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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

outcomes including depression (Kim et al., 2011). Collectively, these results provide preliminary evidence suggesting genetic factors potentially play a significant role in the association between cholesterol levels and various deleterious outcomes.

In line with research examining the influence of genetic factors on cholesterol levels and various behavioral and psychological outcomes, a recent case study provides additional evidence suggesting genetic factors may also play a role in such associations (Reilly et al., 2011). More specifically, upon the administration of a commonly prescribed statin (atorvastatin), a father and his son both displayed a similar set of adverse behavioral effects including irritability, aggression, and depression. Shortly after the use of the prescribed medication was discontinued, behavior in both the father and his son returned to normal. While these results require replication, they provide preliminary evidence suggesting that genetic factors play a role in the association between cholesterol levels and both behavioral and psychological outcomes.

5. The current study

Despite the findings of these studies, to our knowledge, no studies have examined the potential role that genetic factors play in the association between cholesterol and deleterious outcomes. More specifically, no studies have explored whether cholesterol levels significantly predict various behavioral and psychological outcomes within the confines of a genetically informed modeling strategy. This overall lack of attention from prior research is troubling since recent research has indicated that failing to properly account for genetic effects in quasi-experimental research designs results in model misspecification and potential confounding, making it virtually impossible to draw causal conclusions (Johnson et al., 2009; McGue et al., 2010). The current study aims to address this gap in the literature by examining whether cholesterol levels are significantly associated with measures of self-control, anger expression, depressive symptoms, and neuroticism. To do so, a nationally representative sample of twins from the Survey of Midlife Development in the United States (MIDUS) is analyzed (Brim et al., 1996).

6. Methods

6.1. Data

The MIDUS study is a nationally representative two-wave data project funded by the National Institute on Aging (Brim et al., 2004). The first wave of data collection was carried out between 1995 and 1996 and included over 7000 adults ranging in age from 25 to 74 years old. Importantly, a national sample of twins ($N=1914$) is also nested within the full sample. All respondents were selected using random-digit dialing sampling techniques and were asked to report on a range of social, biomedical, and psychological topics via self-administered and phone questionnaires. For example, respondents were asked about their job history, medication use, diet, physical exercise, personal beliefs, and their relationship satisfaction (Brim et al., 2004).

Twin pairs were recruited into the sample with a two-part process. First, a prospective nationally representative sample of approximately 50,000 households was screened for the presence of a twin pair as a part of an ongoing national omnibus survey. Second, households that included at least one twin pair were asked to participate in the MIDUS study. Of the nearly 7500 households reporting twins, 60 percent agreed to participate in first wave of data collection. For families with more than one twin pair, all pairs that agreed to participate in the study were included. In total, 1914 twins (998 pairs) were included in the first wave of data collection. Respondents identified as twins were asked to report on their relationship with their co-twin, perceived zygosity, and physical characteristics. Eight items drawn from the twin-specific interview were used to determine zygosity. Similar methods of determining zygosity have been shown to be over 95 percent accurate (Reitveld et al., 2000).

The second wave of data collection was carried out between 2004 and 2006, when respondents were 32–84 years old. Similar to Wave 1, respondents were asked to report on various aspects of their social lives and physical/mental health via telephone and self-administered questionnaires. In addition to the standard questionnaires, a subset of respondents ($N=1255$) was asked to participate in the Biomarker Project, an extensive physical health assessment. Respondents were eligible to participate in the Biomarker Project if they had already completed the Wave 2 phone interview and self-administered questionnaire and their existing health information indicated that they were able to travel to one of three General Clinical Research Centers: University of California, Los Angeles (UCLA), University of Wisconsin, or Georgetown University. Clinicians and trained staff collected a wide variety of medically related information from each respondent including vital signs, functional capacities, bone density, and medication usage. In addition, each respondent was subjected to a comprehensive physical exam and provided fasting blood draws, 12-hour urine samples, and saliva tissue specimens. Respondents were also asked to complete a self-administered questionnaire covering topics such as sleep quality, medical history, drug use, exercise habits, and diet.

Importantly, a subset of the full twin subsample also participated in the Biomarker Project ($N=388$; Love et al., 2010). The current study draws directly from this pool of respondents, limiting the final analytic sample to dizygotic (DZ; same and opposite sex) and monozygotic (MZ) twin pairs that participated in the Wave 2 Biomarker Project. For households with more than one participating twin pair, one twin pair was selected at random. In addition, a total of 41 twins were dropped from the final analytic sample due to either undetermined or mismatched zygosity (i.e., one twin was coded as MZ while their co-twin was coded as DZ).

7. Measures

7.1. Cholesterol

Fasting blood samples were collected during Wave 2 interviews for all respondents who agreed to participate in the Biomarker Project. Enzymatic colorimetric assays were used to determine each respondent's triglycerides, high-density lipoprotein (HDL), and total cholesterol levels. Low-density lipoprotein (LDL) cholesterol levels were determined using the Fridewald formula. Additional information regarding the collection and processing of tissues used in the Biomarker Project has been provided elsewhere (Love et al., 2010). All four cholesterol measures were recoded into 4-item categorical measures, with each category representing the quartile in which each respondent's respective cholesterol level falls. The final categorical cholesterol measures were coded as follows: 4=75th percentile or higher, 3=greater than the median, but less than the 75th percentile, 2=less than the median, but greater than the bottom 25th percentile, and 1=bottom 25th percentile. Means, standard deviations and sample sizes for all measures included in the current study are reported in Table 1.

7.2. Self-control

A 22-item self-control measure was constructed using responses from the Wave 2 self-administered questionnaire. Respondents were asked how strongly they agree with various statements concerning

Table 1
Means, standard deviations, and sample size for all measures.

	Mean (%)	SD	*N* (MZ/DZ)
Cholesterol measures			
LDL cholesterol level	2.50	1.13	379(196/183)
HDL cholesterol level	2.49	1.13	379(196/183)
Triglycerides level	2.51	1.13	380(196/183)
Total cholesterol level	2.51	1.13	381(196/183)
Outcome measures			
Self-control	44.03	8.13	1110(432/678)
Depressive symptoms	27.16	7.24	377(194/183)
Anger expression	13.79	6.69	373(193/98)
Neuroticism	4.25	2.50	1139(436/703)
Sex			
Male	44.58	–	818(328/490)
Female	55.42	–	1017(370/647)
Race			
White	94.49	–	1578(607/971)
Other race	5.51	–	92(39/53)
Age	44.97	12.09	1835(698/1137)

their social relationships, decision-making process, self-confidence, and coping styles. For example, respondents were asked how likely they were to give up on something after encountering problems and whether they like to make plans for the future. Responses to all 22 items were coded as follows: 1=a lot, 2=some, 3=a little, 4=not at all. Exploratory factor analysis revealed that all 22 items loaded on a common factor. The self-control scale was created by summing all 22 items (α=.81) with higher values indicating higher levels of self-control.

7.3. Depressive symptoms

Depressive symptoms were measured using the Center for Epidemiological Studies Depression (CES-D) scale, which is a validated and widely used measure of depression (Radloff, 1977). Respondents were asked to report how much they felt or experienced things the way described during the past week. For example, respondents were asked how much they "felt lonely" or "felt that people dislike me." Responses were coded using as follows: 1=rarely or none of the time; 2=some or a little of the time; 3=occasionally or a moderate amount of the time; and 4=most or all of the time. Scores on the 20 items were summed to create the depressive symptoms scale (α=.89), where higher scores indicate greater levels of depressive symptoms.

7.4. Anger expression

A 20-item anger expression measure was constructed using items from the Wave 2 Spielberger Anger Expression Inventory, a sub-portion of the State-Trait Anger Expression Inventory (Spielberger, 1996). The measure was created by combining the Anger Expression-In (8-item index), Anger Expression-Out (8-item index), and Anger Expression-Control (4-item index) sub-indices. Respondents were asked to record how they generally respond to various situations when angry or furious. For example, respondents were asked if they harbor grudges, slam doors, say nasty things, lose their temper or strike out at whatever infuriates them, or make threats when they are angry or furious. Responses were coded as follows: 1=almost never, 2=sometimes, 3=often, and 4=almost always. Scores on all 20 items were then summed to create the anger expression scale (α=.81), with higher values representing higher levels of anger expression.

7.5. Neuroticism

Neuroticism was measured using four items drawn from The Midlife Development Inventory (MIDI) Personality scales (Lachman and Weaver, 1997). Respondents were asked how well they believed each of the following four adjectives described them: moody, worrying, nervous, and calm. Responses were coded as 1=a lot, 2=some, 3=a little, and 4=not at all. The calmness item was reverse coded and all four items were then combined into an additive scale (α=.75), where higher values represent higher levels of neuroticism.

7.6. Controls

Three demographic control variables were included in the analyses. First, each respondent's race was recorded during Wave 1 interviews and recoded as a dummy variable (0=White and 1=all other races). Second, gender was also coded as a dichotomous variable where 0=female and 1=male. Third, age was included as a continuous variable measured in years.

8. Plan of analysis

The analyses for the current study were carried out in a series of interrelated steps. First, bivariate correlations were estimated between all variables of interest to determine whether cholesterol levels covary with self-control, depressive symptoms, anger expression, and neuroticism. Second, a series of multivariate ordinary least squares (OLS) regression models were estimated to partial out the effects of race, gender, and age. More specifically, a separate regression equation was estimated for each of the examined outcome measures in which each measure was regressed on the four categorical cholesterol measures and demographic controls.

Third, DeFries–Fulker (DF) analysis was used to control the potentially confounding effects of genetic influences and isolate the effect of cholesterol levels on self-control, depressive symptoms, anger expression, and neuroticism (DeFries and Fulker, 1985). DF analysis is a regression-based statistic that is appropriate when analyzing samples of twin dyads and sibling pairs. This modeling technique is commonly used in behavior genetic research and provides accurate estimates of the proportion of overall variance in the phenotype of interest that is explained by additive genetic (symbolized as h^2) and shared environmental (symbolized as c^2) influences, with the residual variance attributed to nonshared environmental (symbolized as e^2) influences and error. Shared environmental influences make siblings from the same household more similar to one another, while nonshared environmental influences contribute to differences in siblings from the same household.

The original DF equation proposed by DeFries and Fulker (1985) was developed to be used with clinical samples of twins where one twin had an extreme score on the outcome measure of interest. Rodgers et al. (1994) modified the original equation to allow for the use of samples drawn from the general population. The modified equation is as follows:

$$K_1 = b_0 + b_1 K_2 + b_2 R + b_3 (R * K_2) + e \quad (1)$$

where K_1 is the score on the outcome measure (self-control, depressive symptoms, anger expression, or neuroticism) for one twin, K_2 is the score on the same outcome measure for their co-twin. R measures the level of genetic similarity between each twin and their co-twin (R=1.0 for MZ twins, R=.5 for DZ twins), and $R * K_2$ is an interaction term created by multiplying R by K_2. In Eq. (1), b_0= the constant, b_1= the proportion of variance in the

outcome measure that is due to the shared environment (c^2), b_2 is not typically interpreted in Eq. (1), b_3= the proportion of the variance in the outcome explained by genetic factors (h^2). The remaining variance in the outcome measure is captured by the error term (e) which is equal to the proportion of the variance in the outcome measure explained by the nonshared environment (e^2) plus error.

In a recent modification, Rodgers and Kohler (2005) provided an improved equation. The modified DF equation is as follows:

$$K_1 = b_0 + b_1(K_2 - K_m) + b_2[R*(K_2 - K_m)] + e \quad (2)$$

where K_1 is still the outcome measure for one twin, K_2 remains the same outcome measure for their co-twin, and R is still the measure of genetic similarity between the twins. The new term included in Eq. (2) that was not included in Eq. (1) is K_m, which is equal to the mean value of K_2. Also, the main effect of R has been dropped from Eq. (2) but is still included in the interaction term, $[R*(K_2 - K_m)]$. In Eq. (2), b_1= the proportion of variance in the outcome measure that can be explained by c^2, b_2=the proportion of variance in the outcome measure that can be explained by h^2, and e=the proportion of variance in the outcome measure that can be explained by e^2 plus error.

Importantly, the coefficients in the DF equation are latent factors that provide an estimate of the proportion of variance in the outcome measure that can be explained by genetic, shared environmental, and nonshared environmental influences. In this way, the coefficients in the DF equation do not implicate specific genetic or environmental influences on the examined phenotype. In an effort to provide a better understanding of the specific genes or environments that contribute to nonshared influences on the outcome measure, Eq. (2) has been modified to include sources of nonshared variance (Rodgers et al., 1994):

$$K_1 = b_0 + b_1(K_2 - K_m) + b_2[R*(K_2 - K_m)] + b_3 ENVDIF + e \quad (3)$$

Eq. (3) is virtually identical to Eq. (2) with the exception of one new term, ENVDIF. This term is a difference score that is created by subtracting the first twin's score on a given measure from their co-twin's score on the same measure. The resulting term (symbolized as ENVDIF in Eq. (3)) measures the difference between twins on that measure. The corresponding coefficient (b_3) is different from the other coefficients in the DF equation and does not provide an estimation of explained variance. Rather, b_3 does not express the magnitude of the effect but indicates whether ENVDIF significantly contributes to nonshared environmental influences and the direction of the association. The remaining coefficients included in Eq. (3) are interpreted in the same manner as in Eq. (2).

A series of DF models were estimated for each of the outcome measures of interest (i.e., self-control, depressive symptoms, anger expression, and neuroticism). First, a baseline DF model was estimated using Eq. (2). This model provided an estimation of the amount of variance in each of the outcome measures that was explained by genetic, shared environmental, and nonshared environmental influences. Second, each of the categorical cholesterol measures was included in the DF model as a source of nonshared environmental influence using Eq. (3) in a stepwise fashion. This second set of DF models provided coefficients that indicate whether between twin differences in each of the cholesterol measures significantly contributed to each of the examined outcomes, net of the effect of genetic and shared environmental influences.

9. Results

The results of the bivariate correlations between cholesterol levels and each of the outcome measures are presented in Table 2. The results revealed that only HDL cholesterol levels were significantly correlated with each of the outcome measures. Total cholesterol was not significantly associated with any of the examined outcome measures. While the remaining cholesterol measures (i.e., LDL and triglycerides levels) were significantly associated with some of the examined outcomes, the pattern of results was inconsistent with only some significant correlations. In addition, each of the significant associations was positive, suggesting that higher levels of cholesterol were associated with higher levels of depression (both LDL and triglycerides) and anger expression (triglycerides).

The results of the baseline OLS regression models are presented in Table 3. For each model, the examined outcome measure was regressed separately on each of the cholesterol measures and the demographic control variables (age, race, sex). The first two columns from the left of the table report results for the self-control measure. None of the cholesterol measures significantly predicted levels of self-control after controlling for age, sex and race. The next two columns from the left present findings from the OLS model examining the association between cholesterol levels and depressive symptoms. LDL cholesterol levels significantly predicted depressive symptoms (Beta=.12, $p \leq .05$), but the results indicated that higher levels of LDL cholesterol are associated with a greater prevalence of depressive symptoms. A similar pattern of findings was reported for the association between triglycerides and depressive symptoms (Beta=.12, $p \leq .05$). The association between HDL cholesterol levels and depressive symptoms was also significant which indicated that respondents with lower levels of HDL cholesterol were more likely to have experienced depressive symptoms (Beta=−.24, $p \leq .01$). Total cholesterol levels failed to significantly predict depressive symptoms. The next two columns from the left present the results of the OLS model examining the association between cholesterol levels and anger expression. The results revealed that lower levels of HDL cholesterol resulted in higher levels of anger expression (Beta=−.15, $p \leq .01$), net of the effect of age, sex, and race. All other cholesterol levels failed to significantly predict levels of anger expression after including the demographic controls in the model. The final two columns of the table present findings from

Table 2
Correlation matrix of all included measures.

	1	2	3	4	5	6	7	8
1. LDL cholesterol level	1.00							
2. HDL cholesterol level	−.02	1.00						
3. Triglycerides level	.23**	−.53**	1.00					
4. Total cholesterol level	.84**	.19**	.23**	1.00				
5. Self-control	−.07	.13*	−.05	−.06	1.00			
6. Depressive symptoms	.05	−.23**	.13*	.00	−.34**	1.00		
7. Anger expression	−.02	−.18**	.11*	−.02	−.28**	.38**	1.00	
8. Neuroticism	.04	−.13*	.04	.03	−.36**	.44**	.48**	1.00

* $p \leq .05$.
** $p \leq .01$.

the model examining the association between cholesterol levels and neuroticism. Once again, the findings indicated that only HDL cholesterol levels were significantly associated with neuroticism after controlling for age, race, and sex (Beta = −.11, $p \leq .05$). The resulting coefficient revealed that lower levels of HDL cholesterol result in higher levels of neuroticism.

Table 4 presents the results from the DF models for self-control, depressive symptoms, anger expression, and neuroticism. The first three columns from the left report the results of five DF models that examined self-control. The first model is a baseline DF model and indicated that 37 percent of the variance in self-control was explained by genetic influences and shared environmental influences failed to explain any of the variance in self-control. The subsequent models introduced each of the cholesterol difference scores into the equation. The results revealed that none of the cholesterol measures significantly contributed to levels of self-control after holding genetic and shared environmental influences constant. The next set of columns present results from five additional DF models which examined depressive symptoms. The first model is a baseline DF model which revealed that 47 percent of the variance in depressive symptoms was explained by genetic factors. Shared environmental influences failed to explain any of the variance in depressive symptoms. The subsequent models introduced the cholesterol difference scores into the model. Only the HDL cholesterol difference score was significantly associated with depressive symptoms ($b = -1.46$, $p \leq .01$), indicating that the twin within each pair that possessed lower levels of cholesterol was also more likely to experience depressive symptoms, after controlling for genetic and shared environmental influences.

The results of the DF models that examined anger expression are presented in the next set of columns. The first model is a baseline DF model and indicated that 41 percent of the overall variance in anger expression was explained by genetic factors. Shared environmental influences failed to explain any of the variance in anger expression. None of the subsequent models revealed a significant association between cholesterol levels and anger expression, indicating that between twin differences in cholesterol did not significantly predict anger expression after controlling for genetic and shared environmental influences. The results of DF models that examined neuroticism are presented in the final set of columns. The results of the baseline DF model revealed that approximately 41 percent of the variance in neuroticism was explained by genetic influences, while shared environmental influences failed to explain any of the variance in neuroticism. The subsequent models revealed that the HDL cholesterol difference score was marginally significant ($b = -.25$, $p = .06$), indicating that the twin within each pair with lower HDL cholesterol levels was also more likely to possess greater levels of neuroticism. The remaining cholesterol difference scores failed to reach statistical significance.

Table 3
Baseline regression models controlling for age, sex, and race.

	Self-control		Depressive symptoms		Anger expression		Neuroticism	
	Beta	*SE*	*Beta*	*SE*	*Beta*	*SE*	*Beta*	*SE*
LDL cholesterol	−.07	.35	.06	.30	−.06	.30	.01	.11
HDL cholesterol	.08	.41	−.26**	.43	−.15*	.32	−.11*	.13
Triglycerides	−.02	.37	.11*	.36	.09	.30	.02	.12
Total cholesterol	−.06	.36	.01	.31	−.06	.29	.00	.11
N	357		364		360		362	

All models include statistical controls for age, race, and sex (results not reported but available upon request).
Huber/White Standard Errors reported.
* $p \leq .05$.
** $p \leq .01$.

10. Discussion

Based on recent estimates from the Centers for Disease Control (CDC), the overall use of cholesterol-lowering drugs (referred to as antihyperlipidemic agents) has increased from 1.7 percent of all American adults age 20 and older between 1988 and 1994 to 12.5 percent of adults between 2007 and 2010 (National Center for Health Statistics, 2013). Based on this dramatic increase in the use of such drugs, it is not surprising that a large segment of the literature has been devoted to examining the potential health risks associated with their administration and extended use. Comparatively less attention has been paid to the potential behavioral and psychological risks associated with the use of such drugs. Relatedly, a line of research spanning several decades indicates that individuals with lower levels of cholesterol are at an increased risk of suffering from a number of deleterious outcomes such as antisocial and violent behavior (Conklin and Stanford, 2008; Golomb, 1998; Golomb et al., 2000, 2004; Hillbrand and Spitz, 1999; Repo-Tiihnen et al., 2002) and various internalizing problems including depression and impulsivity (New et al., 1999; Ormiston et al., 2003; Pozzi et al., 2003; Steegmans et al., 2000;

Table 4
DeFries–Fulker (DF) analysis of self-control, depressive symptoms, anger expression, and neuroticism.

	Self-control			Depressive symptoms			Anger expression			Neuroticism		
	h^2	c^2	*Cholesterol*	h^2	c^2	*Cholesterol*	h^2	c^2	*Cholesterol*	h^2	c^2	*Cholesterol*
Baseline model	.37**	.00		.31**	.00		.41**	.00		.41**	.00	
	(.05)			(.07)			(.06)			(.05)		
LDL cholesterol levels	.25**	.00	−.20	.31**	.00	−.08	.41**	.00	−.43	.46**	.00	.17
	(.07)		(.34)	(.07)		(.30)	(.06)		(.28)	(.06)		(.10)
HDL cholesterol levels	.25**	.00	.17	.35**	.00	−1.37**	.41**	.00	−.30	.46**	.00	−.25***
	(.07)		(.44)	(.08)		(.39)	(.06)		(.37)	(.06)		(.13)
Triglycerides levels	.25**	.00	−.04	.32**	.00	.45	.41**	.00	.05	.46**	.00	−.04
	(.07)		(.37)	(.07)		(.31)	(.06)		(.29)	(.06)		(.10)
Total cholesterol levels	.25**	.00	−.58***	.31**	.00	−.15	.41**	.00	−.47	.46**	.00	.08
	(.07)		(.33)	(.07)		(.30)	(.06)		(.34)	(.06)		(.11)

Huber/White Standard Errors reported in parentheses.
* $p \leq .05$.
** $p \leq .01$.
*** $p = .06$.

Tedders et al., 2011). A complementary line of research seems to implicate the neurotransmitter serotonin as a significant mediating factor in such associations (Kaplan et al., 1997). Despite partial support for the serotonin–cholesterol hypothesis (Asellus et al., 2010; Buydens-Branchey et al., 2000; Comings et al., 1999; Kim et al., 2011; Marčinko et al., 2007; Scanlon et al., 2001), the potential underlying etiology of the association between cholesterol levels and various deleterious outcomes remains largely unknown.

One possible, yet unexplored, explanation of such associations is a shared genetic etiology in which genetic influences significantly contribute to both cholesterol levels and various outcomes. To our knowledge, there are no studies that have performed a genetically informed study of this association. This gap in the literature is surprising given the important role that genetic influences play in the development of cholesterol levels (de Miranda Chagas et al., 2011; Pérusse et al., 1997), antisocial behaviors (Ferguson, 2010; Miles and Carey, 1997; Rhee and Waldman, 2002), and internalizing problems (Haberstick et al., 2005; Johnson et al., 2002; Sullivan et al., 2000). In addition, a sizable literature has empirically demonstrated the methodological shortcomings that accompany failing to utilize genetically sensitive research models when attempting to draw causal conclusions within quasi-experimental research designs (for an overview see Johnson et al., 2009).

Based on these observed gaps in the extant literature, the current study aimed to examine the potential association between cholesterol levels and a host of deleterious outcomes including self-control, anger expression, depressive symptoms, and neuroticism within the confines of a genetically sensitive model. Three important findings emerged, each of which warrants additional discussion. First, there was a considerable amount of variation in the observed associations between each of the examined subtypes of cholesterol and each of the examined outcomes. Directly in line with previous research (Buydens-Branchey et al., 2000; Sutin et al., 2010; Tedders et al., 2011), HDL cholesterol appeared to be most consistently associated with the observed outcomes in the bivariate, multivariate, and the genetically informed models. The association between triglycerides, LDL cholesterol, and total cholesterol levels and each of the examined outcomes was far less consistent and even resulted in findings in the opposite direction than what was expected. For example, in the baseline multivariate models, *higher* levels of LDL cholesterol and triglycerides both significantly predicted *higher* levels of depressive symptoms. While these associations did not remain significant in the genetically informed models, they still require additional attention in future research. In addition, a significant amount of attention has been devoted to testing the cholesterol–serotonin hypothesis, but far less attention has been devoted to understanding the roles of various forms of cholesterol in the process. In this way, additional empirical and theoretical work must be conducted in an effort to fully understand how cholesterol and serotonin levels are linked.

Second, in both the baseline multivariate and the genetically informed models, cholesterol levels were only significantly associated with some of the observed outcomes. More specifically, in the baseline regression models, respondents with lower levels of HDL cholesterol had significantly higher levels of depressive symptoms, anger expression, and neuroticism. Importantly, these findings were directly in line with prior research (Buydens-Branchey et al., 2000; Sutin et al., 2010; Tedders et al., 2011). However, when adequate controls for genetic influences were applied using DF models, only the association between HDL cholesterol levels and depressive symptoms remained significant (the association between HDL cholesterol and neuroticism remained marginally significant). This finding suggests that failing to control for genetic influences may upwardly bias the probability of detecting a significant association when one does not actually exist.

Relatedly, none of the baseline multivariate models revealed a significant association between cholesterol levels and levels of self-control. This pattern of results directly contrasts with previous research reporting a significant association between cholesterol levels and a related phenotype—impulsivity (New et al., 1999; Ormiston et al., 2003; Pozzi et al., 2003). In light of this finding, we are left to consider the underlying cause of the nonsignificant association between cholesterol levels and levels of self-control. While only speculative, this finding may be a direct result of the trait of low self-control, wherein, individuals with lower levels of self-control are expected to make lifestyle and diet choices that are, on average, less healthy than individuals with relatively higher levels of self-control (Wills et al., 2007). These choices may lead to an increase in cholesterol levels (particularly in LDL cholesterol and triglycerides) effectively masking any association between the trait of self-control and observed levels of cholesterol. This possible explanation remains only speculation at this point and additional research is required to effectively determine the underlying etiology of the nonsignificant association between cholesterol and self-control.

Third, even after controlling for genetic influences, differences in cholesterol levels between twins significantly predicted differences in some of the observed outcomes. For example, lower levels of HDL cholesterol significantly predicted higher levels of depressive symptoms. In addition, the associations between HDL cholesterol and neuroticism and between total cholesterol levels and self-control were marginally significant. This is an important finding since the genetically informed modeling strategy used in the current study is highly conservative, making it more difficult for findings to reach statistical significance. While the findings of the current study still require replication, the associations that did reach statistical significance should be viewed as highly robust.

As with any empirical investigation, the current study should be viewed with caution due to three limitations. First, the association between cholesterol levels and serotonin was not explored due to data limitations. The Biomarker Project of the MIDUS study provided detailed information on a number of important health outcomes; however, respondents were not asked to provide information regarding serotonin levels. Future research would benefit from a more thorough investigation of the specific causal mechanisms that underlie the association between cholesterol levels and overall serotonergic activity. Second, while the initial sample of twins selected for the MIDUS study was nationally representative, the subset of twins that agreed to participate in the Biomarker Project may not be. Due to this limitation, the findings observed in the current study may not extrapolate to the larger population. Finally, cholesterol levels were only measured at one time point (during the Biomarker Project). Future research would benefit from a more longitudinal approach in which the effect of changes in cholesterol levels over time on changes in various outcomes can be observed more effectively. Despite these limitations, the results of the current study indicate that the association between HDL cholesterol levels and various outcomes is likely more complicated than first thought. Taken together, the results of previous studies coupled with findings from the current study provide strong evidence suggesting that lowering cholesterol levels may result in a significant increase in depression and marginal increases in neuroticism. Conversely, the results of the current study seem to indicate that lowering HDL cholesterol levels is not significantly associated with greater levels of anger expression and self-control after accounting for genetic influences on each outcome.

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Conflict of interest

The authors declare no conflicts of interest.

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