From THE DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

CHOLESTEROL AND APOLIPOPROTEIN E IN SUICIDAL BEHAVIOR

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Karolinska Institutet

Stockholm 2016

Published by Karolinska Institutet.
Printed by E-print 2016

ISBN 978-91-7876-392-6

Cholesterol and Apolipoprotein E in Suicidal Behavior

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To the first doctor(s)

facts/clouds
slithering sky;
ever changing

questions/stars
hearthing mind;
never ending

ABSTRACT

Introduction

Low cholesterol has repeatedly been associated with an increased risk of suicidal and violent behavior. The increase in risk is believed to be associated with alterations in serotonergic signaling, which is associated with low cholesterol. Apolipoprotein E is an important factor in cholesterol metabolism, especially in the CNS, where it is involved in uptake, redistribution, and excretion of cholesterol. There are only a few studies dealing with apolipoprotein E in relation to suicide and suicidal behavior.

Aim

The overall aim of this thesis was to study a possible relationship between cholesterol, apolipoprotein E, and serotonin with respect to suicidal and violent behavior in patients with a recent suicide attempt.

Methods

This thesis is based on two clinical studies on patients having made a recent suicide attempt, all recruited at the Karolinska University Hospital. The suicide attempters (N = 181) were diagnosed and evaluated using a number of clinical rating scales measuring suicide intent, interpersonal violence, and depression severity. Samples of blood and cerebrospinal fluid were acquired for the analysis of biomarkers, primarily the serotonergic metabolite 5-HIAA, total serum cholesterol, and ApoE in both plasma and CSF.

Results

Total serum cholesterol was associated with the serotonergic metabolite CSF 5-HIAA. Low serum total cholesterol was found to be associated with the effect of exposure to violence as a child with respect to the risk of violent behavior as an adult. Plasma apolipoprotein E was found to be associated with the number of previous suicide attempts and repeater status, while CSF apolipoprotein E was associated with seriousness of the suicide attempt as measured by reversibility of the method of the current suicide attempt.

Conclusions

Our findings further indicate associations between cholesterol, factors involved in cholesterol metabolism, the serotonergic system, and suicidal and violent behavior. Total serum cholesterol appears to correlate with CSF 5-HIAA in suicide attempters, low total serum cholesterol may be a factor in the “Cycle of Violence” and ApoE may be related to the seriousness of the suicidal behavior.

LIST OF SCIENTIFIC PAPERS

I. **Asellus P**, Nordström P, Jokinen J. Cholesterol and CSF 5-HIAA in attempted suicide. *Journal of Affective Disorders* 2010, 125(1-3):388-92.

II. **Asellus P**, Nordström P, Nordström AL, Jokinen J. Cholesterol and the "Cycle of Violence" in attempted suicide. *Psychiatry Research* 2014, 215(3):646-50

III. **Asellus P**, Nordström P, Nordström AL, Jokinen J. Plasma apolipoprotein E and severity of suicidal behavior. *Journal of Affective Disorders* 2016, 190:137-42.

IV. **Asellus P,** Nordström P, Nordström AL, Jokinen J. CSF apolipoprotein E in attempted suicide. *Manuscript.*

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LIST OF ABBREVIATIONS

CSF	Cerebrospinal fluid
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
VLDL	Very Low Density Lipoprotein
5-HIAA	5-hydroxyindoleaceticacid (a metabolite of serotonin)
5-HTTLPR	Serotonin-Transporter-Linked Polymorphic Region
TPH1	Tryptophan Hydroxylase 1
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
KIVS	Karolinska Interpersonal Violence Scale
DSM-III-R	The Diagnostic and Statistical Manual of Mental Disorders, Third Revised Edition
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
MADRS	Montgomery-Åsberg Depression Rating Scale
SCID	Structured Clinical Interview for DSM-IV or DSM-III-R, Axis 1 Disorders (SCID-I) and Axis 2 Disorders (SCID-II)

1 INTRODUCTION

1.1 SUICIDE AND SUICIDAL BEHAVIOR

Suicide is a leading cause of death, being in the top 10 most common causes of death in most countries and, in younger individuals, age 15–34, suicide is among the top three causes of death (McGirr and Turecki, 2007).

The etiology of suicide and suicidal behavior is diverse. There is, however, considerable evidence that suicide attempts and suicide attempters may be grouped into potentially clinically relevant subgroups (Rapeli and Botega, 2005). In an early classification of suicide attempters by cluster analysis, three main groups were found: (1) a group with repeated suicide attempts, taking small doses of medication and representing a low risk of death with behavior mainly motivated by interpersonal difficulties; (2) a second smaller group, which made severe attempts with high self-destructive motivation using mainly violent methods; and (3) the third and smallest group with a large number of suicidal gestures and many attempts, with the attempts generally being relatively mild in nature and creating reciprocal hostility with regard to the psychiatrists (Paykel and Rassaby, 1978).

Suicide and suicidal behavior have been associated with traumatic or stressful life events, addiction and substance abuse, accidental suicide due to self-harm-gone-wrong, and to untreated depression (Pompili et al., 2011, Turecki and Meaney, 2014). However, whether or not different suicides are etiologically related to each other is less certain (McGirr and Turecki, 2007) since suicide and suicidal behavior may be premeditated or impulsive, violent or nonviolent. Suicidal behavior has been linked to such aspects of personality as extroversion in men (Hirvikoski and Jokinen, 2012) and there may be behavioral phenotypes associated with certain types of suicide and suicidal behavior (Dumais et al., 2005; Turecki, 2005; McGirr and Turecki, 2007)

Furthermore, there are indications that suicide and suicidal behavior may be related to certain executive dysfunctions. Above and beyond the general decline in cognitive performance associated with depression, suicidal behavior has been associated with deficits in memory, working memory, and attention control, unrelated to deficits associated with the afore-mentioned affective disorder (Keilp et al., 2013; Keilp et al., 2014).

It is, in fact, debatable whether suicide and suicidal behavior should be considered to be a psychiatric symptom, an illness in itself, or as a symptom of executive difficulties. Furthermore, there is also the possibility of so-called “rational suicides” (Ho, 2014).

Studying suicide and suicidal behavior poses several difficulties: the nomenclature defining suicide and suicidal behavior is extensive, there are a number of different scales examining suicidality, and, while being a fairly common cause of death, it is only possible to study completed suicide *post-factum*. It may also be difficult to differentiate between accidents and suicides with intent (Silverman et al., 2007a; Silverman et al., 2007b).

There are several methods for studying suicidality, such as epidemiological, clinical, postmortem, psychological autopsy, etc., with each method having its benefits and drawbacks due to the multifactorial etiology of suicide and suicidal behavior. For instance, in epidemiological studies, the specificity of the diagnosis and symptomatology is often limited while, in clinical studies, each subject is thoroughly examined and, by design, the number of subjects will be small and, in effect, generalizability will often be limited.

1.1.1 Suicidal behavior and violence

As mentioned, violence has always been closely linked to suicidal behavior. Violence and death related to violence have long been suggested to be part of the same spectrum of self-destructive behavior (Holinger 1980; Holinger, 1981).

The association between expressed violence and later suicide may start at an early age since current violent behavior in suicide attempters seems to be associated with violence as a child (Moberg et al., 2014). In male suicide attempters, there may be an association with a family history of suicide and exposure to interpersonal violence and the seriousness and degree of planning of suicide attempts, as well as with the actual risk of suicide (Rajalin et al., 2013).

In retrospective studies, a violent suicide method is a marker for a higher overall expression of lifetime violence and aggression (Dumais et al., 2005). Depressed patients displaying either assaultive or suicidal behavior score higher on tests of hostility, compared to nonviolent patients displaying neither suicidal nor assaultive behavior (Maiuro et al., 1989). There is an ostensible aspect of aggression in every suicide or suicide attempt, be it directed towards the self, as a part of impulsive-aggression or passive aggression, or indirectly directed towards others (Turecki, 2005).

In the first years after homicides among homicidal offenders, the perpetrators have a very high risk of suicide. Most suicides in this group are violent ones (Jokinen et al., 2009). In a study on violent criminal offenders in relation to the risk of suicide that reviewed all Danish suicides during 1994–2006, violent criminal offenders were found to have a significantly increased risk of suicide compared to the general population (Webb et al., 2013).

Interestingly, in violent patients, the relationship between depression and suicide may actually be less significant than in nonviolent patients (Apter et al., 1997).

Furthermore, on comparing other violent offenders with violent offenders displaying suicidal behavior, there are indications that there are differences in personality aspects as measured on the Karolinska Personality Scale, violent offenders displaying suicidal behavior scoring very low on sociability and high on impulsive aggression (Stålenheim, 2001).

1.1.2 Suicidal behavior and biomarkers

There is a need for biomarkers in order to understand the neurobiology related to suicidal behavior and to help to predict suicide attempts and prevent suicide. As for peripheral markers, low serum cholesterol has been repeatedly associated with prior suicide attempts and an increased risk of suicide. The predictive value is less certain, however.

The analysis of biomarkers in CSF has long been a priority in suicidology. Since the initial finding by Åsberg and colleagues (Åsberg et al., 1976), CSF 5-HIAA has been the most extensively studied and is perhaps the marker with the highest potential predicitive potential (Åsberg, 1997). It was later suggested that a combination of low 5-HIAA and HPA dysfunction may increase the predictive ability (Mann and Currier, 2007). In a meta-analysis from 2011, where a principal analysis of biomarkers in the CSF of suicide attempters was conducted, it was suggested that a combination of specific markers may help predict the risk of future suicide and discriminate between different types of suicidal behavior (Lindqvist et al., 2011).

It seems increasingly likely that no single biomarker has the predictive value needed in relation to the risk of suicide, and further addition of other biomarkers, such as inflammatory cytokines, cortisol and perhaps cholesterol, increases the predictive value regarding the risk of suicide and suicidal behavior (Coryell and Schlesser, 2007; Lindqvist et al., 2011).

In summary, no single biomarker has the predictive potential needed and several biomarkers are needed to more accurately predict the risk of suicide (Review: Oquendo et al., 2014). At present, the number of useful biological markers with respect to suicide and suicidal behavior is still small, and the predictive effect is limited.

1.1.3 Suicidal behavior and the serotonergic system

The serotonergic system is perhaps the most extensively researched biological system in relation to suicide and suicidal behavior. It has been linked to impulsivity, aggression, and violent suicide methods (Review: Mann, 2013).

Low CSF 5-HIAA has long been associated with the risk of suicide, the frequency of suicide attempts, and more violent methods of suicide (Åsberg et al., 1976). The findings have been replicated, especially with regard to low CSF 5-HIAA and violent methods of suicide (Träskman et al., 1981; Cremniter et., 1994; Åsberg, 1997).

In later studies, such as a post-mortem study of suicide victims, alterations of serotonergic receptor binding in the ventral and ventrolateral prefrontal cortex were been found (Arango et al., 1997). However, research with respect to peripheral serotonergic markers has generally yielded inconclusive results with respect to the risk of suicide (Muller-Oerlinghausen et al., 1997).

The results from genetic studies concerning suicidal behavior have yielded rather unconvincing results. There is insufficient evidence regarding a genetic relationship between genes associated with the serotonergic system and suicidal behavior in general. However, the s-allele of the serotonin transporter gene might be involved in violent suicidal behavior and repetitive suicidal attempts (Bondy et al., 2006). The most replicated genetic findings have been associations of TPH1 and 5-HTTLPR with violent suicides (Bondy et al., 2006; Antypa et al., 2013).

Recently, a prospective imaging study, including 100 patients, was concluded. The study, using Positron Emission Tomography (PET), aimed to investigate whether the binding potential of the serotonin transporter in the lower mid-brain (n=50), and the binding potential of the serotonin$_{1A}$-receptor in the raphe nuclei (n=100), had a predictive value in association with degree of suicidal ideation and intent, number of suicide attempts, and the lethality of suicide attempts. The PET scan(s) were done in a drug-free state, whereafter the patients received standard of care for depression during a 2 year long follow up period. They found neither the binding potential of the serotonin transporter in the mid-brain, nor the binding potential of the serotonin$_{1A}$ receptor to be associated with prediction of future suicide attempts. The binding potential of the serotonin$_{1A}$ receptor was, however, not only in the raphe nuclei, but also in other areas of the brain, associated with a higher degree of suicide ideation and greater lethality of suicide attempts (Oquendo et al., 2016). This large imaging study, conducted in drug-free patients, provides further evidence for the association of the serotonergic system with suicidal behavior.

In summary, the serotonergic system remains firmly associated with suicide and suicidal behavior (Review: Mann, 2013).

1.2 CHOLESTEROL

Cholesterol is a molecule mostly known for its atherogenic properties and its relation to cerebrovascular diseases. However, cholesterol has many vital functions in the organism.

Cholesterol forms an integral part of all cell membranes and is present in cholesterol rafts in the membrane. Areas which are stabilized by cholesterol facilitate the presentation of receptors and may affect the activity of serotonergic signaling (Björk et al., 2010). Cholesterol is vital for the formation of receptors and for synaptogenesis, and it affects neurotransmitter release (Mauch et al., 2001; Goritz et al., 2005), and mitochondrial function is involved in the formation of cholesterol and steroid hormones. Cholesterol is the precursor to all steroid hormones, such as estrogen, testosterone, and cortisol (Review: Miller, 2011).

There are two sources of cholesterol: external or dietary cholesterol and internal cholesterol, which is produced intracellularly.

Dietary cholesterol can be taken up by selective receptor-mediated uptake (Brown et al., 2007), receptor-mediated endocytosis (Osono et al., 1995), or bulk-phase endocytosis (Acton et al., 1996). Cholesterol taken up from the intestines is mixed with triglycerides and taken up into chylomicrons. The chylomicrons are, in turn, transported to the liver, where cholesterol and triglycerides are repackaged into very low-density lipoproteins (VLDLs). As these molecules are transported through the body, free fatty acids are absorbed into cells, leaving an increasingly dense core of cholesterol, thus gradually turning into low-density lipoproteins (LDLs). These LDL molecules bind, through markers known as apolipoproteins, to receptors, which cells present on their membranes. Low intracellular levels of cholesterol prompt cells to increase the presentation of receptors and thus enable uptake of extracellular cholesterol (Review: Dietschy, 2009).

Most cholesterol in the body is not, however, derived from dietary sources, since most cells have the ability to produce cholesterol. In general, dietary cholesterol is considered to be a supplementary source of cholesterol.

There are two major ways of regulating cholesterol levels in serum when the cholesterol intake is high: to reduce synthesis or increase resecretion of cholesterol. The dominant mechanism of change can differ between individuals, but up to a certain level of cholesterol intake, both methods seem to be sufficient to compensate for the increase in cholesterol and avoid increased serum cholesterol levels (Nestel and Poyser, 1976).

An increase in the biologically active pool of cholesterol through high dietary intake inhibits the rate limiting enzyme in cholesterol metabolism, HMG-CoA, and leads, in turn, to the suppression of cholesterologenesis. The next step is inhibition of the production of other enzymes involved in cholesterologenesis, leading to a longer inhibition of the process and, finally, an increase in enzymes involved in the export of cholesterol (Dietschy, 2009).

An excess of intracellular cholesterol is packaged into HDL particles, which are generally rich in cholesterol content. These particles travel through the circulation, where they may pick up cholesterol on the way to the liver. In the liver, cholesterol may be eliminated by secretion into the gastrointestinal tract as bile and conversion into bile acids (Dietschy, 2009).

1.2.1 Cholesterol in the brain

In the central nervous system, practically all cholesterol is manufactured *in situ*. The blood-brain barrier inhibits the passage of lipoproteins and the uptake of peripherally produced or dietary cholesterol is considered to be very low, if any at all (Linton et al., 1991).

The cholesterol content of the CNS is very high compared to the rest of the body. However, the rate of production of cholesterol in the CNS varies across the life span. During the perinatal period, it is very high in all parts of the CNS, allowing to the extensive myelinization taking place in the human brain post-partum. The cholesterol production later stabilizes and excretory pathways are activated. In the adult, the rate of cholesterol synthesis in the brain, based on excretion of cholesterol and cholesterol metabolites from the CNS, is actually rather small compared to the rest of the body. Current opinion is that the half-life of cholesterol in the brain is about 5 years (Dietschy and Turley, 2004).

While neurons possess the ability to produce cholesterol, the forming of synapses and nerve growth is believed to rely mostly on additional cholesterol produced by other cells than neurons, namely, astrocytes (Mauch et al., 2001).

Currently, there is no evidence of a net transport of cholesterol across the BBB (Review: Dietschy, 2009). The major mechanism for elimination of cholesterol from the CNS is likely through 24s-hydroxycholesterol. There is a low ApoE-mediated excretion of cholesterol through cerebrospinal fluid and the possibility of a ApoE mediated ecretion of cholesterol across the blood-brain barrier has been discussed (Dietschy and Turley, 2004). The total amount of excreted sterols is, however, very low compared to the rate of cholesterol excretion in the rest of the body (Björkhem et al., 1998).

1.2.2 Cholesterol and suicidal behavior

As lipid-lowering medication, known as statins, became available, epidemiological studies started to investigate their effect on overall mortality in relation to cholesterol levels. While the use of statins was found to be were associated with a reduction in deaths due to coronary incidents, it was less clear whether they reduced overall mortality. In fact, there were indications of an increase in accidental deaths and suicides in patients treated with statins, perhaps explaining the seeming lack of reduction in overall mortality in the whole group (Muldoon et al., 1990). However, while the relationship between cholesterol reduction and coronary incidents remained strong, the results with respect to suicide and other causes of death were more ambiguous (Neaton et al., 1992). In the early 1990s two large epidemiological studies found low total cholesterol to be associated with an increased risk of suicide in men (Neaton et al., 1992; Lindberg et al., 1992).

In a review from 1996 presented in the British Journal of Psychiatry, it was concluded that there was a considerable amount of evidence indicating an effect of the cholesterol level on mental state and personality (Boston et al., 1996).

In clinical studies, a correlation was found between low total serum cholesterol and para-suicidal acts and, furthermore, in patients with two measurements of cholesterol, both men and women showed lower serum total cholesterol after the para-suicidal act (Gallerani et al., 1995). Low serum total cholesterol was found to be associated with suicidal behavior in suicide attempters with a mood or personality disorder, but not in patients with schizophrenic spectrum disorders (Kunugi et al., 1997) and, in a large Finnish study focusing on middle aged men, low serum total cholesterol was found to be associated with both low mood and risk of suicide (Partonen et al., 1999). Total serum cholesterol has been linked to both para-suicidal acts and increased impulsivity (Garland et al., 2000).

In suicide completers, cholesterol was reduced in areas relevant for decision-making, but only in subjects committing a violent suicide (Lalovic et al., 2007).

All studies did not, however, find a correlation between low serum total cholesterol and the risk of violent death (Vartiainen et al., 1994; Iribarren et al., 1995). In fact, there have also been studies which have found contradictory results, linking high total serum cholesterol and violent suicide (Tanskanen et al., 2000).

Regarding total serum cholesterol, gender, and suicidal behavior, in some clinical studies, a history of suicide attempts has been associated with lower total serum cholesterol regardless of gender (Perez-Rodriguez et al., 2008), while, in other studies, such an association has only been found in men (Diaz-Sastre et al., 2007). Rather recently, two Polish studies found an association between low total serum cholesterol and suicide attempts in patients with both uni- or bipolar depression and schizophrenia (Ainiyet and Rybakowski, 2014; Ainiyet and Rybakowski, 2014).

In summary, a recent meta-analysis, including 65 studies and a total of 510,392 participants, found, however, suicidal patients to have lower total cholesterol in comparison to non-suicidal patients and healthy controls (Wu et al., 2015).

1.2.3 Cholesterol in the prediction of violent and suicidal behavior

The predictive value of serum cholesterol with regard psychiatric illness in general and suicide and suicidal behavior, is still under debate. In 2003, it was found that patients with increased levels of cholesterol had a blunted cortisol response after administration of fenfluramine, which was believed to be potentially associated with a poorer treatment response (Papakostas et al., 2003a). High serum cholesterol was found to be associated with a poor treatment response and a higher rate of relapse in patients with high serum cholesterol (Papakostas et al., 2004) and, in another study, low serum total cholesterol was found to be associated with a risk for mania, but not predictive of depression (Fiedorowicz et al., 2010).

In one review, it was proposed that MDD and low serum cholesterol might be associated with a risk of suicide, while MDD and high serum cholesterol might be associated with a poor treatment response. Ironically, both the increased risk of suicide in the low cholesterol patients and the poor treatment response in the high cholesterol patients may, in theory, be potentially mediated by altered serotonergic activity (Papakostas et al., 2004).

In a prospective study from 2007, low cholesterol did not predict the risk of suicide attempts, despite the finding of an association between a higher prevalence of earlier suicide attempts and low serum cholesterol in the cohort at the start of the study (Fiedorowicz and Coryell, 2007).

A rather recent Norwegian prospective study, previously mentioned in "Introduction", examined serum cholesterol and platelet serotonin in relation to violence and suicidal behavior. The study, which included 254 (out of 489) patients admitted to a psychiatric hospital in Norway (both voluntary and involuntary), found a significant relationship between total serum cholesterol and inpatient suicidal and violent behavior, and to violent behavior three months after discharge. They also found a significant negative relationship between HDL cholesterol and violence at 12 months and with the risk of violence in patients with repeated admissions. The predictive value was, however, apparently greater with regard to violent behavior than to suicidal behavior (Roaldset et al., 2011).

In summary, while there are indications that the predictive value of individual cholesterol level is rather low. Cholesterol and cholesterol subfractions do, however, have a potential use as a marker of the risk for aggressive and suicidal behavior and constitute an area in need of further research.

1.2.4 Cholesterol and violence

Cholesterol, in particular, low serum total cholesterol, has been repeatedly associated with aggressive, impulsive, and violent behavior. In a Finnish study from 1983 on antisocial homicidal offenders, low total cholesterol was associated with violent behavior when under the influence of alcohol. Furthermore, in the same study, there were also associations between low total cholesterol and suicide attempts and self-harm, and between low cholesterol and exposure to parental violence by alcoholic fathers (Virkkunen, 1983).

There have been several findings of associations between low cholesterol and aggression from animal studies. In the early 1990s, a group of researchers conducted a series of experiments on cynomologous monkeys. In the first experiment, monkeys were put on a low versus high cholesterol diet over the course of 22 months. The monkeys on a high cholesterol diet displayed an increase in serum total cholesterol and lower HDL, as well as less contact aggression than their counterparts having been fed a more restrictive diet (Kaplan et al., 1991).

In 1998, a review was presented of the literature examining whether low, or lowered, cholesterol could be considered to have a causal relation to violence and violent behavior. The review intended to investigate whether Hill`s criteria of a causal relationship were fulfilled. After reviewing the current literature, the criteria were found to be fulfilled, and it was concluded that there was indeed enough evidence to claim a causal relation between low cholesterol and violent behavior (Golomb, 1998). The conclusion was not, however, uncontroversial, and was indeed much disputed.

Further indications of a correlation between cholesterol metabolism, suicidality, and violent behavior can be found in the literature on genetic studies with respect to genes involved in cholesterol metabolism. Smith-Lemli-Opitz (S-L-O) is a rare genetic disorder which severely affects cholesterol metabolism and results in hypocholesterolemia. In interviews of carriers of the S-L-O syndrome, it was discovered that relatives to the S-L-O carriers displayed a higher degree of suicidal behavior, but did not display an increase in other psychiatric illnesses, compared to controls (Lalovic et al., 2004).

In another study, a novel mutation of apolipoprotein B was found to be associated with hypocholesterolemia (low total serum cholesterol). The 26-year-old male psychiatric index patient in the study presented with such clinical symptoms as persecutory delusions and suicidal ideation. Upon examination, it was discovered that 5 out of 10 males of his relatives had committed violent suicide and one a double homicide. The father of the index patient and the paternal grandfather were both heterozygotic for the novel mutation and both displayed hypocholesterolemia, further supporting a heritable association between cholesterol metabolism, low cholesterol, and possible violent behavior and violent suicide (Edgar et al., 2007).

The two above-mentioned studies are consistent with a link between cholesterol metabolism, suicide, and violent behavior which is not mediated through other psychiatric illnesses, and perhaps indicating a more direct cognitive effect.

1.2.5 Cholesterol and the Cycle of Violence

That violence begets violence is an old saying and has been studied repeatedly over the years.

In a study presented in 1989, Widom examined current evidence supporting the “Cycle of Violence” concept and conducted an extensive register study on the outcome for abused and neglected children. Abused children were found to have more violent crimes in their criminal records, compared to controls. Those having endured abuse during childhood had, in general, more criminal offenses, debuted in the correctional system at an earlier age, and there was also a higher degree of chronic offenders. In both men and women, criminal records were more common among those previously abused, but, in women, the increase in criminal offenses was not significantly associated with violent crimes. Overall, the conclusion drawn was that abuse and neglect increase the risk of becoming a potentially violent adult, but that there must also be other mediating factors, since most children subjected to abuse or neglect do not become violent adults (Widom, 1989).

While general support for the Cycle of Violence found in Widom's study was rather small, other studies show a strong correlation between exposure to abuse and antisocial behavior (Jaffe et al., 2004).

In a recent twin study, the association between abuse as a child and violent behavior as an adult was again weak and bordering on nonsignificance. Furthermore, genetic effects on the risk of criminal activity were marginal. It was once again concluded that there must be other factors transforming maltreatment and abuse as a child into a violent adulthood (Forsman and Långström, 2012).

In summary, there may be an overrepresentation of violent adults among those who were abused as children and the association between exposure to and expression of violence varies greatly depending on the study.

1.2.6 Cholesterol and serotonin

The link between low serum cholesterol and suicide, violent suicide attempts, impulsive behavior, or aggression, has long been considered to be mediated through alterations in the serotonergic system (Engelberg, 1992; Wallner and Machatschke, 2009; Vevera et al., 2016).

It was initially suggested that the cholesterol content in the cell membrane might affect membrane fluidity and thus reduce the ability of the cell to present serotonergic receptors, which, in turn, would affect serotonergic signaling (Engelberg, 1992*)*. This theory has later been both revised and expanded upon.

The findings from animal studies, which reported a direct association between serum total cholesterol or diet and an effect on the CSF 5-HIAA level (Muldoon et al., 1992; Kaplan et al., 1994; Fontenot et al., 1996), were not, however, replicated in human trials investigating serum total cholesterol and CSF 5-HIAA (Ringo et al., 1994; Engström et al., 1995; Hibbeln et al., 2000; Tripodianakis et al., 2002). In 2010, a positive correlation between CSF 5-HIAA and total serum cholesterol was, however, found, a correlation found to be present only in suicide victims (Jokinen et al., 2010).

It has been noted that gender may be a potential confounder with regard to the association between serum total cholesterol and CSF 5-HIAA. In a study on neurological patients, a gender difference was recorded concerning CSF 5-HIAA and serum total cholesterol. The study consisted of two groups, with one group displaying symptoms of multiple sclerosis and a second group being examined for (and cleared of) neurosyphilis. A correlation between serum cholesterol and CSF 5-HIAA was found in both groups, but only in male patients (Markianos et al., 2010).

In humans, there are also several peripheral, preclinical, and genetic studies on a possible interaction between cholesterol and the serotonergic system. One such study found an association between low-level platelet serotonin and low total cholesterol (Steegmans et al., 1996) and another reported on how a combination of low HDL cholesterol and low

responsivity of the serotonergic system was found to be associated with violent behavior (Buydens-Branchey et al., 2000). There have also been indications of alterations in vascular reactivity to serotonin relative to the serum cholesterol level (Papakostas et al., 2003). Furthermore, it has been shown in preclinical studies that there is a reactive increase in the activity of the serotonin reuptake transporter (SERT) secondary to decreased membrane cholesterol content caused by statin treatment (Vevera et al., 2005). The presence of cholesterol in the membrane also seems to be associated with the function of serotonergic 1A receptors (Chattopadhyay and Paila, 2006; Singh et al., 2007).

Over time, the areas studied with respect to cholesterol metabolism and suicidality have expanded. In a review article from 2013, other possible mechanisms relating cholesterol and suicide are discussed, such as alterations of steroid hormones such as testosterone or cortisol; altered availability and function of lipid rafts; or an effect on brain-derived neurotrophic factor and neurogenesis (da Graca Cantarelli et al., 2014). At present, there are still strong indications of a relationship between cholesterol metabolism, serotonergic signaling, and behavioral effects, particularly violent and impulsive behavior. This is exemplified by a recent study on rats exposed to statins, which displayed increased impulsivity and cognitive difficulties after treatment with the statins (Vevera et al., 2016).

In summary, there is currently a strong basis linking cholesterol and serotonin to aggressive and maladaptive behaviors and possibly suicidality (Wallner and Machatschke, 2009).

1.2.7 Cholesterol and side-chain oxidized oxysterols

One challenge regarding studies on cholesterol in relation to psychiatric illnesses is the apparent lack of communication between peripheral serum cholesterol levels and cholesterol in the CNS. However, an interesting avenue for future research with regard to cholesterol and psychiatry may be the side-chain oxidized oxysterols.

A side-chain oxidized oxysterol has a hydroxyl group in 24S-, 25 or 27-position. Such hydroxycholesterol molecules becomes more polar with increased solubility in water. Passive permeability is reduced, but the exponential increase in solubility has a relatively greater effect. This is what makes it much easier for side-chain oxidized oxysterols cross the blood-brain barrier (Review: Lutjohann, 2006).

The most common oxysterol, 27-OHC, which is both directly related to peripheral cholesterol levels and, after crossing the BBB, influences cholesterol production in the CNS, may thus provide a link between peripheral serum cholesterol and activity in the CNS. 24-OHC, which is only produced in the CNS and is directly related to cholesterol synthesis in the CNS, may also provide insight into the activity of cholesterol synthesis in the CNS.

Deficiencies in 24s-hydroxylase may have direct effects on cognition and result in severe impediment of spatial, motor, and associative learning in mice (Kotti et al., 2006). Furthermore, 27s-hydroxycholesterol suppresses expression of the activity-regulated cyto-skeleton-associated protein (Arc), which is important for the consolidation of memory, thus providing yet another link between oxysterols and cognition (Björkhem et al., 2009).

The fraction of 24s present in the CSF may be useful as a marker of neuronal damage since it better reflects both neuronal damage and neuronal death than the number of metabolically active neurons (Leoni et al., 2004; Review: Björkhem, 2006). It has also been proposed that testing for the ratio 24s/27s may be of value as a diagnostic tool. 24s-OHC may be involved in the modulation of both neuronal death and the NMDA receptor (Zhou et al., 2016; Noguchi et al., 2015). There is a significant increase in the influx of 27s-OHC into the CSF in states of decreased blood-brain-barrier integrity. For instance, the 24s/27s ratio was normal in MS, but significantly increased in patients with meningitis, polyneuropathy, and hemorrhages (Leoni et al., 2003).

While there is a very limited number of studies on oxysterols in psychiatric populations, in a post-mortem study of suicides, increased levels of 24-OHC were found in the prefrontal cortex in suicide victims (Freemantle et al., 2013).

1.3 APOLIPOPROTEIN E

Apolipoprotein E (ApoE) is an important factor in cholesterol metabolism, mostly due to its role in the transportation of cholesterol and the facilitation of cholesterol uptake into the cells. As the name indicates, ApoE attaches itself to lipoproteins and binds to receptors on cell membranes, mainly the LDL receptor.

ApoE is a part of very low-density lipoproteins (VLDL) on secretion from the liver, while chylomicrons acquire ApoE after secretion from the small intestines. Both VLDL and chylomicrons acquire more ApoE, since ApoE can be secreted by most cells when they are transported through the circulatory system. ApoE helps deliver both triglycerides and cholesterol to extrahepatic cells through VLDL association, and to the liver through chylomicron remnants (Mahley and Rall, 2000).

While ApoE mostly mediates the uptake of cholesterol from VLDL, it can also have a direct effect on increased VLDL levels in plasma, since an increased amount of circulating ApoE induces the production and secretion of VLDL from the liver (Huang et al., 1999). Furthermore, ApoE also mediates the uptake of cholesterol into small HDL particles. It is worth noting that ApoE has a higher affinity for LDL receptors than ApoB100, but the effect is isomer-specific and, in the peripheral circulation, ApoB is more important for the transportation of lipids than ApoE (Mahley and Rall, 2000).

Overexpression of ApoE is generally related to decreased levels of plasma cholesterol in animal studies. For instance, ApoE-null mice, have been shown to display high lipid and VLDL levels (Reddick et al., 1994). ApoE mice are susceptible to atherosclerosis and have elevated levels of plasma cholesterol (Review: Hauser et al., 2011). ApoE deficiency has also been associated with hypercholesterolemia in humans (Ghiselli et al., 1981).

1.3.1 Apolipoprotein E in the brain

Apolipoprotein E is mainly produced by astrocytes in the CNS. Astrocytes secrete ApoE, which then associates with cholesterol-rich HDL-particles and mediate uptake of cholesterol into neurons and facilitate transport of cholesterol out of the CNS (Mahley, 1988). However, while ApoE is mainly produced by astrocytes under normal circumstances, during periods of increased cellular stress, ApoE can also be expressed by neurons (Fagan and Holzmann, 2000; Kim et al., 2009).

The presence of ApoE in the CNS is crucial for synaptic formation and neurogenesis. It is believed to have an important role in protecting neurotrauma, and in a subsequent reconstruction. (Lee et al, 2004; Kim et al, 2009). Outside of the CNS, Apolipoprotein E is probably involved in the salvage and redistribution of cholesterol after traumatic injury to nerves (Goodrum, 1991).

1.3.2 Apolipoprotein E in plasma and cerebrospinal fluid

There is a very limited number of studies on ApoE in plasma in relation to psychiatric or cognitive symptoms. In fact, there are very few studies on nongeriatric psychiatric populations and the level of ApoE in plasma or the CSF.

There is currently no evidence supporting an ApoE-mediated uptake of peripherally produced cholesterol in the CNS. According to findings in both mice, and human studies, peripheral ApoE does not seem to cross the BBB. Indicating that ApoE present in the CSF have been produced in the CNS (Liu et al., 2012, Linton et al., 1991,Yamauchi et al., 1999)**.** ApoE-mediated excretion of cholesterol across the blood brain barrier has been discussed (Dietschy and Turley 2004), but never proved.

A low flux of ApoE bound cholesterol through cerebrospinal fluid is known to occur. This flux is, however, considerably lower than the flux of cholesterol in the form of 24S-hydroxycholeterol (Review: Björkhem, 2006).

1.3.3 Apolipoprotein E and the major isomers (E2, E3, and E4)

Apolipoprotein E has three major isomers, E2, E3, and E4. The frequency of the three isoforms, apolipoprotein E2, apolipoprotein E3, and Apolipoprotein E4, varies across the world, but approximate frequencies are E3, 78%, E4, 15%, and E2, 7% (Eisenberg et al., 2010).

Since ApoE has three major isomers, with different affinities for the type of lipoprotein and receptors, it is of interest that approximately 50% of the variance in cholesterol levels is attributed to genetic factors. ApoE is believed to account for approximately 16% of the total genetic variance, mainly by influencing LDL-C and total serum cholesterol levels. ApoE2 is generally associated with lowered total cholesterol and LDL, and ApoE4 with relatively higher total cholesterol and LDL (Sing and Davignon, 1985).

There is a significant decrease in LDL receptor affinity in the ApoE2 isomer, which has approximately 1–2% of the binding affinity of ApoE3 (Weisgraber et al., 1982). Furthermore, both *in vitro* and animal studies have shown results which indicate that ApoE3, in comparison to E4, enhances synaptic plasticity and has fewer neurotoxic effects (Kim et al., 2009).

Previous studies have mainly focused on finding correlations between ApoE isomers and cognitive or psychiatric symptoms. ApoE isomers may therefore affect the plasma level of cholesterol through differences in affinity to LDL receptors, different preferential binding of lipoproteins and by altering the potential to transport cholesterol out of the CNS across the BBB (Mahley et al., 2000; Verghese et al., 2011).

There are, however, some indications that the ApoE genotype might be associated with antagonistic pleiotropy, which means that the different isotypes may have differential protective effects at different developmental stages (Bloss et al., 2010; Zetterberg et al., 2009). While E2 and E3 might be associated with a longer life span and durability, E4, on the other hand, has been associated with better health during the perinatal period and greater survival rates for infants, which might partly explain a still rather high frequency of E4 in the population (Eisenberg et al., 2010).

1.3.4 Apolipoprotein E and mental disorders

Most psychiatric studies on ApoE have focused on finding associations between prevalence or symptom severity in relation to the ApoE isomers. However, the studies have generally yielded negative results.

For instance, a large-scale community-based investigation found no association between ApoE isomers and MDD in a sample of 17,000 subjects aged 41–80 years (Surtees et al., 2008), while a second study found a weak association between the severity of symptoms in bipolar patients (Bellivier et al., 1997) and a third study found no association between symptoms and ApoE isomers in neither unipolar nor bipolar patients (Kessing and Jorgensen, 1999). In a study on 106 unipolar and 21 bipolar patients, no increase in the frequency of apoE4 was found, compared to controls, nor was apoE4 associated with any increase in cognitive deficits (Kessing and Jörgensen, 1999).

In summary, as of yet, clear correlations between isomers of ApoE and psychiatric diagnoses have been scarce (Review: Gibbons et al., 2011).

In theory, the most likely area of psychiatry for finding associations between ApoE isomers and the severity or prevalence of disease would probably be in schizophrenia – partly due to the dementia-like qualities of certain types of schizophrenia and partly due to the competitive binding of ApoE to the reelin receptor. There is actually a considerable theoretical basis for how ApoE might influence or induce schizophrenia or affect the symptomatology. Apart from the earlier-mentioned influence on synaptic plasticity, dendritic formation, and recuperation after trauma, ApoE binds competitively to the same receptor as reelin, a factor which has been implicated in the development of schizophrenia and other neurodevelopmental disorders (Folsom et al., 2013).

1.3.5 Apolipoprotein E and suicidal behavior

There are only a few studies on apolipoprotein E in relation to suicide and suicidal behavior.

The only earlier study of Apolipoprotein E in plasma in relation to suicidal behavior yielded a negative result. No significant difference in plasma ApoE level was found between suicide attempters and controls (Baca-Garcia et al., 2004).

There are no previous studies of ApoE in in CSF in relation to suicidal behavior (Lee and Kim, 2011). Nor are there any studies investigating environmental factors and suicidal behavior in relation to ApoE in plasma (Mandelli and Seretti, 2013).

There are some genetic studies on ApoE in relation to suicidal behavior. An association between ApoE4 and the number of earlier suicide attempts was found in a group of depressed geriatric patients (Hwang et al., 2006). However, a genetic study on 145 suicide completers and 160 controls revealed no difference in the frequency of ApoE alleles. In the same study, the overall expression of ApoE in the brain was investigated, but no significant difference in the expression of ApoE in the brain of suicide completers was found as compared to controls (Lalovic et al., 2004). The results are, as of yet, inconclusive regarding whether ApoE is associated with suicidal behavior (Review: Gibbons et al., 2011).

Suicide and suicide attempts remain, however, a rather rare event and thus the results are influenced by underlying psychiatric disorders and the population base. It is likely that individual genes have, at most, a small effect on suicidality in general and that there is no uni-directional relation between genes and suicidality (Schild et al., 2013).

2 AIMS

2.1 OVERALL AIMS

The overall aim of this thesis was to further study a possible relationship between cholesterol, ApoE, and serotonin with respect to suicidal and violent behavior.

2.2 STUDY I

In Study I, we aimed to test if there is a correlation between the cholesterol and serotonergic systems by measuring serum total cholesterol in peripheral blood and, as a marker of central serotonergic activity, measuring the level of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid.

2.3 STUDY II

In Study II, we aimed to examine whether total serum cholesterol is related to the "Cycle of Violence." The Cycle of Violence is based on a hypothesis which basically states that violence begets violence. The exposure of children and adolescents to violence may increase the risk of individuals displaying aggression and violence as adults. Since low total serum cholesterol has been associated with impulsivity and aggression, we aimed to examine whether low total cholesterol is a factor associated with the Cycle of Violence.

2.4 STUDY III

In Study III, we aimed to examine whether there was a relationship between plasma apolipoprotein E and the severity of suicidal behavior, a phenotype characterized by the number of earlier suicide attempts and the age of onset of suicidal behavior.

2.5 STUDY IV

In Study IV, we aimed to investigate whether ApoE in the cerebrospinal fluid is related to the severity of suicidal behavior as measured by the number of earlier suicide attempts, reversibility/interruptability, and violent methods of attempted suicide.

3 METHODS

3.1 STUDY SETTING

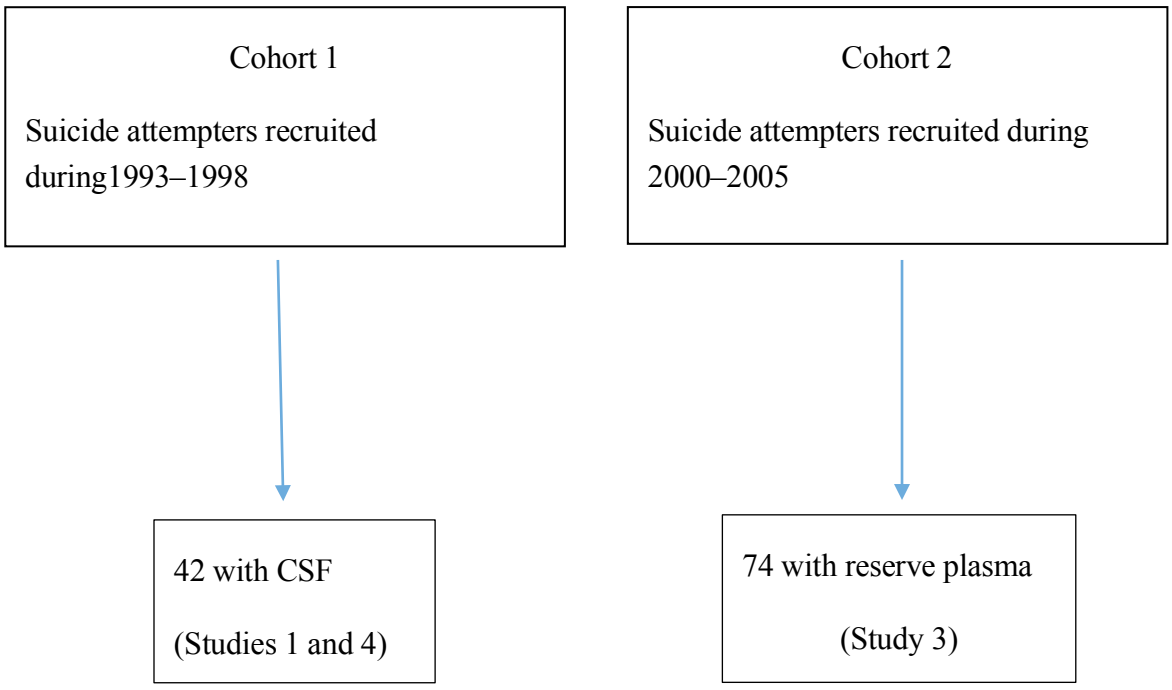
The papers presented in this thesis are based on two clinical studies on patients who had made a recent suicide attempt, all recruited at the Karolinska University Hospital in Solna, Sweden, during the years 1993–2005. The patients were recruited from emergency settings, outpatient care, and as inpatients.

The study protocols (Dnr 93-211; Dnr 00-194; Dnr 2013/917-32.) were approved by the Regional Ethical Review Board in Stockholm, and all patients gave their written informed consent before inclusion in the study

3.2 CLINICAL COHORTS

The inclusion criteria were a recent suicide attempt and with a time limit of one month prior to inclusion in study. The definition of suicide attempt used in the study was "nonfatal self-injurious behavior with some intent to cause death." Other requirements were an age of 18 or older and a fair capacity to communicate in Swedish, both verbally and in writing. Exclusion criteria were schizophrenia spectrum psychotic disorders, intravenous drug-abuse, mental retardation, and dementia.

The flowchart shows the patients in the studies presented in this thesis.



3.2.1 Cohort 1

Patients in the first cohort (n = 81) were recruited between 1993 and 1998.

This cohort comprises 35 men, mean age, 39 years (SD, 11.8 years; range, 20–69 years) and 46 women, mean age, 35 years (SD, 12.1 years; range, 18–68 years). At inclusion, all participants were interviewed by a trained psychiatrist, using the SCID-I research version (Spitzer et al., 1990a) in order to establish an axis I diagnosis according to DSM-III (American Psychiatric Association). The axis II diagnosis was established by trained psychologists using the SCID-II interview (Spitzer et al., 1990b). Nearly all patients in the first cohort (95%) fulfilled the criteria for at least one current psychiatric diagnosis according to DSM-III. Tabel 1 shows the psychiatric diagnoses of the patients. Violent suicide attempt methods were defined according to the criteria proposed by Träskman and colleagues (Träskman, Asberg, Bertilsson et al., 1981). In general, the participants were somatically healthy. At inclusion in the study, the somatic diagnoses were asthma (2), cardiovascular disease (2), morbus Chron (1), migraine (1), pain (6), diabetes (4), celiac disease (1), and kidney stone (2). A high percentage, 78% (n = 51), were drug-naive with regard to antidepressants prior to the suicide attempts. Cerebrospinal fluid was acquired from 42 out of the 81 patients in the study (Studies 1 and 4).

3.2.2 Cohort 2

During the recruitment period, i.e., 2001–2005, there was a total of 258 patients (89 men, 169 women) from the catchment area who had committed a suicide attempt and came into contact with the Suicide Prevention Clinic at Karolinska University Hospital in Solna.

Out of the 258 subjects eligible for the study, 61 fulfilled one or more of the mentioned exclusion criteria and 50 patients declined to participate. Another 47 patients were excluded from the study due to such reasons as declining a clinical follow-up, moving to another part of the country, or difficulties in following up patients due to holiday periods.

The recruitment period ended when 100 patients (67 women, 33 men) had been enrolled into the study. The mean age of the participants was 34 years (SD, 12.4 years; range, 18–67 years) with no significant difference in age between the participating men and women.

To establish Axis I Disorders according to DSM-IV, all participants were interviewed by a trained psychiatrist using the SCID-I Research Interview (First et al., 1996). Axis II Disorders were established by trained psychologists using the DIP-I Interview (Ottosson et al., 1998). The administered self-rating scales were completed under the supervision of a research nurse.

With regard to the comorbidity of Axis 1 diagnoses, 25% of the patients had a comorbid anxiety disorder and 4% a comorbid eating disorder (bulimia nervosa).

Table 1 shows the psychiatric diagnoses of the patients.

Table 1	Cohort 1 (DSM III)	Cohort 2 (DSM IV)
Mood disorder	80%	71%
Anxiety disorder	4%	6%
Adjustement disorder	5%	5%
Other Axis 1 dg	4%	4%
Comorbid substance use disorder	21%	16%
Comorbid personality disorder	39%	28%
Violent suicide attempt method	14%	18%

3.3 CLINICAL RATINGS OF PSYCHIATRIC SYMPTOMS

3.3.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

Depression was rated using the Montgomery-Åsberg Depression rating scale (MADRS). This scale has been widely used as a reliable depression rating scale during the last three decades.

The scale was originally developed by Stuart Montgomery and Marie Åsberg as a depression rating scale intended to be sensitive to change in the severity of depressive symptoms. It was designed using the 17 most frequently occurring symptoms (out of a total of 65 symptoms tested for) in a combined English and Swedish sample of depressed patients.

The 17 remaining symptoms were then evaluated in 64 patients taking part in studies designed to evaluate the efficacy of antidepressive treatment. The ratings were evaluated and the 10 items showing the highest correlation with change of state were selected for a 10-item scale, with scores of 0–6 on each item.

The scale displayed high inter-rater reliability and correlated significantly with scores on a frequently used scale for depression severity, the Hamilton Rating Scale. However, the new scale showed a better ability to distinguish responders to treatment from nonresponders, indicating that the MADRS may be more sensitive to change in state (Montgomery and Åsberg, 1979).

3.3.2 Becks`s Suicide Intent Scale (SIS)

The Suicide Intent Scale was constructed as an instrument to help in the assessment of suicide risk. It contains 15 items and is designed to investigate both objective (such as the circumstances at the time of the suicide attempt) and subjective aspects of the suicide attempts (such as thoughts and feelings of the patient during the suicide attempt).

In addition to questions regarding the present suicide attempt, the SIS also contains additional questions concerning the presence and nature of earlier suicide attempts. Item 18 concerns the presence and frequency of any earlier suicide attempts. Responses to item 18 are divided into three alternatives with regard to previous suicide attempts: (1) none, (2) one or two, and (3) three or more suicide attempts (Beck et al., 1974a).

3.3.3 Beck`s Hopelessness Scale

Beck`s Hopelessness Scale is constructed out of 20 true-false statements. Nine out of the ten items were taken from a test regarding patients' attitudes concerning the future, but were originally structured in a semantically different format. The remaining 11 items were selected from statements made by patients considered to be in a state of "hopelessness" by psychiatrists.

The selected statements were believed to reflect different aspects of the state. The scale was then distributed among a random sample of depressed and nondepressed patients who were asked about the relevance of the content and clarity of the statement. In the next phase, the scale was appraised by several clinicians regarding comprehensibility, after which further revising was done.

In the final form, the scale consisted of 20 statements, with 9 keyed false and 11 true, each question scoring 0 or 1, giving a score of 0–20. The scale has been validated with regard to clinical ratings, in both outpatients and suicide attempters, and showed a high inter-rater reliability. High scores on the Hopelessness Scale are intended to detect higher rates of suicidal intent (Beck et al., 1974b).

3.3.4 Karolinska Self-Harm History Interview

The Karolinska Self-Harm History Interview examines a large number of factors related to suicidal behavior.

It focuses in detail on circumstances of suicide attempts and also elucidates such factors as family history of suicide, nonsuicidal self-injury, age at onset of suicidal behavior and earlier suicide attempts. It also investigates factors elicitating suicide attempts and expectations and wishes surrounding the suicide attempts.

3.3.5 Karolinska Interpersonal Violence Scale (KIVS)

Interpersonal violence was measured using the Karolinska Interpersonal Violence Scale (KIVS). KIVS is based on a semi-structured interview, intended to assess the degree of exposure to, and expression of, violence.

The scale is divided into four subscales, measuring exposure to violence as a child, expression of violence as a child, exposure to violence as an adult, and expression of violence as an adult. Childhood is defined as the period between ages 6 and 14, and adulthood is defined as covering experiences from age 15 and older.

The scoring is 0–5 for all four subscales, giving a score of 0–10 for life-time exposure to violence and of 0–10 for life-time expression of violence. Trained clinicians performed all interviews and ratings in the clinical cohorts presented in this thesis.

While the scale is rated by the interviewing clinician, thus being a one-point-in-time measurement, the rating of childhood experiences gives it a retrospective aspect, making it useful for studying the development of violent behavior over time. The subscales have a high inter-rater reliability ($r > 0.9$) and have been validated against other scales measuring the degree of violent behavior and aggression (Jokinen et al., 2010).

The Karolinska Interpersonal Violence Scale

The steps of this scale are defined by short statements about violent behavior. On the basis of an interview with the subject, the highest score is used where one or more of the statements apply.

A. Used Violence
As a child (age 6–14 years)

0 No violence.
1 Occasional fights, but no cause for alarm among grown-ups in school or in the family.
2 Fighter. Been in fights a lot.
3 Often started fights. Hit a comrade who had been bullied. Continued hitting when the other had surrendered.
4 Initiated bullying. Often hit other children, with fist or object.
5 Caused serious physical injury. Violent toward adult(s). Violent behavior that led to intervention by social welfare authorities.

As an adult (age 15 years or older)

0 No violence.
1 Slapped or spanked children on occasion. Shoved or shook partner or another adult.
2 Occasionally smacked partner or child. Fought when drunk.
3 Assaulted partner, drunk or sober. Repeated corporal punishment of child. Frequent fighting when drunk. Hit someone when sober.
4 Instance of violent sexual abuse. Repeated battering/physical abuse of child or partner. Assaulted/attacked other persons frequently, drunk or sober.
5 Killed or caused severe bodily harm. Repeated instances of violent sexual abuse. Convicted of crime of violence.

B. Victim of violence

Childhood (age 6–14 years)

0 No violence.
1 Occasional slaps. Fights in school, of no great significance.
2 Bullied occasionally for short period(s). Occasionally exposed to corporal punishment.
3 Often bullied. Frequently exposed to corporal punishment. Beaten by drunken parent.
4 Bullied throughout childhood. Battered/beaten up by schoolmates. Regularly beaten by parent or another adult. Beaten with objects. Sexually abused.
5 Repeated exposure to violence at home or in school that resulted at least once in serious bodily harm. Repeated sexual abuse, or sexual abuse that resulted in bodily harm.

Adulthood (age 15 years or older)

0 No violence.
1 Threatened or subjected to a low level of violence on at least one occasion.
2 Beaten by partner on occasion. Victim of purse snatching. Threatened with object.
3 Threatened with a weapon. Robbed. Beaten by someone other than partner. Frequently beaten by partner.
4 Raped. Battered.
5 Repeatedly raped. Repeatedly battered. Severely battered, resulting in serious bodily harm.

3.3.6 Freeman Scale

The Freeman scale is a validated scale intended to evaluate the risk of later suicide after a recent suicide attempt. It is divided into two subscales: one is intended to measure Reversibility and the other Interruption Probability.

The first part, Reversibility, examines the potential lethality of the suicide attempts by taking into account the quantity and type of drug ingested and the extent of the injuries inflicted on the body. A high score on Reversibility indicates a low reversibility of the chosen suicide attempt method, indicating a more serious suicide attempt and a potentially higher risk of death. Methods which may indicate a low chance of reversibility are, for instance, hanging or shooting oneself.

The Interruption Probability is intended to measure the probability of the suicide attempt being interrupted by others, thus preventing completed suicide. A high score indicates a low probability of interruption or discovery by others.

Both subscales are graded 1–5, which gives a total range of 2–10 for scores on the Freeman Scale (Pallis and Sainsbury, 1976).

3.4 MEASUREMENT AND ANALYSIS OF BIOLOGICAL MARKERS

3.4.1 Blood samples (Studies I, II, IV)

Blood samples were collected from the antecubital vein of the participants. All samples were acquired after fasting overnight. Fasting blood samples were collected from 65 of 81 patients recruited for the study. The analysis for total serum cholesterol was performed at the Clinical Chemistry Laboratory, Karolinska University Hospital.

3.4.2 Blood samples (Study III)

Plasma samples were acquired from 74 of the 100 patients enrolled in the Sui-100 clinical cohort. The samples were from venous blood and were frozen at -70^{0}C or lower until analyzed. There had been no prior thawing of the plasma samples.

3.4.3 Lumbarpunctures and collection of cerebrospinal fluid

Cerebospinal fluid (CSF) samples were acquired from 42 patients. All lumbar punctures were performed between 8 a.m. and 9 a.m. The patients had been fasting since midnight. The needle was inserted between lumbar vertebrae IV and V and the patients were in a seated position. Twelve milliliters of cerebrospinal fluid were drawn and immediately centrifuged and stored at -80^{0}C.

3.4.4 Analysis of Apolipoprotein E in plasma and cerebrospinal fluid

The analysis of fS apoliprotein E and CSF apolipoprotein E was performed at the Karolinska Univeristy Hospital in Huddinge using immunonephelometry in a BN Pro-Spec system (http://www.healthcare.siemens.com/plasma-protein/sys tems/bn-prospec-system/technical-specifications), according to accredited routines.

Immunonephelometry of ApoE is based on adding specific antibodies, which then form immune complexes with apolipoprotein E. These complexes capture and scatter light and the concentration of ApoE is calculated as the difference in absorbed light after two measurements, separated by a predefined period of time (Weisweiler and Schwandt, 1983).

In this case, samples were diluted to 1:5 and concentrations of 0.01–0.19g/L (10–190mg/L) were calculated, after which a second dilution to 1:20 was performed and concentrations in intervals of 0.04–0.76 g/L (40–760 mg/L) were calculated. The fixed-time measurements, with timing starting after the mixing of the solution with antiserum at each concentration, were done after 7.5 s and after 6 min. The increase in light intensity was then converted into concentrations using a calibration curve. The results of the tests were given in mg/L, without decimals (Asellus et al., 2016).

3.4.5 5-Hydroxyindoleacetic acid in the cerebrospinal fluid

All lumbar punctures were performed between 8 a.m.and 9 a.m. The patients had been fasting since midnight. The needle was inserted between lumbar vertebrae IV and V with the patients in a seated position. Twelve milliliters of cerebrospinal fluid were drawn and immediately centrifuged and stored at -80^0C.

The method used to analyze the serotonergic metabolite 5-HIAA was mass fragmentography (GC-MS), according to a methodology developed by Bertilsson. The analytical method has a coefficient of variation which is less than 5% (Bertilsson et al., 1981).

3.5 STATISTICAL ANALYSIS

All statistical analyses were performed using the statistical package JMP Software (versions 6-11.2), SAS Institute Inc., Cary, NC, USA) and the cut-off for significance was set at 0.05.

The Shapiro-Wilk test was initially performed in order to evaluate kurtosis and skewness of distributions. Multivariate outliers were identified using Mahalanobis' distance. A median split was performed in order to dichotomize the material into two groups, one with serum total cholesterol above the median and one with serum cholesterol below the median (Study 2). For continuous variables, the Mann-Whitney test was used for the analysis of non-normally distributed data and Student's t test was used for the analysis of normally distributed data.

For tests of non-parametric correlations, Spearman's rho was used, while Pearson's r was used for parametric correlations.

One-way analysis of variance (ANOVA) was used for comparisons between multiple groups with variables displaying a normal distribution. A standard regression analysis was applied to adjust the results for confounding.

4 RESULTS

4.1 STUDY I

4.1.1 Serum cholesterol

The mean serum total cholesterol was 5 mmol/L (standard deviation = 1, with a range of 2.8–7.5, median 5). As expected, we found a significant positive correlation between serum total cholesterol and age ($r = 0.65$, $p < 0.0001$) and BMI ($r = 0.36$, $p = 0.026$).

The correlations between serum total cholesterol, suicide intent, hopelessness, and the severity of depression were not significant. Total serum cholesterol did not differ between violent suicide attempts and nonviolent suicide attempts ($p = 0.3$), nor between suicide attempters and patients who later completed suicide in the follow-up ($p = 0.18$).

4.1.2 CSF 5-HIAA

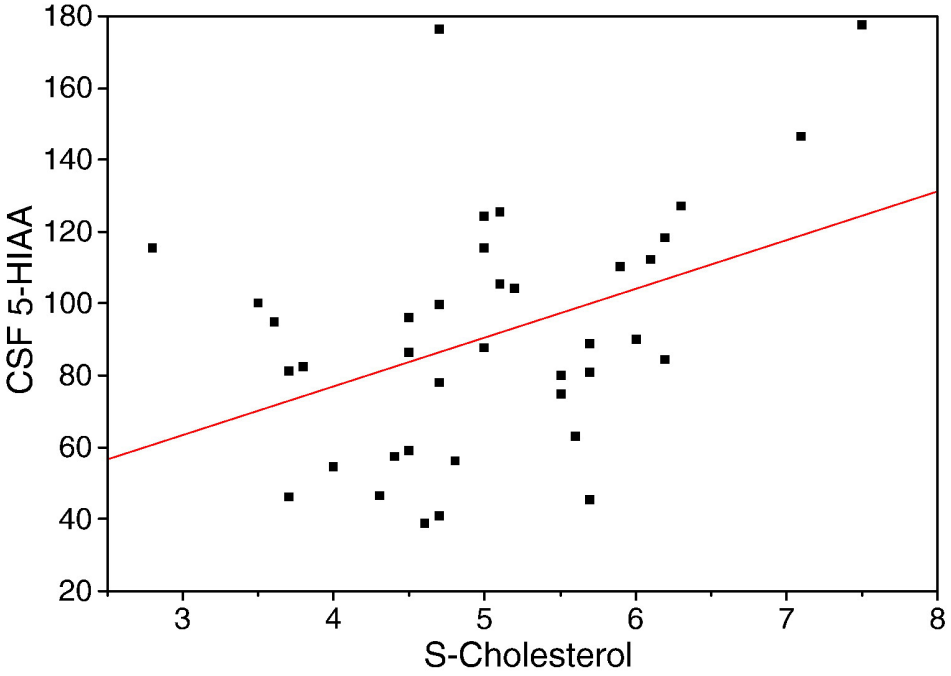
The mean level of CSF 5-HIAA was 92 nm (standard deviation = 34, with a range of 38.6–177, median 88).

There were no significant correlations between CSF 5-HIAA, suicide intent, degree of hopelessness, and severity of depression. There was no significant difference in CSF 5-HIAA according to violent versus nonviolent suicide attempt method ($p < 0.8$), nor between suicide attempters and patients who later committed suicide ($p < 0.22$).

4.1.3 CSF 5-HIAA and cholesterol

CSF 5-HIAA showed a significant positive correlation with serum total cholesterol

($r = 0.40$, $p = 0.012$).



The correlation remained significant after controlling for confounders. We performed a standard regression, with serum total cholesterol as the dependent variable, and with CSF 5-HIAA, gender, age, BMI, and comorbid substance abuse as independent variables. For cholesterol, the R for regression from zero was significantly different from zero, $F = 9.1$, $p < 0.0001$, with R2 0.59 and adjusted R2 0.52. In the regression model, two coefficients were significant predictors of serum total cholesterol, CSF 5-HIAA ($t = 2.59$, $p = 0.014$) and age ($t = 4.51$, $p = 0.0001$).

4.2 STUDY II

4.2.1 Interpersonal violence

Interpersonal violence was measured using the Karolinska Interpersonal Violence Scale (KIVS). The mean value of exposure to violence as a child was 2.2, with a standard deviation = 1.3, range = 0–5, and median = 2. For expression of violence as an adult, the mean value was 1.4, with a standard deviation of 1.1, range 0–5, and median = 2.

4.2.2 Cholesterol

Mean serum cholesterol was 5.0 mmol/L, with a standard deviation of 2.8–7.5 and a median of 4.9 mmol/L. We found no gender difference in cholesterol levels.

4.2.3 Cholesterol and expression of interpersonal violence as an adult

There was a significant negative correlation between serum total cholesterol and expressed interpersonal violence as an adult (rho = -0.26 and $p = 0.04$).

After, however, performing a standard regression, with the expression of violence as an adult as the dependent variable and serum total cholesterol, comorbid substance abuse, and age as independent variables, the association was no longer significant, $p = 0.27$.

4.2.4 Cholesterol and exposure to interpersonal violence as a child

There was a trend toward a negative correlation between serum total cholesterol and exposure to violence as a child (rho = -0.23 and $p = 0.07$).

After, however, performing a standard regression, with exposure to violence as a child as the dependent variable and serum total cholesterol, comorbid substance abuse, and age as independent variables, the association was no longer significant, $p = 0.8$.

4.2.5 Cycle of Violence

In a correlation analysis, exposure to violence as a child showed a significant positive correlation with the expression of violence as an adult (rho = 0.39, $p = 0.002$).

4.2.6 Median split

In order to examine the influence of serum total cholesterol on the Cycle of Violence, i.e., the risk of children exposed to violence becoming violent adults expressing violence toward others, we divided the group into two groups and performed a median split of serum cholesterol levels.

In the "low" group, the mean serum total cholesterol was 4.3 (standard deviation 0.5, range 2.8–4.9, median 4.5), while in the "high" group, the mean serum total cholesterol was 5.7 (standard deviation 0.6, range 4.9–7.6, median 5.6),

There were indications of differences between the groups, apart from serum total cholesterol. The "high" cholesterol group was older (p = 0.0001), with a mean age of 42.4 (standard deviation 10.8, range 24–68, median 42), compared to a mean age of 31.2 (standard deviation 10.8, range 18–55, median 28) in the "low" group.

Furthermore, there was a higher prevalence of substance abuse in the "low cholesterol" group (p = 0.03), with 10 (10/32 = 31.3%) patients having a comorbid substance abuse disorder, compared to 3 (3/32 = 9.4%) patients in the "high cholesterol" group.

Table 2	Suicide attempters Low cholesterol, n = 32				Suicide attempters High cholesterol, l n = 32				
	Mean	Median	SD	Range	Mean	Median	SD	Range	p-value
Gender % F	20/32 62.5%				17/32 53.1%				0.4
Age	31.2	28	10.7	18–55	42.4	42	10.8	24–68	0.0001
Serum cholesterol	4.3	4.5	0.5	2.8–4.9	5.7	5.6	0.6	4.9–7.6	0.0001
Exposure to violence during childhood	2.7	3	1.1	1–5	2.3	2	1.5	0–5	0.2
Used violence as adult	1.7	2	1.2	0–5	1.5	2	1.1	0–4	0.3
Mood disorder	28/32 87.5%				24/32 75%				0.2
Substance Abuse yes %	10/32 31.3%				3/32 9.4%				0.03
Personality disorder %	16/31 51.6%				11/31 35.5%				0.2

4.2.7 Cholesterol and the Cycle of Violence

There was a significant correlation between exposure to violence as a child and expression of violent behavior as an adult in the "low cholesterol" group, rho = 0.52, p = 0.002. In the "high cholesterol" group, there was no significant correlation between exposure to violence as a child end expression of violence as an adult, rho = 0.25, p = 0.2.

We performed two separate standard regression analyses, one for the "low cholesterol" group" and one for the "high cholesterol" group, with the KIVS Subscale "Violent behavior as an adult" as the dependent variable and KIVS subscale "Exposure to violence as a child", age, gender, and comorbid substance abuse as independent variables.

In the group of patients with serum total cholesterol below the median, the R for regression of violent behavior as an adult was significantly different from zero: F = 3.6, DF = 3, p <0.03, and R2 at 0.29 and adjusted R2 0.21. In this group, the only significant predictor of expressed violent behavior as an adult was exposure to violence as a child, t ratio = 3.10, p = 0.005.

In the group of patients with serum total cholesterol above the median, the R for regression of violent behavior as an adult was significantly different from zero: F = 3.6, DF = 3, p <0.03, and R2 at 0.25, and adjusted R2 0.17. In the regression model, the only significant predictor of expressed violent behavior as an adult was comorbid substance abuse, while exposure to violence as a child was no longer significantly correlated with expression of violence as an adult.

	Cholesterol below the median. N = 31		Cholesterol above the median. N = 31	
	t ratio	*p* value	*t* ratio	*p* value
Exposure to violence as a child	3.10	0.0045*	0.13	0.90
Comorbid substance abuse	0.75	0.46	2.59	0.015*
Age	-0.26	0.80	-0.93	0.36

4.3 STUDY III

4.3.1 Characteristics of suicide attempters

Information concerning a previous suicide attempt history was obtained from 82 of the 100 patients included in the study. Fifty patients had made only one suicide attempt, thus having committed their first attempt at inclusion in the study; 19 patients had two attempts (one before the index attempt); 11 patients had a history of 3–5 total attempts; and two patients had a history of more than five suicide attempts. The mean age for onset of suicidal behavior was 31 years (standard deviation, 13.9 years; range, 12–63 years).

Clinical characteristics of suicide attempters with a history of an earlier suicide attempt or attempts, compared to suicide attempters debuting with suicidal behaviour at inclusion in the study, are shown in **Table 3.**

Table 3	Suicide attempters with earlier attempt(s), n = 32				Suicide attempters without an earlier attempt, n = 50				
	Mean	Median	SD	Range	Mean	Median	SD	Range	P value
Gender, % F	21/32 65.6%				33/50 66%				0.97
Age	33.3	30.5	12.1	19–67	35.4	30	13.2	18–63	0.47
Age at first suicide attempt	23.8	20	11.8	12–51	35.6	30	13.2	18–63	0.0001
Number of suicide attempts	2.4	2	0.62	2–4	1	1	0		<0.0001
Exposure to violence during childhood	1.9	1.5	1.6	0–5	1.8	2	1.4	0–5	0.80
Exposure to violence as an adult	2.4	3	1.6	0–5	1.7	2	1.6	0–4	0.047
Exposure to violence total	4.3	4	2.8	0–10	3.4	3	2.5	0–8	0.26
MADRS	14.5	16	6.0	4–24	14.6	14.5	5.1	1–24.5	0.95
Personality disorder, yes, %	9/26 34.6%				12/48 25%				0.38
Substance Abuse, yes, %	8/30 26.7%				10/50 20%				0.49
Smoking, yes, %	12/29 41.4%				26/48 54.2%				0.28
BMI	24.4	23.6	4.7	18–41	25	24.2	4.3	18–40	0.59

4.3.2 Interpersonal violence in suicide attempters

Repeaters reported more exposure to interpersonal violence as an adult compared to suicide attempters without earlier attempts ($p = 0.047$). There was also a significant positive correlation between exposure to interpersonal violence as an adult and the number of earlier suicide attempts (rho = 0.29, $p = 0.012$). Total scores on exposure to violence showed a trend for an positive correlation with number of suicide attempts (rho = 0.20, $p = 0.082$).

Exposure to violence as a child did not correlate with age at the onset of suicidal behavior (rho = 0.16, $p = 0.17$), nor was there any correlation between exposure to interpersonal violence as a child and the number of suicide attempts (rho = 0.09, $p = 0.42$).

4.3.3 Plasma Apolipoprotein E in suicide attempters

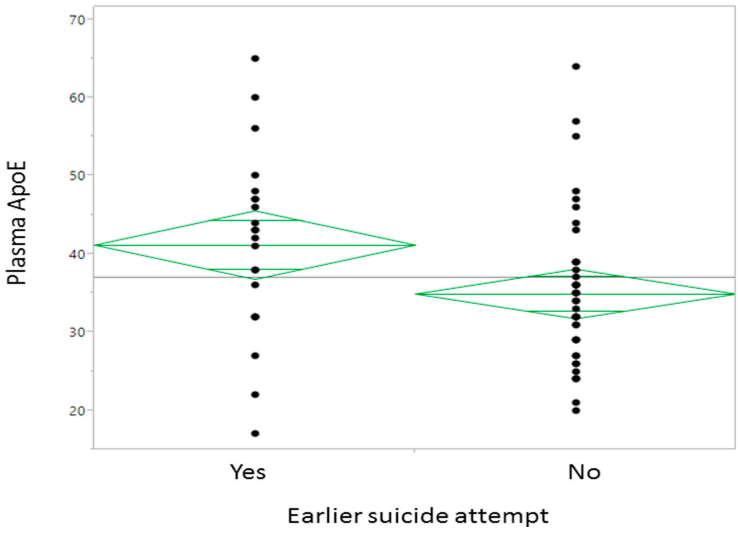
Out of the 100 patients in the cohort, 74 had plasma samples. The mean plasma ApoE level in this cohort of patients with a recent suicide attempt was 36.6 mg/L (SD, 10.7; range, 17–65 mg/L; median, 35 mg/L).

There was no significant difference regarding gender ($p = 0.46$). In the cohort, there were 24 males with a mean plasma ApoE of 34.5 mg/L (SD, 8.0; range, 22–50 mg/L; median, 35 mg/L) and 50 females with a mean plasma ApoE of 37.6 mg/L (SD, 11.8; range, 17–65 mg/L; median, 35.5 mg/L).

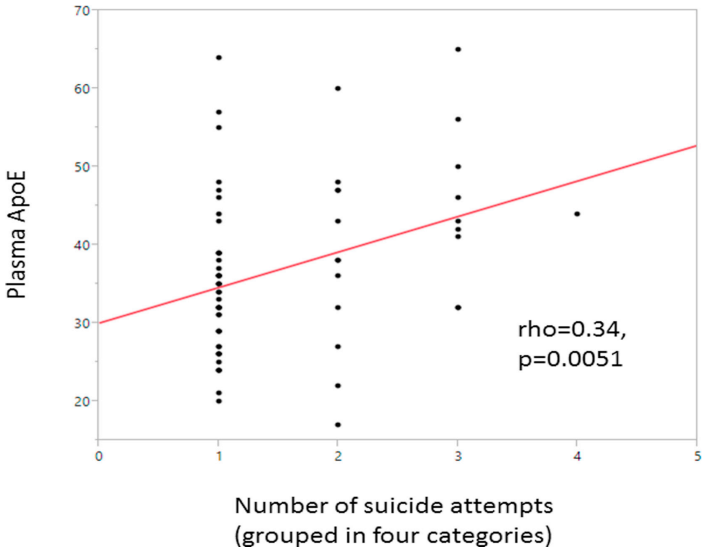
There was a significant positive correlation between age and plasma ApoE (rho = 0.32, $p = 0.005$), but there was no correlation between plasma ApoE and other potential confounders such as tobacco smoking, personality disorder, comorbid substance abuse or with depression severity (according to MADRS) (range of p values, 0.48-–0.91).

4.3.4 Plasma Apolipoprotein E and characteristics of suicidal behavior

The 22 patients with one or more prior suicide attempts had a significantly higher mean plasma ApoE of 41.2 mg/L (standard deviation, 11.6,;range, 17–65; median, 42.5 mg/L), compared to the 42 patients having their first suicide attempt at inclusion in the study, who displayed a mean plasma ApoE of 34.9 mg/L (standard deviation, 9.5; range, 20–64; median, 34 mg/L), (unadjusted value, p = 0.019), a finding which remained significant after correction for age and exposure to violence (p = 0.011).



Plasma Apo E significantly positively correlated with the number of earlier suicide attempts, (rho, 0.34; p = 0.0051). The finding remained significant after correction for the effects of age and interpersonal violence as an adult (p = 0.0048).

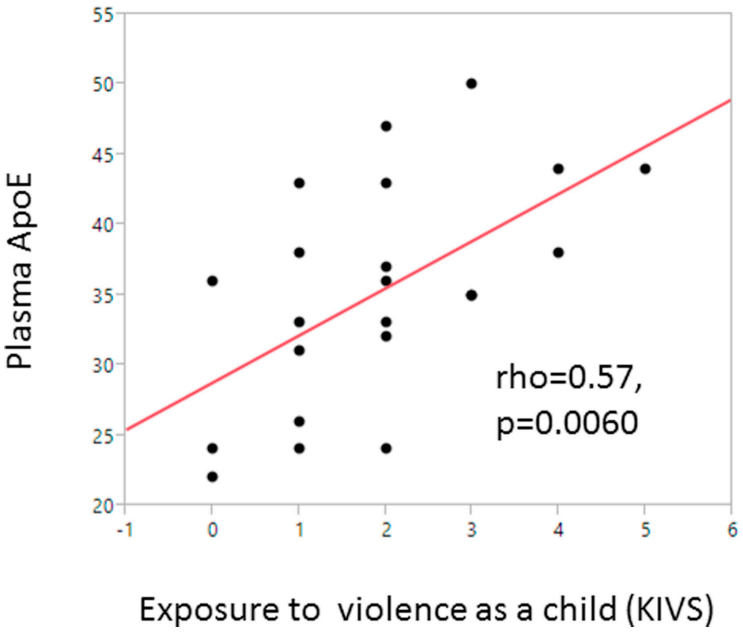


In an unadjusted analysis, age at onset of suicidal behavior did not correlate with plasma ApoE; however, after adjusting for exposure to interpersonal violence as an adult and age, there was a significant negative correlation between age at onset and the level of plasma ApoE (t-ratio, -2.27; p = 0.027).

4.3.5 Plasma Apolipoprotein E and interpersonal violence

There was no significant correlation between total exposure to interpersonal violence and plasma ApoE. Regarding exposure to violence as a child, there was an initial correlation with plasma ApoE (rho = 0.25, p = 0.043). The finding did not remain significant after adjusting for age (p = 0.13).

While there seemed to be no significant correlations between ApoE and exposure to interpersonal violence in the group as whole, after dividing into gender, we found a significant positive correlation between exposure to interpersonal violence and ApoE in the 22 male suicide attempters (rho = 0.45, p = 0.035; adjusted for age, p = 0.021), but not in the 44 women. The correlation between exposure to interpersonal violence and plasma ApoE in males seemed to be borne out by exposure to interpersonal violence as a child (rho = 0.57, p = 0.0055) and remained significant after adjustment for age (p = 0.0059).



4.4 STUDY IV

4.4.1 Characteristics of suicidal behavior

Information regarding an earlier suicide attempt or attempts was obtained from the Suicide Intent Scale in 40 (out of 42) suicide attempters. Since information regarding earlier suicide attempts was the main focus of the study, all further calculations were done based on the 40 suicide attempters with information regarding earlier suicidality.

Seventeen of the patients had made their first suicide attempt at inclusion in the study, 12 patients reported one or two prior suicide attempts, and 11 patients had made 3 or more earlier suicide attempts. Thus, in total, 23 patients (23/40 = 57.5%) were classified as repeaters, while 17 patients (17/40 = 42.5%) were classified as nonrepeaters. There was no significant correlation between repeater status and gender or age.

Nine (9/40 = 23%) of the current suicide attempts were classified as violent and 31 as nonviolent (31/40 = 77%). First-time suicide attempters showed a trend (p = 0.10) toward correlation with a violent method of suicide attempts.

The Freeman Scale mean total score was 5.88 (standard deviation, 1.5; range, 3–9), with a mean Reversibility score of 2.83 (standard deviation, 0.8; range, 1–5), and a mean Interruption Probability of 3.05 (standard deviation, 1; range, 1.5).

4.4.2 CSF 5-HIAA

The mean level of CSF 5-HIAA was 92 nm, with a standard deviation of 34, range of 38.6–177, and a median of 88.

4.4.3 CSF Apolipoprotein E

The mean CSF ApoE level in the 41 suicide attempters was 3.27 mg/L (standard deviation = 1.05; range, 1.35–5.21; median, 3.33 mg/L).

There was no significant difference in CSF ApoE between female suicide attempters (n = 27, 3.24 mg/L, standard deviation =1.18; range, 1.35–5.18; median, 3.33mg/L) and male suicide attempters (n = 14; 3.31mg/L, standard deviation = 0.76; range, 2.49–5.21; median 3.33mg/L) (p = 0.85).

There was no significant correlation between CSF ApoE and depression severity as measured by MADRS. (r = -0.098, p = 0.36).

There was a trend toward a negative correlation between age and CSF ApoE (r = -0.19, p = 0.08).

4.4.4 CSF 5-HIAA, Apolipoprotein E and serum total cholesterol

There were no significant correlations between CSF ApoE and 5-HIAA ($r = 0.079$, $p = 0.46$), nor between CSF ApoE and serum total cholesterol ($r = -0.059$, $p = 0.72$).

4.4.5 CSF Apoliprotein E and characteristics of suicidal behavior

There was a significant negative correlation between CSF ApoE and Freeman Reversibility ($r = -0.31$, $p = 0.049$), but no significant correlation between CSF ApoE and Freeman Interruption Probability ($r = -0.12$, $p = 0.27$).

Violent methods of attempted suicide showed a trend toward lower CSF ApoE ($n = 9$; mean, 2.74 mg/L; standard deviation = 0.64; range, 1.54–3.52; median, 2.79 mg/L), in comparison with nonviolent suicide attempts ($n = 32$; mean, 3.41 mg/L; standard deviation = 1.10; range, 1.35–5.21; median, 2.42 mg/L) ($p = 0.09$).

There was also a trend toward a lower CSF ApoE among the 17 first-time suicide attempters (mean = 2.91 mg/L; SD = 0.90; range, 1.35–4.78; median, 2.81 mg/L), in comparison with the 23 repeaters (mean = 3.49 mg/L; SD = 1.10; range, 1.54–5.21; median, 3.43 mg/L) ($p = 0.09$).

5 DISCUSSION

5.1 CHOLESTEROL - STUDIES I AND II

The main focus of Studies I and II is on serum total cholesterol.

In the first study, we investigated the relationship between serum total cholesterol and CSF 5-HIAA, while the second study examined the relationship between serum cholesterol and the Cycle of Violence. In Study 1, we also examined serum total cholesterol and CSF 5-HIAA in relation to measurements of the severity of psychiatric symptoms.

In clinical studies, it has been difficult to find ways of connecting the seemingly reliable findings of low serum total cholesterol and an increase in suicidal and aggressive behavior with markers of serotonergic activity. Furthermore, there is an apparent lack of direct communication between peripheral serum cholesterol and cholesterol in the CNS, which makes it of vital importance to examine relations with central markers of serotonergic activity (Linton et al., 1991).

Measurements of 5-HIAA in CSF have been used as an indicator of central serotonergic activity. Furthermore, although very seldom used in clinical practice, partly due to the fact that measurements of CSF require a lumbar puncture, CSF 5-HIAA has been repeatedly suggested to be used as a biological marker of risk of suicide (Mann and Currier, 2007; Corryell and Schlesser, 2007; Oquendo et al., 2014). CSF 5-HIAA could thus provide a link between serum total cholesterol levels and central serotonergic activity. There are, however, some problems associated with the use of CSF 5-HIAA as a marker of central serotonergic activity. Even if low 5-HIAA were shown to be a true marker of low serotonergic signaling, this says nothing about which areas of the brain that are affected.

The main finding in Study I, namely, the association between serum total cholesterol and CSF 5-HIAA, provides further support for a potential association between serum cholesterol and central serotonergic activity. It is worth noting, however, that a direct link between serum cholesterol levels and central serotonergic activity is unlikely due to the fact that there is no direct flux of peripheral cholesterol into the CNS. This means that, while the finding provides further evidence of a link between the serotonergic system and cholesterol, the link is most likely mediated by other factors.

We did not find any correlation between the cholesterol level and the scales measuring hopelessness, depression severity, suicide intent, or a violent suicide attempt. In some ways, that was surprising, since low serum cholesterol has been repeatedly associated with suicidal behavior and violent suicide attempts. There have been indications that low total cholesterol is more firmly associated with violent suicide attempts compared to patients with non-violent suicide attempts and to controls, a finding which has been replicated (Alvarez et al., 2000; Vevera et al., 2003; Atmaca et al., 2008).

The increase in risk and alterations in behavior is shown most often in those in the lowest quartile of total serum cholesterol. It is possible that there is no association between serum total cholesterol and behavioral aspects when kept within a certain range, but, at low levels, cholesterol may indirectly or directly be associated with the mentioned behaviors and risk factors. It is even possible that serum total cholesterol is associated with alterations in the risk at both high and low levels (Tanskanen et al., 2000; Partonen et al., 1999).

Linear correlations between serum cholesterol and depression severity as measured by the MADRS, have not been demonstrated in patients with in which most have an active affective disorder (mostly depression) and a recent suicide attempt. On a larger scale, however, associations between serum total cholesterol, suicidal behavior, and depression have generally been demonstrated in comparisons with healthy controls. (Wu et al., 2016).

Unfortunately, the generalizability of our findings is limited due to the lack of a control group. For Study I, a control group would have been useful, primarily in order to see whether the correlation between CSF 5-HIAA and serum total cholesterol was present in controls or merely in depressed and suicidal patients.

The main finding in Study II was that serum total cholesterol may be related to the Cycle of Violence.

In the whole cohort, there was a correlation between exposure to violence as a child and expression of violence as an adult, thus validating the Cycle of Violence.

A combination of abuse during childhood and the development of PTSD has been associated with an increased risk of suicide attempts (Lopez-Castroman et al., 2015) and, as mentioned in the introduction, it has been suggested that impulsive-aggressive suicides may represent a behavioral endophenotype of individuals with behavioral and cognitive difficulties already debuting during childhood, such as, for instance, ADHD or conduct disorder (Turecki, 2005). Furthermore, the development of affective disorders also seems to be associated with the presence of earlier life stressors (Pompili et al., 2011). Since suicidal behavior seems to be associated with earlier traumatization (Lopez-Castroman et al., 2015), exposure to violence as a child might well represent such a trauma, perhaps predicating both suicidal and violent behavior, in vulnerable individuals.

There are earlier findings indicating differential effects of early life stressors according to biological predisposition, as, for instance, studies on the s-allele 5-HTT (Caspi et al., 2003; Uher et al., 2011). Investigating whether cholesterol might be another such a biological marker seemed reasonable. Cholesterol metabolism in the CNS is most active in early years, before the brain is fully formed and myelinized. Cholesterol may thus be a potential factor in sensitivity of an individual to exposure to childhood violence.

Since we intended to explore the association of cholesterol with the Cycle of Violence, we performed a median split and divided the patients into two groups, high and low cholesterol. A method used previously when analyzing the effects of cholesterol on the risk of attempted suicide (Fiedorowicz and Coryell, 2007).

After doing so, we found that the influence of exposure to childhood violence on the use of violence as an adult disappeared in the high cholesterol group and, instead, the expression of violence was associated with substance abuse. On the other hand, in the low cholesterol group, exposure to interpersonal violence as a child was significantly correlated with the use of violence as an adult.

We reported this finding as the first study on cholesterol in relation to the Cycle of Violence. However, depending on the point of view, this was perhaps not an entirely correct statement. In the earlier mentioned study by Virkkunen (Virkkunen, 1983), there was a clear association between low serum total cholesterol and a family history of a violent, and thus potentially abusive, father. The main focus of their study was not, however, on examining whether cholesterol affected the relation between exposure to violence as a child and violent behavior as an adult. Even so, upon closer inspection, the findings seem to be indicative of such a relationship. It is, however, worth mentioning that the study only comprised violent criminal offenders, mostly with antisocial personality disorders, which differs from our cohort of suicide attempters (Virkkunen, 1983).

Another aspect of interest is that earlier studies on the Cycle of Violence (not cholesterol-related) focused mostly on violent crime as an outcome and that most of them search for correlations between abuse and violent criminality. The same outcome is often used in studies on violent behavior and cholesterol. For instance, in an epidemiological study, a strong correlation between low total serum cholesterol and violent crime was found. Subjects with a violent criminal record had significantly lower cholesterol than matching controls (Golomb et al., 2000). Furthermore, another Finnish study on male criminal offenders with antisocial personality disorder found low serum total cholesterol to be associated with an early age of onset with respect to conduct disorder and found low serum total cholesterol to be highly associated with an increased overall risk of death and an increased risk of suicide (Repo-Tiihonen et al., 2002).

It was not unreasonable to expect a fair amount of violence, both experienced and expressed, in this group of patients, which would, in theory, increase the sensitivity for finding a correlation between cholesterol and violence.

Exposure to violence as a child was, as previously mentioned, only related to expression of violence in the low cholesterol group and invalidated the Cycle of Violence in the high cholesterol group. It is not possible, however, to draw any conclusions regarding causality. While the KIVS represents a longitudinal aspect of experienced and expressed violence, it is still a questionnaire administered at a specific time and we have only one measurement of serum total cholesterol.

The findings indicate a potential predictive value of cholesterol measurements in relation to violent behavior, but they do not elucidate whether low cholesterol and violent behavior constitute a trait or a state. The findings of an association between low serum total cholesterol and violent behavior are not, however, limited to studies on adult populations. In a study from the USA, based on the Third National Health and Nutrition Examination Survey, in which 4852 children aged 6–16 had cholesterol levels measured. Non-African-American children with total serum cholesterol in the lowest 25th percentile displayed an almost threefold increase in the risk of suspension or being expelled from school (Zhang et al., 2005). Findings such as these further raise the question of whether low cholesterol in relation to violent behavior constitutes an acquired state or, perhaps, an inborn trait.

In the high cholesterol group, only substance abuse was associated with expression of violence. There was, however, only three substance abusers in the group, which makes the results somewhat unreliable.

The findings from Study II in relation to the KIVS subscales were mostly nonsignificant and mostly determined to ensure that there were no clear confounders, since the main focus was cholesterol levels in relation to the Cycle of Violence.

The lack of a control group is probably less of a problem in Study II since the dividing of the study cohort into two groups enables comparisons. Furthermore, by dividing the group of suicide attempters into two groups, we obtained a control group with mostly similar parameters, except for cholesterol.

Despite our fairly homogeneous clinical group, there were, however, tendencies toward group differences between high and low cholesterol. Substance abuse, mostly alcohol, was more common in the low cholesterol group. As far as we know, alcohol may alter the lipid profile, thereby raising HDL and lowering LDL, but it has less of an impact on total serum cholesterol. This is one of the reasons why an analysis of lipid fractions would have been interesting.

Not unexpectedly, due to the positive correlation between age and serum total cholesterol, the low cholesterol group was almost ten years younger than the high cholesterol group. There was also a tendency toward a slightly lower degree of reported violence as an adult in the high cholesterol group. Age is most certainly a factor in relation to violence, with expression of violence being displayed in a higher degree among younger suicide attempters.

In summary, on exploring the association of cholesterol with the Cycle of Violence, by dichotomizing the group into high and low cholesterol, we found that the Cycle of Violence was only valid in the group of patients with cholesterol below the median.

Our finding could be interpreted either as high cholesterol being associated with less risk of learned violent behavior or that low cholesterol is associated with reduced resilience. Unfortunately, since the measurement of cholesterol was cross-sectional, it is difficult to say whether low cholesterol was present before traumatization or whether it is associated with a

group of individuals with naturally low cholesterol and an “inborn” sensitivity to the Cycle of Violence or a hereditary proclivity for violent behaviors. The findings from the earlier Finnish study may actually indicate the latter (Virkkunen, 1983).

Traumatized patients with a recent suicide attempt and current mood disorder are rare in relation to the general population, but, in clinical psychiatric settings, such as inpatient care, they are well represented, with a potential for clinical use when examining risk factors for violence. Whether the results are applicable to a larger population remains, however, to be seen.

5.2 APOLIPOPROTEIN E - STUDIES III AND IV

Studies III and IV focus mainly on Apolipoprotein E in plasma and in the CSF in two separate groups of suicide attempters.

The main focus of Studies III and IV was to further investigate ApoE in plasma (Study III) and in CSF (Study IV) in relation to the severity of suicidal behavior. The two studies were conducted in two separate groups of suicide attempters. Furthermore, we intended to investigate the relationship between ApoE in the CSF and its relation to serum cholesterol and CSF 5-HIAA. It is somewhat unfortunate that we had no CSF from the group of patients examined in Study III.

The main finding in Study III was that ApoE in plasma was higher in patients with prior suicide attempts. There was also a positive significant correlation between the number of earlier suicide attempts and the level of ApoE in plasma. Both of these findings indicate a possible relation between ApoE and suicidal behavior and may be particularly related to the chronicity of suicidal behavior.

Age of onset correlated negatively with plasma ApoE, further indicating a link between the temporal severity of suicidal behavior and plasma ApoE.

As previously mentioned, there is only one previous study on ApoE in plasma in relation to suicidal behavior and it found no significant difference in ApoE levels between suicide attemters and controls (Baca-Garcia et al., 2004). As far as we know, the only other recent study on psychiatric symptoms of depression in relation to ApoE in plasma investigates depressive symptoms in chronic hepatitis C patients during statin treatment (Sheridan et al., 2014).

Since there are virtually no studies on plasma ApoE in psychiatric populations, the literature available for reference is not always directly related to suicidal behavior, but some of it is still of theoretical interest for the subject of suicidal behavior.

We speculate that the correlation between ApoE and suicidal behavior found in Study III might be related to a stress-induced response and to alterations in the HPA axis. ApoE is involved in inflammatory responses and could thus theoretically be increased in response to chronic stress (Review: Larkin et al., 2000; Colton et al., 2005). The idea that ApoE levels

and the HPA axis are related has been somewhat supported by studies in mice, showing that ApoE levels in plasma may be affected by exposure to corticosteroids (Staels et al., 1991). The effect on ApoE levels in mice seems dependent on the corticosteroid being used and is potentially non cholesterol dependent (Staels et al., 1991, Zuckerman et al., 1993). Furthermore, similar effects were reproduced in rabbits, indicating that the effect may be not specific to species (Zuckerman et al., 1993).

As previously mentioned in "Introduction", there are a number of genetic studies on isomeric effects on suicide which have mostly yielded negative results (Gibbons et al., 2011). Admittedly, none of these studies have specifically investigated the severity of suicidal behavior, nor the relation between interpersonal violence and ApoE. A secondary benefit of including isomeric analyses is, however, that it would have made comparisons with the existing literature on ApoE more reliable.

In Study IV, we examined ApoE in the CSF in relation to CSF 5-HIAA and the severity of suicidal behavior. Our hypothesis was that a suicide attempt might represent a state of stress similar to brain trauma and might thus affect ApoE levels in the CSF. It was, to the best of our knowledge, the first study on ApoE in the CSF in relation to suicidal behavior. In fact, studies on CSF ApoE, in general, are rare in psychiatric populations.

Earlier studies of ApoE in the CSF have almost exclusively focused on its relation to Alzheimer's disease. The findings concerning ApoE in CSF in relation to Alzheimer's disease and other neurodegenerative diseases are ambiguous and, at present, ApoE in the CSF is not regarded as a primary biomarker with respect to neurodegenerative disorders (Review: Genius et al., 2012; Randall et al., 2013).

Interestingly, with regard to physical brain trauma and ApoE, there seems to be a selective depletion of ApoE containing lipoproteins from the CSF after brain damage. An increase in total cholesterol, free cholesterol, and triglycerides was found after subarachnoidal hemorraghe, but no increase in ApoE-containing lipoproteins, which may indicate a role for ApoE in the remodeling of the CNS after traumatic injury, particularly the redistribution of cholesterol (Kay et al., 2003a). Findings after traumatic brain injury were similar. Furthermore, the degree of lowering of ApoE seems to match the severity of the injury, with severe injuries having lower CSF ApoE (Kay et al., 2003b) There also seemed to be a downregulation of beta-amyloids after TBI, something which is at least partly related to ApoE activity and function (Kay et al., 2003c). In summary, ApoE levels seem to be lower in the CSF after brain injury.

We found a significant negative correlation between CSF ApoE and the score on Freeman Reversibility, which appears to indicate an association between low CSF ApoE and more serious suicide attempt methods. There were also trends indicating a correlation between low CSF ApoE and violent suicide attempt methods and low CSF ApoE and first-time suicide attempts. The findings may indicate that low CSF ApoE may be associated with overall seriousness of the suicide attempt.

We did not find any correlations between CSF ApoE and the level of CSF 5-HIAA, nor with serum total cholesterol, which may indicate that the regulatory mechanisms are separate.

In summary, in Study III we found a positive correlation between higher plasma ApoE and repeated suicide attempts, while, in Study IV, we found low CSF ApoE to be associated with the apparent severity of the suicide attempt.

While these findings may at first seem contradictory, it is once again worth noting that suicidal behavior is a an etiologically varied entity. Furthermore, it is uncertain whether ApoE in the CSF correlates with ApoE in plasma. One study, found a mild correlation between ApoE in CSF and ApoE in plasma from Alzheimer patients (Toledo et al., 2014), but there are other studies failing to demonstrate a such a correlation (Yamauchi et al., 1999; Martinez-Morillo et al., 2014).

5.3 STRENGTHS AND LIMITATIONS

5.3.1 Strengths

The patients were carefully examined and well diagnosed. The combination of fasting blood samples and lumbar punctures enabled a correlation analysis of peripheral and central biomarkers. Many of the patients recruited for the study were at the time of inclusion, inpatients being cared for on a psychiatric ward, which made monitoring of samples more reliable and facilitated the collection of complete tests within a relatively short time frame.

There is a diagnostic coherence within the cohort, since most have been diagnosed with a current mood disorder and disorders in the psychotic spectrum have been excluded, which, in turn, limits the number of confounders.

The second cohort (Study III) was also examined extensively and a combination of clinical rating scales and blood samples enabled a detailed analysis.

5.3.2 Limitations

First and foremost is the lack of a control group problematic, primarily because it limits the generalizability in comparisons with the general population, but also with patients with mood disorders and without suicide attempts, or with suicide attempters without mood disorders.

The relatively small sample size might give false negative findings. Furthermore, the cross-sectional design limits the potential for drawing conclusions regarding any causative effects.

Another issue which needs to be addressed is that the cohort upon which Studies I, II, and IV are based was, as mentioned earlier, primarily recruited among inpatients, while the patients in the cohort upon which study IV is based were recruited primarily from outpatient care. The different basis for the recruiting of patients could possibly be associated with an increased severity of illness in the first cohort. However, the criteria for admission to a psychiatric ward was altered over time, as hospital beds were reduced and psychiatric care experienced a shift towards outpatient care. It is therefore reasonable to assume that a large number of patients who would have received inpatient care at the time of recruiting for the first cohort received outpatient care in the period of time during which the second cohort was recruited.

It is very unfortunate that we did not have any whole blood for genotyping since most of the earlier literature on ApoE has taken the genotype into account. The lack of genotyping makes references to the existing literature on the subject of ApoE less reliable. Furthermore, since the metabolization of ApoE varies somewhat according to the isomer, this is, unfortunately, also a potential confounder with regard to the results obtained. Genotyping would, however, have led to even smaller groups and less power to detect group differences. Our studies thus far are mainly descriptive by nature and have demonstrated significant correlations and associations between different factors but do not present convincing evidence for causal relationships. In animal studies it is possible to study the consequences of a knocking out or overexpression of a specific gene, this type of studies are seldom possible in humans.

6 CONCLUSIONS

There are numerous ways in which cholesterol and ApoE could, in theory, affect mood, anxiety, suicidality, and cognition. One difficulty concerning studies on the effects of cholesterol on psychiatric and cognitive disorders is that there can be both direct and delayed effects (Papakostas et al., 2004).

We found a correlation between serum total cholesterol and CSF 5-HIAA in Study I, further strengthening the link between serum total cholesterol and the serotonergic system in suicidal behavior.

In Study II, we found serum total cholesterol to modify the association between exposure to violence as a child and expression of violence as an adult. In fact, in the group with "high" cholesterol, the Cycle of Violence was no longer valid. It is therefore tempting to draw the conclusion that serum total cholesterol is one of the mediating factors involved in the outcome of the Cycle of Violence. However, since we have no prior measurement of cholesterol, it is not possible to draw any causal conclusions with regard to cholesterol with respect to the Cycle of Violence.

We found a positive correlation between plasma ApoE E and the severity of suicidal behavior, as measured by repeated suicidal behavior, the number of suicide attempts, and early age at onset in Study III.We also found a positive correlation between ApoE in plasma and the temporal severity of suicidal behavior and a negative correlation between age at onset of suicidal behavior and ApoE. Exposure to interpersonal violence, particularly exposure to violence as a child, was positively correlated with ApoE in plasma in male suicide attempters. ApoE in plasma may therefore be involved in the humoral response to external and internal stressors, and, in turn, the level of ApoE in plasma may be related to the severity of suicidal behavior.

Finally, in Study IV, we found low ApoE the CSF to correlate with the severity of the current suicide attempt. Among suicide attempters, low CSF ApoE was significantly negatively correlated with reversibility of a suicide attempt method, and there were trends toward an association between lower CSF ApoE and violent suicide attempt and low CSF ApoE and first-time suicide attempts. It is therefore possible that low CSF ApoE may be associated with the degree of trauma associated with the suicide attempt.

We conclude that further studies on both cholesterol and ApoE, especially in violent, impulsive, and suicidal populations, are warranted.

7 FUTURE DIRECTIONS

Most psychiatric disorders are, in one way or another, associated with various degrees of neuronal damage, mostly via inflammatory processes. One could argue that one could also include cognitive decline in dementias and alcohol-induced damage or traumatic brain injury. The severity of the symptoms should be, at least in part, attributable to the individual's ability to reconstruct/rebuild/recycle. Adaptability partly depends on the ability to create and maintain new synaptic formations.

It is not unreasonable to hypothesize that the ability to recover from depressive, manic, or psychotic episodes might be partly due to entirely different aspects than those that led to the illness.

At the moment there is, however, a tendency to use the same treatments and dosages, both psychological and pharmacological, when treating acute symptoms as when the patient is in recovery or remission.

Cholesterol and lipids in general are an area where one could see both potential treatment and diagnostic opportunities in the psychiatric field. It is far from certain that suicidology is the area which has most to gain from further research into the cholesterol metabolism.

7.1 SIDE-CHAIN OXIDIZED OXYSTEROLS

We are currently analyzing oxysterols in the CSF in order to investigate whether these levels, which we know have a direct effect on cholesterol metabolism in the brain, correlate with CSF 5-HIAA.

Due to the unique ability of oxysterols to transverse the blood-brain barrier, they may facilitate a direct link between serum total cholesterol and central cholesterol metabolism.

Furthermore, changes in oxysterol levels, especially 24-OHC and the ratio between 24-OHC and 27-OHC, may be a promising avenue for future research.

Cognitive symptoms associated with psychiatric disorders are generally difficult to treat and are often the last symptoms to remain. Cholesterol is, as mentioned earlier, crucial for neurogenesis and synaptic formation.

Prospective studies on how levels of 24-OHC fluctuate over time would therefore be very interesting, especially with regard to the evaluation of treatment effects and remission, since 24-OHC levels seem to correlate directly with cholesterol synthesis in the CNS.

7.2 STATINS FOR TREATMENT OF PSYCHIATRIC CONDITIONS

At the present state of knowledge a role for statins in the treatment of psychiatric diseases can not be excluded. Some potential examples are manic or psychotic states, in which a reduction in the overall inflammatory activity might be beneficial.

There are some studies in rats which indicate a potential augmentation of the antidepressant effect of fluoxetine by lovastatin (Renshaw et al., 2009) and even a perceived direct positive effect on mood after treatment with simvastatin, particularly when exposed to stress (Can et al., 2012; Lin et al., 2014).

Whether such findings are transferable to humans is less certain. However, in a meta-analysis reviewing the results of three published randomized controlled trials evaluating the effect of statin add-on treatment for depression, the results indicate that statins may indeed be of potential use in the treatment of depression, but that further trials are needed (Salagre et al., 2016).

In a large epidemiological study, concomitant use of statins and SSRI was associated with fewer psychiatric hospital contacts overall and with fewer psychiatric hospital contacts due to depression (Köhler et al., 2016). Furthermore, there are actually some indications that statins may have gender-related effects on aggression. In a large double-blind RCT study, statins were actually found to decrease aggression (and testosterone) in men, while increasing aggression in women (Golomb et al., 2015).

Further studies on the use of statins in psychiatry are clearly warranted.

8 ACKNOWLEDGMENTS

First of all, I wish to thank Jussi Jokinen, my guide, my shining light, my main supervisor. I cannot express the immense gratitude I feel for your guidance, patience, and knowledge. Guiding me through the "Narrows" was no easy task. I am sometimes not the most organized or coherent person in the world, but you were always there for me when I needed it. I am in awe of your skill and your kindness. You are truly the best.

Thank you, Ingemar Björkhem. You were a late addition as co-supervisor, but a very, very appreciated one. When I suddenly had access to true expertise in the field of cholesterol, I realized how much there was that I didn't know. Unfortunately, it was a lot! My questions were, and still are, endless. I am truly in your debt.

Thank you, Anna-Lena Nordström, my first co-supervisor, for asking me what the *purpose* of my research was. I have taken it to heart.

Thank you, Jonas Svensson, my mentor and dear friend. You have been of immense help and you are indeed a true friend. Furthermore, you are probably twice the scientist that I am. When my theories and speculations threatened to balloon out of proportion, you kindly shot me down every time. Much obliged, Dr. Obispo!

I also wish to thank Peter Nordström, for allowing me to use his material, his great scientific advice and for being a really cool guy.

A special thanks to Henrik Nybäck, for insightful comments at the half-time seminar. They helped me a lot.

Thank you, Anna Mademyr for guiding me all the way to becoming a specialist in psychiatry. You always made me feel welcome and at home in psychiatry. Your kindness, warmth, and competence were very much appreciated.

Thanks to Andreas Liliequist for the great scientific discussions (while running), your great advice, and for just being an awesome friend. We talked, we ran, and I destroyed you in board games. It's time to get that Hat, Dr. Liliequist!

Thanks to Martin Lundmark for remaining a true friend over all these years. You have been like an extra brother and I have always counted on you to be there when needed.

I also wish to thank the members of the Book Club, Jonas Svensson, David Bergman, and Alexander Liakos, for allowing me to discuss Science Fiction with the same gravity as real science. There is more to life than just Science, and Spaceships, and Lasers are of particularly importance among them.

Thanks to you, Ayn Rand, for your amazing practical joke.

Thank you, Lisa Sjölin, for being the best boss ever. It was a joy to work for you all those years. I also wish to send a big hug to my colleagues at Upplands Väsby, Henrik, Hiie, Jon, Katarina, Marie and Marja. Every time I took time off for research, you were there to take care of my patients. Thanks also to my team at Upplands Väsby and all my other friends at Sigtuna/Upplands Väsby Psykiatriska Mottagning. I miss you all very much.

I also wish to thank those at my previous clinic, Psykiatri Nordväst, for always allowing me to take time off for research when I needed to and for allowing me to attend both congresses and the National Research School in Psychiatry. It most probably prevented an ulcer or two.

I am very grateful to the Gadelius Foundation and to the Center for Psychiatric Research (CPF) for their financial support.

Thank you, Ioannis Pantziaras. Statistically, I owe you.

Thank you, Mr. Isaac Austin. Use of correct prepositions correlates significantly *with* (not *to!*) you. Bravo, Mr. Austin! I am very grateful.

Thank you for being my brother, Brother. You are awesome. Much love.

Mum and Dad, I am what I am because of you. I love you with all my heart.

Lastly, I am so very grateful for the love and support from my family. My beautiful and clever Emma, my thoughtful Frog, and my energetic Duck. I love you all!

Finally, as I considered this part of my thesis to be the hardest part to write, I saved it for last. There are so many whom I a grateful to and would like to thank. Unfortunately, I cannot mention all of you, as I would have to go on forever. Thank you all!

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