Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Search Terms Used for the Systematic Review and Meta-analysis

We used the following terms to systematically search the current literature: "depression" OR "depressive disorder" OR "depress*[Title]" AND 1) "sICAM-1" OR "sVCAM-1"OR "sE-selectin" OR "vWF" AND 2a) "capillary recruitment" OR "capillaroscopy" OR "laser-Doppler flowmetry" OR "capillaries" AND 2b) "L-NMMA" OR "sodium nitroprusside" OR "plethysmography" OR "forearm blood flow" OR "iontophoresis" OR "intracutaneous injection" AND 3) "urinary albumin excretion" OR "albuminuria" OR "macroalbuminuria" OR "microalbuminuria" AND 4) "retinal arteriolar diameter" OR "retinal venular diameter" OR "arteriovenous ratio" OR "retinal vessels" AND 5) "cerebral small vessel disease" OR "CSVD" OR "white matter lesion" OR "WML" OR "microbleeds" OR "microinfarctions" OR "lacunar infarctions". The references of the identified studies were checked in order to identify additional relevant articles. The search was limited to humans and study populations aged >40 years.
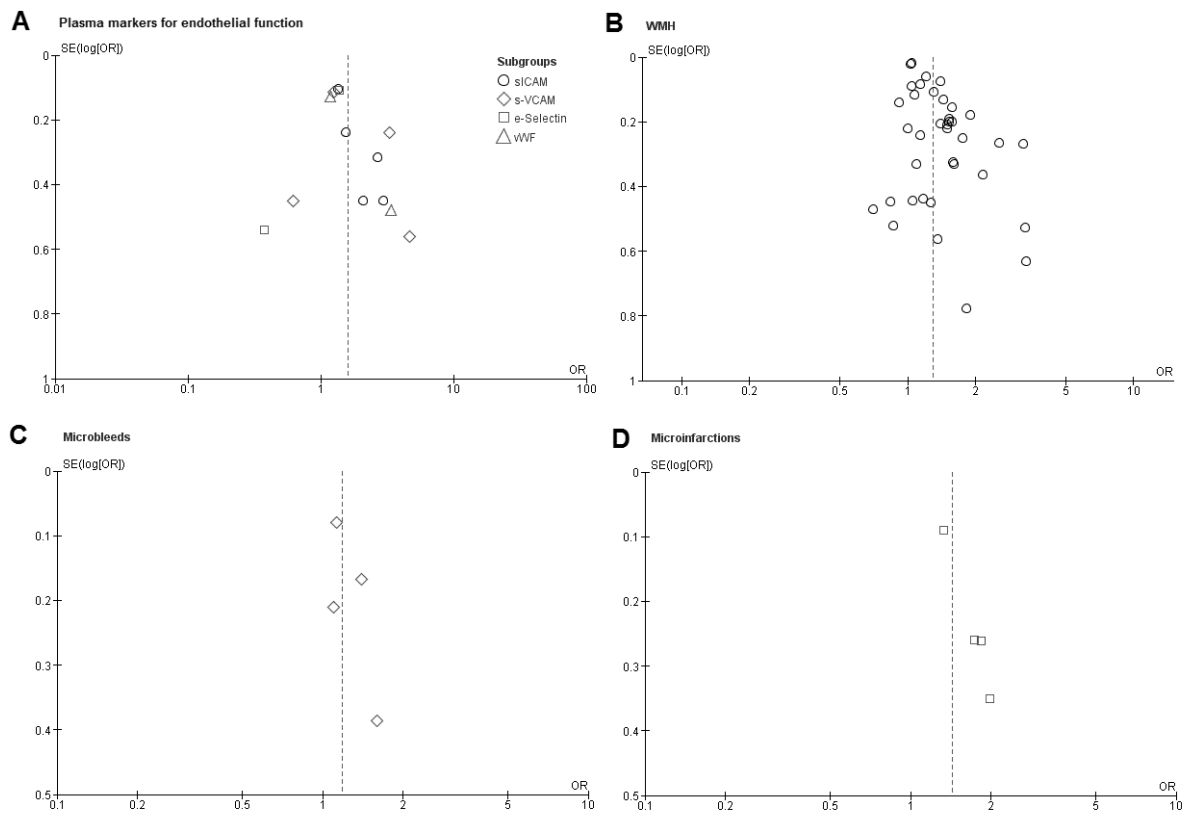
eFigure 1. Funnel Plot of Cross-Sectional Studies on the Association Between Microvascular Dysfunction and Depression; Plasma Markers for Endothelial Function (A), WMH (B), Microbleeds (C) And Microinfarctions (D)

Cerebral microbleeds

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Microbleeds				
Direk 2016	0.33647	0.16652	16.3%	1.40 [1.01, 1.94]
Feng 2013	0.465	0.385	3.0%	1.59 [0.75, 3.39]
van Sloten 2015	0.095	0.21	10.2%	1.10 [0.73, 1.66]
Wu 2014	0.12	0.08	70.5%	1.13 [0.96, 1.32]
Total (95% CI)			100.0%	1.18 [1.03, 1.34]

Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.43 (P = 0.02)
Test for subgroup differences: Not applicable

eFigure 2. Forest Plots With the Odds Ratios and 95% Confidence Intervals for Original Studies and the Pooled Odds Ratios for the Cross-Sectional Association Between Cerebral Microbleeds and Depression

These data represent the odds to have a clinically relevant depression, per standard deviation higher number of cerebral microbleeds.

Cerebral (micro)infarctions

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Microinfarctions				
Direk 2016	0.54812	0.25871	9.7%	1.73 [1.04, 2.87]
Feng 2013	0.68	0.35	5.3%	1.97 [0.99, 3.92]
van Sloten 2015	0.605	0.26	9.6%	1.83 [1.10, 3.05]
Wu 2014	0.28	0.09	75.3%	1.32 [1.11, 1.58]
Total (95% CI)			100.0%	1.43 [1.22, 1.68]

Heterogeneity: Tau² = 0.00; Chi² = 3.04, df = 3 (P = 0.39); I² = 1%
Test for overall effect: Z = 4.43 (P < 0.00001)
Test for subgroup differences: Not applicable

Odds Ratio
IV, Random, 95% CI

0.1 0.2 0.5 1 2 5 10
Favours [no depression]   Favours [depression]
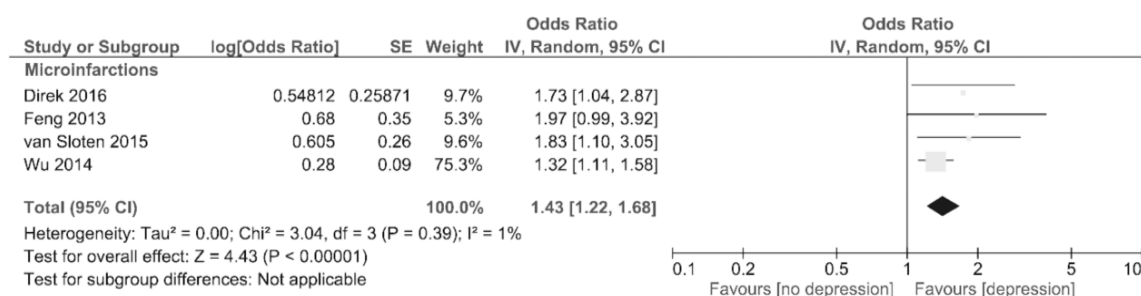
eFigure 3. Forest Plots With the Odds Ratios and 95% Confidence Intervals for Original Studies and the Pooled Odds Ratios for the Cross-Sectional Association Between Cerebral (Micro)Infarctions and Depression
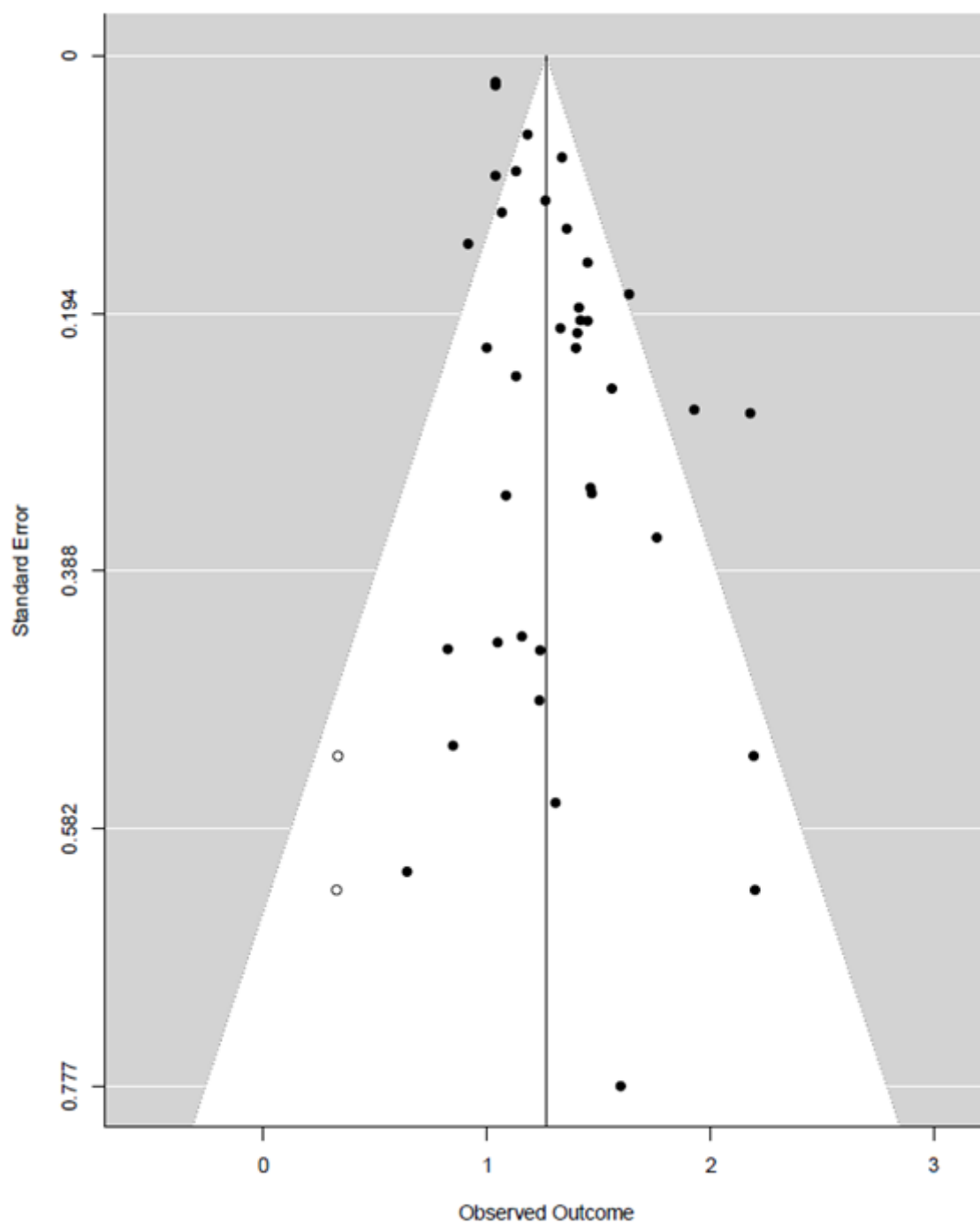
These data represent the odds to have a clinically relevant depression, per standard deviation higher number of cerebral (micro)infarctions.

eFigure 4. Funnel Plot of Cross-Sectional Studies on the Association Between White Matter Hyperintensities and Depression After Trim-and-Fill Analysis

Two theoretical and 38 original studies are indicated with white and black circles, respectively.
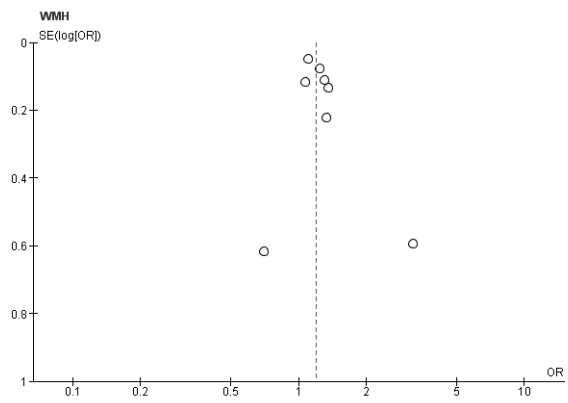
eFigure 5. Funnel Plot of Longitudinal Studies on the Association Between Cerebral Small Vessel Disease and Depression

eTable 1. Quality Assessment of the Included Studies by Use Of the Newcastle-Ottawa Scale (NOS)

Study	Study design	Selection	Comparability	Exposure (c-c only)	Outcome (cohort only)	Overall assessment	Percentage of maximum score
Plasma markers of endothelial function							
Dimopoulos 2006	Case-control	1, 3, 4	1a, 1b	1b, 2		7/8	87.5%
Lesperance 2004	Case-control	1, 2, 4	1a, 1b	1b, 2		7/8	87.5%
Phuong Do 2010	Population based cohort	1a, 2, 3	1a		1a	5/6	83.3%
Rajagopalan 2001	Case-control	1		1b		2/8	25%
Tchalla 2015	Population based cohort	1, 2	1a, 1b		1a	5/6	83.3%
Thomas 2007	Case-control	3, 4	1a	1b, 2		5/8	62.5%
Tully 2016	Population based cohort	1, 2			1a	3/6	50%
van Dooren 2016	Population based cohort	1, 2, 3	1a, 1b		1a	6/6	100%
van Sloten 2013	Population based cohort	1, 2, 3	1a, 1b		1a	6/6	100%
Albuminuria							
Fischer 2013	Population-based cohort	1a, 3a	1a, 1b	1b		5/6	83.3%
Katon 2004	Population-based cohort		1a, 1b	1a		3/6	50%
Retinal diameters							
Nguygen 2010	Case-control	1, 4	1a, 1b	1b, 2		6/8	75%
Ikram 2010	Population based cohort	1, 2, 3b, 4	1a, 1b		1a, 2	8/9	88.9%
Cerebral small vessel disease							
Aizenstein 2011	Case-control	1, 4	1a	1a, 2		5/8	62.5%
Almeida 2004	Case-control	3, 4	1a	1b, 2a		5/8	62.5%
Chatterjee 2010	Case-control	1, 2	1	1a, 2		5/8	62.5%
Chen 2009	Case-control	1, 2	1a, 1b	1a, 2		6/8	75%
Colloby 2011	Case-control	1, 3	1a	1b, 2a		5/8	62.5%
Cyprien 2014	Population-based cohort, prospective (ESPRIT study)	1, 2, 3b, 4	1a, 1b		1a, 2	8/9	88.9%
Dalby 2010	Case-control	1, 2, 3, 4	1a, 1b	1b, 2a		8/8	100%

Study	Study type					Score	%
De Groot 2000	Population-based cohort. Rotterdam scan study.	1a, 2a	1a, 1b		1a	5/6	83.3%
Delaloye 2010	Case-control	1, 4	1a, 1b	1b, 2a		6/8	75%
Devantier 2016	Case-control	1, 3	1a	1a, 2		5/8	62.5%
Direk 2016	Population-based cohort. Rotterdam study.	1a, 2a	1a, 1b		1a	5/6	83.3%
Dotson 2013	Population-based cohort, prospective (Baltimore longitudinal study of aging)	1a, 2a	1a, 1b		1a, 2a, 3a	7/9	77.8%
Feng 2013	Population-based cohort	1a, 2a	1a, 1b		1a	5/6	83.3%
Firbank 2005	Population-based cohort, prospective (LADIS)	1a, 2a	1a, 1b		1a	5/9	55.6%
Fujishima 2014	Case-control	1a, 2a, 3a	1a	1a, 2a		6/8	75%
Godin 2008	Population-based cohort, prospective (3C-Dijon study)	1a, 2a, 3b,	1a, 1b		1a, 2	7/9	77.8%
Greenwald 1998	Case-control	1a, 2a, 3a			1a, 2	5/8	62.5%
Grool 2013	Population-based cohort, prospective (SMART-Medea)	1a, 2a	1a, 1b		1a, 2	6/9	66.7%
Gudmunds-son 2013	Population-based cohort (AGES-Reyklavik study)	1a, 2a, 3b	1a, 1b		1a	6/6	100%
Hannestad 2006	Case-control	1a, 3a, 4a	1a	1a, 2		6/8	75%
Iosifescu 2005	Case-control	1a, 3a, 4a	1a, 1b	1b, 2a		7/8	87.5%
Janssen 2004	Case-control	1a, 3a, 4a	1a	1a, 2		6/8	75%
Janssen 2007	Case-control	1a, 4a	1a	1b, 2a		5/8	62.5%
Jorm 2005	Population-based cohort	1a, 2a	1a, 1b			4/6	66.7%
Kieseppa	Case-	1a, 2a, 3a, 4a	1a	1b, 2a		7/8	87.5%

2013	control						
Kohler 2010	Case-control	1a, 2a, 3a, 4a	1a	1a		6/8	75%
Krishnan 2006	Population-based cohort (LADIS)	1a, 2a	1a, 1b		1a	5/6	83.3%
Kumar 2000	Case-control	1a, 3a, 4a	1a	1a, 2a		6/8	75%
Lavretsky 2008	Population-based cohort	1a, 2a, 3b	1a, 1b		1a	6/6	100%
Lee 2003	Case-control	1a, 2a, 3a	1a	1b, 2a		6/8	75%
Lin 2005	Case-control	2a, 4a		1a, 2a		4/8	50%
MacFall 2005	Case-control	2a, 3a, 4a	1a	2a		5/8	62.5%
Murray 2013	Population-based cohort, prospective	1a, 2a	1a		1a	4/9	44.4%
Nys 2005	Case-control	2a, 4a	1a	1a, 2a		5/8	62.5%
Olesen 2010	Population-based cohort, prospective	1a, 2a, 3b	1a, 1b		1a, 2a	7/9	77.8%
Paranthaman 2010	Case-control	1a, 2a		1b, 2a		4/8	50%
Perez 2012	Population-based cohort (Rotterdam Scan Study)	1a, 2a	1a, 1b		1a	5/6	83.3%
Potter 2007	Population-based cohort	1a, 2a, 3b	1a, 1b		1a	6/6	100%
Sheline 2008	Population-based cohort	1a, 3a	1a, 1b	1b		5/6	83.3%
Shimony 2009	Population-based cohort	1a, 2a, 3b	1a		1a	5/6	83.3%
Steffens 2002	Population-based cohort, prospective (Cardio-vascular Health Study)	1a, 2a, 4a	1a, 1b		1a, 2a	7/9	77.8%
Steffens 1999	Population-based cohort (Cardio-vascular Health Study)	1a, 2a	1a, 1b		1a	5/9	55.6%
Tang 2010	Case-control	1a, 3a, 4a	1a	1b, 2a		6/8	75%
Taylor 2005	Case-control	2a, 3a, 4a	1a, 1b	1b, 2a		7/8	87.5%
Taylor 2007	Case-control	1a, 2a, 3a, 4a	1a	1b, 2a		7/8	87.5%

Teodorczuk 2010	Population-based cohort, prospective (LADIS study)	1a, 2a, 4a	1a, 1b		1a, 2a	7/9	77.8%
Tudorascu 2014	Population-based cohort	1a, 2a	1a, 1b		1a	5/6	83.3%
Tupler 2002	Case-control	1a, 2a, 3a, 4a	1a	1a, 2a		7/8	87.5%
Van Sloten 2015	Population-based cohort, prospective (AGES-Reykjavik)	1a, 2a, 4a	1a, 1b		1a, 2a, 3a	8/9	88.9%
van Uden 2011	Population-based cohort, prospective (RUN DMC study)	2a, 3a	1a	1a		4/9	44.4%
Vardi 2010	Case-control	1a, 4a		1a, 2a		4/8	50%
Vataja 2001	Case-control	1a, 2a, 3a, 4a		1a, 2a		6/8	75%
Versluis 2006	Population-based cohort (Prosper study)	1a, 2a	1a		1a, 2a	5/6	83.3%
Videbech 2000	Case-control	1a, 2a, 3a, 4a	1a	1b, 2a		7/8	87.5%
Wu 2014	Case-control	1a, 3a, 4a	1a	1a, 2a		7/8	87.5%

eTable 2. Characteristics of Studies Included in the Systematic Review and Meta-Analysis

Study	Study design	Characteristics of study population	Age (yrs)	Sex (%F)	Participants (n)	Participants with depression (n)	Microcirculation marker	Definition of depression
Plasma markers of endothelial function (Cross-sectional data)								
Dimopoulos 2006	Case-control	Greece, general population	60+	61	66	33	sICAM-1; s-VCAM-1	GDS, diagnostic interview
Lesperance 2004	Case-control	Canada, consecutive patients coronary syndrome	57	19	481	35	sICAM-1	SCID
Phuong Do 2010	Population based cohort	USA, general population	43	35	434	103	sICAM-1; sE-Selectin	11 item CES-D ≥ 16
Tchalla 2015	Population based cohort (MOBILIZE Boston study)	USA, general population	78	63	668	179	sICMAM-1, sVCAM-1	CES-D ≥ 16
Thomas 2007	Case-control	UK, general population	75	60	48	23	sICAM-1; sVCAM-1	GDS, MDRS, DSM-IV
Tully 2016	Population based cohort (Florey Adelaide Male ageing study)	Australia, general populaton	53	0	688	59	sE-Selectin	BDI
van Dooren 2016	Population based cohort (The Maastricht Study)	the Netherlands, general population	60	45	852	55	sICAM-1, s-VCAM-1, sE-Selectin, vWF	PHQ-9, MINI
van Sloten 2014	Population based cohort (The Hoorn Study)	the Netherlands, general population	70	50	493	63	sICAM-1; s-VCAM-1; sE-Selectin vWF	20 item CES-D ≥ 16
Albuminuria (Cross-sectional data)								
Fischer 2012	Population-based cohort	USA, Hispanic and non-Hispanic CKD patients	58	43	3853	1098	ACR	BDI
Katon 2004	Population-based cohort	USA, primary care patients with predominantly diabetics	60	49	557	78	Micro-albuminuria in spot urine	PHQ-9
Retinal vessel diameters(Cross-sectional data)								
Nguygen 2010	Case-control	USA, Caucasian and African Americans, mean age 70	70	77	146	43	Arteriolar and venular diameters	HDRS, DSM-IV
Retinal vessel diameters(Longitudinal data)								
Ikram 2010	Population based cohort, prospective (Rotterdam Scan study)	the Netherlands, general population, 9 years follow-up	66	55	3605	555	Arteriolar and venular diameters	CES-D, HADS, diagnostic interview
Cerebral Small Vessel Disease (Cross-sectional data)								
Aizenstein 2011	Case-control	Caucasian and African Americans	70	67	60	33	WMH volumetry (semi-automatic)	HDRS
Almeida 2004	Case-control	South America, heart failure	74	53	32	8	Scheltens scale	HDRS
Chatterjee 2010	Case-control	UK, stroke population	70	40	103	33	CT scan WMH rating scale	Diagnostic interview, MDRS
Chen 2009	Case-control	China, stroke population	65	75	127	44	WMH volumetry (semi-automatic)	GDS
Colloby 2011	Case-control	UK, general population	74	69	68	38	WMH volumetry (semi-automatic)	GDS, MDRS, diagnostic

								interview
Cyprien 2014	Population-based cohort, prospective (ESPRIT study)	France, general population	71	45	467	120	WMH volumetry (semi-automatic)	MINI 5, CES-D, current anti-depressive treatment
Dalby 2010	Case-control	Denmark, general population	58	68	44	22	WMH volumetry (semi-automatic)	Physicians diagnosis
De Groot 2000	Population-based cohort	the Netherlands, general population	72	52	1077	185	WMH severity rating scale	CES-D, history of depression
Delaloye 2010	Case-control	Switzerland, non-specified population	70	73	60	11	Scheltens scale	GDS
Devantier 2016	Case-control	Denmark, general population	60	15	56	29	WMH volumetry (semi-automatic)	Diagnostic interview
Direk 2016	Population-based cohort (Rotterdam study)	the Netherlands, general population	59	55	3799	60	WMH volumetry (semi-automatic) Microbleeds Microinfarctions	CES-D, SCAN diagnostic interview in participants with CES-D≥16
Dotson 2013	Population-based cohort, prospective	South-America, general population	72	43	90	9	WMH severity rating scale	20 item CES-D, history of depression
Feng 2013	Population-based cohort	China, general population	72	57	85	57	Fazekas scale	GDS
Firbank 2005	Population-based cohort, prospective (LADIS)	the Netherlands, Denmark, France, Austria, Sweden, Finland, Portugal, Germany, England, general population	74	55	629	169	WMH volumetry (semi-automatic)	GDS
Fujishima 2014	Case-control	Japan, MCI -/+	79	57	322	81	WMH volumetry (semi-automatic)	GDS ≥ 5
Greenwald 1998	Case-control	USA, general population	75	59	66	35	Scheltens scale	HDRS
Gudmundsson 2013	Population-based cohort	Iceland, general population	75	58	4296	185	WMH volumetry (semi-automatic)	MINI, GDS
Hannestad 2006	Case-control	USA, general population	60+	64	246	182	WMH volumetry (semi-automatic)	CES-D, MDRS, history of depression
Iosifescu 2005	Case-control	USA, general population	41	34	85	50	Fazekas scale	Modified HDRS
Janssen 2004	Case-control	the Netherlands, general population	63	100	69	28	WMH volumetry (semi-automatic)	Diagnostic interview
Janssen 2007	Case-control	the Netherlands, general population	70	67	70	50	WMH volumetry (semi-automatic)	MDRS
Jorm 2005	Population-based cohort	Australia, general population	60-64	Not des-cribed	475	38	Fazekas scale	PHQ-9, antidepressant medication
Kieseppa 2013	Case-control	Finland, general population	41	55	65	44	Coffey scale	Physicians diagnosis
Kohler 2010	Case-control	UK, general population	60+	78	64	35	Scheltens scale	MDRS
Krishnan 2006	Population-based cohort (LADIS)	the Netherlands, Denmark, France, Austria, Sweden, Finland, Portugal, Germany, England, general population	74	55	626	92	Scheltens scale	GDS-15
Kumar 2000	Case-control	USA, general population	70	73	81	51	WMH volumetry (semi-automatic)	SCID DMS-IV, HDRS >15
Lavretsky 2008	Population-based cohort	USA, general population	74	21	270	49	WMH volumetry (semi-automatic)	MUDS
Lee 2003	Case-control	USA, general population	60+	67	82	41	Coffey scale	HDRS, history of depression
Lin 2005	Case-control	Taiwan, general population	71	64	55	37	Fazekas scale	17-item HDRS > 15, diagnostic interview
MacFall 2005	Case-control	USA, general population	60+	63	99	50	WMH volumetry (semi-automatic)	CES-D > 16, history of MDD
Murray 2013	Population-based cohort, prospective	UK, general population	64	47	219	n.a.	Scheltens scale	HADS-D

Olesen 2010	Population-based cohort, prospective	Sweden, general population, 5 years follow-up	72	70	525	83	Gothenburg scale	HRSD, MDRS, physicians diagnosis
Paranthaman **2010**	Case-control	UK, general population	72	65	40	20	WMH volumetry (semi-automatic)	Physicians diagnosis, history of depression
Potter 2007	Case-control	USA, general population	72	64	130	83	WMH volumetry (semi-automatic)	MADRS
Sheline 2008	Case-control	USA, depressed inpatients	59+	65	115	83	WMH volumetry (semi-automatic)	MDRS, diagnostic interview based on DMS-IV
Steffens 1999	Population-based cohort (Cardio-vascular Health Study)	USA, general population	75	58	3660	880	WMH severity rating scale	CES-D score in highest quartile
Tang 2010	Case-control	China, post-stroke depression	67	53	156	78	Fazekas scale	Diagnostic interview
Taylor 2005	Case-control	USA, general population	60+	68	399	253	WMH volumetry (semi-automatic)	CES-D, history of depression
Taylor 2007	Case-control	USA, general population	60+	68	370	226	WMH volumetry (semi-automatic)	CES-D, MDRS, history of depression
Tudorascu **2014**	Population-based cohort (Health ABC)	USA, general population	83	64	277	63	WMH volumetry (semi-automatic)	CES-D
Tupler 2002	Case-control	USA, general population	50+	73	267	115	Fazekas scale	Physicians diagnosis
van Uden	Population-based cohort (RUN DMC study)	the Netherlands, consecutive patients with CSVD	65	44	491	101	WMH volumetry (semi-automatic)	CES-D, antidepressant medication
Vardi 2010	Case-control	Israel, general population	55	54	101	37	WMH volumetry (semi-automatic)	Diagnostic interview
Vataja 2001	Case-control	Finland, consecutive stroke patients	71	51	275	109	WMH volumetry (calculated by hand)	Diagnostic interview
Videbech 2000	Case-control	Denmark, inpatients	45	67	137	44	Fazekas scale	Diagnostic interview
Wu 2014	Case-control	Chinese, general population	72	60	335	65	Fazekas scale	Diagnostic interview

Cerebral Small Vessel Disease (Longitudinal data)

Firbank 2012	Population-based cohort, prospective (LADIS study)	Multicenter, general population, 3 years follow-up	64+	54	639	211	WMH volumetry (semi-automatic)	GDS
Godin 2008	Population-based cohort, prospective (3C-Dijon study)	France, general population, 4 years follow-up	72	61	1658	241	WMH volumetry (semi-automatic)	MINI, CESD, antidepressant medication use
Grool 2013	Population-based cohort, prospective (SMART-Medea)	Dutch, symptomatic atherosclerotic disease, 3 years follow-up	62	19	650	No cases described	WMH volumetry (semi-automatic)	PHQ-9 quartiles
Olesen 2010	Population-based cohort, prospective	Sweden, general population, 5 years follow-up	72	70	525	83	Gothenburg scale	HRSD, MDRS, physicians diagnosis
Perez 2012	Population-based cohort (Rotterdam Scan Study)	Dutch, non-demented population, 3.6 years follow-up	60+	52	961	92	WMH severity rating scale	CES-D
Steffens 2002	Population-based cohort, prospective (Cardio-vascular Health Study)	USA, general population, 4 years follow-up	70	40	3236	1821	WMH severity rating scale	Ever CES-D >7
Teodorczuk	Population-	Multicenter, patients	65+	54	399	85	WMH volumetry	GDS

2010	based cohort, prospective (LADIS study)	presenting at neurology department, 3 years follow-up					(semi-automatic)	
van Sloten **2015**	Population-based cohort, prospective (AGES-Reykjavik)	Iceland, general population, 4 years follow-up	75	57	1949	197	WMH volumetry (semi-automatic), microbleeds, subcortical infarcts	GDS
Versluis 2006	Population-based cohort, prospective (Prosper study)	the Netherlands, high CVD risk population, 2.8 years follow-up	75	43	527	43	WMH volumetry (semi-automatic)	15 items GDS

sICAM-1 (Soluble intercellular adhesion molecule-1), s-VCAM-1 (Soluble vascular cell adhesion molecule-1), GDS (Geriatric Depression Scale), SCID (Structured clinical interview for DSM-IV), CES-D (Center for Epidemiological
Studies of Depression), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV), MDRS (Montgomery–Åsberg Depression Rating Scale), HDRS (Hamilton Rating Scale for Depression), WMH (White matter hyper-
intensities), PWMH (Periventricular WMH), DWMH (Deep cortical WMH), AWMH (Anterior WMH), MINI (Mini International Neuropsychiatric Interview), MCI (Mild cognitive impairment), PHQ-9 (Patient health questionnaire-9),
BDI (Beck Depression Index), CSVD (Cerebral small vessel disease), CVD (Cardiovascular disease), CKD (Chronic kidney disease), ACR (Albumin creatinin ratio)

eTable 3. Reported Results of Studies Included in the Systematic Review and Meta-analysis

Study	Marker	Results	Calculated results	Transformation	Adjustments for covariates
Endothelial dysfunction (Cross-sectional data)					
Dimopoulos **2006**	sICAM-1	OR 2.97 [1.23 – 7.18]	NA	None	Sex, smoking, metabolic syndrome
	sVCAM-1	OR 4.66 [1.55 – 13.98]	NA		
Lesperance **2004**	sICAM-1	Depression: 5.34±0.24 Control: 5.20±0.26	OR 2.66 [1.43 – 4.96]	SMD*	Sex, smoking, metabolic syndrome
Phuong Do **2010**	sICAM-1	% change: 17.6	NA	None	Age, sex, systolic blood pressure, cardiovascular condition, inflammation, BMI, smoking status
	E-Selectin	% change: 17.96	NA		
Tchalla 2015	sICAM-1	Depression: 273±87 Control: 258±75	OR 1.41 [1.04 – 1.92]	SMD*	None
	sVCAM-1	OR 1.97 [1.14 – 3.57]	NA	None	Age, sex, race, educational level, BMI, smoking, alcohol use, physical activity, diabetes, comorbidity index
Thomas 2007	sICAM-1	Depression: 289.0 Control: 251.6	OR 2.08 [0.86 – 5.01]	SMD	None
	sVCAM-1		OR 0.61 [0.25 – 1.48]		
Tully 2016	sE-Selectin	Depression: 3.475 Control: 3.469 (Logtransformed)	OR 1.11 [0.68 – 1.82]	SMD*	None
van Dooren **2016**	sICAM-1	Depression: 284.9±71.9 Control: 256.7±67.4	OR 1.35 [1.10 – 1.65]	SMD*	Age, sex, T2DM, eGFR, history of CVD, smoking, alcohol use, BMI
	sVCAM-1	Depression: 428.5±99.3 Control: 402.4±101.0	OR 1.25 [0.99 – 1.58]	SMD*	
	E-Selectin	Depression: 16.5±10.3 Control: 13.2±7.4	OR 1.36 [1.11 – 1.66]	SMD*	
	vWF	Depression: 143.1±44.8 Control: 134.3±47.8	OR 1.19 [0.93 – 1.53]	SMD*	
van Sloten **2013***	sICAM-1	Depression: 257.9±36.5 Control: 248.8±37.5	OR 1.55 [0.96 – 2.49]	SMD*	Age, sex, glucose metabolism status, prior CVD, hypertension, waist-to-hip ratio, cholesterol, education, physical activity, dietary habits, use of antihypertensive, lipid-lowering, glucose-modifying medication
	sVCAM-1	Depression: 427.0±59.1 Control: 390.6±55.8	OR 3.25 [2.03 – 5.21]	SMD*	
	E-Selectin	Depression: 16.6±2.3 Control: 17.9±2.4	OR 0.38 [0.13 – 1.08]	SMD*	
	vWF	Depression: 177.4±19.2 Control: 146.5±16.3	OR 1.21 [1.31 – 8.59]	SMD*	
Albuminuria (Cross-sectional data)					
Fischer 2013	ACR	OR 1.07 [0.90 – 1.26]	NA	None	Age, sex, race, education, hypertension, cholesterol, CVD, diabetes, obesity, eGFR, antidepressant medication
Katon 2004	Microal-buminuria	OR 1.29 [0.96 – 1.73]	NA	None	Smoking, obesity, exercise, triglycerides, LDL, Hb1Ac, hypertension
Retinal vessel diameters (Cross-sectional data)					
Nguygen 2010	Arteriolar diameter	OR 8.3 [4.70 – 11.99]	NA	None	Age, sex, duration of diabetes, systolic blood pressure, cigarette smoking, serum glucose, cerebrovascular risk factor scale, cumulative illness scale, retinopathy
	Venular diameter	OR 2.18 [0.00 - 7.20]	NA	None	
Retinal vessel diameters (Longitudinal data)					
Ikram 2010	Arteriolar diameter	HR 1.01 [0.93 – 1.10]	NA	None	Age, sex, smoking, blood pressure, diabetes mellitus, BMI, carotid artery plaques, cholesterol
	Venular	HR 1.02 [0.94 – 1.12]	NA	None	

		diameter			
Cerebral Small Vessel Disease (Cross-sectional data)					
Aizenstein 2011	WMH rating scale	Depression: 0.0015 Control: 0.0008	NA	None	Age, sex
Almeida 2004	Scheltens scale	correlation coefficient 0.79	NA	None	Age, sex
Chatterjee 2010	WMH Volumetry	OR 1.50 [0.97 – 2.20]	NA	None	None
Chen 2009	Fazekas scale	Depression: 1.23±0.83 Control: 1.19±0.85	OR 1.09 [0.57 – 2.09]	SMD	None
Colloby 2011	WMH Volumetry	Depression: 0.94±1.28 Control: 0.84±0.88	OR 1.17 [0.50 – 2.78]	SMD	Age, sex
Cyprien 2014	WMH Volumetry	Depression: 0.59±0.26 Control: 0.53±0.26	OR 1.52 [1.03 – 2.25]	SMD*	Age, education, global cognitive impairment, ischaemic pathologies, left-handedness, ICV, past depression
De Groot 2000	PWMH rating scale	OR 3.3 [1.20 – 9.50]	NA	None	Age, sex, educational level
Delaloye 2010	Scheltens scale DWMH	Depression: 6.45±6.3 Control: 2.87±4.99	OR 3.32 [0.97 – 11.41]	SMD	None
Devantier 2016	WMH Volumetry	Depression: 1249±9018 Control: 308±4479	OR 1.27 [0.49 – 3.28]	SMD	Age, sex, smoking status
Direk 2016	WMH Volumetry	OR 1.40 [1.20 – 1.62]	NA	None	Age, sex, education, smoking status, hypertension, diabetes mellitus, BMI, total and HDL cholesterol, cognitive function
	Microbleeds	OR 1.40 [1.01 – 1.94]	NA	None	
	Micro-infarctions	OR 1.73 [1.07 – 2.95]	NA	None	
Dotson 2013	WMH rating scale	Regression coefficients -0.06 [0.57] (women) -0.27 [0.42] (men)	NA	None	None
Feng 2013	PWMH Fazekas scale	OR 1.14 [0.71 – 1.83]	NA	None	Age, sex, education, hypertension, diabetes, cognition
	DWMH Fazekas scale	OR 1.87 [1.13 – 3.08]	NA	None	
	Microbleeds	OR 1.59 [0.75 – 3.38]	NA	None	
	Micro-infarctions	OR 1.98 [1.00 – 3.92]	NA	None	
Firbank 2005	WMH Volumetry	OR 1.52 [1.05 – 2.22]	NA	None	Age, sex, cognition, disability, baseline depression, study center, baseline WMH (longitudinal data only)
Firbank 2012	WMH Volumetry	Spearman's rho 0.48	NA	None	Age, sex, cognition, disability, baseline depression, study center, baseline WMH
Fujishima 2014	WMH Volumetry	Depression: 2.35±0.48 Control: 1.29±0.53	OR 3.25 [1.92 – 5.52]	SMD	None
Godin 2008	WMH Volumetry	Depression: 7.6±0.54 Control: 6.8±0.50	OR 1.30 [1.05 – 1.61]	SMD*	Age, sex, hypertension, history of cardiovascular disease, alcohol and tobacco consumption, physical impairment, brain white matter volume
Greenwald 1998	Sum of DWMH, Scheltens scale	Depression: 1.53±1.82 Control: 0.72±1.24	OR 1.57 [1.16 – 2.13]	SMD*	Sex, hypertension
Grool 2011	WMH Volumetry	RR 1.07 [0.85 – 1.35]	NA	None	Age, sex, education, hypertension, diabetes mellitus, physical functioning
Gudmunds-son 2013	WMH Volumetry	Depression: 0.9±0.3 Control: 0.9±0.4	OR 0.92 [0.70 – 1.21]	SMD*	Age, sex, years of follow up, ICV, height, education, systolic and diastolic blood pressure, anti-hypertensive medication use
Hannestad 2006	WMH Volumetry	Depression: 6.68±10.1 Control: 3.88±3.8	OR 1.75 [1.07 – 2.86]	SMD*	Age, sex, ICV
Iosifescu 2005	Fazekas scale	Depression: 0.67±0.66 Control: 0.65±0.59	OR 1.05 [0.44 – 2.50]	SMD*	Age, sex, hypertension, family history of CVD, smoking, diabetes, hypercholesterolemia
Janssen 2004	WMH Volumetry	Depression: 6.93±7.89 Control: 14.15±11.38	OR 0.84 [0.35 – 2.02]	SMD	Age, sex
Janssen 2007	Larger DWMH Volumetry	Depression: 47% Control: 5%	NA	None	Age, cognition, ICV
Jorm 2005	Fazekas scale	OR 1.39 [0.93 – 2.08]	NA	None	Age, sex, education, physical disability, history of stroke, diabetes, hypothyroidism, cognition, systolic and diastolic blood pressure, smoking, alcohol use.
Kieseppa 2014	DWMH Coffey scale	Depression: 1.13±1.15 Control: 0.62±0.97 (obtained through correspondence)	OR 1.59 [0.84 – 3.01]	SMD	Age, sex

Kohler 2010	Scheltens scale	Depression: 12.2±5.4 Control: 13.2±9.9	OR 1.27 [0.53 – 3.06]	SMD*	Age, sex, education
Krishnan 2006	Scheltens scale	OR 1.04 [1.00 – 1.08]	NA	None	Age, cognition, hypertension, prior CVD
Kumar 2000	WMH Volumetry	Depression: 0.00330±0.00460 Control: 0.00037±0.00054	OR 1.43 [1.11 – 1.85]	SMD	Age, sex, ICV
Lavretsky **2008**	WMH volumetry (semi-automatic)	OR 1.14 [0.96 – 1.35]	NA	None	Age, sex, education
Lee 2003	Coffey scale DWMH grade 3	Depression: n=9 Control: n=13	NA	None	Age, sex, ICV
Lin 2005	Fazekas scale	Depression: 2.57±1.44 Control: 1.67±1.14	OR 1.20 [1.07 – 1.35]	SMD	None
MacFall 2005	WMH Volumetry	Depression: 6.11±0.90 Control: 3.09±1.02	OR 5.66 [4.57 – 6.73]	SMD	Age, sex
Murray 2013	Scheltens scale	Pearson correlation coefficient 0.066	NA	None	Sex, living alone
Paranthaman **2010**	WMH Volumetry	Depression: 342.2±748.1 Control: 202.0±881.2	OR 1.36 [0.45 – 4.10]	SMD	None
Per**ez 2012**	WMH rating scale	OR 1.10 [1.00 – 1.22]	NA	None	Age, sex, education, cognition
Potter 2007	AWMH Volumetry	Depression: 0.094±0.026 Control: 0.063±0.186	OR 1.60 [0.84 – 3.05]	SMD*	Age, education, depression severity, anxiety, time between MRI and depression screening
Sheline 2008	WMH Volumetry	Graphic representation of regional differences	NA	None	None
Steffens 2002	WMH rating scale	OR 1.33 [0.86 – 2.06]	NA	None	Age, sex, race, education, antidepressant medication use, cognition, hypertension, coronary heart disease, apoE genotype, ADL, LADL
Steffens 1999	WMH rating scale	OR 1.04 [0.99 – 1.08]	NA	None	Age, sex, race, education, antidepressant medication use, cognition, hypertension, coronary heart disease, apoE genotype, ADL, LADL
Tang 2010	DWMH Fazekas scale	OR 13.8 [1.64 – 115.65]	NA	None	Age, sex
Tang 2014	Pontine Microbleeds rating scale	OR 2.2 [1.16 – 4.16]	NA	None	None
Taylor **2005**	WMH Volumetry	Depression: 7.22±10.71 Control: 4.87±6.47	OR 1.57 [1.06 – 2.32]	SMD*	Age, sex, race, hypertension, diabetes, heart disease
Tudorascu **2014**	WMH Volumetry	OR 1.89 [1.33 – 2.69]	NA	None	Age, sex, cognition, cardiovascular disease, diabetes, hypertension
Tupler 2002	Sum of Fazekas scale	Depression: 3.65±7.05 Control: 1.16±2.43	OR 2.14 [1.05 – 4.36]	SMD	Age
van Sloten **2015**	WMH Volumetry	OR 1.04 [0.89 – 1.21]	NA	None	Age, sex, education, smoking history, alcohol intake, anxiety, gait speed, hypertension, antihypertensive medication, BMI, diabetes, coronary calcium score, cognition
	Microbleeds rating scale	OR 1.15 [0.77 – 1.72]	NA	None	
van Uden **2011**	WMH Volumetry	Depression: 21.8±20.2 Control: 14.7±13.8	OR 1.49 [0.97 – 2.29]	SMD	Age, sex, ICV, lacunar infarcts, amygdala volume
Vardi 2010	WMH Volumetry	Depression: 366.96±1072 Control: 54.7±57	OR 1.82 [0.40 – 8.34]	SMD	None
Vataja 2001	WMH Fazekas	Depression: 3.4±1.5 Control: 3.4±1.6	OR 1.00 [0.65 – 1.54]	SMD	None
Versluis 2006	WMH Volumetry	OR 0.70 [0.28 – 1.76]	NA	None	Age, sex
Videbech **2000**	Fazekas scale	OR 0.86 [0.31 -2.38]	NA	None	Age, sex
Wu 2014	Fazekas scale	Depression: 1.62±1.10 Control: 1.11±0.97	OR 2.53 [1.50 – 4.27]	SMD*	Sex, cognition, microbleeds, microinfarctions

Cerebral Small Vessel Disease (Longitudinal data)

Study	Measure				Adjustments
Firbank **2012**	WMH Volumetry	Depression: 2 (IQR 1 − 4) Control: 1 (IQR 0 -3)	NA	None	Age, sex, cognition, disability, baseline depression, study centre, baseline WMH
Godin 2008	WMH Volumetry	Depression: 2.1±0.35 Control: 1.5±0.31	OR 1.30 [1.05 − 1.62]	SMD*	Age, sex, hypertension, history of CVD, alcohol consumption, smoking, education, diabetes
Grool 2011	PWMH Volumetry	OR 1.07 [0.93 − 1.24]	NA	None	Age, sex, education, vascular risk, cognition
Olesen 2010	Gothenburg scale	OR 3.21 [1.00 − 10.26]	NA	None	Age, sex, hypertension, cholesterol
Perez 2012	WMH rating scale	OR 1.10 [1.00 − 1.22]	NA	None	Age, sex, education, cognition
Steffens 2002	WMH rating scale	OR 1.33 [0.86 − 2.06]	NA	None	Age, sex, race, education, antidepressant medication use, cognition, hypertension, coronary heart disease, apoE genotype, ADL
Teodorczuk **2010**	WMH Volumetry	OR 1.36 [1.04 − 1.76]	NA	None	Age, sex, educational level, history of depression, cognition, history of stroke, hypertension
van Sloten **2015**	WMH Volumetry	OR 1.24 [1.06 − 1.44]	NA	None	Age, sex, education, smoking history, alcohol intake, anxiety, gait speed, hypertension, antihypertensive medication, BMI, diabetes, coronary calcium score, cognition
	Microbleeds rating scale	OR 1.36 [0.98 − 1.86]	NA	None	
Versluis 2006	WMH Volumetry	OR 0.70 [0.21 − 2.34]	NA	None	Age, sex

sICAM-1 (Soluble intercellular adhesion molecule-1), s-VCAM-1 (Soluble vascular cell adhesion molecule-1), GDS (Geriatric Depression Scale), SCID (Structured clinical interview for DSM-IV), CES-D (Center for Epidemiological Studies of Depression), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV), MDRS (Montgomery–Åsberg Depression Rating Scale), HDRS (Hamilton Rating Scale for Depression), WMH (White matter hyperintensities), PWMH (Periventricular WMH), DWMH (Deep cortical WMH), AWMH (Anterior WMH), MINI (Mini International Neuropsychiatric Interview), MCI (Mild cognitive impairment), PHQ-9 (Patient health questionnaire-9), BDI (Beck Depression Index), CSVD (Cerebral small vessel disease), CVD (Cardiovascular disease), CKD (Chronic kidney disease), ACR (Albumin creatinin ratio), SMD (Standardized Mean Difference), NA (not applicable): the original data were used.

* The unadjusted data were used and converted to odds ratios by use of the SMD. Odds ratios were calculated by use of the following formula: SMD = (sqrt 3)/π ln OR

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