RUSH UNIVERSITY MEDICAL CENTER

Blood pressure and neuropathology:
Late-life blood pressure association with cerebrovascular and Alzheimer's disease pathology

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Strategic partners

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Research Participants

Religious Orders Study
Rush Memory and Aging Project
Minority Aging Research Study
African American Core
Latino Core
SANDS

Common conditions of older persons: neurologic and other

Longitudinal, community-based, clinical-pathologic research studies, for more than two decades

Outline

PART 1. Review the association of blood pressure (BP) with common pathologies of dementia, specifically:

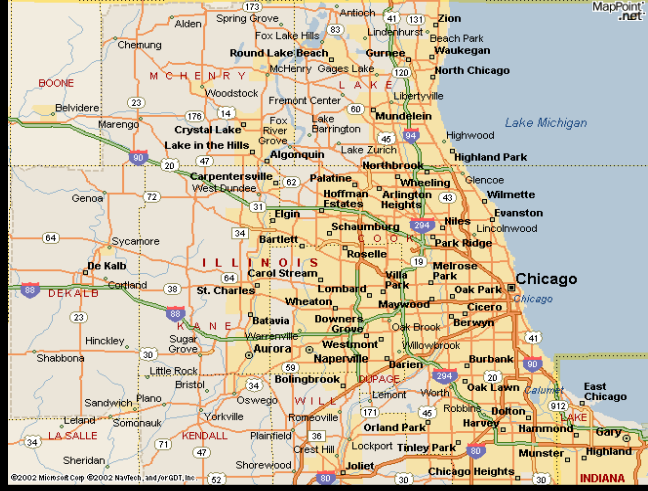
- Cerebrovascular disease and
- Alzheimer's disease (AD) pathology

PART 2. Explore the relation of BP with cognitive decline

Religious Orders Study

- Began in 1993
- Funded by the National Institute on Aging
- > 1,450 older nuns, priests, and brothers without known dementia from >40 groups across the US
- All agreed to annual cognitive and motor testing
  - Complete neurological evaluation performed annually
  - > 95% follow-up of survivors with up to 24 time points
  - > 375 persons have developed dementia
- All agreed to brain donation at the time of death
  - > 90% autopsy rate with > 760 brain autopsies

Memory and Aging Project



- Began in 1997
- Funded by the National Institute on Aging
- > 2,140 residents from about 40 retirement communities and senior housing from across the Chicago area
- All agreed to annual cognitive and motor testing, and blood draw

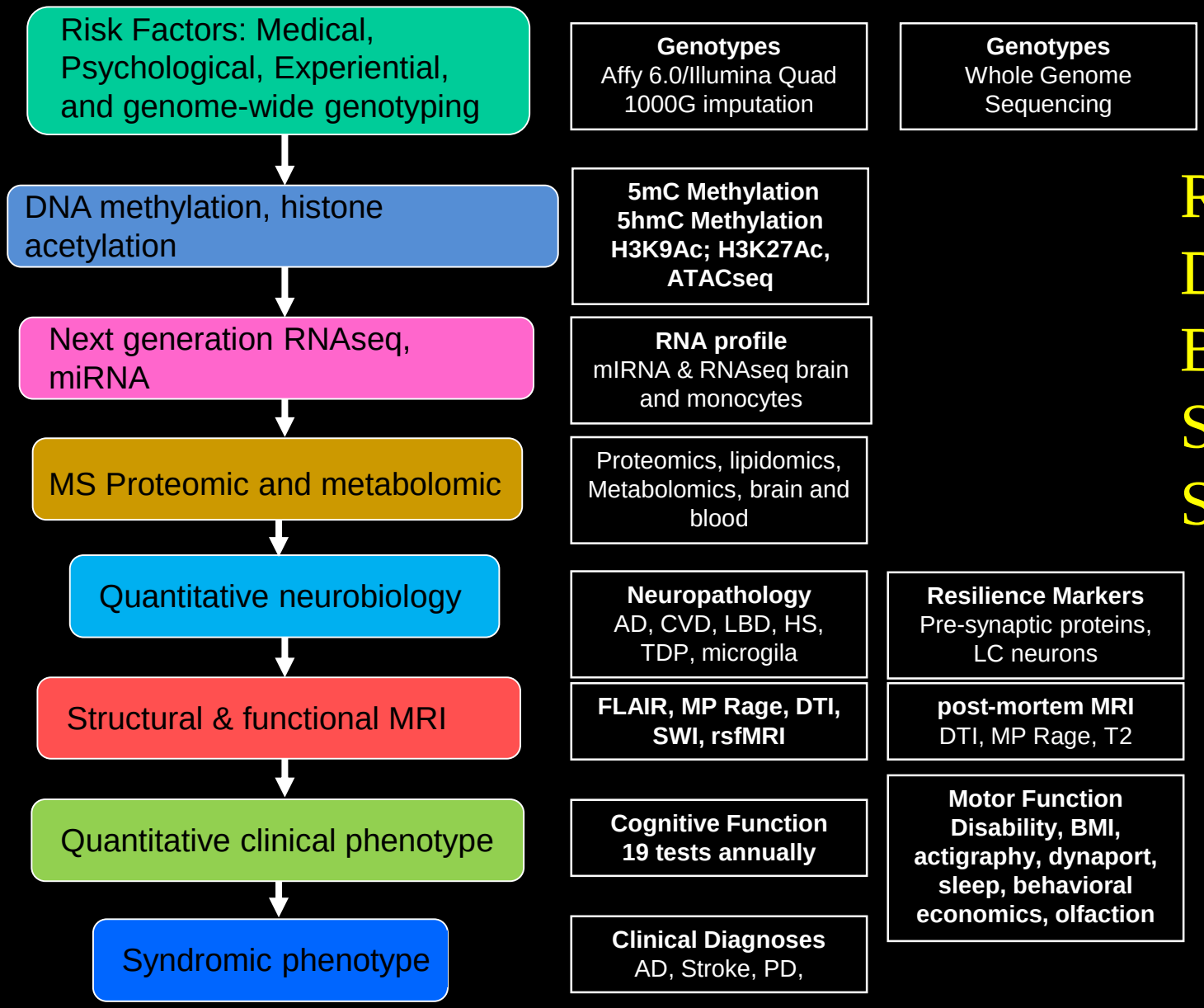
  Complete neurological evaluation performed annually

  > 90% follow-up of survivors with up to 21 time points
- All agreed to donate brain, spinal cord, muscle, and nerve at the time of death

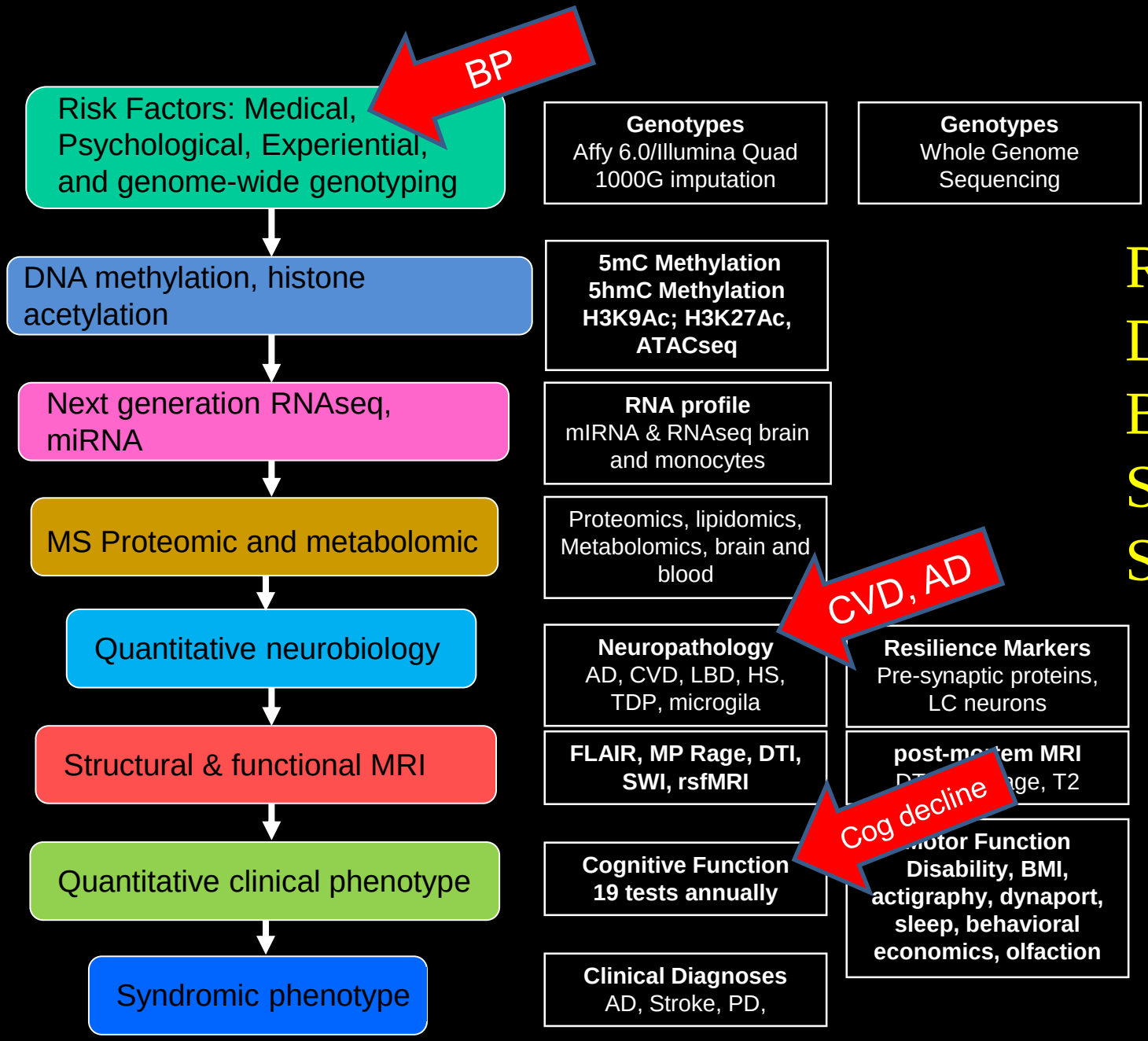
  > 85% autopsy rate with > 815 brain autopsies

Minority Aging Research Study

- Began in 2004
- Funded by the National Institute on Aging
- > 750 older community-dwelling African Americans without known dementia, living in private residences or senior housing across the Chicagoland area
- All agreed to annual cognitive testing
- More recently, invited to participate in brain donation at time of death



RANGE OF DATA FOR BROAD SCOPE OF STUDY



RANGE OF DATA FOR BROAD SCOPE OF STUDY

PART 1:
BP and neuropathology

OBJECTIVE

To examine associations of

average and change in late-life blood pressure (BP) with

cerebrovascular and Alzheimer's disease (AD) neuropathology

in a large group of decedents followed longitudinally in vivo

Neurology 2018

Blood pressure (BP)

- Measured at baseline and annually using an automated sphygmomanometer in an environment familiar to the research participant
- 3 values recorded and averaged
- For analyses, longitudinal data on each individual was aligned at death and we computed the standardized person-specific mean BP over time across the years (level) and slope of change in BP (change over time)
- Mean follow-up of 8 years (SD = 4.8)

Table 1 Demographic, clinical, and neuropathologic characteristics of participants[a]

	Total (n = 1,288)
Demographic	
Age at death, y, mean (SD)	88.6 (6.7)
Female, n (%)	842 (65)
APOE ε4, n (%)	339 (26)
Education, y, mean (SD)	16.3 (3.7)
Clinical	
BP, mm Hg, mean (SD)	
SBP at baseline	136 (18)
SBP mean across study	134 (13)
DBP at baseline	72 (10)
DBP mean across study	71 (8)
History of hypertension at any time, n (%)	843 (66)
Antihypertensive medication use at any time, n (%)	1,122 (87)
Vascular risk factors at baseline, n (%)[b]	853 (66)
Vascular diseases at baseline, n (%)[b]	347 (28)

ROS, MAP, MARS subjects

Neuropathologic	
Brain infarcts, presence	
Any type of infarct (size or location), n (%)	
Single infarct	260 (20)
Multiple infarcts	362 (28)
Gross infarct(s), n (%)	
Single infarct	222 (17)
Multiple infarcts	220 (17)
Microinfarct(s), n (%)	
Single infarct	226 (18)
Multiple infarcts	147 (11)
Cortical infarct(s), n (%)	
Single infarct	215 (17)
Multiple infarcts	124 (10)
Subcortical infarct(s) present, n (%)	
Single infarct	229 (18)
Multiple infarcts	222 (17)
Vessel pathology,[c] n (%)	
Atherosclerosis	452 (35)
Arteriolosclerosis	427 (33)
AD pathology,[d] mean (SD)	
Global score	0.7 (0.6)

Analyses

- All analyses adjusted for age at death, sex, education and years in study
- Ordinal logistic regression analyses to determine the odds of separate cerebrovascular outcomes (one and more than one infarcts, increased severity of vessel pathology)
- Linear regression analyses to determine odds of AD pathology (overall and individual measures of plaques and tangles)

BP and infarcts

Table 2 Relationship of blood pressure with number of brain infarcts[a]

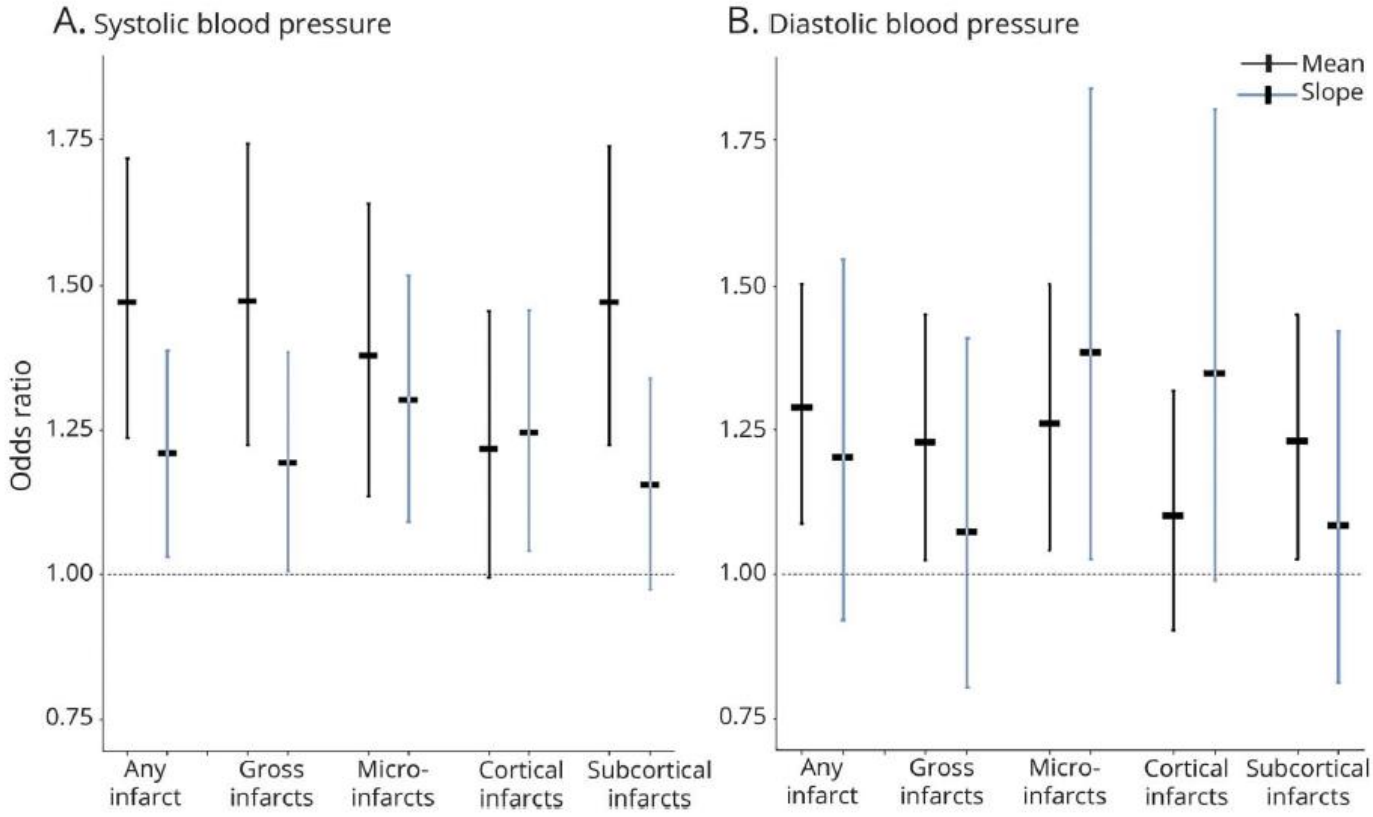
	SBP terms		DBP terms	
Outcome	**Person-specific mean[b]**	**Person-specific slope[b]**	**Person-specific mean[b]**	**Person-specific slope[b]**
Any infarct[c]	1.46 (1.24–1.72)	1.20 (1.03–1.39)	1.28 (1.09–1.50)	1.19 (0.92–1.55)
Gross infarct(s)	1.46 (1.22–1.74)	1.18 (1.01–1.38)	1.22 (1.02–1.45)	1.06 (0.80–1.41)
Microinfarct(s)	1.36 (1.13–1.64)	1.29 (1.09–1.52)	1.25 (1.04–1.50)	1.37 (1.03–1.84)
Cortical infarct(s)	1.20 (1.00–1.46)	1.23 (1.04–1.46)	1.09 (0.90–1.32)	1.34 (0.99–1.80)
Subcortical infarct(s)	1.46 (1.22–1.74)	1.14 (0.97–1.34)	1.22 (1.03–1.45)	1.07 (0.81–1.42)

Abbreviations: DBP = diastolic blood pressure; SBP = systolic blood pressure.
Data represent odds ratio (95% confidence interval).
[a] Ten ordinal logistic regression models, one for each of the 5 infarct outcomes (each categorized into 3 levels, as multiple, single, none [reference]) separately for the 2 predictors of SBP and DBP; all models adjusted for age at death, sex, education, and years in study; all infarcts are chronic.
[b] Terms for the standardized person-specific mean and declining slope of blood pressure are both included in a single analytic model.
[c] Any infarct refers to infarcts of any size (gross or microscopic) and location (cortical or subcortical).

Higher average late-life blood pressure (separately SBP and DBP), and independently a faster decline in SBP before death, are associated with increasing number of brain infarcts, both gross and microinfarcts

A person with a 1 SD SBP above the mean (147 vs 134 mmHg) would have a 46% increased odds of having one or more infarcts

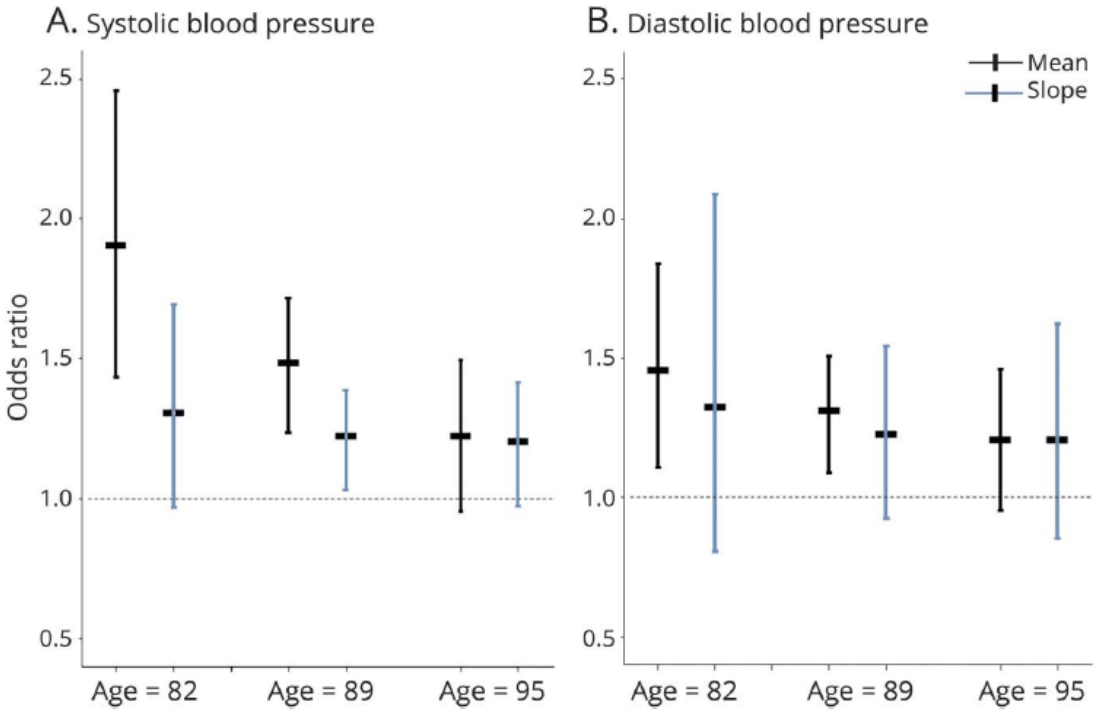
Figure 1 Relation of mean and slope of blood pressure with brain infarcts



Horizontal dashed line represents an odds ratio of 1. (A) Associations between the mean and declining slope of systolic blood pressure with each of the infarct outcomes (categorized as one, and more than one, compared to the reference of none), including any infarcts, gross infarcts and microinfarcts, and cortical and subcortical infarcts. (B) Associations for diastolic blood pressure with the same infarct outcomes.

Effect modification by age

Figure 2 Relation of mean and slope of blood pressure with brain infarcts, according to age



(A) SBP. (B) DBP. The estimated odds of any infarct, and respective 95% confidence interval, for an increase of 1 SD above the mean SBP (or DBP), or 1-unit-faster decline in the slope of SBP (or DBP), on a participant with a mean age of 89 years (center), a participant 1 SD younger than the mean age or 82 years old (left portion of figure), and a participant 1 SD older than the mean age or 95 years old (right portion of figure). DBP = diastolic blood pressure; SBP = systolic blood pressure.

The effect of the mean SBP over time on infarcts was decreased with an increasing age at death (interaction of age with mean SBP)

BP and AD

Table 3 Relationship of blood pressure with Alzheimer disease neuropathology[a]

	SBP		DBP	
Outcome	**Person-specific mean[b]**	**Person-specific slope[b]**	**Person-specific mean[b]**	**Person-specific slope[b]**
Global score	0.031 (0.017), 0.065	0.005 (0.015), 0.727	−0.006 (0.017), 0.701	−0.006 (0.027), 0.826
Neuritic plaques	0.026 (0.022), 0.249	−0.004 (0.020), 0.832	−0.014 (0.022), 0.523	−0.033 (0.036), 0.366
Diffuse plaques	0.039 (0.021), 0.063	0.004 (0.019), 0.837	−0.002 (0.021), 0.926	0.017 (0.034), 0.612
Neurofibrillary tangles	0.037 (0.018), 0.038	0.020 (0.016), 0.212	0.006 (0.018), 0.731	−0.010 (0.003), 0.078

Abbreviations: DBP = diastolic blood pressure; SBP = systolic blood pressure.
Data represent estimate (SE), *p* value.
[a] Eight linear regression models, one for each of the 4 Alzheimer disease pathology outcomes (each transformed using the square root), and separately for SBP and DBP; all models adjusted for age at death, sex, education, and years in study.
[b] Terms for the standardized person-specific mean and declining slope of blood pressure are both included in a single analytic model.

Separately, some evidence for relation of higher SBP with more AD pathology, and with tangles in particular

Weaknesses

- Observational study with cross-sectional design does not establish causation between risk factor and neuropathology
- Extent of neuropathology likely under-reported, as select regions examined
- Pathophysiologic mechanisms need further elucidation, e.g., mediation effects, taking into account range of co-existing clinical and pathologic factors
- White matter pathology not examined

PART 2:
BP and cognitive decline

Level of BP (over the years) and change in cognitive function

	Estimate (SE), p value	
Cognitive decline	**Mean SBP**	**Mean DBP**
Global score	0.001 (0.003), 0.774	**0.010 (0.003), <0.001**
Episodic memory	-0.002 (0.003), 0.600	**0.012 (0.003), <0.001**
Semantic memory	0.003 (0.004), 0.443	**0.011 (0.004), 0.006**
Working memory	-0.001 (0.002), 0.811	**0.008 (0.003), 0.003**
Perceptual speed	0.001 (0.003), 0.661	**0.011 (0.003), <0.001**
Visuospatial abilities	-0.001 (0.002), 0.807	**0.007 (0.002), 0.004**

Results suggest that a lower mean DBP is related to a faster decline in global cognitive function and in each of the cognitive domains

12 mixed effects models controlling for age, sex, education

3631 participants of ROS, MAP, or MARS who were followed annually (mean 9 years)

SBP: relation of level with change (slope)

SBP level (average across study years), in quartiles	N	**SBP slope (mean)**	Lower 95% CL for Mean	Upper 95% CL for Mean
1	907	**-0.23**	-0.27	-0.20
2	908	**-0.39**	-0.43	-0.35
3	908	**-0.51**	-0.55	-0.46
4	908	**-0.76**	-0.81	-0.71

DBP: relation of level with change (slope)

DBP level (average across study years), in quartiles	N	**DBP slope (mean)**	Lower 95% CL for Mean	Upper 95% CL for Mean
1	907	**0.07**	0.05	0.09
2	908	**-0.08**	-0.10	-0.06
3	909	**-0.15**	-0.17	-0.13
4	907	**-0.35**	-0.37	-0.32

Preliminary interpretation

- These results suggest that there may be several pathways through which BP affects the brain:
  - SBP is associated with neuropathology (especially infarcts)
  - DBP is associated with cognitive decline

- More work needed to understand relation of SBP with DBP, and how levels and change in each are inter-related, and how they relate to change in cognition, and whether neuropathology mediates the relation of BP with cognition

Many remaining questions