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Mild depressive symptoms do not influence cognitive functioning in patients with type 2 diabetes

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Summary Type 2 diabetes (T2DM) is associated both with cognitive decrements and depressive symptoms. Since depression in itself has been associated with cognitive decrements we aimed to investigate the influence of depressive symptoms on the relation between T2DM and cognitive functioning.

Data were derived from three independent studies on cognitive functioning in patients with T2DM (n = 366) and controls without diabetes (n = 204), two with longitudinal and one with only cross-sectional assessments. Depressive symptoms were measured with self-report inventories (CES-D or BDI-II). The composite z-score of the domains memory, information-processing speed, and attention and executive function was the primary cognitive outcome measure. Mixed linear regression analyses were used in a stepped approach to compare cognitive functioning between (1) patients with T2DM and controls (cross-sectionally and longitudinally), (2) participants with and without depressive symptoms, separately for patients and controls, and (3) patients and controls after adjustment for depressive symptoms. In addition the mediating effect of depressive symptoms was assessed with a bootstrapping technique.

Depressive symptoms were present in 11% of the patients with T2DM and in 7% of controls (p = 0.15). Cognitive performance in patients with T2DM was worse than in controls (overall difference composite z-score −0.13). However, T2DM was not associated with accelerated cognitive decline over three years of follow-up relative to controls. Controls with depressive

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symptoms performed worse than those without depressive symptoms, although not statistically significant. Performance in patients with T2DM with and without depressive symptoms was similar. Adjustment for depressive symptoms and estimation of the mediating effect showed that the difference between patients and controls was not mediated by depressive symptoms.

In conclusion, the modest cognitive decrements that are associated with T2DM are not due to the presence of mild depressive symptoms.

1. Introduction

In patients with type 2 diabetes (T2DM) small decrements in cognitive functioning are consistently found on the domains memory, information-processing speed, and attention and executive functioning (Awad et al., 2004). Diabetes is also an established risk factor for dementia, with an up to twofold increased risk (Ott et al., 1999; Biessels et al., 2006). In addition, depressive symptoms are more common among patients with T2DM (Anderson et al., 2001; Ali et al., 2006; Mezuk et al., 2008; Pan et al., 2010) with depression occurring twice as often in patients with diabetes compared to individuals without diabetes (Anderson et al., 2001).

In the general population, depressive symptoms are associated with lower cognitive performance and an increased risk for dementia (Jorm, 2000; Ownby et al., 2006). In people with depressive symptoms impairments are found in the domains memory and information-processing speed (Alexopoulos et al., 2002; Butters et al., 2004; Airaksinen et al., 2007). Therefore, the question arises whether depressive symptoms play a mediating role in the relation between T2DM and cognitive functioning and cognitive decline. In a meta-analysis of three studies, all with the same detailed standardized neuropsychological assessment, we studied the influence of depressive symptoms on the relation between T2DM and cognitive functioning in a cross-sectional and longitudinal design.

2. Methods

Data were derived from three studies that assessed cognitive functioning in patients with T2DM relative to controls: the ADDITION-Netherlands study (Koekkoek et al., 2012), the UDES (van den Berg et al., 2010) and the Hoorn study (van den Berg et al., 2008).

2.1. Design of the studies

The ADDITION study (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care) was a cluster-randomised trial in patients with screen-detected T2DM that compared the effectiveness of an intensive multifactorial treatment with routine care on cardiovascular outcome (Griffin et al., 2011). The study started with a population-based screening for diabetes followed by inclusion of newly diagnosed patients with diabetes in the trial. In a subgroup of patients from The Netherlands cognition was assessed through two standardized neuropsychological assessments, in 2006—2007 and again in 2009—2010 (Koekkoek et al., 2012). Control participants without diabetes were recruited among spouses and acquaintances of the patients.

The UDES (Utrecht Diabetic Encephalopathy Study) was a longitudinal study on determinants of impaired cognition in patients with T2DM in The Netherlands (van den Berg et al., 2010). Patients were recruited through their general practitioner. Controls were recruited among spouses and acquaintances of the patients. They were first examined between 2002 and 2004 and again four years later (2006—2009).

The Hoorn study was a population-based cohort study on glucose metabolism, which started in 1989 in the middle-sized town of Hoorn, The Netherlands (Mooy et al., 1995). A random sample of inhabitants of Hoorn was invited to participate in the study. Over the years three follow-up examinations were performed (Mooy et al., 1995; de Vegt et al., 2001; van den Berg et al., 2008). In the third follow-up examination cognitive functioning was assessed (van den Berg et al., 2008). For the present study participants of the Hoorn study were reclassified based on their fasting glucose of the last follow-up examination in patients with T2DM and control subjects.

The ADDITION study and the UDES were approved by the medical ethics committee of the University Medical Center Utrecht, The Netherlands. The Hoorn study was approved by the medical ethics committee of the VU University Medical Center, Amsterdam, The Netherlands. Written informed consent was obtained from all participants.

2.2. Study populations

Fig. 1 represents a flowchart demonstrating drop-out and follow-up of the three studies. The first neuropsychological assessment in the ADDITION study was performed in 183 patients with screen-detected T2DM, aged between 50 and 70 years. Their diabetes was screen-detected approximately three years before, following a standardized protocol (Janssen et al., 2007). Classification was done according to the WHO-criteria (WHO, 1999). Of these patients 135 were re-examined three years later. During the second examination eight patients did not complete a depressive symptoms questionnaire and were therefore excluded for the longitudinal analyses. In the UDES 122 patients aged between 56 and 80 years, known with T2DM for at least one year, underwent the first neuropsychological assessment. Twenty-three patients were excluded from the present analyses as sixteen patients had no baseline depressive symptoms questionnaire and seven had no estimated level of (crystallized) intelligence. Four years later 68 patients completed the second neuropsychological assessment. Participants of the Hoorn study were aged 50—75 years at recruitment. For a diagnosis of diabetes fasting blood glucose was measured and subsequently an oral glucose tolerant test (OGTT) was administered and classified according to the WHO-criteria (WHO, 1999). Participants already known with diabetes and/or using glucose-lowering therapy were categorized as having

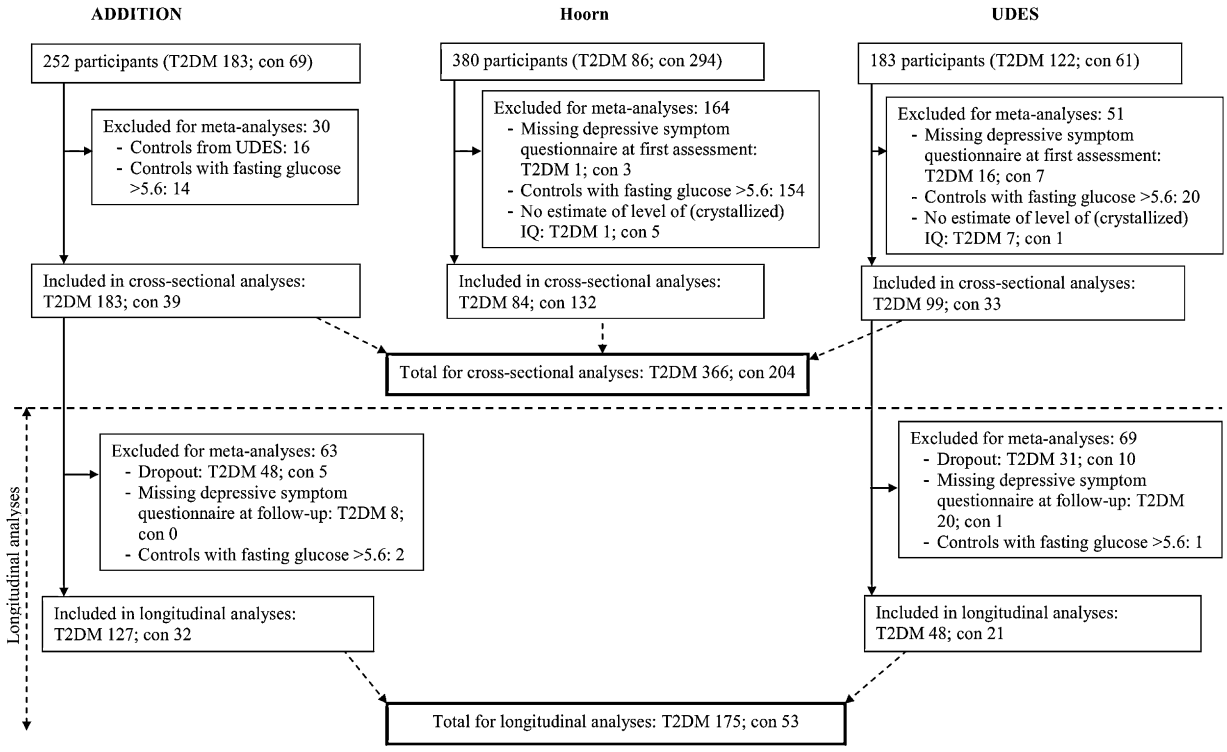

Figure 1 Flowchart of study participants. T2DM: type 2 diabetes; con: controls.

diabetes. Eighty-six patients fulfilled the criteria for diabetes at the third examination and received a neuropsychological assessment. One person with a missing baseline depressive symptoms questionnaire and one without estimated level of (crystallized) intelligence measured were excluded.

Sixteen control participants of the UDES were also used as controls in the ADDITION-study. For the present pooled analyses these sixteen controls were only included in the population of the UDES. From all three studies only control participants with a fasting glucose $\leq$5.6 mmol/L were included. This left 39, 33 and 132 controls from the ADDITION, UDES and Hoorn study respectively for inclusion in the present pooled analysis.

All participants were functionally independent and Dutch speaking. None of them had a history of neurological or psychiatric disorders that could influence cognitive functioning or a history of alcohol or substance abuse. Individuals with a previous non-disabling stroke (i.e. without interference with usual daily activities) could participate.

2.3. Neuropsychological assessment

The neuropsychological assessments in all three studies included the same nine tests addressing three cognitive domains, that are most consistently affected in T2DM in previous studies (Awad et al., 2004): memory, information-processing speed, and attention and executive functioning. The division in cognitive domains was made a priori, according to neuropsychological practice and cognitive theory (Lezak et al., 2004). The domain 'memory' was subdivided in four domains: working memory, immediate memory and learning rate, forgetting rate, and incidental memory. Working memory was assessed by the forward and backward digit span of the Wechsler Adult Intelligence Scale — 3rd edition (WAIS-III) (Wechsler, 1997) and the Corsi Block-tapping Task (Kessels et al., 2000). The product scores of both measures (number correct times span length) were used. Immediate memory and learning rate was assessed with the Rey Auditory Verbal Learning Test (RAVLT) (Van der Elst et al., 2005) and the Location Learning Test (LLT) (Bucks et al., 2000). For the RAVLT the mean of the total number of words remembered in five learning trials was recorded and a learning index was calculated. For the LLT the total number of displacements over five trials and a learning index was calculated. Forgetting rate was calculated in the RAVLT and the LLT by correcting the scores in the delayed recall condition for the score obtained in the fifth learning trial. Incidental memory was measured with the delayed recall of the Rey-Osterrieth Complex Figure Test (Rey, 1941). This score was also corrected for the score obtained in the copy condition. The domain 'information-processing speed' was assessed by the Trail-making Test Part A (TMT-A) (Corrigan and Hinkeldey, 1987), the Stroop Color-Word Test (part 1 and 2) (Stroop, 1935) and the subtest Symbol Digit Substitution of the WAIS-III (SS-WAIS-III). Time to complete the TMT-A task was recorded in seconds; the mean of the total time needed to complete part I and II of the Stroop was calculated and for the SS-WAIS-III the total correct numbers of copied symbols within two minutes was recorded. The domain 'attention and executive functioning' was assessed by the Trail-making Test Part B (ratio score) (Corrigan and Hinkeldey, 1987), the Stroop Color-Word Test (part 3; ratio score), the Brixton Spatial Anticipation Test (Burgess and Shallice, 1997) recording the number of errors, and a letter fluency test using the letters 'N' and 'A' and a category fluency test (animal naming) recording the total number of correct responses

(Deelman et al., 1981). The Dutch version of the National Adult Reading Test was used to estimate level of (crystallized) intelligence (Schmand et al., 1992). The tests were administered in a fixed order by neuropsychologists and neuropsychologists in training and took about 90 min to complete.

Raw test scores at first and second neuropsychological assessment were standardized into *z*-scores per test, using the pooled mean of baseline scores of all control participants of the three studies. The *z*-scores of each domain were calculated by averaging the test scores comprising that domain. The primary cognitive outcome measure was defined as the mean composite *z*-score of the domains memory, information-processing speed and attention and executive function.

In the ADDITION and Hoorn study depressive symptoms were assessed with the validated Dutch version of the 20-item Centre for Epidemiologic Studies Depression Scale (CES-D) (Bouma et al., 1995) and in the UDES with the Dutch version of the Beck Depression Inventory 2nd Edition (BDI-II) (Beck et al., 1996). Both are self-report questionnaires to measure the presence of depressive symptoms on a four-point scale. Higher scores indicate more depressive symptoms. A score $\geq$16 on the CES-D and a score of $>$13 on the BDI is generally accepted as the cut off score for the presence of depressive symptoms (Radloff, 1977; Beekman et al., 1997). The accuracy of these depressive screening instruments was examined by Katz et al., who found comparable sensitivities and specificities for the CES-D and the BDI when the cut off scores were respectively $\geq$16 and $>$13 (Katz et al., 2004). Therefore these cut off scores were used to classify depressive symptoms as absent or present.

2.4. Clinical characteristics

At the time of the neuropsychological assessments body weight, height, waist circumference and blood pressure were measured and body mass index (BMI) was calculated. Demographic variables and medical history were recorded in a standardized interview. Venous blood samples were drawn after an overnight fast to determine fasting blood glucose, HbA1c and total cholesterol. The specific protocols are described in the separate studies (van den Berg et al., 2008, 2010; Koekkoek et al., 2012).

2.5. Statistical analyses

Categorical variables are reported as numbers and percentages, continuous variables as means with standard deviations (SD) and not normally distributed variables as median with interquartile range (IQR). Within the studies, differences between the patients with diabetes and control subjects were analyzed with Chi-square tests for categorical variables, independent *t*-tests for normally distributed continuous variables and Mann–Whitney tests for not normally distributed continuous variables.

Mean cognitive domain scores were calculated by averaging the test scores comprising that domain and comparisons

Table 1 Patient characteristics per study of patients with T2DM and controls.

	ADDITION		UDES		Hoorn	
	Type 2 diabetes	Controls	Type 2 diabetes	Controls	Type 2 diabetes	Controls
n	183	39	99	33	84	132
Age (yr)	63.0 ± 5.4	62.3 ± 6.5	65.6 ± 5.8	64.3 ± 6.0	74.5 ± 6.0	73.6 ± 6.1
Sex (% male)	61.2	28.2*	51.2	42.1	51.2	42.4
Estimated level of (crystallized) IQ	96.8 ± 19.4	106.4 ± 16.1*	97.7 ± 14.3	101.9 ± 14.0	96.4 ± 13.2	100.8 ± 12.8
BMI (kg/m^2)	30.6 ± 4.8	26.2 ± 3.6*	28.4 ± 4.3	25.8 ± 3.6	28.1 ± 4.2	26.1 ± 3.4*
Systolic blood pressure (mmHg)	143.7 ± 19.6	145.1 ± 24.9	147.7 ± 19.8	139.0 ± 19.5	151.9 ± 22.4	145.5 ± 21.6
Diastolic blood pressure (mmHg)	82.0 ± 10.4	83.1 ± 11.8	82.6 ± 10.8	80.0 ± 9.4	75.4 ± 11.8	73.8 ± 11.9
HbA1c (%)	6.2 ± 0.5	5.4 ± 0.2*	6.9 ± 1.2	5.5 ± 0.4*	6.4 ± 0.8	5.5 ± 0.3*
Total cholesterol (mmol/L)	4.1 ± 1.0	5.7 ± 0.8*	5.0 ± 0.9	5.8 ± 1.1*	4.8 ± 1.0	5.4 ± 1.1*
Depressive symptoms present (%)	9.8	10.3	9.5	0	12.9	7.6
CES-D/BDI-score[a]	4 (1–8)	6 (2–11)	6 (3–10)	3 (1–7)*	6 (2–10)	4 (1–8)
Diabetes duration (yr)	3.6 ± 0.6	NA	8.6 ± 6.1	NA	6.2 ± 2.6	NA
Hypoglycemic medication (%)						
Metformin	48.6		61.6		29.8	
Sulfonylurea	18.0		55.6		22.6	
Thiazolidinediones	12.6		6.1		9.5	
Insulin	0		29.3		4.8	

* *p*-Value $<$ 0.01 within a study between patients with T2DM and control subjects.
[a] Median with interquartile range. In the ADDITION and Hoorn-study the CES-D was used; in the UDES the BDI.

between groups were made using mixed linear regression analyses adjusted for age, gender and estimated level of (crystallized) intelligence. First, cognitive performance and depressive symptoms were compared between the diabetic and the control groups. Next, cognitive performance was compared between participants with and without depressive symptoms, separately for the diabetic and the control groups. Finally, to examine whether the relation between cognitive performance and diabetes status was mediated by depressive symptoms, we added the presence of depressive symptoms as a covariate in the first comparison. In addition, we estimated the possible mediating effect of depression and corresponding 99%-confidence interval (CI) with a bootstrapping technique (Preacher and Hayes, 2008). During bootstrapping the data set is sampled repeatedly to estimate the mediating effect in each resampled data set and reconstruct a 99%-CI. When the CI does not contain zero a mediating effect is present. We computed bootstrapped confidence intervals (5000 samples) for the size of the specific mediating effects using SPSS macros provided by Preacher and Hayes (2008).

In the longitudinal analyses, mean change in cognition per year was compared between the groups with and without diabetes using mixed linear models adjusted for age, gender, estimated level of (crystallized) intelligence. Because these analyses did not show accelerated cognitive decline in the group with diabetes, no further analyses on the possible modulating effects of depression were performed.

Secondary analyses were performed for each of the cognitive domains. In addition, to examine the influence of cardiovascular disease, two post hoc analyses were performed. In the first analyses participants with a history of stroke were excluded. The second additionally adjusted the primary comparisons for hypertension (defined by the use of antihypertensive medication or a blood pressure above 160 mmHg systolic and/or 95 mmHg diastolic) and hypercholesterolemia (defined by the use of cholesterol lowering medication or total cholesterol above 6.5 mmol/L). The analyses were performed per study and then combined in a fixed-effect model (Review Manager 5, Cochrane Collaboration). The *I*-squared (I^2) statistic was calculated to quantify

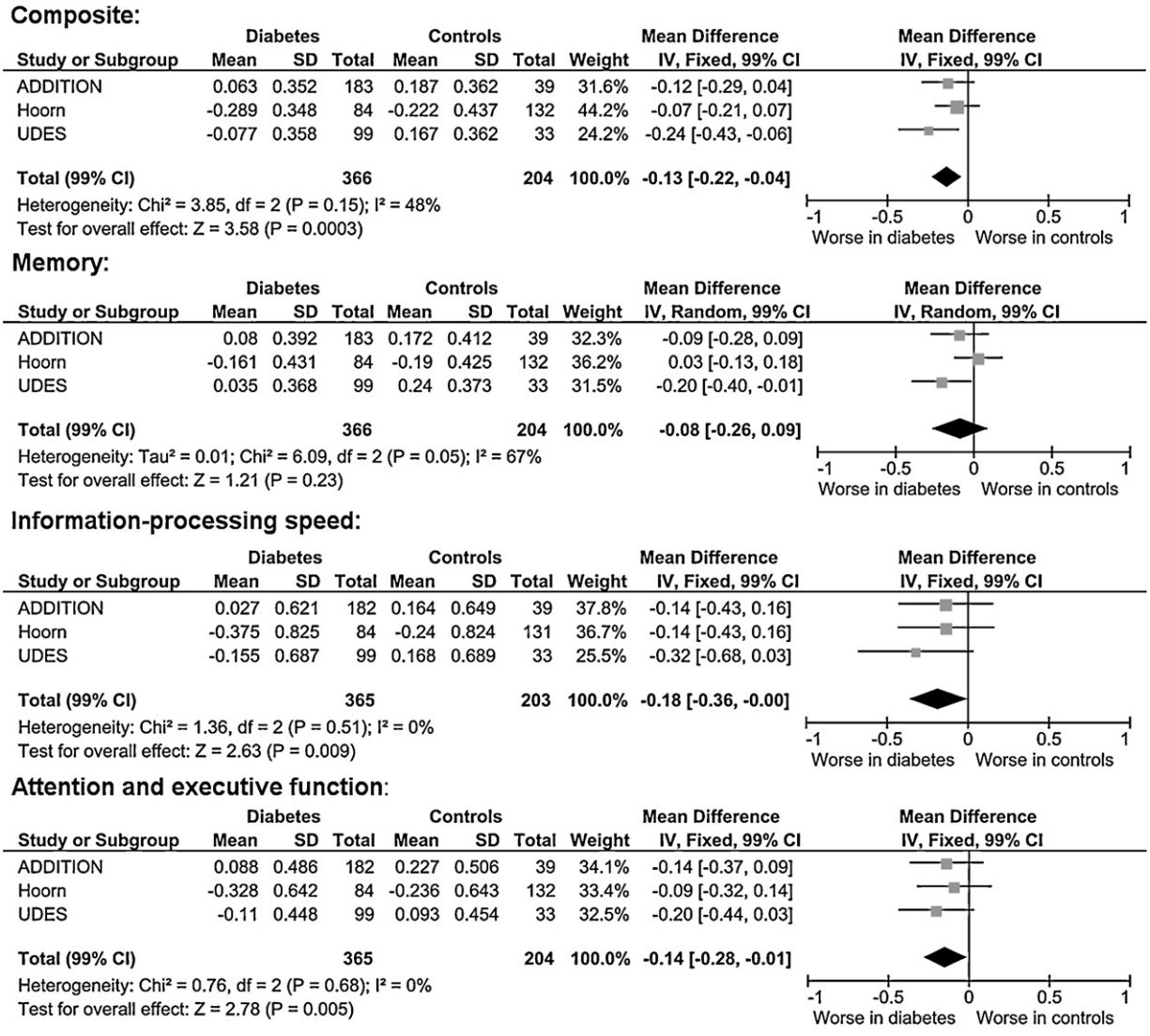

Figure 2 Cognitive scores in T2DM versus controls adjusted for age, gender and IQ.

the percentage of total variation across studies due to heterogeneity (Higgins and Thompson, 2002). In case of an I^2 above 50% a random-effect model was used. To minimize the possibility of type 1 errors, a p-value of less than 0.01 was considered statistically significant; therefore results are reported with a 99%-confidence interval.

3. Results

Table 1 shows the characteristics for the control group and patients with T2DM per study at the first neuropsychological assessment. Participants in the Hoorn study were older and T2DM patients in the UDES had a longer history of diabetes. Depressive symptoms were present in 10—13% of the patients with T2DM compared to 0—10% of the control participants (Table 1). Overall, depressive symptoms were present in 11% of the patients with T2DM and in 7% of controls ($p = 0.15$).

3.1. Cognitive performance

In all three studies, patients with T2DM showed worse cognitive performance than control participants with an overall difference in composite z-score of −0.13 (99%-CI −0.22 to −0.04; $p < 0.001$) (Fig. 2). Secondary analyses for the separate cognitive domains showed overall differences of −0.08 (memory), −0.14 (attention and executive function) and −0.18 (information-processing speed).

Because the UDES had no control participants with depressive symptoms, this study could not be included in the meta-analysis for the comparison of controls with and without depressive symptoms. In the other two studies the controls with depressive symptoms performed worse than those without depressive symptoms, although not significantly (overall difference composite z-score −0.25; 99%-CI −0.54 to 0.03; $p = 0.02$) (Fig. 3). Secondary analyses for the separate domains showed similar results. Also, no difference was found between patients with T2DM with and without depressive symptoms in any of the three studies on any of the domains (overall difference composite z-score 0.01; 99%-CI −0.15 to 0.18; $p = 0.82$) (Fig. 4).

Adjustment for depressive symptoms did not influence the difference in cognitive performance between patients with diabetes and controls; the difference in overall composite score remained −0.13 (99%-CI −0.23 to −0.03; $p < 0.001$) (Fig. 5). These results were confirmed by bootstrapping the mediating effect, with a mediating effect of depressive symptoms below 0.01 for all cognitive domains in all three studies (results not shown).

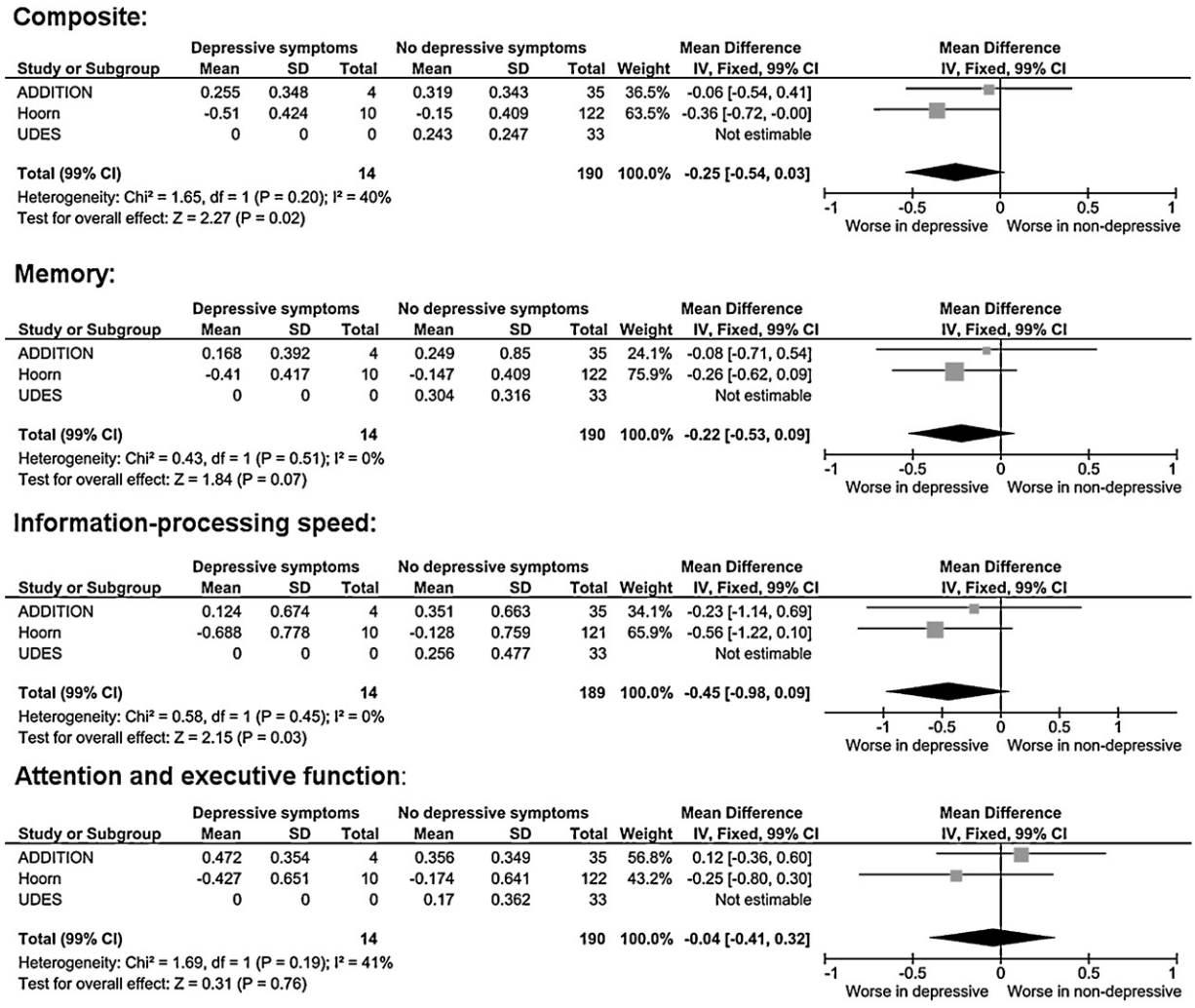

Figure 3 Cognitive scores in controls: depressive symptoms versus no depressive symptoms, adjusted for age, gender and IQ.

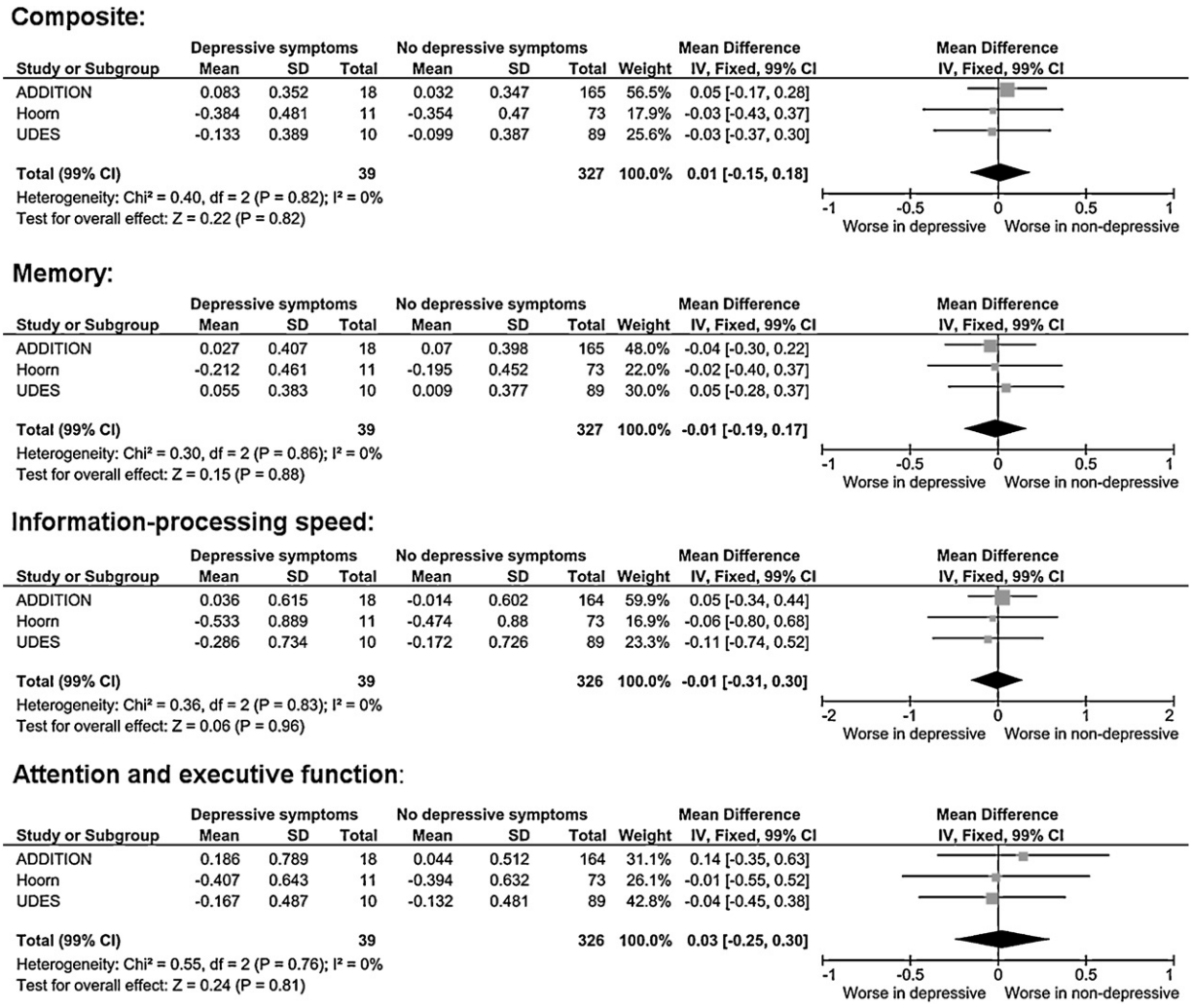

Figure 4 Cognitive scores in T2DM: depressive symptoms versus no depressive symptoms, adjusted for age, gender and IQ.

Post hoc analyses, one excluding participants with a history of stroke, another adjusting for hypertension and hypercholesterolemia, did not change the results (results not shown).

3.2. Cognitive decline

Cognitive decline was assessed in a pooled analysis of the ADDITION study and the UDES. Over a period of three to four years patients with T2DM showed no greater decline than control participants (overall difference in decline per year on composite score −0.01; 99%-CI −0.04 to 0.02; $p = 0.21$) (Fig. 6). We did not perform further longitudinal analyses on the mediating effect of depressive symptoms as no accelerated decline was found.

4. Discussion

The present study demonstrated more cognitive decrements in diabetes patients compared to controls. Controls with depressive symptoms performed worse than those without depressive symptoms, although not statistically significant, but performance in diabetes patients with and without depressive symptoms was similar. The pooled analysis, including over 350 patients and 200 controls, showed that cognitive decrements in patients with T2DM are not influenced by the presence of depressive symptoms.

Previous studies reported similar prevalence rates of co-morbid depressive symptoms in patients with T2DM compared to our sample. In a review examining the prevalence of co-morbid depression in diabetes, measured by self-report questionnaires, prevalence rates ranged from 8 to 31% in patients with T2DM with an overall prevalence of 18% (Ali et al., 2006) and between 5 and 24% in people without diabetes, with an average of 10%. A study in The Netherlands that administered the CES-D to a community-based sample of older adults, aged 55—85 years, found an overall prevalence of depressive symptoms (CES-D $\geq$ 16) of 17% in patients with T2DM (Pouwer et al., 2003). In the three included studies, the prevalence rates of depressive symptoms were in the low range of other studies and were not significantly different between diabetes patients and controls, which might have been influenced by selection bias. People with a depressive disorder often do not participate in research. Besides, they are often excluded from the analyses due to their depressive

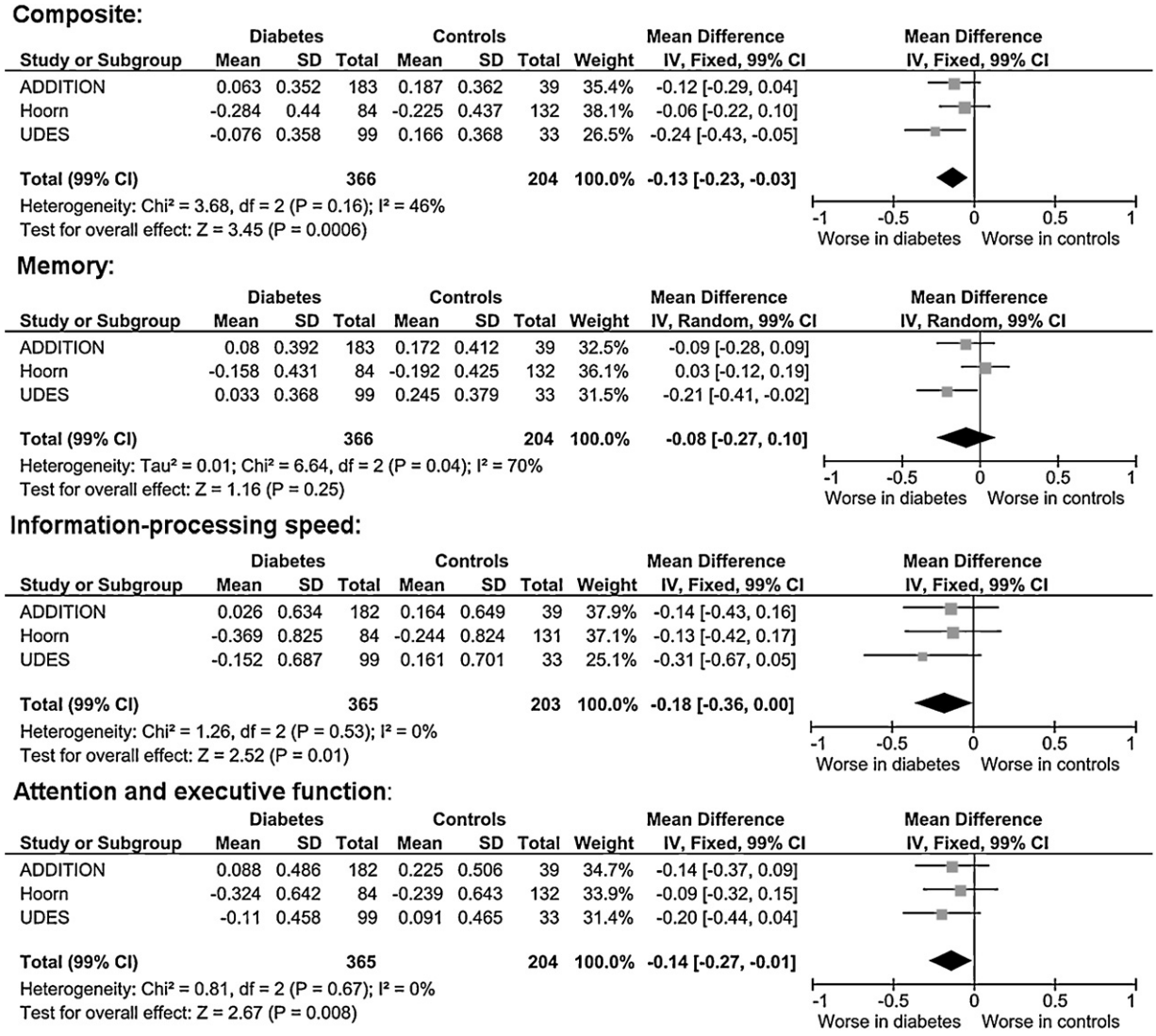

Figure 5 Cognitive scores in T2DM versus controls adjusted for age, gender, IQ and depressive symptoms.

symptomatology. The latter was also the case in the ADDITION study and the UDES; people with a diagnosis of severe depression were excluded.

Over the three studies, the difference in cognitive functioning between patients with T2DM and controls was at the lower end of the range of differences reported in other studies (Awad et al., 2004; van den Berg et al., 2009). Diabetes-associated decrements are often reported in other studies with effect sizes up to 0.6 (Awad et al., 2004; van den Berg et al., 2009). In accordance with the literature the domains information-processing speed and attention and executive functioning are most affected in the pooled analyses. In contrast, the domain memory showed no significant difference between patients and controls in our study (Awad et al., 2004; van den Berg et al., 2009; Reijmer et al., 2010). Several factors may have attenuated the differences in effect sizes. First of all, in our three cohorts patients with diabetes were well controlled for their diabetes and for vascular risk factors relative to control participants. Controls were not excluded if they had elevated vascular risk factor levels, therefore the contrast between participants with and without diabetes may be attenuated, as also hypertension and elevated lipid levels play a role in cognition (van den Berg et al., 2009). Another explanation might be that patients with modest cognitive decrements were reluctant to participate in research.

Both longitudinal studies found no difference in rate of cognitive decline between diabetes patients and controls which is in agreement with recent publication of a large study (Euser et al., 2010). In this study participants were followed for three years and no accelerated decline was found for both those with diabetes and those with elevated fasting glucose or insulin resistance (Euser et al., 2010). Other studies however found an up to 1.5 to two times increased decline in cognition compared to normal aging (Gregg et al., 2000; Fontbonne et al., 2001; Yaffe et al., 2004).

Little research has been done on the effect of depressive symptoms on cognitive functioning in patients with T2DM (Awad et al., 2004). Most previous studies have adjusted their analyses for the presence of depressive symptoms (Alexopoulos et al., 2002; Airaksinen et al., 2004; Butters et al., 2004) and reported that the association between diabetes

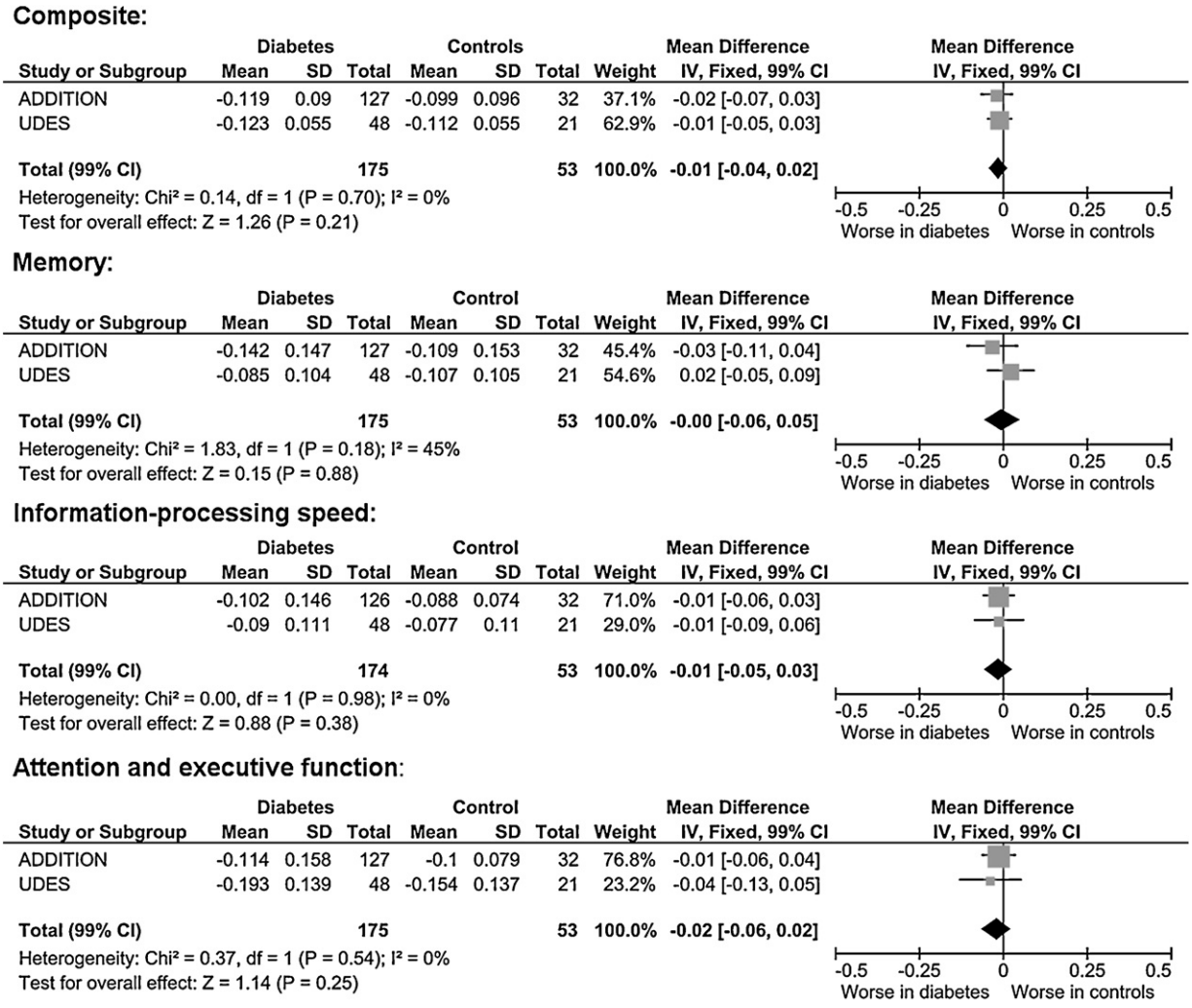

Figure 6 Cognitive decline per year in patients with T2DM versus controls adjusted for age, gender and IQ.

and cognitive functioning did not change after this adjustment (Lowe et al., 1994; Gregg et al., 2000). One study compared cognitive functioning between patients with T2DM with and without a major depressive disorder (Watari et al., 2006). Comparable to our study, they found no difference in cognitive performance between the two groups. Probably, diabetes-associated cognitive decrements and depressive symptoms emerge independently from each other and have different risk factors and etiologies.

In this article we included three studies that investigated cognitive functioning in patients with T2DM through an extensive neuropsychological assessment which was similar in all studies. This gave us the opportunity to examine the influence of depressive symptoms in a large group of patients with diabetes. Participants with comorbid conditions associated with type 2 diabetes (e.g. hypertension, dyslipidemia) were included in the analyses to form a representative group of diabetes patients. Nevertheless, our findings remained the same after adjusting for these potential confounders. The mean age of the participants over the three studies varied. This might be a reason for the variation in prevalence rates of depressive symptoms as elderly people more often have mild depressive symptoms. To minimize the number of statistical tests, we choose to divide the tests into cognitive domains instead of analyzing the effect of depressive symptoms per test. We cannot exclude the possibility that a different approach might have lead to different results. Furthermore, it should be emphasized that cognitive functioning in the study populations was within the range of normal aging and that we only included people with mild depressive symptoms. The results therefore might not be generalizable to people with major depression or pathological cognitive decline.

In conclusion, the cognitive decrements in patients with T2DM compared to people without diabetes are not influenced by the mild depressive symptoms that are known to be present in one out of six of these patients.

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Contributors

GR was principal investigator of the ADDITION study. GJB and LJK were principal investigators of the UDES. JD, CS and GN

were principal investigators of the Hoorn study. EvdB, CR and YR collected the cognitive data in the three studies. PK performed the statistical analysis and wrote the first draft of the manuscript. PK, GR, KG, LK and GJB participated in the interpretation of data and contributed to the discussion. All authors reviewed/edited the manuscript and have approved the final manuscript.

Conflict of interest

The authors report no conflict of interest.

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