Serum cholesterol, body mass index and smoking status do not predict long-term cognitive impairment in elderly stroke patients

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Title: Serum cholesterol, body mass index and smoking status do not predict long-term cognitive impairment in stroke elderly patients

Running title: Stroke, Cardiovascular Factors and Cognition

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ABSTRACT

Objectives: Older stroke survivors are at risk of long-term cognitive impairment, which is associated with a number of modifiable and non-modifiable factors. We aimed to assess the association between the modifiable risk factors, serum cholesterol, low density lipoprotein, high density lipoprotein, serum triglycerides, body mass index (BMI) and smoking status on cognitive function, while controlling for the non-modifiable factors, acute functional impairment, diabetes status and age.

Methods: A cross-sectional study from a metropolitan University Hospital in Sweden involving older adults (n=149). Assessments occurred at 20 months post-stroke, using the Mini Mental State Examination and serum blood levels of cholesterol, low density lipoprotein, high density lipoprotein and serum triglycerides,.

Results: Hierarchical linear regression showed that only acute functional impairment significantly contributed to long-term cognitive impairment in stroke survivors. Only 12% of the sample showed healthy cholesterol levels while the remaining patients showed borderline or high cholesterol levels. In terms of BMI, only 2% of the sample were underweight, 38% were within healthy range and 26% were overweight/obese. Only eight women and four men were smokers, therefore our sample of smokers was likely too small to detect any differences between smokers and non-smokers in regard to cognitive outcomes.

Conclusion: Serum cholesterol, low density lipoprotein, high density lipoprotein, serum triglycerides, BMI or smoking status did not influence cognitive outcomes in older stroke surviving individuals. These findings suggest that modification of these factors may not influence cognitive outcomes in stroke-surviving individuals however should be interpreted as preliminary given limitations in the current study.

Introduction

Ischemic stroke is a leading cause of death and disability worldwide, affecting 15 million people every year[1]. The societal cost of stroke is €27 billion annually in the European Union alone[1]. Stroke results in long-term impairments in a range of abilities, such as cognitive capacity[2]. Cognitive impairment affects over two thirds of stroke survivors, while dementia is present in one third of stroke survivors[2]. Aside from the impact of cognitive impairment on quality of life, it is associated with poorer recovery and functional capacity[3], including increased mortality[4]. In order to achieve the best outcomes for stroke survivors, it is important to understand if modifiable factors may mediate post stroke cognitive outcomes.

Many modifiable risk factors are associated with long term cognitive impairment following stroke, including lifestyle factors such as diet, nutrition[5] and smoking status[6] which may provide possible avenues to moderate the risk of long term cognitive impairment following ischemic stroke.

In non-stroke affected populations, high density lipoprotein (HDL) is associated with better cognitive function, including a lower prevalence of dementia, and less Alzheimer pathology[7]. HDL cholesterol levels have been found to be significantly associated with cognitive function, as measured using the Mini Mental State Examination (MMSE), in approximately 700 Dutch individuals aged 85 years or older[8]. In a subsample of individuals who had previously experienced stroke (n=56), both serum HDL cholesterol concentration and cognitive function were lower, indicating that HDL cholesterol levels may be related to cognitive function following stroke[8]. Further research demonstrates that levels of LDL cholesterol are positively associated with an increased risk of dementia following stroke in 122 individuals aged 65 and above from the United States[9].

Body mass index (BMI) is also reported to influence cognitive function. In a sample of over 7,000 individuals form the United States, higher BMI in later life predicts a lower risk of dementia[10]. Accordingly, in another study of approximately 2800 community dwelling adults from the United States, underweight individuals (BMI <20) aged >65 years had an increased risk of developing dementia[11]. In both of these studies however, only a proportion of the sample were stroke survivors (2% and unreported, respectively)[11, 12]. In stroke survivors specifically, dementia risk has been reported to be decreased in individuals with higher BMI, however this was seen in a small sample of 53 individuals[13], and therefore the association between post stroke cognitive outcomes and BMI is yet to be compressively explored.

Cigarette smoking also appears to influence cognitive function. In approximately 1700 older German adults, cigarette smoking has been reported to be associated with poorer cognitive function[14]. Similarly, in a longitudinal study of approximately 9,000 participants aged >65 years, cognitive function was seen to decline more in smokers compared to non-smokers, as measured using the MMSE[15].

No study has been designed to measure the impact of the modifiable cardiovascular risk factors, cholesterol, low density lipoprotein, HDL, serum triglycerides, smoking and body mass index on cognition following stroke. In previous studies, only a proportion of the participating individuals were stroke survivors, the time since stroke was either variable or not reported[8, 9]. Given this these risk factors are modifiable, it is important to assess if they contribute to ongoing post stroke cognitive impairment. Therefore, in the current study we aimed to assess if cholesterol, BMI, and smoking status are associated with cognitive impairment long term after stroke onset, after controlling for non-modifiable factors known to influence long term cognitive outcome, following stroke[3].

Methods

Participants

Eligible individuals were patients admitted to a stroke unit or medical ward of a metropolitan University Hospital in Gothenburg, Sweden between February 1, 1993, and May 17, 1994. While this data was collected some time ago, the senior author of the current manuscript designed the process and also investigated all patients, ensuring that all of the information was collected reliably and consistently across patients. Eligible patients were aged 70 years or older with no upper age limit, so as to counteract the fact that previous cohorts were biased towards being younger than the typical stroke population. Patients were presenting with an acute cerebrovascular neurological deficit that was diagnosed by routine investigations by the physician on call and an acute computer tomography (CT) scan. Exclusion criteria were coma, extracerebral or subarachnoid haemorrhage, previous cerebral lesion requiring ongoing care, cerebral tumour, or a requirement for care for a specific neurological disorder that cannot be handled in a medicine ward, symptoms for more than 7 days prior to admission, or residing in a nursing home at the time of admission. Patients were only excluded if they were severely cognitively impaired or could not be placed in the stroke unit or medical wards because they required particular facilities that precluded the randomization of the patient to either ward. Thus patents were not excluded if co-morbidities were present, such as diabetes, myocardial infarction, Parkinson's Disease or Multiple Sclerosis. Eligible patients were assessed and included in the study at admission, at the emergency unit of the hospital. The study was naturalistic and the patients received all components of the hospital's standard care including any form of therapy addressing any speech/language/cognitive impairments exhibited post stroke.

Study protocol

The protocol for the follow-up investigation has been detailed previously[2]. In brief, participating individuals (*n*=149) were contacted initially by mail and later by telephone to arrange hospital appointments. The patients were contacted by the primary investigator or a study nurse. In cases when the participant was unable to visit the hospital (n=15, 10%), appointments were offered to take place in patients' homes. All outcomes measured were collected at 20 months following stroke, in order to assess the impact of the modifiable biomarkers on long-term cognitive outcomes following stroke. Written and verbal information was provided to all individuals or their nearest relative when relevant, prior to obtaining informed consent. Ethics approval was granted by The Ethics Committee for Medical Research, at the University of Gothenburg.

Biomarkers collection

Table 1 shows the timeline for collection for data collection. Serum cholesterol, LDL, HDL, and serum triglycerides were collected 20 months post-stroke from peripheral venous blood samples during the hospital appointment. Other biomarkers were also collected at this time, including the acute phase reactant C-reactive protein and the amino acid homocysteine that have been reported elsewhere[16, 17]. Samples were collected into 5ml gel tubes, inverted >5 times, left to coagulate, centrifuged (10 min) and assessed by photometry. Collection and analysis was conducted in an accredited university hospital pathology laboratory, in in the patients' home when necessary. The healthy range of human serum cholesterol is <5mmol/L in adults[18]. Individuals were classified as having healthy (<200 mg/dl), borderline (200-239 mg/dL) or high cholesterol levels (>240 mg/dl).

Cognitive assessments

Cognitive assessments were conducted by a neurologist/psychiatrist according to Mini Mental State Examination (MMSE) at a single time point, 20 months post stroke, selected to reflect cognitive impairments at long term following stroke onset. To ensure the screening tool was consistently administered in the same manner, the same person evaluated all the patients. Before commencing, co-assessments and calibrations were done with researchers who were experienced with the method. Diagnoses were reviewed in a three-physician conference. MMSE scores are compiled based on information obtained from eight criteria: orientation to time and place; registration; attention and calculation; recall; language; repetition; and complex commands. Individuals are given a score for each of these measures that is compiled into an overall cognition score out of 30, with lower scores indicating greater cognitive impairment. A score of 25-30 is considered normal cognition; 21-24 is considered mild cognitive impairment, 10-20 is considered moderate cognitive impairment and <10 is considered severe cognitive impairment[19]. The neurologist/psychiatrist conducting the assessment was unaware of the type, size and location of the index stroke throughout the diagnostic and assessment procedure.

Acute functional impairment assessment

Functional impairment was assessed as either improved or unchanged using the Barthel Index at 3 days following stroke. The Barthel Index consists of 10 items that measure a person's daily functioning as assessed by the ability to perform activities, including feeding, bathing, grooming, dressing, bowel movements, bladder movements, toilet use, transfers from one location to another, mobility, and stair walking, with lower scores indicating higher disability and higher scores indicating less disability[20].

Body mass index (BMI)

BMI was calculated by dividing body weight in kilograms by body height in meters squared. Individuals were classed as either underweight (<18.5), healthy (18.5-25), overweight (25-30) or obese (>30).

Statistical methods

Statistical analyses were conducted using the SPSS version 20 package. Exploratory analyses were used to determine means and standard errors for acute functional impairment, age, diabetes status, BMI, mean serum cholesterol, LDL, HDL, serum triglycerides, smoking status (as measured using a self-report questionnaire), and MMSE scores. Independent sample *t tests* were used to determine differences in outcomes measures between female and males. Hierarchical linear regression was used to assess the predictive value of acute functional impairment, age, diabetes, serum cholesterol, LDL, HDL, serum triglyceride, BMI and smoking status on MMSE scores. For the purpose of multiple regression analysis and descriptive statistics, raw continuous MMSE scores were used. Outliers were screened using box plots. Multicollinearity was checked using collinearity statistics, variance inflation and tolerance. Independence of errors was checked using the Durbin-Watson test. Histograms and The Shapiro-Wilk Test were used to assess normality.

Insert table 1 here

Results

Characteristics of the cross sectional study population

A detailed loss-to-follow-up-analysis has been previously reported elsewhere[2]**.** Table 2 shows mean values of acute functional impairment, age, diabetes status, serum cholesterol, LDL, HDL, serum triglyceride, BMI and MMSE scores at 20 months following stroke onset. The mean level of serum cholesterol was clinically elevated (healthy range <5mmol/L in adults)[18], 13% (n=19) of patients had healthy cholesterol levels (<200mg/dL), 28% (n=41) had borderline high cholesterol (200-239 mg/dL) and 35% (*n*=52) had high cholesterol (>240mg/dL) [21] In 25% (n=37) of patients, cholesterol outcomes were unable to be collected. The mean level of triglycerides in patients was 1.84 mmol/L, which is clinically elevated [30], indeed, only 54% of patients had triglyceride levels considered clinically desirable. The mean LDL levels in patients with a history of coronary artery disease or diabetes (*n*=39) was 4.08 mmol/L which is considered to be high [30]. In patients without a history of coronary artery disease or diabetes (*n*=66) mean LDL levels were 3.90 mmol/L which is considered to borderline high [30]. The mean level of HDL was 1.31 mmol/L for men (*n*=35) and 1.46 mmol/L for women (*n*=74), which is considered to be clinically normal [30]. The mean MMSE scores indicated mild cognitive impairment (21–24 points)[19], 65 individuals (43.6%) had normal cognition, 40 (26.8%) had mild cognitive impairment, 40 (10.7%) had moderate cognitive impairment and 1 (0.7%) had severe cognitive impairment (data was missing for 27 of the 149 individuals). Individuals with cognitive impairment did not differ from individual without cognitive impairment on any of the modifiable risk factors assessed, serum cholesterol, $t(110)=-0.62$, $p=0.53$; triglycerides, $t(109)=-1.52$, $p=0.13$; HDL, $t(107)=1.71$, $p=0.08$; LDL, $t(103)=-0.70$, $p=0.48$; BMI, $t(97)=-1.00$, $p=0.32$; smoker, $t(93)=-0.44$, $p=0.66$. Individuals with cognitive impairment were however found to more

functional impairment, $t(147)=-4.75$, $p=0.00$ (no impairment *M Barthel Index* =2.8, *SD*=0.47, impairment *M Barthel Index* =2.1, *SD*=0.8). Eight women (8.2%) and four men (7.7%) were smokers. In terms of BMI, 2% (n=3) of individuals were underweight, 38% (n=57) were within healthy range, 20% (n=29) were overweight and 7% were obese (n=10). In 34% (n=50) of individuals, BMI was unable to be collected as morphometry could not be done when house-visiting or when the patients were bed-ridden. Independent sample *t tests* showed that men and women did not differ on any of the reported outcomes: acute functional impairment, $t(147)=-0.27$, $p=0.77$; age at follow up, $t(147)=3.12$, $p=0.35$; serum cholesterol, $t(110)=2.23$, $p=0.77$; triglycerides, $t(109)=0.45$, $p=0.66$; HDL, $t(107)=1.73$, $p=0.09$; LDL, $t(103)=0.77$, $p=0.44$; BMI, $t(97)=-0.10$, $p=0.23$; MMSE scores, $t(120)=-1.57$, $p=0.46$. Spontaneous recovery in terms of physical and cognitive function during the first year following stroke has been previously measured and reported elsewhere [2, 22]

Inset table 2 here

The modifiable risk factors cholesterol, BMI and smoking status are not associated with cognitive impairment at 20 months after stroke

To explore the factors affecting MMSE scores long-term after stroke, hierarchical multiple regression was conducted with MMSE scores as the dependent variable and acute functional impairment, diabetes status, age, serum cholesterol, LDL, HDL, serum triglyceride, BMI and smoking status and as predictor variables, at 20 months following stroke. Acute functional impairment (as collected at 3 days post stroke) age and diabetes status were entered into the first block as these were considered to be non-modifiable risk factors. After controlling for these, serum cholesterol, LDL, HDL, serum triglyceride levels, BMI and smoking status were entered into the

second block to determine if these significantly explained the variance in MMSE scores. Acute functional impairment (at 3 days post stroke) diabetes status and age explained 23.3% of the variance in MMSE scores and significantly predicted depression scores ($F(3, 63)=6.08$, $p<0.01$). The addition of serum cholesterol, LDL, HDL, serum triglycerides, BMI and smoking status increased the amount of variance explained to 27.1%, and the model again significantly predicted MMSE scores ($F(9, 63)=2.23$, $p=0.03$). However, serum cholesterol, BMI and smoking status only increased the amount of variance explained by 3.8%. Table 3 shows the slope of the regression line for each of the individual independent variables. Of these, only acute functional impairment (at 3 days) was found to significantly explain the variance seen in MMSE scores.

Inset table 3 here

Discussion

This study examined the relationship between the modifiable risk factors serum cholesterol, LDL, HDL, serum triglyceride, BMI, smoking status and cognitive impairment long-term after stroke onset, after controlling for non-modifiable risk factors, acute functional impairment and age, in community dwelling older individuals. In our study, patients showed a mean MMSE score that indicated mild cognitive impairment at 20 months post-stroke. Mean scores of serum cholesterol, triglycerides and LDL were also elevated. This is not surprising given that the vast majority of the sample had borderline or high cholesterol. Indeed, only 13% of the sample had cholesterol in the healthy range. Using hierarchical regression modelling our study demonstrates that acute functional impairment at 3 days post-stroke is associated with worse cognitive outcomes at 20 months post-stroke. This result is not unexpected given that previous research indicates that acute cognitive function is a predictor of long-term cognitive impairment[3]. Thus, our study confirms the importance of and prognostic value of early neuropsychological examination in regard to identifying individuals at risk of long-term cognitive impairment in clinical settings, however there are some limitation of the MMSE as discussed below.

Interestingly, in this study age was not found to be not associated with cognitive function in stroke survivors; however the sample comprised only older adults, and thus the results could reflect a ceiling effect. Alternately, while multiple studies have previously indicated that increasing age is associated with greater cognitive impairment following stroke[3], a number of other factors have also been demonstrated to be important predictors of longer term cognitive outcomes[3], such as ethnicity, lower social class, left hemispheric stroke, visual field defect, education level and urinary incontinence[3]. A limitation in the current study is that comprised of only elderly Swedish individuals, and did not examine the predictive value of any of the above listed factors such as

ethnicity. It is possible that the predictive role of age is more meaningful when studied in conjunction with other relevant predictive factors.

Our study did not find an association between serum cholesterol, LDL, HDL, serum triglyceride levels and long-term cognitive function following stroke, indicating that these cardiovascular risk factors are not associated with cognitive outcomes in stroke survivors. This finding is inconsistent with previous research which demonstrates that cognitive impairment is associated with increased serum triglycerides and lipoproteins in non-stroke surviving populations[7]. Indeed, membrane cholesterol has been shown to play a role in the formation and aggregation of amyloid-beta[23, 24] the main component of the amyloid plaques that are present in the brains of individuals with Alzheimer's disease[23, 24]. Other studies however have highlighted that decreased cholesterol levels may impair brain function in older individuals, as cholesterol is essential for synapse formation involved in signal transduction as a component of the cell membrane[7]. It appears that when measured in midlife, high cholesterol levels are associated with an increased risk of late-life cognitive decline. However, when measured later in life, high cholesterol levels show no association or an inverse association with cognition decline, whereby low levels of cholesterol are associated with more cognitive impairment[7]. In our sample of older individuals, mean cholesterol levels were clinically elevated at 20 months post stroke (Female M=6.46, SE=0.15, Male M=5.88, SE=0.22). Indeed, only 13% of the sample showed healthy levels of cholesterol, compared to 28% with borderline and 35% with high cholesterol. Therefore the cognitive impairments previously reported to be associated with low cholesterol levels would not likely have been present in the patients who partook in this study, given that most patients had clinically elevated cholesterol levels. This finding is interesting as it indicates that in elderly stroke survivors, that high cholesterol may not contribute to cognitive difficulties[7].

Body mass index was similarly not found to be not associated with cognitive function in stroke survivors. This is inconsistent with previous research that indicates that higher BMI is associated with less cognitive decline in older individuals (>65 years)[11]. In the current study, we may have failed to demonstrate a relationship between BMI and cognitive function as only 2% (n=3) of patients in the current sample were underweight. On the contrary, 38% of patients (n=57) were within healthy range, 20% (n=29) were overweight and 7% were obese (n=10). The Mean BMI of the entire sample was in the healthy range (Female *M*=24.1, *SE*=0.58, Male *M*=24.9, *SE*=0.57), thus these patients were not vulnerable to the mechanisms underlying the cognitive dysfunction seen among underweight older adults.

Finally, smoking status was not found to be associated with cognitive impairment, contrary to previous research demonstrating that cigarette smoking is associated with poorer cognitive outcomes and dementia in older, stroke and non-stroke affected adults[14]. Interestingly, smoking has been reported to be associated with reduced cortical regional grey matter density in brain regions associated with Alzheimer disease, as assessed using voxel-based morphometry[25] and reduced cerebral blood flow, as assessed using single-photon emission computed tomography[26]. Indeed, heavy smoking in midlife is associated with 3-fold increased risk of stroke-related cognitive impairment, even after controlling for various potential vascular confounding factors[6]. In the present cross-sectional study, the smoking status of patients in midlife was not a studied variable, and would be worthwhile to explore in future research. A limitation of our study is that only eight females and four males were smokers, and thus while there may be an effect, our sample of smokers was likely too small and lacked sufficient power to detect any differences between smokers and non-smokers in regard to cognitive outcomes. Furthermore, smoking status was

obtained using self-report and thus it is possible that patients did not accurately report their smoking status.

A further limitation of the current study is that the MMSE is often criticized for being biased toward memory and language, as opposed to executive function and abstract thinking, and therefore could be followed by a more formal assessment in order to more thoroughly assess cognitive impairment [27]. For example, the MMSE does not take into account potential language impairments often associated with a hemisphere stroke[28]. Analysis of a more stringent measure of cognitive ability which is more commonly used in the stroke surviving population and sensitive to cognitive impairment in the post stroke population [29], may have provided a more accurate and specific measure of cognitive ability. While we chose to use the MMSE for this study, in future studies it would be valuable to analyse a more stringent measure of cognitive ability, to examine if cognitive change is associated with various risk factors. Finally, the design of this study does not allow us to determine the cause of cognitive impairment and dementia and therefore, it is unclear whether stroke survivors in the current study experience cognitive impairment resulting from stroke and/or cognitive impairments resulting from other causes. The senior author of this paper has however previously assessed the impact of stroke on cognitive impairment[2], by comparing stroke survivors to a population sample, using the same instruments utilized in the current study[2].

This study is the first to report that modifiable risk factors, serum cholesterol, LDL, HDL, serum triglycerides, BMI and smoking status do not seem to be associated with long term cognitive outcomes in stroke survivors, after controlling for acute cognitive impairment and age. These findings suggest that modification of these factors may not influence cognitive outcomes in stroke-surviving individuals. In light of the limitations of our study, such as a small sample size of

smokers, healthy BMI and elevated serum cholesterol levels among patients, these results should be interpreted with caution. It would be valuable to explore the relationship between BMI, serum cholesterol and cognition in stroke survivors with low BMI and low serum cholesterol levels.

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458

459 **Tables**

460 *Table 1.*

461 **Timeline for data collection**

Timeline for data collection	
3 days post stroke	Acute functional impairment - Barthel Index
20 months post stroke	Serum cholesterol Serum LDL Serum HDL Serum Triglycerides MMSE BMI Age Smoking status Diabetes status

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Table 2.

Key descriptive Statistics in Stroke Survivors

Descriptive Statistics

	Mean	Std. Deviation	N
Mini Mental State Examination	24.08	3.68	122
Stroke Severity (Barthel) at 3 days	2.32	0.80	149
Age at follow-up	81.04	5.33	149
Diabetes	0.13	0.34	149
s-Cholesterol (mmol/L)	6.26	1.31	112
s-Triglycerides (mmol/L)	1.84	0.95	111
s-High density lipoprotein (mmol/L)	1.41	0.41	109
s-Low density lipoprotein (mmol/L)	3.97	0.98	105
BMI	24.40	4.17	99
Smoker	0.13	0.33	95

The healthy range of human serum cholesterol is <5mmol/L in adults[18]. A desirable triglyceride level is less than 1.7 mmol/L [30]. LDL of 3.4-4.1 mmol/L is borderline high if there is no coronary artery disease and high if there is coronary artery disease[30]. An acceptable level of HDL is between 1.0-1.5 mmol/L for men and between 1.3-1.5 mmol/L for women [30]. Mini Mental State Examination = MMSE; age is shown in years. Lower MMSE scores represent more cognitive impairment. Scores of 25-30 out of 30 are considered normal cognition; 21-24 as mild cognitive

impairment, 10-20 as moderate cognitive impairment and <10 as severe cognitive impairment[19]. Means and Standard Errors of acute functional impairment at 3 days post stroke, age, serum cholesterol, LDL, HDL, serum triglycerides, body mass index and MMSE scores at 20 months following stroke onset.

Table 3

Coefficients, Standard Error of the Coefficients, Standardized Beta Values, P Value and Collinearity Statistics of the Regression Model

Model		Unstandardized Coefficients		Standardized Coefficients	Sig.	Collinearity Statistics	
		B	Std. Error	Beta		Tolerance	VIF
1	(Constant)	31.141	6.572		<0.01		
	Stroke Severity at 3 days	1.951	0.523	0.424	<0.01	0.992	1.008
	Age at follow-up	-0.143	0.079	-0.207	0.074	0.988	1.012
	Diabetes	0.003	1.252	<0.01	0.998	0.986	1.014
2	(Constant)	35.761	8.966		<0.01		
	Stroke Severity at 3 days	2.064	0.564	0.448	0.001	0.902	1.109
	Age at follow-up	-0.174	0.089	-0.252	0.057	0.807	1.238
	Diabetes	-0.088	1.336	-0.008	0.948	0.915	1.093
	s-Cholesterol (mmol/L)	-0.640	0.611	-0.229	0.299	0.284	3.524

s-Triglycerides (mmol/L)	0.695	0.603	0.179	0.254	0.559	1.788
s-High density lipoprotein (mmol/L)	0.945	1.319	0.105	0.477	0.631	1.586
s-Low density lipoprotein (mmol/L)	0.079	0.768	0.021	0.918	0.327	3.060
BMI	-0.052	0.119	-0.058	0.667	0.743	1.345
Smoker	-0.234	1.426	-0.021	0.870	0.806	1.240

Dependent Variable: Mini Mental State Examination. Computed using alpha = .05 * is significant at $p<0.05$.