SUPPLEMENTAL MATERIAL

Blood pressure variability and cerebral small vessel disease: A systematic review and meta-analysis of population-based cohorts

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Supplemental Methods

Modified Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Note: In our study, one item regarding the selection of controls (in the selection category) was removed given that it was true for all the studies because all individuals were "exposed" to the risk factor under study (i.e. blood pressure variability). A study can be awarded a maximum of one score for each membered item within the Selection and Outcome categories. A maximum of two scores can be given for Comparability. The total score of eight reflects the highest quality. The individual items of the scale are described below.

Selection

1) **Representativeness of the cohort**

a) truly representative of the general population (i.e. random sampling from community-based population) *****

b) somewhat representative of the general population *****

c) high risk populations (e.g. individuals with: prior stroke, mild cognitive impairment, cardiovascular disease, prior depression (for the association with incident depression), or individuals receiving dialysis)

d) no description or other cohorts

2) **Ascertainment of determinant** (Blood pressure variability)

a) objectively measured blood pressure*

b) not a method described above (e.g. self-reported)

c) no description

3) **Baseline screening** for small vessel disease

a) yes *****

b) no

Comparability

1) Comparability of cohorts based on of the design or analysis

a) study controls for age and sex*****

b) study controls for cardiovascular risk factors; smoking habits, type 2 diabetes, and pre-existing cardiovascular disease*****

c) other

Outcome

1) **Assessment of outcome**

a) use of an MRI scanner with a field strength of 1.5 Tesla or higher and the following (minimal) sequences: for white matter hyperintensities: T2-weighted and fluid-attenuated inversion recovery (FLAIR); for lacunes: T1- and(or) T2-weighted; for cerebral microbleeds: T2*-weighted gradient echo sequence; for perivascular spaces: T2-weighted; and for total cerebral atrophy: T1/FLAIR *

b) Self-report*

c) no description/other

2) Was **follow-up long enough** for outcomes to occur

a) yes (median/mean follow-up duration >=5 year) *****

b) no (median/mean follow-up duration <5 year)

3) **Adequacy of follow-up of cohorts**

a) complete follow-up and/or all subjects accounted for *****

b) subjects lost to follow-up unlikely to introduce bias, small number lost (>80 % follow-up), or description provided of those lost *****

c) follow up rate <80% and no description of those lost to follow-up

d) no statement

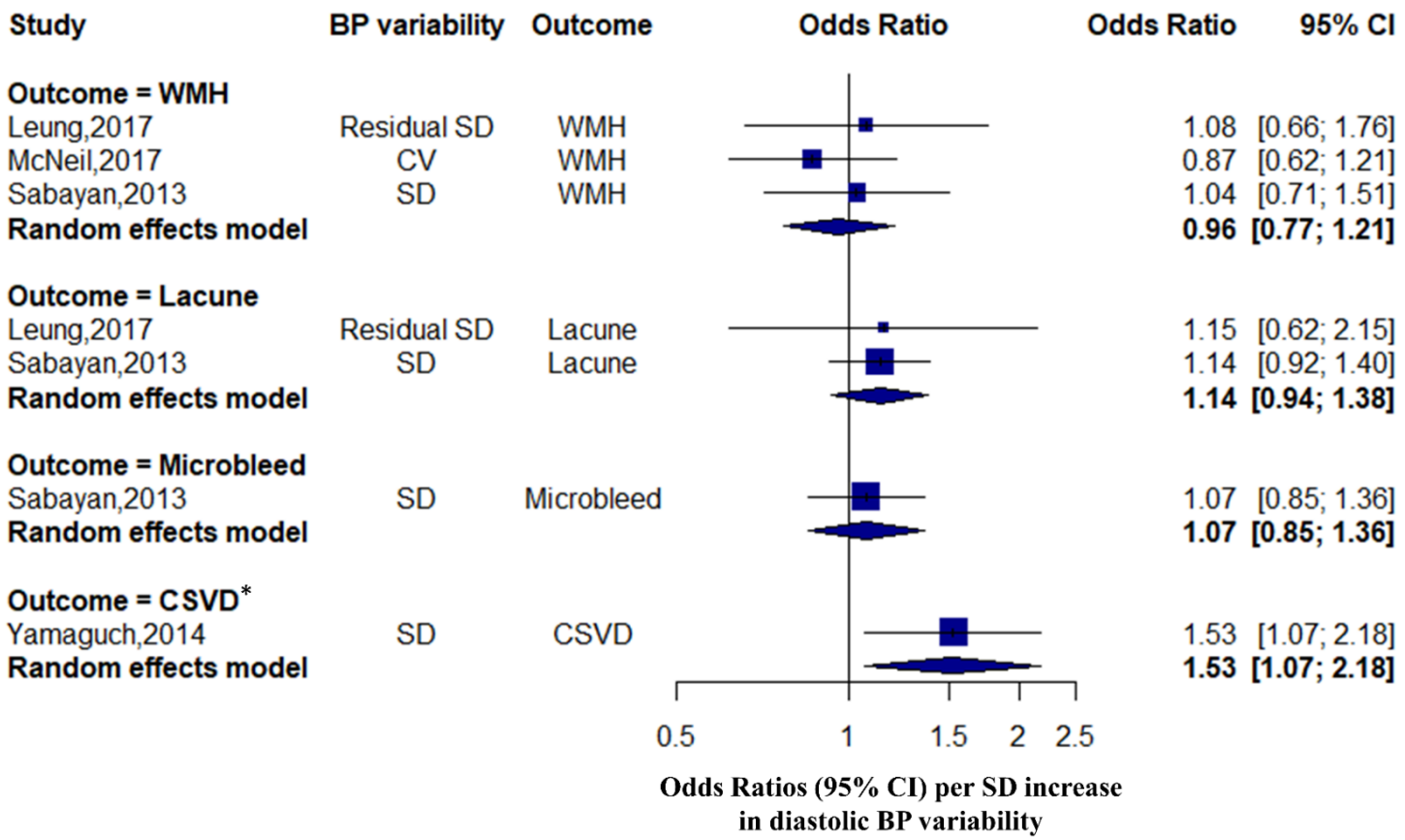
Supplemental Table I Search strategy

Medline (Ovid)
(((blood pressure OR bp OR sbp OR dbp) adj3 (variabilit* OR variation* OR instabilit* OR fluctuat* OR disturbance* OR characteristic* OR profile*)).ab,ti OR ((exp Blood Pressure/ OR exp Blood Pressure Determination/ OR (blood pressure OR bp OR sbp OR dbp).ab,ti) AND (((between OR within) adj3 visit?).ab,ti OR ((between OR within) adj3 day?).ab,ti OR visit to visit.ab,ti OR day to day.ab,ti OR day by day.ab,ti OR (measure* adj measure*).ab,ti OR (reading? adj reading?).ab,ti OR (repeat* adj measure*).ab,ti OR within subject?.ab,ti OR ((ambulatory OR 24 hour OR home) adj3 (monitor* OR measur*)).ab,ti OR ((daytime OR day time OR diurnal) adj5 (nighttime OR nocturnal)).ab,ti))) AND (exp cerebral small vessel diseases/ OR exp leukoaraiosis/ OR small vessel.ab,ti OR csvd.ab,ti OR white matter.ab,ti OR leukoaraiosis.ab,ti OR ((brain OR cerebr*) AND (lacun* OR infarc* OR microbleed* OR microhemorrhag* OR microhaemorrhag* OR atrophy OR volum*)).ab,ti OR (perivascular space* OR virchow robin* OR etat crible).ab,ti)
Embase
('lacunar stroke'/exp OR 'leukoaraiosis'/exp OR 'small vessel':ab,ti OR csvd:ab,ti OR 'white matter':ab,ti OR leukoaraiosis:ab,ti OR ((brain OR cerebr*) AND (lacun* OR infarc* OR microbleed* OR microhemorrhag* OR microhaemorrhag* OR atrophy OR volum*)):ab,ti OR ('perivascular space*' OR 'virchow robin*' OR 'etat crible'):ab,ti) AND (('blood pressure fluctuation'/exp OR (('blood pressure' OR bp OR sbp OR dbp) NEAR/3 (variabilit* OR variation* OR instabilit* OR fluctuat* OR disturbance* OR characteristic* OR profile*)):ab,ti) OR (('blood pressure'/exp OR 'blood pressure measurement'/exp OR ('blood pressure' OR bp OR sbp OR dbp):ab,ti) AND (((between OR within) NEAR/3 (visit OR visits)):ab,ti OR ((between OR within) NEAR/3 (day OR days)):ab,ti OR 'visit to visit':ab,ti OR 'day to day':ab,ti OR 'day by day':ab,ti OR 'measure* to measure*':ab,ti OR 'reading* to reading*':ab,ti OR (repeat* NEXT/1 measure*):ab,ti OR 'within subject*':ab,ti OR ((ambulatory OR '24 hour' OR home) NEAR/3 (monitor* OR measur*)):ab,ti OR ((daytime OR 'day time' OR diurnal) NEAR/5 (nighttime OR nocturnal)):ab,ti)))
Web of Science
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years TS=("small vessel" OR "csvd" OR "white matter" OR "leukoaraiosis" OR (("brain" OR "cerebr*") AND ("lacun*" OR "infarc*" OR "microbleed*" OR "microhemorrhag*" OR "microhaemorrhag*" OR "atrophy" OR "volum*")) OR "perivascular space*" OR "virchow robin*" OR "etat crible") AND (TS=(("blood pressure" OR "bp" OR "sbp" OR "dbp") NEAR/3 ("variabilit*" OR "variation*" OR "instabilit*" OR "fluctuat*" OR "disturbance*" OR "characteristic*" OR "profile*")) OR (TS=("blood pressure" OR "bp" OR "sbp" OR "dbp") AND TS=((("between" OR "within") NEAR/3 ("visit" OR "visits" OR "day" OR "days")) OR "visit to visit" OR "day to day" OR "day by day" OR "measure* to measure*" OR "reading* to reading*" OR ("repeat*" NEAR/1 "measure*") OR "within subject*" OR (("ambulatory" OR "24 hour" OR "home") NEAR/3 ("monitor*" OR "measur*")) OR (("daytime" OR "day time" OR "diurnal") NEAR/5 ("nighttime" OR "nocturnal")))))

Supplemental Table II. Quality assessment of studies included in systematic review*

Study	BP variability	Selection			Comparability		Outcome			Total score
		Sampling	Exposure measurement	Baseline Screening	Age and sex	Vascular risk factors	Outcome assessment	Length of follow-up	Adequacy of follow up	
Goldstein et al, 2005[1]	hour-to-hour	1	1	1	1	1	1	1	1	8
Yamaguchi et al, 2014[2]	hour-to-hour	1	1	1	1	1	1	0	1	7
Liu et al, 2016[3]	day-to-day	1	1	1	1	1	1	0	1	7
Brickman et al, 2010[4]	visit-to-visit	1	1	0	1	1	1	1	1	7
Havlik et al, 2002[5]	visit-to-visit	1	1	0	1	1	1	1	1	7
Leung et al, 2017[6]	visit-to-visit	1	1	1	1	1	1	1	1	8
McNeil et al, 2017[7]	visit-to-visit	1	1	0	1	0	1	0	0	4
Rosano et al, 2014[8]	visit-to-visit	1	1	0	0	0	1	1	0	4
Sabayan et al, 2013[9]	visit-to-visit	1	1	0	1	1	1	0	1	6
Tully et al, 2018[10]	visit-to-visit	1	1	0	1	1	1	1	1	7

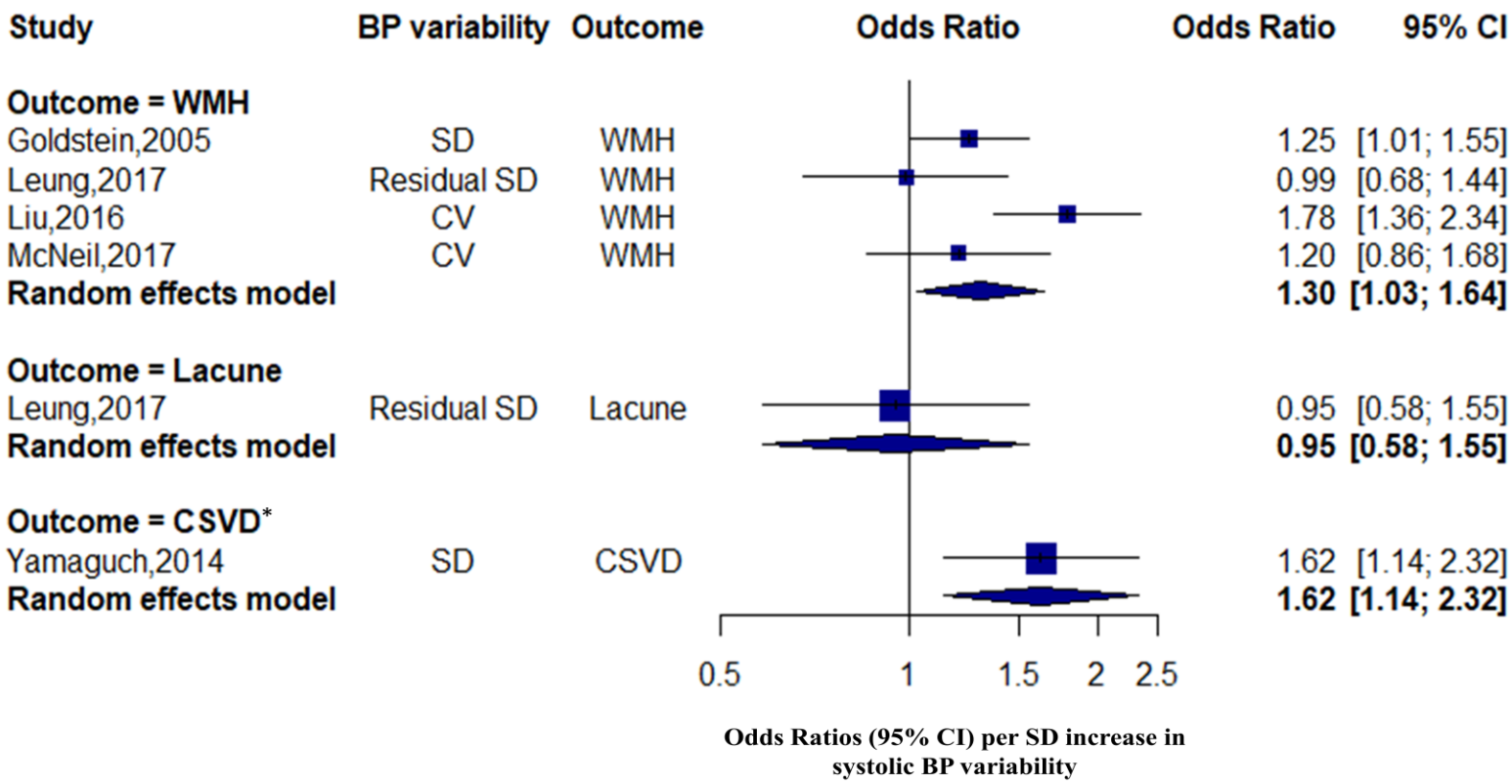
Individuals items are defined as follows: 1) Sampling: 1= representative sampling from community-based population; 2) Exposure measurement: 1=objectively measured blood pressure; 3) Baseline screening for cerebral small vessel disease: 1=yes, 0=no; 4-5) Comparability: assigned one score to studies that controlled for age and sex, and assigned one score to studies with additional adjustment for vascular risk factors; 6) Outcome assessment: 1=use MRI scanner with a filed strength of 1.5T with appropriate sequences; 7) Length of follow-up: 1=median/mean follow-up duration >5 year; 8) Adequacy of follow-up: loss to follow up<20% and description provided of those lost.



Supplemental Figure I. The association of diastolic BP variability with imaging markers of cerebral small vessel disease

*Defined as new WMH or incident lacunes during the follow-up.

SD=standard deviation; CV=coefficient of variation; WMH=white matter hyperintensities; CSVD=cerebral small vessel disease.



Supplemental Figure II. The association of systolic BP variability with imaging markers of cerebral small vessel disease after excluding studies with a small proportion of dementia and stroke cases.

*Defined as new WMH or incident lacunes during the follow-up.

SD=standard deviation; CV=coefficient of variation; WMH=white matter hyperintensities; CSVD=cerebral small vessel disease.

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