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Research report

A genetically informed test of cholesterol levels and self-control, depressive Symptoms, antisocial behavior, and neuroticism

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ABSTRACT

Background: Low cholesterol levels have been found to be associated with a wide range of behavioral problems, including violent and criminal behavior, and a wide range of psychological problems including impulsivity, depression, and other internalizing problems. The casual mechanisms underlying these associations remain largely unknown, but genetic factors may play a role in the etiology of such associations as previous research has found significant genetic influence on cholesterol levels and various deleterious behavioral and psychological outcomes. The current study addressed this existing gap in the literature by performing a genetically sensitive test of the association between cholesterol levels and various outcomes including levels of self-control, depressive symptoms, anger expression, and neuroticism.
Methods: DeFries–Fulker (DF) analysis was used to analyze data from 388 twin pairs nested within the Survey of Midlife Development in the United States (MIDUS).
Results: The results of the genetically informed models revealed that high-density lipoprotein (HDL) cholesterol levels were negatively and significantly associated with depressive symptoms, had a marginally significant effect on neuroticism, and a nonsignificant effect on both anger expression and self-control.
Limitations: The findings may not extrapolate to the larger population of American adults since the subsample of twins with cholesterol information may not be nationally representative.
Conclusions: Genetic influences play a significant role in the association between cholesterol levels and various deleterious outcomes and failing to control for these influences may result in model misspecification and may increase the probability of detecting a significant association when one does not actually exist.

1. Introduction

A substantial body of literature has identified a consistent association between cholesterol levels and a wide range of deleterious outcomes including various forms of antisocial behavioral (Conklin and Stanford, 2008; Golomb, 1998; Golomb et al., 2000, 2004; Hillbrand and Spitz, 1999; Repo-Tiihonen et al., 2002). For example, a number of studies have reported significant associations between overall lower levels of cholesterol and violent criminal behavior (Golomb, 1998; Golomb et al., 2000). A complementary line of literature has also detected a fairly consistent association between lower cholesterol levels and various traits that have been found to be strongly correlated with serious criminal behavior such as aggression, anger, conduct disorder, and antisocial personality disorder (Boston et al., 1996; Hillbrand and Spitz, 1999; Kaplan et al., 1997; Sahebzamani et al., 2013; Sutin et al., 2010). In addition to the fairly consistent association between lower cholesterol levels and externalizing problems, studies have also reported somewhat mixed evidence suggesting a possible association between lower cholesterol levels and various internalizing problems including impulsivity and depression (New et al., 1999; Ormiston et al., 2003; Pozzi et al., 2003; Steegmans et al., 2000; Tedders et al., 2011).

Compared with the large number of studies identifying a significant association between cholesterol levels and various deleterious outcomes, studies which attempt to better specify the underlying etiology of such associations are surprisingly elusive. One of the leading explanations of such associations implicates the role of the neurotransmitter serotonin and proposes that overall lower levels of cholesterol are indicative of overall lower levels of serotonergic

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activity in the brain. Importantly, a substantial body of literature has linked lower levels of serotonin to a host of detrimental outcomes including antisocial behavior (Moore et al., 2002), impulsivity (Dalley and Roiser, 2012; Reist et al., 2004), and depressive symptoms (Nemeroff and Owens, 2009).

A complementary, yet unexplored, explanation for the association between cholesterol levels and various outcomes focuses on underlying genetic influences on the association. Previous research has revealed that cholesterol levels (de Miranda Chagas et al., 2011; Pérusse et al., 1997), antisocial behavior (Ferguson, 2010; Miles and Carey, 1997; Rhee and Waldman, 2002), and various psychological problems (Beaver et al., 2008; Hur and Bouchard, 1997; Haberstick et al., 2005; Johnson et al., 2002; Sullivan et al., 2000) are under moderate to strong genetic influence. These findings indicate that previously observed associations may simply be a result of model misspecification and spurious due to genetic confounding (McGue et al., 2010; Johnson et al., 2009). The current study analyzes a nationally representative sample of twins from the Survey of Midlife Development in the United States (MIDUS) using a genetically sensitive modeling strategy in an effort to isolate the potential effect of cholesterol levels on levels of self-control, depressive symptoms, anger expression, and neuroticism. In this way, the current study is the first to explore the potential association between cholesterol levels and such a wide range of both internalizing and externalizing problems in addition to being the first study to examine such associations within the confines of a genetically informed model.

2. Cholesterol, antisocial behavior, and psychological disorders

A body of research spanning several decades has identified a significant association between cholesterol levels and serious behavioral problems, wherein individuals with lower overall levels of cholesterol display significantly higher levels of antisocial and violent criminal behavior than their counterparts (Conklin and Stanford, 2008; Golomb, 1998; Golomb et al., 2000, 2004; Hillbrand and Spitz, 1999; Repo-Tiihonen et al., 2002). Along the same lines, several studies have revealed that individuals with lower levels of cholesterol are more likely to score higher on measures of aggression and anger (Hillbrand and Spitz, 1999; Sahebzamani et al., 2013), have a higher risk of injury and other sources of non-illness mortality (Jacobs et al., 1995; Muldoon et al., 2001), and are significantly more likely to display impulsive and violent suicidal behaviors (Atmaca et al., 2002; De Berardis et al., 2012; Marčinko et al., 2007) compared to individuals with relatively higher cholesterol levels (but see Brunner et al., 2006; Tanskanen et al., 2000).

Mounting evidence also suggests that lower cholesterol levels are associated with a wide range of psychological traits and disorders. For example, lower cholesterol levels have been found to significantly predict impulsivity (New et al., 1999; Ormiston et al., 2003; Pozzi et al., 2003), greater risk for internalizing problems including conduct disorder and antisocial personality disorder (Boston et al., 1996; Kaplan et al., 1997; Sutin et al., 2010), and depression (Ormiston et al., 2003; Steegmans et al., 2000; Tedders et al., 2011). However, the observed association between lower cholesterol levels and greater prevalence of depressive symptoms remains far from conclusive, with additional studies finding no significant association (Apter et al., 1999; Freedman et al., 1995; Pozzi et al., 2003; Repo-Tiihonen et al., 2002; Sahebzamani et al., 2013).

3. The cholesterol–serotonin hypothesis

Despite the sheer number of studies examining the association between cholesterol levels and various externalizing and internalizing problems, the underlying etiology of such associations remains somewhat unknown. One of the leading explanations is referred to as the cholesterol–serotonin hypothesis and implicates the effect of cholesterol on the neurotransmitter serotonin (5-HT; for a more detailed overview see Kaplan et al., 1997). More specifically, the removal of cholesterol from synapses during neurotransmission may result in lower levels of postsynaptic bonding of 5-HT, resulting in fewer molecules bonding to postsynaptic neurons and a reduction in overall serotonergic activity in the brain (Engelberg, 1992; Kaplan et al., 1997; Kim et al., 2011). In this way, the cholesterol–serotonin hypothesis asserts that lower levels of cholesterol result in lower levels of serotonin in the brain, which in turn, results in a host of behavioral and psychological disorders. Based on this hypothesis, the effect of low cholesterol levels on negative outcomes is mediated by an overall reduction in serotonin.

Although no study has directly assessed all of these associations as they relate to the cholesterol–serotonin hypothesis in a single study, it is possible to link together findings from studies which provide some evidence in favor of this hypothesis. For example, Kaplan et al. (1991) reported that adult monkeys that were fed diets lower in cholesterol and saturated fats displayed significantly higher levels of physical aggression than the comparison group which was fed diets high in cholesterol and saturated fat. In addition, the results of a meta-analytic review indicated that lower levels of 5-hydroxyindoleacetic acid (5-HIAA; a primary serotonergic metabolite) significantly predicted increased levels of antisocial behavior (Moore et al., 2002). Lower levels of serotonergic activity have also been found to significantly predict increases in depressive symptoms (Nemeroff and Owens, 2009), impulsivity (Dalley and Roiser, 2012; Reist et al., 2004), and other internalizing problems (Apter et al., 1999; Graeff et al., 1996). A number of studies have also found more direct evidence in favor of the serotonin–cholesterol hypothesis including significant and positive correlations between cholesterol levels and serotonergic activity (Asellus et al., 2010; Buydens-Branchey et al., 2000; Comings et al., 1999; Marčinko et al., 2007; Scanlon et al., 2001). Despite these findings in favor of the cholesterol–serotonin hypothesis, the extant literature remains somewhat mixed with other studies reporting nonsignificant associations between cholesterol and serotonin levels (Alvarez et al., 1999; Modal et al., 1995; Sarchiapone et al., 2001).

4. The potential role of genetic influences

A complementary line of research indicates that cholesterol levels and many of the deleterious outcomes that have been found to be associated with cholesterol levels are influenced by genetic factors (Beaver et al., 2008; de Miranda Chagas et al., 2011; Ferguson, 2010; Haberstick et al., 2005; Johnson et al., 2002; Pérusse et al., 1997). For example, the results of a number of studies indicate that genetic factors explain between 32 and 83 percent of the variance in cholesterol levels, with environmental factors explaining the remaining variance (de Miranda Chagas et al., 2011; Pérusse et al., 1997). Research has also revealed a significant genetic influence on various outcomes related to other internalizing and externalizing problems including aggression (Ferguson, 2010; Miles and Carey, 1997; Rhee and Waldman, 2002), impulsivity (Beaver et al., 2008; Hur and Bouchard, 1997), depression (Johnson et al., 2002; Sullivan et al., 2000), and additional internalizing problems (Haberstick et al., 2005). One study, moreover, has revealed that measured genetic polymorphisms linked to regulation of serotonergic systems (such as the serotonin transporter gene 5-HTTLPR) significantly moderate the association between cholesterol levels and various deleterious