# The Effects of Type 1 Diabetes on Cognitive Performance

## A meta-analysis

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**OBJECTIVE** — To investigate the exact nature and magnitude of cognitive impairments in patients with type 1 diabetes and the possible association with other disease variables, such as recurrent episodes of hypoglycemia and metabolic control.

**RESEARCH DESIGN AND METHODS** — MedLine and PsycLit search engines were used to identify studies on cognitive performance in patients with type 1 diabetes. Effect sizes (Cohen's *d*), which are the standardized differences between the experimental and the control group, were calculated. In the meta-analysis, a combined *d* value was calculated, expressing the magnitude of associations across studies.

**RESULTS** — A total of 33 studies were identified that met the inclusion criteria. Compared with nondiabetic control subjects, the type 1 diabetic group demonstrated a significantly lowered performance on the following cognitive domains: intelligence ($d = -0.7$), speed of information processing ($d = -0.3$), psychomotor efficiency ($d = -0.6$), visual ($d = -0.4$) and sustained attention ($d = -0.3$), cognitive flexibility ($d = -0.5$), and visual perception ($d = -0.4$). Lowered cognitive performance in diabetic patients appeared to be associated with the presence of microvascular complications but not with the occurrence of severe hypoglycemic episodes or with poor metabolic control.

**CONCLUSIONS** — In patients with type 1 diabetes, cognitive dysfunction is characterized by a slowing of mental speed and a diminished mental flexibility, whereas learning and memory are spared.The magnitude of the cognitive deficits is mild to moderate, but even mild forms of cognitive dysfunction might hamper everyday activities since they can be expected to present problems in more demanding situations.

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Individuals with type 1 diabetes have repeatedly been reported to show modest deficits on a wide range of neuropsychological tests compared with nondiabetic control subjects. However, the results of the different neuropsychological studies are heterogeneous with respect to the affected cognitive domains and the severity of the reported cognitive deterioration. Some studies (1) report impairments on tests relying on problem solving skills, whereas other studies (2) report deficits in psychomotor efficiency, learning and memory (3), and visuospatial (2,4) abilities, or report no difference at all (5). This heterogeneity is probably caused by differences in patient characteristics and the psychometric paradigms used. Consequently, the exact pattern and magnitude of cognitive dysfunction is still unclear.

Both chronic hyperglycemia (6,7) and the consequent occurrence of diabetes complications (2,8), as well as recurrent episodes of severe hypoglycemia (1,4,9), are thought to be associated with cognitive dysfunction in patients with type 1 diabetes. The contribution of these disease variables with respect to cognitive dysfunction is unresolved. The primary aim of the current meta-analysis was to determine the pattern and magnitude of cognitive impairments in adult type 1 diabetic patients compared with nondiabetic control subjects. The secondary aim was to evaluate the possible effects of disease variables and comorbid disorders, such as the level of metabolic control, occurrence of diabetes complications, and repeated hypoglycemic episodes, on cognitive dysfunction.

## RESEARCH DESIGN AND METHODS

### Selection of studies

MedLine and PsycLit search engines were used to identify studies on cognitive performance in patients with type 1 diabetes versus nondiabetic control subjects or comparing different type 1 diabetic patient groups. The following were the key words or truncated versions: cognition, behavioral, attention, learning, memory, executive functioning, information processing, spatial, intelligence, and intellectual. They were also combined with the terms diabetes, type 1 diabetes, insulin dependent diabetes, hypoglycemia, and hyperglycemia. In each database, the search was limited to studies in humans. Studies on cognition in children and on the effects of acute hypo- and hyperglycemia were not included in this review; they have been the subject of previous reports (10,11). Abstracts were examined to establish if the studies fulfilled the following inclusion criteria: *1*) published or available in English after 1980 and before 2004, *2*) included only adults aged >18 years diagnosed with type 1 diabetes (either early onset or late onset), *3*) had a defined control group, *4*) assessed cogni-

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tive performance using standard neuropsychological or reliable experimental testing methods at normal blood glucose values (if studies were designed to measure the effect of acute hypoglycemia, only test results in the euglycemic state before induction of hypoglycemia were considered), and 5) were original studies and test scores were presented for the experimental and control groups (means and SD) or statistics such as the exact *t* or *F* values were given. Reference lists of published studies were examined to identify additional studies.

For each study, the type of control group (healthy control subjects or other diabetic patient groups) was determined. Group characteristics and inclusion and exclusion criteria for both the experimental and the control groups were recorded.

Subsequently, effect sizes (Cohen's *d*), which are the standardized differences between the experimental group and the comparison group (12), were calculated for every test result. If no exact values were reported for nonsignificant results, these results were included as $d = 0.00$ in the analysis, adopting a conservative approach (13). The direction of the effect size was negative if the performance of the experimental group was worse than the control group. Calculations were performed independently by two of the authors (R.P.C.K. and A.M.A.B.). Differences in calculations were resolved by discussion, resulting in an interrater reliability of unity.

In the actual meta-analysis, a combined *d* value was included, expressing the magnitude of associations across studies. This *d* value was weighted for sample size to correct for upwardly biased estimation of the effect in small sample sizes (14). In addition, Stouffer's *Z* (weighted for sample size), as well as the 95% CI on the basis of the SE, provided an indication of the significance of the difference in task performance between the experimental and the control group. The CI was determined by the two-tailed critical value derived from Student's *t* distribution ($\alpha$ set at 0.05). The cumulative effect size *d* thus represents the overall magnitude of the effect present in the studies.

To determine the heterogeneity of a sample, the statistic *Q* is calculated. Since only published results have been included in this meta-analysis, this could potentially lead to a publication bias. Therefore, the fail-safe *N* (14) was calculated to estimate the number of studies needed to falsify the significant result. Furthermore, the actual number of existing nonsignificant studies was estimated (13) to establish if the fail-safe *N* exceeds this estimated number of nonsignificant studies. For each significant effect size, the calculated fail-safe *N* exceeded the estimate of existing unpublished studies reporting nonsignificant results, which indicates that the observed significant effects cannot be explained by publication bias.

Tests measuring the same cognitive domain were taken together in the analysis. An overall *d* value, in which all cognitive domains were pooled, was computed first as a general index of differences in cognitive function (overall cognition). Subsequently, separate meta-analyses were performed for the different cognitive domains.

Tasks from the individual studies were classified according to the following seven cognitive domains: intelligence, learning and memory, (psycho)motor activity and information processing, attention, cognitive flexibility, visual perception, and language. To perform more specific analyses, these general domains were subdivided into more specific cognitive domains. We based these classifications on the exhaustive descriptions of test characteristics by Lezak, Howieson, and Loring (15). The domain intelligence was subdivided into fluid intelligence, which assesses a person's problem solving ability to apply knowledge in a new situation, and crystallized intelligence, which measures acquired scholarly knowledge. The domain learning and memory consisted of the domains working memory, which measures the ability to actively manipulate given information for a limited amount of time; verbal learning and immediate memory, which measures the ability to acquire and store new verbal information; visual learning and immediate memory, which is the ability to acquire and store new visual information; and delayed memory as an index of information retrieval, which was also administered verbally and visually after a delay of approximately half an hour. The domain (psycho)motor activity and information processing consisted of the following domains: psychomotor efficiency to assess cognitively demanding information processing tasks, speed of information processing to measure reaction time, and motor speed to assess basic manual motor activity. The domain attention was divided into visual attention, which assesses the ability to selectively attend to visually presented information; sustained attention, which measures concentration over a longer period of time; divided attention, which is the ability to divide attention among different tasks; and selective attention, which assesses the ability to inhibit automatic responses. Cognitive flexibility, which measures the ability to shift concepts and problem solving strategies; visual perception, which is the ability to accurately perceive visually presented information; and language, which measures naming and language comprehension were not further subdivided. Tasks that could not be classified according to these domains were not included in the meta-analysis (e.g., priming tasks [29]) (see online appendix at http://care.diabetesjournals.org).

Meta-analyses were performed separately for the difference between type 1 diabetic patients versus nondiabetic control subjects and for the possible contribution of disease variables, such as the level of metabolic control, the occurrence of diabetes complications, and repeated hypoglycemic episodes. Due to the limited number of studies focusing on the relation between disease variables and cognition, we combined the cognitive domains visual attention, sustained attention, divided attention, and interference into the overall domain of attention. Furthermore, visual and verbal memory scores were combined. All analyses were performed using the statistical package META (16).

**RESULTS** — The literature search identified a total of 33 studies on neuropsychological functioning in type 1 diabetic patients that met the inclusion criteria. Table 1 displays the studies that have compared diabetic patients with nondiabetic control subjects on cognitive functioning. Table 2 represents the characteristics of the studies that have studied the impact of different disease variables and comorbid conditions on cognition.

The studies included in Table 1 are homogeneous with respect to age; generally participants are relatively young (aged <50 years), and the ages of the case and control groups are similar both within and across studies. Ten studies matched subjects for education, occupation, or both, but nine studies matched partici-

**Table 1—*Characteristics of studies that have assessed cognitive functioning in patients with type 1 diabetes and nondiabetic control subjects***

| First author (ref.) | *n* (grp 1)/ (grp 2) | % Males (grp 1)/ (grp 2) | Age (grp 1)/(grp 2) (years) | Subjects matched for | $HbA_{1c}$ or $HbA_1$ (%) | Duration (years) | Calculated age at onset (years) | Included complications and characteristics | Exclusion criteria or absent characteristics |
|---|---|---|---|---|---|---|---|---|---|
| Meuter et al. 1980 (17) | 112/112 | 50/50 | 38 ± 14.3/ND | E | ND | 10.5 ± 9.3 | 17 | H,Hy,N,R,Ne | ND |
| Franceschi et al. 1984 (18) | 37/26 | 43/42 | 25.8 ± 5/26.4 ± 5 | E,O,SES | 12.7 ± 2.5 | 7.7 ± 5.5 | 18 | Hy,N,R | H,Ne,CI,DL,P |
| Skenazy et al. 1984 (19) | | | | | | | | | |
| Visually impaired | 20/24 | 70/67 | 28 ± 6.1/22.6 ± 5.6 | ND | ND | 18.7 ± 5.9 | 9 | H,Hy,N,R,Ne | ND |
| Nonvisually impaired | 19/24 | 53/67 | 32.1 ± 6.2/22.6 ± 5.6 | ND | ND | 15.3 ± 7.8 | 17 | H,Hy,N,R,Ne | ND |
| Lawson et al. 1984 (5) | 48/40 | 54/48 | 38.3 ± 14.6/38.8 ± 12.8 | ND | 9.1 | 13 ± 10.8 | 15 | Hy,N | P |
| Grill et al. 1990 (20) | 6/5 | ND | 37.1 ± 6.9/30.3 ± 4.5 | ND | 6.9 ± 0.7 | 19.4 ± 5.1 | 18 | Hy,R | CV,Ne,H,CI,N |
| Widom et al. 1990 (21) | | | | | | | | | |
| Poor metabolic control | 9/10 | 44/60 | 22 ± 3/27 ± 3.2 | ND | 11.8 ± 1.2 | 12 ± 6 | 10 | R | N,Ne, |
| Good metabolic control | 8/10 | 50/60 | 27 ± 5.7/27 ± 3.2 | ND | 8 ± 0.6 | 7 ± 2.8 | 20 | ND | N,Ne,R |
| Dejgaard et al. 1991 (22) | 20/120 | ND/ND | 44 ± 9/ND | ND | 9.1 ± 1.4 | 26 ± 9 | 18 | Hy,N,R,Ne | P |
| Pozzessere et al. 1991 (23) | 16/16 | 70/70 | 33.2 ± 12.6/33.4 ± 12.5 | E | 7 ± 1.6 | 9 ± 7.7 | 24 | H | Hy,NA,P,DL |
| Blackman et al. 1992 (24) | 14/10 | 43/50 | 29.5 ± 6/26.7 ± 6 | ND | 11 ± 1.9 | ND | ND | ND | Hy,N |
| Ryan et al. 1992 (2) | 75/75 | 45/25 | 35.5 ± 5.6/36.2 ± 6.8 | E,SES | 10.3 | 26.6 ± 6.7 | 9 | Hy,N,R, | ND |
| Sachon et al. 1992 (3) | | | | | | | | | |
| Severe hypoglycemia | 30/25 | 77/48 | 41 ± 13/38 ± 15 | O,SES | 7.4 ± 1.2 | 18 ± 13 | 23 | Hy,N,Ne,R | ND |
| No hypoglycemia | 25/25 | 60/48 | 34 ± 10/38 ± 15 | O,SES | 8.6 ± 1.9 | 15 ± 11 | 18 | N,Ne,R | Hy,ND |
| Wirsen et al. 1992 (25) | 10/12 | 100/100 | R 20–43/R 18–32 | E, | 7.9 ± 0.6 | ND | ND | Hy | N |
| Cox et al. 1993 (26) | 10/10 | 40/ND | 34/ND | E,O | 9.8 | 18 | 16 | ND | ND |
| Deary et al. 1993 (1) | 100/100 | ND/ND | 40.9 ± 8.8/40.2 ± 6.7 | E | ND | >5 | >19 | Hy,R,N,Ne | P |
| Ryan et al. 1993 (6) | | | | | | | | | |
| Females | 41/41 | 0/0 | 33.4 ± 5.5/35.2 ± 8.4 | E,SES | 10.9 ± 1.8 | 25.3 ± 6.6 | 8 | Hy,N,Ne,R | ND |
| Males | 41/41 | 100/100 | 33.4 ± 5.2/34.7 ± 7.5 | E,SES | 10.6 ± 2 | 27.1 ± 5.5 | 6 | Hy,N,Ne,R | ND |
| Ryan et al. 1993 (27) | 142/100 | 51/47 | 33.5 ± 5.6/34.1 ± 6.7 | E,SES | 10.6 ± 1.8 | 24.8 ± 6.1 | 8 | Hy,N,Ne,R | ND |
| Maran et al. 1995 (28) | | | | | | | | | |
| Good metabolic control | 8/8 | 75/63 | 36 ± 3/31 ± 2 | ND | 7.7 ± 0.3 | 16 ± 2 | 20 | Hy | ND |
| Poor metabolic control | 10/8 | 60/63 | 32 ± 4/31 ± 2 | ND | 10.1 ± 0.2 | 17 ± 3 | 15 | ND | ND |
| Hershey et al. 1997 (29) | | | | | | | | | |
| Severe hypoglycemia | 26/21 | ND/ND | 26.2 ± 6.6/27.8 ± 8.1 | E | ND | >5 | <14 | Hy | R,N |
| No hypoglycemia | 12/21 | ND/ND | 22.8 ± 7.7/27.8 ± 8.1 | E | ND | >5 | <14 | — | Hy,R,N |
| Kramer et al. 1998 (30) | 108/108 | 45/ND | 36 ± 13/36 ± 13 | ND | ND | >1 | >16 | H,Hy,N,R, | P,Ne |
| Snoek et al. 1998 (31) | | | | | | | | | |
| Severe hypoglycemia | 9/9 | 100/100 | 36.9 ± 6.7/ND | ND | 7.4 | 13.4 | 24 | Hy | P, |
| No hypoglycemia | 9/9 | 100/100 | 36.9 ± 6.7/ND | ND | 7.4 | 13.4 | 24 | — | Hy,P, |
| Lobmann et al. 2000 (32) | 12/12 | 33/58 | 31 ± 7/27 ± 3 | ND | 7.4 ± 1.8 | 7.8 ± 8.6 | 23 | Hy | N,R,H,CI,Ne, |

Data are means ± SD, unless otherwise indicated. CI, cardiac insufficiency; DL, dyslipidemia; E, education; H, hypertension or hypertensive treatment; Hy, severe hypoglycemic episodes; N, neuropathy; ND, not specifically defined; Ne, nephropathy and/or microalbuminuria; O, occupation; P, psychiatric problems and/or use of psychoactive drugs and/or addiction to alcohol or other substances; R, retinopathy; SES, socioeconomic status.

**Table 2—*Characteristics of studies that have assessed cognitive functioning in patients with type 1 diabetes, comparing different diabetic characteristics***

| First author (ref.) | Type (grp 1/grp 2) | *n* (grp 1/ grp 2) | % Males (grp 1/ grp 2) | Age (grp 1/grp 2) | $HbA_1$ (grp 1/grp 2) | Duration (grp 1/grp 2) | Calculated age at onset (grp 1/grp 2) | Included complications and characteristics | Exclusion criteria or absent characteristics | Subjects matched for |
|---|---|---|---|---|---|---|---|---|---|---|
| Hung et al. 1984 (33) | Poor MC/good MC | 12/20 | 67/65 | 35.1/34.15 | 13 ± 0.9/10 ± 0.8 | 20.2/22.8 | 15/14 | R,N | Ne | ND |
| Skenazy et al. 1984 (19) | Vis imp/non-vis imp | 20/19 | 70/53 | 28 ± 6.1/32.1 ± 6 | ND/ND | 18.7 ± 5.9/15.3 ± 7.8 | 9/17 | H,N,R,Ne | ND | ND |
| Holmes 1986 (7) | Poor MC/good MC | 8/19 | 100/100 | 20.9 ± 2.4/23.4 ± 5.4 | 12.4 ± 0.7/8.2 ± 1.6 | 7.8 ± 4.1/8.4 ± 5.7 | 13/15 | ND | P | E,SES |
| Holmes et al. 1988 (34) | Poor MC/good MC | 6/10 | 100/100 | 22.2 ± 4.3/24 ± 5.3 | 10.1 ± 1/6.9 ± 0.8 | 7.5 ± 3.8/6.7 ± 4.4 | 15/14 | ND | R | ND |
| Prescott et al. 1990 (35) | Poor MC/good MC | 20/20 | 50/50 | 40.3 ± 11.6/39.8 ± 10 | 13.1 ± 1.6/8.9 ± 1 | 15.2 ± 10.5/14 ± 10.3 | 25/26 | ND | ND | SES |
| Widom et al. 1990 (21) | Poor MC/good MC | 9/8 | 44/50 | 22 ± 3/27 ± 5.7 | 11.8 ± 1.2/8 ± 0.6 | 12 ± 6/7 ± 2.8 | 10/20 | R,ND | N,Ne | ND |
| Wredling et al. 1990 (4) | Sev hy/no sev hy | 17/17 | ND/ND | 49 ± 18/48 ± 17 | 7.9 ± 1.6/8.8 ± 1.6 | 28 ± 18/29 ± 13 | 21/19 | N,R,P | ND | E |
| Langan et al. 1991 (36) | Sev hy/no sev hy | 24/23 | 58/48 | 37.9 ± 6.4/38.5 ± 5.3 | 10 ± 2.3/10.2 ± 1.8 | 10.7 ± 4/13 ± 4 | 27/25 | R,N,Ne,H | CV,P,PD | ND |
| Sachon et al. 1992 (3) | IHA/NHA | 30/25 | 77/60 | 41 ± 13/34 ± 10 | 7.4 ± 1.2/8.6 ± 1.9 | 18 ± 13/15 ± 11 | 24/19 | N,Ne,R | ND | O,SES |
| Ryan et al. 1993 (27) | Compl/no compl | 113/29 | 49/55 | 34.3 ± 5.4/30.7 ± 5.6 | 10.6 ± 1.7/10.7 ± 1.9 | 25.9 ± 5.6/20.5 ± 5.8 | 8/10 | N,Ne,R | ND | E,SES |
| Chabriat et al. 1994 (37) | Sev hy/no sev hy | 15/6 | ND/ND | 47.6 ± 17/42.8 ± 19 | 7.2 ± 1.7/7.1 ± 0.8 | 19.6 ± 16/11.3 ± 7 | 28/32 | | H,R,M,N,CV | E |
| Gold et al. 1995 (38) | IHA/NHA | 10/10 | ND/ND | 35 ± 7.7/37.4 ± 5.1 | 9.7 ± 1/10.3 ± 2.2 | 12.8 ± 4.4/17.9 ± 7.8 | 23/19 | H | P,R,N | ND |
| Maran et al. 1995 (28) | Poor MC/good MC | 10/8 | 60/75 | 32 ± 4/36 ± 3 | 10.1 ± 0.2/7.7 ± 0.3 | 17 ± 3/16 ± 2 | 15/20 | ND | ND | ND |
| DCCT 1996 (39) | | | | | | | | | | |
| >5 episodes | Sev hy/no sev hy | 23/1,045 | ND/ND | <50/<50 | ND/ND | >6/>6 | ND | — | R,Ne,N,P | ND |
| 1–5 episodes | Sev hy/no sev hy | 314/1,045 | ND/ND | <50/<50 | ND/ND | >6/>6 | ND | — | R,Ne,N,P | ND |
| Reichard et al. 1996 (40) | Poor MC/good MC | 48/43 | ND | ND/ND | 8.3 ± 1/7.2 ± 0.6 | ND/ND | ND | R | ND | |
| Hershey et al. 1997 (29) | Sev hy/no sev hy | 26/12 | ND/ND | 26.2 ± 6.6/22.8 ± 7.7 | ND/ND | >5/>5 | <14 | — | R,N | E |
| Kramer et al. 1998 (30) | | | | | | | | | | |
| Hypoglycemia | Sev hy/no sev hy | 55/53 | 35/57 | 38 ± 14/34 ± 12 | 7 ± 1.6/6.9 ± 1.3 | 17.6 ± 11.6/10.8 ± 10.6 | 20/23 | H,N,R | P,Ne | A |
| MC | $HbA_{1c}$ >6.5/ $HbA_{1c}$ <6.5 | ND/ND | ND/ND | ND/ND | ND/ND | ND/ND | >16 | H,N,R | P,Ne | A |
| Snoek et al. 1998 (31) | Sev hy/no sev hy | 9/9 | | 36.9 ± 6.7/36.9 ± 6.7 | 7.4/7.4 | 13.4/13.4 | 24/27 | — | P | A,S |
| Howorka et al. 2000 (41) | Sev hy/no sev hy | 13/14 | 46/36 | 36.1 ± 10.2/36.1 ± 10 | 7.6 ± 1/7.3 ± 1.2 | 16.7 ± 7.4/15.6 ± 8.6 | 19/20 | R | P,CV,N,CI | A,S |
| Strachan et al. 2000 (42) | IHA/NHA | 20/20 | 65/60 | 36.4 ± 14.7/34 ± 12.5 | 8.3 ± 1.3/10 ± 1.7 | 15.5 ± 7.6/13 ± 8.2 | 20/21 | ND | P | A,S |
| Ferguson et al. 2003 (8) | R/no R | 25/46 | 50/40 | 31.5 ± 6/26.4 ± 4.6 | 8.9 ± 1.3/8.4 ± 1.2 | 21.6 ± 5.9/17 ± 4.6 | 10/9 | Hy | N,Ne,H,P | ND |

Data are means ± SD, unless otherwise indicated. A, age; CI, cardiac insufficiency; Compl, diabetes complications; DL, dyslipidemia; E, education; Gluc, hypoglycemia prevented during testing; H, hypertension or hypertensive treatment; Hy, severe hypoglycemic episodes; IHA, impaired awareness of hypoglycemia; MC, metabolic control; N, neuropathy; ND, not specifically defined; Ne, nephropathy and/or microalbuminuria; NHA, normal awareness of hypoglycemia; O, occupation; P, psychiatric problems and/or use of psychoactive drugs and/or addiction to alcohol or other substances; R, retinopathy; S, sex; SES, socioeconomic status; Sev hy, episodes of severe hypoglycemia; Vis imp, visually impaired.

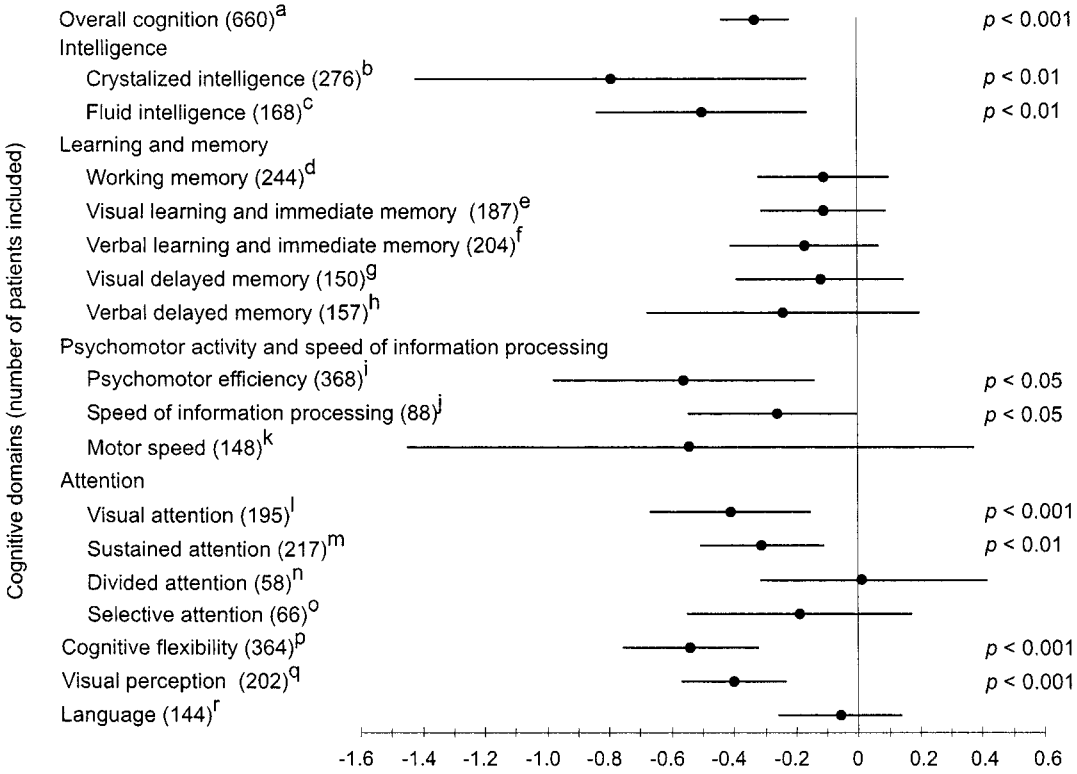


**Figure 1 —***Standardized effect sizes (Cohen's* d*) and 95% CIs for the cognitive domains in patients with type 1 diabetes compared with nondiabetic control subjects. Number of patients included in each domain is listed between brackets. Nonsignificant* P *values are not shown. Refs.: a = (1,3,18,19,20–32), b = (18,19,22,27,29, c = (6,18,19,25), d = (3,6,18,20,22,23,25,31), e = (6,18,22,25,29), f = (3,6,18,22,25), g = (6,22,25,29), h = (3,22,25), i = (3,6,18,19,21,22,25,30), j = (20,24,28,29,32), k = (20,27), l = (2,3,21,25,29), m = (18,27,29), n = (25,26,29), o = (25,29,31), p = (3,18,19,20–22,25,27,29), q = (6,18,19,27,29), and r = (2,19,22,25).*

pants for age only. In one study (5), this resulted in a significant difference between the diabetic and control group with respect to educational level; therefore, the results of this study were not used to calculate domain scores. The results from the study by Meuter et al. (17) were not used for the calculation of effect sizes either, since the cognitive domains defined in that study differed too much from the cognitive domains in this meta-analysis. The studies included in Table 1 are not all homogeneous for sex. Most studies, however, matched their subjects for sex.

Table 1 displays heterogeneity with respect to complications and associated disorders of type 1 diabetes. Four studies only included patients who did not suffer from any diabetes complication or comorbid disorder, whereas eight other studies did not define any specific complication or comorbid disorder as exclusion criterion. Other disease variables and possible comorbid disorders also vary markedly among the studies.

Although Table 1 lists three studies by Ryan et al., we included only one of them (the study with the highest number of persons tested on a specific cognitive domain) in the meta-analyses because they were based on the same pool of patients and control subjects (C.M. Ryan, personal communication).

Figure 1 shows the results of the meta-analyses. Compared with control subjects, the type 1 diabetic group demonstrated a significant reduction of overall cognition, as well as a lowered intelligence (both fluid and crystallized), speed of information processing, psychomotor efficiency, visual and sustained attention, mental flexibility, and visual perception. Psychomotor efficiency just reaches statistical significance ($P = 0.047$). According to the nomenclature of Cohen (12), most effect sizes are in the moderate range ($-0.6 < d < -0.3$). The effect size for crystallized intelligence ($d = -0.8$; 276 patients) approaches a large difference ($d = -0.8$). In a separate subanalysis including only those studies matching on education, both fluid and crystallized intelligence showed a significant effect size ($d = -0.4$; $P < 0.001$ and $d = -0.9$; $P < 0.01$, respectively). All significant effect sizes are accounted for by over 150 diabetic patients per calculated domain score, which is up to a total of 660 patients in the overall calculation.

The inhomogeneity index $Q$ was not significant for most comparisons, with the exception of the domains crystallized intelligence, psychomotor efficiency, and cognitive flexibility. Although much effort was expended to render these domains as homogeneous as possible, one must acknowledge the fact that by definition, the domain intelligence is comprised of a wide variation in neuropsychological tasks, possibly resulting in a relatively large variation in $d$ values.

In studies addressing the role of different disease variables on cognition, two different types of statistical analysis were encountered. Disease variables were either classified as dichotomous variables (e.g., the presence or absence of a history of severe hypoglycemic episodes) or as continuous variables (e.g., duration of diabetes in years). Studies that assessed the

**Table 3—*Domain scores from studies that could not be explored further meta-analytically***

| | | | | Cognitive domains | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Learning | | | Speed of | | | | | |
| First author (ref.) | Group 1 | Group 2 | Overall intelligence | Working memory | immediate memory | Delayed memory | Psychomotor efficiency | information process | Motor speed | Attention | Cognitive flexibility | Visual perception | Language |
| Hung et al. (33) | Poor MC | Good MC | — | 0.18 | −0.71 | — | — | — | — | — | 0.17 | — | — |
| Skenazy et al. (19) | Vis imp | Non vis imp | 0.23 | — | — | — | — | — | — | — | — | — | 0.29 |
| Holmes (7) | Poor MC | Good MC | −0.31 | — | — | — | — | −0.53 | 0.38 | — | — | — | — |
| Holmes et al. (34) | Poor MC | Good MC | −0.10 | — | — | — | 0.14 | −0.73 | 0.64 | — | — | — | — |
| Prescott et al. (35) | Good MC | Good MC | — | — | 0 | — | — | — | — | — | — | — | — |
| Widom et al. (21) | Poor MC | Good MC | — | — | — | — | −0.33 | — | — | 0.17 | 0.89 | — | — |
| Ryan et al. (27) | Compl | No compl | 0.23 | — | −0.24 | — | — | — | −0.80 | −0.28 | 0.10 | −0.35 | — |
| Gold et al. (38) | IHA | NHA | −0.33 | — | — | — | 0 | — | — | — | — | — | — |
| Maran et al. (28) | Poor MC | Good MC | — | — | — | — | — | 0.45 | — | — | — | — | — |
| Kramer et al. (30) | Poor MC | Good MC | 0.28 | — | — | — | 0 | — | — | — | — | — | — |
| Strachan et al. (42) | IHA | NHA | — | — | −0.10 | −0.13 | −0.77 | 0 | — | −0.63 | −0.54 | — | — |
| Ferguson et al. (8) | R | No R | −0.31 | — | — | — | −0.48 | −0.59 | — | −0.40 | −0.34 | — | — |

Data are Cohen's *d*. Negative effects sizes reflect worse performance in group 1. Compl, diabetes complications; IHA, impaired awareness of hypoglycemia; MC, metabolic control; NHA, normal awareness of hypoglycemia; Vis imp, visually impaired; R, retinopathy.

impact of disease variables in a dichotomous design are listed in Table 2.

Cross-sectional studies revealed no consistent relationship between disease duration and cognition (2,5,6,18,19, 30,35). The pattern and severity of cognitive changes in studies based on patient populations with an average age at onset <15 years (5,7,8,19,21,27,29,33) did not differ from the general pattern of cognitive changes represented in Fig. 1. However, the combined effects of juvenile onset and the occurrence of diabetes complications may have an impact on cognition (7,29). The same applies to the effect of $HbA_{1c}$ (in correlational analyses) (2,6,7,18,27,30,35,40), where some studies report that a high level of $HbA_{1c}$ in interaction with diabetes complications such as neuropathy might negatively influence cognition (6,19).

Eleven studies addressed the role of metabolic control, defined as a dichotomous variable, on cognition (3,7,21, 28,30,33–35,37,42,43) (Table 2). A qualitative analysis of the data presented in Table 3 shows no consistent difference between the "well" and "poorly" controlled groups. A formal meta-analysis could not be performed because the cutoff points of $HbA_{1c}$ differed among studies. The three studies that compared cognition in patients with different types and severity of diabetes complications (8, 19,27) report poorer test performance in patients with more complications.

Eight studies compared patients with severe hypoglycemic episodes with patients who had not experienced such episodes (Fig. 2). One of these studies (39) had a longitudinal design and assessed the occurrence of severe hypoglycemic episodes prospectively, whereas the other cross-sectional studies (4,29–31,36,37, 39,41) examined this variable retrospectively by a standardized interview. Three studies (3,38,42) that approached this issue by focusing on hypoglycemic awareness, therefore including patients with recurrent episodes of severe hypoglycemia in both groups, were not included in the formal meta-analysis. It is important to note that the Diabetes Control and Complications Trial study (39) listed is based on cognitive domains that are somewhat different from our classification. Therefore, only the domains similar to those used in this meta-analysis were included, i.e., psychomotor speed, motor

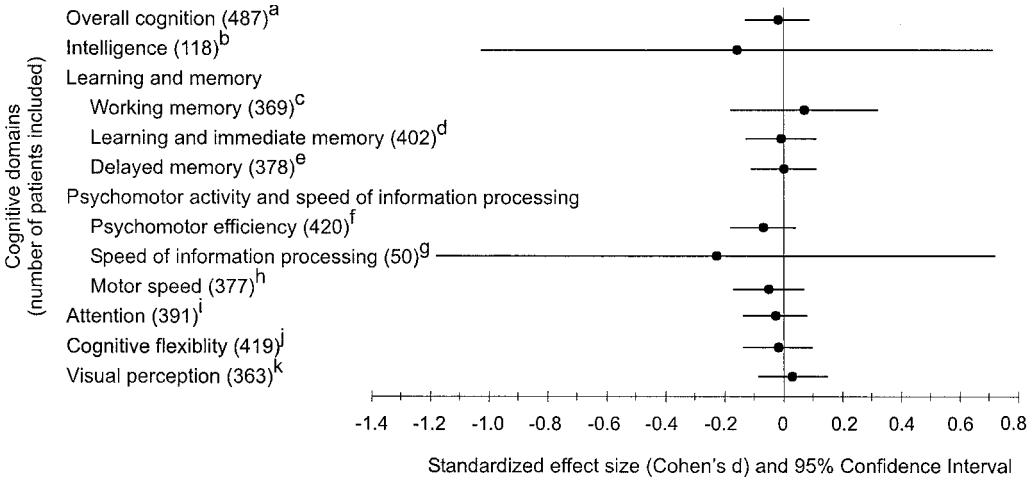


**Figure 2 —***Standardized effect sizes (Cohen's* d*) and 95% CIs for the cognitive domains in patients with compared with patients without recurrent episodes of severe hypoglycemia. Number of patients with recurrent episodes of severe hypoglycemia in each domain is listed between brackets. Nonsignificant* P *values are not shown. Refs.: a = (4,29–31,36,37,39,41), b = (29,30,36,41), c = (4,31,37,39,41), d = (29,36,37,39), e = (29,37,39), f = (30,37,39,41), g = (29,36), h = (4,39,41), i = (29,31,37,39,41), j = (4,29,36,37,39), and k = (29,39)*

speed, verbal learning and immediate memory, and mental flexibility.

Figure 2 shows that patients with recurrent severe hypoglycemic episodes were not significantly more impaired in either overall cognition or in any of the single cognitive domains than patients without hypoglycemic episodes. It should be noted that the large prospective study did not find an effect of the occurrence of severe hypoglycemic events, whereas some of the smaller cross-sectional studies did. This explains some of the heterogeneity in the results as presented in Fig. 2 (e.g., intelligence and speed of information processing). In some of the studies included in the analyses presented in Fig. 2, the patient groups with recurrent hypoglycemic episodes had lower $HbA_{1c}$ values than the groups without these episodes. Differences in $HbA_{1c}$ levels between groups with and without recurrent severe hypoglycemic episodes could be a confounding factor, as lower $HbA_{1c}$ levels (better glycemic control) and severe hypoglycemic episodes may have opposing effects on the brain, thus masking the effects of hypoglycemia per se. A separate analysis, only including those studies with equal levels of $HbA_{1c}$ (within 1% difference), in the group with and without recurrent hypoglycemic episodes (4,30,36, 41) revealed no significant effect either.

From the ten relatively small cross-sectional studies (1,3,4,8,9,19,27,33,42, 44) that looked at the correlation between the frequency of hypoglycemic episodes and cognitive function, about half did find an inverse relationship. The single longitudinal study (40) addressing the same issue did not find such an effect.

**CONCLUSIONS** — The results of the current study strongly support the hypothesis that there is a relationship between cognitive dysfunction and type 1 diabetes. Overall, summarizing all studies and all cognitive domains (i.e., overall cognition), there is a modest but highly significant difference in cognitive performance between patients with type 1 diabetes and nondiabetic control subjects. The pattern of cognitive findings does not suggest an overall impairment of cognitive function but is characterized by a slowing of mental speed and a diminished mental flexibility. Patients with type 1 diabetes seem to be less able to flexibly apply acquired knowledge in a new situation. Crystallized intelligence, especially, is usually not considered to be a domain to show deterioration, but mental slowing and diminished mental flexibility may explain the lowered performance on tests that are used to assess intelligence. However, since not all studies included in this meta-analysis matched subjects on education, one could also hypothesize that these effects are the consequence of imperfect group matching. In a separate subanalysis that included only those studies that did match on education, both crystallized and fluid intelligence showed a statistically significant effect size indicating a deterioration of general intellectual ability that is not the result of differences in educational levels. Learning and memory, contrary to some reports (e.g., 3,29), are spared.

Although the magnitude of most of these cognitive decrements is relatively modest (within one half SD of the control group or an equivalent effect size of $<0.5$), moderate forms of cognitive dysfunction can potentially hamper everyday activities, and they can be expected to present problems in more demanding situations. As such, they can have a negative impact on the quality of life of patients. A study on the impact of cognitive problems in patients with type 1 diabetes on the day-to-day functioning is still missing. It is noteworthy that in type 2 diabetes, cognitive dysfunction is indeed associated with poorer ability in diabetes self-care and greater dependency (45).

Our survey on the impact of metabolic control and disease duration on cognition has produced no consistent results, but microvascular complications such as retinopathy and neuropathy do appear to be associated with impaired cognition. We observed that the pattern and severity of cognitive changes in study populations of adult diabetic patients with an average age at diabetes onset $<15$ years were comparable to those with an average age at onset above this age. It should be noted, however, that studies that assessed cognition in children with diabetes (which were not included in the present meta-analysis) observed that a very early age at onset (before the age of 5 years) does ap-

pear to be associated with more severe impairments of cognitive performance (11,46). Our meta-analysis does not support the idea that there are important negative effects from recurrent episodes of severe hypoglycemia on cognitive functioning.

When addressing the relationship between these disease variables and cognition, it is important to note that studies that examined these issues were mostly (except for two large studies [39,40]) cross-sectional and included relatively low numbers of patients ($n < 50$). Figure 1 clearly indicates that the combined effect of type 1 diabetes and its associated conditions leads to cognitive impairment of a magnitude in the order of an effect size of 0.4 (overall cognition). Although such an effect size is relevant when comparing different groups, one has to acknowledge that in relation to the total variation within a group of individuals, this effect size is rather modest. Therefore, it is questionable whether the studies that have been performed thus far are adequately powered and designed to give a true insight in the exact relation between individual disease variables and cognition. A solution to this problem could be a longitudinal design. The intraindividual change in cognition over time, due to the disease process, should correlate closely with relevant disease variables. In contrast, the interindividual variation in a single cross-sectional assessment is also strongly affected by many other confounding factors such as educational level, socioeconomic background, or genetic factors. Interestingly, a longitudinal study in children (46) and a longitudinal study in adults (47) that could not be included in the formal meta-analysis both demonstrate progression of cognitive deficits in time, thus indicating that diabetes duration is a relevant factor and emphasizing our point that longitudinal studies are of additional value. Another drawback of a cross-sectional design is that the occurrence of hypoglycemic episodes or the history of metabolic control has to be assessed retrospectively. Any effect of metabolic control variables or experienced severe hypoglycemic episodes is therefore contaminated by the lack of precise measurements of these variables.

Another important issue is the interaction among different disease variables. In particular, patients with diabetes onset before the age of 5 years (11) and patients with advanced microangiopathy (48) could be more sensitive to the effects of hypoglycemic episodes or elevated $HbA_{1c}$ levels. In this respect, it is also important to note that in the large longitudinal study that addressed the effects of hypoglycemia on cognition, patients with advanced microvascular complications were excluded (39). Indeed, two cross-sectional studies (27,43) and one prospective study (40) that addressed the effect of hypoglycemic episodes in patients with microvascular complications do report adverse effects of recurrent hypoglycemia in this subpopulation.

When regarding the effect of diabetes on cognition, there are a number of other variables with potential relevance that need to be discussed. Research on type 2 diabetes suggests that there may be an interaction between age and the severity of cognitive problems: cognitive deficits appear to be more pronounced in individuals who are >60–65 years of age (49). Thus far, no studies have addressed the effects of type 1 diabetes on cognition in individuals of more advanced age. This is a subject that warrants further investigation.

Some studies (19,27) but not all (33) have shown that sex is a variable that could be of influence on cognitive performance. Most studies included in Tables 1 and 2 have matched their groups on sex, so no separate analysis could be performed to assess the influence of sex, and this is another topic that warrants further investigation.

Studies in type 2 diabetes also indicate that hypertension and cerebrovascular disease may have synergistically interactive effects with diabetes on cognition (49). However, in the population included in the present meta-analysis (average age ~35 years), clinically overt cerebrovascular disease is very rare (and was often defined as an exclusion criterion), and hypertension is much less prevalent than in type 2 diabetes. Therefore, we do not expect that either cerebrovascular disease or hypertension have a substantial contribution to the cognitive impairments that have been established in this meta-analysis.

Depression is another condition with an impact on cognition that is more prevalent in type 1 diabetic patients than in nondiabetic control subjects (50,51). In fact, the pattern of cognitive impairments as presented in Fig. 1 partially resembles the pattern seen in major depression (15). However, most studies in this meta-analysis have excluded patients with major depression or have used screening instruments to control for depressive symptoms. Both studies that did and did not specifically exclude patients with major depression found similar effects on cognition. Hence, depression does not appear to be a major factor in the cognitive impairments as presented in Fig. 1.

In conclusion, this meta-analysis shows that there is a relationship between cognitive dysfunction and type 1 diabetes. The main open questions that remain relate to the relative contribution of different disease variables, such as diabetes duration, levels of glycemic control and the development of microvascular complications, and the possible influence of comorbid conditions. Longitudinal studies could play an important role in resolving these issues.

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