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The Relationship between Mean Corpuscular Volume and Cognitive Performance in Older Adults

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Abstract

OBJECTIVES—To examine the relationship between erythrocyte mean corpuscular volume (MCV) and cognitive performance over time.

DESIGN—Longitudinal.

SETTING—Sample from the Baltimore Longitudinal Study of Aging (BLSA)

PARTICIPANTS—The sample consisted of 827 participants from the Baltimore Longitudinal Study of Aging (BLSA; *M* age = 67; *range* = 50 – 96).

MEASUREMENTS—MCV and several other blood indices were measured including hemoglobin, iron, ferritin, vitamin B12, folate, white blood cell count, albumin and erythrocyte sedimentation rate. Cognitive performance was examined using neuropsychological measures of visual memory, verbal memory, language, attention, executive function and global mental status.

RESULTS—High MCV levels were significantly associated with lower global mental status even after adjusting for potential confounders. High MCV levels were also significantly associated with accelerated rates of decline on tasks of global mental status, long delay memory, and attention even after adjusting for potential confounders.

CONCLUSION—Our findings confirm a previous observation that larger erythrocytes in older adults are associated with poorer cognitive function. The relationship between MCV and cognition does not appear to be explained by anemia and inflammation. Further research is needed to clarify the mechanisms behind this association.

There is some evidence that the lifespan of red blood cells is shorter in older adults, and as a result, the percentage of red blood cells recently released from the bone marrow increases progressively with age.[1-4] Furthermore, the incidence of vitamin B12 and folate deficiency,

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Author's Contributions

Alyssa Gamaldo analyzed data and wrote the paper. Luigi Ferrucci contributed vital new reagents and assisted in writing the paper. Joseph Rifkind contributed new reagents and assisted in writing the paper. Dan Longo contributed new reagents and assisted in writing the paper. Alan Zonderman assisted in data analyses and writing the paper.

Conflict of Interest

There were no relevant financial interests in our manuscript.

often manifested by macrocytosis, increases with age.[5,6] Larger red blood cells in older adults may have more difficulty passing through narrow capillaries, and transporting adequate quantities of oxygen and nutrients to tissues.[3,7] In the brain, such dysfunction can impair neuronal energetic metabolism and, in turn, negatively affect cognitive functioning.[7] Factors such as folate, and/or vitamin B12 deficiency also produce large red cells by slowing DNA synthesis. This delay in nuclear maturation is not matched by a delay in hemoglobin synthesis and therefore, those cells that survive the ineffective erythropoiesis tend to be larger. Scientists have suggested that older persons with larger red blood cells are more likely to have poorer cognitive functioning.[8]

Both MCV and cognitive performance (i.e. processing speed, memory, attention, and inhibition) change across the lifespan although there is great heterogeneity between individuals for the rate of change in both phenotypes.[9-11] A first stage in understanding whether changes in MCV are causally linked with changes in cognitive performance is to verify whether those individuals who show accelerated rates of cognitive decline also have higher MCV.[3,7] Danon and colleagues (1992) observed that higher MCV values were significantly associated with worse delayed recall, but not general memory performance.[7] Older adults with age-associated memory impairment had significantly higher MCV values than both older adults with normal cognitive functioning and unimpaired younger adults.[7] As already stated above, a possible interpretation of this link is that red cells with greater volumes may have difficulty transporting oxygen and nutrients through capillaries, especially in the brain regions connected with memory performance in older adults.[3,7] Such a direct link, however, may be too simplistic. In fact, it is possible that age-related changes in physiological processes, such as a pro-inflammatory state, vitamin deficiency, and excessive and unopposed oxidative stress, may be responsible for both MCV increases and impaired cognition without a true causal relationship between them.[12-15] To shed light into the relationship between MCV and cognition, we analyzed data from the Baltimore Longitudinal Study of Aging (BLSA). Our analysis addressed two primary aims: 1) to test the hypothesis that MCV is significantly correlated with various domains of cognitive performance independent of demographics, health covariates and other potential confounders (i.e. hemoglobin, folate, vitamin B12, erythrocyte sedimentation rate, ferritin, folate, iron, and white blood cells); 2) to test the hypothesis that age-related changes in cognitive performance are accounted for by changes in MCV independent of demographics and potential confounders. If our hypothesis is correct, and there is indeed a long-term longitudinal coupling between MCV and cognition, it may be worth to explore the mechanism of this association as a possible target of preventive and or therapeutic interventions.

METHODS AND PATIENTS

Participants

The current study included participants from the Baltimore Longitudinal Study of Aging (BLSA; n = 3,002), a prospective study initiated in 1958 that assesses health, cognition, and psychosocial factors in community-dwelling volunteers roughly every 2 years. Although participants were administered standardized psychometric tests starting in 1960, a more extensive neuropysch battery was administered to participants in 1986. For the current study, 2,071 BLSA participants were excluded from the analysis due to missing demographic and cognitive data (n = 1,291) as well as missing blood parameters (n = 780). For those participants who met clinical criteria for Mild Cognitive Impairment (MCI, $n = 4$), using Petersen criteria[16], or dementia ($n = 10$; diagnosis method detailed elsewhere[17]), we excluded any assessments at the time of onset and afterwards from the analysis. This resulted in an additional 104 participants being excluded from the analysis, leaving a sample of 827 (405 women and 422 men) included in our analysis. Participants excluded from the

analyses were not significantly different in age from participants included in the analyses ($t(1999) = -1.63$, $p > .05$), but they tended to have less education ($M = 16.07$, $SD = 2.83$) than participants included in the analyses ($M = 16.42$, $SD = 2.39$; $t(1496) = -2.84$, $p < .05$). Table 1 reports the baseline demographic characteristics, blood parameters, and selected health indices of the current study's sample. At baseline, participants' age ranged from 50 to 96 years ($M = 67$, $SD = 11.14$). The average duration of education was 16 years (range = 8–20, $SD = 2.47$ years). The sample consisted of 635 whites and 192 African Americans. On average, participants had 2.44 (range = 1-8, $SD = 1.42$) follow-up evaluations, with an average time between visits of 1.85 years (range = 0-6, $SD = 1.23$). The Johns Hopkins University and the MedStar institutional review boards approved this study, and all participants provided written informed consent.

Study variables

The current analyses included the demographic variables age, sex, and race. Given that a majority of the participants were highly educated, education was not included in the analyses. Health measures, particularly cerebrovascular disease and stroke, were included in the analyses. In the BLSA, ascertainment of chronic diseases, such as cerebrovascular disease (i.e., ischemic attack, ateriosclerotic cerebrovascular disease, cerebral arteriosclerosis, and stroke) and is based on an accurate medical history, physical exams and analysis on medical documentation and is performed by trained nurse practitioners using standard algorithms.

MCV & Blood Covariates

Blood samples were collected at each BLSA visit. A Coulter Counter was used to measure MCV levels in each participant's blood sample. At baseline, our sample had an average MCV of 91.39 (range = 61 – 107, $SD = 4.83$), which is within the normal range for adults.[18] A more detailed description of the procedures used to measure MCV has been published previously.[19] Since MCV can be strongly affected by many causes of anemia, we adjusted our analysis for hemoglobin, albumin, vitamin B12, ferritin, folate, and iron. We also adjusted the analyses for blood parameters associated with inflammation (i.e., erythrocyte sedimentation rate (ESR) and white blood count).

Cognitive Measurements

Cognitive performance was estimated using several measures from the BLSA's cognitive battery. Visual memory was assessed using the Benton Visual Retention Test –Total Errors (BVRT).[20] Verbal memory was assessed using the California Verbal Learning Test (CVLT, i.e. List A Total Correct, Free Recall Short Delay, and Free Recall Long Delay).[21] Language was assessed using Category Fluency, Letter Fluency,[22, 23] and Boston Naming (BNT).[23] Attention and Executive Function was assessed using Card Rotation,[24] and Trail Making Testing – Part A and B,[25] Digits Span Forward and Backward. Global Mental Status was assessed using the Blessed Information-Memory-Concentration-Test (Blessed)[26] errors and Mini-Mental Status Examination (MMSE).[27]

Analyses

Mixed-effects models,[28] also known as multilevel models (MLM)[29] were conducted to examine the current study's two aims using SAS System software (version 9.1.3; SAS Institute). Four models were fitted for each cognitive measure. The first model examined the association between MCV and performance on each cognitive measure, without adjusting for demographic, health, and blood confounders. The second model examined the association between MCV and cognition after adjusting for demographic and health confounders. The third model examined whether the MCV and cognition relationship

continues to remain significant after additionally adjusting for blood confounders (i.e. hemoglobin, albumin, folate, vitamin B12, ESR, ferritin, iron, and white blood cells). Lastly, the fourth model examined the interaction between age and MCV as it relates to performance on each cognitive measure, after adjusting for the demographic, health, and blood confounders. Given MCV, age, and the blood confounders were assessed at each visit, these measures were included in the models as time-varying predictors/covariates. However, sex, race, cerebrovascular disease, and stroke were included in the models as time-invariant covariates. MCV and/or age were not included as a random effect because the data consistently fit the models better when the mcv and/or age slope was constrained.

RESULTS

Relationship of MCV and Cognition

Greater MCV was significantly associated with worse performance on Category Fluency (*B*: -0.03, *SE*: 0.01, $p < .05$), MMSE (*B*: -0.04, *SE*: 0.01, $p < .05$), Blessed (*B*: 0.02, *SE*: 0.01, $p < .05$) after accounting for demographic and health confounders (Table 2). When the additional blood confounders were included in the model, the MCV main effect was no longer significant for Category Fluency (*B*: -0.02, *SE*: 0.02, $p > .05$). However, the MCV main effect remained significant for the Blessed (*B*: 0.02, *SE*: 0.01, $p < .05$) and MMSE (*B*: -0.04, *SE*: 0.02, $p < .05$) even after additionally accounting for blood confounders (Table 2). There were no other significant associations between MCV and the other cognitive measures.

Age-related changes in Cognition as it relates to MCV

Significant interactions between age and MCV were observed for the CVLT Free Recall Long Delay (*B*: -0.004, *SE*: 0.002, $p < .05$), Digits Span Backward (*B*: -0.003, *SE*: 0.001, $p < .01$), and Blessed (*B*: 0.003, *SE*: 0.008, $p < .001$; Table 2). A marginally significant interaction between MCV and age was observed for the MMSE (*B*: -0.003 *SE*: 0.002, $p = .05$). Simple slopes analyses[30] were used to estimate the association between age and MCV at three levels of MCV (i.e. 1 *SD* above the mean MCV, mean MCV, and 1 *SD* below the mean MCV). Greater MCV values (i.e. 97 or above) had significantly accelerated rates of decline across these tasks than lower MCV values (i.e. 91 or below, see Figure 1 for the standardized simple slope estimates).

We conducted subsequent analyses after removal of non-significant confounders from the MLM models. These adjusted models revealed similar significant main effects and interactions as our unadjusted models described previously. However, greater MCV was significantly associated with worse performance on Category Fluency even after accounting for significant confounders (*B*: -0.03, *SE*: 0.001, $p < .05$). In addition, the interaction between MCV and age was significant for the MMSE (*B*: -0.003 *SE*: 0.002, $p < .05$).

DISCUSSION

Greater MCV appeared to be associated with worse performance on global mental status testing independent of several confounders including anemia and inflammation. This finding may further support a potential vascular metabolic origin for the coupling relationship between MCV and global cognition. Although greater MCV values also appeared to be associated with worse language testing as measured by Category Fluency, this relationship was dependent upon anemia and inflammation. Previous studies have observed a significant relationship between MCV and memory impairment,[2, 7] which we did not observe in our participant sample. These inconsistent findings may be explained by our study's larger and

older sample size as well as our inclusion of memory measures that were not included in previous studies.

Our most intriguing findings are that greater MCV levels were associated with greater age-related changes in global mental status, attention, and verbal, long delay memory performance. In addition, it appeared as though at baseline greater MCV values were associated with better performance on the Digits Backward, but this is likely an artifact of the analysis and may not represent a significant difference in performance. Although our findings did not confirm the notion that MCV is a significant and specific predictor of memory performance, we did observe that greater MCV is associated with a steeper rate of age-related decline on delay memory, but not on other tasks of memory. Indeed, this finding appears to expand upon a previous cross-sectional finding that greater MCV was significantly associated with worse delayed memory, but was not significantly associated with an index of both visual and verbal memory.[7] Furthermore, our findings suggest that greater MCV may be associated with greater age-related changes on measures of global mental status, which are routinely given in a clinical setting, and some measures of attention. MCV does not appear to be associated with significant age-related changes across the cognitive measures, which tap into various specific cognitive abilities. One speculation for these inconsistent results is that age-related changes in vasculature may account for the potential influence of greater MCV on cognitive functioning in a particular ability. Changes in MCV and other red blood cell parameters may be associated with cognitive deficits where there is greater circulatory impairment. Animal studies partially support this hypothesis. For example, Jucker and colleagues (1990) observed in rats that the age-related decline in the density of capillaries, particularly in the parietal lobe and hippocampus, was associated with impaired maze learning, a task of visuospatial processing and memory.[31] In humans, greater circulatory impairment, perhaps due to a reduced density of capillaries and/or decreased capillary diameters in particular brain regions may possibly explain why age-related changes in MCV might be significantly detrimental to specific cognitive abilities. However, more research is needed to evaluate this notion.

Although this study reveals some interesting findings, there are some limitations that should be noted. First, the current sample is highly educated and healthy, which may not be representative of the general population. However, some of our findings appear to be consistent with a previous study that included a different population.[7] A second limitation is that a restricted number of cognitive domains were observed. Thus, it is possible that changes in MCV may also be associated with changes in cognitive constructs (i.e. processing speed and working memory) that were not assessed in the current study.

Despite these limitations, the current study is one of the few studies to explore the association between MCV and cognition, particularly over time. Additional research is needed to clarify the specific mechanisms underlying the coupling relationship between MCV and cognition. For example, research exploring the potential interaction between MCV and red cell deformability may be useful in explaining whether larger red blood cells are also more fragile and have greater difficulty manipulating their shape to fit through narrow vessels (i.e. capillaries) in older adults.[17] Furthermore, research exploring whether differential changes in vasculature across brain regions may explain how greater MCV values appear to influence performance in specific cognitive domains. Lastly, it is possible that other processes associated with aging, such as oxidative stress,[13] that we could not account for in our study may indeed explain the association between cognition and MCV.

Conclusions

Accelerated rates of age-related declines in cognition may be coupled with enhanced MCV levels, and this long-term coupling relationship does not appear to be explained by anemia

and inflammation, but rather is associated with another mechanism. A clearer understanding of the mechanism behind the long-term coupling relationship between MCV and cognition may assist in targeting a clinical preventive intervention for cognitive decline. In addition, these findings expand upon the existing cognitive aging literature by introducing a potentially new area of research which explores how age-related physiological changes in red blood cells might explain inter- and intra-individual differences in cognitive performance. For example, given that MCV values tend to be lower in African Americans than whites,[32-34] we are currently exploring whether differences between age-related changes in cognition between whites and African Americans may be explained by changes in MCV.

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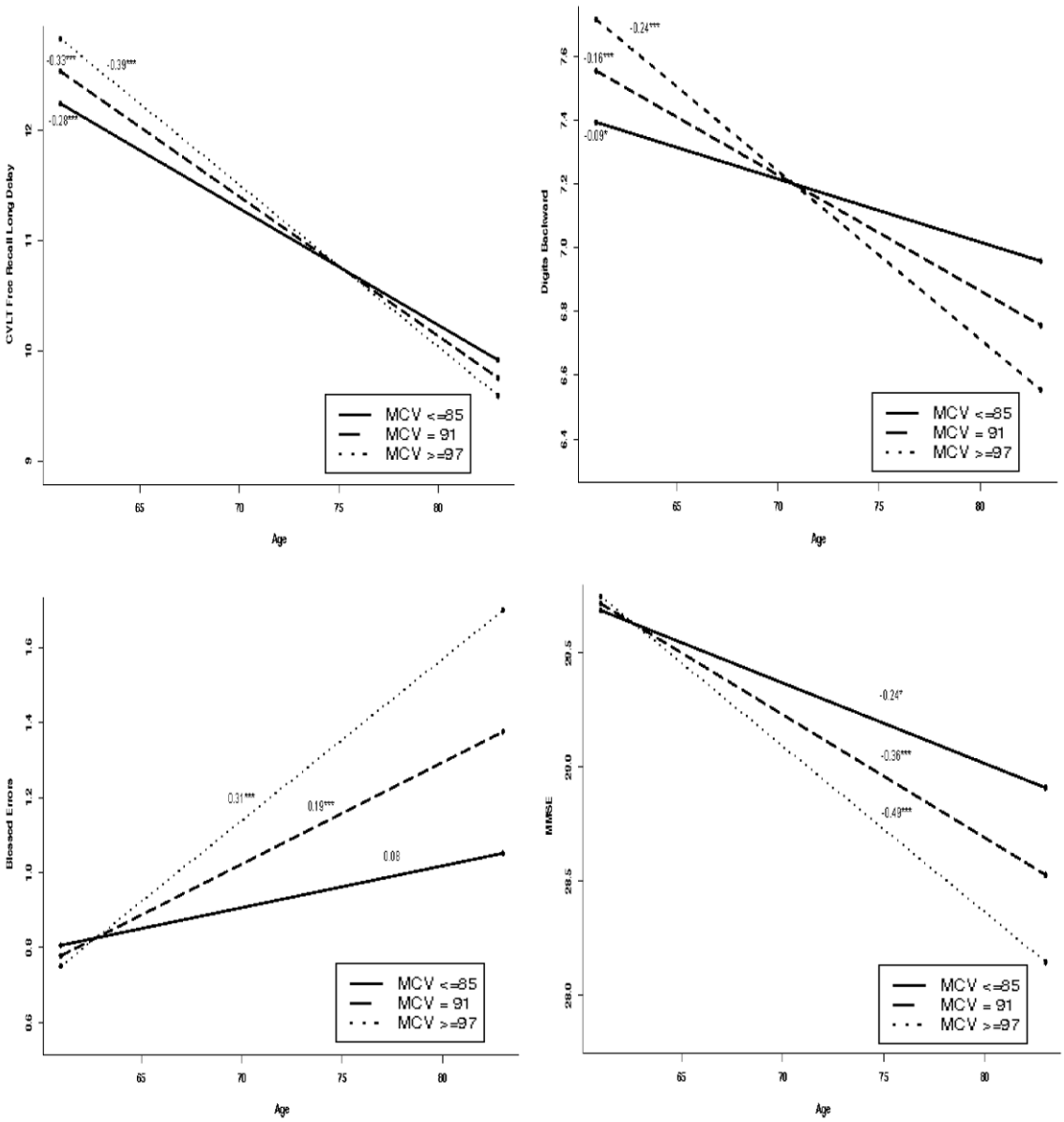

Figure 1.

Age-related changes in CVLT Free Recall Long Delay, Digits Backward, and Global Scales of Cognition as it relates to three MCV levels (i.e., MCV ≤ 85, MCV = 91, MCV ≥ 97).
Note: *p < .05. **p < .01. ***p < .001.

Table 1

Baseline demographic characteristics, blood parameters, and selected health indices (n = 827)

Characteristic	n (%)	Mean (SD)	Range
Age	-	67.00 (11.14)	50 - 96
Education, yrs	-	16.36 (2.47)	8 - 20
Sex, female	405 (49)	-	-
Non-Hispanic white	192 (23)	-	-
MCV	-	91.39 (4.83)	61 - 107
Hemoglobin	-	13.85 (1.39)	7 - 18
Albumin	-	3.87 (0.32)	3 - 6
Vitamin B12	-	521.59 (278.84)	108 - 2474
Erythrocyte sedimentation rate	-	14.18 (15.81)	0 - 128
Ferritin	-	97.62 (101.16)	4 - 898
Folate	-	15.47 (9.44)	3 - 95
Iron	-	82.61 (30.80)	10 - 246
White blood cell count	-	5.69 (1.60)	2 - 18
Cerebrovascular Disease	28 (3)	-	-
Stroke	42 (5)	-	-

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Table 2

Relationship between MCV and Cognitive Measures

	Model 1	Model 2	Model 3	Model 4	
Measures	**MCV**	**MCV**	**MCV**	**MCV**	**Age*MCV**
BVRT	-0.0101 (0.0151)	-0.0151 (0.0147)	-0.0210 (0.0164)	-0.1143 (0.0919)	0.0015 (0.0014)
CVLT-LA	0.0616 (0.0605)	0.0977 (0.0597)	0.1020 (0.0676)	0.4097 (0.3905)	-0.0049 (0.0061)
CVLT-SD	0.0111 (0.0153)	0.0242 (0.0149)	0.0207 (0.0172)	0.1254 (0.0994)	-0.0017 (0.0016)
CVLT-LD	0.0156 (0.0160)	0.0217 (0.0158)	0.0191 (0.0179)	0.2399 (0.1030)	-0.0035 * (0.0016)
Category	-0.0327 * (0.0139)	-0.0303 * (0.0135)	-0.0231 (0.0157)	0.0036 (0.1141)	-0.0004 (0.0017)
Letter	0.0144 (0.0143)	0.0111 (0.0144)	0.0045 (0.0171)	0.0179 (0.1243)	-0.0002 (0.0019)
BNT	-0.0054 (0.0172)	-0.0225 (0.0167)	-0.0369 (0.0203)	0.1415 (0.1483)	-0.0027 (0.0022)
Card Rotation	-0.0251 (0.1041)	-0.0691 (0.1035)	-0.0969 (0.1161)	0.1579 (0.7033)	-0.0041 (0.0112)
Trails A	0.0728 (0.0999)	0.0415 (0.0945)	-0.0244 (0.0970)	0.9254 (0.7150)	-0.0141 (0.0105)
Trails B	0.0947 (0.3773)	0.0569 (0.3564)	-0.1210 (0.3692)	1.3062 (2.7238)	-0.0213 (0.0403)
Digits Forward	-0.0050 (0.0095)	-0.0058 (0.0097)	-0.0126 (0.0110)	0.0964 (0.0627)	-0.0017 (0.0010)
Digits Backward	0.0052 (0.0095)	0.0026 (0.0096)	0.0023 (0.0109)	0.1776 ** (0.0619)	-0.0028 ** (0.0010)
Blessed	0.0075 (0.0095)	0.0217 * (0.0097)	0.0215 * (0.0100)	-0.1493 ** (0.0524)	0.0027 *** (0.0082)
MMSE	-0.0259 (0.0152)	-0.0377 * (0.0149)	-0.0402 * (0.0159)	0.1739 (0.1111)	-0.0032 † (0.0016)

Note:

† p = .05.

* p < .05.

** p < .01.

*** p < .001.

Table illustrates unstandardized estimates and (standard errors). Model 1 does not include confounding variables. Model 2 includes demographic variables (i.e., age, sex, and race), cvd, and stroke. Model 3 includes all confounders, including additional blood parameters (i.e., hemoglobin, albumin, folate, vitamin B12, ESR, ferritin, iron, and white blood cells). Model 4 includes all confounders. Model 4 Bonferonni multiple-comparison adjusted p = 0.003.