As described by Caro and Hershey in this issue (p. 197), it is well established that children and adolescents with type 1 diabetes have small but significant cognitive impairments relative to control subjects, with greater impairment in those with certain diabetes-related risk factors. However, questions remain about the course of cognitive change into adulthood and old age in those with type 1 diabetes.

**Cognitive Impairment in Adults**

As in the literature regarding children and adolescents, there is general consensus from cross-sectional studies that type 1 diabetes is associated with cog-
nitive deficits in adults compared to normal control subjects (1–3). In a meta-analysis of 33 studies of cognition in adults with type 1 diabetes, Brands et al. (1) reported poorer performance compared to control subjects in the domains of intelligence, information processing speed, psychomotor efficiency, attention, cognitive flexibility, and visual perception ($d = 0.3–0.7$). However, in adults with childhood-onset type 1 diabetes, these differences could represent stable cognitive impairments since childhood, with some authors speculating that there is no further cognitive decline in adults apart from the cognitive effects of diabetes complications (4).

In an attempt to address this issue, a meta-analysis of 55 studies (32 in adults and 23 in children) found cognitive differences in more cognitive domains and larger effect sizes in adult compared to child samples (5). This could indicate that the brain continues to be vulnerable to damage associated with type 1 diabetes in adulthood. In support of this hypothesis, Nunley et al. (6) reported more pronounced cognitive impairment in middle-aged adults with type 1 diabetes (28% impaired; mean age 49 years) and twice the rate of clinically significant cognitive impairment compared to that reported in child samples (6).

**Cognitive Decline in Adulthood**

The Diabetes Control and Complications Trial (DCCT) and its subsequent follow-up study measured cognitive functioning from early adulthood to middle age (7). This large and comprehensive study found no evidence of marked cognitive decline over 18 years in the overall cohort. This study has been regarded by some as definitively determining that cognition does not change over time in adults with type 1 diabetes.

Although it is certainly an important study and has contributed much to our understanding of the value of intensive glycemic control with regard to complications, there are several limitations that need to be considered when interpreting the DCCT cognitive data. First, this sample does not appear to be representative of the broader adult population with type 1 diabetes. The majority of participants were diagnosed as adults (mean age 27 years at enrollment with average duration of 6 years), and, more importantly, the average IQ at enrollment was 114 (high average). Furthermore, cognitive performances were at or above the performance of normal control participants on nearly all cognitive tests, and the majority of participants were employed in professional or technical occupations. Given the protective effect of higher cognitive functioning or “cognitive reserve” on cognitive decline (8), a sample with less impressive cognitive skills at baseline may be more vulnerable to brain dysfunction over time. Additionally, the investigators used an average of individual test $z$ scores to calculate cognitive domain scores. Although this reduces the risk for type 1 error associated with multiple comparisons, it can result in above-average test scores canceling out below-average or impaired scores within domains, which would reduce the likelihood of detecting meaningful cognitive impairment if only some tests within a domain were sensitive to type 1 diabetes–related cognitive decline.

In contrast to the DCCT findings, Ryan et al. (9) reported that 39% of their middle-aged sample (average age 40 years) had a cognitive decline of at least 0.5 SD in processing speed over 7 years.

**Cognitive Decline and Dementia in Older Adults**

As a result of advances in medical treatment, the life expectancy of people with type 1 diabetes has increased, resulting in a growing population of older adults with the disease (10). There is a paucity of research on the cognitive status of this population, however.

Although there are strong associations between type 2 diabetes and cognitive decline and dementia in older adults (11–18), the nature, severity, and risk factors for, and trajectory of cognitive impairment in older adults with type 1 diabetes are less clear. No longitudinal studies have reported the incidence of dementia in type 1 diabetes or risk factors for conversion from mild cognitive impairment (MCI) to dementia. However, recent evidence from a national retrospective cohort study from England (19) suggests that type 1 diabetes is associated with increased vascular dementia risk. In contrast, there is also speculation that type 1 diabetes may protect older adults from Alzheimer’s disease due to the protective effects of exogenous insulin in the brain (20).

The only longitudinal study in older adults (average age 60 years) with type 1 diabetes (21) reported mild information processing speed deficits compared to matched control subjects at baseline but no significant cognitive decline over 4 years. Incident severe hypoglycemic events and cardiovascular events were associated with declines in information processing speed, however. Of note, this was a small sample ($n = 36$), so the study may have been underpowered to detect other variables associated with cognitive decline. Given the absence of robust longitudinal data on cognition in those >60 years of age, it is not known how the preexisting cognitive weaknesses associated with type 1 diabetes are affected by the aging process.

**Risk Factors**

It is clear that not all adults with type 1 diabetes have cognitive impairment. It is important to identify cognitive risk factors for several reasons: 1) to understand mechanisms underlying cognitive impairment in type 1 diabetes, 2) to potentially modify risk, and 3) to appropriately refer at-risk patients for detailed evaluation and recommendations regarding the po-
tential impact of cognitive impairment on self-management and other aspects of daily living. It is important to note that, although adults with type 1 diabetes diagnosed in childhood retain the same risk factors for cognitive impairment present in that age-group (see Cato and Hershey in this issue, p. 197), those diagnosed as adults may have a different set of risk factors for cognitive decline. For example, diabetic ketoacidosis, a risk factor for cognitive impairment in children, may not be a risk factor for cognitive impairment in those diagnosed as adults, given evidence that the developing brain may be at greater risk for adverse effects of glycemic extremes (4).

**Age of Onset and Duration of Diabetes**

Age of onset and duration of type 1 diabetes have been linked to cognitive ability in adult samples (5,22–24). Ferguson et al. (24) found that adults with early-onset diabetes ($n = 26$) had lower current intellectual ability (Wechsler Adult Intelligence Scale–Revised performance IQ, $P = 0.03$) and information processing ability (Choice Reaction Time, $P = 0.006$) than those with later-onset diabetes ($n = 45$). Furthermore, lateral ventricular volumes were 37% greater ($P = 0.002$), and ventricular atrophy was more prevalent (61 vs. 20%, $P = 0.01$) in the early-onset group. In addition, in a sample of 150 adults with type 1 diabetes, Brismar et al. (22) reported that age of onset and duration of diabetes were the strongest predictors of neuropsychological performance, with long diabetes duration and young age of onset predicting low scores in psychomotor speed, memory, processing speed, attention, working memory, verbal ability, general intelligence, executive functions, and global score.

**Diabetes Complications**

Micro- and macrovascular complications of diabetes, including retinopathy and neuropathy, have been consistently linked to greater cognitive impairment in adult samples (9,25–27). Using meta-analysis, Brands et al. (1) reported that cognitive deficits in adults with type 1 diabetes were associated with microvascular complications. Retinopathy and polyneuropathy measured 5 years before cognitive testing were predictive of poorer cognitive functioning in middle-aged adults (6). In addition, brain white matter disease occurred earlier and was associated with neuropathy and slowed cognition (28). In a longitudinal study of middle-aged adults with type 1 diabetes (9), the development of proliferative retinopathy and autonomic neuropathy predicted decline in psychomotor speed ($P < 0.01$), as did incident macrovascular complications ($P < 0.05$).

**Glycemic Extremes**

The relationship between glycemic extremes (i.e., hypoglycemia and hyperglycemia) and cognitive functioning remains controversial. In the DCCT, there was no evidence of greater cognitive decline associated with incident severe hypoglycemic episodes, and other studies have also failed to find an association between a history of severe hypoglycemic events and cognitive functioning (1). However, there is an apparent link between hypoglycemia and cognitive impairment in older adults with type 2 diabetes (29–31), and a recent case-control study found that older adults with type 1 diabetes who had recent severe hypoglycemic events had poorer cognitive functioning than those who had not had an event in the past 3 years (32). Thus, the neurological effects of severe hypoglycemia may be greatest during early development and during age-associated neurodegeneration (4).

As described by Cholerton et al. in this issue (p. 210), chronic hyperglycemia has been linked to cognitive decline and dementia risk in type 2 diabetes (18,33). This also appears to be the case in type 1 diabetes. DCCT investigators reported declines in motor speed and psychomotor efficiency (but not in other cognitive domains) in those with the highest A1C (>8.8%) over 18 years in their now middle-aged sample (7). Likewise, average A1C over the previous 14 years was associated with cognition in midlife (6). However, Brands et al. (1) did not find a relationship between cognition and A1C in their meta-analysis.

**Implications for Self-Management**

Researchers studying the relationship between cognitive functioning and chronic disease typically have assumed that chronic disease causes cognitive impairment. However, cognition also may be a risk factor for outcomes in chronic conditions with high self-management demands. For example, there is evidence that lower cognitive ability precedes obesity (34) in children who later become obese. This concept of “reverse causality” provides a rationale for a novel approach to behavioral intervention based on individual cognitive risk factors and using cognitive compensatory strategies, prompts, and environmental modifications to improve patients’ adherence to self-management behaviors despite cognitive barriers.

**Fluid Cognition Declines With Age and Is Related to Medical Self-Management**

Fluid cognition is a broad descriptor of a diverse set of discrete cognitive skills, including executive functioning, working memory, prospective memory, episodic memory, mental flexibility, attention, and complex processing speed and is highly sensitive to the effects of normal aging (35). Many of these cognitive skills also have been linked to medication self-management among diverse populations, including those with HIV (36,37), MCI and dementia (38), and Parkinson’s disease (39).

Executive functioning is the most consistently cited cognitive domain in research focused on predicting instrumental activities of daily living in older adults (40) and neurological...
populations (41). Of note, longitudinal decline in executive functioning and memory is associated with concomitant decline in instrumental activities of daily living in older adults both with and without MCI (38). Typically, when evaluating cognition in older adults, researchers control for the effects of normal age-related cognitive decline. Although this is appropriate when diagnosing a pathological disease state, it may not be appropriate when determining risk for medical mismanagement. It is possible that even normal age-related decline, coupled with the high demands of managing type 1 diabetes, could result in self-management problems. It is therefore crucial to identify the level of absolute cognitive performance that increases risk for self-management problems, even within the normal range.

**Cognitive Impairment Is a Risk Factor for Poor Diabetes Self-Management**

Although data in adults with type 1 diabetes are scarce, cognitive performance in older adults is associated with performance on simulated cognitively demanding diabetes self-management tasks (42). There is also evidence that cognition predicts self-management ability in children with type 1 diabetes and adults with type 2 diabetes. McNally et al. (43) used structural equation modeling to demonstrate that treatment adherence mediated the relationship between executive functioning and glycemic control in their sample of children with type 1 diabetes. The alternative model (that adherence led to glycemic control, which in turn led to executive dysfunction) was not supported by the data. There are also increasing data suggesting that cognitive performance predicts type 2 diabetes self-management (44–46). Most studies have focused on the important role of executive functioning (i.e., planning, problem-solving, and mental flexibility) in managing diabetes.

Prevention of hypoglycemic events is a key self-management task that may be affected by cognitive function. The ACCORD-MIND trial (47) in patients with type 2 diabetes found that cognitive performance at baseline predicted hypoglycemic episodes at the 20-month follow-up in those with no baseline hypoglycemia. In addition, this trial found that cognitive decline from baseline to 20 months was predictive of hypoglycemic episodes at 20 months for those patients who began the trial with average or lower cognitive ability. These data indicate that cognitive ability must cross a functional threshold to begin to affect self-management and hypoglycemia risk (Figure 1). In another longitudinal study in type 2 diabetes, lower cognition at baseline was associated with a twofold higher risk of incident severe hypoglycemia over the next 4 years, and previous hypoglycemia also was associated with steeper cognitive decline (30). Executive functioning, processing speed, and memory (i.e., fluid cognition) had the strongest associations with hypoglycemia. It is possible that those with declining cognition are less able to prevent, recognize, and treat hypoglycemia.

**Psychosocial and Demographic Factors**

Of course, psychosocial variables such as depression (48,49), diabetes distress (50,51), self-efficacy (52), social support (53), and hypoglycemia fear (54) are associated with type 1 diabetes self-management. Demographic factors, including age, sex, and socioeconomic status (i.e., education, income, and insurance status), also have been linked to self-management behaviors (55,56). It is therefore important to account for these factors in addition to cognitive impairment.

**Future Directions**

It is evident from this summary of the literature on cognitive functioning in adults with type 1 diabetes that many questions remain unanswered. Overall, as a group, adults with type 1 diabetes have poorer cognitive performance than those without. Younger age of onset, longer diabetes duration, presence of diabetes complications, and chronic hyperglycemia are associated with poorer performance and greater decline. Cognitive problems in adults with type 1 diabetes appear to be primarily in fluid cognition (i.e., processing speed, executive functioning, and memory), although other domains also can be affected. More research is needed to better understand the course and magnitude of cognitive change over time, particularly in older adults, and the implications of cognitive change on diabetes self-management. With this knowledge, cognitive rehabilitation approaches could be developed to compensate for changing cognition and lessen its impact on diabe-

![FIGURE 1. Hypothesized model linking cognitive decline, self-management, and severe hypoglycemia (SH) risk.](image-url)
tes self-management and quality of life. Elsewhere in this issue (p. 224), Hopkins et al. provide an excellent summary of practical strategies that may be beneficial in this regard.

Duality of Interest
No potential conflicts of interest relevant to this article were reported.

References
1. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-analysis. Diabetes Care 2005;28:726–735
2. Johnston H, McCrimmon R, Petrie J, Astell A. An estimate of lifetime cognitive change and its relationship with diabetes health in older adults with type 1 diabetes: preliminary results. Behav Neurol 2010;23:165–167
3. Ohmann S, Popow C, Rami B, et al. Cognitive functions and glycemic control in children and adolescents with type 1 diabetes. Psychol Med 2010;40:95–103
4. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. Lancet Neurol 2008;7:184–190
5. Tonoli C, Heyman E, Roelands B, et al. Type 1 diabetes-associated cognitive decline: a meta-analysis and update of the current literature. J Diabetes 2014;6:499–513
6. Nunley KA, Rosano C, Ryan CM, et al. Clinically relevant cognitive impairment in middle-aged adults with childhood-onset type 1 diabetes. Diabetes Care 2015;38:1768–1776
7. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group; Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 2007;356:1842–1852
8. Tucker AM, Stern Y. Cognitive reserve in aging. Curr Alzheimer Res 2011;8:354–360
9. Ryan CM, Geckle MO, Orchard TJ. Cognitive efficiency declines over time in adults with type 1 diabetes: effects of micro- and macrovascular complications. Diabetologia 2003;46:940–948
10. Ioacara S, Lichiardopol R, Ionescu-Tirgoviste C, et al. Improvements in life expectancy in type 1 diabetes patients in the last six decades. Diabetes Res Clin Pract 2009;86:146–151
11. Maggi S, Limongi F, Noale M, et al.; ILSA Study Group. Diabetes as a risk factor for cognitive decline in older persons. Dement Geriatr Cogn Disord 2009;27:24–33
12. Mayeda ER, Haan MN, Kanaya AM, Yaffe K, Neuhaus J. Type 2 diabetes and 10-year risk of dementia and cognitive impairment among older Mexican Americans. Diabetes Care 2013;36:2600–2606
13. Möttus R, Luciano M, Starr JM, Deary IJ. Diabetes and life-long cognitive ability. J Psychosom Res 2013;75:275–278
14. Nandipati S, Luo X, Schimming C, Grossman HT, Sano M. Cognition in non-demented diabetic older adults. Curr Aging Sci 2012;5:131–135
15. Ökerene OI, Kang JH, Cook NR, et al. Type 2 diabetes mellitus and cognitive decline in two large cohorts of community-dwelling older adults. J Am Geriatr Soc 2008;56:1028–1036
16. Roberts RO, Knapman DS, Geda YE, et al. Association of diabetes with amnestic and nonamnestic mild cognitive impairment. Alzheimers Dement 2014;10:18–26
17. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol 2011;7:108–114
18. Yaffe K, Falvey C, Hamilton N, et al. Diabetes, glucose control, and 9-year cognitive decline in young adults without dementia. Arch Neurol 2012;69:1170–1175
19. Smolina K, Wotton CJ, Goldacre MJ, et al. Association of diabetes with amnestic and nonamnestic mild cognitive impairment. Alzheimers Dement 2011;7:625–633
20. Rdzak GM, Abdelghany O. Does insulin therapy for type 1 diabetes mellitus protect against Alzheimer’s disease? Pharmacotherapy 2014;34:1317–1323
21. Vonkerenken E, Brands AM, van den Berg E, Henselmans JM, Hoogma RP, Biessels GJ; Utrecht Diabetic Encephalopathy Study Group. Cognition in older patients with type 1 diabetes mellitus: a longitudinal study. J Am Geriatr Soc 2011;59:563–565
22. Brismar T, Maurex L, Cooray G, et al. Predictors of cognitive impairment in type 1 diabetes. Psychoneuroendocrinology 2007;32:1041–1051
23. Kokkekoek PS, Rutten GE, Biessels GJ. Cognitive disorders in diabetic patients. Handb Clin Neurol 2014;128:45–166
24. Ferguson SC, Blane A, Wardlaw J, et al. Influence of an early-onset of type 1 diabetes on cerebral structure and cognitive function. Diabetes Care 2005;28:1431–1437
25. Jacobson AM, Ryan CM, Cleary PA, et al. Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. Diabetologia 2011;54:245–255
26. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. Lancet 2012;379:2291–2299
27. Wessels AM, Scheltens P, Barkhof F, Heine RJ. Hyperglycaemia as a determinant of cognitive decline in patients with type 1 diabetes. Eur J Pharmacol 2008;585:88–96
28. Nunley KA, Ryan CM, Orchard TJ, et al. White matter hyperintensities in middle-aged adults with childhood-onset type 1 diabetes. Neurology 2015;84:2062–2069
29. Aung PP, Strachan MW, Frier BM, Butcher I, Deary IJ, Price JF; Edinburgh Type 2 Diabetes Study Investigators. Severe hypoglycaemia and late-life cognitive ability in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabet Med 2012;29:328–336
30. Feinkohl I, Aung PP, Keller M, et al.; Edinburgh Type 2 Diabetes Study Investigators. Severe hypoglycaemia and cognitive decline in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabet Care 2014;37:507–515
31. Warren RE, Frier BM. Hypoglycaemia and cognitive function. Diabetes Obes Metab 2005;7:493–503
32. Weinstock RS, DuBose SN, Bergenstal RM, et al.; TID Exchange Severe Hypoglycaemia in Older Adults With Type 1 Diabetes Study Group. Risk factors associated with severe hypoglycaemia in older adults with type 1 diabetes. Diabetes Care 2016;39:603–610
33. Feinkohl I, Keller M, Robertson CM, et al. Cardiovascular risk factors and cognitive decline in older people with type 2 diabetes. Diabetologia 2015;58:1637–1645
34. Li Y, Dai Q, Jackson JC, Zhang J. Overweight is associated with decreased cognitive functioning among school-age children and adolescents. Obesity (Silver Spring) 2008;16:1809–1815
35. Heaton RK, Akshoomoff N, Tulsy D, et al. Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in adults. J Int Neuropsychol Soc 2014;20:588–598
36. Poquette AJ, Moore DJ, Gouaux B, Morgan EE, Grant I, Woods SP. Prospective memory and antiretroviral medication non-adherence in HIV: an analysis of ongoing task delay length using the Memory for Intentions Screening Test. J Int Neuropsychol Soc 2013;19:155–161
37. Woods SP, Dawson MS, Weber E, Gibson S, Grant I, Atkinson JH. Timing is everything: antiretroviral non-adherence is associated with impairment in time-based prospective memory. J Int Neuropsychol Soc 2009;15:42–52
38. Farias ST, Cahn-Weiner DA, Harvey DJ, et al. Longitudinal changes in memory and executive functioning are associated with longitudinal change in instrumental activities of daily living in older adults. Clin Neuropsychol 2002;23:446–461
39. Manning KJ, Clarke C, Lorry A, et al. Medication management and neuropsychological performance in Parkinson’s disease. Clin Neuropsychol 2012;26:45–58
40. Overdorp EJ, Kessels RPC, Claassen JA, Oosterman JM. The combined effect of neuropsychological and neuropathological deficits on instrumental activities of daily living in older adults: a systematic review. Neuropsychol Rev 2016;26:92–106
41. Perna R, Loughan AR, Talsa K. Executive functioning and adaptive living skills after acquired brain injury. Appl Neuropsychol Adult 2012;19:263–271
42. Chaytor NS, Riddlesworth TD, Bzdick S, et al. The relationship between neuropsychological assessment, numeracy, and functional status in older adults with type 1 diabetes. Neuropsychol Rehabil 2015. Electronically published ahead of print (DOI: 10.1080/09602011.2015.1116448)
43. McNally K, Rohan J, Pendley JS, Delamater A, Drotar D. Executive functioning, treatment adherence, and glycemic control in children with type 1 diabetes. Diabetes Care 2010;33:1159–1162
44. Primožič S, Tavčar R, Avbelj M, Dernovšek MZ, Oblak MR. Specific cognitive abilities are associated with diabetes self-management behavior among patients with type 2 diabetes. Diabetes Res Clin Pract 2012;95:48–54
45. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. Diabetes Res Clin Pract 2000;50:203–212
46. Yaffe K, Ackerson L, Hoang TD, et al.; CRIC Study Investigators. Retinopathy and cognitive impairment in adults with CKD. Am J Kidney Dis 2013;61:219–227
47. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787–793
48. Pouwer F, Nefs G, Nouwen A. Adverse effects of depression on glycemic control and health outcomes in people with diabetes: a review. Endocrinol Metab Clin North Am 2013;42:529–544
49. Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment non-adherence: a meta-analysis. Diabetes Care 2008;31:2398–2403
50. Martyn-Nemeth P, Quinn L, Hacker E, Park H, Kujath AS. Diabetes distress may adversely affect the eating styles of women with type 1 diabetes. Acta Diabetol 2014;51:683–686
51. Strandberg RB, Graue M, Wentzel-Larsen T, Peyrot M, Rokne B. Relationships of diabetes-specific emotional distress, depression, anxiety, and overall well-being with HbA1c in adult persons with type 1 diabetes. J Psychosom Res 2014;77:174–179
52. Chih AH, Jan CF, Shu SG, Lue BH. Self-efficacy affects blood sugar control among adolescents with type 1 diabetes mellitus. J Formos Med Assoc 2010;109:503–510
53. Feil DG, Pearlman A, Victor T, et al. The role of cognitive impairment and caregiver support in diabetes management of older outpatients. Int J Psychiatry Med 2009;39:199–214
54. Polonsky WH, Fisher L, Hessler D, Edelman SV. Identifying the worries and concerns about hypoglycemia in adults with type 2 diabetes. J Diabetes Complications 2015;29:1171–1176
55. Simmons JH, Chen V, Miller KM, et al.; T1D Exchange Clinic Network. Differences in the management of type 1 diabetes among adults under excellent control compared with those under poor control in the T1D Exchange Clinic Registry. Diabetes Care 2013;36:3573–3577
56. Weijman I, Ros WJ, Rutten GE, Schaafeli WB, Schabraaq MJ, Winnubst JA. The role of work-related and personal factors in diabetes self-management. Patient Educ Couns 2005;59:87–96