and platelet MAO activity have a complex, non-linear relationship with impulsivity (Paaver et al., 2008).

5.3.2. Cholesterol, and *HTR2A* and *HTT* genes (Paper I)

Several studies have shown interaction of the 5-HTTLPR polymorphism and serum lipid levels as well as lipid metabolism linked psychiatric and behavioural disorders in an elderly population (Grünblatt et al., 2006.; Partonen et al., 1999). We found this trend present already during late stages of puberty. Our study demonstrates a significant interaction between 5-HTTLPR polymorphism and lipid levels in adolescents at age 15 and 18, whilst no changes were noted in the lipid levels of 9 year old children. The longitudinal analysis revealed a main effect on LDL cholesterol within the older cohort (measured at the ages of 15, 18 and 25) whilst in the comparison of S/S genotype against L/L and S/L genotype at different age groups with pooled cohorts, we found that L allele carriers had significantly higher levels of LDL and total cholesterol. Furthermore, 25 year olds carrying the L allele had significantly lower levels of HDL cholesterol.

Total cholesterol levels were significantly ($p<0.05$) higher in 15 year old, but not 9 year old L allele carriers. The same trend ($p=0.09$) was found also in 18 year olds. LDL levels were influenced by the 5-HTTLPR polymorphism in 15, 18 and 25 year olds with L/L genotype having the highest levels of LDL. In 25 year olds also HDL cholesterol levels were affected by 5-HTTLPR genotype whilst L/L genotype carriers had lower levels of HDL cholesterol compared with other genotypes. Genotype was not associated with triglyceride levels at any age (data not shown). Contrasting L/L genotype with the S/S and S/L genotype did not yield in any statistically significant interactions between 5-HTTLPR polymorphism and serum lipid levels. Cohort and pubertal stage effects were added to the statistical model, but did not show any main effect on the serum lipid levels. Sex, calorie intake, BMI and physical activity were associated with the lipid levels, but did not affect the association of the 5-HTTLPR polymorphism with lipid levels (data not shown). Separate analysis of males and females did not reveal sex-specificity of this association.

Longitudinal analysis with linear mixed-effects models did not show any significant interaction of 5-HTTLPR genotype with LDL cholesterol ($F(4, 1522)=0.52$, $p=0.72$ for the older cohort (Figure 3A)) and $F(4, 1492)=0.68$, $p=0.61$ for the younger cohort (Figure 3B). The model revealed a trend for a main effect of the 5-HTTLPR polymorphism on LDL cholesterol in the older cohort, though it did not reach a statistically significant level ($F(2, 1522)=2.89$, $p=0.056$). When the L/L and S/L genotypes were pooled, the L allele carriers did show higher LDL cholesterol levels ($F(1, 1522)=5.60$, $p=0.018$). In younger cohort no main effect of 5-HTTLPR polymorphism on LDL cholesterol levels was found.

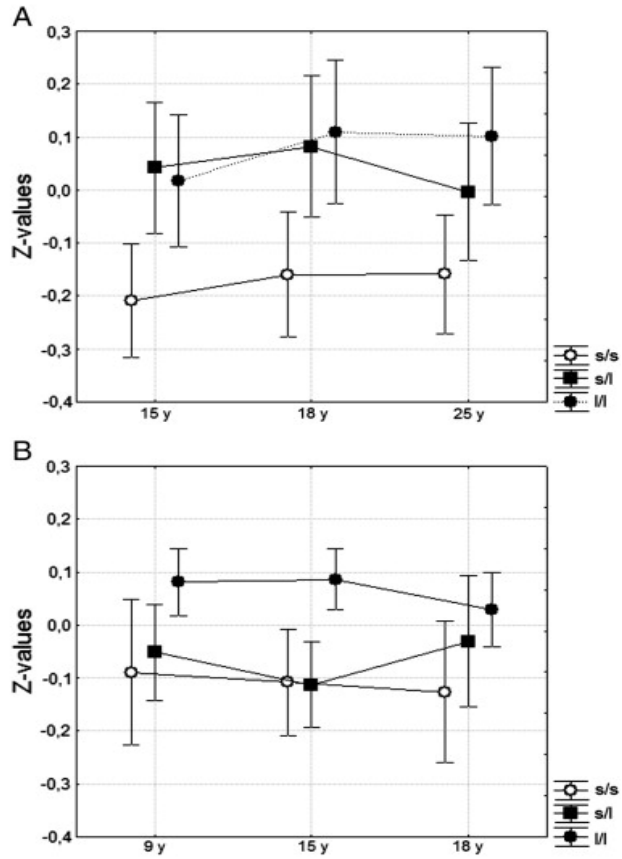

Figure 3. Levels of LDL cholesterol longitudinally in two cohorts (A – older cohort, B – younger cohort) by serotonin transporter gene linked promoter region (5-HTTLPR) polymorphism. Levels are expressed as mean ± SEM. Z-scores stand for cohort-adjusted value

Very little is known on the association between the gene variants that regulate the serotonergic system and lipid metabolism in children and adolescents. Majority of the studies on lipid metabolism and cholesterol have been conducted in elderly population because of the increasing role of cholesterol levels on prevalence of coronary disease in the elderly population. As previously noted, the large Vienna Trans-Danube Aging study found that L allele is an independent risk factor for higher mean fasting LDL-cholesterol levels (Fischer et al., 2006). Though conducted in an elderly population, this finding is in accordance with our data. The findings concerning the levels of blood lipids and 5-HTTLPR have not, however, always been consistent even in elderly populations. A study on non-Hispanic Caucasians (mean age of 55.4 ± 7.5 years) from the Loma Linda University Centre for Health Promotion, California, Comings et al. (1999) reported that total

cholesterol and triglyceride levels were significantly higher in S/L heterozygotes than either in S/S or L/L homozygotes. However, that study consisted of a very limited sample, 99 subjects in total. In elderly Korean population it was the S allele of the 5-HTTLPR polymorphism that had an elevating effect on the LDL cholesterol levels (Kim et al., 2011). Although the study consisted of 732 people with an age 72.8 ± 5.9 years, it is important to note that studies of populations with Asian ancestry should be compared with care with the studies based on Caucasian ancestry, as the S allele is the more frequent allele in Asians.

It is important to note that different studies have controlled for different confounding factors. In our analysis cohort, sex, calorie intake, physical activity, body mass index, oral contraceptive use in women, and the pubertal stage were all independently added to the model to investigate the possible effects of interaction. None of them had a main effect on the lipid levels and there was no interaction between those factors and 5-HTTLPR polymorphism on the different cholesterol fractions.

It is known that sex differences exist in lipid levels as well as in depression prevalence, and thus sex stratification may have an impact on results (Buydens-Branchey et al., 2000; Steegmans et al., 1996; Steiner, 2011). A study conducted in elderly men has found a significant interaction effect of 5-HTTLPR and LDL cholesterol on risk of depression, low LDL and the S allele together increasing the risk, but no significant association between this polymorphism and lipid levels (Ancelin et al., 2010). Our analysis shows, however, that the interaction between serum lipid levels and 5-HTTLPR is present in both young men and women. At older age, the impact of a variety of lifestyle factors on lipid levels is likely to be higher.

Another possibility to explain the inconsistent findings would be to take into account the rs25531 polymorphism. Since the effect of Lg allele on mRNA expression is similar to the one of the S alleles, studies that include many Lg allele carriers within S/L or L/L genotypes may underestimate the effect of the 5-HTTLPR polymorphism. The present study has also considered the A→G SNP and has shown that accounting for A→G SNP does not change the high levels of LDL cholesterol present in L allele (or La allele) carriers. In our study the percentage of people with either Lg/S or Lg/Lg genotype was only 5.91 which also might be too low for a significant A→G SNP impact.

A recent study using a genome-wide association study (GWAS) summary-statistics-based approach found a significant association between 5-HTTLPR polymorphism, human adult height, body mass index, and total cholesterol levels (Majumdar et al., 2022). Since the polymorphism cannot be tested via available SNP arrays, the study used a machine learning algorithm to predict the genotypes of 5-HTTLPR based on the genotypes of eight nearby SNPs. Given the non-linear relationships between cholesterol, impulsivity, and genotype associations, the absence of a straightforward and linear correlation with neurological and neurobehavioral phenotypes in the extensive dataset is unsurprising.

To summarize, the observation that the 5-HTTLPR polymorphism interacts with serum lipid levels, specifically LDL-cholesterol, at a young age implies that this genotype associated to personality may have an early influence that is rele-

vant for lifestyle choices. Though it is known that the *SLC6A4* gene is associated with cholesterol levels and has an influence on cardiovascular diseases through vascular constriction, platelet aggregation and thrombosis (Yildiz et al., 1998) and on risk of death by suicide (Engelberg, 1992), we do not know at present why or how this mechanism works. It is possible that serum cholesterol levels and central serotonergic function co-vary without being in fact causally linked because their association is brought about by associations with a third variable.

Serum lipid and BMI levels did not differ between *HTR2A* -1438A/G polymorphism genotypes.

5.3.3. The effect of *HTR2A* gene polymorphism on impulsivity depends on cholesterol levels (Paper II)

While *HTR2A* -1438A/G polymorphism is associated with Maladaptive Impulsivity, this effect can differ according to serum lipid levels. Our analysis indicated that LDL cholesterol and sex had an interaction effect on Disinhibition, Thoughtlessness and Maladaptive Impulsivity ($F(2, 462)=3.97$, $p<0.05$ $F(2, 462)=6.30$, $p<0.05$ and $F(2, 462)=6.27$, $p<0.05$, respectively), while total cholesterol had an interaction effect with sex on Thoughtlessness and Maladaptive Impulsivity ($F(2, 462)=4.45$, $p<0.05$ and $F(2, 462)=4.42$, $p<0.05$, respectively), but not on Disinhibition. Female sex and higher LDL or total cholesterol levels together had a positive (raising) interaction effect on impulsivity measures ($t(2, 462)=2.10$, $p<0.05$ for total cholesterol and Maladaptive impulsivity and $t(2, 462)=2.50$, $p<0.05$ for LDL cholesterol and Maladaptive Impulsivity). Only for Maladaptive Impulsivity there was an interaction effect between genotype and sex ($F(2, 462)=3.02$, $p<0.05$ for total cholesterol and $F(2, 462)=3.43$, $p<0.05$ for LDL cholesterol). Genotype interaction effect with sex and LDL cholesterol levels was found for Disinhibition, Thoughtlessness and Maladaptive Impulsivity ($F(2, 462)=4.16$, $F(2, 462)=3.87$, $p<0.05$ and $F(2, 462)=4.72$, $p<0.01$, respectively). Total cholesterol had an interaction effect with genotype and sex in Thoughtlessness and Maladaptive Impulsivity ($F(2, 462)=3.31$, $p<0.05$ and $F(2, 462)=3.73$, $p<0.05$, respectively). Contrast analysis indicated that female A/A homozygotes with high total or LDL cholesterol had higher impulsivity measures ($t(2, 462)=2.22$, $p<0.05$ for both LDL and total cholesterol), but in female G/G homozygotes, high total or LDL cholesterol resulted in lower impulsivity measures ($t(2, 462)=-2.72$, $p<0.01$ and $t(2, 462)=-3.07$, $p<0.01$, respectively).

For better interpretation of the results, impulsivity measures were divided in addition to sex and genotype according cholesterol quartiles (Table 12). In the lowest quartile there were no differences in impulsivity, but in the highest quartile of total cholesterol the female G/G homozygotes had the lowest Thoughtlessness and Maladaptive Impulsivity measures (($F(2,118)=4.62$, $p=0.02$) and ($F(2,118)=6.19$, $p=0.02$), respectively) and female A allele carriers had the highest measures. Only in highest quartile of LDL cholesterol, males with the A/G genotype had the lowest Thoughtlessness that was significantly different from the corresponding female group ($F(2,110)=4.58$, $p=0.02$).

Table 12. Descriptive statistics depicting different facets of impulsivity in the first and fourth quartile of total and LDL cholesterol based on *HTR2A* genotype.

	Female			Male		
	A/A	A/G	G/G	A/A	A/G	G/G
Disinhibition						
TC 1	19.57 ± 5.83	18.31 ± 3.86	16.82 ± 3.73	19.67 ± 3.06	17.00 ± 4.64	16.08 ± 3.10
TC 4	20.44 ± 3.50	18.37 ± 5.40	15.86 ± 4.14	13.83 ± 3.25	16.00 ± 3.97	17.63 ± 4.30
LDL 1	17.70 ± 4.83	17.76 ± 3.88	16.76 ± 3.72	23.50 ± 0.71	17.86 ± 4.87	16.84 ± 3.93
LDL 4	20.33 ± 3.93	18.41 ± 3.94	17.32 ± 4.36	15.70 ± 5.60	16.57 ± 4.18	17.59 ± 4.54
Thoughtlessness						
TC 1	16.86 ± 4.14	17.40 ± 4.70	16.77 ± 4.72	21.00 ± 2.65	15.88 ± 4.41	15.96 ± 4.33
TC 4	18.56 ± 7.11	**18.04 ± 5.10***	13.94 ± 5.08	14.67 ± 5.82	14.58 ± 4.35	16.00 ± 3.68
LDL 1	16.20 ± 3.79	16.13 ± 4.81	15.95 ± 4.58	22.00 ± 1.41	16.79 ± 5.21	15.82 ± 5.07
LDL 4	19.00 ± 8.15	18.50 ± 4.16	15.00 ± 4.64	16.10 ± 5.02	**14.39 ± 4.09****	16.32 ± 3.86
Maladaptive Impulsivity						
TC 1	36.43 ± 9.47	35.71 ± 7.82	33.59 ± 7.42	40.67 ± 5.51	32.88 ± 8.33	32.05 ± 6.86
TC 4	**39.00 ± 10.16***	**36.41 ± 9.58***	29.81 ± 8.33	28.50 ± 8.96	30.58 ± 7.37	33.63 ± 7.04
LDL 1	33.90 ± 7.52	33.89 ± 7.91	32.71 ± 7.23	45.50 ± 0.71	34.64 ± 9.28	32.67 ± 8.59
LDL 4	39.33 ± 11.48	36.91 ± 6.63	32.32 ± 8.12	31.80 ± 9.85	30.96 ± 7.38	33.91 ± 7.50

Impulsivity: means ± SD. CHL1<4.1 mmol/l, CHL4>5 mmol/l, LDL1<2.26 mmol/l and LDL>43.22 mmol/l.

* $p<0.05$, vs female G/G.

** $p<0.05$, vs female A/G.

To summarize, subjects with the risk genotype, the A/A, of the *HTR2A* -1438A/G polymorphism had higher scores of Maladaptive Impulsivity, but not Adaptive Impulsivity. In females, high LDL and total cholesterol levels increased the genotype effect. In males, in the highest quartile of total or LDL cholesterol the genotype effect was altered, with G/G homozygotes having the highest Maladaptive Impulsivity levels.

The essential symptoms of substance use disorder and attention deficit hyperactivity disorder include elevated levels of impulsivity, which have been found to be associated with aggressive behaviour and suicidal tendencies. A wide range of studies has shown a linkage between disinhibition and thoughtlessness and the serotonergic neurotransmission (Tarter et al., 2004). Interestingly, the other side of the coin, a cognitive style characterized by fast decision making and excitement seeking, was not found associated with this genotype, supporting the notion by Dickman (1990) on distinct functional and dysfunctional components of impulsivity.

Cholesterol levels are related to impulsivity and may also reflect central serotonergic activity. 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 association between elevated and low cholesterol levels and serotonergic dysfunction is expected to occur through separate pathways. In the present analysis cholesterol levels did not have a main effect on impulsivity measures, but rather had complex interaction effect with the *HTR2A* genotype and sex where high cholesterol levels were associated with higher impulsivity measures. Thus, in females high LDL or total cholesterol levels increased the -1438A/G genotype effect, resulting in very high Maladaptive Impulsivity, but in males high cholesterol levels lowered the effect of the A allele of the -1438A/G polymorphism and rather resulted in G/G homozygotes having high Maladaptive Impulsivity levels.

Several studies have already suggested that the relationship between cholesterol and psychological variables may be non-linear. For example, Troisi (2011) displayed a significant difference in attentional impulsivity between individuals with total cholesterol levels lower than 4.3 mmol/l and the remainder of the sample, with low cholesterol related to high impulsivity. Yet, only a weak linear association was discovered over the whole cholesterol range (2.8–7.6 mmol/l). A study by Pozzi et al. (2003) used a similar cut-off point. They found that the significant negative relationship between total and HDL cholesterol and impulsivity was only present in men whose total cholesterol levels were less than 3.7 mmol/l. In our analysis, cholesterol was used as a continuous variable. No cut-off values emerged where the effect on impulsivity would have been greater than in the rest of the sample. When the impulsivity levels of people from the first (≤3.8 mmol/l) and last quartiles (≥5.3 mmol/l) of cholesterol were compared, no differences emerged.

The *HTR2A* -1438A/G polymorphism effect was present in Maladaptive Impulsivity in both sexes. When looking at subscales, the effect of Disinhibition

was found only in women and not in men, while in the case of Thoughtlessness, the effect was clearer in men. The role of sex in impulsivity levels can be linked with sex differences in central serotonergic function that have previously been described (Soloff et al., 2014). In the highest quartile of both total and LDL cholesterol, the elevating effect of the A/A genotype was strengthened in females, but for males in the highest quartile of both total and LDL cholesterol, carrying the A/A genotype resulted in lowering Maladaptive impulsivity measures compared to men with the A/A genotype in the lowest cholesterol quartile. This finding highlights the importance of sex in the analysis of gene and behavioural interactions. While taken separately, higher total and LDL cholesterol levels, female sex, and *HTR2A* -1438A/G polymorphism all lead to higher impulsivity measures. Yet, the complexity of the interaction is emphasized by the finding that, despite not being a statistically significant effect, male A/A homozygotes in the lowest quarter of total or LDL cholesterol had very high measures of Maladaptive Impulsivity that would be compatible with the majority of findings in the literature.

5.4 Impulsivity and environment

5.4.1 Impulsivity and stressful life events

Environmental factors, including stress, have been shown to be important risk factors for the development of impulsivity and impulsivity-related psychopathologies. Our analysis indicated that males who reported greater numbers of stressful life events (SLEs) at 15 years had higher Thoughtlessness and Disinhibition levels at the same age ($F(1, 210)=5.89$, $p=0.02$; $F(1, 212)=11.68$, $p<0,001$, respectively). Males with greater reported numbers of SLE at 18 years had higher Thoughtlessness and Excitement seeking levels at the respective age ($F(1, 381)=7.20$, $p=0.008$; $F(1, 381)=8.21$, $p=0,004$, respectively).

Females who reported greater numbers of stressful life events at 15 or at 18 years had at both respective ages higher Thoughtlessness levels ($F(1, 250)=5.66$, $p=0.02$; $F(1, 498)=5.87$, $p=0.02$, respectively). Additionally, females with higher numbers of SLEs at 18 years had higher Disinhibition levels ($F(1, 500)=6.12$, $p=0.01$), Table 13.

Table 13. ANOVA analysis indicating the effect of high or low SLEs reported at 15 and 18 years on different facets of impulsivity measured at the same age in males and females separately.

	MALES					FEMALES				
	Low SLE		High SLE			Low SLE		High SLE		
15 years	Mean	SEM	Mean	SEM	F	Mean	SEM	Mean	SEM	F
Disinhibition	17.00	0.29	**18.48****	0.32	11.68	18.12	0.31	18.88	0.33	2.87
Thoughtlessness	17.40	0.37	**18.72***	0.40	5.89	17.69	0.38	**18.98***	0.39	5.66
Excitement seeking	22.67	0.39	23.63	0.43	2.75	22.08	0.40	23.05	0.42	2.80
Fast decision making	19.12	0.35	19.39	0.38	0.28	17.89	0.36	18.22	0.37	0.43
18 years										
Disinhibition	16.52	0.29	17.30	0.30	3.38	17.79	0.25	**18.76***	0.30	6.12
Thoughtlessness	16.87	0.32	**18.12***	0.34	7.20	17.54	0.27	**18.58***	0.33	5.87
Excitement seeking	21.01	0.30	**22.27***	0.32	8.21	21.08	0.28	21.20	0.34	0.08
Fast decision making	18.96	0.27	19.29	0.29	0.70	17.48	0.25	17.36	0.30	0.09

Data are expressed as mean ± SEM, means marked in bold and * have significant difference between SLE groups at $p < 0.05$, ** are significant at $p < 0.001$.

Environmental factors, such as stress, pose a substantial risk for impulsivity and psychopathologies associated with impulsivity. There is a positive correlation between the number of SLEs experienced by males at 15 and 18 years and their levels of Thoughtlessness and Disinhibition. Similarly, women who have experienced more SLEs at 18 years also exhibit greater levels of Thoughtlessness and Disinhibition.

5.4.2. Serum lipid levels, impulsivity and stressful life events

Previous results have revealed that a high number of SLEs leads to higher Maladaptive Impulsivity levels. To study additionally how impulsivity differs according to both high and low serum lipid levels as well as high and low reported stressful life events, an ANOVA was conducted with SLEs and serum lipid levels as independent variables at both 15 and 18 years of age.

While SLEs reported at 15 years together with serum lipid levels did not have an effect on impulsivity (data not shown), males or females who had experienced more SLEs reported at 18 years had higher levels of the Maladaptive Impulsivity traits, Disinhibition and Thoughtlessness. In both sexes, in addition to high SLEs, high triglyceride levels were associated with high levels of Maladaptive Impulsivity traits, but only in men did high levels of BMI lead to high levels of Maladaptive Impulsivity traits (Table 14). Men with high SLE and low CHL, HDL, and LDL cholesterol had highest level of Thoughtlessness when compared with other groups.

When analysing the Adaptive Impulsivity traits, it was observed that males with low SLE number at 18 years and low total cholesterol had significantly lower Excitement seeking levels (20.3 ± 0.59) than males with high SLE number and low total cholesterol (22.4 ± 0.58, $p<0.05$) or males with low SLE number and high total cholesterol (22.3 ± 0.57, $p<0.05$). Males with low SLE number and low HDL cholesterol had significantly lower Excitement seeking levels (19.7 ± 0.62) than males with high HDL cholesterol and high SLE number (22.1 ± 0.61, $p<0.01$). There was no effect of serum lipids and SLEs on Fast Decision making in men. Fast Decision making was low in females with a low BMI, regardless of SLEs. There was no effect of serum lipids and SLEs on Excitement seeking in women.

Table 14. Levels of Disinhibition and Thoughtlessness based on high and low SLE at 18 years and first and fourth quartile of BMI or serum lipid levels in males and females separately.

18 years	MALES								FEMALES							
	Disinhibition				Thoughtlessness				Disinhibition				Thoughtlessness			
	Low SLE		High SLE		Low SLE		High SLE		Low SLE		High SLE		Low SLE		High SLE	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Low BMI	**15.1***¤	0.59	17.6	0.61	**16.4**¤	0.69	17.4	0.69	17.7	0.45	18.4	0.61	16.9¤	0.49	19.0	0.67
High BMI	17.1	0.58	17.9	0.63	17.2	0.67	19.6	0.72	17.5	0.48	18.9	0.54	18.0	0.51	18.9	0.58
Low CHL	16.5	0.59	17.8	0.58	**16.7**#	0.62	19.0	0.61	17.5	0.49	18.6	0.59	17.4	0.55	18.5	0.66
high CHL	16.1	0.57	18.0	0.66	16.9	0.59	18.3	0.67	18.6	0.50	19.1	0.60	17.5	0.55	18.8	0.66
low HDL	17.1	0.57	**18.3**¤	0.60	17.2	0.65	18.4	0.66	17.7	0.57	18.8	0.59	18.4	0.61	18.8	0.64
high HDL	15.6	0.56	16.0	0.64	**16.5**¤	0.63	18.0	0.71	18.0	0.51	19.1	0.67	17.6	0.55	18.2	0.73
Low LDL	16.5	0.64	17.8	0.58	**16.7**¤	0.68	19.2	0.62	17.7	0.56	18.6	0.65	17.0	0.57	18.0	0.66
High LDL	16.5	0.58	18.1	0.66	16.5	0.61	17.8	0.69	18.0	0.54	18.9	0.67	17.3	0.54	18.8	0.67
Low TRG	16.5	0.61	17.0	0.56	**16.4**¤	0.66	17.4	0.60	**16.9**¤	0.51	18.1	0.66	17.1	0.54	18.1	0.70
High TRG	16.7	0.57	17.6	0.61	18.1	0.62	19.0	0.65	18.2	0.55	19.0	0.62	17.6	0.59	18.7	0.67

Body mass index (BMI), total cholesterol (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG). Serum lipid levels and BMI were divided based on the quartiles. Low lipid levels mark the first quartile and high lipid levels mark the fourth quartile. #$p<0.05$ different from high SLE, low serum lipids; * $p<0.05$ different from low SLE, high serum lipids; ¤ $p<0.05$ different from high SLE, high serum lipids.

In men, but not women, the combination of high levels of stressful life events (SLE) and low cholesterol levels appears to have an additive effect on the high levels of Maladaptive Impulsivity. This finding aligns with previous research indicating that men are more vulnerable to the adverse effects of low serum lipid levels (Jokinen et al., 2010). Similarly, the heightened vulnerability to stressful life events among men suggests a heightened susceptibility to environmental stressors, further contributing to the severity of Maladaptive Impulsivity. This underscores the complex interplay between biological and environmental factors in shaping impulsivity and highlights the need for sex-specific considerations in understanding and addressing impulsive behaviours.

5.4.3. Serum lipid levels as predictors of impulsivity in subjects with high or low number of stressful life events

To learn whether stressful life events (SLE) reported before or during the school years have a predictive value on impulsivity in young adulthood, predictive analysis was conducted. SLEs reported at 15 years did not influence impulsivity at 25 years (data not shown). In males, SLEs reported at 18 years were a significant predictive factor for all impulsivity measures at 25 years. In females, stressful life events reported at 18 years of age predicted only Maladaptive Impulsivity traits measured at 25 years of age (Table 15).

Table 15. ANCOVA predicting impulsivity measures at 25 years based on stressful life events at 18 years in males and females separately.

	MALES					FEMALES				
	Low SLE		High SLE			Low SLE		High SLE		
	Mean	SEM	Mean	SEM	F	Mean	SEM	Mean	SEM	F
Disinhibition	15.51	0.31	**17.52****	0.33	20.03	17.37	0.24	**18.47***	0.32	8.84
Thoughtlessness	15.20	0.36	**16.48***	0.38	5.90	15.18	0.30	**17.04****	0.37	15.40
Excitement seeking	20.72	0.34	**22.05***	0.36	7.28	19.33	0.31	19.39	0.39	0.02
Fast decision making	19.33	0.33	**20.28***	0.35	3.99	17.65	0.29	16.96	0.37	2.16

Data are expressed as mean ± SEM, means marked in bold and * have significant difference between groups at $p < 0.05$, marked with ** are significant at $p < 0.001$. N for males was 300 and for females 432.

To further analyse predictive value of serum lipid levels on impulsivity measures depending on the high or low number of SLEs at either 15 or 18 years, analysis were conducted with serum lipid levels as independent variables separately in subjects with high or low SLE number. To illustrate the strength of the association of serum lipids with impulsivity measures, Pearson correlation analysis is additionally presented. Previous results indicated that only Maladaptive Impulsivity

traits Disinhibition and Thoughtlessness are predicted by serum lipids (Table 5) in both sexes, so results for Adaptive Impulsivity traits Fast decision making and Excitement seeking are not presented. SLEs reported at 15 years were not predictive of impulsivity measured at 25 years, so only the results for SLEs reported at 18 years are presented (Table 16).

In both males and females, serum lipid levels predicted impulsivity mostly when SLEs reported were low. In males with low reported SLEs, both low total and LDL cholesterol measured at 9, 15, and 18 years were predictors of high Disinhibition at 25 years. In males with high reported SLE, low total cholesterol measured at 15 and 25 years predicted high Thoughtlessness at 25 years. In females with low reported SLEs, high BMI levels at 9, 15, 18, and 25 years predicted high Disinhibition at 25 years. As an exception to the trend, in women with high reported SLEs high total and LDL cholesterol measured at 9 years old led to high Disinhibition levels at 25 years old. This deviation highlights the different effect high and low lipid levels have on impulsivity in different sexes.

Both, stressful life events and cholesterol levels, have a correlation with Maladaptive Impulsivity. In the current analysis it became evident, that in males total and LDL cholesterol predicts Disinhibition only when the stressful life events number remains low. It is possible, that environmental influences exert an effect that conceals the impact of serum lipids on impulsivity. This finding suggests a potential masking effect of environmental influences on the impact of serum lipids on impulsivity.

Serum lipid levels predict impulsivity differently depending on the presence of stressful life events (SLEs). The sex-specific impacts highlight the differential effects of high and low lipid levels on impulsivity in men and women.

Table 16. BMI and serum lipids measured at 9, 15, 18 and 25 years predicting Disinhibition and Thoughtlessness at 25 years in subjects with low or high number of SLEs at 18 years males and females separately.

		MALES								FEMALES							
		Disinhibition				Thoughtlessness				Disinhibition				Thoughtlessness			
		Low SLE		High SLE		Low SLE		High SLE		Low SLE		High SLE		Low SLE		High SLE	
		F	r	F	r	F	r	F	r	F	r	F	r	F	r	F	r
9	BMI	0.00	0.00	0.94	0.02	4.92*	**-0.21**	0.53	0.12	4.17*	**0.17**	0.90	0.17	0.87	-0.10	0.22	0.11
	CHL	8.01**	**-0.31**	0.45	-0.13	3.24	-0.23	0.53	-0.06	0.10	0.01	2.82	**0.28**	0.07	-0.03	1.62	0.14
	HDL	0.99	-0.12	0.15	-0.06	0.50	-0.07	0.00	-0.04	4.38*	**0.18**	0.00	-0.07	0.68	0.07	1.31	0.08
	LDL	6.02*	**-0.30**	0.80	-0.09	2.14	-0.21	0.55	-0.03	0.18	-0.06	3.78	**0.30**	0.39	-0.06	1.15	0.10
	TRG	2.36	-0.14	0.30	-0.15	2.10	-0.16	1.42	-0.10	0.00	0.00	1.59	0.24	0.06	0.02	0.00	0.08
15	BMI	3.33	0.15	4.34	**0.20**	0.35	-0.04	0.96	0.20	10.01**	**0.15**	3.17	0.26	1.86	-0.16	0.13	0.22
	CHL	8.92**	**-0.39**	3.82	-0.10	2.07	**-0.25**	4.74*	-0.17	2.08	0.08	3.09	0.14	0.35	0.06	0.14	0.16
	HDL	4.59*	-0.20	1.58	-0.06	0.56	-0.05	0.64	0.01	0.02	0.11	0.16	-0.15	0.35	0.08	0.27	0.05
	LDL	4.98*	**-0.36**	3.49	-0.10	0.90	**-0.25**	3.81	-0.16	0.85	0.05	3.91	0.23	0.02	0.03	0.20	0.15
	TRG	1.03	0.01	0.06	-0.05	1.56	0.01	0.34	-0.01	0.35	-0.02	0.00	0.17	0.88	0.15	0.54	0.11
18	BMI	2.88	0.18	7.88*	**0.23**	0.12	0.05	1.48	0.19	6.01*	**0.12**	1.72	0.19	0.83	-0.16	0.02	0.10
	CHL	4.31*	**-0.29**	0.38	-0.06	4.45*	-0.20	0.21	0.04	0.48	0.01	0.08	0.12	0.17	0.03	1.04	0.16
	HDL	2.22	-0.18	0.42	0.15	1.36	-0.19	0.02	0.17	0.76	0.17	0.60	-0.13	0.04	0.15	0.20	0.09
	LDL	2.91	**-0.24**	0.81	-0.11	4.26*	-0.19	0.51	-0.03	0.01	-0.03	0.26	0.21	0.05	-0.04	0.80	0.12
	TRG	0.04	0.08	4.48	0.10	0.00	0.15	1.64	0.05	0.00	-0.02	0.25	**0.27**	0.08	0.07	0.18	**0.29**
25	BMI	2.48	0.15	0.97	0.13	0.82	-0.04	0.56	0.21	7.42**	**0.12**	1.32	0.12	0.00	-0.13	0.09	0.18
	CHL	1.14	-0.21	1.94	-0.14	1.15	-0.17	4.82*	-0.10	0.00	0.04	0.51	0.12	1.75	-0.07	0.50	-0.06
	HDL	3.34	-0.21	0.15	0.15	0.65	-0.18	0.05	0.00	0.17	0.20	0.00	-0.07	2.64	0.04	0.01	-0.04
	LDL	0.45	-0.15	2.22	-0.17	0.21	-0.12	4.85*	-0.07	0.07	-0.09	0.34	0.11	0.57	-0.13	0.25	-0.05
	TRG	0.08	0.09	2.04	-0.19	0.27	0.16	3.61	-0.10	0.20	-0.03	0.02	0.10	0.38	0.00	0.97	-0.14

F statistic of ANCOVA and correlation coefficient r. Body mass index (BMI), total cholesterol (CHL), HDL cholesterol (HDL), LDL cholesterol (LDL), triglycerides (TRG). F statistic is significant at *$p<0.05$, **$p<0.01$. Correlations marked in bold are significant at $p<0.05$.

CONCLUDING REMARKS

The goal of this thesis was to shed light on how the different functional gene variants of the serotonin system, serum lipid levels, and impulsivity interact with each other. We have found that these factors, all major factors in psychopathologies and behaviour disturbances, do not have a straightforward cause-and-effect relationship and instead interact in a complex and dynamic way. Both low and high ends of central serotonergic functioning are associated with high impulsivity levels, suggesting a non-linear relationship. Several factors, including age, sex, cholesterol fractions, genetic variability, and different facets of impulsivity, further complicate the interactions. Our study used a longitudinal approach and was based on a representative birth cohort sample, giving us an opportunity to gain insights into the nuanced interactions of these parameters. We found that the significance of these factors varied across demographic groups, highlighting the importance and necessity of considering them in impulsivity research.

The findings of our study highlight the fact that there are huge inconsistencies in previous literature, but also provide a fresh perspective for understanding why this heterogeneity of results exists in the first place. Significant factors contributing to the discrepancies in previous studies include neglecting environmental influences and relying on convenience samples or small sample sizes, potentially biassing their results. In contrast, our study addressed these limitations by incorporating a diverse and representative sample, thereby ensuring the broad applicability of our findings. The longitudinal design of our study provided the opportunity to monitor how the interaction effects vary as the subjects transition from children into adults. Additionally, we showed results for both men and women separately, thus eliminating any sex bias and visualising how associations between impulsivity, genes of the serotonergic system, and serum lipid levels differ between sexes.

There are numerous opportunities for further research in this field. Additional studies could explore factors that influence impulsivity, such as socioeconomic status or cultural measures, to provide a more comprehensive understanding of this complex phenomenon. Furthermore, longitudinal studies tracking impulsivity over extended periods of time could explain the fundamental principles of impulsive behaviour and its subsequent impact on psychological health.

Finally, our study adds to what we know about impulsivity by looking at how it is connected to serum lipid levels and different functional genes in the serotonin system in different demographic groups. The study emphasizes complex and interconnected associations between those factors, which rely not only on current environmental effects but also on past experiences. Further research in this area may contribute to our better comprehension of the multifaceted nature of impulsivity and its implications on mental health and general well-being.

CONCLUSIONS

This dissertation aimed to elucidate the association of impulsivity with genetic markers of the serotonin system and serum lipid levels during childhood and young adolescence in highly representative birth cohort samples. Papers I–IV and data presented first in the current thesis have led to the following answers to the research questions:

1. Summary of the recent findings on the association of serum lipid levels with impulsivity and violence was given. Demographic factors and presence of psychiatric disorders can play a role in the discrepancies present in previous literature. Men seem to be more sensitive to low cholesterol levels as the association between low cholesterol levels and aggression is found mostly in men. Cholesterol may play a role as a moderator of the serotonergic function and interact with associations between relevant gene variants and impulsivity. Lowering cholesterol levels with statins brings about several changes in the serotonergic system, nerve cell membrane microviscosity and behaviour, and needs to be done with precaution in susceptible individuals. Cholesterol levels could serve as a biological risk marker for violence and suicidal tendencies in psychiatric patients with depression and schizophrenia. **(Paper III).**
2. Cross-sectional analysis of impulsivity and risk behaviour with serum lipid levels did not result in systematic outcomes. The serum lipid levels did not have an effect on suicide tendency or suicide ideation in 18 year old males or females and had no effect on suicide risk in 25 year old females. In 25 year old males high total and LDL cholesterol and triglyceride levels and low HDL cholesterol levels were associated with recent suicide risk, but not with lifetime suicide risk. Suicide risk is most likely in subjects with a mismatch with the general association of cholesterol with impulsivity. **(Paper IV, unpublished data).**
3. Risk behaviour correlated with different facets of impulsivity according to age and sex. In males most of risk behaviours were correlated with Adaptive Impulsivity and only to some extend in the youngest years with Maladaptive Impulsivity. In women however risk behaviour correlated more with Maladaptive Impulsivity though all ages. Men and women who had suicide ideation or attempted suicide at 18 or had been rated to have high suicide lifetime risk at 25 had high Maladaptive Impulsivity levels. **(Unpublished data).**
4. Low total and LDL cholesterol levels predict high impulsivity in adult males starting from early childhood itself, which continues throughout adolescence. Total and low-density lipoprotein cholesterol measured in boys aged 9, 15 and 18 years predicted Disinhibition and Thoughtlessness in 25 year old young adults. **(Paper IV).**

5. In men, but not in women high stressful life events and low cholesterol levels have an additive effect on high levels of Maladaptive Impulsivity. In both males and females, serum lipid levels predicted Maladaptive Impulsivity mostly when reported stressful life events were low. In males with low reported stressful life events, both low total and LDL cholesterol measured at 9, 15, and 18 years were predictors of high Disinhibition at 25 years. In females with low reported stressful life events, high BMI levels at 9, 15, 18, and 25 years predicted high Disinhibition at 25 years. The number of stressful life events experienced by men and women at 18 years and males at 15 years correlated positively with levels of Maladaptive Impulsivity. (**Unpublished data).**
6. Children and adolescents carrying the L allele of the 5-HTTLPR polymorphism had higher levels of cholesterol and in particularly LDL cholesterol. Serum lipid levels did not differ different between *HTR2A* -1438A/G polymorphism genotypes. **(Paper I, unpublished data).**
7. The A/A genotype of -1438A/G *HTR2A* polymorphism was associated with significantly higher Maladaptive, but not Adaptive Impulsivity traits in both females and males in 25 year olds. High LDL or total cholesterol levels in females increased the -1438A/G genotype effect resulting in very high Maladaptive Impulsivity. In males with highest quartile total or LDL cholesterol levels the genotype effect was modified with A allele carriers having lower Maladaptive Impulsivity levels than G/G homozygotes. Serum lipid levels did not differ between *HTR2A* -1438A/G polymorphism genotypes. There was no main effect of 5-HTTLPR polymorphism on impulsivity. **(Paper II, unpublished data).**

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SUMMARY IN ESTONIAN

Impulsiivsus, seerumi lipiidid ja serotoniinisüsteemi funktsionaalsed geenivariandid

Impulsiivsus mängib olulist rolli erinevate psüühikahäirete, sealhulgas isiksuse- ja käitumishäirete, sõltuvussündroomi ja enesetappude puhul. Impulsiivsus väljendub tavaliselt ebaküpsetes ja sageli ohtlikes tegevustes, mis toovad oma mõtlematusega kaasa negatiivseid tagajärgi. Kui traditsioonilised seisukohad rõhutavad ainult impulsiivsuse patoloogilisi aspekte, siis Dickman (1990) teeb vahet funktsionaalsel ja düsfunktsionaalsel impulsiivsusel. Funktsionaalne impulsiivsus hõlmab kiiret, kuigi vigadele kalduvat otsustamist, mis võib olla optimaalsetes tingimustes mõnikord kasulik. Seevastu düsfunktsionaalset impulsiivsust iseloomustab aeglase, metoodilise mõtlemise puudumine siis, kui see on vajalik. Enamik uuringuid on leidnud, et impulsiivsus on seotud madalama serotonergilise võimekusega.

Kolesteroolitaset on seostatud psühhiaatriliste ja käitumishäiretega, samas on üldtunnustatud, et just madalama kolesteroolitasemega inimestel on nendeks häireteks suurem risk. Mitmed uuringud on siiski näidanud, et kolesterooli ja psühholoogiliste näitajate vaheline seos ei pruugi olla sirgjooneline ja seda võivad mõjutada sellised tegurid nagu sugu ja vanus. Madal kolesteroolitase võib avaldada negatiivset mõju käitumisele mõjudes läbi serotoniinisüsteemi.

Enamik lipiidide ainevahetust ja impulsiivsust käsitlevaid uuringuid on läbi viidud kas eakatel või kliinilistes valimitel. Käesoleva väitekirja eesmärk oli selgitada impulsiivsuse seost serotoniinisüsteemi geneetiliste markerite ja seerumi lipiidide tasemega lapsepõlves ja noorukieas esinduslikus sünnikohordis. Analüüs põhines Eesti laste isiksuse käitumise ja tervise uuringu (ELIKTU) sünnikohordi representatiivsete valimite andmetel.

Madalad LDL- ja üldkolesterooli tasemed, mida mõõdeti lapsepõlves ja noorukieas vanuses 9, 15 ja 18, ennustasid kõrget maladaptiivset impulsiivsust täiskasvanud meestel. See, et seos oli olemas ainult maladaptiivse impulsiivsuse ja kolesteroolitaseme vahel näitab, et kolesterool mõjutab selektiivselt neuroloogilisi mehhanisme, mis vastutavad impulsiivsuse düsfunktsionaalsete aspektide eest. Meie tulemused rõhutavad lapsepõlve seerumi lipiidide taseme tähtsust impulsiivsusele täiskasvanueas ja on kooskõlas neuroloogiliste uuringutega, mis käsitlevad kolesterooli rolli lapsepõlves ja varases noorukieas.

Meie uuring näitas seost 5-HTTLPR polümorfismi ja seerumi lipiidide taseme vahel. Täpsemalt, L-alleeli kandvatel lastel ja noorukitel olid kõrgemad LDL- ja üldkolesterooli tasemed. Samas puudus 5-HTTLPR polümorfismil otsene mõju impulsiivsusele nii lastel, noorukitel kui ka täiskasvanutel. Seerumi lipiidide tase ei erinenud *HTR2A* -1438A/G polümorfismi genotüüpide vahel. 5-HTTLPR polümorfism mõjutab seerumi lipiidide taset, eriti LDL-kolesterooli, juba noores eas, ning viitab sellele, et see isiksusega seotud genotüüp võib varakult mõjutada elustiili valikuid.

Serotoniini 2A retseptori geeni -1438A/G polümorfismi A/A genotüüp korreleerus oluliselt kõrgema maladaptiivse impulsiivsusega, kuid mitte adaptiivse impulsiivsusega 25-aastastel meestel ja naistel. Naistel suurendas -1438A/G genotüübi mõju kõrgem LDL- või üldkolesterooli tase. Seevastu kõrge kolesterooliga A alleeliga meestel oli maladaptiivse impulsiivsuse tase võrreldes G/G homosügootidega madalam. Need leiud rõhutavad seerumi lipiidide tasemetega arvestamise tähtsust, kuna nad mõjutavad serotonergilisi funktsioone ja võivad mõju omada psühhiaatrilistele häiretele, sealhulgas impulsiivsusele ja suitsidaalsusele.

Riskikäitumine varieerub koos impulsiivsuse erinevate aspektidega, mida mõjutavad vanus ja sugu. Meie valimis oli meestel riskikäitumine nooremas eas enamasti seotud adaptiivse impulsiivsusega ja vähemal määral maladaptiivse impulsiivsusega. Naiste puhul oli riskikäitumine aga tugevamalt seotud maladaptiivse impulsiivsusega kõigis vanusegruppides. Meie analüüs ei näidanud siiski selget seost riskikäitumise, impulsiivsuse ja seerumi lipiidide taseme vahel.

Maladaptiivne impulsiivsus oli kõrgem inimestel, kellel oli 18-aastaselt enesetapumõtteid või -katseid või kellel hinnati 25-aastaselt eluaegne enesetapurisk kõrgeks. Samas ei mõjutanud seerumi lipiidide tase 18-aastaste seas enesetapukatseid ega -mõtteid ja 25-aastaste naiste puhul enesetapuriski. 25-aastastel meestel oli aga kõrgem üldkolesterool ja LDL-kolesterool koos madalama HDL-kolesterooliga seotud hiljutise enesetapuriskiga, samas seost ei leitud eluaegse enesetapuriskiga. Tulemus viitab sellele, et meie valimis on enesetapu risk kõrgem nendel inimestel, kelle puhul kolesterooli ja impulsiivsuse seos ei allu üldmustrile.

Leidsime 18-aastaste meeste ja naiste ja 15-aastaste meeste stressirohkete elusündmuste arvu ja nende maladaptiivse impulsiivsuse taseme vahel positiivse korrelatsiooni. Meestel oli stressirohkete elusündmuste suurel arvul madala kolesteroolitasemega koosmõju maladaptiivsele impulsiivsusele, muutes mehed naistest haavatavamaks nende tegurite kombineeritud mõju suhtes.

Nii meestel kui ka naistel ennustas madal seerumi lipiidide tase kõrget maladaptiivset impulsiivsust ainult siis, kui stressirohkeid elusündmusi oli vähe. Meestel, kellel stressirohkeid elusündmusi oli vähe, ennustasid nii 9, 15 kui ka 18 aasta vanuses mõõdetud madal LDL-ja üldkolesterooli tase kõrget pidurdamatust 25 aasta vanuses. Naistel, kellel stressirohkeid elusündmusi oli vähe, ennustas kõrget pidurdamatust 25 aasta vanuses hoopis kõrge kehamassiindeksi tase mõõdetuna 9, 15, 18 ja 25 aasta vanuselt. Soospetsiifilised mõjud rõhutavad kõrgete ja madalate lipiidide tasemete erinevat mõju impulsiivsusele meestel ja naistel. Võimalik, et keskkonna mõju impulsiivsusele on tugevam kui seerumi lipiidide mõju. Seega on keskkonnal potentsiaalselt maskeeriv efekt seerumi lipiidide mõjule impulsiivsusele.

Antud väitekiri toob selgust varasemas kirjanduses esinevate lahknevuste võimalikesse põhjustesse. Kuigi mõnes varasemas uuringus on jõutud meie järeldustest erinevate tulemusteni, ei ole meie uuring otsese vastuolus nendega, vaid toob pigem juurde täiendavaid selgitusi. Üks põhitegur, mis aitab kaasa varasema kirjanduse vastuolu mõistmisele, on segavate faktoritega arvestamine. On erine-

vaid tegureid nagu vanus, sugu, kolesterooli fraktsioonid, geneetiline varieeruvus ja impulsiivsuse erinevad tahud, mis muudavad koostoimed keeruliseks. Paljudes varasemates uuringutes on kas keskkonnamõjud tähelepanuta jäetud või on tuginetud mugavusvalimitele või väikestele valimitele ning see võis tulemusi moonutada. Seevastu meie uuringus kasutati mitmekesist ja representatiivset valimit, suurendades seeläbi tulemuste üldistatavust. Leidsime, et segavate faktorite olulisus varieerus erinevates demograafilistes rühmades, rõhutades kõigi asjakohaste muutujate arvestamise tähtsust impulsiivsuse uurimisel veelgi.

Kokkuvõttes aitavad meie tulemused selgitada impulsiivsuse, seerumi lipiidide taseme, geneetiliste tegurite ja keskkonnategurite omavahelist keerulist koostoimet ja anda väärtusliku ülevaadet impulsiivsuse mitmekülgsest olemusest.

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仕方がない

ORIGINAL PUBLICATIONS

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Publikatsioonid

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