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C-Reactive Protein, Homocysteine, And Cognitive Performance In Healthy Adults

Cheryl Dahle
Wayne State University

C-REACTIVE PROTEIN, HOMOCYSTEINE, AND COGNITIVE PERFORMANCE IN HEALTHY ADULTS

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CHERYL L. DAHLE

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CHAPTER 1

INTRODUCTION

Cognitive aging is a complex phenomenon that reflects multiple biological and behavioral changes. There is growing evidence that vascular risk is one of the important contributors to the development of age related cognitive declines. In recent years, one contributor to vascular risk, systemic inflammation (Hansson, 2005), has been increasingly examined as a source of cognitive decline and dementia. Cardiovascular disease (CVD) is the leading cause of death in the United States (Kung, Hoyert, Xu, & Murphy, 2007) and several modifiable risk factors (e.g., smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, nutritional intake, alcohol consumption, and physical activity) for the development of CVD have been identified (Calabrò, Golia, & Yeh, 2009). Together, these modifiable risk factors contribute to nearly 90% of all cases of mortality (Danaei et al., 2009). Nonetheless, nearly half of all cases of CVD have no identifiable risk factor other than age and gender, a finding which has sparked interest in identifying additional markers (Calabrò et al., 2009). Within the past decade, a new group of risk factors for CVD has emerged, several of which have also been implicated as modifiers of cognitive aging, presumably through their inflammatory effects in the central nervous system (CNS). Elevations in plasma levels of C-reactive protein (CRP) and homocysteine (Hcy) are two such risk factors that have been assessed in this capacity.

Role of CRP and Hcy in the Development of Atherosclerosis

Following an injury or infection, risk factors for atherosclerosis (e.g., hypertension, smoking, hyperglycemia, and viruses) contribute to endothelial

dysfunction by altering the intimal layer, increasing its permeability, and allowing the adhesion of leukocytes and platelets to the endothelium. These in turn facilitate monocyte adhesion to the endothelial wall and their subsequent migration into the intima, which then become macrophages with the ingestion and oxidation of lipids and low-density lipoproteins (LDL). The macrophages in an attempt to correct the tissue damage, become foam cells and initiate the fatty streak, which contributes to the formation of an atheromatous lesion by releasing enzymes that break down the collagen and smooth muscle cells in the atherosclerotic cap, causing it to weaken, and thereby exposing the atherosclerotic core, rendering it susceptible to rupture and thrombosis (Katrinchak & Fritz, 2007; Patrick & Uzick, 2001; Pearson et al., 2003).

A disturbance in immunological homeostasis such as that caused by injury or infection also leads to a parallel activation of cytokines (e.g., interleukin [IL]-6, IL-1, and tumor necrosis factor [TNF]-α), acute phase reactants (e.g., CRP, serum amyloid A), and other proteins (Patrick & Uzick, 2001; Pearson et al., 2003). A growing body of evidence supports CRP as a causal factor in every aspect of atherogenesis, from the initial recruitment of leukocytes to endothelial dysfunction (Calabrò et al., in 2009). The evidence includes *in vivo* experimentation in humans, where a single bolus infusion of CRP provoked an immediate and simultaneous decline in endothelial-dependent vasodilation and stimulation of CRP-mediated coagulation processes (Bisoendial et al., 2007).

Conversely, the link between atherosclerosis and Hcy is less clear. However, several plausible mechanisms for Hcy-induced atherosclerosis have been suggested including putative effects on monocytes, coagulation factors, and adhesion molecules;

reduced endothelial reactivity; increased proliferation of smooth muscle cells; promotion of lipoprotein oxidation and platelet activation (Miller, 2001; Seshardi, 2006; Spence, 2007; Trabetti, 2008); and in human cells, there is evidence for increased cytokine expression and activation of monocytes and their proliferation, while inhibiting macrophage migration inhibitory factor (Su, Huang, Pai, Liu, & Chang, 2005). Moreover, studies have demonstrated a positive association between hyperhomocysteinemia and CRP, and CVD is accompanied by elevations in both CRP and Hcy (Holven et al., 2006; van den Kommer, Dik, Comijs, Jonker, & Deeg, in press; Youssef, Mojiminiyi, & Abdella, 2007), suggesting there is also a point of interaction for CRP and Hcy in the development of atherosclerosis.

Biochemistry and Synthesis of CRP and Hcy

CRP is a pleiotropic plasma protein, having both pro-inflammatory (e.g., up-regulation of adhesion molecule expression in endothelial cells, enhancement of phagocytosis, stimulation of cytokines) and anti-inflammatory (e.g., interactions with ligands, binding with immunoglobulin receptors) effects. In plasma, CRP is a pentameric structure, having five sub-units. With the loss of this structure however, a modified or monomeric CRP results which is naturally occurring in tissue, and also exerts atherogenic effects, although to a lesser degree than pentameric CRP. In all likelihood, the function of CRP is context-dependent and can either enhance or dampen inflammatory responses depending on the circumstance (Black, Kushner, & Samols, 2004; Paffen & deMaat, 2006).

CRP is primarily synthesized in the liver by hepatocytes and regulated by IL-6 and to a lesser extent by IL-1 and TNF, although extrahepatic synthesis of CRP has

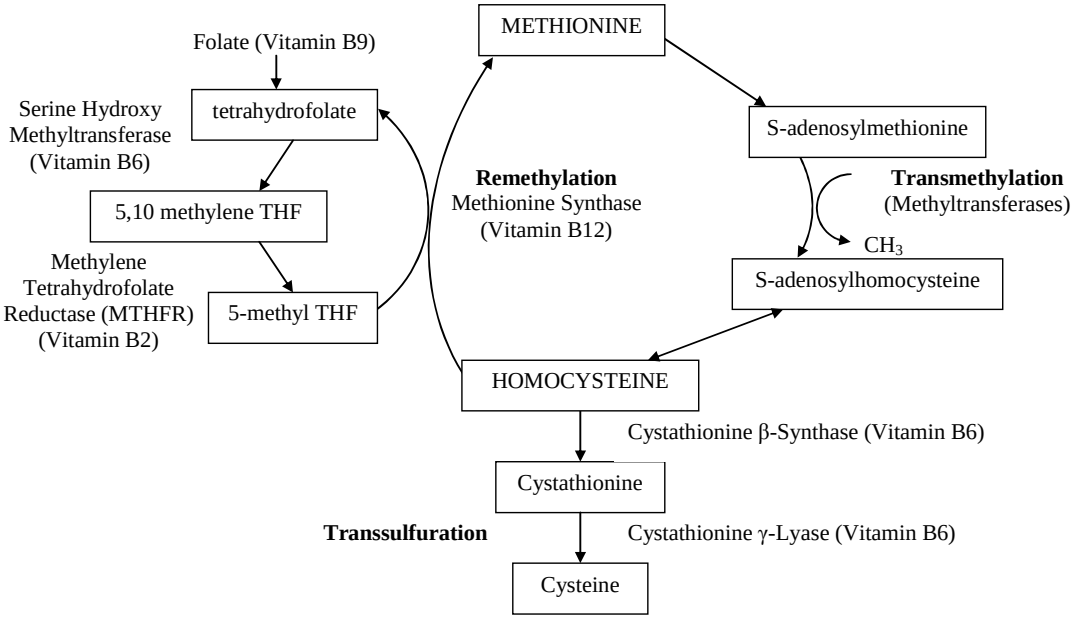
also been reported in neurons, atherosclerotic plaques, monocytes, and lymphocytes (Black et al., 2004; Katrinchak & Fritz, 2007). CRP is an acute phase reactant, and as such, plasma levels of CRP increase markedly, as much as 1000-fold, in response to tissue injury including that caused by infection, trauma, malignant disease, and chronic inflammatory conditions. Post-injury, CRP can be found in high levels in areas of tissue damage, such as the intimal layer of the atherosclerotic artery and in foam cells of atherosclerotic plaques (Black et al., 2004; Hackam & Shumak, 2004). Hcy, a non-essential sulfur-containing amino acid linking the methionine and cysteine cycles, can be derived from the addition of a methylene group to the naturally occurring amino acid cysteine (transsulfuration), or the loss of a methyl group from thiol (remethylation) via S-adenosyl methionine. The latter is a positive allosteric effector for the transsulfuration pathway, and a negative allosteric effector for the remethylation pathway (see Figure 1).

The bulk of circulating Hcy is cellular in origin and is derived from the metabolism of methionine. However, a limited amount of Hcy is of a dietary origin, and varies according to protein content and vitamin sufficiency. With the consumption of a protein-rich meal, methionine concentration is increased, and the transsulfuration pathway takes the dominant role, resulting in Hcy catabolism to cysteine. Conversely, when dietary methionine is low, the remethylation pathway is favored with the conversion of Hcy back to methionine. At least three B-complex vitamins are essential for Hcy homeostasis: B_6 (pyridoxine), B_9 (folate), and B_{12} (cobalamin), though to variable degrees in the two pathways. Methionine synthase, the enzyme involved in converting Hcy to methionine in the remethylation reaction requires both B_9 and B_{12} as

cofactors. In the transsulfuration pathway, Hcy is converted to cysteine by the enzymes cystathionine-β-synthase and cystathionine-γ-lyase, which require B_6 as a cofactor (see Figure 1). Therefore, B_6, B_9, and B_{12} deficiency causes hyperhomocysteinemia, with low folate being the strongest determinant of total plasma Hcy (tHcy; Jacobsen, 2000; Joubert & Manore, 2006).

Figure 1

Homocysteine Metabolism. Adapted from Chanson et al., 2007; Joubert & Manore, 2006



Role of Inflammation in Cognitive Decline

Inflammation has been associated with cognitive decline with some consistency suggesting systemic inflammation may be involved in the pathophysiology of cognitive decline, and in particular Alzheimer's Disease (AD). Several lines of evidence support

this hypothesis. First, areas of the brain affected by AD also show signs of astro- and microgliosis in response to activation of the inflammatory cascade, of which CRP is a part. Specifically, cellular byproducts of this complementary cascade are seen in higher concentrations in the serum of AD patients and co-localize at areas affected by AD pathology (i.e., neuritic plaques, neurofibrillary tangles). Second, inflammatory cytokines and β-amyloid (Aβ) reciprocally act on one another: proinflammatory cytokines augment amyloid precursor protein expression, which in turn, through β-amyloid, induces the release of inflammatory cytokines. Third, several inflammatory single nucleotide polymorphisms (SNPs) have been associated with reductions in AD risk. Last, non-steroidal anti-inflammatory drugs have been shown to delay the onset or slow the progression of AD in several epidemiological studies (Casserly & Topol, 2004; Dziedzic, 2006).

Similarly, Hcy has also been implicated in the pathophysiology of AD because in high concentrations, Hcy is neurotoxic and can cause neuronal degeneration and alterations in plasticity (Obeid & Hermman, 2006; Sachdev, 2005). Several mechanisms for hyperhomocysteinemia neurotoxocity have been proposed including increased oxidative stress through the generation of oxygen free radicals and the reduced activity or bioavailability of endogenous antioxidants; excitotoxicity through activation of glutamatergic N-methyl-D-aspartate (NMDA) receptors; promotion of apoptosis through impaired transmethylation leading to DNA breakage; and alterations to protein function resulting in inhibition of Na^+/K^+ ATP-ase activity. Hcy also interacts directly with amyloid and tau pathways to accelerate dementia. Specifically, it induces an Hcy-responsive endoplasmic reticulum stress protein, Herp, which interacts with presenilin 1 and 2 to

increase Aβ generation in culture, and Hcy sensitizes hippocampal neurons to the neurotoxic effects of insoluable Aβ. Hcy also promotes tau phosphorylation by inhibiting protein phosphatase 2 activity (Obeid & Hermann, 2006; Raman et al., 2007; Sachdev, 2005; Seshardi, 2006).

Alzheimer's type pathology is only one cause of cognitive decline however, and a large body of evidence suggests CRP and Hcy have a causal role in the development of other forms of cognitive decline, such as vascular dementia (VaD). VaD frequently results from a cerebrovascular disease, which in itself may stem from an accumulation of cardiovascular risk factors. Endothelial damage seems to be the final common pathway of several vascular risk factors with the brain as the major target for end-organ damage because of its large small-vessel microcirculatory endothelial surface (Román, 2005). Several cardiovascular and cerebrovascular diseases have been independently linked with elevations in CRP including myocardial infarction, peripheral arterial disease, sudden cardiac death, transient ischemic attack, and stroke, many of which are associated with the development of VaD (Black et al., 2004; Paffen & deMaat, 2006). Indeed, in a prospective population study of Japanese men, elevations in CRP at midlife predicted AD, VaD, and AD with contributing cerebrovascular disease in late life independent of other vascular risk factors (Schmidt et al., 2002).

With regard to Hcy, diet-induced hyperhomocysteinemia in mice is associated with microvascular and spatial memory deficits in the absence of neurodegeneration (Troen et al., 2008). Similarly, a study conducted in humans showed a direct association between hyperhomocysteinemia and cognitive deficits in the absence of mediation through white matter burden (Dufouil, Alpérovitch, Ducros, & Tzourio, 2003).

Combined, these studies suggest an etiology that is distinct from AD. Additional studies have demonstrated that the risk of having Hcy values in the upper tertile among persons with VaD after adjustment for demographic, nutrition, and vascular factors is higher, albeit not significantly (odds ratio, OR = 4.9) than that of persons with mild cognitive impairment (OR = 2.0), AD (OR = 2.0 – 3.7), AD plus VaD (OR = 4.3), or histologically confirmed AD (OR = 4.5). Those findings suggest that cerebrovascular causes are not limited to the development of VaD (Clarke et al., 1998; McIlroy, Dynan, Lawson, Patterson, & Passmore, 2002; Quadri et al., 2004). Some studies, however, showed no association between hyperhomocysteinemia and incident VaD. For example, in a prospective study of Italian elders hyperhomocysteinemia predicted the development of AD but not VaD after controlling for additional vascular risk factors, while elevated CRP was predictive of the development of VaD but not AD (Ravaglia et al., 2007).

Elevated CRP and Hcy and Their Effects on the Central Nervous System

Neuroimaging studies lend further support to the notion that elevations in either CRP or Hcy are associated with changes in the brain. Lacunar infarcts are linked to inflammatory markers independent of traditional cardiovascular risk factors (Hoshi et al., 2005). Higher levels of circulating CRP have been associated with more severe periventricular and subcortical white matter lesions at baseline, as well as greater white matter hyperintensity (WMH) expansion at follow-up (van Dijk et al., 2005). CRP is a graded risk factor for the presence of both white matter lesions and brain infarcts (Fornage et al., 2008; Hoshi et al., 2005), particularly among women (Sachdev et al., 2006).

Similarly, studies have shown an association between total serum Hcy levels and WMH volume (Wright et al., 2005) as well as the number and severity of silent brain infarcts and white matter lesions (de Lau, Smith, Refsum, Johnston, & Breteler, 2009; Polyak et al., 2003; Prins et al., 2002; Sachdev, 2004; Sachdev et al., 2003; Vermeer et al., 2002; Wong et al., 2006), though the effect may be stronger for men (Sachdev et al., 2004). Elevated Hcy has also been associated with medial temporal (Williams, Pereira, Budge, & Bradley, 2002; den Heijer et al., 2003; Refsum et al., 2004) and general cortical (Prins et al., 2002; Sachdev et al., 2003) atrophy. Moreover, high levels of total serum Hcy in combination with low levels of serum vitamin B_{12} and folate have been associated with atrophy and histological changes in persons diagnosed with AD (Clarke et al., 1998). However, low levels of vitamin B_{12} (Vogiatzoglou et al., 2008) and folate (Snowdon, Tully, Smith, Riley, & Markesbery, 2000) are independently associated with brain volume loss and severity of brain atrophy. In addition, several studies have shown elevations in either CRP or Hcy are unrelated to the presence and severity of lacunar infarcts and white matter disease burden, or whole brain volume (Dufouil, et al., 2003; Gunstad et al., 2006; Longstreth et al., 2004; Quadri et al., 2004). Thus, the relationship between CRP and Hcy levels and brain structure is far from fully understood.

Elevated CRP and Hcy and Cognitive Performance

Elevations in CRP and Hcy have been associated with an increased incidence of AD and VaD (Schmidt et al., 2002), which exhibit different patterns of cognitive deficits. In AD, declarative memory declines are predominant from the start. Conversely, in VaD, a relative sparing of memory is accompanied by executive dysfunction (Pantoni, Poggesi, & Inzitari, 2009; Román, 2005; Solfrizzi et al. 2006). It is not surprising then

that numerous studies have examined the relationship between elevations in blood biomarker levels and cognitive performance across a plethora of cognitive domains from crude indices of global cognition (e.g., Mini Mental State Exam; MMSE) to higher-order processing (e.g., executive functions), with deficits observed in many of these.

With regards to CRP, the findings are mixed, with the majority of studies showing either no relationship or a negative correlation. However, most studies have examined older adults within a relatively narrow age range, with very few studies examining a lifespan sample. A summary of studies conducted in cross-sectional populations can be found in Table 1, and longitudinal studies in Table 2. Similarly, elevated levels of Hcy have been linked to poorer cognitive outcomes in some studies, whereas others have found no association, and still others have shown both no association and a negative association for the same domain depending on the type of neuropsychological tests used for assessment. The reasons for the latter discrepancy are unclear and may include questionable validity of some cognitive measures. Finally, one study has shown a positive effect of elevated Hcy levels among females with eating disorders (Freiling et al., 2005). A summary of findings from cross-sectional studies can be found in Table 3, longitudinal studies in Table 4, and placebo-controlled and parallel-group trials in Table 5.

It has been suggested that the potential for cognitive decline is heightened by combined effects of CRP and Hcy (Gunstad et al., 2006). However, few studies have examined both biomarkers in conjunction with measures of cognitive performance. Moreover, the majority of these studies found no relation between CRP and Hcy levels, thereby precluding analysis of their cumulative effects (Fischer et al., 2006; Gunstad et

Table 1
Relationship between elevated C-reactive protein levels and cognition: Findings from cross-sectional studies

Author(s)	Domains Assessed/Association	Sample Description	Covariates
Arai et al., 2006	global cognition (-), manual dexterity (-)	outpatients in geriatric clinic over 62 years	age, sex
Chin et al., 2008	global cognition (0), psychomotor speed (0), visuospatial ability (0), declarative memory (0), executive functions (0)	medically stable non-demented community elders over 65 years	age, sex, education, social class, alcohol, tea intake, depression, life satisfaction, HBP, psychotropic medication use, smoking, stroke, fruit intake
Dickerson et al., 2007	global cognition (-)	outpatients with schizophrenia aged 13-65 years	none
Dimopoulos et al., 2006a	global cognition (-)	community-dwelling older adults over 60 years	none
Fischer et al., 2006	global cognition (0)	residents of Vienna aged 75 years	none
Gunstad et al., 2006	global cognition (-), psychomotor speed (-), manual dexterity (-), visuospatial ability (-), construction praxis (-), attention (0), declarative memory (0), reasoning (-), executive functions (0)	persons with a documented history of CVD aged 55-85 years	age, sex, HBP, diabetes, smoking, B6, B12, folic acid
Hogue et al., 2006	global cognition (0), psychomotor speed (-), manual dexterity (0), visuospatial ability (0), declarative memory (0), executive functions (0)	women over 55 or had undergone oophorectomy or hysterectomy scheduled for elective cardiac surgery and matched controls	none
Laudisio et al., 2008	global cognition (0)	residents of Tuscania over 75 years	age, sex, education, alcohol, smoking, comorbid conditions, medication use, protein, creatinine, sodium, potassium, GDS, activities of daily living
Licastro et al., 2001	global cognition (0)	patients with probable AD, VaD and nondemented controls	none
Mangiafico et al., 2006	global cognition (0), psychomotor speed (-), construction praxis (-), attention (0), working memory (-), executive functions (-)	persons with asymptomatic perherial arterial disease and matched controls	age, sex, education, GDS score

Table 1 cont.

Author(s)	Domains Assessed/Association	Sample Description	Covariates
Ravaglia et al., 2003a	reasoning (-)	cognitively intact residents of Conselice over 65 years	age, sex, education, history of cancer, history of CVD, serum glucose
Ravaglia et al., 2005	global cognition (-)	cognitively intact residents of Conselice over 65 years	age, education, sex, plasma fibrinogen, leukocyte count, serum albumin, BMI, number of comorbid diseases, edentulism
Shawcross et al., 2007	psychomotor speed (-), declarative memory (-), executive functions (0)	patients with cirrhosis	age
Shucard et al., 2007	premorbid intelligence (0), attention (-)	female patients with systemic lupus erythematosus	none
Suzuki et al., 2006	global cognition (-), psychomotor speed (0), declarative memory (0), executive functions (0)	outpatients with diabetes aged 65-77 years	none
Weuve et al., 2006	global cognition (0), declarative memory (0), executive functions (0)	women health professionals over 66 years	age, education, income, delay between testing, smoking, alcohol, physical activity, BMI, HBP, cholesterol ratio, triglycerides, HRT meds
Wright et al., 2006	global cognition (0)	stroke-free residents of Manhattan	age, sex, race, education, HBP, CVD, smoking, tHcy, diabetes, BMI, alcohol

Note: The direction of the association between heightened C-reactive protein levels and specific cognitive domains is indicated by the sign where (-) is a negative association and (0) is no association. Covariates are listed in the order indicated by the individual studies. Abbreviations: HBP = high blood pressure/ hypertension, CVD = cardiovascular disease, B6 = vitamin B6, B12 = vitamin B12, GDS = Geriatric Depression Scale, AD = Alzheimer's disease, VaD = vascular dementia, BMI = body mass index, HRT = hormone replacement therapy, tHcy = total homocysteine

Table 2
Relationship between elevated C-reactive protein levels and cognition: Findings from longitudinal studies

Author(s)	Domains Assessed/Association	Sample Description	Covariates
Alley et al., 2008	global cognition (-), visuospatial ability (0), declarative memory (0), reasoning (-)	high-functioning persons aged 70-79 years at baseline	none
Blasko et al., 2007	global cognition (0)	outpatients with probable AD	none
Dik et al., 2005	global cognition (0), psychomotor speed (0), declarative memory (0), reasoning (0)	participants of Longitudinal Aging Study of Amerstam aged 62-85 years	age, sex, education
Jordanova et al., 2007	global cognition (0), psychomotor speed (0), declarative memory (0)	African-Carribean elders aged 55-75 years	age, sex, education, stroke, HBP, diabetes, smoking, alcohol, BMI, NSAID use, disability
Komulainen et al., 2007	global cognition (0), psychomotor speed (0), declarative memory (-)	women aged 50-60 years at baseline	none
Koster et al., 2005	global cognition (0)	well-functioning adults aged 70-79 years	none
Rafnsson et al., 2007	psychomotor speed (0), declarative memory (0), reasoning (0), executive functions (0)	outpatients at general practitioner aged 55-74 years at baseline	age
Ramlawi et al., 2006	global cognition (-)	patients scheduled for coronary artery bypass graft and/or valvular surgery	age, aprotinin, cardiotomy suction, CPB time, preoperative creatinine levels
Schram et al., 2007 (Leiden)	global cognition (0), declarative memory (0), executive functions (0)	inhabitants of Leiden born between 1912 and 1914	sex, education
Schram et al., 2007 (Rotterdam)	global cognition (-/0), declarative memory (-), executive functions (-)	inhabitants of Rotterdam over 55 years	age, sex, education
Szwast et al., 2007	global cognition (0)	African American elders over 65 years	age, sex, education
Teunissen et al., 2003	psychomotor speed (0), declarative memory (-), executive functions (-)	primary care facilities registrants over 30 years at baseline	age, sex, education
Tilvis et al., 2004	global cognition (0)	inhabitants of Helsinki born in 1904, 1909, or 1914	age, sex

Table 2 cont.

Author(s)	Domains Assessed/Association	Sample Description	Covariates
van den Biggelaar et al., 2007	global cognition (0)	inhabitants of Leiden aged 85 years	sex, education, depression symptoms
Yaffe et al., 2003	global cognition (-)	community-dwelling elders aged 70-79 years	age
Yaffe et al., 2004	global cognition (-)	community-dwelling elders aged 70-79 years	none

Note: The direction of the association between heightened C-reactive protein levels and specific cognitive domains is indicated by the sign where (-) is a negative association, (0) is no association, and (-/0) means the domain was assessed by multiple measures with mixed results. Reported associations are on baseline findings. Covariates are listed in the order indicated by the individual studies. Abbreviations: AD = Alzheimer's disease, HBP = high blood pressure/hypertension, BMI = body mass index, NSAID= nonsteroidal anti-inflammatory drug, CPB = cardiopulmonary bypass

al., 2006; Ravaglia et al., 2005; Silbert, Evered, Scott, McCutcheon, & Jamrozik, 2008). To date, only one study has found a combined negative effect. In the Longitudinal Aging Study Amsterdam, the potential modifying effect of inflammatory markers on the relationship between tHcy and cognitive function was assessed. Persons with the highest tertile of CRP who also had a high level of tHcy performed the worst on delayed recall of a verbal learning task. CRP also had a modifying effect on longitudinal rate of decline for processing speed, such that persons with a high tHcy showed the fastest rate of decline for the lowest and middle tertiles of CRP (van den Kommer et al., in press).

Genetic Regulation of CRP and Hcy in CVD

Blood levels of both CRP and Hcy depend in part on genetic factors. However little is known about how specific SNPs influence inflammation and its effects on cognition. The *CRP* gene has been localized to the proximal long arm of chromosome 1 in the q21-q23 region, and contains two coding regions (exons 1 and 2) consisting of a 204-amino acid chain and separated by a single 280-base pair intron encoding a dinucleotide repeat (GT), and flanked by a 5'- and 3'-untranslated region on either side (Danik & Ridker, 2007; Hage & Szalai, 2007; Lee et al., 2009). The *CRP* gene is polymorphic and it has over 40 SNPs forming 29 different haplotypes, with the largest haplotypic diversity occurring in African Americans (Crawford et al., 2006; Hage & Szalai, 2007). With the exception of exon 1, SNPs have been identified in all other areas of the *CRP* gene. Although many of these have been shown to affect baseline blood levels of CRP, few have been linked to cardiovascular risk, and only one of them is functional: the triallelic C>T>A polymorphism (rs3091244), occurring at two different

Table 3
Relationship between elevated homocysteine levels and cognition: Findings from cross-sectional studies

Author(s)	Domains Assessed	Sample Description	Covariates
Adunsky et al., 2005	global cognition (-)	residents of long-stay geriatric medical center over 60 years	albumin, cholesterol, age over 72 years, total protein, transferin, BMI, education
Aleman et al., 2005	global cognition (0), psychomotor speed (-), declarative memory (0), executive functions (0)	independently living men aged 40-80 years	age, education, SBP, glucose, smoking, alcohol, cholesterol, peak expiratory flow, BMI
Almeida et al., 2004	global cognition (0)	community-dwelling women over 70 years	age, folate, B12
Almeida et al., 2005	global cognition (0), manual dexterity (0), visuospatial ability (0), declarative memory (0), executive functions (0)	community-dwelling women over 70 years	none
Araki et al., 2003	global cognition (-), psychomotor speed (-), visuospatial ability (0), reasoning (0), working memory (0)	outpatients with type 2 diabetes over 60 years	age, education, HbA1c, systolic blood pressure, insulin treatment, cerebral infarction, vitamins
Ariogul et al., 2005	global cognition (0)	outpatients with MCI, dementia, or normal cognitive function	none
Bell et al., 1992	global cognition (-)	young and old inpatients with diagnosis of depression	none
Bottiglieri et al., 2001	global cognition (-)	patients with dementia diagnosis and controls	none
Budge et al., 2000	global cognition (-/0)	community-dwelling self-caring elders over 60 years	sex, age, IQ, GDS
Budge et al., 2002	global cognition (-)	community-dwelling self-caring elders over 60 years	age, sex, systolic blood pressure, cystatin C
Camicioli et al., 2009	global cognition (0)	patients with idiopathic PD and healthy controls over 65 years	age, Levodopa dose
Chin et al., 2008	global cognition (-), psychomotor speed (-), visuospatial ability (-), declarative memory (0), executive functions (0)	medically stable non-demented community elders over 65 years	age, sex, education, social class, alcohol, tea intake, depression, life satisfaction, hypertension, psychotropic med use, smoking, stroke, fruit intake

Table 3 cont.

Author(s)	Domains Assessed	Sample Description	Covariates
Clark et al., 2005	declarative memory (-), executive functions (0)	women undergoing menopausal transition aged 45-55 years at baseline	smoking, age, HRT, education
de Luis et al., 2002	global cognition (-)	persons with type 2 diabetes	none
Dias et al., 2009	premorbid intelligence (-), psychomotor speed (-), visuospatial ability (-), attention (-), declarative memory (-), reasoning (-), executive functions (-)	outpatients with euthymic type 1 bipolar disorder and healthy controls	age, sex, education
Dimopoulus et al., 2006b	global cognition (-)	community-dwelling persons with dementia and healthy controls over 60 years	none
Dittmann et al., 2007	premorbid intelligence (0), language (0), psychomotor speed (0), construction praxis (0), attention (0), declarative memory (-), executive functions (-)	outpatients with euthymic bipolar disorder and healthy controls	age, sex, number of bipolar episodes, HAM-D scores, number of psychotropic meds
Dittmann et al., 2008	psychomotor speed (0), visuospatial ability (0), declarative memory (-), working memory (0), executive functions (-)	outpatients with euthymic bipolar disorder and healthy controls	age, sex, number of bipolar episodes, HAM-D scores, time of being euthymic, number of medications, current use of meds, lifetime symptoms
Durga et al., 2006	psychomotor speed (-/0), declarative memory (0), executive functions (-)	inhabitants from Gelderland region aged 50-70 years	age, sex, education
Elias et al., 2005	psychomotor speed (-), visuospatial ability (0), construction praxis (-), declarative memory (-), reasoning (-), executive functions (-)	offspring to original cohort of Framingham study aged 60-82 years	age, education, sex, creatinine, alcohol, cholesterol, BMI, coffee, APOE, stroke risk profile
Elias et al., 2006	global cognition (-), psychomotor speed (-), visuospatial ability (-), declarative memory (0), reasoning (-), executive functions (-)	community dwellers aged 26-98 years	age, sex, education, practice effects, ethnicity, folate, B6, B12, CVD risk profile, CVD
Elias et al., 2008	global cognition (-), psychomotor speed (0), visuospatial ability (0), declarative memory (0), reasoning (-), executive functions (-)	community dwellers aged 26-98 years	age, sex, education, practice effects, ethnicity, folate, B6, B12, CVD risk profile, CVD

Table 3 cont.

Author(s)	Domains Assessed	Sample Description	Covariates
Feng et al., 2006	global cognition (0), psychomotor speed (-), manual dexterity (-), visuospatial ability (0), construction praxis (-), attention (0), declarative memory (0), executive functions (0)	random selection of participants from Singapore Longitudinal Ageing Study over 55 years	age, sex, education
Fischer et al., 2006	global cognition (0)	inhabitants of Vienna aged 75 years	none
Forti et al., 2001	global cognition (-), language (-), visuospatial ability (0), construction praxis (0), declarative memory (0), reasoning (0), executive functions (0)	random selection of participants from Conselice Study over 65 years	none
Freiling et al., 2005	premorbid intelligence (0), psychomotor speed (0), construction praxis (0), attention (0), declarative memory (+), executive functions (0)	patients with a diagnosis of anorexia or bulimia nervosa aged 18-51 years	ICD-10 diagnosis, age, BMI, full scale IQ
Garcia et al., 2004a	global cognition (0), declarative memory (0), executive functions (-)	community-dwelling volunteers over 65 years	age, education, sex, methylcitric acid, creatinine
Gorgone et al., 2009	global cognition (-)	patients with cognitive impairment and matched controls	age
Gunstad et al., 2006	global cognition (0), psychomotor speed (0), manual dexterity (0), visuospatial ability (0), construction praxis (0), attention (0), declarative memory (0), reasoning (0), executive functions (0)	persons with a documented history of CVD aged 55-85 years	age, sex, HBP, diabetes, smoking, B6, B12, folic acid
Haapaniemi et al., 2007	global cognition (-)	individuals with first-ever ischemic stroke	none
Hassin-Baer et al., 2006	gloabal cognition (0), psychomotor speed (0), attention (0), declarative memory (0), working memory (0), executive functions (0)	paitients with PD	age, duration of PD, sex
Hengstermann et al., 2009	global cognition (0)	geriatric patients with acute medical conditions over 65 years	none
Hestad et al., 2005	global cognition (0)	residents of Hedmark over 80 years	none

Table 3 cont.

Author(s)	Domains Assessed	Sample Description	Covariates
Irizarry et al., 2005	global cognition (- for PD/0 others)	patients with MCI, AD, PD, or cerebral amyloid angiopathy and their caregivers	age, levodopa use
Jensen et al., 1998	language (0), visuospatial ability (-), attention (0), declarative memory (-/0), reasoning (-), working memory (0)	residents of Lund aged 80 years	none
Leblhuber et al., 2000	global cognition (-)	patients with probable AD, VD, and age-matched controls	none
Lehmann et al., 1999	global cognition (-)	persons with subjective memory complaints over 50 years	none
Lewis et al., 2005a	global cognition (0), reasoning (0), executive functions (0)	elders recruited from senior centers	creatinine
Manders et al., 2006	global cognition (0)	institutionalized elderly with cognitive deterioration	age
Marengoni et al., 2004	global cognition (0)	patients admitted to acute geriatric ward over 65 years	age, sex, education, creatinine, albumin, B12, folate, disability, atherosclerotic disease
McCaddon et al., 2003	global cognition (0)	patients with primary degenerative dementia of Alzheimer type and matched controls	glutathione, cysteine
Miller et al., 2003	global cognition (-), visuospatial ability (-), attention (-), declarative memory (0), reasoning (-/0)	community-dwelling Latinos over 60 years	folate, B12, creatinine, age, sex, education, acculturation
Mizrahi et al., 2003	global cognition (0)	patients with probable AD and matched controls	none
Morris et al., 2001	declarative memory (-)	persons from the second wave of NHANES over 60 years	sex, age, race, income, folate
Osher et al., 2008	psychomotor speed (0), visuospatial ability (0), attention (0), declarative memory (0), executive functions (-/0)	euthymic type 1 bipolar disorder outpatients and controls	age

Table 3 cont.

Author(s)	Domains Assessed	Sample Description	Covariates
O'Suilleabhain et al., 2004	global cognition (0), manual dexterity (-), construction praxis (-), attention (0), declarative memory (0), working memory (0), executive functions (-/0)	patients with diagnosis of PD aged 35-90 years	levodopa dose, age, sex, duration of PD
Ozer et al., 2006	global cognition (-), visuospatial ability (-/0), construction praxis (0), declarative memory (0), reasoning (0), executive functions (-/0)	patients with idiopathic PD and matched controls	none
Paulionis et al., 2005	global cognition (0)	residents of a long-term care facility	none
Prins et al., 2002	global cognition (-), psychomotor speed (-), declarative memory (-)	community dwellers aged 60-90 years	age, sex, education, CESD score, creatinine, alcohol, smoking
Quadri et al., 2004	global cognition (-)	persons with AD, VaD or healthy controls over 60 years	none
Raeder et al., 2006	global cognition (0)	patients admitted for acute medical/surgical conditions	none
Ramos et al., 2005	global cognition (0), declarative memory (0)	community-dwelling Latinos over 60 years	RBC folate, B12, creatinine, age, sex, education, acculturation, CESD score
Ravaglia et al., 2003b	global cognition (-)	cognitively intact residents of Conselice over 65 years	age, education, income, creatinine, B vitamin, active lifestyle, coffee, meat consumption
Ravaglia et al., 2004b	global cognition (-/0), language (0), visuospatial ability (0), construction praxis (0), declarative memory (0), reasoning (0), executive functions (-)	random selection of participants from Conselice study over 65 years	none
Ravaglia et al., 2000a	global cognition (0)	centenarians living in two provinces of Italy	none
Ravaglia et al., 2000b	global cognition (0), language (0), visuospatial ability (0), construction praxis (0), declarative memory (0), reasoning (0), executive functions (0)	cognitively intact residents of Conselice over 65 years	none

Table 3 cont.

Author(s)	Domains Assessed	Sample Description	Covariates
Ravaglia et al., 2005	global cognition (-)	cognitively intact residents of Conselice over 65 years	age, education, sex, plasma fibrinogen, leukocyte count, serum albumin BMI, number of comorbid diseases, edentulism
Riggs et al., 1996	premorbid intelligence (0), construction praxis (-/0), attention (0), declarative memory (0), working memory (0), executive functions (0)	participants of VA Normative Aging Study aged 54-81 years	none
Robbins et al., 2005	global cognition (- for diabetics/0 others)	community-dwelling dementia and stroke-free persons, some diabetic	age, education, sex, folate, B6, B12, cigarette, SBP, renal dysfunction, cholesterol, coffee, depressed mood
Rodriguez-Oroz et al., 2009	global cognition (0), psychomotor speed (0), construction praxis (0), attention (0), declarative memory (0), reasoning (0), executive functions (0)	patients with PD over 60 years	age, B12, B6, folate
Sachdev et al., 2003	language (0), psychomotor speed (-), attention (-), declarative memory (0), executive functions (-)	patients with recent ischemic stroke and healthy controls aged 55-87 years	age, folate, creatinine
Sachdev et al., 2004	global cognition (-), psychomotor speed (0), manual dexterity (-), declarative memory (-)	community-dwelling residents aged 60-64 years	age, sex, folate, B12, creatinine, HBP, smoking, diabetes
Sachdev, 2004 (Path)	global cognition (0), psychomotor speed (0), manual dexterity (0), declarative memory (0)	community-dwelling residents aged 60-64 years	age, sex, folate, B12, creatinine
Sachdev, 2004 (Sydney)	language (-), psychomotor speed (0), attention (-), declarative memory (0), executive functions (-)	patients with recent ischemic attack and healthy controls aged 55-87 years	age, folate, creatinine
Sala et al., 2008	global cognition (0), psychomotor speed (0), visuospatial ability (0), construction praxis (0), declarative memory (0), reasoning (0), executive functions (0)	patients with subjective memory complaints, MCI, AD, VaD	age, education, sex, creatinine, B12, folate

Table 3 cont.

Author(s)	Domains Assessed	Sample Description	Covariates
Schafer et al., 2005	psychomotor speed (-), manual dexterity (-), construction praxis (-), declarative memory (-), reasoning (-), executive functions (-)	residents of Baltimore aged 50-70 years	race, tester, smoking, alcohol, BMI, cholesterol
Stewart et al., 2002	global cognition (-)	persons of African-Caribbean heritage aged 55-75 years	age, occupation, HBP, diabetes, physicl activity, cholesterol, triglycerides, fibrinogen, folate, BMI, waist/hip ratio, smoking, alcohol, MMSE score below 20
Tabet et al., 2006	global cognition (0)	patients with AD living with a carer in the community	none
Tassino et al., 2009	global cognition (-)	low income Brazilians over 60 years	education, age, folic acid
Tay et al., 2006	global cognition (0)	patients post first stroke	education, age, stroke subtype
van Asselt et al., 2001	global cognition (0), psychomotor speed (0), attention (0), declarative memory (-/0), reasoning (0), working memory (0), executive functions (0)	community-dwelling elders with low cobalamin	none
van Raamt et al., 2006	construction praxis (-), attention (-), declarative memory (-), executive functions (-)	patients with artieral disease or risk factors aged 18-79 years	age, sex, education, intelligence, intima media thickness, location of arterial disease
Whitmer et al., 2003	global cognition (-), declarative memory (-)	community-dwelling Latinos over 60 years	folate, B12, creatinine, HDL, LDL, triglyceride, age, education, income, acculturation
Wong et al., 2006	global cognition (0), declarative memory (0), executive functions (0)	patients post stroke due to small vessel disease	age, education
Wright et al., 2004	global cognition (-)	community-dwelling stroke-free persons over 40 years	age, creatinine, B12 deficiency, sex, race, education, medicaid status, HBP, diabetes, cardiac disease, smoking, alcohol, BMI

Note: The direction of the association between heightened homocysteine levels and specific cognitive domains is indicated by the sign where (-) is a negative association, (0) is no association, (+) is a positive association, and (-/0) means the domain was assessed by multiple measures with mixed results. Covariates are listed in the order indicated by the individual studies. Abbreviations: BMI = body mass index, SBP = systolic blood pressure, B12 = vitamin B12, HbA1c = glycosylated hemoglobin, MCI = mild cognitive impairment, IQ = intelligence quotient, GDS = Geriatric Depression Scale, PD = Parkinson's disease, HRT = hormone replacement therapy, HAM-D = Hamilton Depression Rating Scale, APOE = apolipoprotein E, B6 = vitamin B6, CVD = cardiovascular disease, ICD-10 = International Classification of Diseases, 10th revision, AD = Alzheimer's disease, NHANES = National Health and Nutrition Examination Survey, CESD = Center for Epidemiologic Studies Depression Scale, VaD = vascular dementia, RBC = red blood cell, VA = Veteran's Affairs, HBP = high blood pressure/hypertension, MMSE = Mini-Mental State Exam, HDL = high-density lipoprotein, LDL = low-density lipoprotein

Table 4
Relationship between elevated homocysteine levels and cognition: Findings from longitudinal studies

Author(s)	Domains Assessed	Sample Description	Covariates
Clarke et al., 2007	global cognition (-)	residents of Oxford over 65 years	none
Dufouil et al., 2003	global cognition (-), psychomotor speed (-), executive functions (0)	inhabitants of Nantes born between 1922 and 1932	age, gender, education, BMI, alcohol, smoking, HBP, hypercholesterolemia, glycemic status, vascular disease history, folate, B12
Duthie et al., 2002 (1921 cohort)	premorbid intelligence (0), global cognition (-), psychomotor speed (-), manual dexterity (-), declarative memory (0), reasoning (-)	independent living survivors of Aberdeen survey of all Scottish schoolchildren	childhood IQ
Duthie et al., 2002 (1936 cohort)	premorbid intelligence (0), global cognition (0), psychomotor speed (0), manual dexterity (0), declarative memory (0), reasoning (0)	independent living survivors of Aberdeen survey of all Scottish schoolchildren	childhood IQ
Garcia et al., 2004b	global cognition (0), declarative memory (0), executive functions (-)	community-dwelling volunteers over 65 years	none
Kado et al., 2005	global cognition (0)	high functioning community-dwelling elders aged 70-79 years	age, sex, education, physical function, smoking, folate, B6, B12
Kalmijn et al., 1999	global cognition (0)	random selection of individuals with baseline MMSE and Hcy over 55	age, sex, education
Luchsinger et al., 2004	language (0), visuospatial ability (0), declarative memory (0), reasoning (0)	Medicare recipients over 65 years	age, sex, APOE, education
Mooijaart et al., 2005	global cognition (-), psychomotor speed (-), declarative memory (-), executive functions (-)	inhabitants of Leiden over 85 years	sex, education
Nurk et al., 2005	declarative memory (-)	inhabitants of Bergen born between 1925 and 1927	none
Rowan et al., 2007	global cognition (0)	elderly individuals 3-months post stroke at baseline	none
Teunissen et al., 2008	attention (-)	MS patients and healthy controls aged 20-75 years	age, sex

Table 4 cont.

Author(s)	Domains Assessed	Sample Description	Covariates
Teunissen et al., 2003	processing speed (0), declarative memory (-), executive functions (0)	generally healthy participants from Maastricht Aging Study aged 30-80 years	age, sex, education
Tucker et al., 2005	global cognition (0), construction praxis (-), declarative memory (-), working memory (0), executive functions (0)	generally healthy men living in Boston	baseline cognitive measures, age, education, smoking, alcohol, BMI, diabetes, SBP, delay between measure and folic acid supplementation, delay between cognitive assessments, creatinine, total energy intake
van den Kommer et al., in press	global cognition (-), psychomotor speed (0), declarative memory (-), reasoning (0)	inhabitants of Netherlands over 65 years	time, age, education, B12, creatinine, ACT, CRP, IL-6, cholesterol, triglycerides, fructosamine, APOE, CESD, comorbid disease, medication, physical activity, BMI, smoking, alcohol

Note: The direction of the association between heightened homocysteine levels and specific cognitive domains is indicated by the sign where (-) is a negative association and (0) is no association. Reported associations are on baseline findings. Covariates are listed in the order indicated by the individual studies. Abbreviations: BMI = body mass index, HBP = high blood pressure/hypertension, IQ = intelligence quotient, B6 = vitamin B6, B12 = vitamin B12, MMSE = Mini-Mental State Exam, Hcy = homocysteine, APOE = apolipoprotein E, MS = multiple sclerosis, SBP = systolic blood pressure, ACT = alpha-1-antichymotrypsin, CRP = C-reactive protein, IL-6 = interleukin-6, CESD = Center for Epidemiologic Studies Depression Scale

Table 5
Relationship between elevated homocysteine levels and cognition: Findings from randomized double-blind placebo-controlled/parallel group trials

Author(s)	Domains Assessed/Association	Sample Description	Covariates
Aisen et al., 2008	global cognition (0)	persons with probable AD over 50 years	none
Clarke et al., 2003	global cognition (-)	diagnosis of MCI or dementia	none
Connelly et al., 2008	global cognition (0), psychomotor speed (-)	patients with probable AD	age, creatinine
Eussen et al., 2007	psychomotor speed (-), construction praxis (-), attention (-), declarative memory (0), executive functions (-)	community-dwelling elders over 70 years	age, education
Hvas et al., 2004	global cognition (-)	individuals with increased plasma methylmalonic acid	age, education
Lewerin et al., 2005	language (-), manual dexterity (-), psychomotor speed (-), visuospatial ability (-), attention (-), declarative memory (0), reasoning (0), working memory (-)	community-dwelling elders	age, sex
Pathansali et al., 2006	psychomotor speed (0), attention (0), declarative memory (0)	generally healthy and cognitive intact elders over 65 years	none
Wolters et al., 2005	premorbid intelligence (0), psychomotor speed (0), attention (0)	females not taking vitamins or medications known to interfere with vitamin absorbtion over 60 years	none

Note: The direction of the association between heightened homocsyteine levels and specific cognitive domains is indicated by the sign where (-) is a negative association and (0) is no association. Reported associations are on baseline findings prior to enrollment in the clinical trial. Covariates are listed in the order indicated by the individual studies. Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment

sites -286 and -390 (Hage & Szalai, 2007). Genotypic variants in the triallelic C>T>A polymorphism have been differentially linked with higher CRP levels among non-Hispanic blacks (AA, TT, AT, CT) and Hispanics (TT, CT) compared to the referent CC genotype. Conversely, among non-Hispanic whites, the AA genotype has been associated with incident coronary heart disease, but not baseline CRP levels (Crawford et al., 2006).

With regards to Hcy, several candidate genes which encode the enzymes involved in Hcy regulation have been examined including cystathionine β-synthase (*CBS*), methylenetetrahydrofolate reductase (*MTHFR*), methionine synthase (*MTR*), and methionine synthase reductase (*MTRR*), of which the most extensively studied is *MTHFR* (Kluijtmans et al., 2003; Trabetti, 2008). MTHFR catalyses the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which serves as a methyl donor in the reaction converting Hcy to methionine (Trabetti, 2008). A thermolabile variant in *MTHFR* positioned at 1p36.3 and caused by a mutation in the C to T transition at base pair 677 (exon 4) leading to an amino acid substitution (alanine to valine) at codon 222 has been associated with decreased enzymatic activity and consequently, increased Hcy concentrations (Kang, Zhou, Kong, Kowalisyn, & Strokosch, 1988). Homozygosity for the T genotype tends to be associated with the highest Hcy levels (Albert et al., 2009; Dedoussis et al., 2005). However, sex differences in the effects of that SNP have been reported. The association between *MTHFR* 677T allele and Hcy levels is particularly strong among males (Kluijtmans et al., 2003), and is not related to Hcy levels among black, Asian, or Hispanic women (Albert et al., 2009). Consistent evidence linking the *MTHFR* 677C>T to vascular risk is lacking,

and meta-analyses have produced conflicting results. In one study, the TT variant was not associated with incremental risk for coronary heart disease (Lewis, Ebrahim, & Davey Smith, 2005b), whereas another showed a 16% greater risk among persons with the TT variant compared to persons with the CC variant (Klerk et al., 2002). Notably, T carriers are disproportionately represented among persons with VaD, suggesting the link is not spurious (McIlroy, et al., 2002).

Genetic Regulation of CRP and Hcy in Cognition

With regards to cognition, few polymorphisms of the *CRP* gene have been examined for a role in cognitive decline. However, because systemic inflammation has been implicated in the development of AD and VaD, and elevations in CRP are related to white matter lesions and brain infarcts, there is sufficient reason to suspect cognitive decline is under genetic regulation through the *CRP* gene. To date, five studies have examined elevations in CRP within the context of genetic regulation (Dik et al., 2005; Haan, Aiello, West, & Jagust, 2008; Mathew et al., 2007; Schram et al., 2007; Szwast et al., 2007), all but one of which (Mathew et al., 2007) examined apolipoprotein E (ApoEε2/3/4) and not *CRP* polymorphisms. In the latter, two *CRP* SNPs (2147 C>T, 1059 G>C) were examined in the context of post-operative cognitive deficits following a coronary artery bypass graft, of which only the less prevalent SNP 1059 G>C was associated with cognitive deficits post-surgery (Mathew et al., 2007).

Conversely, several studies have examined cognitive outcomes in the context of *MTHFR* with equivocal results. Some reported no cognitive reduction in T carriers (Bottiglieri et al., 2001; Flicker et al., 2004; Gussekloo et al., 1999; Matsui et al., 2001; Nurk et al., 2005; Ravaglia et al., 2004a; Rodriguez-Oroz et al., 2009), even in the

presence of higher Hcy levels (Almeida et al., 2005; Bathum et al., 2007; Camicioli, Bouchard, & Sommerville, 2009; de Lau et al., in press; Russo et al., 2008). Other studies however have found an association between the T allele and reduced performance among older women (Elkins et al., 2007), hypertensives (Deshmukh et al., 2009), depressed persons (Naismith et al., 2002), schizophrenics (Roffman et al., 2007; Roffman et al., 2008), and persons with a diagnosis of mild cognitive impairment or dementia (Gorgone et al., 2009; Religa et al., 2003; Yoo, Choi, & Kang, 2000). Finally, some reported a benefit of carrying the *MTHFR* 677T allele, but only for measures of processing speed (Araki et al., 2003; Durga et al., 2006). However the latter of these studies recruited only persons with elevated Hcy (> 13 µmol). Thus, the sample included a disproportionate number of T homozygotes compared to other samples, and could have been affected by an upwardly biased selection of survivors.

Methodological Problems

Both CRP and Hcy are readily assessed and widely available, and studies measuring these biomarkers and their correlates are proliferating. Although the literature supports the use of elevated CRP and Hcy blood levels as measures of cardiovascular risk, their use as markers of cognitive decline is less clear. While several studies have examined elevated blood levels of CRP or Hcy in relation to cognition, there is no consensus as to what specific domains are affected. Further, crude indices of cognitive function (e.g., MMSE) are frequently the only outcome measure assessed, contributing to the lack of specificity of the findings. Whereas several studies have shown an inverse association between elevations in CRP or Hcy and cognitive function, several others have not. Still, others have reported a positive correlation. The reason for

the disparity has largely been attributed to study design and the inclusion of multiple confounds.

Among the prominent confounds are physiologic and lifestyle factors known to alter plasma levels of either CRP or Hcy. Although CRP is not susceptible to food intake and has little seasonal or diurnal variation, several characteristics of the metabolic syndrome (e.g., elevated blood pressure, elevated body mass index, diabetes mellitus, low high-density lipoprotein/high triglycerides), as well as cardiovascular risk factors associated with lifestyle (e.g., cigarette smoking), hormonal status as affected by estrogen/progesterone use, chronic infections (e.g., gingivitis, bronchitis), and systemic inflammatory conditions (e.g., rheumatoid arthritis, lupus, gout) are all known to increase CRP levels, whereas moderate alcohol consumption, increased activity/exercise, weight loss, and medication use (e.g., statins) and nutrition (e.g., fibrates, niacin) have all been shown to decrease CRP levels (Katrinchak & Fritz, 2007; Pearson et al, 2003). Several physiologic characteristics (e.g., older age, male sex), lifestyle determinants (e.g., protein intake, alcohol and caffeine consumption, smoking history) as well as various disease states (e.g., vitamin deficiency, renal failure, hypothyroidism, late-stage diabetes) have been associated with Hcy elevations, while vitamin intake and overactivity or minor aberrations in disease states (e.g., hyperthyroidism, early-stage diabetes) are associated with decreases in Hcy (Refsum et al., 2004). The literature to date is marred by a failure to recognize the impact of many of these factors, and when addressed, there is a general lack of adequate statistical control over their impact and an underreporting of effects by specific groups or stratifications (e.g., sex, ethnicity, supplement use, smoking status).

Neither physiologic or lifestyle factors act alone however, and there is an interplay among the various risk factors that leads to the development of high levels of CRP and Hcy, though the relative contribution of each is unknown (Kluijitmans et al., 2003). Moreover, this interplay may be differentially associated with race, as various disease states occur more frequently among minority populations, diet is somewhat culturally regulated, and minor alleles are observed less frequently among minority populations (Albert et al., 2009), though population-specific effects are virtually unstudied at this juncture.

Rationale and Hypotheses

The reviewed literature suggests that elevated blood levels of CRP or Hcy may be independently associated with increased cardiovascular risk, poorer cognitive function, and increased risk for AD and VaD. However, efforts to examine the combined effects of CRP and Hcy elevations have been tenuous at best. Few studies (Fischer et al., 2006; Gunstad et al., 2006; Ravaglia et al., 2005; Silbert et al., 2008; van den Kommer et al., in press) have examined the combined impact of elevations in CRP and Hcy on cognition, and at present, only one study has demonstrated a relationship between genetic factors and biomarkers of inflammation. Namely, homozygosity for the T variant of the *MTHFR* 677C>T SNP was associated with higher baseline levels of both Hcy and CRP in seemingly healthy adults (Dedoussis et al., 2005). Perhaps most notable however, there has not been a study linking both genetic factors and the blood biomarkers of inflammation and cardiovascular disease under their regulatory control, to cognitive outcomes. To that end, the current study proposes to examine baseline blood levels of CRP and Hcy, and polymorphisms of the C>T>A -286 *CRP* and the 677C>T

MTHFR alleles, and their association with cognitive function across a variety of domains in a large and exceptionally healthy sample. In this way, many of the problems inherent to studies conducted thus far (e.g., small, heterogeneous sample selection) will be circumvented. Further, special care will be taken to rigorously control for other potential confounds on CRP and Hcy blood levels.

Hypotheses

1.) Elevations in blood levels of either CRP or Hcy will be associated with poorer cognitive performance. Specifically, as elevations in both CRP and Hcy have been associated with an increased incidence of AD and VaD (Schmidt et al., 2002), conditions with distinct cognitive impairments (Pantoni et al., 2009; Román, 2005; Solfrizzi et al. 2006), it is expected that declarative memory and executive functions domains will be most adversely affected.

2.) Blood levels of CRP and Hcy will be moderately correlated.

3.) The combined effect of elevated blood levels of CRP and Hcy on cognitive outcomes will be stronger than either CRP or Hcy alone.

4.) Carriers of a T allele for either -286 C>T>A *CRP* or 677C>T *MTHFR* will experience higher blood levels of CRP and Hcy compared to the referent CC carriers.

5.) Carriers of the T allele for either -286 C>T>A *CRP* or 677C>T *MTHFR* will exhibit poorer cognitive performance compared to the referent CC carriers, particularly for declarative memory and executive functions domains.

6.) The combined effect of T allele of both -286 C>T>A *CRP* and 677C>T *MTHFR* on cognitive performance will be stronger than that of T allele status

for either -286 C>T>A *CRP* or 677C>T *MTHFR* alone particularly for declarative memory and executive functions domains.

CHAPTER 2

METHOD

Participants

Participants were recruited from the community of a large Midwestern metropolitan area in the United States through posted flyers and media announcements as part of an ongoing five-year longitudinal study of healthy brain and cognitive aging. At baseline, a written questionnaire and telephone interview were used to exclude participants with a history of cardiovascular, neurological, endocrinological, metabolic, and psychiatric disease, head trauma associated with a loss of consciousness, drug or alcohol abuse, and uncorrected visual or hearing impairments. In addition, participants were screened for depression and dementia, using the Center for Epidemiologic Studies-Depression Scale (Radloff, 1977; cutoff = 16) and the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975; cutoff = 26/30) respectively. Participants who reported the use of glucose-lowering agents as well as centrally-acting medications such as anxiolytics, antidepressants, or anticonvulsants were also excluded. All participants were native English speakers, with a minimum of a high school education, right-hand dominant for basic manual activities (75% or greater on the Edinburgh Handedness Questionnaire; Oldfield, 1971), corrected visual acuity of 50/20 or better (assessed by Optec 2000 apparatus, Stereo Optical Co. Inc., Chicago, IL), and hearing of 40 dB or better for frequencies of 500-4000 Hz (assessed by Maico, MA27 audiometer, Maico Diagnostics, Eden Prairie, MN). All participants were given informed consent in compliance with Institutional Review Board and American Psychological Association requirements, and were monetarily compensated for their efforts.

Cognitive, blood marker, and genomic data were available for a total of 198 participants (134 women). However, data from 9 participants (8 women) met criteria for an acute inflammatory condition (CRP > 10 mg/L), and data from 26 participants (13 women) met criteria for hyperhomocysteinemia (Hcy > 12 μmol/L). Two participants (both women) met criteria for both an acute inflammatory condition and hyperhomocysteinemia. As values outside the normal reference range are indicative of inflammatory or subclinical cardiovascular processes, further analyses were restricted to participants whose CRP and Hcy values were within the reference range. As is shown in Table 6, persons with values outside the reference range for either CRP or Hcy were on average older, had higher diastolic blood pressure, higher CRP and Hcy blood levels, and poorer MMSE performance than persons with values within the reference range limits.

An additional 10 participants (three Hispanic, three Asian, two Indian, one Egyptian, and one Pacific Islander) were removed from analysis in order to conduct population analyses for the SNPs on a more homogenous genetic sample. These persons were on average younger and performed more poorly on the MMSE than persons retained for the final sample (Table 7).

All told, the final sample was comprised of 151 persons (106 women). There were no differences between men and women in age, education, systolic or diastolic blood pressure, CRP levels, or MMSE performance, however men did have higher Hcy levels than women ($t = 3.80$, $p = .001$) in accord with the literature (Refsum et al., 2004). Descriptive statistics for the final sample by sex are reported in Table 8.

Table 6

Comparison of Participants by Normal Reference Range CRP and Hcy Values

Variable	Within Range (n = 161) Mean ± SD	Outside Range (n = 37) Mean ± SD	*t*	*p*
Age (years)	51.21 ± 14.81	57.65 ± 14.15	-2.41	< .02
Education (years)	15.83 ± 2.54	15.92 ± 2.36	-.20	.84
Systolic Blood Pressure (mmHg)	120.79 ± 13.24	124.98 ± 12.33	-1.76	.08
Diastolic Blood Pressure (mmHg)	74.68 ± 7.99	77.84 ± 6.61	-2.24	< .03
C-Reactive Protein (mg/L)	2.20 ± 2.22	8.03 ± 11.13	-6.16	< .001
Homocysteine (µmol/L)	8.32 ± 1.71	13.05 ± 4.56	-10.37	< .001
MMSE	28.92 ± 1.03	28.51 ± 1.24	2.08	< .04

Note. SD = standard deviation; *t* = student t-test value; *p* = significance; MMSE = Mini Mental State Exam

Table 7

Comparison of Participants by Population

Variable	CA/AA (n = 151) Mean ± SD	Other (n = 10) Mean ± SD	*t*	*p*
Age (years)	51.88 ± 14.53	41.00 ± 16.10	2.28	< .03
Education (years)	15.75 ± 2.52	17.00 ± 2.79	-1.52	.13
Systolic Blood Pressure (mmHg)	121.08 ± 13.40	116.47 ± 10.05	1.07	.29
Diastolic Blood Pressure (mmHg)	74.75 ± 8.05	73.6 ± 7.28	.44	.66
C-Reactive Protein (mg/L)	2.28 ± 2.26	1.08 ± 0.64	1.66	.10
Homocysteine (µmol/L)	8.32 ± 1.70	8.31 ± 1.99	.02	.99
MMSE	28.98 ± 0.98	28.00 ± 1.33	2.98	< .01

Note. CA = Caucasian American; AA = African American; SD = standard deviation; *t* = student t-test value; *p* = significance; MMSE = Mini Mental State Exam

Table 8

Sample Characteristics: Means, Standard Deviations and t-tests for Sex Differences

Variable	Range	Men (n = 45) Mean ± SD	Women (n = 106) Mean ± SD	*t*	*p*
Age (years)	18-77	52.84 ± 14.39	51.47 ± 14.64	.53	.60
Education (years)	12-21	15.93 ± 2.81	15.67 ± 2.39	.59	.56
Systolic Blood Pressure (mmHg)	91.33-156.67	123.61 ± 12.38	120.01 ± 13.73	1.52	.13
Diastolic Blood Pressure (mmHg)	60.00-106.67	76.67 ± 8.51	73.93 ± 7.74	1.93	.06
C-Reactive Protein (mg/L)	0.10-9.51	1.86 ± 1.57	2.45 ± 2.49	-1.48	.14
Homocysteine (µmol/L)	3.70-11.80	9.10 ± 1.70	7.99 ± 1.59	3.80	.001
MMSE	26-30	28.78 ± 1.00	29.01 ± 0.97	-1.66	.10

Note. SD = standard deviation; *t* = student t-test value; *p* = significance; MMSE = Mini Mental State Exam

Blood Biomarker Measurements

Following an overnight fast of 12 hours, participants reported to the clinic between 9 and 10 am, where venipuncture was done to obtain approximately 20 cc of whole blood for the analysis of plasma CRP, Hcy, and vitamins B_6, B_{12}, and folate. Samples for Hcy and vitamin B_6 were placed in EDTA tubes, immediately placed on ice, and then centrifuged to separate plasma (within 30 minutes post-venipuncture). Vitamin B_6 samples were additionally wrapped in paper to protect them from sunlight. The remaining samples were placed in serum separator tubes. With the exception of vitamin B_6, all samples were processed in-house within four hours of venipuncture. Vitamin B_6 was shipped locally on dry ice for same day processing. CRP was determined by

immunoturbidimetry, Hcy by fluorescence polarization immunoassay, vitamin B_6 by radioenzymatic immunoassay, and vitamin B_{12} and folate by chemiluminescence.

Genomic Analysis

DNA was isolated from buccal cultures obtained in mouthwash. Isolation was performed using a Gentra Autopure LS (QIAGEN Inc., Valencia, CA) with the standard buccal cell protocol. For genotyping quality control, 10% direct repeats and DNA sequencing for verification were performed using both control DNA and no-template controls, whereby beta-globin was used as the amplification control. All 5'-nuclease assays were adapted from a quantitative PCR method (Lo et al., 2000) and implemented on an Applied Biosystems 7900. The *CRP* -286C>T>A polymorphism (rs3091244) utilized sense 5′-GAGGAGCAAGGAGAAGGAGTA-3′ and anti-sense 5′-GGTCACGTCCTGCTGCCAGTGATA-3′ primers, and was amplified using a biotinylated antisense primer 5′-Bio-AGGGCTCCACTTTGGCTATC-3′. The *MTHFR* 677C>T polymorphism (rs1801133) was interrogated using the TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA) under the 0.5X protocol for ABI PRSIM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems). Sequencing extension products were purified using Sephadex and the purified products were analyzed on an ABI PRISM 3700 DNA Analyzer using a 50 cm capillary array.

Almost 80% of the sample was evenly split among C homozygotes (39.1%, 59 individuals) and C/T heterozygotes (39.7%, 60 individuals) for the *CRP* gene. The remaining 20% was approximately evenly split among T homozygotes (8.6%, 13 persons), A/C heterozygotes (6.6% 10 persons), and A/T heterozygotes (6%, 9 persons). There were no A homozygotes in the sample. The distribution of T

homozygotes conformed to the Hardy-Weinberg equilibrium: χ^2 = 0.16, *p* = .70. With regards to the *MTHFR* allele, approximately half the sample was homozygous for the C allele (52%, 79 individuals), whereas 38% (57 individuals) were heterozygous, and a mere 10% (15 individuals) were homozygous for the T allele. The distribution of *MTHFR* C>T alleles did not deviate from Hardy-Weinberg equilibrium: χ^2 = 0.86, *p* = .33.

There were both population and sex differences in the distribution of the various polymorphisms for the *CRP* gene, as can be seen in Figures 2 and 3 respectively. Similarly, the *MTHFR* gene was associated with differential distributions by both population (Figure 4) and sex (Figure 5), particularly for T homozygotes which were unrepresented among African Americans.

Figure 2

CRP Gene Polymorphism Distribution by Population

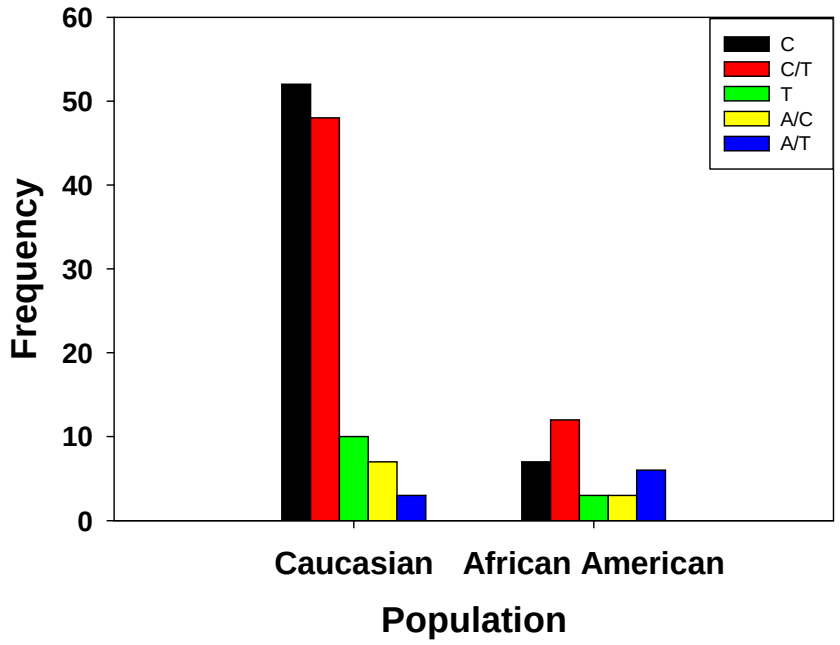


Figure 3

CRP Gene Polymorphism Distribution by Sex

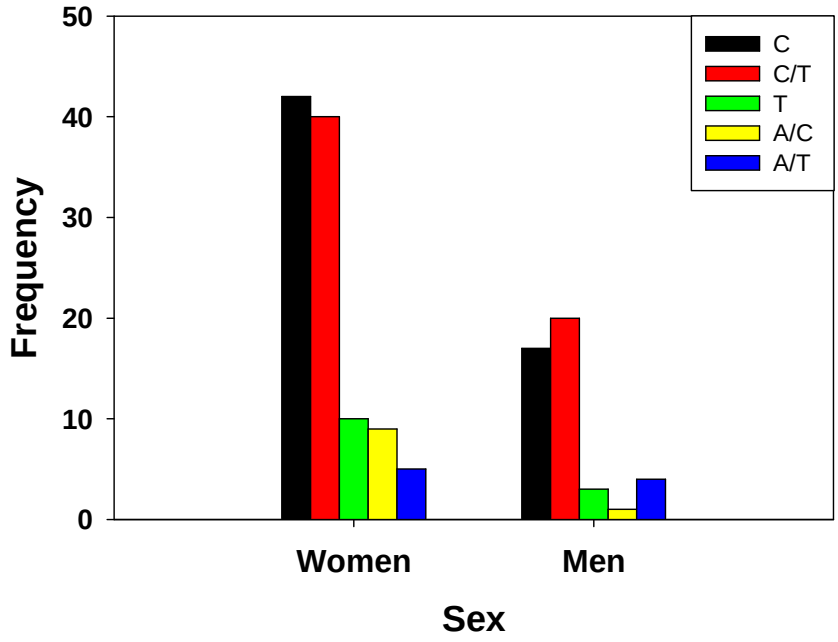


Figure 4

MTHFR Gene Polymorphism Distribution by Population

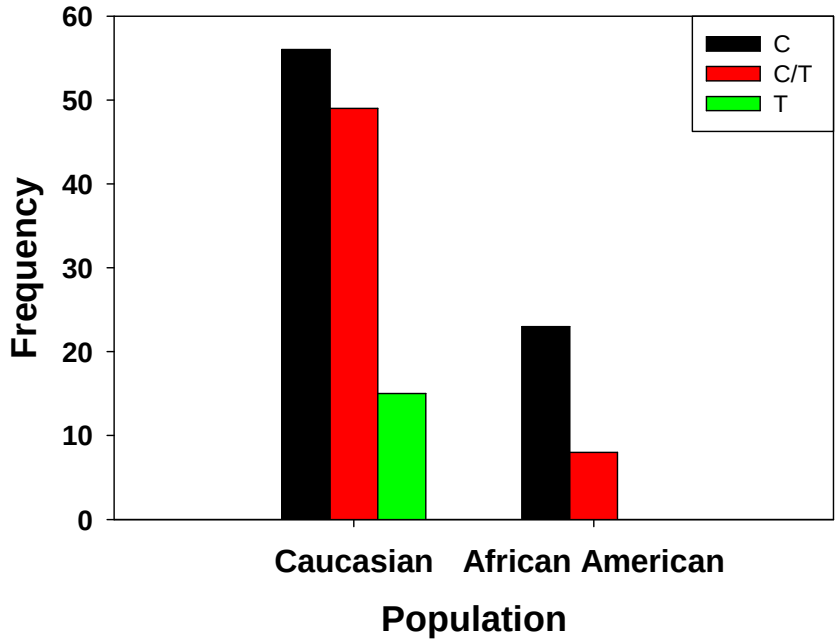
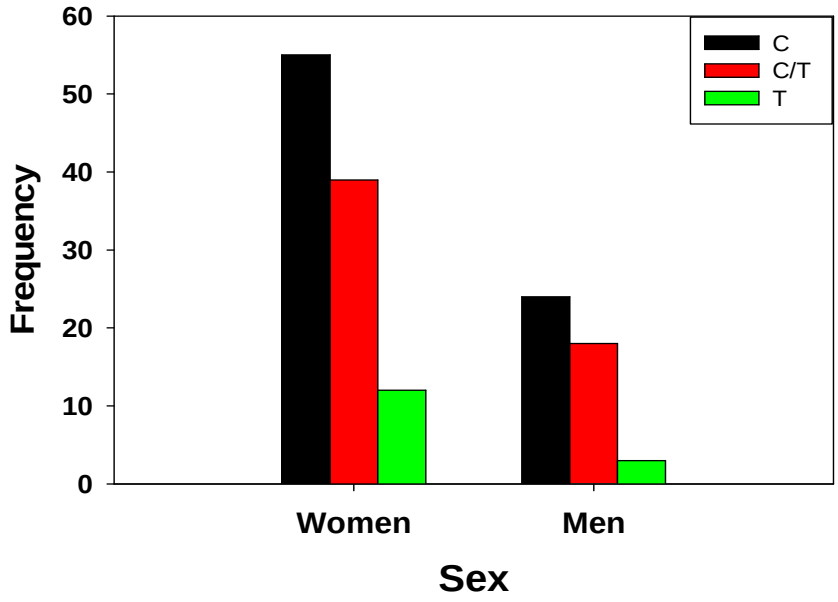


Figure 5

MTHFR Gene Polymorphism Distribution by Sex



Supplementary Questionnaire

As participants for the current study had already completed the baseline assessment, an additional questionnaire was mailed to all participants to inquire about current and past dietary and nutrition supplements, alcohol and caffeine consumption, cigarette and other tobacco use, as well as anitlipidemic, anti-inflammatory, and estrogen use (Appendix A). Questionnaire responses were available on a subsample of 94 participants (66 women). Survey respondents were on average older; had higher blood levels of Hcy, folate, vitamin B_{12}, cholesterol, LDL, triglyceride, cholesterol ratio, and blood glucose; a higher diastolic blood pressure; and better MMSE performance than non-respondents. Only age and folate reached significance however ($p > .05$, all other's *ns*). Conversely, non-respondents were better educated, had a higher systolic blood pressure, pulse pressure, and higher blood levels of CRP and HDL, though not significantly (all p's > .18). There were fairly equal numbers of respondents and non-

respondents across sex (70.21% vs. 70.18% for women and 29.79 vs. 29.83% for men), population (17.02% vs. 26.32% for African American, vs. 82.98% vs. 73.68% for Caucasian), and persons with a diagnosis of hypertension and/or characterized as hypertensive based on systolic and diastolic means (23.40% vs. 24.56%). Characteristics for survey respondents versus non-responders are reported in Table 9.

Cognitive Tasks and Procedures

Participants reported to the laboratory on three separate occasions for cognitive testing. At the start of each session, blood pressure was measured using a mercury sphygmomanometer (BMS 12-S25; Omron Healthcare, Bannockburn, IL) with a standard blood pressure cuff on the left arm with participants seated. The systolic and diastolic means were averaged for each participant and a mean systolic of 140 mmHg or a mean diastolic of 90 mmHg or more were classified as hypertensive. The cognitive tasks were administered to each participant individually in quiet, well-lit rooms with strict adherence to task and session order for all participants. For those tests requiring the administration of more than one block of trials, block order was counterbalanced across subjects. For tests requiring a delay within administration, every effort was made to maintain an equal period of delay across subjects. The cognitive tests were administered by extensively trained graduate and undergraduate students.

Crystallized intelligence. Several subtests from the Educational Testing Service Referenced Factors Test Kit (Ekstrom, French, Harman, & Dermen, 1976a) were administered as a measure of crystallized intelligence. In these multiple-choice paper-pencil tests designed to test word knowledge, participants chose from 4 or 5 alternatives the synonym for the given word. Each of the five subtests has two parts, with a variable

Table 9

Sample Characteristics by Survey Response

Variable	Responders (n = 94) Mean ± SD	Non-responders (n = 57) Mean ± SD	*t*	*p*
Age (years)	54.03 ± 13.97	48.33 ± 14.86	2.37	< .05
Education (years)	15.53 ± 2.46	16.11 ± 2.59	-1.36	.18
Systolic Blood Pressure (mm Hg)	121.07 ± 13.29	121.10 ± 13.70	-.01	.99
Diastolic Blood Pressure (mm Hg)	74.89 ± 7.22	74.52 ± 9.31	.28	.78
Pulse Pressure (mm Hg)	46.18 ± 9.15	46.59 ± 9.02	-.27	.79
C-Reactive Protein (mg/L)	2.27 ± 2.21	2.29 ± 2.37	-.05	.96
Homocysteine (µmol/L)	8.39 ± 1.62	8.21 ± 1.83	.62	.54
Folate (ng/mL)	19.04 ± 5.15	17.21 ± 4.93	2.15	< .05
Vitamin B_{12} (pg/mL)	572.65 ± 238.49	569.46 ± 272.80	.08	.94
Cholesterol (mg/dL)	202.16 ± 39.72	193.02 ± 38.55	1.39	.17
LDL Cholesterol (mg/dL)	123.26 ± 34.06	114.19 ± 34.13	1.58	.12
HDL Cholesterol (mg/dL)	55.62 ± 13.88	56.75 ± 15.82	-.46	.64
Triglycerides (mg/dL)	116.54 ± 68.07	110.19 ± 66.68	.56	.58
Cholesterol Ratio (mg/dL)	3.82 ± 1.11	3.63 ± 1.14	1.02	.31
Blood Glucose (mg/dL)	88.46 ± 12.27	85.04 ± 10.69	1.71	.09
MMSE	29.05 ± 0.96	28.86 ± 1.03	1.17	.24

Note. SD = standard deviation; *t* = student t-test value, *p* = significance, LDL = low density lipoprotein; HDL = high-density lipoprotein; Cholesterol Ratio = Cholesterol/ HDL Cholesterol; MMSE = Mini Mental State Exam

number of items. For the current study, these have been modified from the standard test battery to eliminate words that have fallen out of usage or those that are not native to the English language. The complete set of words was then randomly assigned across six comparable lists of 26 items each, so that each original list was equally represented across each of the newly derived lists. Participants were given subtests one and two at baseline. The internal reliability for one of the subtests in its original form ranges from .81 to .89 (Ekstrom, French, Harman, & Dermen, 1976b).

Fluid intelligence. Scale 3B of the Cattell-Culture-Fair Intelligence Test (Cattell & Cattell, 1960) was administered in its entirety as a measure of fluid intelligence. In this paper-pencil based task, participants view geometric designs and are asked to discover rules according to which the designs are arranged in series and matrices. In test one, participants are asked to find the drawing among six alternatives that would best complete the series. In test two, participants are instructed to find two drawings among five alternatives that are different in some way from the remaining choices. In the third part, participants are asked to identify which of six alternatives best completes the geometric matrix. Lastly, in part four, participants are given an abstract figure containing a dot and are asked to replicate the position of the dot among five alternatives. Internal consistency using Cronbach's alpha has been estimated at .63, and construct validity at .81 for scale 3B (Cattell & Cattell, 1973).

Declarative memory. Two declarative memory functions were assessed. Associative memory measured by the Memory for Names subtest from the Woodcock-Johnson Psychoeducational Battery-Revised ([WJ-R], Woodcock & Johnson, 1989), and free recall by the Logical Memory subtest from the Wechsler Memory Scale-

Revised ([WMS-R], Wechsler, 1987). In Memory for Names, participants are shown cartoons of “space creatures” and read aloud creatures “names” (nonsense one- or two-syllable words). After presentation of name-picture pairs, participants are asked to point to the named space creature first alone, then among other space creatures. With each successive trial, participants are asked to learn the identity of a new space creature and retain the identity of all the preceding space creatures until all twelve are presented. Corrections are provided throughout acquisition. After a 20 min delay, participants are given three trials with no correction to identify the named space creature by pointing. The split-half reliability of the immediate and delayed recognition scores is .91 (Woodcock & Mather, 1989).

In Logical Memory, participants are read two short stories of just a few lines each and are asked to retell the story, verbatim. After a 20 min delay, participants are asked to repeat the stories. If they are unable to do so, a simple reminder cue is provided for one or both stories. The split-half reliability of this task is .74 for immediate and .75 for delayed presentation (Wechsler, 1987).

Working memory. Participants performed two computerized versions of the *n*back task modeled after Dobbs and Rule (1989). In the verbal version, a series of digits (1-9) of variable length was presented. After the presentation, participants were asked to name the digit shown 1-, 2-, or 3-back in blocked trials of the same *n*back. Participants were aware of the condition being tested and were familiarized with each condition before the test trials. In the nonverbal version, a series of abstract drawings was presented, and at the end of each presentation, the participants were asked to indicate the drawing shown 1-, 2-, or 3-back. Trials were blocked and the participants

were aware of the condition prior to starting. For both versions, the indices of performance included both reaction time and number of errors. The test-retest reliability for the verbal version of the task is .68, .88, and .91, for 1-, 2-, and 3-back conditions respectively (Salthouse, Hancock, Meinz, & Hambrick, 1996).

Executive functions. Two executive functions were assessed: inhibition of pre-potent response and perseveration. The response inhibition measures are in paper-and-pencil format, whereas administration of the perseveration task is computerized.

Two variants of a modified Stroop task (Stroop, 1935) modeled after Salthouse and Meinz (1995) were administered. In the color version, participants read aloud a page of words rendered in colors that are congruent or incongruent with the written word meaning, e.g., the word *red* printed in red ink (compatible) or in green ink (incompatible). In the position Stroop task, participants view a page of boxes bisected by either a horizontal or vertical line with a word printed in each box. The task is to identify the position of the word relative to the internal line. The position of the word is either consistent or inconsistent with its meaning, e.g., the word *above* could appear above (compatible) or below (incompatible) the line. Split-half reliability estimates of these tasks as a measure of interference are .72 for the color version and .70 for the position version (Salthouse & Meinz, 1995).

A computerized version of the Wisconsin Card Sorting Task (WCST: Computer Version 4 – Research Edition, Psychological Assessment Resources, Inc. Lutz, FL) was administered. Participants are to match the target card presented in the lower portion of the screen, to one of the four key cards presented at the top of the screen according to the color, shape, or number of geometric figures on the target card, using one of four

designated keys on the keyboard. Categories are presented in two repeated sets of blocks ordered as color, shape, number, with category switch occurring after 10 successive correct trials. Participants are informed of their accuracy after each trial and continue until achieving all six categories, or after 128 trials. The total number of errors (incorrect matches), the number of perseverative errors (incorrect match according to current rule, but correct for the previous sorting rule), and the number of non-perseverative errors (all other incorrect matches) were the indices of performance.

Psychomotor speed. Psychomotor speed was assessed by two comparison tasks, both of which are modeled after Salthouse and Meinz (1995). In Letter Comparison, participants are presented with two columns of letter strings, three to nine letters each. Letter strings are either the same in both columns or differ by one letter. For each set of letter strings, participants are required to indicate whether the strings are the same or different. Pattern Comparison has two columns of abstract patterns that are either the same in both columns or with one line having a different orientation. For each set of abstract patterns, participants are required to indicate whether the patterns are the same or different. Participants are instructed to work as quickly and accurately as possible on each of two pages, with a time limit of 30 s per page. Test-retest reliability estimates for the Letter Comparison task have ranged from .77 to .80, and between .76 and .87 for Pattern Comparison (Salthouse et al., 1996; Salthouse & Meinz, 1995; Salthouse, Fristoe, McGuthry, & Hambrick, 1998).

CHAPTER 3

RESULTS

Data Conditioning and Analyses

For the *n*-back tasks, trials resulting in errors were removed from analysis, as were trials in which reaction time was less than 500 ms or in excess of 10,000 ms, as these were deemed to reflect chance responding or motivational problems. The application of these criteria produced missing data for one block of trials in four cases (one verbal, three nonverbal). A computer malfunction resulted in three missing cases on the WCST task. In order to examine inhibition of the pre-potent response, the ratio of incompatible trials to neutral trials was examined separately for each Stroop task. Distributions for reaction time values on both versions of the *n*-back task, comparison tasks, and Stroop interference were skewed, as were distributions for error scores on both versions of the *n*-back and WCST, thus logarithmic transformation was applied to those variables. Scatterplots with blood level on the x-axis and cognition on the y-axis for the total sample and by SNP were analyzed for nonlinearity, as were 2-D mosaic surface plots with blood level on the x-axis, age on the y-axis, and cognition on the Z-axis for both the total sample and by SNP. In all cases, there was little evidence for nonlinearity.

Pearson product moment correlations were used to assess potential relationships among variables. In the full sample *(n* = 198), age and Hcy were significantly correlated (r = .32, p < .001), but CRP was unrelated to either age (r = .02, *ns*) or Hcy (r = -.02, *ns*). A similar pattern was found for the reduced sample (n = 151), such that age and Hcy were significantly correlated (r = .31, p <.001), but CRP was

unrelated to either age (*r* = .01, *ns*) or Hcy (*r* = .01, *ns*). Results were unchanged when Spearman's rho for highly skewed variables was used (data not shown). Correlations among biological variables and cognitive indices in the final sample were similar to those of the full sample and are reported in Table 10.

As the cognitive variables were moderately to highly correlated with one another on different measures of the same construct (*r*'s from .34 to .90), a factor analysis was conducted in order to create fewer, more parsimonious composite variables of similar constructs. Response time on the 3-back trials of the *n*back task was associated with considerable error (5.05 ± 3.60 for verbal; 9.45 ± 4.61 for nonverbal) and significant variability nearly double that of the easier trials (3728.23 ± 906.85 for 3-back, vs. 2149.36 ± 459.49 for 1-back and 2566.59 ± 573.56 for 2-back), whereas accuracy on the 1- and 2-back *n*back trials resulted in near ceiling performance (0.32 ± 0.93 for 1-back and 1.44 ± 2.14 for 2-back vs. 7.25 ± 3.53 for 3-back); therefore factor analysis was restricted to reaction time for 1- and 2-back trials, and errors for 3-back trials.

The factor analysis with varimax rotation revealed five factors with eigenvalues greater than one. The first factor was predominantly categorized by measures of speed, and included both the 1- and 2-back trials from the verbal and nonverbal *n*back, as well as Letter and Pattern Comparison (factor loadings from .58 to .81). The second factor was predominantly a measure of general intelligence ('g') and inhibition, and included the CFIT, vocabulary, color and position Stroop interference, and WCST perseverative and nonperseverative errors (factor loadings from .43 to .82). The third factor constituted prose memory and included both the immediate and delayed administrations of Logical Memory (factor loadings of. 91). The fourth factor was associative memory

Table 10

Correlation Matrix of Biological and Cognitive Study Variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1. Age	1.00																						
2. CRP	.01	1.00																					
3. Hcy	.31	.02	1.00																				
4. PP	.42	.22	.10	1.00																			
5. Vocab	.34	-.12	.06	.08	1.00																		
6. CFIT	-.28	-.04	-.15	-.14	.34	1.00																	
7. LM	-.23	-.12	.03	-.14	.22	.41	1.00																
8. LMD	-.19	-.07	.11	-.11	.27	.44	.90	1.00															
9. Names	-.41	.04	-.10	-.19	.24	.52	.37	.43	1.00														
10. NamesD	-.42	.00	-.13	-.22	.27	.48	.37	.42	.89	1.00													
11. NbV1rt	.44	-.02	.33	.15	-.00	-.40	-.25	-.23	-.24	-.27	1.00												
12. NbV2rt	.36	.09	.21	.12	-.13	-.44	-.27	-.23	-.32	-.34	.70	1.00											
13. NbV3rt	.36	-.07	.01	.23	-.09	-.20	-.18	-.12	-.23	-.25	.38	.53	1.00										
14. NbNV1rt	.60	-.11	.33	.30	.06	-.33	-.26	-.26	-.42	-.42	.59	.54	.41	1.00									
15. NbNV2rt	.58	-.06	.23	.36	.12	-.35	-.35	-.32	-.42	-.42	.59	.53	.41	.71	1.00								
16. NbNV3rt	.42	-.01	.11	.14	.03	-.27	-.17	-.12	-.28	-.28	.37	.44	.44	.40	.40	1.00							
17. NbV3er	.22	-.03	.02	.09	-.24	-.38	-.22	-.24	-.40	-.38	.22	.21	.05	.15	.13	.18	1.00						
18. NbNV3er	.32	.03	-.05	.16	-.21	-.39	-.31	-.30	-.37	-.39	.27	.26	.25	.22	.26	.17	.47	1.00					
19. Cinterfer	.40	-.02	.11	.10	-.13	-.60	-.30	-.31	-.47	-.46	.36	.38	.25	.43	.46	.28	.37	.38	1.00				
20. Pinterfer	.26	-.00	.12	.09	-.18	-.47	-.26	-.27	-.45	-.41	.29	.29	.12	.32	.33	.26	.28	.27	.64	1.00			
21. WCSTPE	.26	-.06	.07	.10	-.31	-.60	-.35	-.37	-.35	-.39	.43	.37	.21	.37	.32	.12	.34	.40	.43	.35	1.00		
22. WCSTNPE	.25	.01	.06	.15	-.21	-.46	-.29	-.32	-.28	-.32	.35	.36	.21	.35	.31	.09	.39	.39	.44	.28	.78	1.00	
23. LetComp	-.50	.07	-.30	-.15	.03	.35	.36	.37	.51	.53	-.40	-.40	-.29	-.51	-.51	-.26	-.37	-.28	-.38	-.28	-.26	-.26	1.00
24. PatComp	-.51	.02	-.30	-.17	.04	.40	.34	.34	.38	.40	-.38	-.39	-.25	-.47	-.42	-.29	-.29	-.33	-.45	-.27	-.24	-.25	.68

Note. All $r \geq .28$ significant at $p < .001$, $r \geq .22$ significant at $p < .01$, and $r \geq .17$ significant at $p < .05$. After adjustment for multiple comparisons, only $r \geq .31$ significant, CRP = C-reactive protein; Hcy = homocysteine; PP = Pulse Pressure; LM & LMD = Logical Memory Immediate & Delayed; Names & NamesD = Memory for Names Immediate & Delayed; NbV1rt, NbV2rt, & NbV3rt = Nback Verbal 1-, 2-, & 3-back Reaction Time; NbNv1rt, NbNv2rt, & NbNv3rt = Nback Nonverbal 1-, 2-, & 3-back Reaction Time; NbV3er = Nback Verbal 3-back Errors; NbNV3er = Nback Nonverbal 3-back Errors; Cinterfer & Pinterfer = Color & Position Stroop Interference; WCSTPE & WCSTNPE = Wisconsin Card Sorting Task Perseverative & Nonperseverative Errors; LetComp & PatComp = Letter & Pattern Comparison.

and included both the immediate and delayed administrations of the Memory for Names task (factor loadings of .78 and .82). Lastly, the fifth factor was an accuracy factor and comprised errors from both versions of the *n*back (factor loadings of .64 and .83). Results from the factor analysis are summarized in Table 11.

The General Linear Model (GLM) approach was used to assess the relationship between age, sex, hypertension status (diagnosis or mean systolic ≥ 140 mmHg and/or mean diastolic ≥ 90 mmHg), blood biomarkers, and cognitive functions. In such analyses, the respective cognitive function(s) served as the dependent variable, whereas age, CRP, and Hcy were centered at their sample means and entered as continuous independent variables. Sex and hypertension status were categorical independent variables.

In a separate set of GLM analyses assessing the relationship between SNPs and cognitive function, allele status (three levels for *CRP* -286 C>T>A and two levels for *MTHFR* 677C>T), hypertension status, and sex were entered as categorical variables, and age, CRP, and Hcy were centered to the mean and entered as continuous independent variables; whereas cognitive function was entered as the dependent variable. Given the small number of participants homozygous for the T allele in either SNP (13 for *CRP*, and 15 for *MTHFR*), carriers homozygous for the T allele were grouped with heterozygote carriers. Similarly, there were no homozygous carriers for the A allele for the *CRP* SNP, therefore, A carriers comprised A/C and A/T heterozygotes.

Table 11

Factor Loadings for Exploratory Factor Analysis with Varimax Rotation of Cognitive Variables

Variable	Speed	'g'/Inhibition	Prose	Association	Accuracy
NbV1rt	**.81**	.26	.07	.04	-.05
NbV2rt	**.71**	.32	.07	-.04	-.13
NbNV1rt	**.80**	.12	.09	-.29	.03
NbNV2rt	**.79**	.11	.20	-.23	-.01
LetComp	**-.58**	.07	-.21	.42	.37
PatComp	**-.59**	-.02	-.19	.29	.37
CFIT	-.28	**-.52**	-.28	.30	.29
Vocab	.33	**-.43**	-.23	.25	.24
Cinterfer	.42	**.51**	.02	-.45	-.11
Pinterfer	.12	**.54**	.06	-.56	.17
WCSTPE	.26	**.82**	.13	-.15	-.19
WCSTNPE	.21	**.78**	.16	-.04	-.24
LM	-.20	-.16	**-.91**	.14	.10
LMD	-.16	-.20	**-.91**	.20	.11
Names	-.21	-.15	-.21	**.82**	.24
NamesD	-.21	-.19	-.21	**.78**	.30
NbV3er	.02	.17	.09	-.17	**-.83**
NbNV3er	.18	.36	.09	-.12	**-.64**

Note. Parsimonious factor loadings are in boldface. NbV1rt & NbV2rt = Nback Verbal 1- and 2-back reaction time; NbNV1rt & NbNV2rt = Nback Nonverbal 1- and 2-back reaction time; LetComp & PatComp = Letter and Pattern Comparison; CFIT = Culture Fair Intelligence Test Scale 3B; Vocab = Educational Testing Services Vocabulary Test; Cinterfer & Pinterfer = Color and Position Stroop Interference; WCSTPE & WCSTNPE = Wisconsin Card Sorting Task perseverative and nonperseverative errors; LM & LMD = Logical Memory immediate and delayed administrations; Names & NamesD = Memory for Names immediate and delayed administrations; NbV3er = Nback Verbal 3-back errors; NbNV3er = Nback Nonverbal 3-back errors.

For each analysis, a full model that included all second-order interactions was tested first. All interactions that did not reach statistical significance ($p < .10$) were removed from analyses, and the analyses repeated without their inclusion. Reduced models of the GLM analyses were followed by univariate analyses of simple effects, and testing the differences among the levels of categorical variables with Fisher's Least Significant Difference (LSD) test, or slope of regression on the continuous variables by comparing the 95% confidence intervals around them.

Pair-wise comparisons on the use/abstinence of various medications/activities (e.g., hormone replacement therapy, dietary supplements, statins, anti-inflammatories, exercise, alcohol, caffeine) and presence/absence of various conditions (e.g., arthritis, high-cholesterol, impaired fasting glucose, infections) known to affect CRP and Hcy levels were also conducted on a subsample of participants with completed supplementary questionnaire data.

Hypothesis 1: Elevations in CRP or Hcy will be associated with poorer cognition

In order to test whether elevated blood levels of CRP or Hcy were related to cognitive performance, a series of 10 GLM (five for each blood biomarker) analyses were conducted with each of the five factors entered as continuous dependent variables in turn. With the exception of prose and associative memory, the other factors were highly skewed and were therefore log transformed before entry into the GLM. In each GLM, age and the blood biomarker (either CRP or Hcy) were centered to the mean and entered as continuous independent variables, whereas sex and hypertension status were categorical independent predictors.

Psychomotor speed. The composite score of psychomotor speed was derived by averaging performance on both versions of the *n*back for 1- and 2-back trials, as well as the number of items correctly completed on each of the comparison tasks. The composite score was then entered as the continuous dependent variable in each of two separate GLM analyses. In each of the GLMs, results indicated a significant main effect of age attributed to slower performance with increasing age ($\beta = .39$, $p < .001$). The GLM with CRP as an independent variable additionally revealed a significant main effect of hypertension status attributed to slower performance among hypertensives (Fisher's LSD $p = .04$). No other significant main effects or interactions were found. Significant effects for CRP are summarized in Table 12, and for Hcy in Table 13.

Examination of *n*-back RT and comparison task performance separately resulted in additional effects. Namely, all models revealed significant main effects of age, as well as a significant interaction of Sex × Hypertension status, reflective of slower performance and fewer comparisons among female hypertensives. Additionally, the analysis conducted on *n*-back RT with CRP alone revealed a significant main effect of hypertension, whereas the analysis on the comparison tasks with Hcy alone resulted in a significant main effect of Hcy reflective of fewer comparisons with higher Hcy levels (data not shown).

'g' and inhibition. A composite score of 'g'/inhibition was derived by averaging performance from the CFIT, vocabulary, each of two measures of Stroop interference, and perseverative and non-perseverative errors from the WCST. First, a summary variable was created for each of the cognitive variables included in the composite. Performance on scale 3B of the Cattell Culture Fair Intelligence Test was created by

Table 12

General Linear Model Analysis: Summary of Significant Effects and Trends of CRP Singularly

Task	Effect	df	*F*	*p*
Psychomotor Speed	Age	1, 144	19.94	< .001
	Hypertension	1, 144	4.32	< .05
‘g’/Inhibition	Age	1, 139	36.57	< .001
Prose Memory	Age	1, 145	6.89	= .01
	CRP	1, 145	3.69	< .06
	CRP × Sex	1, 145	3.05	< .09
Associative Memory	Age	1, 146	24.57	< .001
Accuracy	Age	1, 145	12.19	= .001

Note. df = degrees of freedom; *F* = F statistic derived from GLM; *p* = significance level; ‘g’ = general intelligence; CRP = C-reactive protein

Table 13

General Linear Model Analysis: Summary of Significant Effects and Trends of Hcy Singularly

Task	Effect	df	*F*	*p*
Psychomotor Speed	Age	1, 142	17.85	< .001
‘g’/Inhibition	Age	1, 137	35.72	< .001
Prose Memory	Age	1, 144	9.20	< .01
	Hcy	1, 144	3.46	< .07
Associative Memory	Age	1, 144	24.98	< .001
Accuracy	Age	1, 143	14.88	< .001

Note. df = degrees of freedom; *F* = F statistic derived from GLM; *p* = significance level; ‘g’ = general intelligence; Hcy = homocysteine

summing all items answered correctly under the untimed administration in each of the four subtests. For vocabulary, a composite score was derived by summing the total number of items answered correctly and multiplying this by a fraction (0.25) of the total number of items answered incorrectly on each of the two subtests during the untimed administration. Interference on the Stroop task was first computed as the ratio of response time on the average of the incompatible trials to the average of response time on the neutral trials for each task. The composite variable of all measures combined was then entered as the continuous dependent variable in the GLM. Both GLMs revealed only a significant main effect of age attributed to greater 'g' with increasing age ($\beta = .46$, $p < .001$). No other significant main effects or interactions were found. Significant effects for CRP are summarized in Table 12, and Hcy in Table 13.

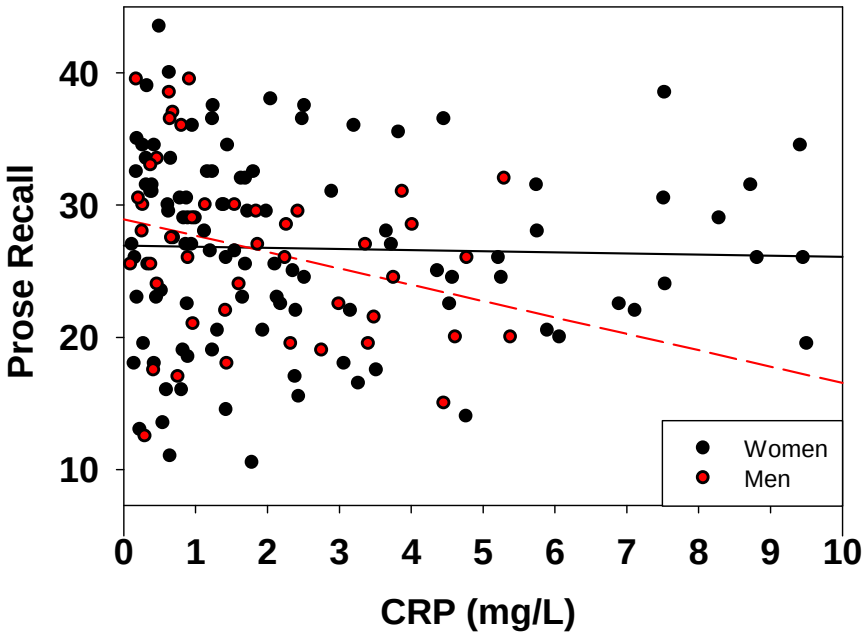
When the results were analyzed separately for each of the tests within the factor, all models yielded significant effects of age, and most revealed effects or trends of sex, and Age × Sex interactions. For the analysis conducted on Vocabulary in CRP alone, there was a main effect of CRP, such that higher levels were associated with reduced performance (data not shown).

Prose memory. A composite for prose memory was derived by averaging performance on the Logical Memory task for the immediate and delayed administrations, and then entered as a continuous dependent variable in the GLM. Both analyses indicated a significant main effect of age reflective of poorer performance among older persons ($\beta = -.22$, $p < .01$). Additionally, in the GLM conducted on CRP as an independent predictor, the main effect of CRP approached significance [$F(1, 145) = 3.69$, $p = .057$] as did the CRP × Sex interaction [$F(1, 145) = 3.05$, $p = .083$], reflective

of poorer performance with higher blood levels of CRP (β = -.08, *ns*), particularly among men (β = -.29, *p* = .05 vs. β = -.03, *ns;* Figure 6). Conversely, the GLM conducted on Hcy identified a main effect of Hcy that approached significance [*F*(1, 144) = 3.46, *p* = .065] reflective of better performance with higher blood levels of Hcy (β = .06, *ns*). Results from the GLM conducted on CRP are summarized in Table 12, and for Hcy in Table 13.

Figure 6

Prose Recall and C-Reactive Protein by Sex



Associative memory. The composite for associative memory was derived by averaging performance from the Memory for Names immediate and delayed administrations then entered as the continuous dependent variable in the GLM. The analysis revealed only a significant main effect of age reflective of poorer performance

with older age (β = -.41, *p* <.001). These results are summarized in Tables 12 (CRP) and 13 (Hcy).

Accuracy. The composite for accuracy was derived by averaging the number of errors made on the 3-back condition for each version of the *n*back and then entered as the continuous dependent variable in the GLM. Results indicated only a significant main effect of age, reflective of more errors made with older age (β = .31, *p* <.001). These results are summarized in Tables 12 (CRP) and 13 (Hcy).

Hypothesis 2: Blood levels of CRP and Hcy will be moderately correlated

In both the full sample *(n* = 198) and the reduced sample (*n* = 151), CRP and Hcy were unrelated with one another (*r* = -.02 and *r* = -.01 respectively). Although restriction of analysis to CRP values above the reference range (≥ 10 mg/L, *n* = 11) resulted in a strengthening of the association (*r* = .20), as did restriction of analysis to values outside the reference range for Hcy (≥ 12 µmol/L, *n* = 27; *r* = -.12), neither was significant. Only when the analysis was restricted to those cases above the reference range for either CRP or Hcy (*n* = 36) was there a significant correlation between the two (*r* = -.48, *p* < .01). There was an insufficient number of cases (*n* = 2) to analyze persons with elevations in both.

Hypothesis 3: The combined effect of elevated blood levels of CRP and Hcy on cognitive outcomes will be stronger than either CRP or Hcy alone.

In order to test whether the combined effects of elevated blood levels of CRP and Hcy on cognition were stronger than either effect alone, the GLM analyses were repeated with both CRP and Hcy centered to the mean and entered as continuous independent variables.

Psychomotor speed. Results indicated a significant main effect of age attributed to slower performance with increasing age (β = .39, $p < .001$). Although there was not a main effect of Hcy within the GLM, there was a significant Age × Hcy interaction, reflective of a slowing of response time with higher Hcy levels, but only among the most aged. Age most likely was functioning as a suppressor variable, as the inclusion of Hcy in the regression analysis explained additional variance over age alone (β = .39 vs. β = .388). The CRP × Hcy interaction approached significance, $F(1, 139) = 3.76$, $p < .06$, and reflected the fact that CRP and Hcy had slopes in the opposite direction of one another (β = -.06, *ns* vs. β = .16, $p < .05$). These interactions are shown in Figure 7, and results for the combined analysis are summarized in Table 14.

Analysis of *n*-back RT and comparison task performance separately resulted in the same age effects, as well as significant interactions of Sex × Hypertension status, and a significant main effect of Hcy on comparison task performance as in the analyses conducted on CRP and Hcy separately. Moreover, the CRP × Hcy interaction reached significance in the analysis conducted on *n*-back RT alone, as did the Hcy × Sex interaction (data not shown).

'g' and inhibition. The GLM on the 'g'/Inhibition factor revealed only a significant main effect of age attributed to greater 'g' with increasing age (β = .46, $p < .001$). No other significant main effects or interactions were found. Results are summarized in Table 14.

Interestingly, when the analyses were repeated on each of the tests comprising the 'g'/inhibition factor alone, many of the same effects emerged as when CRP and Hcy were analyzed separately. Namely, the analysis on the CFIT revealed a significant main

Figure 7

Age and C-Reactive Protein on Speed as a Function of Homocysteine Levels

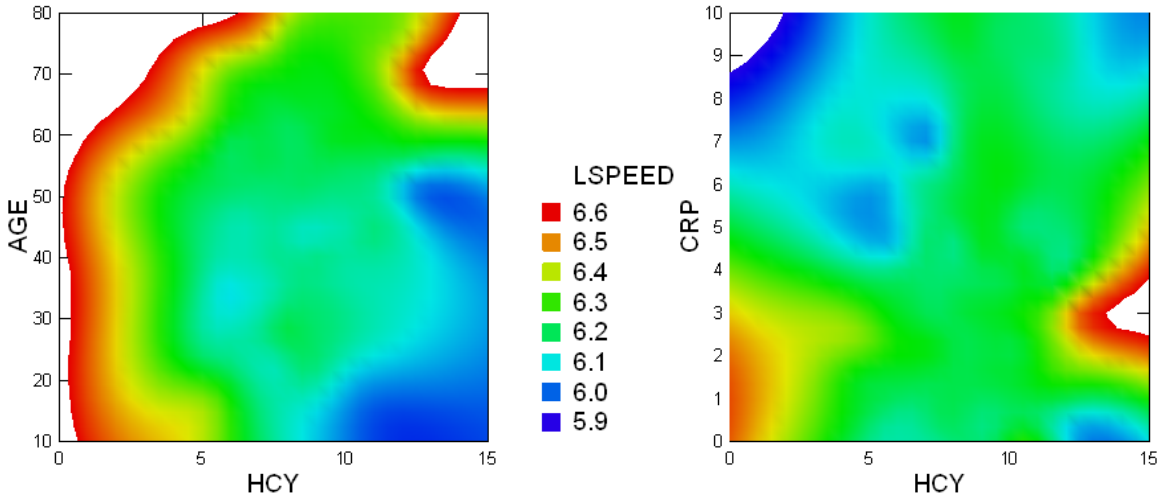


Table 14

General Linear Model Analysis: Summary of Combined Significant Effects and Trends

Task	Effect	df	*F*	*p*
Psychomotor Speed	Age	1, 139	22.57	< .001
	Age × Hcy	1, 139	5.04	< .05
	CRP × Hcy	1, 139	3.76	< .06
‘g’/Inhibition	Age	1, 135	37.26	< .001
Prose Memory	Age	1, 142	10.38	< .01
	Hcy	1, 142	7.42	< .01
	Hcy × Sex	1, 142	7.24	< .01
Associative Memory	Age	1, 143	34.54	< .001
Accuracy	Age	1, 142	14.74	< .001

Note. df = degrees of freedom; *F* = F statistic derived from GLM; *p* = significance level; ‘g’ = general intelligence; CRP = C-reactive protein; Hcy = homocysteine

effect of sex, and the analysis on the Stroop revealed a significant Sex × Age interaction. Additionally, the analysis conducted on Vocabulary revealed a significant CRP × Hcy interaction, reflective of the fact that CRP and Hcy had slopes in the opposite direction of one another (data not shown).

Prose memory. The GLM on prose memory indicated a significant main effect of age reflective of poorer performance among older persons (β = -.22, *p* <.01). Although the main effect of Hcy was significant [*F*(1, 142) = 7.42, *p* < .01], the post-hoc regression analysis was not (β = .06, *ns*), thus indicating a suppressor effect of age on Hcy. As is shown in Figure 8, the significant Hcy × Sex interaction indicated higher blood levels of Hcy were associated with more items recalled in men (β = .28, *p* <.07), but not women (β = -.07, *ns*). Results from the GLM are summarized in Table 14.

Associative memory. As with the analyses conducted on CRP or Hcy singularly and shown in Table 14, the combined analysis revealed only a significant main effect of age reflective of poorer performance among older persons (β = -.41, *p* <.001).

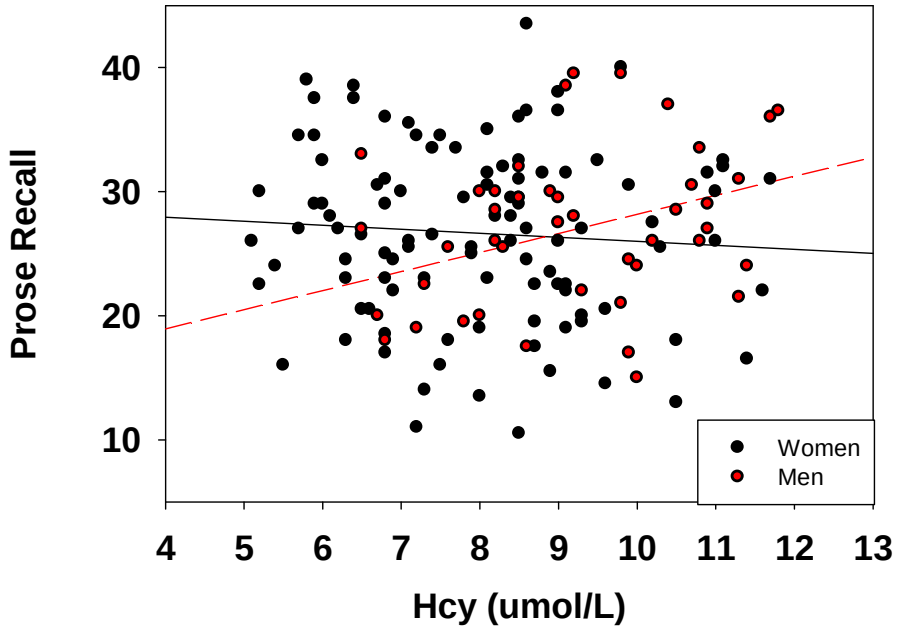
Accuracy. Similarly, results on the combined GLM for accuracy revealed only a significant main effect of age, reflective of more errors made with older age (β = .31, *p* <.001; Table 14).

Hypothesis 4: Carriers of the T allele for either -286 C>T>A *CRP* or 677C>T *MTHFR* will experience higher blood levels of CRP and Hcy compared to the referent CC carriers.

In order to test whether blood levels were higher among carriers of the T allele, a series of two-sample t-tests were conducted where carrier status was the grouping variable, and blood levels of either CRP or Hcy the dependent variable. Blood levels

Figure 8

Prose Recall and Homocysteine by Sex



were not significantly different among carriers of the T allele for either CRP (t = .74, *ns*) or Hcy (t = -1.22, *ns*) compared to the referent homozygous C carriers. However, carriers of the A allele had significantly higher blood levels of CRP than C homozygotes (t = 2.01, p < .05). Moreover, when blood levels were evaluated by T allele homozygosity, T homozygotes had CRP blood levels intermediary between CC and C/T carriers at the low end, and A/C and A/T carriers at the high end (Figure 9). Hcy levels among T homozygotes were the lowest relative to either C/T or C/C carriers (Figure 10).

Figure 9

C-Reactive Protein Blood Level by CRP Polymorphism

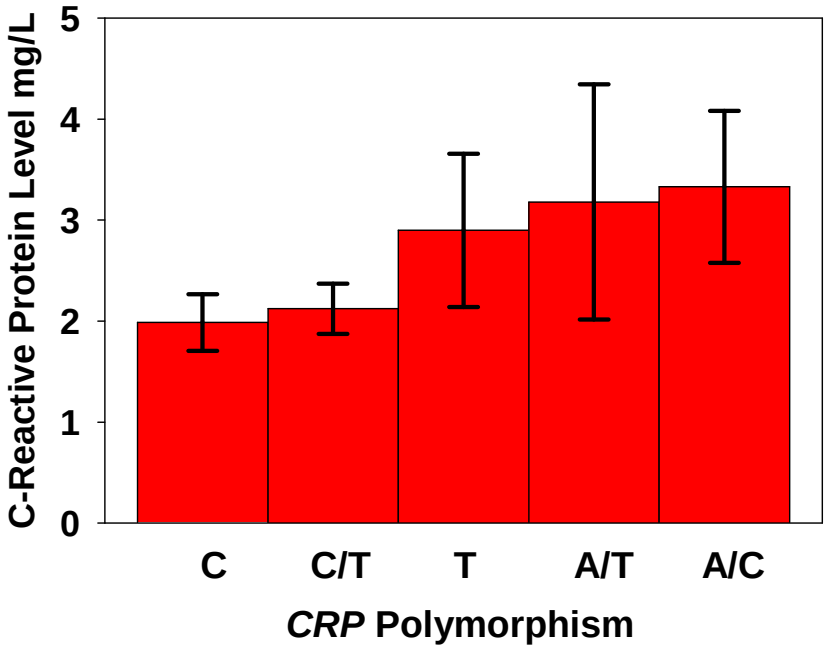
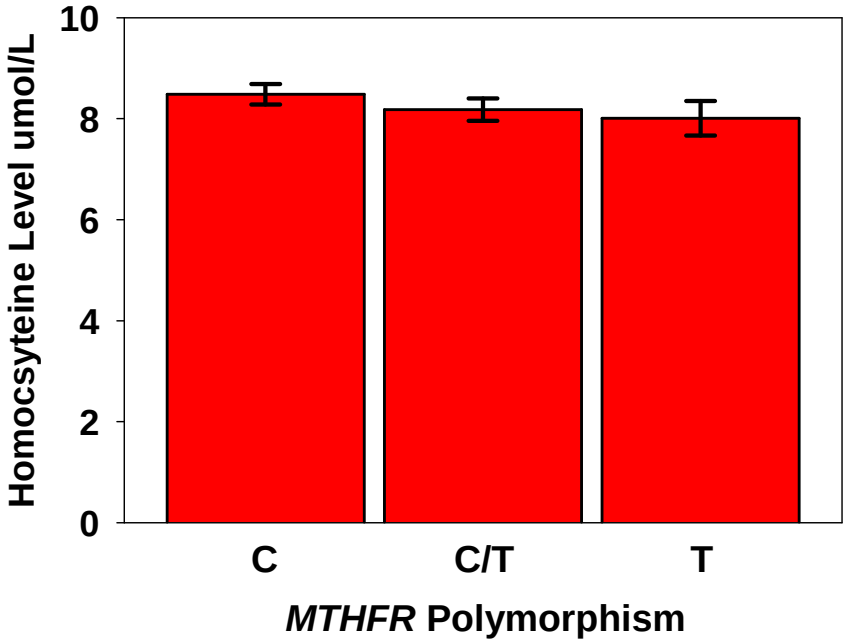


Figure 10

Homocysteine Blood Level by MTHFR Polymorphism



Hypothesis 5: Carriers of the T allele for either -286 C>T>A *CRP* or 677C>T *MTHFR* will exhibit poorer cognitive performance compared to the referent CC carriers.

To test T allele effects on cognition, GLM analyses were repeated with age and the respective blood biomarker centered to the mean and entered as continuous independent variables, and allele, sex, population (Caucasian/African American), and hypertension entered as categorical independent variables on separate GLM analyses for each of the five dependent cognitive factors.

Psychomotor speed. Both the GLM analysis on *CRP* and *MTHFR* revealed significant main effects of age reflective of slower response times among older persons ($\beta = .39$, $p < .001$). The GLM on *CRP* identified additional main effects of population and *CRP* polymorphism, reflective of slower response times among African Americans (Fisher's LSD $p < .001$) and carriers of the T allele relative to either the A (Fisher's LSD $p = .003$) or C (Fisher's LSD $p = .004$) alleles. Results from the GLM for *CRP* are summarized in Table 15, and for *MTHFR* in Table 16.

When *n*-back RT and comparison task performance were analyzed separately, the same age and population effects emerged, but the *CRP* main effect was no longer significant. Instead, the analysis conducted on *n*-back RT alone revealed a main effect of hypertension status and a significant Sex × Hypertension status interaction for both models. Similarly, the analysis conducted on the comparison tasks alone revealed significant interactions of Sex × Hypertension status and Race × Gene polymorphism. There was also a main effect of Hcy in the analysis conducted on Hcy alone (data not shown).

Table 15

General Linear Model Analysis: Summary of Significant Effects and Trends of CRP Gene

Task	Effect	df	*F*	*p*
Psychomotor Speed	Age	1, 141	21.74	< .001
	CRP	2, 141	5.02	< .01
	Population	1, 141	15.01	< .001
'g'/Inhibition	Age	1, 132	53.85	< .001
	CRP	1, 132	3.24	< .08
	Population	1, 132	21.11	< .001
	Age × Sex	1, 132	4.23	< .05
	CRP × Sex	2, 132	4.37	< .05
Prose Memory	Age	1, 141	3.94	< .05
	Age × Sex	1, 141	6.36	< .05
	Hypertension × Population	1, 141	6.12	< .05
Associative Memory	Age	1, 143	26.47	< .001
	Population	1, 143	5.86	< .05
Accuracy	Age	1, 142	14.75	< .001
	Population	1, 142	9.09	< .01

Note. df = degrees of freedom; *F* = F statistic derived from GLM; *p* = significance level; 'g' = general intelligence; *CRP* = -286 C>T>A *CRP* gene

'**g' and inhibition.** Each of the GLM's conducted on *CRP* and *MTHFR* revealed significant main effects of age and population reflective of better 'g' performance among older persons (β = .47, *p* <.001) and Caucasians (Fisher's LSD *p* < .001). Although not significant, there was a trend for a main effect of CRP in the GLM conducted on *CRP*: *F*(1, 132) = 3.24, *p* < .08. Also in this GLM and as shown in Figure 11, the age effect was additionally modified by a significant Age × Sex interaction, which showed greater 'g' performance among men with older age (β = .59, *p* <.001 vs. β = .42, *p* < .001). As is shown in Figure 12, a significant *CRP* × Sex interaction indicated better performance

Table 16

General Linear Model Analysis: Summary of Significant Effects and Trends of MTHFR Gene

Task	Effect	df	*F*	*p*
Psychomotor Speed	Age	1, 138	24.48	< .001
'g'/Inhibition	Age	1, 132	49.11	< .001
	Population	1, 132	25.45	< .001
Prose Memory	Hcy	1, 138	8.83	< .01
	Hypertension	1, 138	4.04	< .05
	Population	1, 138	12.17	= .001
	Age × *MTHFR*	1, 138	5.08	< .05
	Age × Hypertension	1, 138	7.01	< .01
	Hcy × Sex	1, 138	10.13	< .01
	MTHFR × Hypertension	1, 138	5.91	< .05
Associative Memory	Age	1, 142	27.13	< .001
	Population	1, 142	5.18	< .05
Accuracy	Age	1, 141	18.19	< .001
	Hcy	1, 141	4.43	< .05
	Population	1, 141	11.51	= .001
	Sex	1, 141	4.14	< .05

Note. df = degrees of freedom; *F* = F statistic derived from GLM; *p* = significance level; 'g' = general intelligence; Hcy = homocysteine; *MTHFR* = 677C>T *MTHFR* gene

among men compared to women with the A allele (Fisher's LSD *p* = .046), and better performance among women compared to men with the T allele (Fisher's LSD *p* = .029). Additionally, men with the A allele performed better compared to women homozygous for the C allele (Fisher's LSD *p* = .013). Within sex differences were also noted, namely among women, performance was better among carriers of the T allele compared to C homozygotes (Fisher's LSD *p* =.021); and among males, performance was better among carriers of the A allele relative to either carriers of the T allele (Fisher's LSD *p* =

.012) or C homozygotes (Fisher's LSD p = .04). Results from the GLM on *CRP* are summarized in Table 15, and on *MTHFR* in Table 16.

When the analyses were repeated with the individual tests separately, analyses conducted on Hcy alone revealed only significant main effects of age and population. For those conducted on CRP however, several significant interactions with age were revealed such that fluid intelligence was higher among T carriers relative to A carriers, and males had more interference on the Stroop. A significant Sex × Gene polymorphism interaction on the WCST revealed fewer perseverative errors among female C carriers than female T carriers, but more errors among male A carriers than male T carriers (data not shown).

Figure 11

'g' and Age by Sex

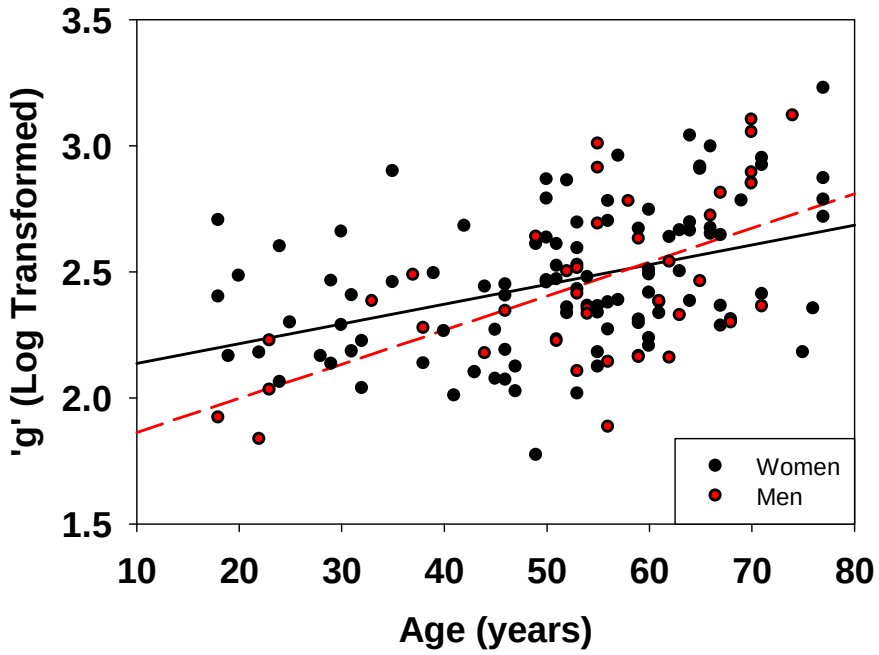
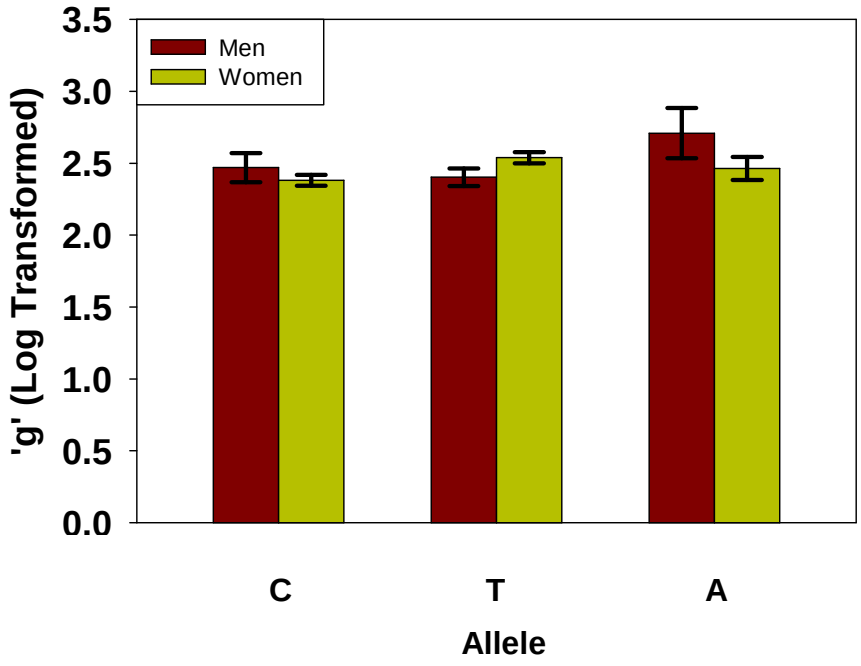


Figure 12

'g' by CRP Polymorphism and Sex



Prose memory. The GLM analysis conducted on *CRP* identified a significant main effect of age which was modified by a significant interaction of Age × Sex. Older persons recalled fewer items (β = -.22, $p < .01$), particularly women (β = -.32, $p = .001$ vs. β = .03, *ns*; Figure 13). As shown in Figure 14, the Hypertension × Population interaction reflected the fact that African American persons without hypertension recalled fewer items than African Americans with hypertension (Fisher's LSD $p = .03$), Caucasians without hypertension (Fisher's LSD $p < .001$), or Caucasians with hypertension (Fisher's LSD $p = .018$). GLM results are summarized in Table 15.

Conversely, in the GLM conducted on *MTHFR*, the main effect of age was not significant ($F < 1$), however, significant main effects of hypertension and population were found, reflective of fewer items recalled among hypertensives (Fisher's LSD $p =$

.046) and African American's (Fisher's LSD p = .001) as summarized in Table 16. As with the analysis conducted on CRP and Hcy blood levels on cognition, the main effect of Hcy was significant in the absence of a significant effect on post-hoc regression analysis (β = .06, *ns*). However, as the standardized coefficient was in the opposite direction to that of the one for age (β = -.22) and added additional variance to that of age alone (β = -.26), it is likely age was acting as a suppressor variable. Several significant interactions modified the main effects for the GLM on *MTHFR*. The Age × *MTHFR* reflected the fact that with older age, C homozygotes performed more poorly than T carriers (β = -.29, p < .01 vs. β = -.11, *ns*; Figure 15). As shown in Figure 16 and demonstrated by the significant Age × Hypertension interaction, prose recall was poorer among older normotensives (β = -.24, p = .01 vs. β = -.05, *ns*). A significant interaction

Figure 13

Prose Recall and Age by Sex

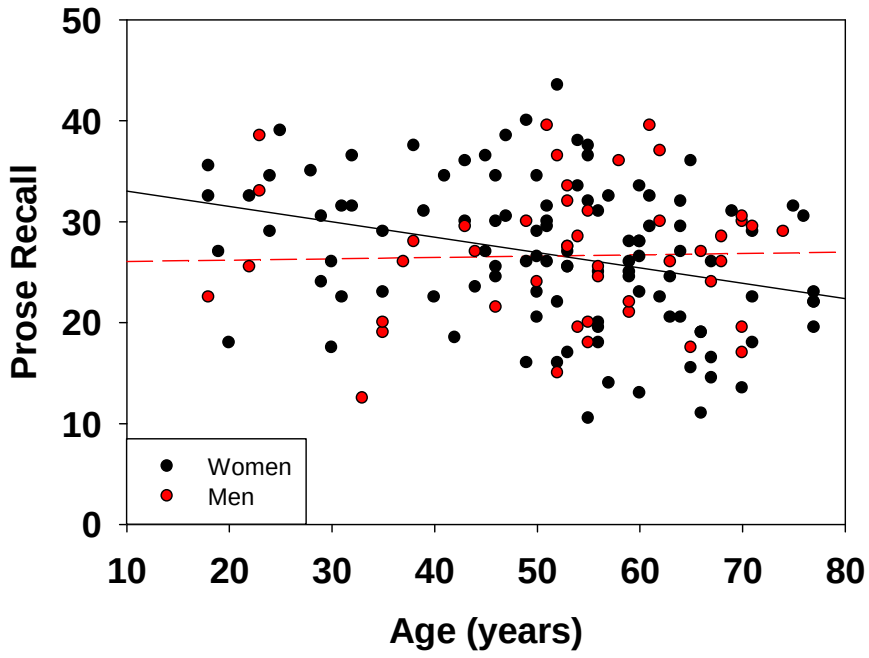


Figure 14

Prose Recall by Population and Hypertension Status

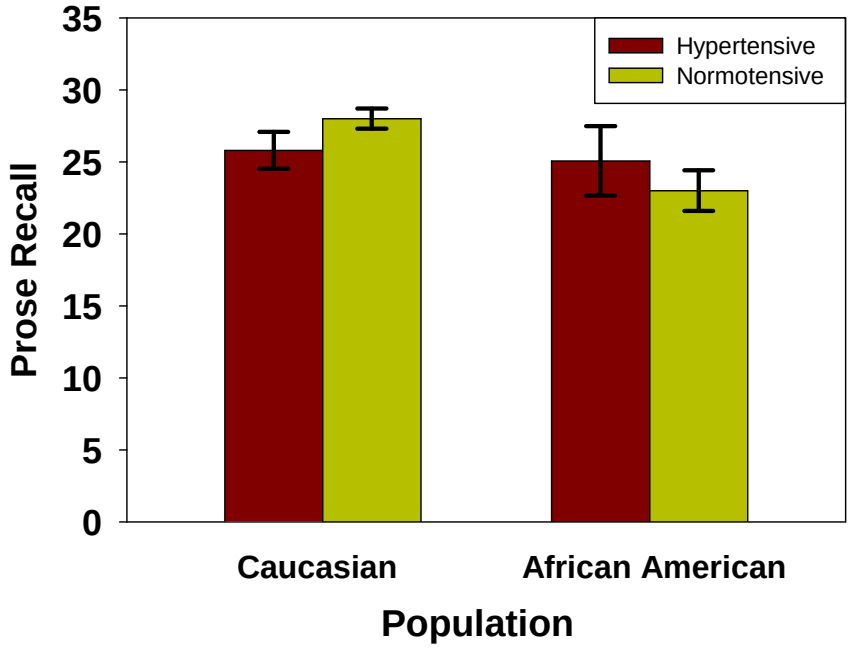


Figure 15

Prose Recall and Age by MTHFR Polymorphism

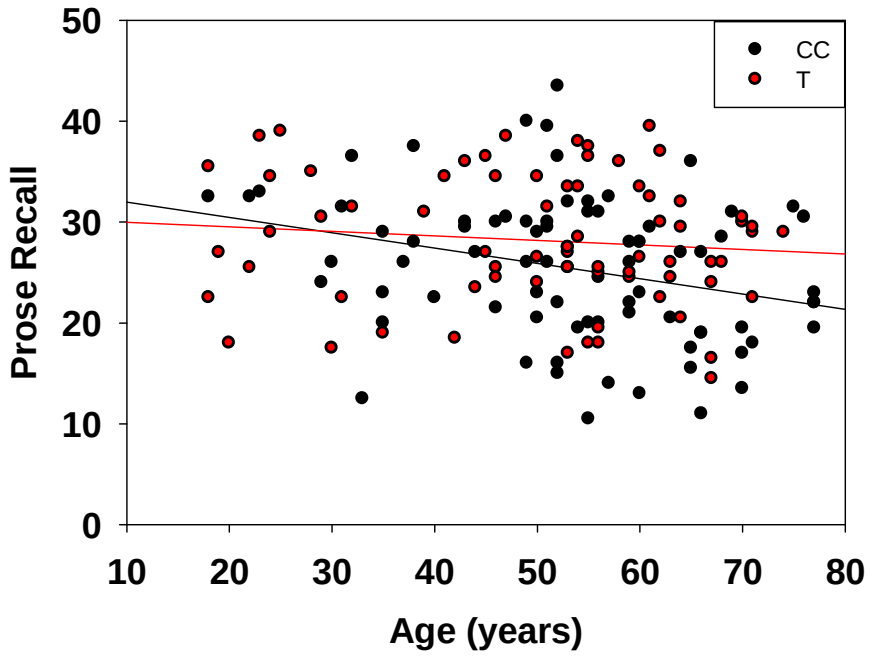
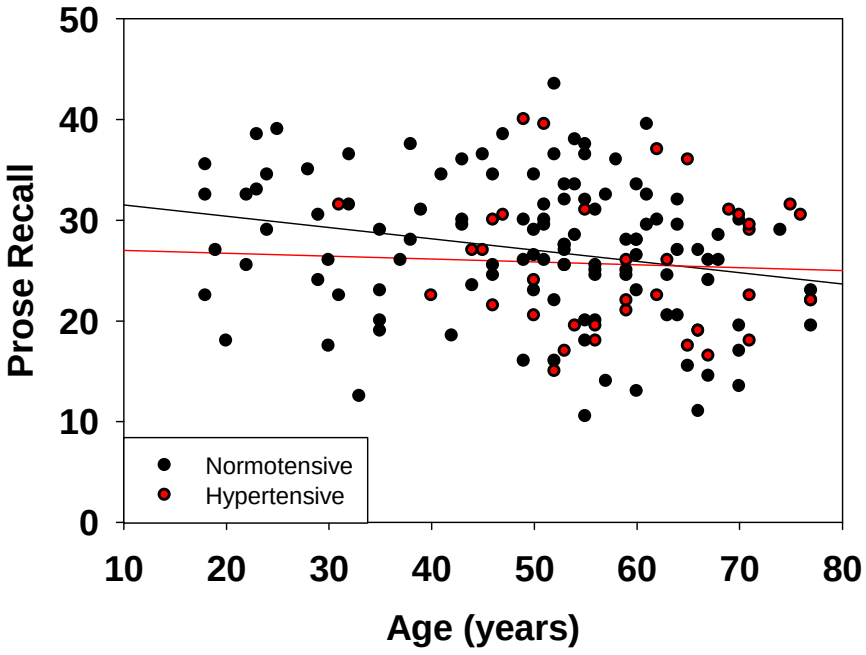


Figure 16

Prose Recall and Age by Hypertension Status



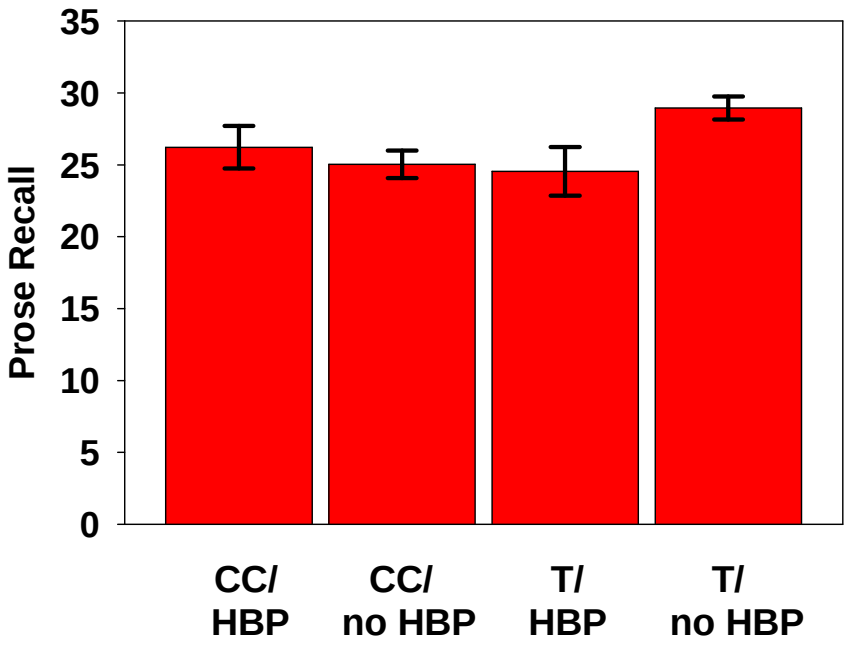
of Hcy × Sex showed men with higher Hcy levels recalled more items than women (β = .28, $p < .07$ vs. β = -.07, *ns*; Figure 8). Lastly, a significant interaction of *MTHFR* × Hypertension revealed hypertensives with T carriage recalled fewer items than normotensives with T carriage (Fisher's LSD $p = .006$; Figure 17). Results for the GLM conducted on *MTHFR* are summarized in Table 16.

Associative memory. The GLM analyses for both *CRP* and *MTHFR* on associative memory revealed only significant main effects of age and population, reflective of fewer associations made by older persons (β = -.41, $p < .001$) and African Americans (Fisher's LSD $p = .017$) as shown in Table 15 (*CRP*) and Table 16 (*MTHFR*).

Accuracy. Similarly, the GLM on accuracy revealed significant main effects of age and population, reflective of more errors made with older age (β = .31, $p < .001$) and

Figure 17

Prose Recall by Hypertension Status and MTHFR Polymorphism



among African Americans (Fisher's LSD p = .003) as shown in Table 15 (*CRP*) and Table 16 (*MTHFR*). The GLM on *MTHFR* revealed a main effect of sex, reflective of more errors made by men (Fisher's LSD p = .044). The significant main effect of Hcy in the absence of a significant post-hoc regression most likely is indicative of a suppressor effect of age on Hcy given the additional variance explained with the inclusion of Hcy over age alone (β = .32 vs. β = .31).

Hypothesis 6: The combined effect of T allele of both -286 C>T>A *CRP* and 677C>T *MTHFR* on cognitive performance will be stronger than that of T allele status for either -286 C>T>A *CRP* or 677C>T *MTHFR* alone.

In order to test the combined effect of *CRP* and *MTHFR* T carrier status on cognitive function, the GLMs were repeated with age, CRP, and Hcy centered to the

mean and entered as continuous independent variables; and sex, hypertension, population, and allele status (three levels for *CRP* and two levels for *MTHFR*) entered as categorical independent variables. Each of the cognitive factors was entered in turn as the dependent variable.

Psychomotor speed. Similar to the GLM conducted on *CRP* alone, the GLM on the combined analysis of *CRP* and *MTHFR* revealed significant main effects of age, *CRP*, and population, reflective of faster response times among younger persons (β = .39, $p < .001$), carriers of the A allele relative to either the T (Fisher's LSD $p = .007$) or C alleles (Fisher's LSD $p = .007$), and Caucasians (Fisher's LSD $p = .008$). Although not significant, the interaction of CRP × Hcy approached significance, $F(1, 135) = 3.74$, $p = .055$, and reflected the fact that CRP and Hcy were inversely related to processing speed (β = -.07, *ns* for CRP vs. β = .16, $p < .05$ for Hcy). Results for the combined GLM are summarized in Table 17.

Similarly, the results on *n*-back RT and Comparison analyzed separately revealed significant age and population effects for both models, as well as a significant main effect of *CRP* for the *n*-back RT task. The CRP × Hcy reached significance in both models, reflective of the fact that CRP and Hcy were inversely related with cognition. Several additional effects and interactions were noted for the analysis conducted on *n*-back RT, namely, significant interactions of Hcy × Age, Hypertension status × Age, and *CRP* gene × Hcy (data not shown).

'**g' and inhibition.** The GLM for 'g'/inhibition revealed significant main effects of age and population indicative of better 'g' performance among older persons (β = .47, $p < .001$) and among Caucasians (Fisher's LSD $p < .001$). Though not significant, the main

Table 17

General Linear Model Analysis: Summary of Significant Effects and Trends of both SNPs

Task	Effect	df	*F*	*p*
Psychomotor Speed	Age	1, 135	24.95	< .001
	CRP	2, 135	4.17	< .05
	Population	1, 135	7.18	< .01
	CRP × Hcy	1, 135	3.74	< .06
‘g’/Inhibition	Age	1, 129	47.13	< .001
	CRP	1, 129	3.54	< .07
	Population	1, 129	18.85	< .001
	CRP × Sex	2, 129	3.17	< .05
Prose Memory	Age	1, 136	9.41	< .01
	Hcy	1, 136	6.69	< .05
	Population	1, 136	8.36	< .01
	Age × *MTHFR*	1, 136	3.28	< .08
	Hcy × *MTHFR*	1, 136	3.02	< .09
	Hcy × Sex	1, 136	6.87	= .01
Associative Memory	Age	1, 139	26.35	< .001
	Population	1, 139	4.62	< .05
Accuracy	Age	1, 132	19.57	< .001
	Hcy	1, 132	6.48	< .05
	Population	1, 132	10.07	< .01
	Sex	1, 132	2.97	< .09
	Age × *CRP*	2, 132	2.36	< .10
	CRP × Sex	1, 132	3.35	< .07
	CRP × *MTHFR*	2, 132	2.78	< .07

Note. Note. df = degrees of freedom; *F* = F statistic derived from GLM; *p* = significance level; ‘g’ = general intelligence; CRP = C-reactive protein; Hcy = homocysteine; *CRP* = -286 C>T>A *CRP* gene; *MTHFR* = *MTHFR* = 677C>T *MTHFR* gene

effect of CRP approached significance, $F(1, 129) = 3.54$, $p < .07$, indicative of a trend towards poorer 'g' performance with higher CRP levels (β = -.11, *ns*). As shown in Figure 12, the *CRP* × Sex interaction indicated better performance among T carriers in women relative to women C homozygotes (Fisher's LSD $p = .035$), and among A carriers in men relative to either C homozygotes in women (Fisher's LSD $p = .03$), or T carriers in men (Fisher's LSD $p = .034$). Results are summarized in Table 17.

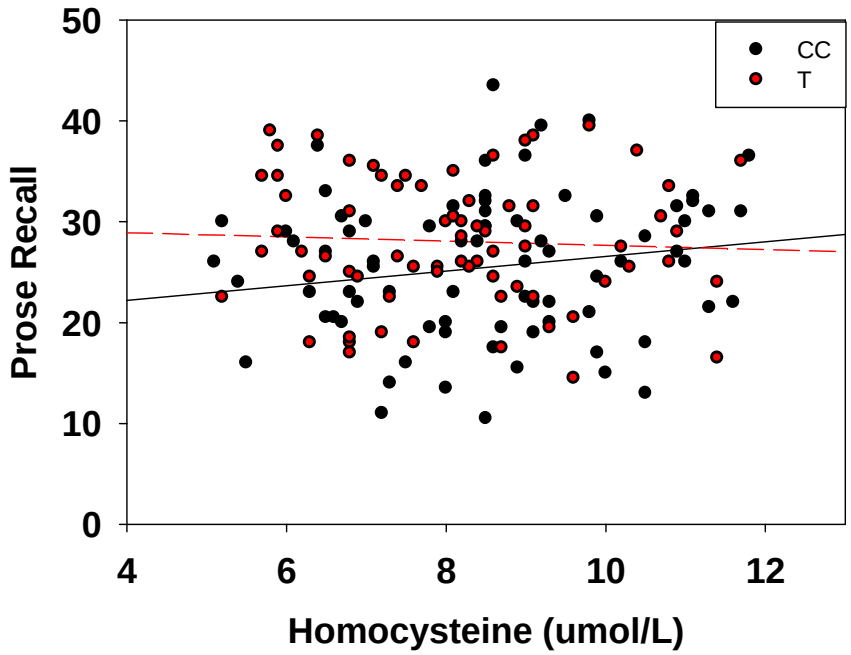
An analysis conducted on each of the tasks separately revealed the same significant main effects of age and population, and a *CRP* × Sex interaction which was only significant for the model conducted on Stroop. Additional interactions of *CRP* gene polymorphism were found such that older age was associated with reduced fluid intelligence in C carriers, T carriage with higher Hcy levels was associated with better vocabulary performance, and females homozygous for the C allele made fewer perseverative responses than females with the T allele.

Prose memory. The GLM conducted on prose memory revealed significant main effects of age and population indicative of fewer items recalled among older age (β = -.22, $p < .01$), and among African Americans (Fisher's LSD $p = .004$). As with the GLM conducted on Hcy alone, the main effect of Hcy was significant [$F(1, 136) = 6.69$, $p < .05$] in the absence of a significant beta on post-hoc regression (β = .06, *ns*), thus indicating a suppressor effect of age on Hcy. The significant Hcy × Sex interaction indicated lower blood levels of Hcy were associated with more items recalled in men (β = .28, $p < .07$), but not women (β = -.07, *ns*; Figure 8). Neither the Age × *MTHFR* nor the Hcy × *MTHFR* interactions were significant, but there was a trend for worse performance among C homozygotes than T carriers with age (β = -.29, $p < .01$ vs. β = -

.11, *ns*; Figure 15); and worse among T carriers versus C homozygotes with higher Hcy levels (β = .18, *ns* vs. β = -.05, *ns*; Figure 18). Results for the GLM are summarized in Table 17.

Figure 18

Prose Recall and Homocysteine by MTHFR Polymorphism



Associative memory. The GLM on associative memory identified only significant main effects of age and population, again reflecting fewer associations among older persons (β = -.41, $p < .001$) and African Americans (Fisher's LSD $p = .033$). These results are summarized in Table 17.

Accuracy. The GLM on accuracy revealed significant main effects of age and population, reflective of more errors in older persons (β = .31, $p < .001$) and among African Americans (Fisher's LSD $p = .002$). As with previous analyses, the main effect of Hcy was significant in the absence of a significant beta on post-hoc regression (β = .01,

ns) with an additive contribution to the total variance explained over age alone (β = .33 vs. β = .31). Both the main effect of sex and the CRP × Sex interaction approached significance as males tended to make more errors than females (Fisher's LSD p = .072), but in the presence of higher CRP blood levels, the opposite was true (β = -.10, *ns* for men vs. β = .11, *ns* for women; Figure 19). The *CRP* × *MTHFR* interaction also approached significance namely due to the fact that carriers of the A allele for *CRP* and the T allele for *MTHFR*, made more errors than either C (Fisher's LSD p = .028) or T carriers of *CRP* (Fisher's LSD p = .016) who were T carriers for the *MTHFR* allele (Figure 20). Lastly, the non-significant interaction of Age × *CRP* indicated that although there was a linear increase in the number of errors made across all polymorphisms, the slope was less steep among T carriers in older age (β = .22, *ns* vs. β = .43, *ns* in A carriers, and β = .40, $p < .01$ in C carriers, Figure 21).

Supplementary Questionnaire: Exploratory Analyses.

A series of two-sample t-tests was conducted, where CRP and Hcy blood levels were continuous independent variables, and survey responses the grouping variable on dichotomous yes/no questions, the results of which are summarized in Table 18. Significant t-test results were followed by linear regressions conducted separately by group (e.g., yes/no responses) with the significant blood biomarker as the continuous independent variable and each cognitive factor examined as the dependent variable in turn. Survey responses measured continuously (e.g. duration of medication use, daily intake of caffeine or alcohol consumption) were examined with CRP and Hcy blood levels using Pearson's correlations.

Figure 19

N-back Errors and C-Reactive Protein by Sex

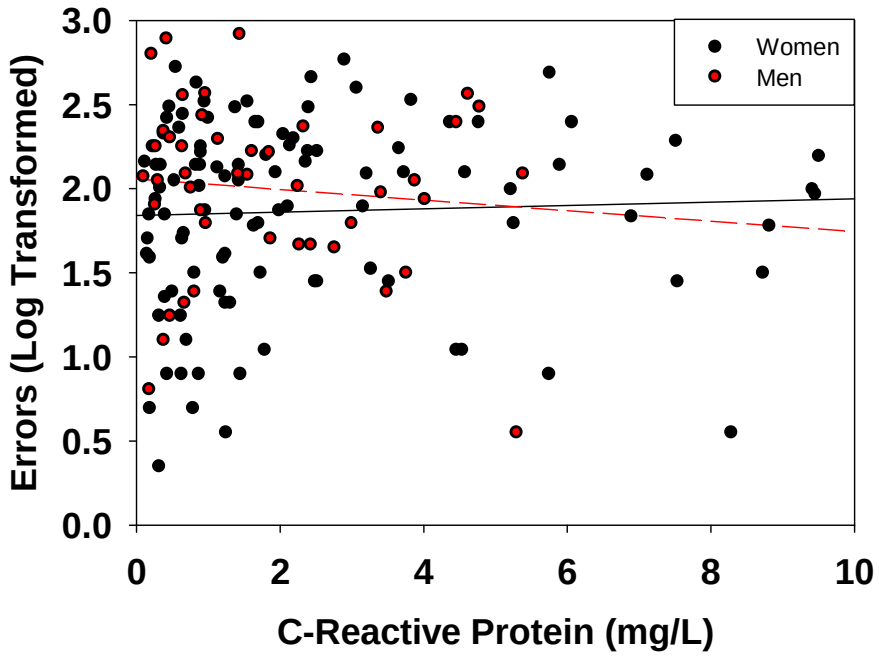


Figure 20

N-back Errors by CRP/MTHFR Polymorphism Carrier Status

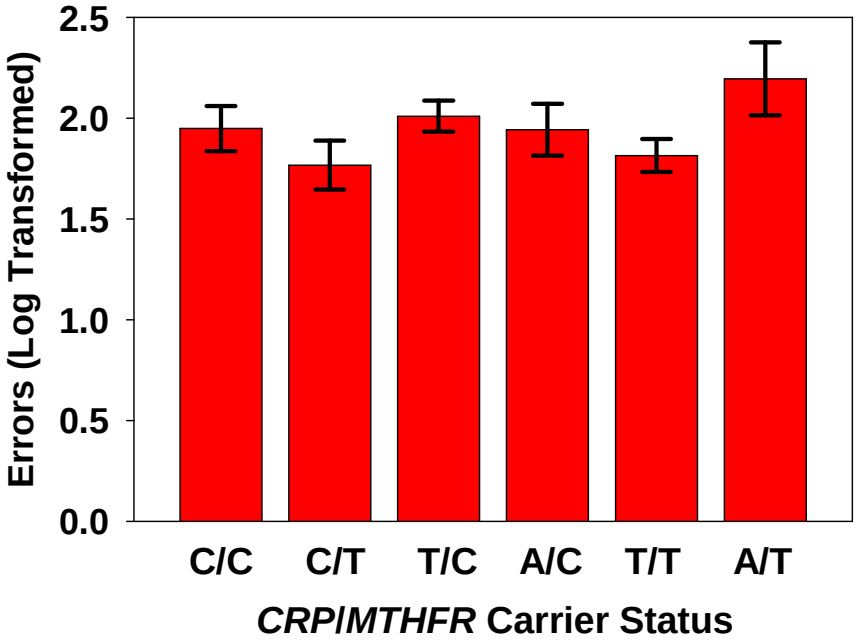
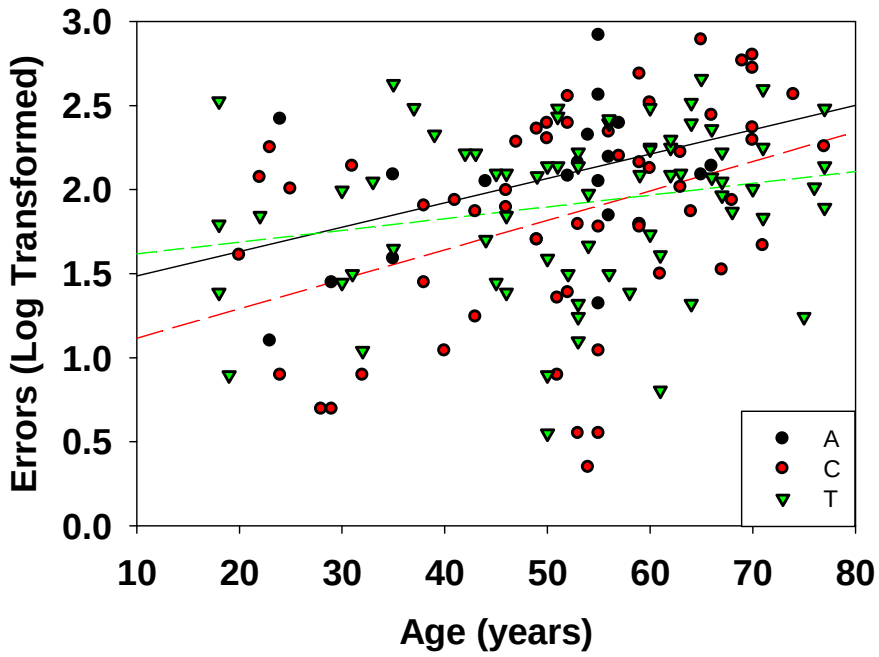


Figure 21

N-back Errors and Age by CRP Polymorphism



Vitamin/nutrition supplementation. Neither current nor past vitamin use was associated with either CRP or Hcy blood levels (*t*'s < 1.69). However, when the responses were examined in further detail by type of vitamin use (e.g., multivitamin, vitamin B), current use of a multivitamin was associated with lower CRP blood levels compared to non-users (1.72 ± 1.44 vs. 2.71 ± 2.61, $t = -2.21$, $p < .05$). This difference was not bore out in relation to cognition however, as none of the regression analyses was significant. There was a trend however for multivitamin users to perform worse on the 'g' factor than non-users (β = -.28, $p < .07$ vs. β = -.04, *ns*). No relationship was found for current or past use of a B complex vitamin (*t*'s < 1.35). With regard to length of time on a vitamin supplement, neither current nor past multivitamin duration were

Table 18

Means and Standard Deviations of Supplementary Questionnaire Responses

	C-Reactive Protein (mg/L)			Homocysteine (μmol/L)		
Variable	'Yes'	'No'	*t*	'Yes'	'No'	*t*
Current Vitamin Use	1.90 ± 1.53	2.66 ± 2.71	-1.69	8.30 ± 1.60	8.47 ± 1.66	-.52
Vitamin B Use	2.50 ± 1.86	2.25 ± 2.25	.30	8.14 ± 1.16	8.41 ± 1.66	-.45
Multivitamin Use	**1.72 ± 1.44**	**2.71 ± 2.61**	**-2.21**	8.31 ± 1.66	8.45 ± 1.60	-.43
Vitamin Deficient	2.59 ± 2.61	2.11 ± 1.97	1.00	**7.91 ± 1.62**	**8.63 ± 1.58**	**-2.06**
Frequent Protein Intake	2.40 ± 2.19	1.58 ± 2.23	1.32	8.37 ± 1.57	8.48 ± 1.92	-.25
High Cholesterol	2.20 ± 2.15	2.30 ± 2.29	-.20	8.55 ± 1.50	8.13 ± 1.81	1.21
Prescribed Antilipidemic	1.94 ± 1.62	2.40 ± 2.45	-.95	**8.84 ± 1.53**	**8.14 ± 1.64**	**2.00**
Diagnosis Unmedicated	2.56 ± 2.64	2.11 ± 2.01	.88	8.20 ± 1.38	8.46 ± 1.72	-.68
Inflammatory Medication	2.58 ± 2.29	1.67 ± 1.96	1.91	8.37 ± 1.61	8.41 ± 1.69	.13
NSAID Use	2.35 ± 2.28	1.93 ± 2.02	.91	8.50 ± 1.64	8.38 ± 1.62	.37
Acetaminophen Use	1.57 ± 1.26	2.27 ± 2.28	-1.07	8.40 ± 1.74	8.45 ± 1.61	.11
Current Alcohol Use	2.37 ± 2.21	1.93 ± 2.22	.80	**8.20 ± 1.54**	**9.02 ± 1.77**	**-2.07**
Current Caffeine Use	2.45 ± 2.33	1.41 ± 1.20	1.73	8.47 ± 1.63	7.99 ± 1.59	1.08
Current Smoking	2.62 ± 2.03	2.22 ± 2.24	.56	9.22 ± 1.58	8.28 ± 1.61	1.84
Current Exercise	2.17 ± 2.05	2.74 ± 2.88	-.94	8.51 ±1.59	7.79 ± 1.71	1.63
Aerobic	2.14 ± 1.93	2.43 ± 2.59	-.58	8.44 ± 1.56	8.07 ± 1.78	.97
Strength/Resistance	1.96 ± 1.68	2.30 ± 2.24	-.66	8.25 ± 1.78	8.37 ± 1.58	-.32
Stretching	2.16 ± 2.11	2.23 ± 2.13	-.12	8.08 ± 1.45	8.40 ± 1.66	-.72
Infection History	2.09 ± 2.00	2.60 ± 2.45	-1.04	8.35 ± 1.58	8.24 ± 1.69	.29
Inflammation History	**3.03 ± 2.26**	**1.97 ± 2.17**	**2.11**	8.74 ± 1.58	8.13 ± 1.57	1.69
Hormone Use History	2.45 ± 2.34	2.78 ± 2.98	-.39	**7.74 ± 1.41**	**9.26 ± 1.64**	**-3.06**
Hormone Replace	1.79 ± 1.65	2.65 ± 2.63	1.33	8.17 ± 1.31	8.11 ± 1.73	.13
Birth Control	2.37 ± 2.27	2.21 ± 2.39	.25	7.77 ± 1.53	8.61 ± 1.51	-1.94

associated with CRP or Hcy blood levels (*r*'s < -.33, n = 32). Similarly, the time since vitamin use was discontinued was also unrelated to blood biomarker levels (*r*'s < .14, n = 12). Neither current nor past vitamin B use duration could be examined, as too few people reported this (n = 3 for current, n = 1 for past).

To the question "have you ever been told you have a vitamin or nutritional deficiency," a positive endorsement was associated with lower Hcy levels (7.91 ± 1.62 vs. 8.63 ± 1.58, $t = 2.06$, $p < .05$). Regression analyses indicated Hcy levels in vitamin/nutritionally deficient persons was associated with better performance on the 'g' factor (β = .44, $p < .05$ vs. β = -.08, *ns*). None of the other regression analyses were significant (*p*'s > .11).

With regard to protein intake, there was no association between CRP or Hcy blood levels and a positive endorsement of characterisitically eating a lot of meat or other protein (*t*'s < 1.32). Similarly, reported daily protein intake as estimated by number of portions was unrelated to blood biomarker levels (*r*'s < -.04, n = 84).

Medications. Neither CRP nor Hcy blood levels were related to a diagnosis of hypercholesterolemia or the diagnosis of hypercholesterolemia in the absence of a current anti-lipidemic prescription (*t*'s < 1.21). However, for those persons with a diagnosis and currently prescribed an anti-lipidemic, Hcy levels were elevated compared to those persons who were not (8.84 ± 1.53 vs. 8.14 ± 1.64, $t = 2.00$, $p < .05$). This difference was not bore out in relation to significant regression analyses on cognition (all *p*'s > .16). Pearson's correlations revealed no significant associations with blood biomarkers in terms of the time since a diagnosis of hypercholesterolemia was

made (*r*'s < .01, n = 45) or the duration of treatment with an anti-lipidemic (*r*'s < .36, n= 24).

Use of an anti-inflammatory medication was not associated with CRP or Hcy blood levels (*t*'s < 1.91). This was true regardless of whether participants were taking nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, *t*'s < .91) or those containing acetaminophen (e.g., Tylenol, *t*'s < 1.07). There was a nonsignificant association with anti-inflammatory use and CRP levels, such that CRP blood levels were higher in those persons taking an anti-inflammatory medication versus those who were not (2.58 ± 2.29 vs. 1.70 ± 1.96, $t = 1.91$, $p = .06$). However, there was no association between the duration of the treatment with an anti-inflammatory medication and blood biomarker levels (*r*'s < -.12, n = 27).

Alcohol/caffeine consumption. With regard to alcohol consumption, current alcohol use was associated with lower Hcy blood levels compared to abstainers (8.20 ± 1.54 vs. 9.02 ± 1.77, $t = -2.07$, $p < .05$). Although none of the regression analyses on cognition were significant (*p*'s > .06), there was a trend for Hcy levels to be associated with a faster processing speed among persons who currently drink alcohol relative to abstainers ($\beta = .22$, $p < .07$ vs. $\beta = .35$, *ns*). The estimated daily intake of alcohol in number of drinks was unrelated to blood biomarker levels (*r*'s < -.12, n = 86), as was the number of years of alcohol use (*r*'s < .13, n = 71). Neither current nor former caffeine consumption was associated with CRP or Hcy blood levels (*t*'s < 1.73). Similarly, estimated daily caffeine intake and number of years of caffeine use were also unrelated to blood biomarker levels (*r*'s < .07, n = 82 and *r*'s < .12, n = 74 respectively).

Cigarette/tobacco use. Although not significant, there was a trend for current smoking to be associated with Hcy blood levels, such that Hcy levels were higher among smokers than non-smokers (9.22 ± 1.58 vs. 8.28 ± 1.61, t = 1.84, p = .07). As with all the previous analyses, estimated daily intake (in number of cigarettes) and duration of smoking history were unrelated to CRP and Hcy levels (r's < -.21, n = 79 and r's < .37, n = 34 respectively).

Exercise/physical activity. Current exercise was unrelated to either CRP or Hcy levels (t's < 1.63). This was true regardless of whether the exercise consisted of aerobic exercise, strength/resistance training, or stretching (all t's < 0.97). On the other hand, estimated body type (e.g., overweight, underweight, normal-weighted) was associated with Hcy blood levels, such that persons self-described as overweight had lower Hcy levels than those who considered themselves normal-weighted (8.05 ± 1.58 vs. 8.78 ± 1.49, t = 2.19, p < .05). Self-described underweighted individuals were not included in these analyses, as there were too few cases (n = 5). Though not significant, there was a trend for persons self-described as overweight, to have higher CRP levels than those who considered themselves to be normal-weighted (2.74 ± 2.22 vs. 1.85 ± 2.20, t = 1.86, p < .07). The significant difference in Hcy levels by body type was associated with 'g', such that Hcy levels in normal-weighted individuals was associated with better 'g' performance compared to over-weight persons (β = .38, p < .05 vs. β = -.14, *ns*). Neither the frequency (number of exercise occasions) nor the duration (in minutes per exercise occasion) were associated with blood biomarker levels, either as a whole or by exercise type (r's < -.16, n ≈ 80). The estimated discrepancy between an individual's

body weight and normal-weighted (in pounds) was also unrelated to blood biomarker levels (*r*'s < .31, n = 81).

General health. Neither a current nor past history of an infection was associated with CRP or Hcy blood levels. Similarly, neither the duration (*r*'s < .18, n = 43) nor the length of time since the most recent infection (*r*'s < -.27, n = 46) was associated with CRP or Hcy blood levels. Though a current inflammatory condition was not related to CRP levels (*t* = 0.95), when any history (either current or past) was compared to no history of an inflammatory condition, higher CRP levels were noted among those with any history (3.03 ± 2.26 vs. 1.97 ± 2.17, *t* = 2.11, *p* < .05). This difference was unrelated to cognitive function (*p*'s > .09). Neither the length of time of the inflammatory condition (*r*'s < -.22, n= 20), nor the time since the most recent inflammatory condition was related to blood biomarker levels (*r*'s < .67, n = 6).

Estrogen use. Current use of hormones (either hormone replacement therapy or birth control) was unrelated to CRP or Hcy levels (*t*'s < 0.47). However, when any history of hormone use was compared to no history, a history was associated with reduced Hcy levels (7.74 ± 1.41 vs. 9.26 ± 1.64, *t* = -3.06, *p* < .01). This difference was substantiated on cognitive function as well, such that a past history of hormone use was associated with reduced processing speed relative to never users (β= .28, *p* < .05 vs. β = -.13, *ns*). When the sample was examined for past history dependent on the type of hormone (e.g., HRT or birth control), no significant differences emerged. However, there was a trend for birth control users to have lower Hcy levels than non-users (7.77 ± 1.53 vs. 8.61 ± 1.51, *t* = -1.94, *p* < .06).

CHAPTER 4

DISCUSSION

Summary of Results

Relationship of CRP and Hcy blood levels to cognition. The results of this study showed neither CRP nor Hcy were independently associated with poorer cognitive performance on any of the cognitive factors measured. Rather, and as expected, age was a significant predictor of reduced processing speed, better 'g' performance, fewer prose memory items recalled, fewer correct name-space creature associations, and reduced accuracy in both models. The only other significant predictor occurred in the GLM conducted on CRP alone, where hypertension diagnosis was associated with reduced processing speed. Though not significant, a few trends emerged, such that higher levels of CRP and lower levels of Hcy were associated with poorer prose recall, and this was particularly true of men with regard to CRP blood levels.

Elevated CRP blood levels have most frequently been associated with performance decrements on measures of global cognition, though decrements have been observed in other areas as well (see Tables 1 and 2). For those studies which specifically assessed declarative memory, only three studies examined prose recall (Rafnsson et al., 2007; Shawcross et al., 2007; Suzuki et al., 2006), and of the three, only one of which (Shawcross et al., 2007), found a negative correlation between CRP blood levels and prose recall. In that study, deterioration on prose recall following an amino acid load (a model of hyperammonemia) was associated with markedly elevated levels of inflammatory markers, including CRP. However, all the participants had biopsy

proven cirrhosis of the liver with inflammatory markers indicating the presence of an acute inflammatory condition and thus are not a suitable comparison group to a healthy aging sample as in the present study. Thus the findings with CRP in relation to prose recall are in accord with the majority of studies conducted.

Performance decrements in relation to elevated CRP blood levels in the literature have not been limited to declarative memory. However, a direct comparison of previous findings with those of the present study is precluded given several methodological differences. The majority of studies have been conducted on age-restricted populations (≥ 50 years), persons with overt inflammatory conditions (e.g., systemic lupus erythematosus, peripheral arterial disease, coronary artery bypass graft or valvular surgery), or patient populations (e.g., schizophrenics). Only one study (Teunissen et al., 2003) has observed performance decrements among elevated CRP levels in a normal aging lifespan sample. In the Teunissen et al. (2003) study however, exclusion criteria were minimal, and the range of CRP values was much broader than the current study (0.5 – 27.83 mg/L) thereby including persons with an acute inflammatory condition. In the present study, the inclusion of persons with CRP levels ≥ 10 mg/L did not result in any significant associations between CRP levels and cognitive function (all *r*'s < ± .11).

With regards to Hcy, the literature has identified impairments across a broad array of cognitive domains including declarative memory (see Tables 3, 4 and 5). As with CRP however, many of these studies have been conducted on age-restricted populations, persons with overt disease, or among patient populations. Of those studies conducted on a lifespan sample (Elias et al., 2006; 2008; Teunissen et al., 2003; Wright et al., 2004), performance decrements have been observed for global cognition,

psychomotor speed, visuospatial ability, declarative memory, reasoning, and executive functions. However, as was the case with CRP, inclusion criteria across the studies were minimal, with large percentages of the samples being diagnosed with conditions known to alter Hcy levels (e.g., cardiovascular disease, diabetes, vitamin B deficiency). Moreover, in the Wright et al. (2004) study, about half the sample had less than a high school education, many of whom additionally had MMSE scores consistent with a diagnosis of mild cognitive impairment or dementia. Lastly, the range of Hcy values was considerably larger than that of the present study, and all studies included values that met criteria for hyperhomocysteinemia. Indeed, in the Elias et al samples (2006; 2008), 20% of the sample had Hcy values higher than the uppermost point of the range (11.8 μmol/L) in the present study. Similarly, in the Wright et al. (2004) study, 10% of the sample had values ≥ 15 μmol/L. In this regard, there may have been an apparent bias in previous studies to find a significant negative correlation between Hcy and cognitive function, as values were well outside the normal range and may be indicative of subclinical cardiovascular disease.

It may be the case that elevated Hcy levels in and of themselves are not problematic. Rather, elevations in Hcy are concomitant with conditions known to affect cognitive function (e.g., cardiovascular disease), and it may be the underlying disease process rather than elevated Hcy levels per se that are responsible for impairments in cognitive functioning. Given Hcy levels are a graded risk factor for cardiovascular disease (Refsum, Ueland, Nygård, & Vollset, 1998), there may be subclinical factors at work in persons with Hcy elevations, despite a lack of overt cardiovascular disease.

Indeed, in the present study of exceptionally healthy adults, although there were no effects of Hcy levels on cognition, the one trend observed was for an improved performance on prose recall. This is in accord with one other study which found a positive effect of elevated Hcy levels on the Logical Memory task. Namely, persons with an impaired Logical Memory performance had significantly lower Hcy levels than persons with normal performance (Frieling et al., 2005). However, this sample was considerably younger than the current study (mean ~ 25 years) and was comprised of persons with a diagnosis of either anorexia or bulimia nervosa, two eating disorders that should theoretically result in nutritional deficiencies and subsequent higher Hcy levels, so it is unclear how well the results generalize to the current study.

Relationship of CRP and Hcy blood levels to each other. The second hypothesis postulated that CRP and Hcy blood levels would be moderately correlated with one another. This was not the case. A nonsignificant and negative correlation was found for both the reduced sample and the total sample. Restriction of the analyses to either persons with CRP levels ≥ 10 mg/L or persons with Hcy levels ≥ 12 μmol/L, strengthened the association, but the correlation remained nonsignificant. Only when the analyses were restricted to persons with elevations in both, did a significant negative correlation ensue. This is in accord with several studies which found no association between CRP and Hcy levels (Fischer et al., 2006; Gunstad et al., 2006; Ravaglia et al., 2005; Silbert et al., 2008). On the other hand, several studies have shown CRP and Hcy blood levels are significantly and positively correlated with one another (Holven et al., 2006; van den Kommer et al, in press; Youssef et al., 2007)

however, these studies were conducted in hyperhomocysteinemic persons with overt cardiovascular disease.

Regardless of whether or not the previous literature has found the correlation between CRP and Hcy to be significant, all studies agree that the two variables are positively related to one another. There are several potential explanations for this. As has previously been discussed, there are differences in the samples with regards to the range of CRP and Hcy values. In the Holven sample (2006), the correlation was only significant among hyperhomocysteinemics, who had Hcy levels as high as 75 μmol/L. In the Youssef et al., study (2007), correlations between CRP and Hcy were evidenced 24 hours post-stroke, where inflammatory mechanisms and hence CRP levels are expected to be high. Both of which suggest the positive correlation is only found when one or the other is elevated outside the normal range, but not both.

A second possibility pertains to the assays used, their lower detection limits, and the coefficient of variation in their day-to-day analytical precision. With regards to CRP, the vast majority of emerging studies use a high-sensitivity immunonephelometric assay (hs-CRP), unlike the current study which used the immunoturbidmetry method (imCRP). The conventional imCRP method although suitable for the measurement of CRP concentrations during infection, has a lower detection limit far less sensitive than the newer hs-CRP method (≥ 3 mg/L versus > 0.1 mg/L) and could thus potentially fail to detect values below a certain threshold, particularly in a healthy sample where values are lower. For this reason, the imCRP method has been regarded as unsuitable for CRP values within the normal reference range (< 10 mg/L) in recent years (Ledue & Rifai, 2003). But given CRP levels in the current study were detected as low as 0.1

mg/L and 41% of the values in this sample were 1 mg/L or less, it would indicate there was not a failure of detection. At worst, it may be an issue of sensitivity, such that CRP levels may be overestimated, thereby making the effects of elevated CRP levels more readily observed. However, given no significant effects of CRP were found, this is likely not a concern.

Differences in sensitivity may also be an issue when comparing across studies. Lower detection limits have been reported as low as 0.8 ng/mL (van den Kommer et al., in press) to as high as 0.5-1.0 mg/dL (Gunstad et al., 2006). According to one study, more than 97% of healthy adults have CRP values less than 0.5 mg/dL (Ravaglia et al, 2005). If this is true, depending on the assay used, many measurements may fall outside the detectable limits thereby causing a range restriction to higher levels. With regards to Hcy, the assays of choice have typically been either fluorescence polarization immunoassay (FPIA), or high-performance liquid chromatography (HLPC). As with CRP however, there are distinct differences in precision. In a study by Ubbink, Delport, Riezler and Vermaak (1999), four different assays of plasma Hcy were compared including FPIA and HPLC. Mean tHcy concentrations were measured a full µmol/L higher using the FPIA method versus HPLC. However, the coefficient of variation in inter-measure analytical precision was considerably better for the FPIA versus the HPLC assay (4.5% vs. 8.4%). Hcy also has special handling procedures which require samples to be drawn in the fasting state, immediately placed on ice, and centrifuged within one hour (Refsum et al., 2004). Failure to adopt these practices unnecessarily inflates Hcy levels in a manner completely removed from differences in

sample characteristics, all of which point to the inherent difficulty in generalizing across studies.

Combined effect of elevated blood levels of CRP and Hcy on cognition. Although neither CRP nor Hcy had a significant effect on cognition independently, when both terms were entered into a GLM, a nonsignificant trend for CRP × Hcy on psychomotor speed was found, such that high Hcy levels, but low CRP levels, were associated with reduced processing speed. Additional significant interactions for Hcy with age on psychomotor speed and with sex on prose memory were also identified. In terms of the domains affected, the results are consistent with the one study conducted thus far that has looked at the combined impact of elevations in both CRP and Hcy blood levels.

In the Longitudinal Aging Study Amsterdam (LASA), CRP had a modifying effect on longitudinal rate of decline for processing speed, such that persons with a high tHcy showed the fastest rate of decline for the lowest and middle tertiles of CRP (van den Kommer et al., in press). In the current study, slowing of psychomotor speed was associated with older age, and higher blood levels of Hcy, but only among the most aged. Among younger persons, higher Hcy levels were actually associated with faster response times, while lower levels were associated with universally slower response times, regardless of age. Among persons with elevated CRP, response time was fastest when Hcy levels were low. Conversely, among persons with elevated Hcy, response times were slowest when CRP levels were low.

Persons with the highest tertile of CRP who also had a high level of tHcy also performed the worst on delayed recall of a verbal learning task in the LASA study (van

den Kommer et al., in press). For prose memory in the current study, a main effect of Hcy was identified in the absence of a significant post-hoc beta (β = .06, *ns*). The direction of the beta suggested however that higher levels of Hcy were associated with better prose memory performance, and this was particularly true of men who showed better recall than women with higher Hcy levels. The fact that Hcy carried a beta in the opposite direction to that of age and it's inclusion in the GLM added additional variance explained over that of age alone (β = -.26, *p* = .005 vs. β = -.22, *p* = .007) however, indicates that age has a suppressor effect on Hcy. As age in itself is associated with cardiovascular risk, and Hcy levels increase with age (Refsum et al., 2004), such an argument is not outside the realm of possibility. Indeed, when age and Hcy were included in the post-hoc regression, the beta for Hcy approached significance (β = .15, *p* = .08).

Substantial differences exist between the LASA sample and the current study however which may in part explain the discrepant results. The LASA study is comprised of adults over the age of 65 years, with a mean education of less than the 9th grade and a high prevalence of hypertension, cardiovascular disease, and hyperhomocysteinemia. Compare this to a lifespan sample, with a mean education nearing 4-years college, a prevalence of hypertension less than half that of LASA, and a complete absence of cardiovascular disease and hyperhomocysteinemia, Moreover, not only were hyperhomocysteinemics excluded, but male sex is a risk factor for elevated Hcy levels (Refsum et al., 2004), a group who was underrepresented in the present sample (~30%), and hence their relative absence may have driven down the mean Hcy level further.

Relationship of T allele carrier status to blood levels of CRP and Hcy. Neither T carrier status for *CRP* or *MTHFR* was associated with higher blood levels of their respective blood biomarker. Although for the *CRP* gene, T carrier status had higher blood levels than the referent C carriers, the difference was not significant (t = .74, *ns*). When C/T heterozygous carriers were excluded, the difference was larger but remained non-significant (t = 1.31, *ns*). On the other hand, A carrier status was associated with the highest CRP levels. This is in accord with one study in which A and T homozygosity was associated with higher CRP levels, but only among non-Hispanic blacks. Among Hispanics, T homozygotes were associated with higher CRP levels, whereas in non-Hispanic whites, CRP blood levels were not different among any polymorphism (Crawford et al., 2006). In the present sample, no participants were homozygous for the A allele, thus, when A carrier status was compared to C homozygous carriers, the result approached significance in blacks, but not whites (t = 1.89, p < .08 vs. t = 0.56, *ns*). A similar relationship did not exist for T homozygosity in either blacks or whites (t = 0.67, *ns* in blacks, vs. t = 1.25, *ns* for whites). The reason for the discrepancy may be because in the current sample, African Americans were underrepresented as a group, particularly those homozygous for the T allele (n = 3).

Quite unexpectedly, for the *MTHFR* allele, T carrier status was associated with the lowest Hcy blood levels. In previous studies, homozygosity for the T allele has been associated with the highest Hcy levels (Albert et al., 2009; Dedoussis et al., 2005), particularly among males (Kluijtmans et al., 2003), while in women, the *MTHFR* 667C>T variant is related to Hcy levels in Caucasians, but not among black, Asian, or Hispanic women (Albert et al., 2009). In the current study, the highest Hcy levels among men

were for C/T heterozygotes, and for women, C homozygotes. For both sexes, T homozygotes had the lowest Hcy blood levels. For both blacks and whites, the highest Hcy levels were found in C homozygotes, followed by C/T heterozygotes. There were no African Americans homozygous for the T allele.

Genetics studies examining population differences require large numbers of participants. The current sample was considerably underpowered to study differential genetic distributions in Caucasians or African Americans given the number of variants (particularly for *CRP*) and the prevalence of the minor variants in the general population. However, as T carriage is more prevalent among persons with cardiovascular disease (Klerk et al., 2002) and VaD (McIlroy et al., 2002), it may be the case that the inclusion criteria for the current study necessarily selected out the T homozygotes.

Relationship of T allele carrier status to cognition. With regards to the *CRP* gene, in addition to the significant age and population effects across all domains, significant effects of *CRP* were found in relation to psychomotor speed and 'g'/inhibition. As no studies have examined the -286 *CRP* C>T>A gene in relation to cognition, it is hard to frame the findings within the context of the literature. However, the one study to examine *CRP* SNPs found the minor allele variant of 1059 G>C was associated with cognitive deficits post cardiopulmonary bypass surgery on a composite of several cognitive domains (psychomotor speed, visuospatial ability, attention, declarative memory, executive functions). In the present study, T allele status was associated with reduced processing speed compared to either A carriers or C homozygotes. With regards to 'g'/inhibition, both inter and intra-sex differences were evident. Among A carriers, men performed better than women, whereas in T carriers, the opposite was

true. Men with the A allele also performed better than C homozygous women. In women, T carrier status was associated with better performance than C homozygosity, whereas in men, A carrier status was associated with better performance than either T carrier status or C homozygosity.

With regards to *MTHFR*, allele status was a significant interaction term in combination with age and hypertension for prose memory. With older age, carriers of the T allele recalled more items than C homozygotes. Several studies have observed no detriment in relation to T carrier status (Bottiglieri et al., 2001; Flicker et al., 2004; Gussekloo et al., 1999; Matsui et al., 2001; Nurk et al., 2005; Ravaglia et al., 2004a; Rodriguez-Oroz et al., 2009), and indeed, two studies have shown a benefit to T carriage on measures of processing speed (Araki et al., 2003; Durga et al., 2006). However the latter of these studies recruited only persons with elevated Hcy (> 13 µmol). Thus, the sample included a disproportionate number of T homozygotes compared to other samples, and could have been affected by upwardly biased selection of survivors.

Conversely, among hypertensives in the current study, T carriage was associated with the fewest items recalled, whereas T carriage in normotensives was associated with the most items recalled. This is in accord with a previous study in which spatial navigation performance was impaired among hypertensive T carriers (Deshmukh et al., 2009). More generally, as both hypertension and T carrier status are vascular risk factors, it may be the case that multiple risk factors confer an additive risk for poor cognitive performance, whereas T carrier status alone in the absence of other vascular risk factors is not detrimental.

Combined effect of T allele carrier status for both *CRP* and *MTHFR* on cognition. When both SNPs and their respective blood biomarkers were entered into the GLM, several of the same trends were obtained as when each SNP was entered into separate GLM analyses, albeit for the most part, they were no longer significant. For psychomotor processing speed, the T allele of the *CRP* SNP was associated with reduced speed, whereas for ‘g’/inhibition, A carriage among males was associated with better performance than A carriers in women, C homozygosity in either men or women, and T carriers in men. In women on the other hand, T carriage was associated with better performance than either T carriers in men or C homozygotes in women. Although not significant, the Age × *CRP* for accuracy showed a trend such that with older age, A carriers made the most errors, and T carriers the least, with C homozygotes making an intermediary number of errors.

For the *MTHFR* SNP, the same Age × *MTHFR* interaction for prose memory was found, such that with older age, fewer items were recalled for C homozygotes compared to T carriers. An additional trend for an interaction between the *MTHFR* SNP and Hcy was found such that with higher Hcy levels, T carriers recalled fewer items than C homozygotes.

The one point of interaction for the two SNPs was for accuracy, where a non-significant trend emerged. Accuracy was lowest among A carriers of the *CRP* SNP and T carriers of the *MTHFR* SNP. Conversely, T carriage for both *CRP* and *MTHFR* was on the high end of accuracy and only made more errors than C homozygotes on the CRP *SNP* who were T positive for *MTHFR*.

Supplementary questionnaire exploratory analyses. In the supplementary analyses, few variables were related to CRP and Hcy blood levels. Namely, lower CRP levels were associated with current multivitamin use, whereas higher CRP levels were associated with a past history of an inflammatory condition versus no history. Among Hcy levels, lower levels were associated with being told of a nutritional or vitamin deficiency, current alcohol use, a past history of hormone use, and having a self-described overweight body type; whereas higher Hcy levels were associated with being prescribed an anti-lipidemic for high cholesterol.

Several studies support an association between CRP blood levels and lifestyle factors. Namely, elevated CRP levels are observed with vigorous exercise, current smoking, increased body mass index, abstinence or infrequent alcohol use, and current hormone therapy (Ledue & Rifai, 2003). In the present study, neither exercise as a whole nor exercise by subtypes was associated with elevations. This may be because in the current study, aerobic exercise consisted of any type of exercise in which heart rate may be expected to be elevated (e.g., walking, running, elliptical machine). However, there was no objective measure of whether or not exercise was of sufficient intensity to elevate heart rate, so some people may have been misclassified as aerobic exercisers. On the other hand, strength/resistance training and stretching are not considered vigorous, so it is not surprising that CRP levels were lower in relation to these. However, in accord with previous findings, current smoking, a self-described overweight body type, and current birth control use were associated with higher CRP levels, though not significantly.

Conversely, lower CRP levels have been associated with statin use for the treatment of high cholesterol, moderate alcohol consumption, and use of an anti-inflammatory medication (Ledue & Rifai, 2003). Although a diagnosis of high cholesterol should result in higher CRP levels, this was not the case in the present study. Further examination suggested that many of the persons with a diagnosis of high cholesterol were also on lipid lowering medications, which should result in lower CRP levels. It may be the case then that treated persons in effect had lower cholesterol levels and thus lower CRP levels. Indeed, among those with a diagnosis and no prescription, CRP levels were higher. With regard to alcohol use, although the majority of the sample reported drinking, about 80% did not consume alcohol on a daily basis, thus higher CRP levels may be expected. Use of an inflammatory medication was associated with higher CRP levels. This is interesting given NSAIDs are prescribed for inflammation reduction. It may be the case however that persons who use inflammatory medications have higher baseline CRP levels than those who do not, and the result may be a net reduction in CRP levels, but not below those of persons without a need for anti-inflammatory medication.

Given CRP is a marker of inflammation (Black et al., 2004), it is of no surprise that persons indicating any type of history of an inflammatory condition had higher CRP levels than those indicating no such history. It was expected that a similar relationship would exist for those persons indicating a past history of infection, as CRP is an acute phase reactant and increases markedly to such insults to the body (Black et al., 2004), but this was not the case. Responses to the type of past infection were highly variable however, with participants indicating anything from the presence of minor colds and

sore throats, to hepatitis C. More than likely, persons indicating no past history of infection failed to report such minor infections, and a simple dichotomous division was not specific enough to accurately assess infection history.

B vitamins though essential for the 1-carbon metabolism cycle have also been inversely related to CRP levels in a large population study (Friso, Jacques, Wilson, Rosenberg, & Selhub, 2001), and to reductions in CRP levels in a randomized placebo-controlled trial (Church, Earnest, Wood, & Kampert, 2003). Although vitamin B itself was not predictive of CRP levels, more than likely as a result of power (n = 8), use of a multivitamin was.

With regards to Hcy, vitamin B deficiency has been associated with elevations in Hcy levels (Refsum et al., 2004). Interestingly, being told of a vitamin or nutritional deficit was associated with significantly reduced Hcy levels in the present study. However, the deficiencies reported only included deficiencies in vitamin K, vitamin D, and iron. Indeed, vitamin B levels (folate and vitamin B_{12}) as measured in the present study were not indicative of a deficiency. Along these same lines, supplementation with vitamin B has been shown to reduce Hcy levels (Refsum et al., 2004), which was also the case in the present study. Although not significant, both vitamin B and multivitamin supplementation resulted in lower Hcy levels. Conversely, diets rich in protein have the effect of elevating Hcy levels (Refsum et al., 2004). In the present study, the habit of characteristically eating a lot of meat or other protein was associated with lower Hcy levels however. This may have been attributed to the interpretation of ‘a lot’ however, as responses to this varied anywhere from less than daily intake, to 10 portions per day.

With regard to lifestyle factors, elevated Hcy levels are associated with smoking and caffeine consumption, whereas exercise and alcohol intake have been associated with both increased and decreased Hcy levels (Refsum et al., 2004). In the current study, albeit not significant, both smoking and caffeine intake were associated with higher Hcy levels. With regards to exercise, low impact activities such as strength training and stretching were associated with non-significant lower Hcy levels, whereas exercise as a whole and aerobic activity were associated with non-significant increases. On a related note, an overweight self-described body type was associated with significantly lower Hcy levels compared to self-described normal-weighted individuals. Alcohol was related to lower Hcy levels in the present study, perhaps in par with studies that have shown alcohol in moderation is associated with reduced risk for heart disease, peripheral vascular disease, and stroke.

As Hcy is a cardiovascular risk factor and is associated with the development of atherosclerosis (Seshardi, 2006), it is logical for there to be an association with cholesterol levels. Indeed, in the present sample, cholesterol diagnosis was associated with higher Hcy levels compared to persons without a diagnosis. Use of an anti-lipidemic was associated with significantly higher Hcy levels, perhaps because cholesterol levels may be high enough to warrant treatment with medication, whereas among persons who are told they have high cholesterol and are not medicated may only be borderline high. Indeed, persons who had a diagnosis but were not prescribed an anti-lipidemic had non-significantly lower Hcy levels.

Use of estrogen post-menopausally has been shown to decrease Hcy levels (Refsum et al., 2004). In the current study use of a hormone was associated with

significantly lower Hcy levels, but interestingly, hormone replacement therapy in post-menopausal women was related to higher Hcy levels, whereas birth control was related to lower levels.

General Discussion

Quite contrary to the majority of the previous research, there was not a negative effect of elevated blood levels of CRP or Hcy. Also in contrast to previous literature, there was not a detrimental effect to being a T carrier, except perhaps for psychomotor processing speed and in conjunction with male sex on 'g' for the *CRP* SNP, and in conjunction with hypertension status on prose recall for the *MTHFR* SNP. Rather, T carrier status in the absence of other vascular risk factors (e.g., hypertension) was beneficial to cognitive performance in older persons.

The discrepancy in results may in large part be due to the stringency in which potential participants are selected into the current study relative to other studies. Participants in the current study represent the best-case scenario of aging and are free of self-reported cardiovascular, neurological, endocrinological, metabolic, and psychiatric disease, as well as being free of drug and alcohol abuse, and central acting stimulants or depressants. An extensive blood work-up and MRI scans additionally support the general health of the sample, as there was no evidence of vitamin insufficiency (as defined by folate and vitamin B_{12} reference range values), or signs of stroke or white matter degradation beyond expected with normal aging.

The current sample also reports a reduced prevalence of various risk factors and poor life choices than the national average as polled by a 2008 National Health Interview Survey by the Centers for Disease Control and Prevention's National Center

for Health Statistic (Pleis, Lucas, & Ward, 2009). Less than a quarter of the sample had either a diagnosis of hypertension or a mean systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg, compared to the national average of 32% among non-institutionalized adults over the age of 20 years. Similarly, only 12% of the survey respondents reported currently smoking, compared to 21% of United States adults over the age of 18 years. The 2008 survey also reports that more than half of the adult U.S. population drank alcohol in the past 30 days, with 5% reporting heavy drinking, and 15% reporting binge drinking. Contrast that to the present study, where although about 78% of the respondents report drinking alcohol, only 20% of those report daily consumption, and only one female's consumption (1%) was high enough to be considered binge drinking. Finally, the survey states that 59% of the respondents reported that they had never participated in vigorous exercise, compared to 70% in the current sample who reported some sort of aerobic activity, and 75% of whom did so at least once weekly.

Further, the exclusion of persons with values outside the reference range for either CRP or Hcy resulted in a far more homogenous sample than previous studies. While this was mainly done in order to understand the relationship of CRP and Hcy values to one another, cognition, and genetics without confound of potential inclusion of persons with an acute inflammatory condition or hyperhomocysteinemics, it had the added benefit of reducing variability among other vascular risk factors and indices of health (e.g., systolic and diastolic blood pressure), which also resulted in a better educated sample with a higher mean MMSE score. Taken together, these factors further attest to the general health of participants in the present study relative to previous studies.

The inability to detect significant effects of CRP and Hcy may have additionally been hampered by the use of the exploratory factor analysis. Although the consideration was to reduce the number of dependent variables, the resultant factors may not have been particularly representative of the individual tests comprised of these factors, particularly for the speed and ‘g’/inhibition factors. Indeed, when the results were repeated on each of the individual tests for these factors, additional main effects and interactions emerged. Namely, hypertension either as a main effect or in interaction with sex emerged as a significant predictor of working memory speed and number of comparisons made for both the CRP and Hcy GLMs. Additionally, when CRP and Hcy were analyzed in the same model, a significant interaction of CRP × Hcy emerged for vocabulary and working memory speed.

Similarly, in the GLMs conducted with SNPs as a categorical independent variable, in addition to a main effect of *CRP* on working memory speed, several interactions of SNP emerged in the analysis conducted on CRP alone or in the combined analysis, where *CRP* interacted with age on CFIT performance, with Hcy on vocabulary and working memory speed, with sex on number of perseverative errors, and with population on the number of comparisons made. These findings suggest that both the effects of blood levels and SNPs may be very specific, and may only be observed on select tests or in select subpopulations within the context of fine grained analysis, rather than on larger factors.

One final point of divergence from the literature concerns Hcy levels and correction for vitamin B levels. Given the constrained sample to normal CRP and Hcy blood levels, folate and vitamin B_{12} levels were not expected to be lower than the

accepted norm, and indeed they were not. However, given the importance of the B-complex vitamins in the regulation of Hcy, the effect of folate and vitamin B_{12} were examined post-hoc. Neither folate nor B_{12} were significantly associated with Hcy levels or any of the cognitive factors (all *p*'s > .40). In partial correlations, the removal of folate, vitamin $B_{12,}$ or both from the dependent variable(s) resulted in universally stronger associations of Hcy with cognition, which were significant for the speed factor (*p*'s < .051) and approached significance for the associative memory factor (*p*'s < .10).

However, when Hcy, folate, and vitamin B_{12} were centered to the mean and entered as continuous independent variables along with age, and sex and hypertension status as categorical variables in the GLM analyses, differential effects were observed. Hcy was a significant predictor of the prose memory and accuracy factors, while folate emerged as a significant main effect on the speed and prose memory factors, and vitamin B_{12} was a significant predictor in the 'g'/inhibition and associative memory factors. Interestingly however, with the exception of vitamin B_{12} which remained significant at post-hoc and indicated higher levels were associated with better 'g' performance and reduced associative memory, no other main effects were significant at post-hoc. All effects were trumped by age however, and post-hoc regression analyses with age, Hcy, folate, and B_{12} entered an independent effects were significant for all variables and explained an average of .05 more variance than age alone, indicating a suppressor effect of age on each of these.

Limitations and Conclusions

There are several limitations to the current study that should be addressed. First, although the focus on healthy aging inherently reduced some confounds seen in the

literature, it may also be viewed as a limitation, as results do not generalize to a typical aging population. Second, the cross-sectional nature of the study precludes making any inferences about causality, though few correlations were observed among the variables of interest. Third, the relatively small sample size precluded analysis of higher-order interactions to further probe the potential association among inflammatory blood biomarkers, genetic factors, and cognition. The small sample size also presented a challenge for studying genetic variations, particularly as it relates to population effects, as polymorphisms of the two genes differ across populations. In the current study, African Americans as a group were severely underrepresented, as were specific alleles within them. Fourth, many analyses were run which were not corrected for by multiple comparisons, so any observed effects are liable to be the result of random error and would likely be more conservative if corrected for. Finally, for the supplementary questionnaire data, there was a reliance on self-report data. Self-report is often unreliable, particularly when probing retrospective memories from extended periods of time. Although blood work is available on these participants to corroborate some of the information obtained in the supplementary questionnaire (e.g., cholesterol, vitamin levels, presence of an infection), this was not explored in the present study.

In conclusion, among an exceptionally healthy aging population free of any overt signs of cardiovascular disease, normal range elevations in blood levels of CRP or Hcy, either alone or in combination, are not associated with cognitive impairments across several domains. Moreover, T carriage for either the -286 *CRP* C>T>A or *MTHFR* C>T SNPs is not associated with blood levels of CRP or Hcy, and is only associated with cognition in a task and subpopulation specific manner. Namely, T carriers of the *CRP*

SNP have reduced processing speed, and among men, reduced ‘g’ performance. Whereas for the *MTHFR* SNP, T carriage is associated with fewer prose items recalled among hypertensives. Several lifestyle factors may alter CRP and Hcy levels. However, their inclusion/exclusion in a sample of this health caliber does not significantly alter cognitive outcomes. Based on the evidence, within a healthy sample, subclinical inflammatory mechanisms do not appear to exert much control on cognitive outcomes.

Vitamin/Nutrition Supplementation:

1. Do you currently take vitamins or nutrition supplements? Yes No
If yes, please list:
a. Vitamin/supplement name _____ Dose _____ Length of time _____
b. Vitamin/supplement name _____ Dose _____ Length of time _____
c. Vitamin/supplement name _____ Dose _____ Length of time _____
d. Vitamin/supplement name _____ Dose _____ Length of time _____

2. Has the dose changed over the course of time for any of the above? Yes No
If yes, please explain: _____
_____

3. If you do not currently take vitamins or nutrition supplements, have you ever? Yes No
If yes, please list:
a. Vitamin/supplement name _____ Dose _____ Length of time _____
b. Vitamin/supplement name _____ Dose _____ Length of time _____
c. Vitamin/supplement name _____ Dose _____ Length of time _____
d. Vitamin/supplement name _____ Dose _____ Length of time _____

4. If you do not currently take vitamins or nutrition supplements but did in the past, how long has it been since you stopped? _____
_____

5. Have you ever been told you have a vitamin or nutritional deficiency? Yes No
If yes, please explain: _____

6. If you have been told of a vitamin or nutritional deficiency, what was the suggested course of treatment? _____
_____
Did you follow the prescribed advice? Yes No
If no, please explain _____

7. Do you characteristically eat a lot of meat or other proteins (e.g., nuts, legumes, seeds, eggs)? Yes No
If yes, how many meat or other protein portions on average do you consume daily? _____ weekly? _____

Medications

1. Have you ever been told you have high cholesterol? Yes No
If yes, how long ago were you first told? _____

2. Are you currently prescribed an antilipidemic (for high cholesterol)? Yes No
If yes, please list: _____

3. If you currently take an antilipidemic, for how long have you been taking this medication? _____
Has this been continuous use? Yes No
If no, please explain: _____

4. If you do not currently take an antilipidemic, have you ever taken one in the past? Yes No
If yes, please list: _____

5. If you are not currently taking an antilipidemic, but did in the past, for how long did you take the medication? _____
Was this continuous use? Yes No
If no, please explain: _____

6. Do you take any prescribed or over-the-counter medications for pain or inflammation (e.g., Ibuprofen, Motrin)? Yes No
If yes, please list: _____

7. If you currently take a pain or anti-inflammatory medication, for how long have you been taking this medication?_____
Has this been continuous use? Yes No
If no, please explain: _____

8. If you do not currently take a pain or anti-inflammatory medication, have you ever taken one in the past? Yes No
If yes, please list: _____

9. If you are not currently taking a pain or anti-inflammatory medication but did in the past, for how long did you take the medication?
_____
Was this continuous use? Yes No
If no, please explain: _____

Alcohol/Caffeine Consumption:

1. Do you currently drink alcoholic beverages? Yes No
If yes, how many drinks on average do you have daily? _____ weekly? _____ monthly? _____

2. If you do not currently drink alcoholic beverages, have you ever? Yes No
If yes, how many drinks on average did you drink daily? _____ weekly? _____ monthly? _____

3. What type of alcoholic beverages do/did you typically consume? Beer Wine Liquor Other _____
If liquor, what type? Shot Cocktail (single liquor) Cocktail (multiple liquors) Other _____

4. For how many years have you drunk alcoholic beverages? _____

5. Has the number of alcoholic drinks consumed changed over time? Yes No
If yes, please explain _____

6. Please estimate the number of ounces of alcohol consumed daily _____ weekly _____ monthly _____
(shot = 1.5 oz.; cocktail = 1.5 oz. per alcohol; standard wine glass = 5 oz.; standard beer can = 12 oz; a pint = 12 oz.)

7. Do you currently drink caffeinated beverages? Yes No
If yes, how many drinks on average do you have daily? _____ weekly? _____ monthly? _____

8. If you do not currently drink caffeinated beverages, have you ever? Yes No
If yes, how many drinks on average did you drink daily? _____ weekly? _____ monthly? _____

9. What type of caffeinated beverages do/did you typically consume? Coffee Tea Energy Drink Other _____

10. For how many years have you drunk caffeinated beverages? _____
11. Has the number of caffeinated drinks consumed changed over time? Yes No
If yes, please explain _____

12. Please estimate the number of ounces of caffeine consumed daily _____ weekly _____ monthly _____
(cup = 6 oz.; mug = 8 oz.; travel mug = 16 oz.)

Cigarette/Tobacco Use

1. Do you currently smoke or use tobacco products? Yes No

2. What type of tobacco product do you generally use? Cigarette Cigar Chewing tobacco Pipe Other _____

3. For how long have you been smoking or using tobacco products? _____
Has this been continuous use? Yes No
If no, please explain: _____

4. Please estimate the number of cigarettes/cigars/chewing tobacco/pipes you use daily_____ weekly_____ monthly_____

5. Has the number of cigarettes/cigars/chewing tobacco/pipes you use changed over the course of time? Yes No
If yes, please explain: _____

6. Has the type of tobacco product used changed over time? Yes No
If yes, please explain: _____

7. If you do not currently smoke or use tobacco products, have you ever? Yes No

8. What type of tobacco product did you generally use? Cigarette Cigar Chewing tobacco Pipe Other _____

9. For how long had you smoked or used tobacco products? _____
Was this continuous use? Yes No
If no, please explain: _____

10. Please estimate the number of cigarettes/cigars/chewing tobacco/pipes you used daily _____ weekly _____ monthly _____

11. Did the number or type of cigarettes/cigars/chewing tobacco/pipes you used change over the course of time? Yes No
If yes, please explain: _____

12. If you do not currently smoke or use tobacco products but did in the past, how long ago did you stop? _____

Exercise/Physical Activity

1. Do you get regular (at least once/weekly) exercise? Yes No
If yes, please list:
a. Exercise/physical activity _____ frequency per week _____ duration per occasion _____
b. Exercise/physical activity _____ frequency per week _____ duration per occasion _____
c. Exercise/physical activity _____ frequency per week _____ duration per occasion _____
d. Exercise/physical activity _____ frequency per week _____ duration per occasion _____

2. Has the amount or type of exercise that you engage in changed over time?
If yes, please explain: _____
_____

3. If you do not currently get regular exercise, have you ever? Yes No
If yes, please list:
a. Exercise/physical activity _____ frequency per week _____ duration per occasion _____
b. Exercise/physical activity _____ frequency per week _____ duration per occasion _____
c. Exercise/physical activity _____ frequency per week _____ duration per occasion _____
d. Exercise/physical activity _____ frequency per week _____ duration per occasion _____

4. If you do not currently get regular exercise but did in the past, how long has it been since you stopped? _____
_____

5. If you do not currently get regular exercise but did in the past, what was the reason(s) for stopping? _____
_____

6. Please estimate your current body type: Overweight Underweight Normal-weighted

7. If you are over or underweight, please estimate by how many pounds:
Less than 10 10 to less than 20 20 to less than 30 30 to less than 40 40 to less than 50 More than 50

General Health

1. Do you currently have an infection (e.g., pneumonia, gingivitis, bronchitis)? Yes No
If yes, what kind of infection do you have? _____ for how long? _____

2. If you do not currently have an infection, have you ever? Yes No
If yes, what type of infection did you have? _____ for how long? _____

3. If you do not currently have an infection but had one in the past, how long ago was the infection? _____

4. If you currently have an infection or had one in the past, did you undergo any type treatment? Yes No
If yes, please explain: _____

5. If you received treatment for a current or past infection, did you follow the prescribed advice? Yes No
If no, please explain: _____

6. If you received treatment for a current or past infection, did the treatment help? Yes No
Please explain: _____

7. Do you currently have an inflammatory condition (e.g., rheumatoid arthritis, lupus, gout)? Yes No
If yes, what kind of inflammatory condition do you have? _____ for how long? _____

8. If you do not currently have an inflammatory condition, have you ever? Yes No
If yes, what type of inflammatory condition did you have? _____ for how long? _____

9. If you had a past inflammatory condition, how long ago was the inflammatory condition? _____
10. If you currently have an inflammatory condition or had one in the past, did you undergo any type treatment? Yes No
If yes, please explain: _____

11. If you received treatment for a current or past inflammatory condition, did you follow the prescribed advice? Yes No
If no, please explain: _____

12. If you received treatment for a current or past inflammatory condition, did the treatment help? Yes No
Please explain: _____

For Females Only:

1. Are you currently on birth control, estrogen, or other hormone replacement therapy (HRT)? Yes No
If yes, please list: _____

2. If you are currently on birth control, estrogen, or another HRT, for how long have you been medicated? _____
Has this been continuous use? Yes No
If no, please explain: _____

3. If you are not currently on birth control, estrogen, or another HRT, have you ever been in the past? Yes No
If yes, please list: _____

4. If you were previously on birth control, estrogen, or another HRT, for how long were you medicated?_____
Was this continuous use? Yes No
If no, please explain: _____

APPENDIX B

Aβ	amyloid beta	HBP	high blood pressure	PD	Parkinson's disease
ACT	alpha 1 antichymotrypsin	Hcy	homocysteine	RBC	red blood cell
AD	Alzheimer's disease	HDL	high-density lipoprotein	SBP	systolic blood pressure
ApoE	apolipoprotein E	HRT	hormone replacement therapy	SNP	single nucleotide polymorphism
B6	vitamin B6	ICD-10	International Classification of Disease, 10th Revision	tHcy	total homocysteine
B12	vitamin B12	IL	interleukin	TNF	tumor necrosis factor
BMI	body mass index	IQ	intelligence quotient	VA	Veteran's Affairs
CBS	cystathionine β-synthase	LDL	low-density lipoprotein	VaD	vascular dementia
CES-D	Center for Epidemiological Studies on Depression Scale	MCI	mild cognitive impairment	WCST	Wisconsin Card Sorting
CNS	central nervous system	MMSE	Mini Mental State Exam	WJ-R	Woodcock-Johnson Psychoeducational Battery
CPB	cardiopulmonary bypass	MS	multiple sclerosis	WMS-R	Wechsler Memory Scale – Revised
CRP	C-reactive protein	MTHFR	methylenetetrahydrofolate reductase		
CVD	cardiovascular disease	MTR	methionine synthase		
GDS	Geriatric Depression Scale	MTRR	methionine synthase reductase		
HAM-D	Hamilton Depression Rating	NHANES	National Health and Nutrition Examination Survey		
HbA1c	glycosylated hemoglobin	NSAID	non-steroidal anti-inflammatory drug		

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ABSTRACT

C-REACTIVE PROTEIN, HOMOCYSTEINE, AND COGNITIVE PERFORMANCE IN HEALTHY ADULTS

by

CHERYL L. DAHLE

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Advisor: Dr. Naftali Raz

Major: Psychology

Degree: Doctor of Philosophy

Elevated blood levels of C-reactive protein (CRP) and homocysteine (Hcy) have received a great deal of attention as biomarkers for the development of cardiovascular disease. Their utility in predicting cognitive function has also been assessed, though the findings are equivocal. The current study examined the relationship between elevated blood levels of CRP and Hcy and their effect on cognition across several cognitive domains. As baseline blood levels of CRP and Hcy and cognition are in part regulated by genetic factors, the impact of T carrier status for variants in the *CRP* -286 C>T>A and the *MTHFR* 677C>T alleles was also examined. In an exceptionally healthy aging population free of overt signs of cardiovascular disease, normal range elevations in blood levels of CRP or Hcy, either alone or in combination, were not associated with cognitive impairments in any domain. Moreover, T carriage for either SNP was unrelated CRP or Hcy blood levels, and was only related to cognition in a task and subpopulation specific manner. Namely, T carriers of the *CRP* gene had reduced processing speed, and among men, reduced ‘g’ performance. Whereas for the *MTHFR* gene, T carriage was associated with fewer prose items recalled among hypertensives.

AUTOBIOGRAPHICAL STATEMENT

Education:

Institution and Location	Degree	Year	Field of Study
Augsburg College, Minneapolis, MN	B.A.	1996	Psychology
Minnesota State University, Mankato, MN	A.B.T.	1999	Clinical Psychology
University of Memphis, Memphis, TN	transferred	2000	Experimental Psychology
Wayne State University, Detroit, MI	M.A.	2007	Psychology
Wayne State University, Detroit, MI	Ph.D.	2010	Psychology

Recent Professional Positions:

2000 – present ***Neuropsychology of Aging and Cognitive Neuroscience of Aging Labs***
Lab Head: Naftali Raz, Ph.D.

Selected Awards and Honors:

2009 Organization **Travel Award** Recipient, Wayne State University, Dean of Student's Office, Detroit, MI

2008 Behavioral and Social Sciences Section **Travel Award** Recipient, Gerontological Society of America Annual Meeting, National Harbor, MD

2008 **Second Place**, Institute of Gerontology Fall Poster Session, Wayne State University, Detroit, MI

2008 **Technical Assistance Workshop** Participant, National Institute of Aging, National Harbor, MD

2008 – 2009 **Graduate Professional Scholarship** Recipient, Wayne State University Graduate School, Detroit, MI

Publications:

Raz, N., **Dahle, C. L.**, Rodrigue, K. M., Kennedy, K. M., & Land, S. (in press). Effects of age, genes, and pulse pressure on executive functions in healthy adults. *Neurobiology of Aging.*

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