

# Analysis of pleiotropic genetic effects on cognitive impairment, systemic inflammation, and plasma lipids in the Health and Retirement Study



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## ABSTRACT

Variants associated with modulation of c-reactive protein (CRP) and plasma lipids have been investigated for polygenic overlap with Alzheimer's disease risk variants. We examined pleiotropic genetic effects on cognitive impairment conditioned on genetic variants (SNPs) associated with systemic inflammation as measured by CRP and with plasma lipids using data from the Health and Retirement Study. SNP enrichment was observed for cognitive impairment conditioned on the secondary phenotypes of plasma CRP and lipids. Fold enrichment of 100%–800% was observed for increasingly stringent *p*-value thresholds for SNPs associated with cognitive impairment conditional on plasma CRP, 80%–800% for low-density lipoprotein, and 80%–600% for total cholesterol. Significant associations (false discovery rate  $Q \leq 0.05$ ) between cognitive impairment, conditional with either CRP, low-density lipoprotein, or total cholesterol, were found for the locus on chromosome 19 that contains the *APOE*, *TOMM40*, *APOC1*, and *PVRL2* genes. Relative numbers of significant SNPs in each of the genes differed by the conditional associations with the secondary phenotypes. Biological interpretation of both the genetic pleiotropy results and the individual genome-wide association results showed that the variants and proximal genes identified are involved in multiple pathological processes including cholesterol metabolism, inflammation, and mitochondrial transport. These findings are potentially important for Alzheimer's disease risk prediction and development of novel therapeutic approaches.

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## 1. Introduction

The association between lipid levels, inflammation, and cognitive impairment is complex. Lipid metabolism is related to inflammatory markers (Ravaglia et al., 2007) and apolipoprotein E (ApoE) is a ligand for cholesterol transport (Poirier et al., 2014). As many reports have noted the involvement of inflammatory and lipid metabolism pathways for Alzheimer's disease (AD) (Akiyama et al., 2000; Di Paolo and Kim, 2011), studies that investigate cognitive impairment conditioned on phenotypes that are linked with these pathways provide the potential to identify variants associated with the earliest changes in the development of AD,

vascular contributions to cognitive impairment and dementia, and other neurodegenerative diseases of aging.

Genome-wide association (GWA) studies for late-onset AD have demonstrated associations between AD and the *APOE* genotype as well as genetic variants involved in inflammatory and microglial activation pathways (Broussard et al., 2012; Efthymiou and Goate, 2017; Gonzalez-Reyes et al., 2017; Pimenova et al., 2018). Variants associated with modulation of c-reactive protein (CRP) and plasma lipids have been identified by GWA and investigated for polygenic overlap with AD risk variants with the results showing that SNPs associated with CRP and plasma lipids (high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides) were also associated with increased risk for AD (e.g., genetic pleiotropy) (Desikan et al., 2015). By testing for association using conditional phenotypes, novel loci were identified that were not reported in large AD case-control studies, and they provided information about the involvement of pathways related to systemic inflammation,

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plasma lipids (HDL, LDL, and triglycerides), and AD (Desikan et al., 2015). Using multiple phenotypes for genetic studies enabled investigation of shared overlap between the phenotypes, genetic variants, genes, and pathways. This approach has been utilized to examine genetic pleiotropy between multiple diverse diseases and phenotypes including schizophrenia and cognitive traits (Smeland et al., 2017), bipolar disorder (Andreassen et al., 2013b), multiple sclerosis (Andreassen et al., 2015b), cardiovascular disease risk factors (Andreassen et al., 2013a), as well as schizophrenia and educational attainment (Le Hellard et al., 2017). Other diseases and phenotypes to which the approach has been applied include Parkinson's disease and autoimmune diseases (Witoelar et al., 2017), blood lipids and immune-related diseases (Andreassen et al., 2015a), and others (Andreassen et al., 2014a,b; Liu et al., 2013).

Cognitive impairment in aging develops as a consequence of genetic and environmental factors. *APOE*  $\epsilon$ 4 carriers have both a higher risk of developing cognitive impairment and AD and developing symptoms earlier than *APOE*  $\epsilon$ 4 noncarriers (Raber et al., 2004). Large, consortium GWA studies of AD have identified SNPs in genes involved in lipid metabolism—clusterin (*CLU*), ATP-binding cassette subfamily A member 7 (*ABCA7*) and inflammation complement C3b/C4b receptor 1 (*CR1*), major histocompatibility complex, class II, DR beta 5 (*HLA-DRB5*) (Hollingworth et al., 2011; Jones et al., 2010; Lambert et al., 2013, 2009; Naj et al., 2011); rare coding variants in phospholipase C gamma 2 (*PLCG2*), ABI family member 3 (*ABI3*), and triggering receptor expressed on myeloid cells 2 (*TREM2*) have also been reported that support a role for innate immune response contributing directly to the development of AD (Sims et al., 2017). Genome-wide analysis to identify variants affecting the rate of age-related cognitive decline have shown a strong association with *APOE* (Wilson et al., 2002), a coding variant in the *CR1* gene (Chibnik et al., 2011), and with a common SNP that influences the expression of phosphodiesterase 7A (*PDE7A*) and mitochondrial fission regulator 1 (*MTFR1*) which are potential regulators of inflammation and oxidative injury (De Jager et al., 2012). For environmental factors, several longitudinal studies have shown an association between inflammatory markers including CRP and interleukin 6 with dementia in the elderly (Teunissen et al., 2003; Weaver et al., 2002); one study noted that increased CRP levels may precede clinical symptoms of dementia by 25 years (Schmidt et al., 2002). While genetic factors are not modifiable, control of plasma lipids (e.g., reduction of LDL levels) and systemic inflammation are risk factors that are potentially modifiable by lifestyle changes and/or medication (Georgiosopoulou et al., 2016; King et al., 2003; Livingston et al., 2017; Ma et al., 2008).

In the present study, we investigated pleiotropic genetic effects on cognitive impairment conditioned on genetic variants associated with systemic inflammation and with plasma lipids (LDL, HDL, total cholesterol [TC]) in a large, nationally representative longitudinal panel study of aging of older adults: the Health and Retirement Study (HRS) (Juster and Suzman, 1995).

## 2. Materials and methods

The HRS has been assembled from several different studies including the Asset and Health Dynamics among the Oldest Old study (begun in 1993) and the HRS, which began in 1992. Other studies have been folded into the HRS including the War Baby Study and the Children of the Depression Study. Today, these ongoing studies are collectively referred to as the HRS and form a large, longitudinally followed, representative cohort of Americans aged 50 years and older. All participants provided informed consent; interviews take place biennially and are conducted by the Survey Research Center at the University of Michigan. The study protocol

was approved by the University of Michigan Institutional Review Board. The current project was approved by the Wake Forest School of Medicine and the Duke University Medical Center Institutional Review Boards.

### 2.1. Participants

HRS participants are geographically dispersed across the United States and are a representative sample of older Americans. Repeated biennial cognitive evaluations begin once participants turn age 65 years. As such the present study included only participants' observations once they turn age 65 years and is further limited to those who participated in DNA collection in 2006 or 2008.

### 2.2. DNA samples, genotyping, and imputation

HRS genotype data were obtained from dbGAP ([www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000428.v1.p1](http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000428.v1.p1)). Briefly, saliva samples were collected for DNA extraction and GWA studies in 2006 and 2008. A total of 12,507 study individuals were genotyped on the Illumina HumanOmni2.5-4v1 array. The median call rate was 99.7% and the mean genotyping error rate estimated based on sample genotype discordance from 336 pairs of study sample duplicates was  $6 \times 10^{-5}$  errors per SNP per sample. Details for the genotyping procedure and the quality control approach that was applied for all of the genotypes used in the analyses in this article were provided in the Quality Control Report for Genotypic Data for dbGaP users of the HRS genotypic data ([http://hrsonline.isr.umich.edu/sitedocs/genetics/HRS\\_QC\\_REPORT\\_MAR2012.pdf](http://hrsonline.isr.umich.edu/sitedocs/genetics/HRS_QC_REPORT_MAR2012.pdf)).

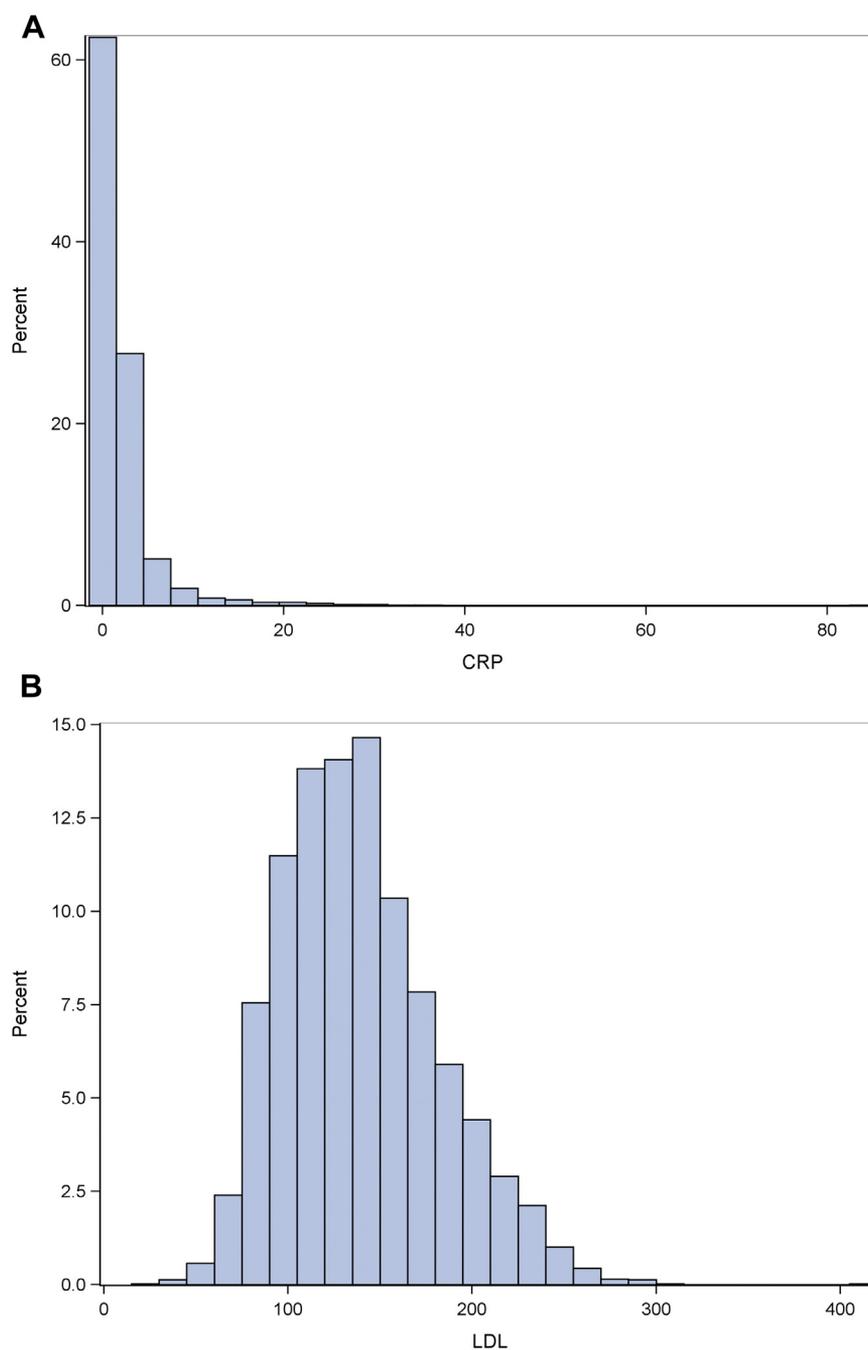
Genotype imputation to dense haplotype reference panels is considered an essential tool in GWA. We used the imputed genotypes, provided by the University of Washington Genetics Coordinating Center for all GWA analyses. Details of the imputation process were provided at [http://hrsonline.isr.umich.edu/sitedocs/genetics/1000G\\_IMPUTE2report\\_HRS2\\_2006\\_2008\\_2010.pdf](http://hrsonline.isr.umich.edu/sitedocs/genetics/1000G_IMPUTE2report_HRS2_2006_2008_2010.pdf). In brief, the worldwide reference panel from the 1000 Genomes project of all 1092 samples from the phase I integrated variant set (v3, released March 2012) was used with the IMPUTE2 software for genotype imputation. The imputation output provided a set of

**Table 1**

Summary statistics for demographic, *TICS*, *APOE* genetics, and biomarkers for the sample

Measurement	Full cohort	Impaired	Unimpaired	<i>p</i> value for difference between affected and unaffected
n	6545	355	6190	
Age, mean (SD), y	72.22 (7.48)	78.85 (7.46)	71.84 (7.30)	<0.0001
% Female	57.51	57.69	54.37	ns
Education	12.57 (3.05)	11.32 (3.78)	12.64 (2.99)	<0.0001
CRP mean (SD)	2.12 (3.75)	1.96 (3.72)	2.13 (3.75)	ns
HDL mean (SD)	55.36 (15.37)	53.38 (13.70)	55.48 (15.46)	0.033
LDL mean (SD)	139.06 (42.42)	138.15 (43.37)	139.11 (42.37)	ns
TC mean (SD)	191.55 (44.36)	189.49 (46.50)	191.67 (44.23)	ns
<i>APOE</i> genotypes				
<i>APOE</i> $\epsilon$ 2/ $\epsilon$ 2	0.98%	0.28%	1.02%	ns
<i>APOE</i> $\epsilon$ 2/ $\epsilon$ 3	16.24%	14.93%	16.32%	ns
<i>APOE</i> $\epsilon$ 2/ $\epsilon$ 4	2.31%	4.23%	2.20%	0.013
<i>APOE</i> $\epsilon$ 3/ $\epsilon$ 3	61.57%	51.55%	62.15%	<i>p</i> < 0.0001
<i>APOE</i> $\epsilon$ 3/ $\epsilon$ 4	17.82%	24.79%	17.42%	0.0004
<i>APOE</i> $\epsilon$ 4/ $\epsilon$ 4	1.08%	4.23%	0.90%	<i>p</i> < 0.0001
<i>APOE</i> $\epsilon$ 4 carrier	21.21%	33.24%	20.52%	<i>p</i> < 0.0001

Key: *APOE*, apolipoprotein E; CRP, c-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol.



**Fig. 1.** Histograms of the plasma CRP and lipid biomarkers. Ordinate shows the proportion of values represented by the histogram bars for CRP (A), LDL (B), HDL (C) and TC (D).

21,632,048 SNPs for the downstream analysis (GWA and conditional analysis).

For *APOE*, 1000 Genomes imputation dosages were used for estimation of *APOE* genotype based on the method described in the HRS documentation ([http://hrsonline.isr.umich.edu/sitedocs/genetics/candidategene/FileDescription\\_Longevity.pdf](http://hrsonline.isr.umich.edu/sitedocs/genetics/candidategene/FileDescription_Longevity.pdf)).

### 2.3. CRP and plasma lipid measurement

Extensive documentation on the sample collection, laboratory procedures for CRP and plasma lipid measurements were provided in the HRS documentation, available at <http://hrsonline.isr.umich.edu/modules/meta/bio2008/desc/Biomarker2006and2008.pdf>.

For this study, laboratory measurements from 2008 were used if available (>95% of individuals) and from 2006 if not available in 2008. CRP and plasma lipid data from a total of 6545 participants was available for the study. Direct measurement of LDL was not available for this cohort; therefore, to approximate LDL, the equation  $LDL = TC - HDL$  was used.

### 2.4. HRS Telephone Interview for Cognitive Status for identification of cognitive impairment

The HRS instrument used to collect data on cognitive status is a version of the modified Telephone Interview for Cognitive Status (TICS) (Welsh et al., 1993) that was modified further specifically for

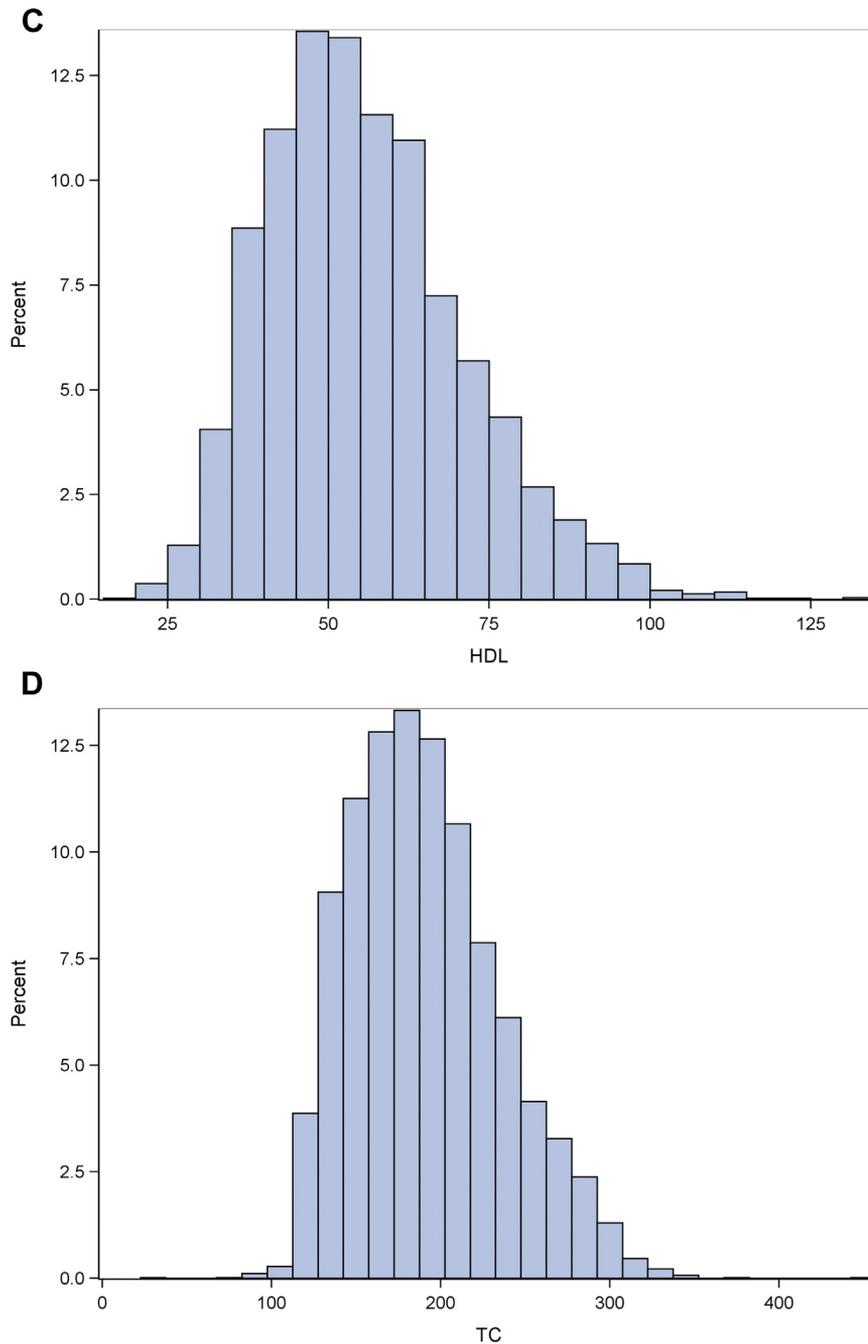
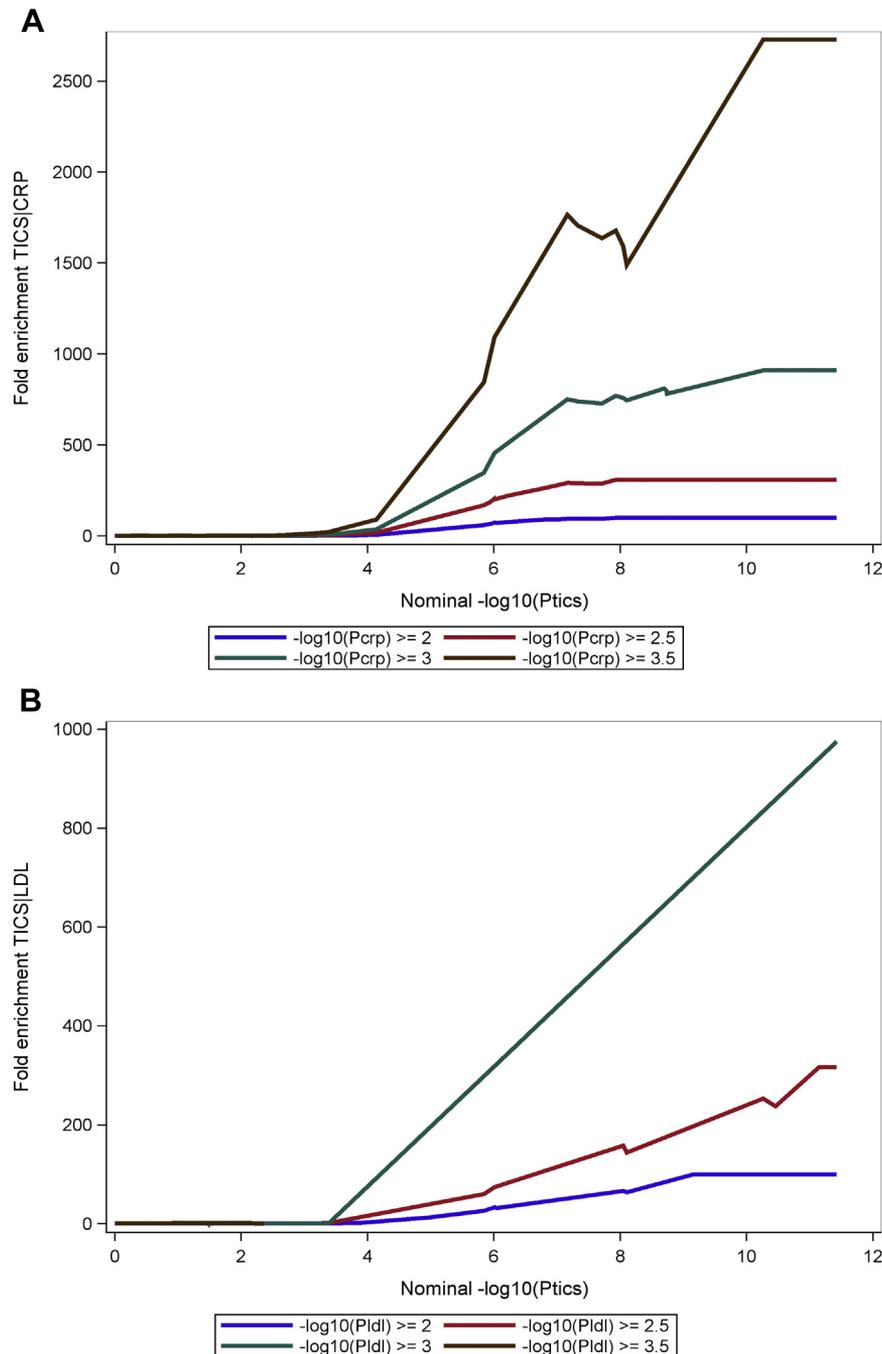


Fig. 1. Continued.

the HRS. The TICS (Brandt et al., 1988) was modeled after the Mini-Mental State Examination (Folstein et al., 1975), a standard measure of global cognitive function, and has good sensitivity and specificity for the identification of dementia (Manly et al., 2011). For the HRS, the TICS was modified to an abbreviated version with a total of 35 points. For the present study, we augmented TICS scores with 3 other approaches to identify cases of cognitive impairment. Using TICS scores, we determined cognitive impairment by using a 2-step process that provides a bivalued response (cognitively normal or cognitive impairment). First we applied a cutoff of 10 points on the TICS, which is a validated cut point for cognitive impairment (Langa et al., 2008). We then added a second criterion of requiring

participants to score at or below this cutoff over 2 consecutive interviews to avoid the inclusion of false positive participants. We used informant reports of impairment based on a cutoff of 3.6 or higher on the Informant Questionnaire on Cognitive Decline in the Elderly (Jorm, 1994, 2004) indicating a severe decline in cognitive functioning. Probabilities of dementia were previously calculated in the HRS (Hurd et al., 2015). We examined these probabilities and after evaluating concordance with other methods, we applied a cutoff of probability of impairment of 65% or higher to identify impairment. We also used 2 self-report indicators where participants were asked if they had been told they have a diagnosis of Alzheimer's disease or dementia. In most cases, where the data



**Fig. 2.** Fold-enrichment plots. Ordinate is fold enrichment, abscissa is nominal  $-\log_{10}(P)$  for cognitive impairment below the standard genome-wide association study threshold of  $p < 10^{-9}$  as a function of significance of association with CRP (A), LDL (B), HDL (C), and TC (D). Curves are differentiated by the threshold for level of statistical significance in the secondary phenotype (CRP and plasma lipids).

were available, these varied methods of case ascertainment were in agreement.

## 2.5. Statistical and bioinformatics analysis

### 2.5.1. Genome-wide association analysis

Separate GWA analyses were run for each of the phenotypes: cognitive impairment, CRP, HDL, LDL, and TC. Imputed genotypes for the 21,632,048 SNPs were used for the GWA. Association with presence of cognitive impairment (yes/no) was tested using

logistic regression modeling in PLINK while linear regression was used to model associations with the CRP and plasma lipid phenotypes. For all GWA analyses, an additive allelic genetic model was assumed.

Filtering for identity by descent reduced the initial sample size from 12,507 to 12,484. GWA analyses were limited to samples identified as non-Hispanic white background to minimize the potential for unaccounted population stratification which can lead to potential spurious associations or lead to important real associations being missed. As described in Arpawong et al., we further

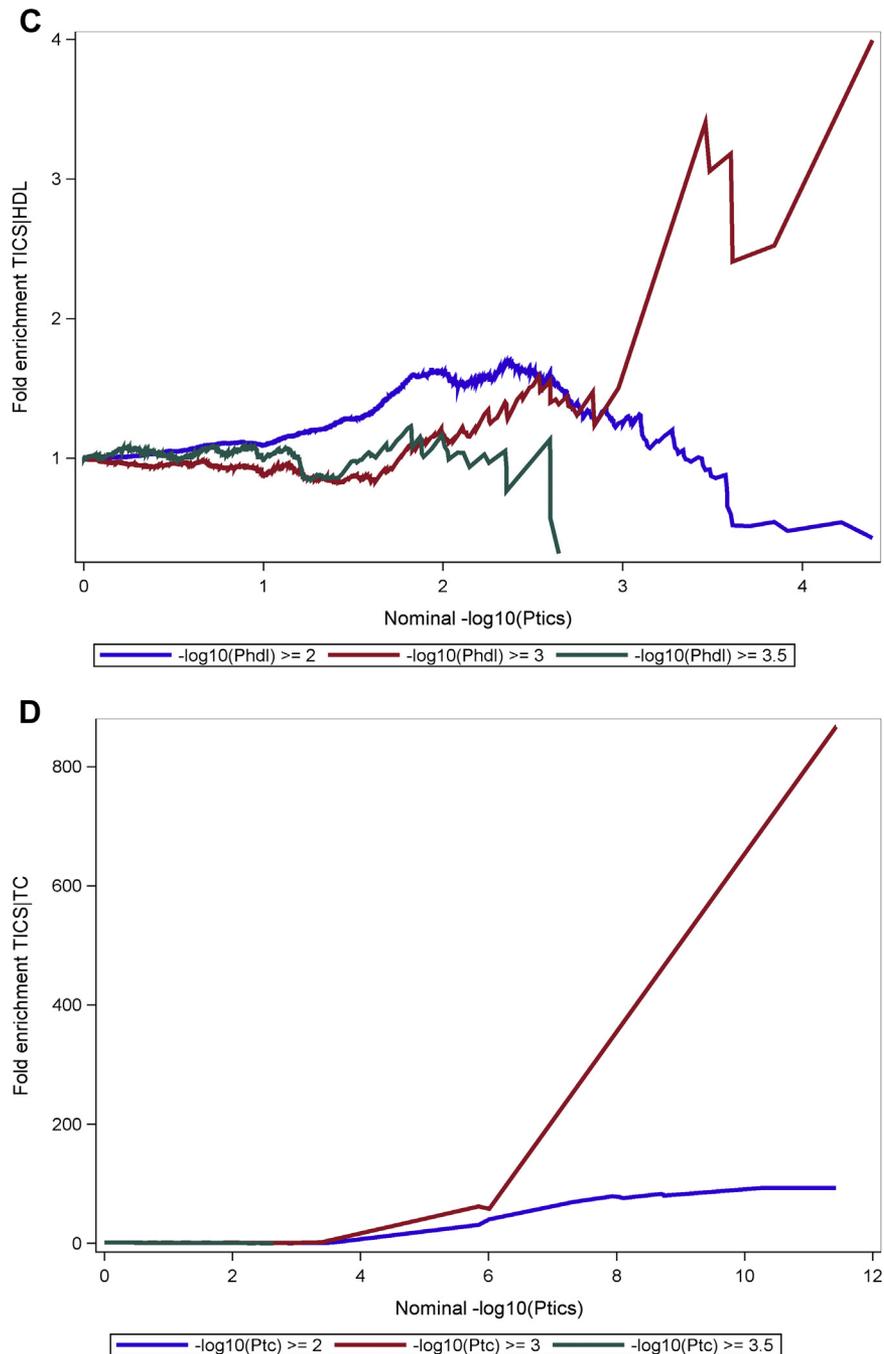
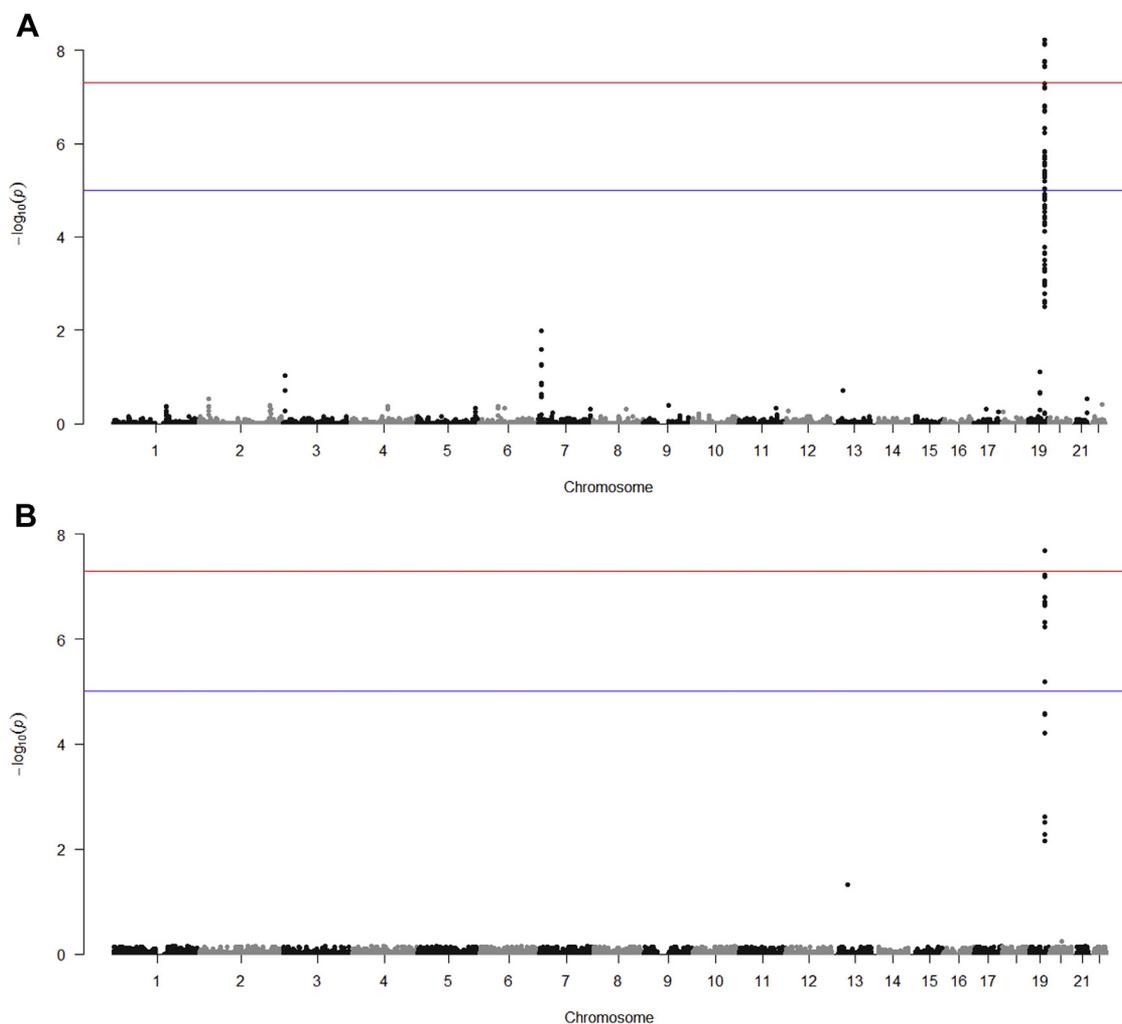


Fig. 2. Continued.

adjusted for population stratification by performing principal component analysis and using the first 4 principal components as covariates (Arpawong et al., 2017). The principal component analysis was performed on the 12,484 unrelated individuals using the R package, *SNPRelate* (Zheng et al., 2012). The top 4 principal components were included as covariates for all of the GWA (cognitive impairment, CRP, and plasma lipids). For the GWA analysis, after filtering, there were 10,307 individuals available for the analysis data set; however, this number was reduced to 6545 where CRP and plasma lipid measurements were available, this set of individuals were used for all of the GWA. All genetic association analyses were performed using PLINK 1.9 (Purcell et al., 2007). Because we used

imputed genotypes, the INFO criteria provided by PLINK were used for postassociation analysis as a quality control measure before the pleiotropy analysis (Purcell et al., 2007). The INFO metric is based on the ratio of empirical and expected variance in dosage. Values closer to 1 indicate better expected quality of imputation. Values can be above 1; values much greater than 1 can indicate strong departure from Hardy-Weinberg equilibrium. To achieve a balance between stringency and coverage, we restricted analysis to SNPs that had INFO scores between 0.6 and 1.06. This criteria included 90% of the imputed SNPs (19,468,843 SNPs); 0.5% of SNPs had INFO scores above 1.06 and 9.5% had scores below 0.6. Manhattan plots, quantile-quantile (Q-Q) plots, and summary tables of the genetic



**Fig. 3.** Conditional Manhattan plots of the conditional FDR  $-\log_{10}(Q)$  values for cognitive impairment given CRP (A), LDL (B), HDL (C), and TC (D). Conditional Manhattan plots show the FDR  $Q$  value for cognitive impairment conditional on each of the 4 secondary phenotypes: CRP (A), LDL (B), HDL (C), and TC (D). Genome-wide significant line (red) is drawn at  $-\log_{10}(5 \times 10^{-8})$ , suggestive line (blue) is drawn at  $-\log_{10}(1 \times 10^{-5})$ .

association results for the individual GWA are provided in the [Supplement](#).

### 2.5.2. Pleiotropy analysis

The pleiotropy analysis strategy, based on conditional false discovery rates, fold-enrichment plots and conditional Q-Q plots is described in detail elsewhere (Desikan et al., 2015). In brief, for 2 phenotypes A and B, pleiotropic enrichment of phenotype A conditional on phenotype B exists if the proportion of variants (SNPs) statistically significantly associated with phenotype A increases as a function of increased statistically significant SNP associations with phenotype B. The number of SNPs associated with phenotype A was determined for several thresholds of SNP association with phenotype B; the proportions are calculated relative to a baseline of all SNPs statistically significantly associated with phenotype A. For this study, phenotype A, the primary phenotype, was cognitive impairment and phenotype B, the conditional phenotypes, were the biomarkers (CRP, LDL, HDL, and TC). Fold enrichment plots graphically depict pleiotropy by showing fold enrichment in terms of numbers of SNPs on the ordinate and nominal  $-\log_{10}(P)$  values for association with cognitive impairment on the abscissa. Separate curves were shown for subsets of SNPs that reach specific levels of significance for their association with CRP, LDL, HDL, and TC,

respectively. Conditional quantile-quantile plots for the same data shown in the fold enrichment plots provided additional assessment of genetic pleiotropy for each set of GWA results. Following the previous analysis strategy (Desikan et al., 2015), we focused the analysis for polygenic enrichment on SNPs below the standard GWA Bonferroni-corrected  $p$ -value thresholds for association with cognitive impairment by using subsets of SNPs with a nominal  $-\log_{10}(P) < 9.0$ .

For identification of specific SNPs conditionally associated with cognitive impairment and one or more of the secondary phenotypes, a conditional false discovery rate (FDR) statistic was calculated as described in the previous implementation of this analysis strategy (Desikan et al., 2015) and other publications (Andreassen et al., 2013a,b, 2014a, 2015a,b; Le Hellard et al., 2017; Witoelar et al., 2017). This framework was an extension of the standard analysis for FDR calculations and uses information from the secondary phenotypes (CRP and plasma lipids) to rerank the  $p$ -values for the primary phenotype (cognitive impairment). We used a conditional FDR of  $Q < 0.05$  to show statistical significance; note that this level must be exceeded in both phenotypes for the overall test to be declared significant. The significance threshold of  $Q = 0.05$  for the conditional FDR (Hochberg and Benjamini, 1990) corresponds to 5 false positives per 100 reported associations.

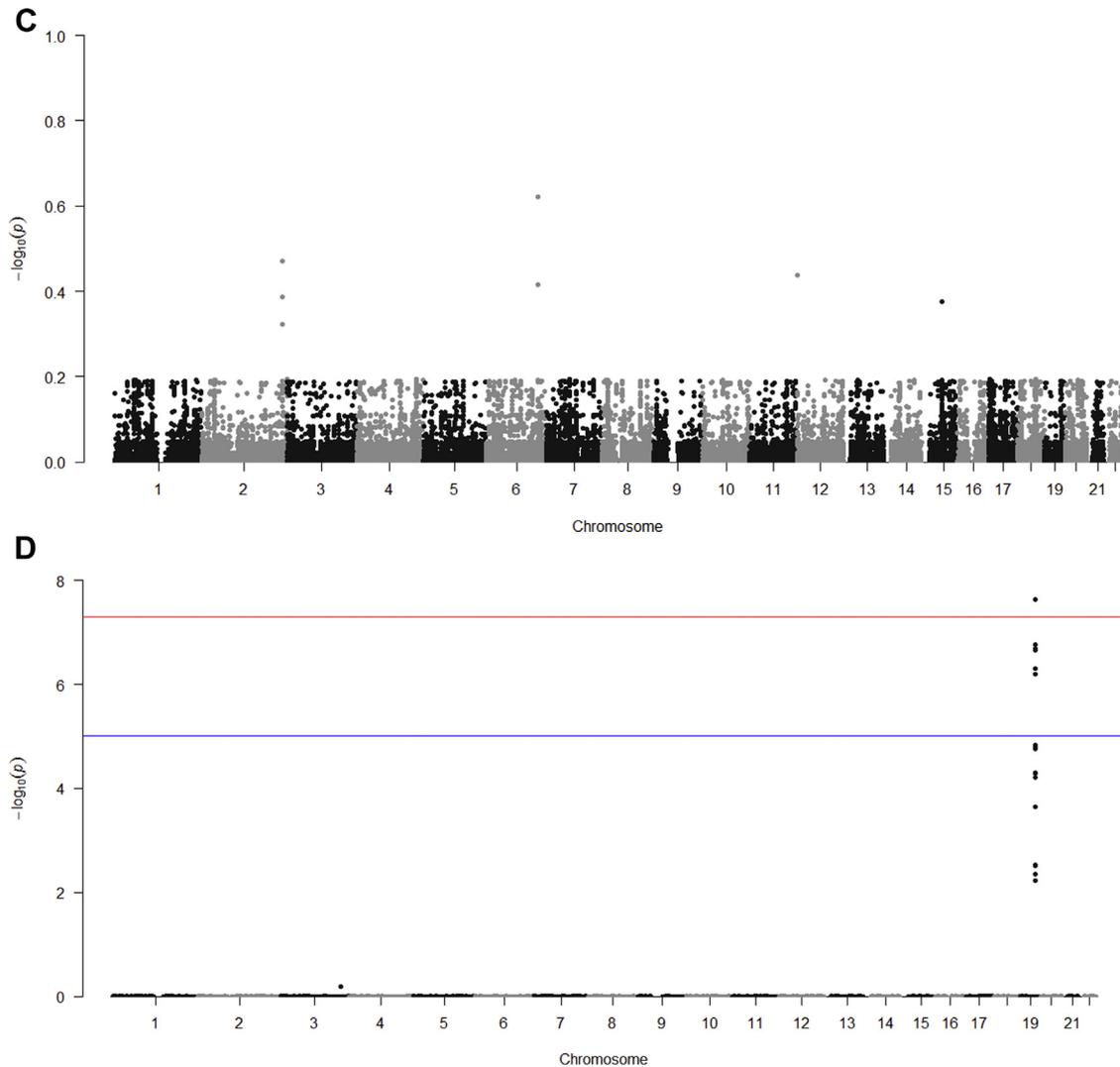


Fig. 3. Continued.

Manhattan plots of the FDRs for conditional association of cognitive impairment on CRP and on the plasma lipids were used to summarize the data.

### 2.5.3. Functional genomics bioinformatics analysis

Functional bioinformatics analysis was performed to evaluate the biological significance of the SNPs that were found to be significantly associated with cognitive impairment, conditional on the CRP and plasma lipid phenotypes. Three bioinformatics analysis tools were used to map the SNPs to genes by proximity, define the genomic context for the variant, annotate effects on phenotypes, and identify relevant literature about the variant. The UCSC genome browser (<http://genome.ucsc.edu/>) was used to map each variant to proximate genes and to provide the first level of information about the genes and biological consequences of the genes (Kent et al., 2002). The Variant Effect Predictor that is part of the Ensembl genome database project (<http://www.ensembl.org/>) was used to provide information about the effects of the SNPs on genes, transcripts, and regulatory regions (McLaren et al., 2016). SNPnexus (<http://www.snp-nexus.org/>) was used to provide additional annotation on gene/protein consequences and phenotype and disease association for the variants (Chelala et al., 2009; Dayem Ullah et al., 2013).

## 3. Results

### 3.1. Descriptive characteristics of the sample

Descriptive characteristics of the sample were summarized in Table 1. The sample consisted of 6545 individuals interviewed from 1992 to 2010 who provided both DNA and biomarker samples. Demographic data, TICS scores, biomarker (CRP, HDL, LDL, and TC) and APOE genotype were summarized for the entire sample, impaired individuals (classified as cognitively impaired as defined in Methods) and unimpaired individuals. For the entire sample, the mean age was 72.2 years (SD 7.5) with a higher proportion (58%) of females. There was a statistically significant ( $p < 0.0001$ ) difference of 7.0 years in age between the impaired (78.9 years, SD 7.5) and the unimpaired (71.8 years, SD 7.3) groups. There was no statistically significant difference in the proportion of females between the impaired and unimpaired groups. There were highly statistically significant differences ( $p < 0.0001$ ) in education between the impaired (11.3 years, SD 3.8) and unimpaired (12.6 years, SD 3.0) groups. There were highly statistically significant differences in APOE genotype frequencies between the impaired and unimpaired groups with higher APOE  $\epsilon 4$  frequencies in the impaired group (Table 1).

There were no statistically significant differences between the impaired and unimpaired groups for the plasma CRP, LDL, or TC biomarkers. There was a marginally statistically significant ( $p = 0.03$ ) difference for HDL between the impaired and unimpaired groups. Histograms of the plasma CRP and lipid biomarkers were constructed (Fig. 1). The distributions of the CRP and lipid biomarkers showed a slight departure from normality ( $p = 0.01$  for all of the biomarkers) based on the Kolmogorov-Smirnov-Lilliefors test. A log transformation did not correct for normality; therefore, the untransformed data were used.

### 3.2. Genome-wide association summary results for the individual phenotypes

Before assessment of polygenetic overlap between cognitive impairment and CRP/plasma lipids, the individual GWA studies for each phenotype were analyzed for quality control and overall genetic association statistics. Summaries for each phenotype are contained in the supplement: Manhattan plots (Supplementary Fig. S1), Q-Q plots (Supplementary Fig. S2), and association statistics (Supplementary Table S1). The genome-wide significance level was  $p < 8.3 \times 10^{-9}$  based on a Bonferroni correction for the number of SNPs. For the primary cognitive impairment phenotype, numerous genome-wide significant SNPs in the *APOE-TOMM40* region of chromosome 19 were observed (Supplementary Fig. S1E), as was a single SNP near the *SMYD3* gene on chromosome 1. For the HDL phenotype, SNPs in the genomic region on chromosome 16 overlapping and near the cholesteryl ester transfer protein (*CETP*) gene reached genome-wide significance, with  $p$  values as low as  $p = 1 \times 10^{-13}$ . An objective of this study was to test for polygenic effects below the standard GWA significance threshold ( $p < 5 \times 10^{-8}$ ), therefore the results (Supplementary Table S1) report on SNPs associated with nominal levels of significance ( $-\log_{10}(P) \geq 6$  corresponding to  $p \leq 10^{-6}$ ). Inspection of the Manhattan plots (Supplementary Fig. S1) showed several regions of the genome with nominal levels of association ( $p \leq 10^{-6}$ ) for the different phenotypes. The Q-Q plots (Supplementary Fig. S2) showed that population stratification was accounted for in the association analysis. A notable result for the CRP phenotype was the identification of the *APOE* coding SNP, rs429358, at an association significance level of  $p < 2.38 \times 10^{-7}$ . The minor allele (C) for this variant had a frequency of 14% in the HRS cohort, which was comparable with the 15% reported for the 1000 Genomes phase 3 combined population.

### 3.3. Assessment of polygenic overlap between cognitive impairment and CRP/plasma lipids

The fold enrichment plot (Fig. 2A) demonstrated SNP enrichment for cognitive impairment across different levels of significance with CRP association. This result and the associated conditional FDR Manhattan plot (Fig. 3A) supported polygenic overlap between CRP and cognitive impairment. Notably, the fold enrichment plot for CRP was monotonic increasing and supported fold enrichment of 100%–800% for increasingly stringent  $p$  value thresholds for the SNPs associated with cognitive impairment; this relationship was observed for all  $p$  value thresholds for the CRP association; these associations were largely driven by the high level of enrichment of SNPs in the *APOE-TOMM40* region of chromosome 19. For LDL and TC, selection of SNPs with the highest threshold for association ( $-\log_{10}(P_{\text{HDL}}) \geq 3.0$ ) showed fold enrichment of approximately 80%–800% for LDL and approximately 80%–600% for TC for increasingly stringent  $p$  value thresholds associated with cognitive impairment. As with CRP, the high level of enrichment of SNPs in the *APOE-TOMM40* region of chromosome 19 was the

primary region driving the enrichment. HDL did not demonstrate fold enrichment above a level of 2.0%, and therefore, the hypothesis of polygenic overlap between cognitive impairment and HDL was not supported by the data.

### 3.4. Specific variants and genes identified by conditional false discovery rate analysis

FDR analysis to identify SNPs associated with cognitive impairment conditional on association for each secondary phenotype with a conditional FDR  $Q \leq 0.05$  are summarized in Table 2. The locus on chromosome 19 that contained the *APOE*, *TOMM40*, *APOC1*, and *PVRL2* genes was shown to have a strong, statistically significant association of cognitive impairment conditional with either CRP, LDL, or TC. The odds ratios for the association of the SNPs in these loci with cognitive impairment ranged from 1.4 to 1.9, consistent with a moderate effect size for the *APOE*  $\epsilon 4$  allele. Relative numbers of significant SNPs in each of the genes: *APOE*, *TOMM40*, *APOC1*, and *PVRL2* differed by the secondary phenotypes. Two additional loci showed modest, statistically significant associations of cognitive impairment conditional on a secondary phenotype: conditional with CRP, a locus on chromosome 7 (near gene *AC009500.2*) ( $p = 0.01$ ) and conditional with LDL, a locus on chromosome 13 (near gene *SPERT*) ( $p = 0.05$ ). The same direction of allelic effects was observed for all SNPs associated with cognitive impairment conditional on association with CRP, LDL, or TC.

## 4. Discussion

This study showed that genetic variants associated with cognitive impairment are also associated with CRP and plasma lipids (LDL and TC) in a large study of older adults. The fold enrichment and conditional Q-Q plots showed similarity to previously published results for conditional association with AD as a function of stringency for levels of significance of association with CRP or plasma lipids (Desikan et al., 2015), with the results for CRP being the most consistent and replicative in terms of congruency of the fold enrichment curves. Enrichment was observed for the plasma lipids LDL and TC but not for HDL. A locus on chromosome 19 that contains the *APOE*, *TOMM40*, *APOC1*, and *PVRL2* genes showed a statistically significant conditional association with cognitive impairment for 3 secondary phenotypes, CRP, LDL, and TC. SNPs in this locus were found to show a strong, genome-wide significant association in the GWA for cognitive impairment; however, the strength of this association was greatly amplified when the conditional analysis was performed. While this locus showed a strong effect in the conditional analysis where all of the phenotypes were measured in the same individuals, larger cohorts and/or meta-analyses of GWA data have the potential to identify additional loci with common variants that demonstrate pleiotropic genetic effects on cognitive impairment, systemic inflammation, and plasma lipids.

Considering that the HRS cohort is a large, nationally representative longitudinal panel study of aging, the fact that few genome-wide significant results were identified for the individual GWA was not surprising; as a comparator, a GWA meta-analysis of general cognitive function report from the COGENT consortium identified 2 genome-wide significant SNPs (Trampush et al., 2017). For the present study, the odds ratios reported for the nominally significant loci were consistent with the low effect size common SNPs, while the odds ratio reported for the chromosome 19 SNPs were consistent with those reported for the association between *APOE* and cognitive impairment (OR=1.68, 95% CI:1.03–2.75) (Jefferson et al., 2015). The present study utilized stringent selection criteria for SNPs based on the imputed genotypes. High stringency was used to maximize the likelihood that the results will replicate.

**Table 2**  
Loci reaching statistical significance at FDR  $\leq 0.05$  for association with cognitive impairment conditional on association for the plasma lipids and CRP phenotypes

Biomarker	SNP	Chr	Position	Nearest gene	Minor allele	MAF	Conditional FDR	Cognitive impairment p value	Cognitive impairment OR (95% CI)	Biomarker beta (95% CI)
CRP	rs73058377	7	9,080,297	AC009500.2	T	0.40	1.03E-02	7.28E-05	1.31 (1.12–1.60)	–0.26 (–0.39 to –0.13)
CRP	rs1541411	7	9,081,364	AC009500.2	A	0.46	5.78E-02	4.38E-04	1.25 (1.08–1.49)	–0.24 (–0.37 to –0.11)
CRP	rs11561890	7	9,086,743	AC009500.2	G	0.42	9.54E-02	2.90E-04	1.28 (1.09–1.55)	–0.23 (–0.36 to –0.10)
CRP	rs118110581	19	31,450,347	CTC-400I9.3	C	0.06	7.92E-02	1.13E-04	1.63 (1.16–2.74)	–0.44 (–0.71 to –0.17)
CRP	rs12972156	19	45,387,459	PVRL2	C	0.13	1.81E-06	1.83E-09	1.72 (1.32–2.47)	0.35 (0.16–0.54)
CRP	rs12972970	19	45,387,596	PVRL2	G	0.13	1.57E-06	1.85E-09	1.72 (1.32–2.46)	0.35 (0.16–0.54)
CRP	rs34342646	19	45,388,130	PVRL2	G	0.13	1.49E-06	2.02E-09	1.71 (1.32–2.45)	0.35 (0.16–0.54)
CRP	rs283812	19	45,388,568	PVRL2	T	0.21	3.22E-04	1.02E-07	1.50 (1.23–1.94)	0.24 (0.07–0.41)
CRP	rs283815	19	45,390,333	PVRL2	A	0.24	8.92E-04	9.69E-07	1.41 (1.18–1.75)	0.25 (0.09–0.40)
CRP	rs6857	19	45,392,254	PVRL2	C	0.14	7.42E-09	3.75E-12	1.79 (1.38–2.53)	0.48 (0.30–0.65)
CRP	rs71352238	19	45,394,336	TOMM40	T	0.12	4.32E-06	1.97E-08	1.65 (1.28–2.32)	0.38 (0.20–0.57)
CRP	rs184017	19	45,394,969	TOMM40	T	0.24	1.64E-04	1.59E-07	1.45 (1.21–1.82)	0.24 (0.08–0.40)
CRP	rs2075650	19	45,395,619	TOMM40	A	0.13	1.23E-05	6.86E-08	1.57 (1.25–2.11)	0.37 (0.18–0.56)
CRP	rs157581	19	45,395,714	TOMM40	T	0.24	9.33E-04	1.17E-06	1.41 (1.18–1.75)	0.24 (0.08–0.40)
CRP	rs34404554	19	45,395,909	TOMM40	C	0.13	2.92E-06	1.18E-08	1.62 (1.28–2.21)	0.37 (0.18–0.56)
CRP	rs11556505	19	45,396,144	TOMM40	C	0.13	9.33E-06	4.72E-08	1.58 (1.26–2.14)	0.37 (0.18–0.56)
CRP	rs157582	19	45,396,219	TOMM40	C	0.24	8.85E-04	1.06E-06	1.41 (1.18–1.75)	0.24 (0.08–0.40)
CRP	rs59007384	19	45,396,665	TOMM40	G	0.22	5.58E-04	5.75E-07	1.43 (1.19–1.80)	0.26 (0.10–0.42)
CRP	rs769449	19	45,410,002	APOE	G	0.10	1.74E-08	3.51E-11	1.87 (1.39–2.85)	0.42 (0.22–0.63)
CRP	rs429358	19	45,411,941	APOE	T	0.14	2.16E-08	5.47E-11	1.69 (1.34–2.31)	0.50 (0.31–0.69)
CRP	rs10414043	19	45,415,713	APOE	G	0.12	1.62E-04	9.84E-07	1.53 (1.21–2.07)	0.42 (0.22–0.63)
CRP	rs7256200	19	45,415,935	APOE	G	0.12	2.19E-04	1.44E-06	1.52 (1.21–2.06)	0.42 (0.22–0.63)
CRP	rs73052335	19	45,420,082	APOC1	A	0.10	5.92E-09	8.97E-12	1.94 (1.42–3.06)	0.41 (0.20–0.62)
CRP	rs12721046	19	45,421,254	APOC1	G	0.12	2.07E-06	7.10E-10	1.78 (1.34–2.63)	0.30 (0.10–0.50)
CRP	rs12721051	19	45,422,160	APOC1	C	0.15	7.07E-09	7.15E-12	1.79 (1.38–2.54)	0.38 (0.19–0.56)
CRP	rs56131196	19	45,422,846	APOC1	G	0.16	2.62E-06	7.94E-09	1.59 (1.27–2.12)	0.38 (0.19–0.56)
CRP	rs4420638	19	45,422,946	APOC1	A	0.16	2.56E-06	9.06E-09	1.59 (1.27–2.11)	0.38 (0.19–0.56)
CRP	rs111789331	19	45,427,125	APOC1	T	0.12	1.20E-05	6.87E-09	1.75 (1.32–2.62)	0.34 (0.13–0.54)
CRP	rs66626994	19	45,428,234	APOC1	G	0.13	2.39E-03	8.92E-07	1.59 (1.23–2.24)	0.31 (0.10–0.52)
LDL	rs11620068	13	46,300,824	SPERT	A	0.14	4.71E-02	1.04E-05	1.45 (1.17–1.90)	–3.39 (–5.81 to –0.98)
LDL	rs6857	19	45,392,254	PVRL2	C	0.14	2.08E-08	3.75E-12	1.79 (1.38–2.53)	–4.02 (–6.41 to –1.63)
LDL	rs769449	19	45,410,002	APOE	G	0.10	1.99E-07	3.51E-11	1.87 (1.39–2.85)	–4.31 (–7.07 to –1.55)
LDL	rs429358	19	45,411,941	APOE	T	0.14	2.33E-07	5.47E-11	1.69 (1.34–2.31)	–4.10 (–6.64 to –1.57)
LDL	rs10414043	19	45,415,713	APOE	G	0.12	2.40E-03	9.84E-07	1.53 (1.21–2.07)	–4.57 (–7.33 to –1.82)
LDL	rs7256200	19	45,415,935	APOE	G	0.12	3.06E-03	1.44E-06	1.52 (1.21–2.06)	–4.56 (–7.32 to –1.80)
LDL	rs73052335	19	45,420,082	APOC1	A	0.10	1.62E-07	8.97E-12	1.94 (1.42–3.06)	–4.25 (–7.09 to –1.42)
LDL	rs12721046	19	45,421,254	APOC1	G	0.12	6.41E-06	7.10E-10	1.78 (1.34–2.63)	–3.75 (–6.40 to –1.10)
LDL	rs12721051	19	45,422,160	APOC1	C	0.15	6.09E-08	7.15E-12	1.79 (1.38–2.54)	–3.86 (–6.34 to –1.39)
LDL	rs56131196	19	45,422,846	APOC1	G	0.16	2.71E-05	7.94E-09	1.59 (1.27–2.12)	–3.98 (–6.45 to –1.51)
LDL	rs4420638	19	45,422,946	APOC1	A	0.16	2.57E-05	9.06E-09	1.59 (1.27–2.11)	–3.98 (–6.45 to –1.51)
LDL	rs66626994	19	45,428,234	APOC1	G	0.13	5.37E-03	8.92E-07	1.59 (1.23–2.24)	–3.78 (–6.58 to –0.98)
TC	rs12972156	19	45,387,459	PVRL2	C	0.13	1.77E-05	1.83E-09	1.72 (1.32–2.47)	–3.22 (–5.62 to –0.83)
TC	rs12972156	19	45,387,459	CTB-129P6.4	C	0.13	1.77E-05	1.83E-09	1.72 (1.32–2.47)	–3.22 (–5.62 to –0.83)
TC	rs12972970	19	45,387,596	PVRL2	G	0.13	1.53E-05	1.85E-09	1.72 (1.32–2.46)	–3.22 (–5.62 to –0.83)
TC	rs12972970	19	45,387,596	CTB-129P6.4	G	0.13	1.53E-05	1.85E-09	1.72 (1.32–2.46)	–3.22 (–5.62 to –0.83)
TC	rs34342646	19	45,388,130	PVRL2	G	0.13	1.46E-05	2.02E-09	1.71 (1.32–2.45)	–3.22 (–5.62 to –0.83)
TC	rs34342646	19	45,388,130	CTB-129P6.4	G	0.13	1.46E-05	2.02E-09	1.71 (1.32–2.45)	–3.22 (–5.62 to –0.83)
TC	rs6857	19	45,392,254	PVRL2	C	0.14	2.34E-08	3.75E-12	1.79 (1.38–2.53)	–3.83 (–6.08 to –1.58)
TC	rs6857	19	45,392,254	CTB-129P6.4	C	0.14	2.34E-08	3.75E-12	1.79 (1.38–2.53)	–3.83 (–6.08 to –1.58)
TC	rs34404554	19	45,395,909	TOMM40	C	0.13	6.21E-05	1.18E-08	1.62 (1.28–2.21)	–3.19 (–5.55 to –0.83)
TC	rs11556505	19	45,396,144	TOMM40	C	0.13	2.28E-04	4.72E-08	1.58 (1.26–2.14)	–3.18 (–5.54 to –0.82)
TC	rs769449	19	45,410,002	APOE	G	0.10	5.08E-07	3.51E-11	1.87 (1.39–2.85)	–4.17 (–6.76 to –1.59)
TC	rs429358	19	45,411,941	APOE	T	0.14	6.33E-07	5.47E-11	1.69 (1.34–2.31)	–3.87 (–6.24 to –1.49)
TC	rs10414043	19	45,415,713	APOE	G	0.12	3.06E-03	9.84E-07	1.53 (1.21–2.07)	–4.62 (–7.20 to –2.04)
TC	rs7256200	19	45,415,935	APOE	G	0.12	2.98E-03	1.44E-06	1.52 (1.21–2.06)	–4.60 (–7.18 to –2.02)
TC	rs73052335	19	45,420,082	APOC1	A	0.10	1.73E-07	8.97E-12	1.94 (1.42–3.06)	–3.84 (–6.48 to –1.19)
TC	rs12721051	19	45,422,160	APOC1	C	0.15	2.07E-07	7.15E-12	1.79 (1.38–2.54)	–3.07 (–5.39 to –0.76)
TC	rs56131196	19	45,422,846	APOC1	G	0.16	5.11E-05	7.94E-09	1.59 (1.27–2.12)	–3.17 (–5.48 to –0.86)
TC	rs4420638	19	45,422,946	APOC1	A	0.16	5.24E-05	9.06E-09	1.59 (1.27–2.11)	–3.17 (–5.48 to –0.86)

Key: APOE, apolipoprotein E; CRP, c-reactive protein; FDR, false discovery rate; LDL, low-density lipoprotein; MAF, minor allele frequency; TC, total cholesterol.

The borderline significance of the association of the *APOE* coding SNP, rs429358, with CRP merits discussion. Previous large studies have shown that plasma CRP levels are influenced by the common genetic polymorphisms within the *APOE* gene, specifically, that the *APOE*  $\epsilon 4$  allele is associated with low levels of plasma CRP (Hubacek et al., 2010). The minor allele frequency for this SNP in our study was also consistent with the frequency reported for the 1000 Genomes phase 3 combined population, an important result

considering the moderate effect size of this variant on many diseases of aging including AD. The finding of genome-wide significant SNPs in the genomic region on chromosome 16 overlapping and near the *CETP* gene that are identified for the HDL phenotype was consistent with the biological function of this gene. The *CETP* gene encodes cholesteryl ester transfer protein. This protein is found in plasma, where it is involved in the transfer of cholesteryl ester from HDL to other lipoproteins.

There are several aspects of our findings that are important in consideration of the role of inflammation with the development of cognitive impairment. First, the strong conditional associations between cognitive impairment and the biomarkers were observed only for CRP, LDL, and TC but not HDL. This finding pointed to the involvement of inflammation-related biological processes that are tagged by these biomarkers with the development of cognitive impairment. Although *APOE* is clearly a genetic factor which is common to cognitive impairment (Jefferson et al., 2015; Qian et al., 2017; Welsh-Bohmer et al., 2009), LDL (Radwan et al., 2014), and CRP (Kahri et al., 2006), it is interesting to note that numerous (8) SNPs were observed in the *TOMM40* gene for the CRP conditional association, but not for LDL. Only 2 *TOMM40* SNPs are identified in the conditional association of cognitive impairment with TC. Recent literature has suggested that haplotypes of *APOE-TOMM40* have complex effects of multiple late-onset disease-related phenotypes (Bekris et al., 2010, 2012; Chiba-Falek et al., 2018; Gottschalk et al., 2014; Li et al., 2013; Linnertz et al., 2014). Interestingly, in another study of the HRS, *TOMM40* effects independent of *APOE* were identified for aging-related verbal memory (Arpawong et al., 2017). The finding that the CRP phenotype alone had the most number of associated *TOMM40* SNPs warrants further investigation to understand whether there is a biological basis rooted in metabolic or mitochondrial dysfunction for the genetic association.

The locus on chromosome 19 that contains the *CTB-129P6.4* that was statistically significant for the cognitive impairment association conditional with TC is located close to the *TOMM40* and *PVRL2* genes and therefore the association was likely a consequence of linkage disequilibrium. The locus on chromosome 7 containing *AC009500.2* constitutes a pseudogene of unknown biological function; however, the conditional FDR for this locus ( $Q = 0.013$ ) was several orders of magnitude greater than observed for the chromosome 19 loci containing *APOE*. The locus on chromosome 13 containing the *SPERT* (spermatid associated) gene has unclear biological relevance to the phenotypes and had a conditional FDR ( $Q = 0.047$ ) that was narrowly significant at the  $Q = 0.05$  level.

The availability of cognitive and CRP/plasma lipid biomarker data for the sample allowed the genetic pleiotropy analysis to be performed within the same set of individuals. Although genetic pleiotropy analysis can be performed on GWA summary-level statistics (beta coefficients and  $p$  values), the present study utilized independent GWA for cognitive impairment, CRP, and the plasma lipids. As noted in Desikan et al., the conditional FDR framework can detect genetic pleiotropy independent of directionality and that both phenotypes are utilized to identify genetic association that may not be detected with a single phenotype GWA (Desikan et al., 2015). The results of this study set the stage to examine how genetic variation in genes and pathways involved in inflammation as measured by CRP and plasma lipid metabolism may identify individuals at risk to develop cognitive impairment, mild cognitive impairment, and AD later in life.

This study had several limitations. The conditional FDR framework controls for the likelihood of false positive results and was based on the number of statistical tests; however, replication in additional cohorts of the conditional associations would strengthen statistical support. Future planned work will replicate the analysis in other cohorts; specifically the Women's Health Initiative Memory Study, which has both the cognitive phenotype and the biomarker measurements available. The cognitive phenotype considered in the study was comparable with other studies of cognitive impairment but cannot be applied to a specific differential diagnosis for dementia. Further work will assess genetic pleiotropy using alternative measures of cognitive impairment and cognitive decline based on the HRS and other studies.

## Disclosure

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.neurobiolaging.2018.10.028>.

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