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Review

Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition

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ABSTRACT

Vascular risk factors, such as type 2 diabetes mellitus, hypertension, dyslipidemia and obesity, have been associated with an increased risk of cognitive dysfunction, particularly in the elderly. The aim of this systematic review was to compare these risk factors with regard to the nature and magnitude of the associated cognitive decrements. Cross-sectional and longitudinal studies that assessed cognitive functioning in non-demented persons in relation to diabetes/impaired glucose metabolism ($k=36$), hypertension ($k=24$), dyslipidemia ($k=7$) and obesity ($k=6$) and that adjusted or matched for age, gender and education were included. When possible, effect sizes (Cohen's d) were computed per cognitive domain. Diabetes and hypertension were clearly associated with cognitive decrements; the results for obesity and dyslipidemia were less consistent. Effect sizes were moderate (median ~ −0.3) for all risk factors. Decline was found in all cognitive domains, although the effects on cognitive speed, mental flexibility and memory were most consistent. Methodological aspects of included studies and implications of these findings are discussed.

1. Introduction

As the world's population gets older, cognitive dysfunction will be an increasing burden for society and health-care resources. Although age remains the main risk factor for cognitive decline and dementia, it is increasingly recognized that a substantial number of cases with dementia may be attributable to vascular risk factors (i.e. type 2 diabetes mellitus, hypertension, dyslipidemia, obesity [1–4]), and consequently these risk factors emerge as major targets for therapeutic intervention.

Although vascular risk factors often co-occur and have shared consequences, such as atherosclerosis, there are also differences in their impact on different organ systems. Type 2 diabetes and hypertension, for example, are strongly associated with end-organ damage in the retina and kidney, through pathophysiological mechanisms that are at least in part specific to these conditions [5–8]. For obesity and dyslipidemia the association with retinal and kidney damage is less evident [9,10]. This raises the question whether the impact on the brain, in particular on cognitive functioning, is similar across these vascular risk factors. Longitudinal population-based studies that assess the risk of dementia in association with diabetes, hypertension, dyslipidemia and obesity show that each of these factors is associated with a relative risk of dementia of approximately 1.5 (systematic review: [11]). There are, however, also some differences between these risk factors, particularly with regard to the modulation effect of age at the time of exposure (e.g. [12,13]). Although dementia is obviously a highly relevant clinical end-point it should be regarded as a final stage of cerebral damage. Based on the observation that different risk factors convey a similar risk of dementia, one may not conclude that the initial damage associated with each factor is identical. This initial damage, which may be reflected in decrements in cognitive functioning short of dementia, is of particular interest from the viewpoints of pathophysiology and prevention. The aim of the present study is therefore to quantify and compare the profile and size of cognitive decrements associated with type 2 diabetes, hypertension, dyslipidemia, and obesity in non-demented persons.

2. Materials and methods

2.1. Identification of studies

This systematic review aimed to include all published studies that examined cognitive functioning associated with type 2 diabetes

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mellitus or impaired glucose metabolism, hypertension, dyslipidemia or obesity and that met the following inclusion criteria: the study (1) was published after 1990, (2) had a population-based or case–control design, (3) matched or adjusted the exposed and the non-exposed groups for the basic confounders age, sex and educational level, (4) addressed at least two cognitive domains with validated neuropsychological tests or, if only one domain was examined, used at least two different tests on that domain. Studies that assessed cognitive functioning only with a global screening instrument, such as the Mini-Mental State Examination, or reported only a composite measure of cognition were not included. Studies that specifically involved patients with type 1 diabetes were also not included.

Medline (1990 to March 2008) and bibliographies from included papers were used to identify relevant papers. The search was limited to papers that were written in English and concerned human participants. We used the search terms ("diabetes", "hyperglycaemia" or "glucose tolerance"), ("hypertension" or "blood pressure"), ("dyslipidemia", "hypercholesterolemia", "cholesterol", "high-density lipoprotein", "low-density lipoprotein" or "triglycerides"), ("waist circumference", "obesity", "overweight", "abdominal fat" or "body-mass index") in combination with ("cognitive" or "neuropsychological") in full or

Table 1a
Description of included studies for type 2 diabetes mellitus and impaired glucose metabolism

	Design	*N*	% with risk factor	Age	% male	Risk factor definition	Exclusion criteria	Additional adjustment/matching*
Diabetes								
Cross-sectional								
Dey et al. [30]	C–C	56	50	47	63	History	Stroke, N/P comorbidity	
Fuh et al. [31]	C–C	284	25	48	0	History, GT	Stroke	
Ryan et al. [32]	C–C	100	50	51	27	History	N/P comorbidity	
Van Boxtel et al. [33]	P	1360	3	24–81	51	History	Dementia, N/P comorbidity	
Cerhan et al. [14]	P	13913	11	45–64	45	History, GT	Stroke, N/P comorbidity, old age	ethnicity
Cosway et al. [34]	C–C	76	50	57	41	History	Stroke, N/P comorbidity, blindness	
Vanhanen et al. [35]	C–C	83	42	65	43	GT	Dementia	
Brands et al. [36]	C–C	174	68	66	48	History	Dementia, N/P comorbidity	
Elias et al. [20]	P	1811	10	68	ND	History, GT	Stroke, DM1	BP, VD, smoking, alcohol
Reaven et al. [37]	C–C	59	49	69	59	History	Dementia, stroke, N/P comorbidity	
Atiea et al. [38]	C–C	40	50	69	68	History	Stroke, N/P comorbidity	
U'ren et al. [39]	C–C	38	50	71	16	History	Stroke, N/P comorbidity	
Desmond et al. [18]	P	249	12	71	34	History	Stroke	
Kilander et al. [40]	P	504	15	72	100	GT	Not specified	
Vanhanen et al. [41]	P	915	20	73	35	History, GT	Dementia	
van Harten et al. [42]	C–C	136	68	73	44	History	Stroke, dementia, N/P comorbidity	BP
Scott et al. [43]	P	1131	16	74	42	GT	Not specified	BP, BMI, DEP, estrogen use
Grodstein et al. [44]	P	2374	3	74	0	History	VD	BP, BMI, DEP, vitamin E, hormone therapy, quality of life
Lindeman et al. [45]	P	664	28	74	ND	GT	None	DEP, ethnicity
Wahlin et al. [46]	P	338	9	84	20	History, GT	Dementia, N/P comorbidity, MD	VD
Longitudinal								
Kumari et al. [47]	P	5647	5	~45	72	History, GT	Not specified	
Knopman et al. [22]	P	10963	12	47–70	44	History, GT	Stroke	
Fontbonne et al. [48]	P	926	6	65	40	History, GT	MMSE<27	
Kanaya et al. [49]	P	999	12	70	40	History, GT	Not specified	DEP, APOE, estrogen use
Gregg et al. [50]	P	9679	7	72	0	History	Not specified	BP, VD, DEP, smoking, estrogen use, visual impairment, perceived health
Hassing et al. [51]	P	274	13	83	29	History	Dementia	
van den Berg et al. [52]	P	596	16	85	34	History, GT	Not specified	
Impaired glucose metabolism								
Cross-sectional								
Fuh et al. [31]	C–C	248	27	48	0	GT	Stroke	
Vanhanen et al. [53]	C–C	83	27	65	43	GT	Dementia	
Scott et al. [43]	P	1131	16	74	42	GT	Not specified	BP, BMI, DEP, estrogen use
Lindeman et al. [45]	P	664	26	74	ND	GT	None	DEP, ethnicity
Longitudinal								
Kumari et al. [47]	P	5647	12	~45	72	GT	Note specified	
Fontbonne et al. [48]	P	926	11	65	40	GT	MMSE<27	
Kanaya et al. [49]	P	999	25	70	40	GT	Not specified	DEP, APOE, estrogen use
Vanhanen et al. [54]	P	586	14	73	37	GT	Dementia	

C–C, case–control design.
P, population-based design.
APOE, apolipoprotein E status.
DM1, type 1 diabetes.
MMSE, Mini-mental State Examination.
GT, glucose tolerance assessed with fasting, or random glucose measurement or formal oral glucose tolerance test using standardized cut-off point.
BP, blood pressure (including systolic blood pressure, history of hypertension, use of antihypertensive medication).
VD, vascular disease (including cerebrovascular disease, stroke, tia, cardiac disease).
DEP, depression (including scores on the Beck Depression Inventory, use of antidepressive medication, measures of anxiety and stress).
N/P comorbidity, neurological or psychiatric comorbidity (including epilepsy, Parkinson's disease, malignancies in central nervous system, sensory of motor neuron disease, depression, psychoactive medication such as sedatives, anticonvulsants, substance abuse, mental retardation, head trauma).
MD, metabolic disturbances (including hyperlipidemia, thyroid disease, renal failure, systemic disease).
* All studies were age-, sex- and education-adjusted or -matched, additional adjustments are listed.

Table 1b
Description of included studies for obesity

	Design	*N*	% with risk factor	Age	% male	Risk factor definition	Exclusion criteria	Additional adjustment/matching*
Cross-sectional								
Gunstad et al. [55]	P	408	49	33	48	BMI ≥25 kg/m2	N/P comorbidity, MD	DEP
Kuo et al. [56]	P	2684	38	73	24	BMI ≥30 kg/m2	Dementia, N/P comorbidity, vision or hearing disability	BP, VD, DM2, MD, ethnicity, smoking, study site
Dik et al. [16]	P	1183	52	75	49	Waist circumference>102 cm for men, >88 cm for women	>65 years old	Smoking, alcohol
Longitudinal								
Cournot et al. [57]	P	2223	20	~44	49	Quintiles of baseline BMI	Dementia	BP, DM2, alcohol, perceived health
Wolf et al. [17]	P	1814	ND	53	53	Quartiles of BMI and Waist/Hip ratio	Stroke, dementia	
Elias et al. [58]	P	1423	11	76	39	BMI ≥30 kg/m2	Stroke, dementia, VD	BP, DM2, MD, alcohol, smoking

P, population-based design.
DM2, type 2 diabetes.
MMSE, Mini-mental State Examination.
BMI, Body-mass Index.
BP, blood pressure (including systolic blood pressure, history of hypertension, use of antihypertensive medication).
VD, vascular disease (including cerebrovascular disease, stroke, tia, cardiac disease).
DEP, depression (including scores on the Beck Depression Inventory, use of antidepressive medication, measures of anxiety and stress).
N/P comorbidity, neurological or psychiatric comorbidity (including epilepsy, Parkinson's disease, malignancies in central nervous system, sensory of motor neuron disease, depression, psychoactive medication such as sedatives, anticonvulsants, substance abuse, mental retardation, head trauma).
MD, metabolic disturbances (including hyperlipidemia, thyroid disease, renal failure, systemic disease).
* All studies were age-, sex- and education-adjusted or -matched, additional adjustments are listed.

truncated versions. Titles and abstracts were scanned and potentially eligible papers were collected in full-text versions. RPK and EvdB independently judged eligible papers according to the inclusion criteria. In case of disagreement a consensus judgment was made, together with GJB.

This review focuses on cognitive dysfunction in the absence of dementia. However, only a subset of the papers that met our inclusion criteria specifically mentioned exclusion of demented subjects in their methods section. More often exclusion of subjects with dementia or other neurological or mental conditions was mentioned in more global terms. Table 1a, Table 1b, Table 1c and Table 1d list the exclusion criteria for individual studies.

2.2. Included studies

For diabetes/impaired glucose metabolism the search yielded 1702 hits, 27 of which met our inclusion criteria for diabetes and 9 for impaired glucose metabolism. The search yielded 2406 hits for hypertension (24 studies were included), 653 hits for dyslipidemia (7 studies were included) and 1113 hits for obesity (6 studies were included). Papers that addressed more than one vascular risk factor were included in multiple risk factor sections in this review (e.g. [14–18]). When more than one paper reported on the same population, the paper with the largest sample size and/or the most detailed information on that risk

Table 1c
Description of included studies for dyslipidemia

	Design	*N*	% with risk factor	Age	% male	Risk factor definition	Exclusion criteria	Additional adjustment/matching*
Cross-sectional								
Zhang et al. [59]	P	4110	ND	37	100	Tertiles of total cholesterol, HDL-cholesterol, non-HDL cholesterol	Stroke	WHR, alcohol, physical activity, diet
Dik et al. [16]	P	1183	ND	75	49	Triglycerides ≥1.7 mmol/l or HDL cholesterol <1.0 (men) //<1.3 (women) mmol/l	>65 years old	smoking, alcohol
Longitudinal								
Henderson et al. [60]	P	438	ND	49	0	Quartiles of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides	Not specified	DEP, medication or estrogen use, demographics, smoking, alcohol, exercise
Teunissen et al. [21]	P	144	ND	57	60	Total cholesterol as continuous variable	Stroke, N/P comorbidity	
Komulainen et al. [61]	P	101	ND	64	0	HDL cholesterol <50 mg/dl	Not specified	DEP, estrogen use
de Frias et al. [62]	P	524	ND	67	49	Total cholesterol and triglycerides as continuous variables	Dementia	VD
Reitz et al. [63]	P	1147	50	76	32	Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides as continuous variables	Stroke, dementia, N/P comorbidity	Ethnicity, APOE

P, population-based design.
WHR, waist-to-hip ratio.
APOE, apolipoprotein E status.
VD, vascular disease (including cerebrovascular disease, stroke, tia, cardiac disease).
DEP, depression (including scores on the Beck Depression Inventory, use of antidepressive medication, measures of anxiety and stress).
N/P comorbidity, neurological or psychiatric comorbidity (including epilepsy, Parkinson's disease, malignancies in central nervous system, sensory of motor neuron disease, depression, psychoactive medication such as sedatives, anticonvulsants, substance abuse, mental retardation, head trauma).
* All studies were age-, sex- and education-adjusted or -matched, additional adjustments are listed.

factor and/or cognitive functioning was included (e.g. [19,20], [15,21] or [14,22]).

2.3. Data extraction

2.3.1. Demographics, risk factor, study design

Data on study design, sample size, sex and baseline age were extracted from the studies and details were included in Tables 1a through d. When available, the proportion of participants with the risk factor (e.g. diabetes or hypertension), risk factors definitions, and the exclusion criteria of the different studies were extracted. Only studies with age-, sex-, and education-matched or -adjusted results were included. Additional adjustments are listed in the final column of Tables 1a through d.

2.3.2. Data analysis

The included studies used variable domain classifications, which hampers comparison of the effects between studies. All test scores were therefore regrouped into the domains general intelligence, memory, processing speed, attention, cognitive flexibility, perception/visuoconstruction and language [23] according to a predefined classification of tests per domain, as listed in the appendix. When available, means and SDs were extracted from the included studies and converted into Cohen's *d* as an estimate for effect size [24]. Negative effect sizes indicate worse cognition in the group with the risk factor. Median effect sizes per cognitive domain are presented in Table 2a Table 2b, Table 2c, and Table 2d. In neuropsychological studies, effect sizes <0.2 are considered small, 0.2–0.8 medium and >0.8 large [24].

The results of studies that did not present data that could be converted into effect sizes are presented in Table 2 by means of direction of effect ('−' meaning 'elevated levels of risk factor are associated with worse cognition', '+' meaning 'elevated levels of risk factor are associated with better cognition or decreased levels of risk factor are associated with worse cognition (inverse effects)', '+/−' meaning 'both elevated and decreased levels of risk factor are associated with worse cognition (U or J-shaped associations)', '=' meaning 'no statistically significant association between risk factor and cognition'). Results from cross-sectional and longitudinal studies

Table 1d
Description of included studies for hypertension

	Design	*N*	% with risk factor	Age	% male	Risk factor definition	Exclusion criteria	Additional adjustment/matching*
Cross-sectional								
Schmidt et al. [64]	C–C	55	64	38	71	History or >160/95 mmHg	Stroke, N/P comorbidity, MD, DM	
Waldstein et al. [65]	C–C	40	50	43	100	≥140/95 mmHg, untreated	VD, N/P comorbidity, antihypertensive medication	
Van Boxtel [15]	P	936	22	24–80	51	≥140/90 mmHg	Stroke, dementia, N/P comorbidity	
Cerhan et al. [14]	P	13840	11	45–64	45	≥160/95 or medication	Stroke, N/P comorbidity, old age	Ethnicity
Andre-Petersson et al. [66]	P	500	78	68	100	≥140/90 (subdivided in stages 1 to 3)	None	
Scherr et al. [67]	P	3627	ND	≥65	38	≥140/90 mmHg	Not specified	VD, DEP, medication use, smoking, alcohol, perceived health
Morris et al. [68]	P	5816	55	≥65	38	History and/or duplicate measurement	Not specified	Ethnicity
Desmond et al. [18]	P	249	42	71	34	History	Stroke	
Kuusisto et al. [69]	P	744	51	73	36	≥160/95 mmHg or medication	Sroke, DM2	Fasting glucose
Dik et al. [16]	P	1183	63	75	49	≥160/90 mmHg or medication	>65 years old	Smoking, alcohol
Harrington et al. [70]	C–C	223	48	76	52	>160/90 mmHg, untreated	Dementia, MD, antihypertensive medication	
Longitudinal								
Pavlik et al. [71]	P	3270	19	30–59	50	≥140/90 mmHg or medication	Stroke, N/P comorbidity	Ethnicity
Swan et al. [72]	P	717	5	39–59	100	SBP ≥140 mmHg throughout adult life	Not specified	DEP, VD, antihypertensive medication
Elias et al. [73]	P	529	64	46	49	≥140/90 mmHg+ as continuous variables	Stroke, dementia, N/P comorbidity	BMI, DEP, alcohol, smoking
Swan et al. [74]	P	392	15	47	100	SBP ≥140 mmHg	VD	Stroke
Kilander et al. [75]	P	502	ND	50	100	DBP ≤70 mmHg	Not specified	
Wolf et al. [17]	P	1814	ND	53	53	≥140/90 mmHg or medication	Stroke, dementia	
Knopman et al. [22]	P	10963	32	47-70	44	≥140/90 mmHg or medication	Stroke	Ethnicity, psychoactive medication
Elias et al. [19]	P	1702	ND	55–88	40	≥160/95 mmHg	Stroke	Alcohol, smoking
Elias et al. [20]	P	1811	32	68	ND	>160/95 mmHg	Stroke, DM1	DBP, antihypertensive medication, VD, smoking, alcohol
Reinprecht et al. [76]	P	186	51	68	100	≥160/90 mmHg or medication + tertiles of DBP	None	MD, smoking, alcohol
Waldstein et al. [77]	P	847	ND	71	59	Duplicate measurement, continuous variables	Stroke, dementia, MD	Antihypertensive medication, DEP, alcohol, smoking
Hebert et al. [78]	P	4284	ND	74	38	Duplicate measurement, continuous variables	Not specified	Ethnicity
Paran et al. [79]	P	495	71	77	28	SBP ≥140 mmHg	Stroke, dementia, N/P comorbidity	'Chronic conditions' (unspecified)

C–C, case–control design.
P, population-based design.
DM, diabetes mellitus.
SBP, systolic blood pressure.
DBP, diastolic blood pressure.
VD, vascular disease (including cerebrovascular disease, stroke, tia, cardiac disease).
DEP, depression (including scores on the Beck Depression Inventory, use of antidepressive medication, measures of anxiety and stress).
N/P comorbidity, neurological or psychiatric comorbidity (including epilepsy, Parkinson's disease, malignancies in central nervous system, sensory of motor neuron disease, depression, psychoactive medication such as sedatives, anticonvulsants, substance abuse, mental retardation, head trauma).
MD, metabolic disturbances (including hyperlipidemia, thyroid disease, renal failure, systemic disease).
* All studies were age-, sex- and education-adjusted or -matched, additional adjustments are listed.

Table 2a
Results of included studies for diabetes and impaired glucose metabolism

	General intelligence	Memory	Processing speed	Attention	Cognitive flexibility	Perception/ construction	Language	Comment
Diabetes								
Cross-sectional								
Dey et al. [30]	−	−*	..	−*	−	..	−	
Fuh et al. [31]	..	−0.2	−0.2	..	−0.2	..	..	
Ryan et al. [32]	−0.4	−0.3	−0.4*	−0.6	−0.3	−0.4	..	
Van Boxtel et al. [33]	..	−*	−*	−*	−*	..	..	
Cerhan et al. [14]	..	−*	−*	..	−*	..	..	
Cosway et al. [34]	−0.1	−0.1	−0.4	..	−0.3	..	..	
Vanhanen et al. [35]	..	−0.7*	−1.4*	−1.4*	−0.6*	−0.7	..	
Brands et al. [36]	−0.2	−0.3*	−0.4*	−0.4*	−0.3*	−0.2	..	
Elias et al. [20]	−	−*	..	..	−	−	..	Hypertensive DM2 patients were at greatest risk of cognitive impairment (<25%)
Reaven et al. [37]	−0.1	−0.7*	−0.7*	..	−0.9*	..	..	
Atiea et al. [38]	−0.4	−0.4	−0.2	−0.5	−0.7	..	..	
U'ren et al. [39]	−2.3*	−1.2*	−0.6	−1.9*	−0.3	..	..	
Desmond et al. [18]	−0.8*	−0.3	..	−0.1	..	−0.5*	−0.4	
Kilander et al. [40]	−	−	−	..	−	−	..	DM2 was associated with a significantly lower composite *z*-score
Vanhanen et al. [41]	..	0	−0.4*	..	−0.2	..	..	
van Harten et al. [42]	..	−0.4	−0.4*	..	−0.4*	..	..	
Scott et al. [43]	..	=	..	..	=	..	..	No association between DM2 and cognitive functioning
Grodstein et al. [44]	..	−0.2	..	..	−0.2	..	..	DM2 was associated with a significantly lower composite *z*-score
Lindeman et al. [45]	..	−0.1	0	..	−0.1	−0.1	..	
Wahlin et al. [46]	..	−0.2*	..	..	−0.3*	..	..	Largest between-group difference on least structured tests
Longitudinal								
Kumari et al. [47]	−*	−	..	..	−	..	−*	Baseline DM2 was associated with worse cognitive performance after 12 years.
Knopman et al. [22]	..	−	−*	..	−*	..	..	DM2 was associated with greater decline over 6 years
Fontbonne et al. [48]	−	−*	−*	−	−*	−*	..	DM2 patients had a 1.5 to 2-fold increased risk of serious worsening (<15%) over 4 years
Kanaya et al. [49]	..	..	..	..	−0.2	..	..	DM2 was associated with significant decline in verbal fluency over 4 years, but only in women.
Gregg et al. [50]	..	..	−0.1*	..	−0.1	..	..	DM2 was associated with greater decline over 3 to 6 years and a twofold increased risk of impairment (<10%)
Hassing et al. [51]	−*	−*	−*	..	..	−	..	No baseline differences but DM2 patients showed greater cognitive decline over 6 years
van den Berg et al. [52]	..	−	−	−	..	..	..	DM2 patients was associated with worse attention and speed at baseline, but not with accelerated decline over 5 years
Impaired glucose metabolism								
Cross-sectional								
Fuh et al. [31]	..	0.1	0.2	..	0	..	..	
Vanhanen et al. [53]	..	−1.0*	−1.4*	−1.0*	−0.9*	−0.7	..	
Scott et al. [43]	..	−	..	..	−	..	..	Persons with IGT tended to perform worse than both DM2 patients and NGT participants
Lindeman et al. [45]	..	0.1	−0.1	..	−0.1	0.1	..	
Longitudinal								
Kumari et al. [47]	=	=	=	=	=	=	..	IFG participants did not show greater cognitive decline over 4 years than NGT participants.
Fontbonne et al. [48]	=	=	..	..	=	..	=	
Kanaya et al. [49]	..	..	..	..	−0.1	..	..	
Vanhanen et al. [54]	..	−0.1	−0.1	..	−0.1	..	..	

Median effect size per domain.
.. cognitive domain not evaluated.
− cognitive domain evaluated, elevated levels of risk factor associated with worse cognition.
+ cognitive domain evaluated, decreased levels of risk factor associated with worse cognition.
+/− cognitive domain evaluated, both elevated and decreased levels of risk factor associated with worse cognition.
= cognitive domain evaluated, no association between risk factor and cognition.
*$p<0.05$.

Table 2b
Results of included studies for obesity

	General intelligence	Memory	Processing speed	Attention	Cognitive flexibility	Perception/ construction	Language	Comment
Cross-sectional								
Gunstad et al. [55]	..	..	..	−0.1	−0.2*	..	..	
Kuo et al. [56]	0.1	0.1	0.1	..	..	..	..	Inverted U-shaped association between BMI and cognition
Dik et al. [16]	−	−	−	..	..	..	..	
Longitudinal								
Cournot et al. [57]	..	−*	−*	−	..	..	..	Highest quintile BMI associated with worse cognitive performance at 5y follow-up
Wolf et al. [17]	..	−*	..	..	−*	−*	..	Highest baseline quartile of waist/hip ratio, but not BMI, associated with worse cognitive performance, particularly in hypertensive individuals
Elias et al. [58]	−0.1	−0.1	..	..	0	−0.2	..	Obesity was associated with significantly worse cognitive performance, but only in men

Median effect size per domain.
.. cognitive domain not evaluated.
− cognitive domain evaluated, elevated levels of risk factor associated with worse cognition.
+ cognitive domain evaluated, decreased levels of risk factor associated with worse cognition.
+/− cognitive domain evaluated, both elevated and decreased levels of risk factor associated with worse cognition.
= cognitive domain evaluated, no association between risk factor and cognition.
*$p<0.05$.

are presented separately. To obtain insight into the potential modifying role of age at the time of exposure the studies are listed according to age at baseline.

Risk factors in the included studies were mostly dichotomized (e.g., diabetes yes/no). In a minority of studies the risk factors were analyzed as continuous variables in statistical analyses. The majority of studies included both participants who were either treated or untreated for a particular risk factor. If data on untreated patients were available, these were included in the tables.

We did not perform a formal meta-analysis because of the heterogeneity of risk factor assessment and the variety of assessment procedures of cognitive functioning, study design (e.g. cross-sectional/longitudinal or case–control/population-based), and presentation of the analyses and results (e.g. risk factor presented dichotomously or as continuous variable, differences in adjustment for confounding variables).

3. Results

3.1. Methodological aspects

Despite the strict inclusion criteria, the studies included in this review differed substantially in design and outcome measures. Case–control studies generally provided limited information about partici-

Table 2c
Results of included studies for dyslipidemia

	General intelligence	Memory	Processing speed	Attention	Cognitive flexibility	Perception/ construction	Language	Comment
Cross-sectional								
Zhang et al. [59]	..	+	+*	..	..	..	..	Low total and non-HDL cholesterol associated with *decreased* cognitive speed in men
Dik et al. [16]	−*	−*	−	..	..	..	..	Low HDL cholesterol, but not high triglycerides was associated with worse speed and fluid intelligence
Longitudinal								
Henderson et al. [60]	..	+*	..	..	..	..	..	Highest quartile of LDL and increase in LDL and total cholesterol over 8y associated with *better* memory performance
Teunissen et al. [21]	..	=	=	=	..	..	..	Total cholesterol was not associated with cognitive function at baseline or after a 6y follow-up
Komulainen et al. [61]	..	−*	−	..	..	..	..	Low HDL-cholesterol was associated with increased risk of poor memory (<median) after 12y follow up
de Frias et al. [62]	−*	−	..	..	−	−	..	High triglyceride levels were associated with greater 10y decline in verbal knowledge. Associations were strongest for APOE e4 allele carriers.
Reitz et al. [63]	..	=	..	..	..	=	=	Lipid levels were not associated with 7 year changes in cognitive function

Median effect size per domain.
.. cognitive domain not evaluated.
− cognitive domain evaluated, elevated levels of risk factor associated with worse cognition.
+ cognitive domain evaluated, decreased levels of risk factor associated with worse cognition.
+/− cognitive domain evaluated, both elevated and decreased levels of risk factor associated with worse cognition.
= cognitive domain evaluated, no association between risk factor and cognition.
*$p<0.05$.

Table 2d
Results of included studies for hypertension

	General intelligence	Memory	Processing speed	Attention	Cognitive flexibility	Perception/ construction	Language	Comment
Cross-sectional								
Schmidt et al. [64]	..	−0.9*	−0.2	−0.4	..	..	..	
Waldstein et al. [65]	..	−2.2*	−	..	..	..	..	
Van Boxtel [15]	..	0	−0.1	..	−0.1	..	..	Hypertensive participants only showed significantly worse performance on 1 measure of cognitive speed
Cerhan et al. [14]	..	−*	−*	..	−*	..	..	Differences were statistically significant for women only
Andre-Petersson et al. [66]	0.2*	−0.1*	−0.1	..	..	..	..	Blood pressure>180/110 mmHg was associated with poorer performance, >140−159/90−99 mmHg with better performance compared to normotensives
Scherr et al. [67]	..	=	..	=	..	..	..	Diastolic blood pressure was not associated with cognitive function
Morris et al. [68]	..	+/−	+/−	..	..	..	..	Modest inverted U-shape between blood pressure and cognitive function
Desmond et al. [18]	=	=	..	=	..	=	=	No relation between blood pressure and cognitive function
Kuusisto et al. [69]	..	−0.1	..	..	−0.1	..	..	
Dik et al. [16]	−	=	=	..	..	..	..	
Harrington et al. [70]	..	−0.4*	−0.3*	−0.8*	..	..	..	
Longitudinal								
Pavlik et al. [71]	..	−	−	..	..	..	..	Hypertension was only associated with cognitive function when combined with DM2
Swan et al. [72]	..	−*	−	..	−	..	..	Persistent elevated SBP and SBP decrease over 38y follow-up was associated with worse cognition
Elias et al. [73]	−*	−	−	..	..	..	..	High baseline blood pressure was associated with increased cognitive decline in both young and old age-groups
Swan et al. [74]	..	−	−*	..	−	..	..	High midlife SBP was associated with greater 10-year decline in cognitive speed
Kilander et al. [75]	−	−	−	..	−*	−	..	High midlife DBP was associated with worse performance, DBP<70 mmHg was associated with *better* cognitive flexibility than normal DBP
Wolf et al. [17]	..	−*	..	..	−*	−	..	Hypertension was associated with worse cognitive performance, particularly in obese individuals
Knopman et al. [22]	..	−	−*	..	−	..	..	Baseline blood pressure was associated with greater 6-year decline in cognitive speed
Elias et al. [19]	−	−*	..	..	−	−*	..	
Elias et al. [20]	−	−*	..	..	−	−	..	Hypertensive DM2 patients were at greatest risk of cognitive impairment (<25%)
Reinprecht et al. [76]	−0.4	−0.4*	−0.4	..	..	..	..	DBP at age 68 was associated with decreased cognitive function at age 81
Waldstein et al. [77]	..	+/−	+/−	..	+/−	..	+/−	U- and J-shaped relation between blood pressure and cognition.
Hebert et al. [78]	..	=	=	..	..	..	..	Blood pressure was not associated with 6-year cognitive decline
Paran et al. [79]	..	+*	..	..	+*	..	..	J-shaped relation where normotensives showed *worse* cognitive performance than hypertensive individuals

Median effect size per domain.
.. cognitive domain not evaluated.
− cognitive domain evaluated, elevated levels of risk factor associated with worse cognition.
+ cognitive domain evaluated, decreased levels of risk factor associated with worse cognition.
+/− cognitive domain evaluated, both elevated and decreased levels of risk factor associated with worse cognition.
= cognitive domain evaluated, no association between risk factor and cognition.
*$p<0.05$.

pant selection and specific in- and exclusion criteria. Several studies specifically selected participants who were treated in outpatient clinics of hospitals, whereas other studies were population-based. There was also considerable variation in the extent to which co-morbid conditions (e.g. depression, stroke) and vascular risk factors other than the studied factor were dealt with. Large population-based studies generally used less detailed measures of cognitive functioning, but often assessed possible confounding or interaction effects across different risk factors more rigorously.

Ten studies on diabetes specifically excluded participants who had a stroke. For obesity, dyslipidemia and hypertension these numbers were 2, 3 and 13, respectively. Eight diabetes-studies specifically mentioned exclusion of persons who were demented (at baseline). For obesity, dyslipidemia and hypertension these numbers were 4, 2 and 6, respectively.

3.2. Cognitive functioning

The methods of neuropsychological assessment differed markedly among the included studies, ranging from an evaluation limited to one or two cognitive domains to a comprehensive examination across all major cognitive domains. The three domains that were assessed in most studies were memory, processing speed and cognitive flexibility.

Memory function was usually assessed by means of a verbal memory test where participants had to recall a list of unrelated words that was presented to them repeatedly (Rey Auditory Verbal Learning Test [25]) or had to recall a short paragraph (Wechsler Memory Scale — Logical Memory [26]). Generally, participants were asked to recall the words or the text immediately (immediate recall) and/or after a delay period of 20 to 30 min. Visuospatial memory was assessed in only a minority (<15%) of studies. Working memory was commonly assessed

with the subtest Digit Span of the Wechsler Adults Intelligence Scale, third edition (WAIS-III [27]), where participants were asked to verbally repeat series of digits of increasing length in the same fixed order as the experimenter or in backward order. Tests of cognitive speed often included the Digit Symbol Test (WAIS-III) in which participants had to copy as many symbols according to a code key in 2 min. Cognitive flexibility was most often assessed by means of the Trail Making Test Part B [28] that required participants to alternatively connect letters and digits and Verbal Fluency, where participants are asked to reproduce as many words as possible that begin with a specified letter of the alphabet over 1 min [29].

3.3. Type 2 diabetes mellitus/impaired glucose metabolism

Twenty-seven included studies [14,18,20,22,30–52] compared cognitive functioning in patients with type 2 diabetes mellitus to non-diabetic persons (Table 1a.). Half of the cross-sectional studies had a case–control design. In the population-based studies diabetes was most commonly identified by medical history combined with fasting or random blood glucose levels (9 out of 17 studies). The studies generally did not distinguish between type 1 and type 2 diabetes, but given the age of the populations involved the vast majority of the participants is likely to have had type 2 diabetes mellitus. The cognitive domains that were assessed most often were memory (25 studies), processing speed (19 studies) and cognitive flexibility (24 studies). Language was assessed in three studies only.

Diabetes was associated with statistically significant worsening of cognitive performance in one or more cognitive domains in 13 out of 20 cross-sectional and 5 out of 7 longitudinal studies. The association between diabetes and cognition differed across the individual domains: processing speed was significantly affected in 63% of studies assessing that domain, attention in 50%, memory in 44%, cognitive flexibility in 38%, language in 33%, general intelligence in 31% and perception and construction in 22% of the studies. For the domains most commonly affected effect sizes ranged from 0 to −1.9, with a median effect size of −0.4 for processing speed, −0.5 for attention and −0.3 for memory.

The cross-sectional studies in relatively older populations (average age >65) showed somewhat larger effect sizes than studies with younger populations. Six studies adjusted their results for the effects of other vascular risk factors [20,42–44,46,50]. Analyses with or without these adjustments generally showed similar results.

Eight included studies [31,43,45,47–49,53,54] reported on the association between impaired glucose metabolism (IGM) short of diabetes and cognitive functioning (Table 1a.). Two out of 4 cross-sectional studies had a case–control design. All population-based studies used an oral glucose tolerance test (OGTT) or fasting blood glucose to define impaired glucose metabolism (impaired fasting glucose (IFG): >6.1 but ≤7.0 mmol/l or impaired glucose tolerance (IGT): 2 h glucose >7.8 but <11.0 mmol/l). The cognitive domains that were assessed most often were memory (7 studies), cognitive flexibility (8 studies) and processing speed (5 studies).

IGM was associated with statistically significant worsening of cognitive performance in 1 out of 4 cross-sectional and none out of 4 longitudinal studies. Effect sizes across the different domains ranged from −1.4 to 0.2, with a median effect size of −0.1. Interestingly, two studies showed opposing effects. One cross-sectional study [31] showed that IGT participants tended to perform better than control participants and another [43] showed that IGT participants performed worse than both the control group and the DM2 patients. Only one study adjusted the result for other vascular risk factors [43]. The results from this study did not differ from the results of other studies.

3.4. Obesity

Six included studies [16,17,55–58] assessed the association between obesity and cognitive functioning (Table 1b.), all with a population-based design. Five out of six studies used body-mass indexe (BMI) as a measure of obesity and compared cognitive performance in participants above a certain cut-off (25 or 30 kg/m2) or in the highest quartile/quintile to normal-weight individuals. One study used waist circumference as a measure of obesity. Memory was assessed most often (5 studies), general intelligence, processing speed and cognitive flexibility were each assessed in 3 studies.

Obesity was associated with statistically significant worsening of cognitive performance in one or more cognitive domains in 1 out of 3 cross-sectional and 2 out of 3 longitudinal studies. The association between obesity and cognition differed across the individual domains: cognitive flexibility was significantly affected in 67% of the studies assessing that domain, perception and construction in 50%, memory in 40%, processing speed in 33% of the studies. General intelligence, attention and language were affected in none of the studies assessing those domains. For the domains most commonly affected the effect sizes range from −0.2 to 0.1, with a median effect size of −0.1 for cognitive flexibility, −0.2 for perception and construction and 0 for memory.

Studies that assessed obesity at midlife generally showed a more consistent relation with worse cognitive performance than studies that assessed obesity at late-life (>65 years). One late-life study actually reported an inverted U-shaped association showing that both low and high BMI was associated with worse cognition [56]. Three studies adjusted their results for the effects of other vascular risk factors [56–58]. Analyses with or without these adjustments generally showed similar results.

3.5. Dyslipidemia

Seven studies [16,21,59–63] that assessed the association between dyslipidemia and cognitive functioning were included (Table 1c.), all were population-based. Studies on dyslipidemia mostly assessed serum cholesterol levels (6 studies). Several studies also measured triglycerides, HDL-cholesterol and LDL-cholesterol. Results were either expressed dichotomously (4 studies), for example by comparing the highest quartile of cholesterol to the lowest quartile, or continuously (3 studies), for example per mmol/l or SD increase. The cognitive domains that were assessed most often were memory (7 studies) and processing speed (4 studies). The other cognitive domains were assessed in only 1 or two studies.

One out of 2 cross-sectional studies and two out of 5 longitudinal studies reported a statistically significant association with one or more measures of dyslipidemia and worse cognitive performance. Effect sizes and the frequency of reported abnormalities could not be calculated. Two studies actually reported an inverse relation where low total cholesterol was associated with decreased cognitive speed [59] and high LDL was associated with better memory performance [60]. No differences could be observed between different lipid measures. One study [62] reported an interaction with APOE where the association between triglyceride level and a decrease in cognitive functioning over 10 years was strongest in APOE ε4 allele carriers.

The two studies that reported an inverse relation between dyslipidemia and cognitive functioning assessed cholesterol levels in midlife. Apart from this observation, no clear differences were found between the results of midlife and late life studies. Three studies adjusted their results for the effects of other vascular risk factors [59,62,63]. Analyses with or without these adjustments generally showed similar results.

3.6. Hypertension/Blood pressure

Twenty-four studies [14–20,22,64–79] that assessed the association between blood pressure and cognitive functioning were included (Table 2d). Three out of 11 cross-sectional studies and none of the longitudinal studies had a case–control design. In the population-based studies hypertension was most commonly defined by means of

repeated blood pressure measurement, with various cut-off points (e.g. >140/90 or 160/95 mmHg; 19 studies). Three studies (also) used systolic and diastolic blood pressure as continuous variables in the analysis and expressed the result per SD or 10 mmHg increase. The cognitive domains that were assessed most often were memory (24 studies), processing speed (16 studies) and cognitive flexibility (12 studies).

Elevated blood pressure was associated with statistically significant worsening of cognitive performance in one or more cognitive domains in 7 out of 11 cross-sectional and 10 out of 13 longitudinal studies. Two studies [65,68] reported an inverted U-shaped relation where both high and low blood pressure levels were associated with worse cognitive performance. One study [79] showed an inverse relation where normotensive individuals performed worse than hypertensive persons. The association between blood pressure and cognition differed across the individual domains: memory was significantly affected in 42% of the studies assessing that domain, processing speed and general intelligence in 29%, cognitive flexibility and attention in 25%, perception and construction in 20% of the studies. Language was affected in none of the studies assessing that domain. For the domains most commonly affected effect sizes ranged from 0.2 to −2.2, with a median effect size of −0.4 for memory, −0.1 for general intelligence, −0.2 for processing speed, −0.4 for attention and −0.1 for cognitive flexibility.

Small differences can be observed between the results of studies that assessed blood pressure at midlife and at late life: studies that fail to show an association between elevated blood pressure and cognitive function or show U-shaped associations were all performed in late life (>65 years). The size of the effects, however, does not differ between midlife and late life studies. Nine studies adjusted their results for the effects of other vascular risk factors [67,69,72–74,76,77,79]. Analyses with or without these adjustments generally showed similar results.

3.7. Comparison

Comparison of the results over the four vascular risk factors shows that most consistent associations with cognitive decrements are found for diabetes (18 of 27 studies) and hypertension (17 of 24 studies). Results for impaired glucose metabolism obesity and dyslipidemia are less consistent, with 1 out of 8, 3 out of 6 and 2 out of 5 studies showing associations with cognitive decrements, respectively. The cognitive domains most commonly affected (memory, processing speed and cognitive flexibility) and the effect sizes on affected domains (median ~ −0.3) are similar across risk factors.

4. Discussion

In this review the association between type 2 diabetes, obesity, dyslipidemia, and hypertension and cognitive functioning was examined. The results show that all four vascular risk factors are associated with decrements in cognitive functioning, but the association was most consistent for type 2 diabetes and hypertension. For obesity and dyslipidemia a substantial proportion of studies did not show an association with worse cognitive performance.

Before further discussing these findings, some methodological issues regarding the included studies and the approach we used for our review should be addressed. Regarding the approach of our review, it is important to emphasize that we aimed to provide a direct comparison between vascular risk factors. We therefore aimed to rigorously standardize inclusion criteria for eligible studies, both with regard to design as to outcome measures. Where possible, test results from individual studies were converted to effect sizes and regrouped in predefined cognitive domains. A potential disadvantage of this method is that a substantial number of studies had to be excluded that did not meet our criteria. Moreover, studies with negative results may be underrepresented in this review due to the effects of publication bias.

Despite our strict inclusion criteria, the study design of included studies varied markedly, from cross-sectional to longitudinal and from sampling at population level to recruitment of patients from hospital clinics. These differences in design lead to differential forms of selection bias. Whereas hospital-based studies may have been biased to the recruitment of individuals whose risk factors were more difficult to manage, hence their treatment in a hospital, population-based studies may have failed to recruit people who were more severely affected, because they were less willing to participate. Another point of concern are the exclusion criteria that were applied in the individual studies. The majority of studies excluded individuals with clinically manifest cognitive impairments, such as dementia. Obviously, differences in the way such individuals were identified and subsequently excluded leads to variations in the observed effect sizes across studies and exclusion of persons with more severe cognitive impairments could potentially lead to underestimation of the effects. The extent in which co-morbid conditions (e.g. depression, stroke) and vascular risk factors other than the factor under study were taken into account also varied greatly. Depression in particular is known to hamper cognitive functioning and the prevalence of depression may vary across different risk factors. Finally, there are some inherent differences between the risk factors included in the present review that need to be considered. Blood glucose, lipid levels, blood pressure and body weight are essentially continuous variables. Cut-off points that define diabetes, dyslipidemia, hypertension and obesity are to some extent arbitrary and are subject to change over time due to evolving medical insights. Consequently, the proportion of individuals that is labelled as "abnormal" varies across risk factors and across time, as can be seen in Tables 1a through d. It will be evident that the using higher cut-off points will result in a smaller proportion of individuals who are is labelled as abnormal and a potentially higher contrast for finding effects on cognition. There are also differences in the evolution of the risk factors throughout the lifespan, with the proportion of individuals diagnosed with type 2 diabetes increasing sharply after 50 to 60 years of age, whereas overweight often starts to develop at a much younger age. Consequently, comparison between risk factors is hampered by inherent differences in duration and levels of exposure. Despite these limitations, this paper provides the first systematic review that allows a quantitative comparison between individual vascular risk factors.

The domains of memory, processing speed and cognitive flexibility were most consistently affected. This profile of cognitive decrements appears to be rather nonspecific and resembles the profile found in normal aging, which is thought to reflect a decline in general-purpose processing resources considered necessary for efficient cognitive functioning [80]. It should be noted here, however, that the cognitive domains most commonly affected were also the domains most frequently assessed. Particularly the domains of language and perception and construction have been examined in only a minority of studies.

The size of the cognitive decrements showed remarkable similarity across risk factors and was generally small to medium, with effect sizes ranging from −0.1 to −0.5 across cognitive domains and vascular risk factors. Effect sizes of studies that showed statistically significant associations were about the same size as those of studies that fail to reach statistical significance. This suggests that some of the studies with negative results had insufficient sample sizes. It is also important to note that some of the relations between risk factors and cognition may be nonlinear, in that there may be interaction between vascular risk factors, or modulation by other factors such as age. Indeed, for dyslipidemia, obesity and hypertension, but not for diabetes, several studies show inverse of U-shaped or inverse effects, where decreased levels of the risk factor were associated with worse cognitive performance or increased levels were associated with better performance. These results raise questions about what levels of certain risk factors may be considered as 'normal'. In this respect age may be a modulating factor, although this age effect appears to be less

evident for the studies included in the present review than for studies that use dementia as an outcome measure [11].

Different vascular risk factors were previously reported to convey a similar risk of dementia [11]. The present review shows that early, more subtle cognitive decrements are also largely similar across vascular risk factors. Imaging studies also show similar cerebral changes across vascular risk factors, in particular more accentuated global atrophy and white matter hyperintensities and an increased occurrence of infarcts, although the magnitude of the effects may differ across factors [81,82]. Nevertheless, it should be noted that not all individuals that present with these early cerebral abnormalities progress to dementia. Therefore, the cognitive decrements that are reported in the present review do not necessarily reflect a 'pre-dementia' stage. Still, these early changes may represent a window of opportunity for early intervention studies.

In sum, diabetes and hypertension and, to a lesser extent, obesity and dyslipidemia are associated with mild to moderate decrements in cognitive functioning in non-demented persons. The profile of cognitive decrements is rather nonspecific, with most consistent results found in the domains of memory, processing speed and cognitive flexibility.

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Appendix 1

Cognitive domain	Included test
General intelligence	
Crystallised intelligence	Verbal IQ
	Similarities (WAIS)
	Vocabulary (WAIS)
	Information (WAIS)
	Comprehension (WAIS)
	National Adult Reading Test
	Synonyms
Fluid intelligence	Performal IQ
	Picture Completion (WAIS)
	Picture Arrangement (WAIS)
	Arithmetic (WAIS)
	Raven (Colored) Progressive Matrices
	Category Test
	Alice Heim 4
	Identities and Oddities (Mattis DRS)
	Word Series, Letter Series, Letter Sets
Memory	
Working memory	Digit Span Forward and Backward
	(Corsi) Block Span Forward and Backward
	Brown–Peterson task
	Four-Word Short Term Memory
Learning and Immediate memory	(Rey) Auditory Verbal Learning Test Immediate Recall
	Word List Learning (10, 12, 15, 16 or 20 words) Immediate Recall
	California Verbal Learning Test Immediate Recall
	Paired Associate Learning (WMS) Verbal and Nonverbal Immediate Recall
	Logical Memory (WMS) Immediate Recall
	Immediate Prose Recall (Rivermead)
	Hopkins Verbal Learning Test Related Word Lists Immediate Recall
	Babcock Paragraph Story Recall Immediate
	(Buschke) Selective Reminding Test Immediate Recall
	(Russell's) Visual Reproductions Test Immediate Recall
	(Benton) Visual Retention Test Immediate Recall
Memory	
Learning and Immediate memory	Visual Reproductions (WMS) Immediate Recall
	Location Learning Test Immediate Recall
	Rey Complex Figure Test Immediate Recall
	(Fuld) Object Learning Test
	Picture Recognition Test
	Spatial Memory Test
	Claeson–Dahl Immediate Recall
	East Boston Memory Test Immediate Recall
	Bäumler Lern-und Gedächtnistest
	Serial Digit Learning Test
	Continuous Recognition Paradigm
Delayed memory	(Rey) Auditory Verbal Learning Test Delayed Recall
	Word List Learning (10, 12, 15, 16 or 20 words) Delayed Recall
	California Verbal Learning Test Delayed Recall
	Paired Associate Learning (WMS) Verbal and Nonverbal Delayed Recall
	Logical Memory (WMS) Delayed Recall
	Delayed Prose Recall (Rivermead)
	Hopkins Verbal Learning Test Related Word Lists Delayed Recall
	Babcock Paragraph Story Recall Delayed
	(Buschke) Selective Reminding Test Delayed Recall
	(Russell's) Visual Reproductions Test Delayed Recall
	(Benton) Visual Retention Test Delayed Recall
	Visual Reproductions (WMS) Delayed Recall
	Location Learning Test Delayed Recall
	Rey Complex Figure Test Delayed Recall
	Claeson–Dahl Delayed Recall
	East Boston Memory Test Delayed Recall
	Object Memory Delayed Recall
Processing speed	
Psychomotor efficiency	Digit Symbol Substitution (WAIS)
	Letter Digit Coding/Substitution Test
	Symbol Digit Modalities Test
	Grooved Pegboard
	Perceptual Speed
	Choice Reaction Time
	Trail Making Test Part A
	Useful Field of View
Motor speed	Simple Reaction Time
	Finger Tapping
Attention	
Visual attention	Stroop Color Word Test Part I and II
	Target Finding Task
Sustained attention	Digit Vigilance Test
	D2
	Quatember and Maly's Vigilance Test
Divided attention	Paced Auditory Serial Addition Test
Selective attention	Stroop Color Word Test Part III
Cognitive flexibility	Category Test
	Concept Shifting Task
	Brixton Spatial Anticipation Test
	Wisconsin Card Sorting Test
	Verbal Fluency (lexical, category)
	Trail Making Test Part B (also C, D and Color)
	Serial Subtraction (1's, 3's, 7's)
	Austin Maze
Perception and Construction	Tactual Performance Test
	Object Assembly (WAIS)
	Block Design (WAIS)
	Embedded Figures
	Rey Complex Figure Copy
	(Russell's) Visual Reproductions Test Copy
	(Benton) Visual Retention Test Copy
	Rosen Figure Drawing Test
	Pentagon Drawing
	Clock Drawing
	Facial Recognition Test
	Hooper Visual Organization Test

Appendix 1 (*continued*)

Cognitive domain	Included test
Language	(Boston) Naming Test
	Mill Hill
	Verbal Meaning Test
	Boston Diagnostic Aphasia Examination

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