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Review

Diabetes and other vascular risk factors for dementia: Which factor matters most? A systematic review

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Abstract

Vascular risk factors, such as type 2 diabetes, hypertension, obesity and dyslipidaemia often co-occur. Each of these factors has been associated with an increased risk of dementia, but it is uncertain which factor imposes the greatest risk. Moreover, the effect of age at time of exposure may differ across factors. This paper systematically reviews the evidence for the association of each of these risk factors with dementia. Longitudinal population-based studies that assessed the incidence of dementia in relation to diabetes ($n=14$), hypertension ($n=13$), dyslipidaemia ($n=8$) or obesity ($n=9$) were included. All four risk factors were indeed associated with an increased risk of dementia, but the results of studies on diabetes and obesity were most consistent. The magnitude of the effects was comparable across the risk factors, with odds ratios for 'any dementia' around 1.5. For hypertension, obesity and dyslipidaemia age appeared to modulate the association: the risk of dementia was generally largest in studies that measured the risk factor in midlife (compared to late life) and had a long follow-up time. At midlife, the population attributable risk of dementia was highest for hypertension, up to 30% of cases of late life dementia. Later in life diabetes appears to convey the highest risk of dementia. This review shows that vascular risk factors should be regarded as a major target for preventive measures, but that timing of such measures appears to be critical.

Keywords: Dementia; Vascular risk factor; Diabetes; Hypertension; Dyslipidaemia; Obesity

Contents

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1. Introduction

Type 2 diabetes mellitus is a well-known risk factor for cardiovascular disease. Diabetes is also associated with cognitive decline and an increased risk of dementia in the elderly (Awad et al., 2004; Biessels et al., 2006). Type 2 diabetes develops in the context of insulin resistance and is often accompanied by other vascular risk factors such as hypertension, dyslipidaemia and obesity. The co-occurrence of these risk factors is generally referred to as 'the metabolic syndrome' (Reaven, 1988). There is evidence that each of the individual risk factors of the metabolic syndrome is associated with cognitive decline and dementia. As these risk factors are potential targets for therapeutic intervention it is important to examine the contribution of each of these risk factors to the risk of dementia. In this context it is also important to assess whether the effects of the individual risk factors are independent from each other.

Several studies suggest that the association between dementia and vascular risk factors varies with age. High blood pressure in middle-age, for example, is a clear risk factor for dementia in old age (Whitmer et al., 2005b). In old age, however, *low* blood pressure may be associated with an increased risk of dementia (Verghese et al., 2003).

In this paper we systematically reviewed studies on the risk of dementia associated with type 2 diabetes mellitus, hypertension, obesity and dyslipidaemia. We aimed to quantify and compare the association with dementia for these four risk factors, and to address the potential modifying role of age at the time of exposure.

2. Materials and methods

2.1. Identification of studies

This systematic review aimed to include all published studies that provide an estimate of the incidence of dementia associated with type 2 diabetes mellitus or impaired glucose metabolism, hypertension, dyslipidaemia or obesity and that met the following inclusion criteria: (1) the study population was recruited at the population level; (2) the study had a longitudinal design; (3) the results were adjusted for the basic confounders age, sex as well as educational level; and (4) adjusted odds ratios, relative risks or hazard ratios could be calculated or extracted from the paper. Studies on the prevalence of vascular risk factors in patients with established dementia were excluded.

Medline 1966 to June 2007 and bibliographies from included papers were used to identify relevant papers. The search was limited to papers that were written in English and concerned humans. We used the search terms ("diabetes", "hyperglycaemia" or "glucose tolerance"), ("hypertension" or "blood pressure"), ("dyslipidaemia", "hypercholesterolaemia", "cholesterol", "high-density lipoprotein", "low-density lipoprotein" or "triglycerides"), ("waist circumference", "obesity", "overweight", "abdominal fat" or "body-mass index") in combination with ("dementia" or "Alzheimer's disease") in full or 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.

2.2. Included papers

For diabetes/impaired glucose metabolism the search yielded 1423 papers, 14 of which met our inclusion criteria for diabetes and two for impaired glucose metabolism. The search yielded 1597 hits for hypertension (13 studies were included), 1291 hits for dyslipidaemia (eight studies were included) and 274 hits for obesity (nine studies were included). Papers that addressed more than one vascular risk factor were included in multiple risk factor sections in this review (Whitmer et al., 2005b; Yamada et al., 2003; Yoshitake et al., 1995; Kalmijn et al., 2000). When more than one paper reported on the same population (e.g. Honolulu-Asia Aging Study, Kungsholmen project), the paper with the largest sample size and/or the most detailed information on that risk factor and/or dementia was included.

2.3. Data extraction and analysis

Odds ratios, relative risks and hazard ratios were extracted from the included studies and are presented in Table 1a–d. Age, sex and education-adjusted analyses are presented. When available, analyses that additionally adjusted for other factors are also presented. Information on baseline and follow-up sample size, follow-up time and age at baseline was recorded. To obtain insight in 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 either dichotomized (e.g. diabetes yes/no) or analysed as continuous variables in statistical analyses. To increase the clarity of this review, these different ways of expressing the risk of dementia are presented separately in Table 1a–d. Since only population-based studies were included in this review the majority of the study populations included both participants who were and were not treated for a particular risk factor. When data on untreated participants were available (i.e. Qiu et al., 2003; Launer et al., 2000) these were included in the tables. We did not perform a formal meta-analysis because of the heterogeneity of risk factor and dementia assessment, study design (e.g. age at

Table 1a
Risk of dementia associated with type 2 diabetes mellitus

						Any dementia		Alzheimer's disease		Vascular dementia		
	FU (y)	*N* baseline/FU	Diabetes baseline/FU	Age baseline	QR	Results [a] (95% CI)	Additionally adjusted results [b]	Results (95% CI)	Additionally adjusted results	Results (95% CI)	Additionally adjusted results	Additional adjustments [c]
Whitmer et al., 2005b	~35	ND/8845	ND/1004	42	5	1.5 (1.2–1.8)	–	–	–	–	–	Race
Yamada et al., 2003	30	ND/1774	ND/ND	43	7	–	–	4.4 ($p<0.01$)	–	1.3 ($p=0.06$)	–	–
Schnaider-Beeri et al., 2004	35	10059/1892	825/42	45	7	–	2.8 (1.4–5.7)	–	–	–	–	BP, DL, BMI, smoking
Curb et al., 1999	25	8006/3734	ND/259	53	5	1.1 (0.7–1.8)	–	1.0 (0.5–2.0)	–	1.5 (0.8–2.8)	–	–
Ott et al., 1999	2.1	6370 [d]	692/ND	69	9	1.9 (1.3–2.8)	–	1.9 (1.2–3.1)	–	2.0 (0.7–5.6)	–	–
Akomolafe et al., 2006	12.7	2210 [d]	202/ND	70	6	1.2 (0.8–1.8)	1.2 (0.7–2.0)	1.1 (0.7–1.8)	1.2 (0.7–2.1)	1.8 (0.6–5.2)	0.8 (0.2–3.7)	BP, VD, BMI, smoking, alcohol, homocysteine
Yoshitake et al., 1995	7	828 [d]	70/ND	74	7	–	–	2.2 (1.0–4.9)	–	2.8 (2.6–3.0)	–	–
MacKnight et al., 2002	5	9131/5574	ND/503	74	7	1.2 (0.9–1.7)	1.3 (0.9–1.8)	1.2 (0.8–1.8)	1.3 (0.8–2.0)	2.2 (1.3–3.6)	2.0 (1.2–3.6)	BP, VD
Arvanitakis et al., 2004	5.5	847/824	91/127	75	6	–	–	1.7 (1.1–2.5)	–	–	–	–
Luchsinger et al., 2001	4.3	1799/1262	229/255	76	6	–	–	–	–	4.2 (2.2–8.3)	3.4 (1.7–6.9)	BP, DL, smoking, race
Luchsinger et al., 2005	5.5	1786/1138	313/231	76	6	–	–	2.4 (1.8–3.2)	2.0 (1.4–2.9)	–	–	BP, VD, APOE, smoking
Peila et al., 2002	2.9	3508/2574	ND/900	77	7	1.5 (1.0–2.2)	1.5 (1.0–2.2)	1.7 (1.0–2.8)	1.8 (1.1–2.9)	2.2 (1.1–4.7)	2.3 (1.1–5.0)	BP, DL, VD, DM medication, BMI, APOE, smoking, alcohol
Xu et al., 2004	4.7	130 [d]	114/ND	81	7	1.5 (1.1–2.1)	1.5 (1.0–2.1)	1.3 (0.8–1.9)	1.3 (0.9–2.1)	2.2 (1.1–5.0)	2.6 (1.2–6.1)	BP, VD, BMI
Hassing et al., 2002	6	702 [d]	ND/108	83	4	–	1.2 (0.8–1.7)	–	0.8 (0.5–1.5)	–	2.5 (1.4–4.8)	BP, VD, smoking

Studies are listed according to age at baseline, data are presented as odds ratios, relative risks or hazard ratios.
ND, not determined; FU, follow-up; QR, quality rating.

[a] All studies adjusted for or matched on age, sex and education.

[b] Analyses additionally adjusted for other vascular risk factors are listed in this column, the variables that were adjusted for are listed in the last column.

[c] Additional adjustments: BP, blood pressure (including hypertension, systolic blood pressure, diastolic blood pressure, antihypertensive medication); DL, dyslipidaemia (including total cholesterol, HDL-, LDL-cholesterol, triglycerides); VD, vascular disease (including cerebrovascular disease, stroke, tia, cardiac disease, myocardial infarction, coronary artery disease, congestive heart failure, angina pectoris, ankle-brachial index); BMI, body-mass index; APOE, apolipoprotein E status; DM medication, oral antidiabetic medication or insulin.

[d] Studies that actively pursued the occurrence of dementia in participants who did not attend follow-up, for example by checking medical records.

Table 1b
Risk of dementia associated with hypertension

	FU (y)	*N* baseline/FU	Hypertensive baseline/FU	Age baseline	QR	Any dementia		Alzheimer's disease		Vascular dementia		Additional adjustments[c]
						Results (95% CI)[a]	Additionally adjusted results[b]	Results (95% CI)	Additionally adjusted results	Results (95% CI)	Additionally adjusted results	
Hypertension												
Studies that compare the risk of dementia in subjects with hypertension to subjects without hypertension.												
Whitmer et al., 2005b	27	ND/8845	ND/1713	42	5	1.2 (1.04–1.5)	–	–	–	–	–	Race
Kuller et al., 2003	7	5888/3608	ND/1491	65	4	1.1 (0.9–1.4)	1.0 (0.9–1.3)	–	0.9 (0.7–1.2)	–	1.4 (0.96–2.1)	VD, APOE, MMSE
Tyas et al., 2001	5	1355/694	ND/223	69	5	–	–	1.1 (0.5–2.5)	–	–	–	–
Lindsay et al., 2002	5	6434/4615	ND/ND	68	6	–	–	0.9 (0.6–1.3)	–	–	–	–
Posner et al., 2002	7	1799/1259	ND/731	76	8	–	–	–	0.8 (0.6–1.1)	–	1.6 (0.9–2.9)	VD
Systolic blood pressure												
Studies that compare the risk of dementia in subjects above a cut-off for high SBP to subjects with normal SBP or the highest quartile to the lowest quartile												
Kivipelto et al., 2001	21	2293/1449	ND/~330	50	8	–	–	–	2.8 (1.1–7.2)	–	–	VD, BMI, smoking, alcohol
Launer et al., 2000	25	8006/3734	ND/~300	53	6	–	3.9 (1.5–10.0)	–	1.2 (0.4–4.0)	–	11.8 (3.5–39.5)	VD, APOE, smoking, alcohol
Morris et al., 2001	14	2313/634	ND/ND	72	7	–	–	0.3 (0.1–0.9)	0.2 (0.1–0.7)	–	–	hist hyp, VD, DM, BMI, APOE
Verghese et al., 2003	6.7	488[d]	204/ND	79	8	0.9 (0.5–1.4)	–	0.7 (0.4–1.3)	–	1.0 (0.3–3.2)	–	–
Qiu et al., 2003	6	1440/1270	~145/ND	81	7	–	1.5 (0.9–2.4)	–	1.6 (0.9–2.6)	–	–	DBP, VD, MMSE
Studies that express the results per 10 mm Hg increase or per S.D. increase												
Yamada et al., 2003	30	ND/1774	ND/ND	43	7	–	–	1.03 ($p<0.001$)		1.0 ($p<0.001$)	1.3 (1.1–1.6)	DM, BMI, diet
Morris et al., 2001	14	2313/634	ND/ND	72	7	–	–	0.8 (0.7–0.95)	0.8 (0.7–0.95)	–	–	Hist hyp, VD, DM, BMI, APOE
Ruitenberg et al., 2001	2.1	7162/5785	ND/ND	70	7	0.9 (0.9–0.99)	–	1.0 (0.9–1.03)	–	0.9 (0.8–1.06)	–	–
Yoshitake et al., 1995	7	828[d]	ND/ND	74	9	–	–	1.0 (0.8–1.4)	–	1.5 (1.2–2.0)	–	–
Verghese et al., 2003	6.7	488[d]	204/ND	79	8	0.9 (0.9–1.01)	–	0.9 (0.8–1.02)	–	1.0 (0.8–1.1)	–	–
Diastolic blood pressure												
Studies that compare the risk of dementia in subjects above a cut-off for high DBP to subjects with normal DBP or the highest quartile to the lowest quartile												
Kivipelto et al., 2001	21	2293/1449	ND/~330	50	8	–	–	–	1.7 (0.8–3.6)	–	–	VD, BMI, smoking, alcohol
Launer et al., 2000	25	8006/3734	ND/~300	53	6	–	4.0 (1.6–10.3)	–	4.5 (1.5–13.1)	–	2.5 (0.5–13.4)	VD, APOE, smoking, alcohol
Morris et al., 2001	14	2313/634	ND/ND	72	7	–	–	0.7 (0.2–2.4)	0.8 (0.2–2.6)	–	–	Hist hyp, VD, DM, BMI, APOE
Verghese et al., 2003	6.7	488[d]	204/ND	79	8	0.6 (0.4–1.02)	–	0.6 (0.3–12.3)	–	0.7 (0.3–2.2)	–	–
Qiu et al., 2003	6	1440/1270	~145/ND	81	7	–	1.0 (0.7–1.6)	–	1.0 (0.6–1.6)	–	–	SBP, VD, MMSE
Studies that express the results per 10 mm Hg increase or per S.D. increase												
Ruitenberg et al., 2001	2.1	7162/5785	ND/ND	70	7	0.9 (0.8–1.0)	–	0.9 (0.8–1.1)	–	1.0 1(0.8–1.3)	–	–
Morris et al., 2001	14	2313/634	ND/ND	72	7	–	–	0.7 (0.5–1.01)	0.8 (0.6–1.08)	–	–	Hist hyp, VD, DM, BMI, APOE
Yoshitake et al., 1995	7	828[d]	ND/ND	74	9	–	–	1.1 (0.8–1.5)	–	1.5 (1.1–1.9)	–	–
Verghese et al., 2003	6.7	488[d]	204/ND	79	8	0.8 (0.6–0.97)	–	0.8 (0.5–1.0)	–	0.9 (0.4–1.2)	–	–

Studies are listed according to age at baseline, data are presented as odds ratios, relative risks, hazard ratios.
ND, not determined; FU, follow-up; QR, quality rating.

[a] All studies adjusted for or matched on age, sex and education.

[b] Analyses additionally adjusted for other vascular risk factors are listed in this column, the variables that were adjusted for are listed in the last column.

[c] Additional adjustments: SBP, systolic blood pressure; DBP, diastolic blood pressure; his hyp, history of hypertension; VD, vascular disease (including cerebrovascular disease, stroke, tia, cardiac disease, myocardial infarction, coronary artery disease, congestive heart failure, angina pectoris, ankle-brachial index); DM, diabetes mellitus (including type 1 and type 2 diabetes mellitus, hyperglycaemia, impaired glucose tolerance, antidiabetic medication or insulin); BMI, body-mass index; APOE, apolipoprotein E status; MMSE, (modified) mini-mental state examination or cognitive abilities screening instrument (CASI).

[d] Studies that actively pursued the occurrence of dementia in participants who did not attend follow-up, for example by checking medical records.

Table 1c
Risk of dementia associated with dyslipidaemia

	FU (y)	*N* baseline/FU	Dyslipidaemia baseline/FU	Age baseline	QR	Any dementia		Alzheimer's disease		Vascular dementia		Additional adjustments [c]
						Results [a] (95% CI)	Additionally adjusted results [b]	Results (95% CI)	Additionally adjusted results	Results (95% CI)	Additionally adjusted results	
Total cholesterol												
Studies that compare the risk of dementia in subjects above a cut-off for high cholesterol to subjects with normal cholesterol levels or the highest quartile to the lowest quartile												
Whitmer et al., 2005b	27	ND/8845	ND/2844	42	5	1.4 (1.2–1.7)	–	–	–	–	–	Race
Kivipelto et al., 2002	21	2293/1449	ND/ND	50	9	–	2.6 (1.2–6.0)	–	2.8 (1.2–6.7)	–	–	APOE, smoking, alcohol
Mielke et al., 2005	18	392 [d]	ND/ND	70	8	–	0.3 (0.1–0.9)	–	–	–	–	BP, BMI, smoking
Li et al., 2005	5.6	2581/1496	ND/ND	75	6	–	1.2 (0.8–1.7)	–	1.0 (0.6–1.6)	–	–	BP, VD, DM, BMI, MMSE
Solfrizzi et al., 2004	3.5	5632/2963	ND/ND	~75	7	0.8 (0.1–4.4)	–	–	–	–	–	–
Reitz et al., 2004	7	1168 [d]	ND/ND	76	7	–	–	0.6 (0.3–0.95)	0.5 (0.3–0.9)	1.6 (0.7–3.7)	1.1 (0.4–2.6)	BP, VD, DM, BMI, APOE, race
Studies that express the results per mmol/l increase or per S.D. increase												
Kalmijn et al., 2000	25	8006/3734	ND/ND	53	8	1.1 (1.0–1.3)	–	–	–	–	–	–
Mielke et al., 2005	18	392 [d]	ND/ND	70	8	–	0.8 (0.6–0.96)	–	–	–	–	BP, BMI, smoking
Hall et al., 2006	9	ND/1075	ND/ND	70	5	–	–	1.02 (p=0.03)	–	–	–	–
Triglycerides												
Studies that compare the risk of dementia in subjects above a cut-off for high triglycerides to subjects with normal triglyceride levels or the highest quartile to the lowest quartile												
Mielke et al., 2005	18	392 [d]	ND/ND	70	8	–	0.5 (0.2–1.1)	–	–	–	–	BP, BMI, smoking
Reitz et al., 2004	7	2126/1168	ND/ND	76	7	–	–	0.8 (0.4–1.3)	0.8 (0.4–1.4)	1.5 (0.7–3.3)	1.3 (0.6–3.3)	BP, VD, DM, BMI, APOE, race
Studies that express the results per mmol/l increase or S.D. increase												
Kalmijn et al., 2000	25	8006/3734	ND/ND	53	8	1.3 (1.1–1.5)	–	–	–	–	–	–
Mielke et al., 2005	18	392 [d]	ND/ND	70	8	–	0.6 (0.3–1.2)	–	–	–	–	BP, BMI, smoking
Hall et al., 2006	9	ND/1075	ND/ND	70	5	–	–	1.0 (p=0.8)	–	–	–	–

Studies are listed according to age at baseline, data are presented as odds ratios, relative risks or hazard ratios.
ND, not determined; FU, follow-up; QR, quality rating.

[a] All studies adjusted for or matched on age, sex and education.

[b] Analyses additionally adjusted for other vascular risk factors are listed in this column, the variables that were adjusted for are listed in the last column.

[c] Additional adjustments: BP, blood pressure (including hypertension, systolic blood pressure, diastolic blood pressure, antihypertensive medication); VD, vascular disease (including cerebrovascular disease, stroke, tia, cardiac disease, myocardial infarction, coronary artery disease, congestive heart failure, angina pectoris, ankle-brachial index); DM, diabetes mellitus (including type 1 and type 2 diabetes mellitus, hyperglycaemia, impaired glucose tolerance, antidiabetic medication or insulin); APOE, apolipoprotein E status; MMSE, (modified) mini-mental state examination or cognitive abilities screening instrument (CASI).

[d] Studies that actively pursued the occurrence of dementia in participants who did not attend follow-up, for example by checking medical records.

Table 1d
Risk of dementia associated with obesity

	FU (y)	*N* baseline/FU	Obese baseline/FU	Age baseline	QR	Any dementia		Alzheimer's disease		Vascular dementia		Additional Adjustments [c]
						Results (95% CI) [a]	Additionally adjusted results [b]	Results (95% CI)	Additionally adjusted results	Results (95% CI)	Additionally adjusted results	
Studies that compare the risk of dementia in subjects above a cut-off for obesity to subjects with normal weight or the highest quartile to the lowest quartile												
Whitmer et al., 2005a	27	10276 [d]	1029/ND	42	5	1.6 (1.2–2.0)	1.7 (1.3–2.3)	–	–	–	–	BP, DL, VD, DM, race
Kivipelto et al., 2005	21	2293/1449	222/ND	50	9	2.4 (1.2–5.1)	1.9 (0.8–4.6)	1.9 (0.8–4.2)	1.8 (0.7–4.6)	–	–	BP, DL, VD, DM, APOE, smoking, FU–time
Rosengren et al., 2005	30	9998/7402	ND/ND	52	7	2.0 (1.1–3.6)	1.8 (1.0–3.3)	–	–	–	–	BP, DL, DM, smoking
Luchsinger et al., 2007	5.1	1484/893	ND/223	77	7	0.9 (0.6–1.5)	0.8 (0.5–1.2)	1.2 (0.7–2.1)	0.9 (0.5–1.6)	0.9 (0.4–2.1)	0.8 (0.4–1.7)	APOE, race
Nourhashemi et al., 2003	8	3646/ND	ND/ND	78	4	–	0.7 (0.4–1.2)	–	–	–	–	smoking, alcohol
Studies that express the results in terms of weight change or per BMI point or S.D. increase												
Kalmijn et al., 2000	25	8006/3734	ND/ND	53	8	1.2 (1.1–1.4)	–	–	–	–	–	–
Gustafson et al., 2003	18	392 [d]	ND/ND	70	8	–	1.1 (1.04–1.2)	–	1.4 (1.2–1.6)	–	1.0 (0.9–1.2)	BP, VD, smoking
Yoshitake et al., 1995	7	828 [d]	ND/ND	74	9	–	–	0.8 (0.5–1.03)	–	1.3 (0.98–1.7)	–	–
Buchman et al., 2005	5.5	918/820	245/ND	75	7	–	–	0.9 (0.9–0.98)	–	–	–	–

Studies are listed according to age at baseline, data are presented as odds ratios, relative risks, hazard ratios.
ND, not determined; FU, follow-up; QR, quality rating.
[a] All studies adjusted for or matched on age, sex and education.
[b] Results additionally adjusted for other vascular risk factors, listed in the last column.
[c] Additional adjustments: BP, blood pressure (including hypertension, systolic blood pressure, diastolic blood pressure, antihypertensive medication); DL, dyslipidaemia (including total cholesterol, HDL-, LDL-cholesterol, triglycerides); VD, vascular disease (including cerebrovascular disease, stroke, tia, cardiac disease, myocardial infarction, coronary artery disease, congestive heart failure, angina pectoris, ankle-brachial index); DM, diabetes mellitus (including type 1 and type 2 diabetes mellitus, hyperglycaemia, impaired glucose tolerance, antidiabetic medication or insulin); APOE, apolipoprotein E status.
[d] Studies that actively pursued the occurrence of dementia in participants who did not attend follow-up, for example by checking medical records.

time of risk factor assessment, duration of follow-up), and presentation of the analyses and results (e.g. risk factor presented dichotomously or as continuous variable, differences in adjustment for confounding variables). However, to allow comparison of the risk of dementia between factors we did calculate the population attributable risk of dementia for each factor (Table 2). The population attributable risk can be defined as the proportion of dementia cases attributable to a particular risk factor. The population attributable risk takes in to account both the magnitude of the relative risk imposed by a particular factor and the prevalence of this factor. We estimated prevalence of each risk factor using published prevalence rates in western countries (Wild et al., 2004; Wolf-Maier et al., 2003; Ogden et al., 2006; National Center for Health Statistics, 2006). The population attributable risk was estimated for each factor based on the median odds ratio of studies presented in Table 1a–d. Only the odds ratios of studies that analysed the risk factors dichotomously were included. To calculate the median odds ratio we primarily used the odds ratio of "any dementia" for each study population. When this outcome measure was not provided, the odds ratio for Alzheimer's disease or vascular dementia was used instead. When both Alzheimers's disease and vascular dementia were assessed, the mean of the two odds ratios was used. Population attributable risks were calculated using the formula $[(OR-1)*PF]/[1+(OR-1)*PF]$ in which OR is the median odds ratio for a particular risk factor and PF the population fraction with that risk factor (Ott et al., 1999). To address the potential modifying role of age at the time of exposure on the risk of dementia we distinguished between midlife and late life exposure, the first being defined as <65 years and the latter as over 65 years of age.

2.4. Dementia diagnosis

The majority of studies used a standardized diagnostic protocol and internationally accepted diagnostic criteria for dementia. For a diagnosis of Alzheimer's disease the NINCDS-ADRDA work-group criteria were used most commonly (McKhann et al., 1984). Diagnostic criteria for vascular dementia were more variable, but the NINDS-AIREN workgroup criteria were used most commonly (Roman et al., 1993). The sensitivity or specificity of diagnostic criteria for dementia, particularly with regard to dementia subtypes, is subject to ongoing debate, but beyond the scope of this review. Two studies based the diagnosis of dementia on the participant's medical records (Whitmer et al., 2005b; Rosengren et al., 2005).

2.5. Quality assessment

The methodological quality of reporting of all included studies was assessed with a rating scale (Biessels et al., 2006) based on previously established criteria for longitudinal observational study designs (Tooth et al., 2005; Stroup et al., 2000). Two points were given for each of the following five criteria: population selection and recruitment; participation at follow-up; risk factor assessment; dementia assessment and diagnosis; data analysis (for details see (Biessels et al., 2006)). Each study could obtain a maximum score of 10 points. RPK and EB independently evaluated each of the included studies according to these criteria.

3. Results

3.1. Type 2 diabetes mellitus/impaired glucose metabolism

We included 14 studies that compared the risk of one or more types of dementia in patients with type 2 diabetes mellitus to non-diabetic persons (Table 1a). Diabetes was most commonly identified by fasting or random blood glucose levels combined with an oral glucose tolerance test. Six studies based the diagnosis of diabetes on medical history or medication use only, or did not assess blood glucose concentration in all participants (Yoshitake et al., 1995; MacKnight et al., 2002; Arvanitakis et al., 2004; Luchsinger et al., 2001, 2005; Hassing et al., 2002). The studies did generally 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 type 2 diabetes mellitus.

The risk of 'any dementia' was increased in five out of nine studies reporting on this aggregate outcome. For Alzheimer's disease and vascular dementia these proportions were six out of 11 and six out of 10, respectively. The odds ratios for vascular dementia were generally larger than for Alzheimer's disease (Table 1a). There was no clear difference between the results of studies that assessed diabetes at midlife or at late life.

Although none of the studies provided an in depth analysis of the modulating effect of comorbid conditions, some studies

Table 2
Risk of dementia attributable to vascular risk factors

	Midlife (45–65 years) risk factor assessment			Late life (>65 years) risk factor assessment		
	Odds ratio for dementia[a]	Estimated prevalence[b] (%)	Estimated population attributable risk (%)	Odds ratio for dementia	Estimated prevalence (%)	Estimated population attributable risk
Diabetes	2.2 (4)	2–8	2–9	1.6 (10)	10–15	6–8%
Hypertension	2.3 (3)	30–40	28–36	1.1 (7)	55–80	5–7%
Dyslipidaemia	2.1 (3)	20–25	18–22	1.0 (4)	10–20	≤0
Obesity	2.0 (3)	35–40	26–29	0.8 (2)	25–30	≤0

[a] Median odds ratio based on the studies presented in Table 1a–d; each study that presented the risk factor dichotomously was included once; the number of studies from which the median OR was derived is presented in brackets.

[b] Prevalence diabetes (Wild et al., 2004; National Center for Health Statistics, 2006), hypertension (Wolf-Maier et al., 2003; National Center for Health Statistics, 2006), dyslipidaemia (National Center for Health Statistics, 2006), and obesity (Ogden et al., 2006; National Center for Health Statistics, 2006).

reported on an additive (Whitmer et al., 2005b) or a synergistic (Xu et al., 2004; Luchsinger et al., 2005; Peila et al., 2002) association between diabetes and vascular disease, hypertension or apolipoprotein E status. Eight studies adjusted their analyses for the effects of other vascular risk factors. Analyses with or without these adjustments generally showed similar results.

Two studies reported on the association between impaired glucose metabolism short of diabetes and dementia (Curb et al., 1999; Xu et al., 2007). One study observed a significant association of midlife impaired glucose metabolism with late life incidence of vascular dementia, but not with 'any dementia' or Alzheimer's disease (Curb et al., 1999). The other reported a significantly increased risk of any dementia and Alzheimer's disease associated with impaired glucose metabolism (Xu et al., 2007).

3.2. Hypertension/blood pressure

We included 13 studies that examined the association between blood pressure and dementia. (Table 1b) Hypertension was mostly diagnosed based on repeated blood pressure measurement with various cut-off points (e.g. >140/90 or 160/95 mm Hg). Several studies did not use a specific cut-off point but expressed the risk of dementia per 10 mm Hg or standard deviation (S.D.) increase. Results were often presented for systolic and diastolic blood pressure separately. Five studies based the diagnosis of hypertension on self-report, medical history or medication use only (Kuller et al., 2003; Tyas et al., 2001; Lindsay et al., 2002; Yamada et al., 2003; Yoshitake et al., 1995).

The risk of 'any dementia' was increased in two out of six studies. For Alzheimer's disease and vascular dementia these proportions were three out of 12 and three out of five, respectively (Table 1b). One of the five studies that examined hypertension dichotomously reported an increased risk of dementia (Whitmer et al., 2005b). The four studies that did not find an association assessed hypertension at late life and based the diagnosis of hypertension solely on self-report or medical records. Eight studies examined systolic and diastolic blood pressure separately, four of which showed an increased risk of dementia associated with either elevated systolic or diastolic blood pressure. The associations were generally more consistent for systolic than for diastolic blood pressure.

Regardless of the method of analysis there was a marked difference between the results of studies that assessed blood pressure at midlife or at late life. All of the studies that assessed blood pressure at midlife showed an association between elevated blood pressure and dementia. In contrast, only one (with the longest follow-up period) out of nine studies that assessed blood pressure at late life showed such an association (Yoshitake et al., 1995). In fact, three late life studies actually reported an inverse relation, where high blood pressure was associated with a *decreased* risk of dementia (Morris et al., 2001; Ruitenberg et al., 2001) or low blood pressure was associated with an increased risk of dementia (Verghese et al., 2003).

Seven studies took the potential confounding effects of other vascular risk factors into account. In general, analyses with or without adjustment for other vascular risk factors showed similar results.

3.3. Dyslipidaemia

We included eight studies that examined the association between dyslipidaemia and dementia. Studies on dyslipidaemia mostly assessed serum cholesterol levels. Several studies also measured triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol. Similar to hypertension, some studies used specific cut-offs for dyslipidaemia, while others expressed the results per mmol/l or S.D. increase. One study based the diagnosis of dyslipidaemia on medical records only (Li et al., 2005).

The results for total cholesterol and triglycerides are presented in Table 1c. Two out of six studies observed an association between high total cholesterol and an increased risk of 'any dementia'. For Alzheimer's disease this proportion was two out of four; the single study that assessed vascular dementia did not find a significant association. Only four studies examined the association between high triglycerides and dementia, one of which found a significant association with any dementia. None of the studies observed a significant association between high triglycerides and Alzheimer's disease or vascular dementia. From four studies on HDL- and LDL-cholesterol (Reitz et al., 2004; Solfrizzi et al., 2004; Li et al., 2005; Hall et al., 2006; data not included in Table 1c), two found no association with dementia, one reported an association between low HDL-cholesterol and an increased risk of vascular dementia (but not Alzheimer's disease) (Reitz et al., 2004), and one reported an association between high LDL-cholesterol (but not low HDL-cholesterol) and Alzheimer's disease (Hall et al., 2006).

The two studies that found the strongest association between high cholesterol and dementia both assessed cholesterol levels in midlife (Whitmer et al., 2005b; Kivipelto et al., 2002). The six studies that assessed cholesterol in late life did not find such an association and two of these six studies actually reported an inverse relation showing an association between high cholesterol and a *decreased* risk of dementia (Solfrizzi et al., 2004; Mielke et al., 2005).

Four out of the eight included studies adjusted their analyses for the effects of other vascular risk factors. In general, studies that adjusted their analyses showed somewhat smaller effects, suggesting that the association between cholesterol and dementia may not be independent of other risk factors. Two studies specifically examined the interaction with apolipoprotein E status (Hall et al., 2006; Li et al., 2005), but only one of these demonstrated such an interaction (Hall et al., 2006).

3.4. Obesity

We included nine studies that examined the association between obesity and dementia. All studies used body-mass index (BMI) as a measure for obesity, which was generally defined as BMI above a certain cut-off (e.g. >30 kg/m^2). Some studies expressed the results per BMI point or S.D. increase.

Two studies based the diagnosis of obesity on self-report or medical records only (Nourhashemi et al., 2003; Yoshitake et al., 1995).

Five out of nine studies reported an association between high BMI and an increased risk of dementia. The risk of 'any dementia' was increased in five out of seven studies, of Alzheimer's disease in one out of five studies and of vascular dementia in one out of three studies (Table 1d).

Studies that measured BMI at midlife generally showed a more consistent association and larger odds ratios for dementia. The four studies that did not find an association between high BMI and dementia all examined BMI and dementia in late life (>75 years). Two of these actually found an association between low BMI and dementia (Buchman et al., 2005; Luchsinger et al., 2007), and one found a J-shaped association where the lowest risk of dementia was found in men with low but healthy BMI (Rosengren et al., 2005).

Six out of nine studies adjusted their analyses for the effects of other vascular risk factors. Analyses with or without such adjustments generally showed similar results.

3.5. Population attributable risk of dementia

Population attributable risks of dementia for the vascular risk factors are presented in Table 2. Since the results suggest that the risk of dementia associated with the risk factors varies with age, we present the population attributable risk of dementia for risk factors measured at middle-age (40 to 65 years of age) and late life (>65 years) separately. It should be noted that these estimated population attributable risks are highly dependent on the data that are entered in the equation and should therefore be interpreted with some caution. At midlife, the population attributable risk was highest for hypertension, up to 30% of cases of late life dementia. Later in life diabetes appears to convey the highest risk of dementia. It should be noted that the population attributable risks presented in Table 2 cannot simply be added up across risk factors to obtain an estimate of the combined effects of the risk factors, because it is unlikely that these risks are independent. Nevertheless, these data indicate that a substantial number of dementia cases can be attributed to these vascular risk factors, pointing out an obvious target for therapeutic intervention.

4. Discussion

This paper systematically reviewed the evidence for the association of type 2 diabetes mellitus, hypertension, dyslipidaemia and obesity with dementia. All four risk factors were associated with an increased risk of dementia, but the results of studies on diabetes and obesity were most consistent. The magnitude of the effects was comparable across the risk factors, with odds ratios for 'any dementia' around 1.5. For hypertension, obesity and dyslipidaemia age appeared to modulate the association: the risk of dementia was generally largest in studies that measured the risk factor in midlife (compared to late life) and had a long follow-up time. At midlife, the population attributable risk of dementia was highest for hypertension, up to 30% of cases of late life dementia. Later in life diabetes appears to convey the highest risk of dementia.

Before discussing the implications of our findings, some limitations of our review need to be addressed. Firstly, our aim was to review the association between vascular risk factors and dementia and to compare the available evidence across these risk factors. Therefore we applied rigorous inclusion criteria and excluded papers from which no adjusted odds ratios or relative risks could be extracted. We also excluded all studies that did not take the confounding effects of age, sex and educational level into consideration. Secondly, the effect of publication bias in relation to negative findings is unknown. Finally, because of the heterogeneity of study design and outcome measures we did not perform a formal meta-analysis. Nevertheless this paper provides the first systematic review that allows a direct semi-quantitative comparison of individual vascular risk factors.

It is to date uncertain whether each of the vascular risk factors is an independent determinant of dementia. Only a proportion of studies, particularly those on diabetes (8 out of 14) and hypertension (7 out of 13), took other vascular risk factors into account in their analyses. Confounding or interacting effects between different factors can therefore not be ruled out. Studies that specifically addressed these interactions had inconsistent results, reporting both cumulative (Kalmijn et al., 2000; Kivipelto et al., 2001; Whitmer et al., 2005b) and opposing effects (Luchsinger et al., 2005) on dementia. In this context it is also remarkable that the strength of the association with dementia appears to be comparable across the vascular risk factors. This could indeed indicate that the studies included in this review did not manage to disentangle the clustering of risk factors. An alternative explanation, however, would be that the different factors share a common aetiology, or exert their adverse effects on the brain through shared pathways. Ischemic cerebrovascular disease is likely to be one of the pathways, but other mechanisms, including inflammation, or even interaction with degenerative changes in the brain could also play a role. The clustering of these risk factors and their shared aetiology and consequences is entailed in the concept of the 'metabolic syndrome' (Reaven, 1988). Insulin resistance is thought to play a central role in the underlying pathophysiological mechanism of the metabolic syndrome, but recent reports show that inflammation may also be involved (Rutter et al., 2004). The metabolic syndrome is associated with an increased risk of cardiovascular disease (Lakka et al., 2002) but also of dementia (Yaffe et al., 2004). It might well be that, regardless of the risk factor profile that is involved in the development of vascular disease in a particular individual, vascular disease itself ultimately determines the impact on dementia.

For the risk factors hypertension, dyslipidaemia and obesity the associations clearly were strongest and most consistent in studies with longer follow-up periods, where the risk factor was assessed in middle-age and dementia in old age. A substantial number of studies that assessed both the risk factor and dementia in (very) old age reported an inverse relation. This may reflect that declining levels of blood pressure, cholesterol and body weight are markers of declining health or even neurodegenerative changes in the brain. Alternatively, there

may be a "survivor effect", where individuals who reach old age, despite having multiple vascular risk factors, are survivors who might be relatively less susceptible to the adverse effects of these risk factors. A third explanation may be that in old age low blood pressure, low cholesterol and low body weight are particularly detrimental or even that high blood pressure, high cholesterol, and overweight might actually be protective against cognitive decline in the oldest old, but there is as yet no solid proof for this latter assumption. Interestingly, the association between diabetes and dementia appeared to be largely independent of age. This could simply reflect the rising prevalence of diabetes in older study populations. An alternative explanation may be that diabetes develops in the context of other vascular risk factors that are often present long before the actual onset of the diabetes. When diabetes eventually develops, hyperglycaemic damage could develop on top of the damage already done by the other vascular risk factors in the preceding years. In any case, beyond the age of 65 diabetes is the strongest predictor of dementia among these risk factors and may thus help to identify persons at increased risk.

In the majority of the studies reviewed herein the study populations included both participants with and without treatment for hypertension, dyslipidaemia or diabetes. Observational studies cannot, however, provide reliable estimates of treatment efficacy. Thus far, relatively few randomized controlled trials have examined the effect of treatment of vascular risk factors on incident dementia. A recent Cochrane meta-analysis did not show a beneficial effect of treatment with anti-hypertensive drugs on the risk of dementia (McGuinness et al., 2006). Randomized controlled trials with statin treatment, in which dementia was a secondary outcome measure, also failed to show an effect (Shepherd et al., 2002; Heart Protection Study Collaborative Group, 2002). However, mean baseline age in these studies was high and treatment duration was short. With duration of exposure and initiation at midlife being most important, this could be "too little, too late".

The results of this systematic review pose several leads for the treatment of vascular risk factors in relation to the risk of dementia. As pointed out in the preceding paragraphs it is yet unclear whether the consistent risk of dementia across risk factors is the result of the clustering of factors or shared underlying pathophysiological mechanisms. In our opinion, it might be more rewarding to adapt treatment approaches that target this "cross-talk" between factors rather than to try and tease out the individual effect of each factor through elaborate analyses that may even produce statistical artefacts. Hence, treatment could focus on shared causes of the different vascular risk factors, such as insulin resistance, or on the shared consequences of these factors, such as atherosclerosis. In addition, multifactorial treatment, targeting multiple risk factors may be a fruitful approach (Gaede et al., 2003). The results of this review also show that timing of the intervention appears to be crucial. The observed interaction with age for hypertension, dyslipidaemia and obesity suggests that treatment may be more effective when initiated in midlife than at a more advanced age.

In conclusion, vascular risk factors predispose to the development of dementia. Age at exposure and duration of exposure are critical variables; the risk of dementia is higher when exposure is measured at midlife compared to late life, with the exception of diabetes. The contribution of each of the individual factors is difficult to assess. Rather than teasing out the individual contributions of risk factors it could be more rewarding to assess shared aetiology or consequences and develop multifactorial treatment strategies.

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