Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes — The ADDITION-Netherlands study: A cluster-randomized trial

Paula S. Koekkoek [a,*], Carla Ruis [b], Maureen van den Donk [a], Geert Jan Biessels [b], Kees J. Gorter [a], L. Jaap Kappelle [b], Guy E.H.M. Rutten [a]

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands
[b] Department of Neurology, Rudolf Magnus Institute of Neurosciences, University Medical Center Utrecht, The Netherlands

ARTICLE INFO

ABSTRACT

Aim: To assess whether an intensive multifactorial treatment can reduce cognitive decrements and cognitive decline in screen-detected type 2 diabetes.
Methods: The multinational ADDITION-study, a cluster-randomized parallel group trial in patients with screen-detected type 2 diabetes, compared the effectiveness of intensive multifactorial treatment (IT; lifestyle advice and strict regulation of metabolic parameters) with routine care (RC) on cardiovascular outcome. In The Netherlands randomization was stratified according to practice organization. Allocation was concealed from patients. The present study assessed the effect of IT on cognition through two neuropsychological assessments (NPA) on two occasions. The assessments took place three and six years after the start of the intervention. Non-diabetic controls served as reference group. The first NPA was performed in 183 patients (IT: 97; RC: 86) and 69 controls. The second NPA was performed in 135 patients (IT: 71; RC: 64) and 55 controls. Primary outcome was a composite score, including the domains memory, information-processing speed and attention and executive function. Comparisons between the treatment groups were performed with multi-level analyses.
Results: The first NPA showed no differences between the treatment groups (mean difference composite z-score: 0.00; 95%-CI −0.16 to 0.16; IT vs RC). Over the next three years cognitive decline in the diabetic groups was within the range of the reference group and did not differ between the treatment arms (difference decline between diabetic groups −0.12; −0.24 to 0.01; IT vs RC).
Conclusions: Six years of IT in screen-detected type 2 diabetes had no benefit on cognitive functioning over RC.

© 2011 Elsevier B.V. Open access under the Elsevier OA license.

1. Introduction

With the increasing incidence of type 2 diabetes, the prevalence of associated complications increases as well. Besides well-known complications, diabetes is also associated with decrements in learning and memory, mental flexibility and information-processing speed [1–3] and with an increased risk of developing dementia [4–6]. These cognitive decrements may already start to develop in pre-diabetic stages [7] and are slowly progressive over the years [3].

The ADDITION study (Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care) [8], started with a population-based screening for type 2 diabetes.

In those identified through screening, the effectiveness of intensive multifactorial treatment on cardiovascular outcome was compared with routine care according to national guidelines. At start of the ADDITION-study it was known that patients with type 2 diabetes have a twofold increased risk for developing dementia. Studies also suggested that cognitive functioning in patients with type 2 diabetes might benefit from several months of improved glycemic control [9,10]. It was unknown, however, what the rate of cognitive decline was in people with early type 2 diabetes relative to controls. It was also unknown whether we could prevent or diminish cognitive decline in patients with screen-detected type 2 diabetes with for example lifestyle advice and strict regulation of glucose levels, blood pressure and lipid levels. Therefore we performed an add-on study in a subgroup of patients of the ADDITION-Netherlands study in which cognition was assessed on two occasions. The assessments took place three and six years after start of the intervention. Our aim was to investigate whether cognitive functioning benefited from intensive multifactorial treatment compared to routine care after three years and whether a further three years of intensive treatment attenuated cognitive decline.

* Corresponding author at: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Huispostnr STR.6.131, P.O. Box 85500, 3508 GA Utrecht, The Netherlands. Tel.: +31 88 75 55110; fax: +31 88 75 68099.
E-mail address: p.s.koekkoek-3@umcutrecht.nl (P.S. Koekkoek).

2. Methods

2.1. Embedding

The ADDITION study is a pragmatic multinational cluster-randomized parallel group trial that compared screening plus intensive multifactorial treatment to screening and routine care. Mean follow-up was 5.3 years [8]. Between 2002 and 2004, a population-based screening among 79 general practices in The Netherlands, screened 56 978 individuals between 50 and 70 years for type 2 diabetes. In total 586 patients were identified with type 2 diabetes according to the WHO-criteria [11,12]. To avoid contamination, randomization was done on the level of the general practice. Before screening, general practices were therefore randomly allocated to intensive multifactorial treatment or routine care using computer-generated random numbers, stratified according to practice organization (single-handed vs. group practice) (Fig. 1). Allocation was concealed from patients throughout the trial. Exclusion criteria for participation in the intervention study were: life expectancy of less than twelve months, being housebound, or psychological or psychiatric problems that were likely to invalidate informed consent [13]. Sixty-nine patients declined participation and nineteen did not meet the eligibility criteria. Subsequently, 498 individuals were included in the Dutch part of the ADDITION intervention study [14]. Patients started the intervention within six weeks after screening.

2.2. Treatment protocols

Intensive multifactorial treatment consisted of lifestyle advice regarding diet, physical activity and smoking and promotion of protocol-driven strict regulation of metabolic parameters [8]. HbA1c level had to be kept <53 mmol/mol (7.0%). Glucose-lowering therapy with a biguanide, prandial glucose regulator or sulphonylurea had to be altered when HbA1c was >48 mmol/mol (6.5%). Antihypertensive treatment with an ACE inhibitor was prescribed if blood pressure was >120/80 mmHg. When blood pressure was >135/85 mmHg calcium channel blockers, thiazides or beta-blockers were added in a stepwise approach. Patients receiving antihypertensive treatment were also treated with aspirin 80 mg/day. Treatment with a statin was indicated if total cholesterol was >3.5 mmol/L; dose needed to be increased when total cholesterol was >5.0 mmol/L or >4.5 mmol/L in patients with known cardiovascular disease (CVD). Although targets were specified and classes of medication recommended, decisions about medication were made by general practitioners and patients.

In the routine care group, general practitioners were only informed about diagnostic test results. Patients received treatment according to the current guidelines of the Dutch College of General Practitioners. At start of ADDITION the guideline from 1999 was followed with target levels for HbA1c, blood pressure and cholesterol below 69 mmol/mol (8.5%), 150/85 mmHg and 5.0 mmol/L respectively [15]. In 2006 a new guideline was introduced with stricter goals for HbA1c and systolic blood pressure respectively being below 53 mmol/mol (7.0%) and 140 mmHg [16]. Furthermore a statin was advised for almost all patients. Patients with CVD received aspirin 80 mg/day. Education and lifestyle advice were also given.

2.3. Study population and cognitive assessment

In the present add-on study, patients were invited to participate in a project in which cognition was assessed. We intended to include approximately one hundred patients per treatment group, allowing to detect a difference between the groups of an effect size of 0.3 standard deviation units, which is considered to be a small to medium effect in neuropsychological studies [17], with 80% power and α of 5%. Patients were not eligible for the cognition sub-study if they had a known psychiatric or neurological disorder that could influence cognitive functioning, history of alcohol or substance abuse or were unable to complete a neuropsychological assessment (NPA). Individuals with a previous non-invalidating stroke could participate. Patients were randomly sampled from both groups, after their records had been checked for exclusion criteria, and subsequently invited to participate. A reference group of participants without diabetes was recruited among spouses and acquaintances of the patients, matched for age, sex and educational level. An additional exclusion criterion for control participants was a fasting blood glucose >7.0 mmol/L. Because some of the exclusion criteria only became evident at a face to face interview (e.g. alcohol abuse), a second assessment against exclusion criteria was done after the first NPA by investigators unknown to group allocation and cognitive status. The study was approved by the medical ethics committee of the University Medical Center Utrecht, The Netherlands. Written informed consent was obtained from all participants.

2.4. Neuropsychological assessment

Participants underwent a detailed NPA on two occasions, in 2006–2007 and 2009–2010. Both NPAs consisted of twelve verbal and nonverbal tasks addressing six cognitive domains. The division in cognitive domains was made a priori, according to standard neuropsychological practice and cognitive theory [18]. For the present study we focused on the domains which have previously been shown to be affected in type 2 diabetes, namely the domains memory, information-processing speed and attention and executive function [1–3]. The domain 'memory' was assessed by the forward and backward digit span of the Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III) [19], the Corsi Block-tapping Task [20], the Rey Auditory Verbal Learning Test [21], the Location Learning Test [22] and the delayed recall of the Rey–Osterrieth Complex Figure Test [23]. The domain 'information-processing speed' was assessed by the Trail-making Test Part A [24], the Stroop Color-Word Test (part 1 and 2) [25] and the subtest Symbol Digit Substitution of the WAIS-III. The domain 'attention and executive function' was assessed by the Trail-making Test Part B (ratio score) [24], the Stroop Color-Word Test (part 3; ratio score), the Brixton Spatial Anticipation Test [26], a letter fluency test using the letters 'N' and 'A' and category fluency (animal naming) [27]. Furthermore, premorbid level of intelligence (IQ) was estimated by the Dutch version of the National Adult Reading Test [28]. Educational level was divided into seven categories (1,<6 years of education; 2, 6 years; 3, 8 years; 4, 9 years; 5, 10–11 years; 6, 12–18 years and 7,>18 years). The tests were administered in a fixed order at the patients' home by neuropsychologists and neuropsychologists in training. The entire battery took about 90 minutes to complete.

To assess possible selective loss to follow-up at the second NPA we invited all non-participants and participants of the second NPA to take part in the modified Dutch version of the Telephone Interview for Cognitive Status (TICS-m), a 12 item screening instrument designed to identify persons with dementia (maximum score 50) [29].

2.5. Timeline

The first NPA took place three and a half years (mean 3.6 ± 0.6 ($\pm$SD)) after screening and start of the intervention (Fig. 2). The second NPA was performed 6.8 ($\pm$0.6) years after the screening, at the end of the main ADDITION study, and 3.2 ($\pm$0.3) years after the first NPA. There was a mean interval of 4.6 ($\pm$3.6) months between the second NPA and the last measurements of the main ADDITION study.

2.6. Risk factor assessment

At time of the NPAs body weight, height and blood pressure were measured and BMI was calculated. Systolic and diastolic blood pressures were measured at the beginning and the end of the NPA with an
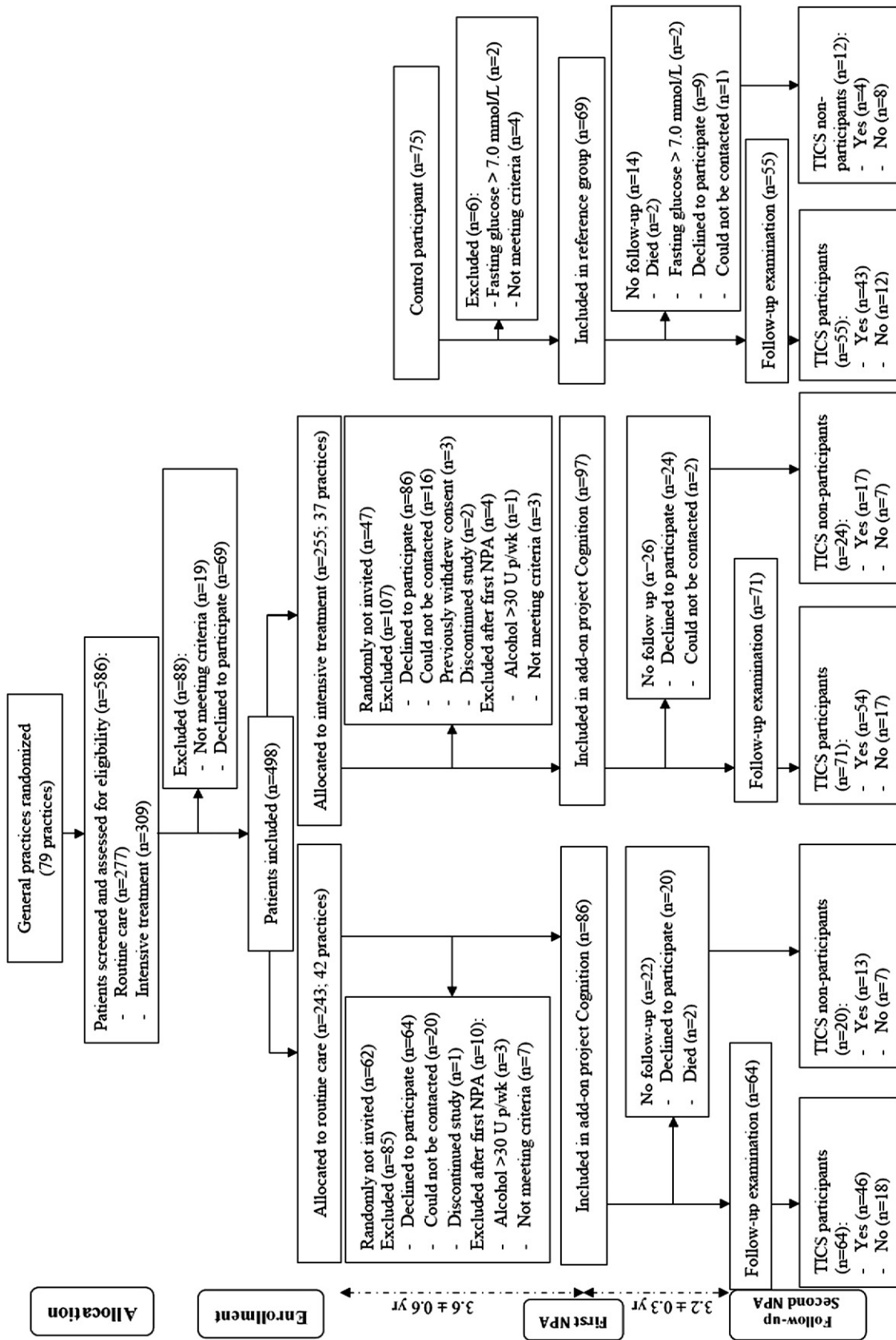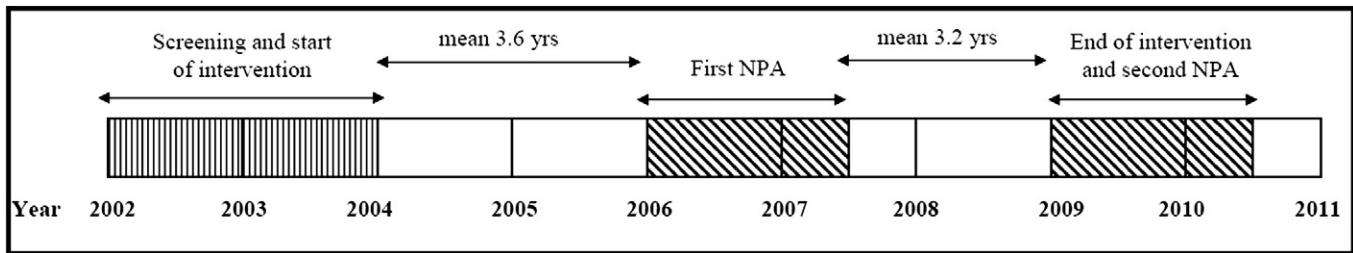
Fig. 1. Flow diagram participants.

Fig. 2. Study timeline.

automatic tonometer (Omron M6, Omron Healthcare Europe, Hoofddorp, The Netherlands); measurements were averaged. Demographic variables and medical history were recorded in a standardized interview. Smoking was classified as current, past or never. 'Any macrovascular event' was defined as self-reported history of myocardial infarction, stroke or surgery or endovascular treatment for carotid, coronary or peripheral arterial disease.

Venous blood samples were drawn after an overnight fast to determine HbA1c and total cholesterol. HbA1c was analyzed by DCCT aligned ion-exchange high-performance liquid chromatography using Menarini 8160 (A.Menarini Diagnostics, Florence, Italy). Lipids were measured using standard enzymatic techniques using a Beckman LX-20 (Beckman Coultier inc., USA) until November 2008 and thereafter a Roche Hitachi Modular P (Roche Diagnostics, USA). Because the second NPA was not performed simultaneously with the close-out of the intervention, we reassessed some risk factors (i.e. blood pressure, height, weight) during the NPA.

2.7. Analysis

Non-parametric data and proportions were analyzed respectively with Wilcoxon test and McNemar test for changes over time and Mann–Whitney test and Chi-square test for differences between groups. Normally distributed continuous data on risk factors levels were analyzed with multi-level linear regression analyses.

Raw test scores at first and second NPA were standardized into z-scores per test, using the pooled mean of the first NPA scores of the reference group. The individual's z-score reflects the number of standard deviations a measurement deviates from the mean of this group. The z-score of each domain was calculated by averaging the test z-scores comprising that domain. In between group comparisons, a mean difference in z-score below 0.2 is considered a small, between 0.2 and 0.8 a medium and above 0.8 a large effect [17]. The primary outcome measure was defined a priori, as the mean difference between the intensive treatment group and the routine care group in the composite z-score of the domains memory, information-processing speed and attention and executive function. These three domains were selected because they are most consistently affected in type 2 diabetes [1,3]. The z-score on each of the separate domains was the secondary outcome measure. For the first NPA we calculated the z-scores per diabetic group compared to the reference group and the difference between the diabetic groups. To asses cognitive decline from the first to the second NPA we calculated a mean change over time per group and a difference between the groups in change over time. Again the performance of the non-diabetic group served as reference. Analyses were done with multi-level linear regression analyses to take into account the cluster-randomization at the general practice level. Analyses for differences between groups were adjusted for IQ-score as the reference group had a higher premorbid estimated intelligence. The change over time was additionally adjusted for time between the end of the intervention and the second NPA.

3. Results

3.1. Study population

For the reference group 75 participants without diabetes underwent the first NPA. Six were excluded after the first NPA, because they were discovered to meet an exclusion criterion at the standardized face to face interview, leaving 69 controls for the analyses. The mean age of this group was 63 years, 48% were male and the mean IQ was 104. Further characteristics have been described elsewhere [2]. As this group acted as reference group, their mean z-scores at the first NPA were zero. At the second NPA two participants from the reference group had died, one could not be contacted, nine declined to participate and two had developed a fasting glucose above 7.0 mmol/L (Fig. 1). The decline on the composite score over the three years was −0.07 (95%-CI −0.14 to 0.01).

From the intensive treatment group 101 patients underwent the first NPA. Four were excluded after checking the results of the interview against the exclusion criteria, leaving 97 patients for the first analyses. From the routine care group 96 patients were examined of which ten were excluded, leaving 86 patients for the analyses. At the second NPA 24 patients from the intensive treatment group declined to participate and two patients could not be contacted. In the routine care group two patients had died and 20 patients declined to participate (Fig. 1). The second NPA was performed between February 2009 and September 2010, with a mean interval of 3.2 ± 0.3 years after the first NPA. Participants and non-participants at the second NPA did not differ with respect to age (63.2 vs 62.8 years; p = 0.69), sex (53.4% vs. 58.9% male; p = 0.47) and estimated premorbid IQ (97.4 vs 99.2; p = 0.53), but cognitive performance at the first NPA differed with a mean difference on the composite z-score of −0.18 (95%-CI −0.31 to −0.04; participants are reference). The TICS-m was obtained in 34 of the 58 surviving non-participants (58.6%) and in 143 of the 192 participants at the second NPA (74.5%).

Within each of the three groups no difference was found between participants and non-participants at the second NPA with respect to age, sex and estimated premorbid IQ. For participants and non-participants at the second NPA from the reference group both the composite score of the first NPA (0.03 ± 0.4 vs -0.2 ± 0.6) and the TICS-score at follow-up (37.4 ± 3.8 vs 35.0 ± 4.4) were comparable. In the intensive treatment group participants of the second NPA scored higher than non-participants on the composite score of the first NPA (-0.2 ± 0.5 vs -0.6 ± 0.8), but TICS-scores at follow-up were similar (35.1 ± 4.7 vs 33.1 ± 5.8). In the routine care group the composite z-scores of the first NPA were comparable (-0.2 ± 0.5 vs -0.2 ± 0.5), but the TICS-score at follow-up was slightly lower in those participating at the second NPA (34.8 ± 4.4 vs 37.8 ± 5.4).

Among the whole group of non-participants, those participating in the TICS (n = 34) did not differ from those that did not perform a TICS (n = 26) with respect to age (63.7 ± 5.0 vs 62.4 ± 6.7; p = 0.40), sex (54.5% vs 52% male; p = 0.85), estimated premorbid IQ (99.9 ± 19.1

Table 1
Patient characteristics of diabetic patient groups.

	Intensive treatment group			Routine care group			p-values		
	Baseline	First NPA	Final[a]	Baseline	First NPA	Final[a]	Group difference first NPA	Group difference final	Difference in change from first NPA to final
N	97		71	86		64			
Sex (% males)	57.7		62.0	64.3		62.5	0.37	0.91	
Age (years)	59.3 ± 5.6	62.9 ± 5.6	66.0 ± 5.7	59.5 ± 5.3	63.1 ± 5.2	66.3 ± 5.6	0.83	0.71	
Educational level (median (IQR))	4 (4–5)		4 (4–5)	5 (4–5)		5 (4–5)	0.19	0.79	
Estimated premorbid intelligence	95.2 ± 19.4		96.5 ± 19.3	98.6 ± 19.4		98.8 ± 20.5	0.24	0.82	
BMI (kg/m²)	31.4 ± 4.9	30.8 ± 4.8[b]	31.4 ± 5.3	30.4 ± 4.3	30.2 ± 4.9	30.8 ± 5.1	0.38	0.50	0.88
Systolic blood pressure (mmHg)	164.7 ± 22.8	140.7 ± 20.7[b]	136.9 ± 17.6	162.4 ± 20.5	147.0 ± 17.7[b]	148.4 ± 19.4	0.08	<0.01	0.06
Diastolic blood pressure (mmHg)	89.6 ± 10.9	81.3 ± 10.6[†]	75.9 ± 8.5	89.8 ± 9.3	82.7 ± 10.2[b]	81.2 ± 10.1	0.44	<0.01	<0.01
Use of antihypertensive drugs (%)	25.8	89.7[b]	94.4	26.5	72.1[b]	78.1	<0.01	<0.01	
Current smoking (%)	22.7	20.0	19.4	19.8	22.6	14.3	0.67	0.63	
HbA1c (mmol/mol; %)	56.2 ± 14.4; 7.3 ± 1.3	43.4 ± 4.5; 6.1 ± 0.4[b]	44.2 ± 4.9; 6.2 ± 0.4	56.1 ± 17.0; 7.3 ± 1.6	45.9 ± 5.8; 6.4 ± 0.5[b]	47.2 ± 6.3; 6.5 ± 0.6	0.15	<0.01	0.99
Total cholesterol (mmol/L)	5.5 ± 1.1	3.9 ± 0.8[b]	4.0 ± 0.8	5.5 ± 1.2	4.4 ± 1.1[b]	4.3 ± 0.8	<0.01	0.04	0.84
Use of lipid-lowering medication (%)	16.5	91.8[b]	90.1	18.1	64.0[b]	81.3	<0.01	0.13	
Any macrovascular event (%)	13.4	13.4	17.6	11.6	16.3	21.9	0.58	0.66	

Data are presented as mean ± SD or percentage unless otherwise specified.
[a] Physical and laboratory measurements measured at end of intervention; medication use, smoking and 'any macrovascular event' assessed during second NPA.
[b] Significant difference between baseline measurement and first NPA.

vs 94.1 ± 16.3; p = 0.22) and cognitive performance at first NPA (mean difference composite z-score 0.02; 95%-CI −0.36 to 0.39; participants are reference).

3.2. Patient characteristics

Table 1 shows the patient characteristics of the routine care and intensive treatment group at baseline of the ADDITION-study, at first NPA and at the final measurements. The groups were similar in age, sex and IQ. Both groups improved significantly on blood pressure, HbA1c and total cholesterol during the first three years. Although the risk factor levels in the intensive treatment group decreased more, the differences between the groups were not significant, except for total cholesterol. In both groups the proportion of patients using antihypertensive and lipid-lowering medication increased. Over the next three years the group difference for total cholesterol remained and significant between group differences developed for blood pressure and HbA1c.

Table 2
Raw test scores of the reference group and the two diabetes groups at the first and second examination (mean ± SD).

Cognitive domain	Cognitive test	Intensive treatment group		Routine care group		Reference group	
		First NPA (n = 97)	Second NPA (n = 71)	First NPA (n = 86)	Second NPA (n = 64)	First NPA (n = 69)	Second NPA (n = 55)
Memory	WAIS-III Digit Span forward	49.1 ± 21.2	40.4 ± 24.4	50.3 ± 23.4	42.8 ± 24.0	57.3 ± 27.8	47.7 ± 19.4
	WAIS-III Digit Span backward	24.1 ± 13.6	23.0 ± 18.5	24.9 ± 16.1	25.6 ± 19.5	29.3 ± 18.7	27.9 ± 18.1
	Corsi Block-Tapping Test forward	37.3 ± 10.5	35.7 ± 12.2	39.0 ± 13.7	41.1 ± 11.8	37.9 ± 12.4	39.7 ± 13.1
	Corsi Block-Tapping Test backward	38.7 ± 17.1	35.3 ± 14.7	36.9 ± 15.4	38.2 ± 16.1	40.8 ± 15.3	41.3 ± 15.4
	RAVLT total trials 1–5	35.5 ± 9.4	41.1 ± 11.8	36.1 ± 8.3	41.0 ± 10.2	41.3 ± 10.6	46.6 ± 11.1
	RAVLT delayed recall	6.6 ± 2.6	8.3 ± 3.5	6.9 ± 2.7	8.1 ± 3.0	7.8 ± 3.1	10.0 ± 3.3
	RAVLT recognition	27.1 ± 3.2	28.5 ± 2.2	27.6 ± 2.5	28.5 ± 2.2	28.4 ± 1.6	29.0 ± 1.4
	LLT total trails 1-5[a]	15.1 ± 16.7	25.4 ± 21.5	15.7 ± 17.7	23.6 ± 18.9	15.9 ± 20.8	15.6 ± 18.1
	LLT learning index	0.8 ± 0.3	0.6 ± 0.3	0.7 ± 0.3	0.6 ± 0.3	0.8 ± 0.3	0.7 ± 0.3
	LLT delayed trial[a]	1.5 ± 3.0	2.6 ± 4.9	1.4 ± 3.0	1.9 ± 3.3	1.5 ± 3.0	5.7 ± 12.4
	Complex Figure Test -Delay	16.5 ± 5.6	16.5 ± 6.3	16.6 ± 5.4	16.2 ± 5.9	19.4 ± 5.2	18.6 ± 6.4
Information-processing speed	Stroop Color Word Test I[a]	48.1 ± 7.1	50.2 ± 8.4	46.4 ± 8.1	50.1 ± 11.6	44.9 ± 8.5	47.3 ± 9.0
	Stroop Color Word Test II[a]	62.7 ± 10.5	62.3 ± 10.6	62.6 ± 10.4	65.9 ± 13.2	59.9 ± 12.9	61.2 ± 13.7
	TMT Part A	48.2 ± 20.7	41.5 ± 11.8	42.8 ± 15.5	43.4 ± 17.0	42.1 ± 17.1	39.5 ± 16.5
	WAIS-III Digit Symbol	56.0 ± 14.7	55.6 ± 17.4	59.6 ± 14.3	57.0 ± 15.5	61.8 ± 17.0	64.3 ± 16.6
Attention and executive functioning	Stroop Color Word Test III[a]	115.8 ± 29.4	110.8 ± 27.1	108.9 ± 24.6	110.3 ± 29.3	105.4 ± 37.2	107.6 ± 39.0
	TMT Part B	101.2 ± 44.9	93.5 ± 39.4	102.2 ± 48.7	96.5 ± 50.2	89.7 ± 29.2	81.6 ± 29.4
	Letter fluency (mean of N + A)	10.2 ± 4.0	11.2 ± 4.9	10.1 ± 4.7	10.9 ± 4.8	11.8 ± 4.4	12.4 ± 3.9
	Category fluency (animals)	29.9 ± 8.1	30.0 ± 9.4	31.4 ± 8.5	32.4 ± 9.1	34.5 ± 8.8	35.5 ± 8.8
	Brixton Spatial Anticipation Test[a]	16.2 ± 6.9	17.6 ± 5.6	16.2 ± 5.8	17.3 ± 5.7	14.6 ± 5.4	16.4 ± 5.2

RAVLT, Rey Auditory Verbal Learning Test; LLT, Location Learning Test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale – Third edition.
[a] Higher test scores reflect worse performance.

Table 3

Mean difference per group compared to the reference group without diabetes in cognitive domain z-scores first NPA and difference between the groups corrected for estimated premorbid intelligence (95%-CI).

	Intensive treatment group (n = 97)	Routine care group (n = 86)	Difference between groups
Composite score	−0.15 (−0.31 to −0.01)	−0.15 (−0.31 to −0.01)	0.00 (−0.16 to 0.16)
Memory	−0.11 (−0.27 to 0.04)	−0.17 (−0.33 to −0.01)	0.06 (−0.09 to 0.21)
Information-processing speed	−0.19 (−0.42 to 0.03)	−0.04 (−0.27 to 0.18)	−0.15 (−0.36 to 0.06)
Attention and executive function	−0.13 (−0.42 to 0.15)	−0.19 (−0.48 to 0.09)	0.06 (−0.21 to 0.33)

Composite score was the primary outcome measure. Secondary analyses were done for the separate domains. Negative z-score indicates worse performance.

3.3. Cognitive functioning

Raw test scores of the reference group and the two diabetes groups at the first and second examination are presented in Table 2. At the first NPA there was no difference between the groups with respect to the primary cognitive outcome measure (mean difference composite z-score 0.00; 95%-CI −0.16 to 0.16) (Table 3). Similar results were found in secondary analyses for the separate domains with mean differences ranging from −0.15 to 0.06 (Table 3). In the following three years the patients showed a slight decline in cognition (mean change composite z-score intensive treatment: -0.14 (−0.23 to 0.06); routine care: -0.02 (−0.12 to 0.07)). The mean difference between the groups in change over time for the composite score was −0.12 (−0.24 to 0.01) (Table 4). Secondary analyses on the separate domains showed mean differences between the groups in change over time between −0.22 to 0.09 (Table 4).

4. Discussion

In this study with cognitive assessments after three and six years of intensive treatment we could not show a positive effect above routine care on cognitive functioning in patients with screen-detected type 2 diabetes. After the first three years of treatment both diabetic groups had similar but modest decrements compared to the non-diabetic reference group. Over the next three years cognitive decline in the diabetic groups was within the range of the reference group and did not differ between the treatment arms.

To the best of our knowledge, this was the first study that compared the effect of six years of intensive multifactorial treatment with routine care on cognition in screen-detected type 2 diabetes. Strengths of our study are the extensive NPA, which was performed in a substantial number of patients with type 2 diabetes, and the longitudinal assessment of cognition over a period of three years. Moreover, treatment could be initiated at an early stage of type 2 diabetes. A limitation of our study is the timing of the NPAs. We were not able to perform a NPA at baseline. As a result we may have missed a change in cognition in the first three years of treatment. Nevertheless, there is no indication that the groups differed in cognition at baseline, as they were comparable in demographic variables and IQ. The second NPA and the final measurements of the main ADDITION study were not administered simultaneously; however we found no differences in the contrast in risk factors between the groups at the two time points (data not shown). Other potential limitations are possible selection bias at the first NPA and possible selective attrition during follow-up. Although the lost to follow up

was random and equally divided over the two treatment groups it might have led to an over- or underestimation of the cognitive functioning in one of the groups. The latter we examined with the TICS-m, which demonstrated no differences in cognitive functioning between participants and non-participants.

We previously reported that this population of screen-detected type 2 diabetes patients has mild cognitive decrements compared to people without diabetes (effect sizes up to −0.2) [2]. Other cross-sectional studies found similar results with respect to impaired cognitive function in type 2 diabetes (effect sizes −0.3 to −0.6) [1]. In agreement with our study, recent longitudinal studies demonstrated that the rate of cognitive decline in people with type 2 diabetes is generally slow and only slightly exceeds the rate of decline in normal ageing [3,30]. Probably, the process of cognitive decrements starts already in (pre-)diabetic stages and the decrements progress only slowly thereafter. Nevertheless, people with type 2 diabetes are overrepresented in the subgroup of individuals that show frank cognitive decline or progress to dementia [4–6]. These recent insights into the course of development of cognitive decrements in people with type 2 diabetes do have important implications for future intervention studies. Possibly such studies should target the prevention of accelerated decline rather than average change in cognition across a whole population of patients, but this will require much larger study cohorts.

The intensive treatment in the main ADDITION-study resulted in a small but significant difference in change from baseline for several risk factors relative to routine care. In addition the intensive multifactorial treatment was associated with a non-significant 17% reduction of cardiovascular events. We did not find an effect of the six years intervention on cognitive functioning. In addition to the relative benign course of cognitive decline in the patients with diabetes, this might be caused by the well-controlled cardiovascular risk factors in both groups. At time of the first NPA, risk factor levels in our participants had already dropped significantly in both the routine care and the intensive treatment group, with minor differences between these groups. After six years of treatment the differences between the groups did become significant. Both groups however were treated well, which is probably the result of the high standard of care in general practice for patients with type 2 diabetes. In The Netherlands routine care improved by a new evidence based guideline in 2006 [16].

Some previous studies did report effects of improved glycemic control on cognitive functioning in people with type 2 diabetes [9,10]. However, these studies did not include a non-diabetic reference group, the follow-up time in these studies was short (≤24 weeks) and the

Table 4

Mean change over time in z-scores per group and difference in change over time between the groups (95%-CI).

	Intensive treatment group (n = 71)	Routine care group (n = 64)	Adjusted difference between groups in change over time[a]
Composite score	−0.14 (−0.23 to −0.06)	−0.02 (−0.12 to 0.07)	−0.12 (−0.24 to 0.01)
Memory	−0.27 (−0.38 to −0.15)	−0.05 (−0.17 to 0.07)	−0.22 (−0.38 to −0.05)
Information-processing speed	−0.05 (−0.17 to 0.07)	−0.13 (−0.27 to 0.00)	0.09 (−0.09 to 0.26)
Attention and executive function	−0.15 (−0.28 to −0.02)	0.07 (−0.07 to 0.21)	−0.21 (−0.41 to −0.02)

Composite score was the primary outcome measure. Secondary analyses were done for the separate domains. Negative z-score indicates worse performance.

[a] Adjusted for time between end of intervention and second NPA and estimated premorbid intelligence.

HbA1c levels before the intervention were relatively high (>60 mmol/mol (7.6%)). Because of the interval between start of treatment at baseline of the ADDITION study and first NPA we may have missed improvement of cognition with lowering of HbA1c. Furthermore, other studies indicate that mid-life hypertension might affect cognitive functioning later in life [31] and that hypertension is one of the factors involved in diabetes-associated cognitive decline [32]. Therefore strict control of blood pressure in mid-life might be a way to prevent cognitive decline. In our study the intensive treatment protocol resulted in a significantly lower blood pressure at close-out compared to routine care, but our follow-up time may have been too short to result in a significant effect on cognition.

It should be emphasized that cognitive functioning in our study population was within the range of normal ageing. The observed treatment effects on cognitive functioning may therefore not be generalizable to prevention of pathological cognitive decline, such as (early) dementia.

In conclusion, patients with screen-detected type 2 diabetes did not suffer from accelerated decline compared to participants without diabetes. In addition, we could not demonstrate that intensive multifactorial treatment had a beneficial effect on decline of cognitive functioning above routine care.

Author's contribution

G.R. was initiator of the study. C.R., M.D., G.J.B., K.G., L.K. and G.R. collectively designed the study. P.K. and C.R. managed the study and data collection. P.K. researched the data, conducted the data analyses and wrote the manuscript. All authors participated in the interpretation of data, contributed to discussion and reviewed/edited the manuscript.

Acknowledgements

References

[1] Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. J Clin Exp Neuropsychol 2004;26:1044–80.

[2] Ruis C, Biessels GJ, Gorter KJ, van den Donk M, Kappelle LJ, Rutten GE. Cognition in the early stage of type 2 diabetes. Diabetes Care 2009;32:1261–5.

[3] van den Berg E, Reijmer YD, de Bresser J, Kessels RP, Kappelle LJ, Biessels GJ. A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. Diabetologia 2010;53:58–65.

[4] Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64–74.

[5] Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. Diabetologia 2005;48:2460–9.

[6] Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurology 1999;53:1937–42.

[7] Van den Berg E, Dekker JM, Nijpels G, Kessels RP, Kappelle LJ, de Haan EH, et al. Cognitive functioning in elderly persons with type 2 diabetes and metabolic syndrome: the Hoorn study. Dement Geriatr Cogn Disord 2008;26:261–9.

[8] Sandbaek A, Griffin SJ, Rutten G, Davies M, Stolk R, Khunti K, et al. Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. Diabetologia 2008;51:1127–34.

[9] Naor M, Steingruber HJ, Westhoff K, Schottenfeld-Naor Y, Gries AF. Cognitive function in elderly non-insulin-dependent diabetic patients before and after inpatient treatment for metabolic control. J Diabetes Complications 1997;11:40–6.

[10] Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, Strachan MW. Improving metabolic control leads to better working memory in adults with type 2 diabetes. Diabetes Care 2006;29:345–51.

[11] Janssen PG, Gorter KJ, Stolk RP, Rutten GE. Low yield of population-based screening for Type 2 diabetes in the Netherlands: the ADDITION Netherlands study. Fam Pract 2007;24:555–61.

[12] WHO. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation; 1999.

[13] Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. Int J Obes Relat Metab Disord 2000;24(Suppl 3):S6–S11.

[14] Janssen PG, Gorter KJ, Stolk RP, Rutten GE. Randomised controlled trial of intensive multifactorial treatment for cardiovascular risk in patients with screen-detected type 2 diabetes: 1-year data from the ADDITION Netherlands study. Br J Gen Pract 2009;59:43–8.

[15] Rutten G, Verhoeven S, Heine R, de Grauw W, Cromme P, Reenders K. Practice guideline diabetes mellitus type 2. [in Dutch]Huisarts Wetenschap 1999;42:67–84.

[16] Rutten GEHM, De Grauw WJC, Nijpels G, Goudswaard AN, Uitewaal PJM, Van der Does FEE, et al. Practice guideline diabetes mellitus type 2. [in Dutch]Huisarts Wetenschap 2006;49:137–52.

[17] Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. New Jersey: Laurence Erlbaum; 1988.

[18] Lezak M, Howieson D, Loring D. Neuropsychological assessment. 4th ed. New York: Oxford University Press; 2004.

[19] Wechsler D. Wechsler Adult Intelligence Scale. 3rd ed. San Antonio, Texas: Psychological Corporation; 1997.

[20] Kessels RP, van Zandvoort MJ, Postma A, Kappelle LJ, de Haan EH. The Corsi Block-Tapping Task: standardization and normative data. Appl Neuropsychol 2000;7:252–8.

[21] Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. J Int Neuropsychol Soc 2005;11:290–302.

[22] Bucks RS, Willison JR, Byrne LMT. Location Learning Test. Bury St. Edmunds, UK: Thames Valley Test Company; 2000.

[23] Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique: Les problemes. Arch Psychol 1941;28:286–340.

[24] Corrigan JD, Hinkeldey NS. Relationships between parts A and B of the Trail Making Test. J Clin Psychol 1987;43:402–9.

[25] Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–62.

[26] Burgess PW, Shallice T. The Hayling and Brixton Tests. Thurston, UK: Thames Valley Test Company; 1997.

[27] Deelman BG, Koning-Haanstra M, Liebrand WBG. SAN test, een afasietest voor auditief en mondeling taalgebruik (SAN test, an aphasiatest for auditory and oral linguistics). Lisse, The Netherlands: Swets & Zeitlinger; 1981.

[28] Schmand B, Lindeboom J, van Harskamp F. Nederlandse leestest voor volwassenen (Dutch adult reading test). Lisse, The Netherlands: Swets & Zeitlinger; 1992.

[29] Kempen GI, Meier AJ, Bouwens SF, van DJ, Verhey FR. The psychometric properties of the Dutch version of the Telephone Interview Cognitive Status (TICS). Tijdschr Gerontol Geriatr 2007;38:38–45.

[30] Euser SM, Sattar N, Witteman JC, Bollen EL, Sijbrands EJ, Hofman A, et al. A prospective analysis of elevated fasting glucose levels and cognitive function in older people: results from PROSPER and the Rotterdam Study. Diabetes 2010;59:1601–7.

[31] Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol 2008;585:97–108.

[32] Van den Berg E, Dekker JM, Nijpels G, Kessels RP, Kappelle LJ, de Haan EH, et al. Blood pressure levels in pre-diabetic stages are associated with worse cognitive functioning in patients with type 2 diabetes. Diabetes Metab Res Rev 2009;25:657–64.