oped, we will be able to study the effect of this SNP on clinical and paraclinical in patients with this disorder.

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**Validation of Plasma Branched Chain Amino Acids as Biomarkers in Huntington Disease**

*While investigating body weight in a cohort of 32 patients at an early stage of Huntington disease (HD) and presymptomatic HD gene carriers, we found a significant decrease in the plasma branched-chain amino acids (BCAA) valine, leucine, and isoleucine in the HD group compared with 21 healthy controls. This systemic metabolic defect, which is indicative of hypercatabolism, was associated with early body weight loss in the HD group.¹ We wanted to (1) try to replicate our initial findings in a larger HD cohort, and (2) assess the feasibility of using plasma BCAA as a biomarker in HD, ie, in a less controlled research environment than the initial study.¹*

**Methods.** After approval by the institutional ethics committees (Institut National de la Santé et de la Recherche Médicale, Recherche Biomédicale 03-48), we measured fasting levels of plasma BCAA as previously described¹ in 16 presymptomatic HD gene carriers and 70 patients with HD at a mild, moderate, or severe stage of the disease who were seen consecutively at our outpatient clinic. Our control group consisted of 21 healthy individuals, previously described.¹ To evaluate the multivariate associations, the LASSO (Least Absolute Shrinkage and Selection Operator) model selection technique was used with the adjusted $^2$ statistic as the model selection criterion.

The number of CAG codons was forced into these models with the Unified Huntington Disease Rating Scale (UHDRS), age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), sex, and their 2-way interactions as possible covariates.

**Results.** Plasma valine, leucine, and isoleucine levels were significantly lower in the HD group compared with controls ($P < .02$, $< .001$, and $< .002$, respectively). In addition, we found a significant decrease of valine, leucine, and isoleucine in moderately affected patients and patients at a severe stage of the disease (Figure). Leucine...
was also significantly decreased in patients at a very mild stage of the disease and in presymptomatic individuals (Figure). Simple linear regression showed that plasma BCAA were not correlated with the UHDRS. However, we found that valine was negatively correlated with the number of CAG repeats (P = .01, adjusted r² = 0.086). After adjusting for BMI and sex, we confirmed that there was a negative association between valine and CAG repeats (P = .02, adjusted r² = 0.309). For every 1-unit increase in CAG, valine decreased by ~3.33. We also found a significant association between leucine and CAG repeats (P = .04, adjusted r² = 0.372), with an association dependent on BMI due to the interaction. For every 1-unit increase in CAG, leucine decreased by ~1.50 for the mean value of BMI (23.2).

Comment. We confirmed, in a larger cohort of patients with HD at different stages of the disease as well as presymptomatic HD gene carriers sampled consecutively, that plasma BCAA are relevant and accessible biomarkers in HD. After adjusting for BMI and sex, we showed an inverse correlation between the plasma levels of valine and leucine and number of CAG repeats, the primary determinant of HD severity. Of the 3 BCAA, leucine was of particular interest because it was significantly reduced in patients at an early stage of the disease and, more remarkably, in presymptomatic individuals. Leucine is a well-known activator of mTOR (mammalian target of rapamycin), which regulates protein synthesis and whose inhibition results in increased autophagic proteolysis. Akt, which has been shown to be altered in HD rat brain and in peripheral blood cells of patients with HD, also mediates the activity of mTOR. Therefore, reduced leucine levels and altered Akt activation in HD may both result in mTOR inhibition and exacerbation of proteolysis in HD. The significant correlation of BCAA with CAG repeats but not with UHDRS stages suggests that this biomarker is closely related to the primary defect in HD rather than to neuronal degeneration.

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Vascular Risk Scores for Dementia: Age Matters

Reitz et al1 presented published a summary risk score for prediction of Alzheimer disease (AD) in elderly individuals based on their vascular risk profiles. The risk score was developed using data from 1051 Medicare recipients aged 65 years and older who were followed up for an average period of 4 years. The risk score included the factors age, sex, education, ethnicity, APOE ε4 genotype, history of diabetes, hypertension, smoking, high-density lipoprotein levels, and waist to hip ratio. Based on the β coefficients of these factors, a weighted risk score was assigned to each factor and the dementia score was the sum of these scores. Using this approach, the risk of developing late-onset AD was 20 times higher for individuals with a summary score in the highest compared with the lowest quintile.

The role of vascular risk factors in the development of dementia is increasingly recognized. However, recent findings indicate that the relation between vascular risk factors and dementia strongly depends on the age at which risk factors are assessed. For example, while obesity and hypertension at midlife are associated with an increased risk of late-life dementia, the same risk factors are associated with a decreased risk when present at a very old age.5,6 This may be explained by a drop in blood pressure and weight loss in the years immediately preceding dementia onset.3,4 Previous studies by the coauthors of Reitz and colleagues’ article,1 have demonstrated a U-shaped relation between body weight and dementia risk.5,6 This relation was clearly dependent on age at the time of body weight assessment. The presented summary risk score included high waist to hip ratio as a predictor for dementia. In contrast, others included low body mass index as a risk factor in a dementia risk score designed for older populations.7 Because the summary risk score targets individuals in a rather wide age range, we would assume that its accuracy can be further improved by considering nonlinearity and the interaction with age for the relation between obesity and dementia risk in the model. This may also apply to other vascular risk factors such as hypertension. Practically, this could entail giving separate scores to high and low levels of vascular risk factors below and above a certain age.

We also noted that 37 of 61 points in the risk score were attributed to age, education, and ethnicity. This is consistent with the strong relation between these factors and dementia risk. However, these factors are not modifiable, and it would be interesting to know the accuracy of the risk score independent of these factors. The authors do report that the summary risk score still performs fairly well independent of education and ethnicity. We wonder what the performance of the model would be independent of age.

Risk scores such as the presented summary risk score may help to identify people at risk of dementia in the context of vascular factors at an early stage and allow for the development and efficient targeting of lifestyle and treatment interventions. We suggest that the interaction between vascular risk factors, age, and dementia should be considered in future risk scores.

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Improving Risk Scores for Dementia

Recently, Reitz and colleagues1 proposed a risk score for AD. Risk scores for AD are virtually nonexistent compared with the numerous etiological studies on individual risk factors for AD. We give 3 suggestions for improving the accuracy of the absolute risks assessed with the risk score.

First, more advanced methods could have been used to estimate absolute risks from the interval-censored data.2 To establish the diagnosis of dementia, follow-up data were collected at sequential visits with 18-month intervals. As a result, the time of onset of dementia was not exactly observed. The authors assumed that the onset occurred at the end of each interval. This approach can lead to inaccurate estimates of absolute risks.

Second, the presented absolute risks result from a logistic regression model rather than from the Cox model, ignoring the time to event character of the data. We disagree that regression coefficients from the Cox model are less practical for clinical use. In fact, the Cox model allows for risk estimates at different points in time, eg, 1-, 2- and 5- years risks.