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Ethnicity/culture modulates the relationships of the haptoglobin (Hp) 1-1 phenotype with cognitive function in older individuals with type 2 diabetes

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Abstract

Objective—The haptoglobin (Hp) genotype has been associated with cognitive function in type 2 diabetes. Because ethnicity/culture has been associated with both cognitive function and Hp genotype frequencies, we examined whether it modulates the association of Hp with cognitive function.

Methods—This cross-sectional study evaluated 787 cognitively normal older individuals (>65 years of age) with type 2 diabetes participating in the Israel Diabetes and Cognitive Decline study. Interactions in two-way analyses of covariance compared Group (Non-Ashkenazi *versus* Ashkenazi Jews) on the associations of Hp phenotype (Hp 1-1 *versus* non- Hp 1-1) with five cognitive outcome measures. The primary control variables were age, gender, and education.

Results—Compared with Ashkenazi Jews, non-Ashkenazi Jews with the Hp 1-1 phenotype had significantly poorer cognitive function than non-Hp 1-1 in the domains of Attention/Working Memory (p=0.035) and Executive Function (p=0.023), but not in Language/Semantic Categorization (p=0.432), Episodic Memory (p=0.268), or Overall Cognition (p=0.082). After controlling for additional covariates (type 2 diabetes-related characteristics, cardiovascular risk

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Conflict of interest

Dr. Andrew Levy is employed by the Technion Israel Institute of Technology, which owns patents that claim that the Haptoglobin genotype can predict diabetic complications.

factors, Mini-mental State Examination, and extent of depressive symptoms), Attention/Working Memory (p=0.038) and Executive Function (p=0.013) remained significant.

Conclusions—Older individuals from specific ethnic/cultural backgrounds with the Hp 1-1 phenotype may benefit more from treatment targeted at decreasing or halting the detrimental effects of Hp 1-1 on the brain. Future studies should examine differential associations of Hp 1-1 and cognitive impairment, especially for groups with high prevalence of both, such as African–Americans and Hispanics.

Keywords

cognitive function; cognitive domains; diabetes; haptoglobin; ethnicity/culture; older adults

Introduction

Older individuals with type 2 diabetes tend to perform more poorly on some neuropsychological tests, especially those assessing the domains of attention, executive function, and psychomotor speed, compared with controls (Nandipati *et al.,* 2012). Cognitive deficits in type 2 diabetes have been associated with brain abnormalities such as white matter lesions, lacunar infarcts, and cortical atrophy (van Harten 2006b; Nelson *et al.,* 2009); they may also be indicators of further decline and dementia. Indeed, there is increased risk for dementia (Luchsinger, 2001; Schnaider Beeri *et al.,* 2004) in patients with type 2 diabetes, and those carrying the apolipoprotein E-epsilon 4 allele may have even higher risk (Peila *et al.,* 2002). The latter suggests that genetic factors may be contributing to this association.

In type 2 diabetes, the haptoglobin (Hp) gene has received much attention. Hp produces a hemoglobin binding protein that prevents oxidative tissue damage (Langlois and Delanghe, 1996). It has been linked to lacunar stroke (Staals, 2008) and dementia (Mattila, 1994), in the general population and to cardiovascular disease in type 2 diabetes (Levy, 2004). However, there is scarcity of research examining the association of Hp with cognitive function, and only one study in type 2 diabetes—we recently reported that Israeli older individuals with type 2 diabetes with the Hp 1-1 phenotype had poorer performance on several cognitive domains compared with non-Hp 1-1 phenotype participants (Ravona-Springer, 2013).

Moreover, despite evidence showing ethnic/cultural discrepancy in normal cognitive function (Byrd, 2004), as well as ethnic/cultural differences in Hp distribution (Goldschmidt, 1962; Langlois and Delanghe, 1996), to our knowledge, there is no investigation on the potential impact that ethnicity/culture may have on the association of Hp with cognition in type 2 diabetes. Thus, in this cross-sectional study, we sought to examine whether prior findings on the association of Hp 1-1 with cognition in Israeli older individuals with type 2 diabetes (Ravona-Springer, 2013) differed by ethnicity/culture, that is, by being from Non-Ashkenazi *versus* Ashkenazi descent. Non-Ashkenazi Jews are descended groups from the Middle East and North Africa, in contrast to Ashkenazi descendants of those from Central and Eastern Europe (Kwon, 1999). These two groups differ not only by ethnic and socio-cultural characteristics but also by genetic, disease frequency, and disease complications

(Wolak, 2007; Feder *et al.,* 2008). This study builds on the Israel Diabetes and Cognitive Decline (IDCD) study, an investigation of the effects of long-term type 2 diabetes-related characteristics on cognitive decline in initially non-demented older individuals with type 2 diabetes.

Methods

Participants

The IDCD study design has been previously described in detail (Beeri, 2014). Briefly, the IDCD recruited community-dwelling older individuals with type 2 diabetes (65+ years old) living in central Israel, from approximately 11,000 clients enrolled in the diabetes registry of the Maccabi Healthcare Services (MHS). MHS is the second largest health maintenance organization, treating a representative cross section of two million citizens. The MHS diabetes registry was established in 1998 to facilitate diabetes management and to improve treatment. Any of the following criteria is sufficient for enrollment into the registry: (1) hemoglobin A1c (HbA1c) >7.25%; (2) glucose >200 mg/dL on two exams more than 3 months apart; (3) purchase of diabetic medication twice within 3 months supported by an HbA1c >6.5% or glucose >125 mg/dL within half a year; (4) diagnosis of type 2 diabetes (ICD9 code) by a general practitioner, internist, endocrinologist, ophthalmologist, or type 2 diabetes advisor, supported by an HbA1c >6.5% or glucose >125 mg/dL within half a year. These criteria have been validated by 20 physicians in MHS against their own practice record (Heymann *et al.*, 2006). IDCD inclusion criteria were having type 2 diabetes, normal cognition at entry, being free of any neurological (e.g., Parkinson's disease and stroke), psychiatric (e.g., schizophrenia), or other diseases (e.g., alcohol or drug abuse) that might affect cognition, and having an informant. Participants were assessed by a physician experienced in assessment and diagnosis of dementia and by a neuropsychologist, who administered the broad neuropsychological battery.

The electronic medical records of potential participants were screened by the MHS team for diagnosis of dementia, and its subtypes, and for cholinesterase inhibitors. Then, MHS personnel asked potential participants, on the phone, whether a doctor had ever told them that they have a memory problem, or if they had ever been treated for a memory problem. Those who responded positively were excluded from the study, and those who passed this screen were then assessed for dementia by the study physicians, and were administered the Clinical Dementia Rating (CDR) scale (Hughes, 1982), described in the succeeding text. Those with a CDR >0 (reflecting questionable or increasing levels of dementia severity) were excluded from the IDCD study and referred back to their primary physician. It is important to note that the neuropsychological battery was not used in the process of screening for normal cognition because it was used to calculate the cognitive outcome measures. For descriptive purposes, global assessment of cognitive function was assessed with the Mini-mental State Examination (MMSE) (Folstein, 1975). All participants were discussed by a diagnostic consensus conference that included neurologists, psychiatrists, and neuropsychologists experienced with dementia, with at least two specialties present.

The CDR scale assesses the severity of cognitive and functional impairment in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies,

and personal care) through an interview with the participant and an informant. A score of 0 represents normal cognition (an inclusion criterion for the IDCD study), 0.5 represents questionable dementia, and scores of 1 through 3 reflect increasing severity of dementia (Hughes, 1982; Fillenbaum, 1996). The MMSE, which assesses various areas of cognitive functions (orientation, concentration, memory, language, and visual construction), is widely used as a cognitive screening instrument for dementia.

Analyses include prospective historical diabetes-related data from the Maccabi Health Services and the baseline cognitive data collected by the IDCD study.

The sample for this study consisted of 787 IDCD participants (80 with the Hp 1-1 phenotype and 707 with the non-Hp 1-1 phenotype) with normal cognitive function as described previously. All participants had complete data on Hp genotyping, cognitive domains, demographic characteristics (age, gender, education, and ethnic/cultural background, that is, non-Ashkenazi and Ashkenazi Jews), type 2 diabetes-related characteristics (HbA1c, number of follow-up years in the registry, and a surrogate for duration of disease (West *et al.,* 2015.) and whether medication for type 2 diabetes was taken: no medication, hypoglycemic medication, and insulin or insulin + hypoglyceemic medication), and cardiovascular risk factors (BMI, creatinine, total cholesterol, triglycerides, and diastolic and systolic blood pressure).

Table 1 describes the region of origin for the participants. They were referred to as non-Ashkenazi (n = 343) or Ashkenazi (n = 444) Jews based on their reported birth region and country; this information was also confirmed by an informant.

The study was approved by the Icahn School of Medicine at Mount Sinai, Sheba Medical Center, and MHS IRB committees.

Cognitive function/outcomes

Cognitive function at entry was assessed using 12 neuropsychological tests, grouped into cognitive domains according to the factor with the highest loading: Episodic Memory: Word List Memory, Word List Recall, and Word List Recognition from the Consortium to Establish a Registry for Alzheimer's disease (CERAD) neuropsychological battery (Welsh *et al.,* 1994; Beeri *et al.,* 2006); Attention/Working Memory: Shape Cancellation and Digit Span (forward and backward) from the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987); Language/Semantic Categorization: Similarities (Godeau *et al.,* 1981), Letter Fluency (Spreen and Spreen and Benton, 1977), and Animal Fluency (Newcombe, 1969); and Executive Function: Trail Making Test (A and B) (Reitan, 1958), CERAD-Constructional Praxis, and Digit Symbol from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Godeau *et al.,* 1981). Raw scores were converted to z scores using participants' means and SDs. A composite measure of global cognitive function (Overall Cognition) was created by averaging all the z scores. Scores for the four cognitive domains were calculated as averages of z scores.

Statistical analyses

Two-way analyses of covariance (ANCOVAs) were performed in order to compare group (non-Ashkenazi *versus* Ashkenazi Jews) and Hp phenotype (Hp 1-1 *versus* non-Hp 1-1 phenotype) differences on the outcome measures, the four cognitive domains and Overall Cognition. These analyses evaluated the interaction of Hp phenotype with Group (i.e., Were the differences in the outcome measures for the two Hp phenotypes discrepant between non-Ashkenazi and Ashkenazi participants?). The primary control variables were age, gender, and education. Results with $p < .05$ were considered significant.

Results

Differences in demographic and clinical characteristics by Hp phenotype were assessed for non-Ashkenazi and Ashkenazi Jews (Table 2). Non-Ashkenazi Jews with the Hp 1-1 phenotype had significantly lower MMSE scores than non-Ashkenazi Jews with the non-Hp 1-1 phenotype. Table 2 (last column) also presents overall ethnicity/culture Group differences: Non-Ashkenazi Jews were younger and less educated than Ashkenazi Jews and had lower MMSE scores. Similarly to previously reported results (Goldschmidt, 1962), the proportion of the Hp 1-1 phenotype did not differ substantially between non-Ashkenazi (11.4%) and Ashkenazi Jews (9.2%).

As shown in Table 3, the two-way ANCOVAs, which compared non-Ashkenazi and Ashkenazi Jews, showed significant Group effects, after controlling for demographic variables, for three of the cognitive outcomes, with non-Ashkenazi performing more poorly than Ashkenazi Jews in Attention/Working Memory ($p < 0.001$), Executive Function ($p < 0.001$), and Overall Cognition ($p < 0.001$) with Language/Semantic Categorization ($p = 0.056$) approaching significance, but not Episodic Memory ($p = 0.827$). However, there were not significant main effects for Hp phenotype. There were significant Group× Hp phenotype interaction effects for two of the outcome measures, Attention/Working Memory ($p = 0.035$), and Executive Function ($p = 0.023$), with Overall Cognition approaching significance ($p = 0.082$); Episodic Memory ($p = 0.268$) and Language/Semantic Categorization ($p = 0.432$) were not significant. The interactions showed that the extent to which Hp 1-1 phenotype participants performed more poorly on the outcome measures than non-Hp 1-1 phenotype participants depended on the ethnic/cultural background of the participants. Specifically, the discrepancy in cognitive performance between the two phenotypes was significant only in non-Ashkenazi Jews.

Table 4 shows that in non-Ashkenazi Jews, performance in the Hp 1-1 phenotype was significantly poorer than that in the non-Hp 1-1 phenotype in Attention/Working Memory ($p = 0.032$) and Overall Cognition ($p = 0.026$), with Executive Function approaching significance ($p = 0.059$). In contrast, in Ashkenazi Jews, the differences in performance between the phenotypes were not significant.

In supplementary analyses, in addition to controlling for demographics, we also controlled for variables that can be potential confounders because they have been associated with cognitive function (Wilson, 2002; Ravona-Springer, 2013) and may account for some of the variance in cognition: type 2 diabetes-related characteristics, cardiovascular risk factors, and

MMSE (described in the research design and Section on Methods). We also controlled for extent of depressive symptoms (associated with both type 2 diabetes and cognition), as measured by the 15-item Geriatric Depression Scale (Sheikh and Yesavage, 1986). After taking into account all these covariates in the analyses, results were generally similar to those from the main analyses. There were significant Group effects for Attention/Working Memory [$F(1, 767)=16.023$, $p<0.001$] and Executive Function [$F(1, 767)=27.773$, $p<0.001$]. However, in contrast to Table 3 result, the Group effect for Overall Cognition only approached significance [$F(1, 767)= 3.395$, $p = 0.066$]. Similar to Table 3 results, there were also significant Group× Hp phenotype interaction effects for Attention/Working Memory [$F(1, 767)=4.309$, $p =0.038$] and Executive Function [$F(1, 767)=6.195$, $p = 0.013$].

Discussion

To our knowledge, this study represents the first examining of the modulating effects of ethnicity/culture on the relationship of Hp phenotype with cognitive function. This study extends our previous findings (Ravona-Springer, 2013) by showing that the poor performance observed in Hp 1-1 phenotype participants with diabetes is modified by ethnicity/culture, after controlling for demographics. Compared with Ashkenazi Jews, whose performance on the cognitive outcomes was not significantly affected by Hp phenotype status, non-Ashkenazi Jews with the Hp 1-1 had significantly poorer cognitive function than non-Ashkenazi Jews with the non-Hp 1-1 phenotype in the domains of Attention/Working Memory and Executive Function.

One explanation for these results is the possibility that non-Ashkenazi Jews have poorer management of type 2 diabetes than Ashkenazi older individuals. Ashkenazi Jews have been reported to have genetic factors that are protective against type 2 diabetes complications (Feder *et al.*, 2008). Poorer cognitive function is another complication of type 2 diabetes, which may be less impacted in Ashkenazi Jews, as reflected in our results. In this vein, when we also controlled for diabetes-related characteristics such as HbA1c, results remained essentially unchanged.

The interaction effects between ethnicity/culture and Hp suggest that Hp 1-1 may be one possible biological mechanism explaining the susceptibility of specific conditions (impaired cognition) in some ethnic groups, but not others. Although other investigators have found that having a particular Hp phenotype is associated with specific disease outcomes (Langlois and Delanghe, 1996), the potential modulating effects of ethnicity remain to be investigated. Similarly, Jewish populations differ in prevalence of diseases and in the involvement of genetic factors associated with disease complications (Wolak, 2007; Feder *et al.*, 2008). For instance, Beeri and colleagues reported on the higher risk of dementia in non-Ashkenazi Jews compared with Ashkenazi Jews (Beeri, 2008), but it is unknown whether this heightened risk is affected by Hp phenotype. Thus, our findings should encourage investigations to examine whether differential prevalence of dementia, in different ethnicities/cultures, is affected by Hp phenotype.

It is noteworthy that Episodic Memory [the primary cognitive function affected by Alzheimer's disease (AD)] was not affected by the interaction effects of Group and Hp, thus

suggesting possible involvement of non-AD-type pathology, such as cerebrovascular-related pathology. Cerebrovascular disease pathology such as cerebral small vessel disease (van Harten, 2006a; Nelson, 2009) is consistently associated with both type 2 diabetes and increased risk of dementia. Cerebral small vessel disease may be a mechanism through which Hp 1-1 exerts its deleterious effects on the brain. Compared with other phenotypes, Hp 1-1 has poorer angiogenic effects (Langlois and Delanghe, 1996), which could explain susceptibility to vascular disease. Hp 1-1 has deleterious effects on endothelial progenitor cells, compromising endothelial repair and affecting proper functioning of the endothelium (Rouhl *et al.*, 2009; Rouhl *et al.*, 2012). Endothelial dysfunction leads to a deficiency in forming of new blood vessels and functioning of the blood brain barrier and is one of the first steps in the progression of cerebral small vessel disease (e.g., lacunar infarcts and white matter lesions). The latter has a negative impact on cognitive functioning, and in particular, attention/working memory domains (e.g., working memory and processing speed) (O'Brien, 2002; Viana-Baptista, 2008; Eilaghi, 2013), the cognitive domain with significant interaction effect in our study.

This study had several limitations, including its cross-sectional design. Longitudinal studies are needed to examine whether ethnicity/culture modulates the relationship of Hp phenotype with cognitive decline and incident dementia. The lack of a control group without type 2 diabetes prevents the generalizability of these findings to all the older population. Of note, however, Hp phenotype effects are found primarily in individuals with diabetes and less so in those without diabetes (Levy, 2002; Levy, 2004). Neuroimaging data were not available, thus, impeding examination of potential contribution of cerebral small vessel disease to Hp 1-1 effects on cognition. To the extent that cerebrovascular disease may be a biological mechanism linking the associations found in this study, excluding participants with stroke (an eligibility criterion in the IDCD study), could have diminished the significance of our results. Although we controlled for demographic variables, it is important to note that, as a whole, non-Ashkenazi Jews were, on average, significantly younger than Ashkenazi Jews (71.1 *versus* 72.5, respectively) and with fewer years of formal education (12.0 *vs.* 14.1, respectively). Future studies of Hp phenotype can be aimed at examining potential confounders such as quantity and quality of education, socioeconomic status, and diet, which may help explain the association of ethnicity/culture with cognitive performance. In this context, even after matching groups on important demographic characteristics, group differences in test performance, favoring advantaged groups, have been reported (Jacobs, 1997). It is important to note that although participants in this study resided in Israel for at least 40years and spoke He-brew fluently, the extent to which prior language experience influenced cognitive performance is unknown (Boone, 2007). Moreover, the non-Ashkenazi Jews were mainly from three different regions, so the extent to which our results can be generalized to specific non-Ashkenazi subgroups remains unknown. Because of the small sample size of Hp 1-1, we did not perform additional stratifications such as region of origin.

Strength of this study included a well-characterized diagnosis of type 2 diabetes, a plethora of potential confounders, and a comprehensive neuropsychological battery, which elucidated Attention/Working Memory and Executive Function as important cognitive domains in the context of the relationships of Hp with ethnicity/culture.

Studies in the USA have consistently reported that compared with White people, minority older individuals perform more poorly in neuropsychological tests (Stricks *et al.*, 1998; Byrd, 2004), have higher prevalence of both type 2 diabetes (Harris, 2011) and dementia, including AD (Gurland *et al.*, 1999; Tang *et al.*, 2001), and have poorer glycemic control (Suh, 2010). In non-Jewish populations, the distribution of Hp differs by ethnicity: The Hp 1-1 phenotype is more frequent in Africans and Hispanics than White people, thus suggesting that it may be a potential risk factor for type 2 diabetes complications, including compromised cognitive function and dementia, in these ethnic groups. Thus, future studies should examine the association of Hp with cognition in minority older groups with type 2 diabetes. To the extent that effective clinical interventions become available, because there is high prevalence of diabetes, Hp 1-1, and cognitive impairment in the minority population (Langlois and Delanghe, 1996; Gurland *et al.*, 1999; Harris, 2011), treatment targeted at decreasing or halting the detrimental effects of Hp 1-1 on the brain may be of particular benefit to individuals from this ethnic/cultural group.

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References

Beeri MS. Religious education and midlife observance are associated with dementia three decades later in Israeli men. J Clin Epidemiol. 2008; 61:1161–1168. [PubMed: 18538995]

Beeri MS. The Israel Diabetes and Cognitive Decline (IDCD) study: Design and baseline characteristics. Alzheimers Dement. 2014; 10:769–778. [PubMed: 25150735]

Beeri MS, Schmeidler J, Sano M, et al. Age, gender, and education norms on the CERAD neuropsychological battery in the oldest old. Neurology. 2006; 67:1006–1010. [PubMed: 17000969]

Boone KB. The association between neuropsychological scores and ethnicity, language, and acculturation variables in a large patient population. Arch Clin Neuropsychol. 2007; 22:355–365. [PubMed: 17320344]

Byrd DA. Cancellation test performance in African American, Hispanic, and White elderly. J Int Neuropsychol Soc. 2004; 10:401–411. [PubMed: 15147598]

Eilaghi A. Normal-Appearing White Matter Permeability Distinguishes Poor Cognitive Performance in Processing Speed and Working Memory. American journal of neuroradiology: AJNR. 2013

Feder J, Blech I, Ovadia O, et al. Differences in mtDNA haplogroup distribution among 3 Jewish populations alter susceptibility to T2DM complications. BMC Genomics. 2008; 9:198. [PubMed: 18445251]

Fillenbaum GG. Estimating the validity of the clinical Dementia Rating Scale: the CERAD experience. Consortium to Establish a Registry for Alzheimer's Disease. Aging (Milan, Italy). 1996; 8:379–385.

Folstein MF. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

Godeau P, Frances-Michel C, Wechsler J, et al. Immunofluorescence study of skin biopsies of healthy skin in bacterial endocarditis. La Revue de medecine interne/fondee … par la Societe nationale francaise de medecine interne. 1981; 2:29–32.

Goldschmidt E. Haptoglobin frequencies in Jewish communities. Ann Hum Genet. 1962; 26:39–46. [PubMed: 13899848]

Gurland BJ, Wilder DE, Lantigua R, et al. Rates of dementia in three ethnoracial groups. Int J Geriatr Psychiatry. 1999; 14:481–493. [PubMed: 10398359]

Harris SS. Does vitamin D deficiency contribute to increased rates of cardiovascular disease and type 2 diabetes in African Americans? Am J Clin Nutr. 2011; 93:1175S–1178S. [PubMed: 21367947]

van Harten B. Brain imaging in patients with diabetes: a systematic review. Diabetes Care. 2006a; 29:2539–2548. [PubMed: 17065699]

van Harten B. Brain imaging in patients with diabetes: a systematic review. Diabetes Care. 2006b; 29:2539–2548. [PubMed: 17065699]

Heymann AD, Chodick G, Halkin H, et al. The implementation of managed care for diabetes using medical informatics in a large Preferred Provider Organization. Diabetes Res Clin Pract. 2006; 71:290–298. [PubMed: 16112245]

Hughes CP. A new clinical scale for the staging of dementia. British Journal of Psychiatry. 1982; 140:566–572. [PubMed: 7104545]

Jacobs DM. Cross-cultural neuropsychological assessment: a comparison of randomly selected, demographically matched cohorts of English- and Spanish-speaking older adults. J Clin Exp Neuropsychol. 1997; 19:331–339. [PubMed: 9268808]

Kwon OJ. HLA class II susceptibility to multiple sclerosis among Ashkenazi and non-Ashkenazi Jews. Archives of Neurology (Chicago). 1999; 56:555–560. [PubMed: 10328250]

Langlois MR, Delanghe JR. Biological and clinical significance of haptoglobin polymorphism in humans. Clin Chem. 1996; 42:1589–1600. [PubMed: 8855140]

Levy AP. Haptoglobin phenotype is an independent risk factor for cardiovascular disease in individuals with diabetes: The Strong Heart Study. J Am Coll Cardiol. 2002; 40:1984–1990. [PubMed: 12475459]

Levy AP. Haptoglobin: A major susceptibility gene for diabetic cardiovascular disease. Isr Med Assoc J. 2004; 6:308–310. [PubMed: 15151377]

Luchsinger JA. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. Am J Epidemiol. 2001; 154:635–641. [PubMed: 11581097]

Mattila KM. Altered blood-brain-barrier function in Alzheimer's disease? Acta Neurol Scand. 1994; 89:192–198. [PubMed: 8030400]

Nandipati S, Luo X, Schimming C, Grossman HT, Sano M. Cognition in non-demented diabetic older adults. Curr Aging Sci. 2012; 5:131–135. [PubMed: 22023096]

Nelson PT. Human cerebral neuropathology of Type 2 diabetes mellitus. Biochimica et biophysica acta Molecular Basis Of Disease. 2009; 1792:454–469.

Nelson PT, Smith CD, Abner EA, et al. Human cerebral neuropathology of Type 2 diabetes mellitus. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2009; 1792:454–469. [PubMed: 18789386]

Newcombe, F. Missile wounds of the brain: a study of psychological deficits. Oxford University Press; Oxford: 1969.

O'Brien JT. Cognitive associations of subcortical white matter lesions in older people. Ann N Y Acad Sci. 2002; 977:436–444. [PubMed: 12480784]

Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes. 2002; 51:1256–1262. [PubMed: 11916953]

Ravona-Springer R. Haptoglobin 1-1 genotype is associated with poorer cognitive functioning in the elderly with type 2 diabetes. Diabetes Care. 2013; 36:3139–3145. [PubMed: 23990521]

Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills. 1958; 8:271–276.

Rouhl RPW, Van Oostenbrugge RJ, Damoiseaux JGMC, et al. Haptoglobin phenotype may alter endothelial progenitor cell cluster formation in cerebral small vessel disease. Curr Neurovasc Res. 2009; 6:32–41. [PubMed: 19355924]

Rouhl RPW, Mertens AECS, Van Oostenbrugge RJ, et al. Angiogenic T-cells and putative endothelial progenitor cells in hypertension-related cerebral small vessel disease. Stroke. 2012; 43:256–258. [PubMed: 21980212]

Schnaider Beeri M, Goldbourt U, Silverman JM, et al. Diabetes mellitus in mid-life and the risk of dementia three decades later. Neurology. 2004; 63:1902–1907. [PubMed: 15557509]

Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. Clin Gerontol. 1986; 5:165–172.

Spreen, O., Benton, AL. Neurosensory center comprehensive examination for aphasia (NCCEA), 1977 revision: manual of instructions. Neuropsychology Laboratory, University of Victoria; Victoria, B.C: 1977.

Staals J. Haptoglobin polymorphism and lacunar stroke. Curr Neurovasc Res. 2008; 5:153–158. [PubMed: 18691072]

Stricks L, Pittman J, Jacobs DM, Sano M, Stern Y. Normative data for a brief neuropsychological battery administered to English- and Spanish-speaking community-dwelling elders. Journal of the International Neuropsychological Society: JINS. 1998; 4:311–318. [PubMed: 9656604]

Suh DC. Impact of comorbid conditions and race/ethnicity on glycemic control among the US population with type 2 diabetes, 1988–1994 to 1999–2004. J Diabetes Complications. 2010; 24:382–391. [PubMed: 19716320]

Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. Neurology. 2001; 56:49–56. [PubMed: 11148235]

Viana-Baptista M. Cognitive function correlates with frontal white matter apparent diffusion coefficients in patients with leukoaraiosis. J Neurol. 2008; 255:360–366. [PubMed: 18338199]

Wechsler, D. Wechsler Memory Scale-Revised Manual. San Antonio Psychological Corporation; San Antonio, TX, USA: 1987.

Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology. 1994; 44:609–614. [PubMed: 8164812]

West RK, Ravona-Springer R, Schmeidler J, et al. The Association of Duration of Type 2 Diabetes with Cognitive Performance is Modulated by Long-Term Glycemic Control. Am J Geriatr Psychiatry. 2015; 22(10):1055–1059.

Wilson RS. Depressive symptoms, cognitive decline, and risk of AD in older persons. Neurology. 2002; 59:364–370. [PubMed: 12177369]

Wolak T. Target organ damage in hypertensive patients of different ethnic groups. Int J Cardiol. 2007; 116:219–224. [PubMed: 16824630]

Key points

- In older Israelis with type 2 diabetes, the association of the haptoglobin 1-1 phenotype with poorer cognitive function differed according to the ethnic/cultural background.
- Our results emphasize the relevance of investigating the contribution of differences in ethnicity/culture to the relationship of risk factors with poor cognitive function.

Table 1

Region of origin by Hp phenotype for non-Ashkenazi and Ashkenazi participants

	Non-Ashkenazi				Ashkenazi			
	Hp 1-1		Non-Hp 1-1		Hp 1-1		Non-Hp 1-1	
Region of origin	***n* = 39**	**%**	***n* = 304**	**%**	***n* = 41**	**%**	***n* = 403**	**%**
Israel	1	2.6	6	2.0	1	2.4	13	3.2
Northern Africa	8	20.5	81	26.6	—	—	—	—
Southern Africa	—	—	—	—	1	2.4	3	0.7
Eastern Africa	—	—	—	—	—	—	2	0.5
Middle East	17	43.6	114	37.5	—	—	—	—
Eastern Europe	10	25.6	93	30.6	33	80.5	343	85.1
Western Europe	—	—	—	—	2	4.9	24	6.0
Asia	2	5.1	9	3.0	—	—	1	0.2
North America	—	—	—	—	1	2.4	5	1.2
South America	1	2.6	1	0.3	2	4.9	11	2.7
Caribbean	—	—	—	—	—	—	1	0.2
Other	—	—	—	—	1	2.4	—	—

Hp, haptoglobin.

Table 2

Mean (*SD*) of demographic and clinical characteristics by Hp phenotype for non-Ashkenazi and Ashkenazi Jews

	Non-Ashkenazi			Ashkenazi			Non-Ashkenazi *versus* Ashkenazi *p*-value*
	Hp 1-1	Non-Hp 1-1	*p*-value*	Hp 1-1	Non-Hp 1-1	*p*-value*	
N	39	304	—	41	403	—	—
Age	72.0 (4.6)	71.0 (4.2)	0.173	73.8 (5.3)	72.4 (4.8)	0.081	<**0.001**
Education	11.6 (3.2)	12.0 (3.0)	0.429	13.8 (3.9)	14.1 (3.3)	0.519	<**0.001**
Male (%)	9.3	90.7	0.128	9.4	90.6	0.908	0.520
Number of follow-up years in the registry	10.4 (2.2)	10.4 (1.4)	0.851	10.6 (0.9)	10.5 (1.3)	0.543	0.493
Body mass index (kg/m^2)	28.3 (5.0)	28.3 (4.0)	0.929	28.3 (4.2)	28.5 (4.7)	0.803	0.472
Creatinine (mg/dL)	0.9 (0.1)	1.0 (0.2)	0.061	1.0 (0.2)	1.0 (0.3)	0.913	0.059
Total cholesterol (mg/dL)	186.4 (24.8)	181.2 (25.3)	0.221	179.0 (18.1)	180.0 (25.4)	0.808	0.302
Triglycerides (mg/dL)	141.4 (62.7)	162.7 (71.4)	0.076	161.2 (52.0)	154.8 (58.9)	0.506	0.288
Diastolic BP (mmHg)	76.9 (4.9)	76.7 (4.9)	0.796	78.0 (5.6)	76.8 (4.7)	0.144	0.516
Systolic BP (mmHg)	135.8 (8.8)	135.0 (10.0)	0.629	136.0 (9.3)	134.6 (9.0)	0.329	0.542
Hemoglobin A1c (%), (mmol/mol)	6.8 (1.00)	6.8 (0.9)	0.988	6.7 (0.7)	6.7 (0.7)	0.597	0.090
	50.8	50.8		49.7	49.7		
Type 2 diabetes medication (%)							
No medication	17.1 (*n* = 7)	82.9 (*n* = 34)	0.145	8.9 (*n* = 5)	91.1 (n = 51)	0.995	0.917
Hypoglycemic medication	9.6 (*n* = 26)	90.4 (*n* = 244)		9.3 (*n* = 32)	90.7 (*n* = 312)		
Insulin or Insulin + hypoglycemic medication	18.8 (*n* = 6)	81.2 (*n* = 26)		9.1 (*n* = 4)	90.9 (40)		
GDS[a]	1.9 (2.0)	2.3 (2.5)	0.331	2.2 (1.9)	2.1 (2.2)	0.843	0.306
MMSE score[a]	27.1 (2.0)	27.7 (1.7)	**0.039**	27.9 (2.0)	28.4 (1.7)	0.141	<**0.001**

Hp, haptoglobin; BP, blood pressure; GDS, Geriatric Depression Scale; MMSE, Mini-mental State Examination; SD, standard deviation.

[a] $n = 402$.

* *p*-value by student's *t*-test or Pearson's chi-square for percentages.

Bold items shows significant results.

Table 3

Associations of Group with cognition, Hp with cognition, and interactions of Group and Hp on cognition

	Main effect of group[a]		Main effect of Hp[a]		Group × Hp interaction[a]	
Cognitive domain	***F* (*d.f.* = 1, 780)**	***p*-value**	***F* (*d.f.* = 1, 780)**	***p*-value**	***F* (*d.f.* = 1, 780)**	***p*-value**
Episodic Memory	0.048	0.827	0.883	0.348	1.231	0.268
Language/Semantic Categorization	3.656	0.056	3.314	0.069	0.618	0.432
Attention/Working Memory	23.363	<**0.001**	1.541	0.215	4.461	**0.035**
Executive Function	34.347	<**0.001**	0.810	0.368	5.180	**0.023**
Overall Cognition	22.197	<**0.001**	2.927	0.087	3.033	0.082

Hp, haptoglobin; *d.f.*, degrees of freedom.

[a]Controlling for age, gender, and education.

Bold items shows significant results.

Table 4

Means and standard error of the mean (SEM) of *Z* scores of cognitive performance in non-Ashkenazi and Ashkenazi Jews by Hp phenotype

	Non-Ashkenazi				Ashkenazi			
Cognitive domain	**Hp 1-1**	**Non-Hp 1-1**	***F* (*d.f.* = 1, 338)**	***p*-value**	**Hp 1-1**	**Non-Hp 1-1**	***F* (*d.f.* = 1, 439)**	***p*-value**
n	39	304	—		41	403	—	
Episodic Memory	−0.395 (0.328)	0.123 (0.125)	2.207	0.138	0.133 (0.336)	0.073 (0.107)	0.029	0.864
Language/Semantic Categorization	−0.751 (0.318)	−0.492 (0.113)	0.588	0.444	−0.069 (0.333)	0.567 (0.106)	3.298	0.070
Attention/Working Memory	−1.223 (0.325)	−0.480 (0.116)	4.612	**0.032**	0.677 (0.299)	0.472 (0.095)	0.425	0.515
Executive Function	−1.714 (0.455)	−0.796 (0.162)	3.599	0.059	1.155 (0.352)	0.760 (0.112)	1.146	0.285
Overall Cognition	−4.083 (1.027)	−1.645 (0.366)	4.988	**0.026**	1.897 (0.918)	1.871 (0.292)	0.001	0.979

Hp, haptoglobin; *d.f.*, degrees of freedom.

Note: Controlling for age, gender, and education.