RUSH

Excellence is just the beginning.

International Society for Neurovascular Disease (ISNVD)

The Association of Diabetes with Dementia

NYU Langone Health
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DISLOSURES

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Consulting as expert witness and medical expert, including on Advisory Boards (academic and industry – Eisai)
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Cohort study participants
Clinic participants

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National Institutes of Health
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Collaborators
Nationally
Internationally

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Agenda

1. Context: brief overview of dementia and diabetes
2. Objective of the studies
3. Methods: Rush Alzheimer's Disease Center (RADC) cohorts and data
4. Select results:
   a. Published results on diabetes, cognition, and neuropathology
   b. Works in progress
5. Conclusions

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Context:
Complex diseases with large public health impact

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DEMENTIA

- All-cause dementia (most commonly attributed to Alzheimer's disease or Vascular Dementia, but most often mixed pathologies):
  - 47 million persons worldwide, mostly elderly
  - Projected to affect 131 million by 2050
- Dementia = enormous and rapidly growing public health and societal burden worldwide
  →urgent need for more effective approaches to address

Alzheimer's Disease International 2015

JAMA | Review

Diagnosis and Management of Dementia: Review

Zoe Arvanitakis, MD, MS; Raj C. Shah, MD; David A. Bennett, MD

JAMA 2019

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A potentially modifiable risk factor for dementia: DIABETES MELLITUS (DM)

- Epidemiology of DM in the US:
  - 7th leading cause of death (CDC)
  - Associated with significant medical, psychological, and societal costs
  - Very common, especially with aging: affects 1/5 older persons
  - Increasingly common
  - Potential times of intervention at all stages: no insulin resistance (normal), pre-diabetes stage, and frank diabetes (especially if early stage)

- Clinical data linking DM with
  - Cognitive impairment and cognitive decline
  - More recent large epidemiologic studies consistently showing there is a **TWO-FOLD increased risk of dementia**

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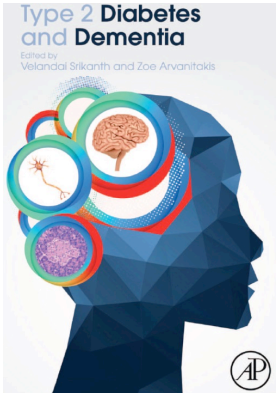
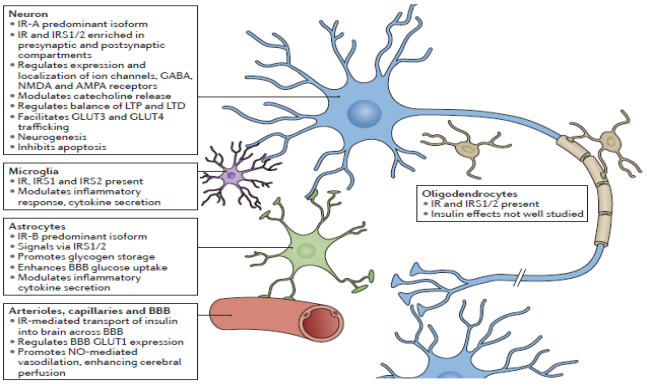
Textbook and reviews on diabetes, brain insulin resistance, Alzheimer's disease, neuropathology



Academic Press: Elsevier 2018

Brain Insulin Resistance in Type 2 Diabetes and Alzheimer's Disease: Concepts and Conundrums



Nature Reviews Neurology 2018

Nature Reviews | Neurology

F1000Research F1000Research 2016, 5:253 Last updated: 03 JUN 2016

REVIEW

REVISED **Complex mechanisms linking neurocognitive dysfunction to insulin resistance and other metabolic dysfunction [version 2; referees: 2 approved]** F1000Res 2016

Relationship of Type 2 Diabetes to Human Brain Pathology

Neuropath Applied Neurobiol 2018

Diabetes Therapies for Dementia

Current Neurology Neurosci Reports 2019

The Relation of Diabetes to Memory Function

Current Neurology Neurosci Reports 2020

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OBJECTIVE: To elucidate the relation of

diabetes and insulin resistance
to
brain structure and function (cognition)

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Methods:
RADC cohorts and data

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Cohorts at the Rush Alzheimer's Disease Center (RADC)

Select Rush prospective, longitudinal, clinical-pathologic, community-based cohort studies of aging:

- Religious Orders Study (ROS)
- Rush Memory and Aging Project (MAP)
- Minority Aging Research Study (MARS)

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Religious Orders Study (ROS)

- Began in 1993
- Funded by the National Institute on Aging
- > 1,497 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 29 time points
  - > 430 persons have developed dementia
- All agreed to brain donation at the time of death
  - > 90% autopsy rate with > 876 brain autopsies

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Memory and Aging Project (MAP)

- Began in 1997
- Funded by the National Institute on Aging
- > 2,275 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 25 time points
- All agreed to donate brain, spinal cord, muscle, and nerve at the time of death
  > 85% autopsy rate with > 1033 brain autopsies

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The Minority Aging Research Study (MARS)

- Began in 2004
- Funded by the National Institute on Aging
- > 816 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

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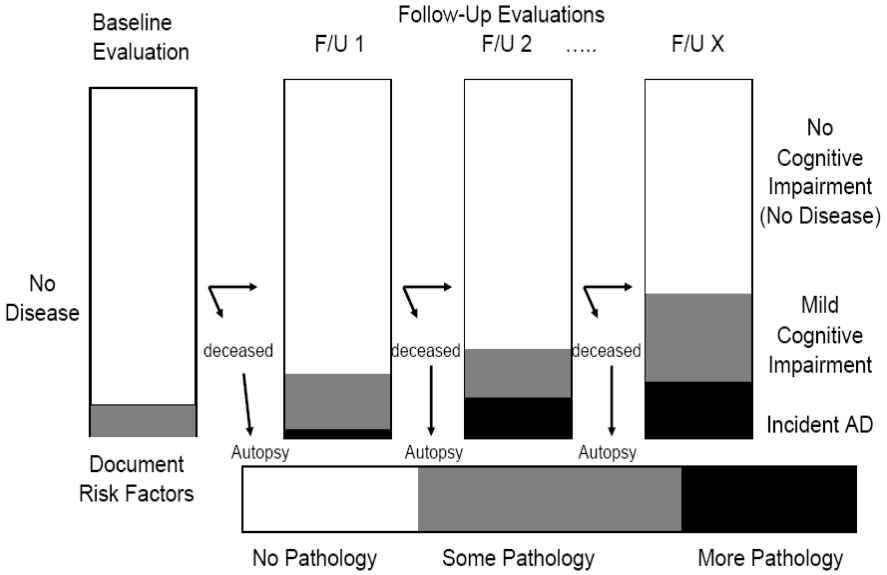
The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort

Bennett DA et al., Neuroepidemiology 2005



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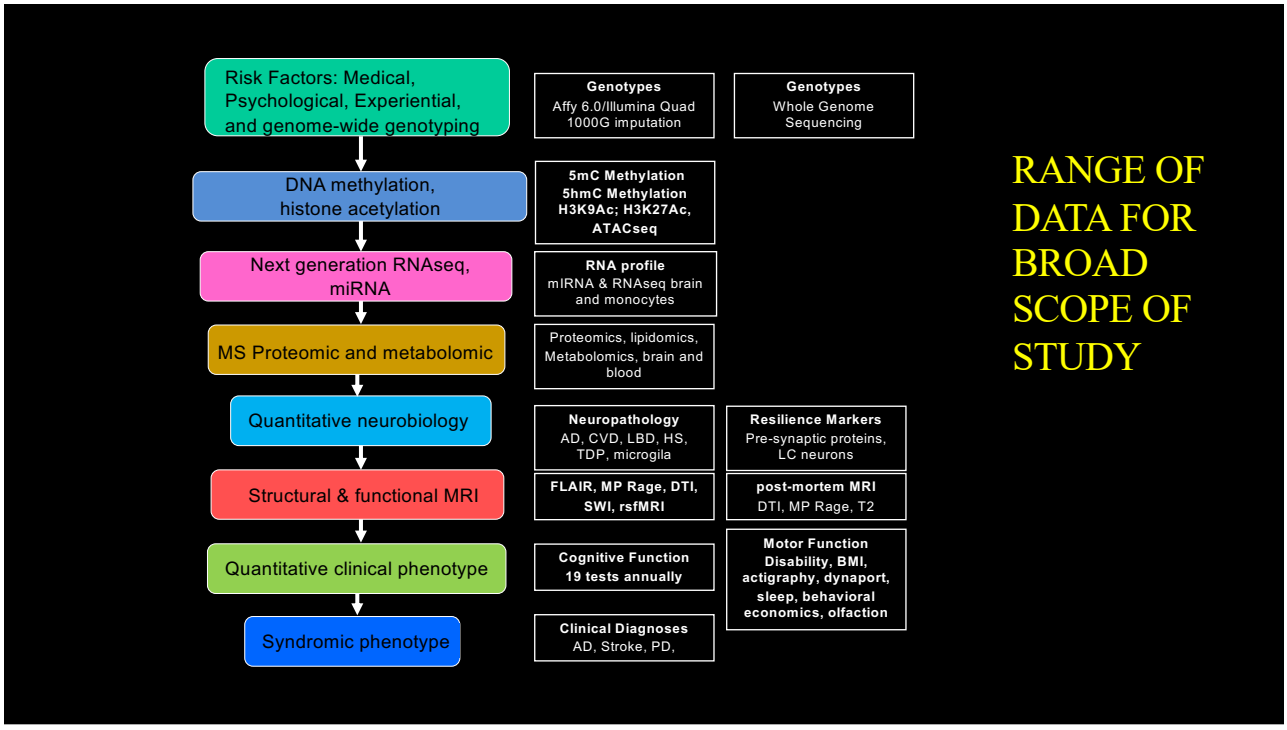

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Neuropsychological tests	ROS	MAP	MARS
MMSE	X	X	X
Complex Ideational Material	X	X	X
Episodic Memory			
Logical Memory Ia	X	X	X
Logical Memroy IIa	X	X	X
East Boston Story Immediate recall	X	X	X
East Boston Story Delayed recall	X	X	X
Word List Memory	X	X	X
Word List Recall	X	X	X
Word List Recognition	X	X	X
Semantic Memory			
Boston Naming Test	X	X	X
Verbal Fluency	X	X	X
National Adult Reading Test	X	X	
Working Memory			
Digit Span Forward	X	X	X
Digit Span Backward	X	X	X
Digit Span Ordering	X	X	X
Perceptual Speed			
Symbol Digit	X	X	X
Number Comparison	X	X	X
Stroop Word Reading		X	X
Stroop Word Color Naming		X	X
Visuospatial Ability			
Line Orientation	X	X	X
Progressive Matrices	X	X	X

COMPOSITE MEASURES:

Global Cognition
- Episodic Memory
- Semantic Memory
- Working memory
- Perceptual speed
- Visuospatial ability

CLINICAL DIAGNOSES:

Dementia
Alzheimer's disease
Mild cog impairment

Wilson et al., Psych Aging 2002
Barnes et al., JINS 2016

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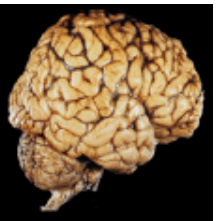
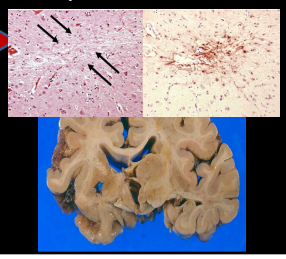
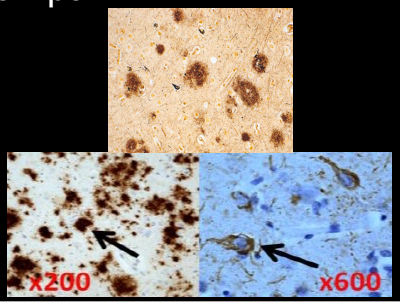
Neuropathology



- Standardized procedure, blinded to clinical data
  - mean post-mortem interval = 8 hrs
- Alzheimer's disease (level, diagnostic criteria)
- Other common pathologies, including
  - Neurodegenerative (Lewy bodies, hippocampal sclerosis, LATE, other)
  - Vascular
  - Other





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Diabetes (DM) data in RADC cohorts

- Assessed at baseline and annually by
  - medical history (4 questions), and
  - visual inspection of all medications (which identify use of insulin and oral hypoglycemic agents) which are recorded and coded using MediSpan
- HbA1c in blood started being collected in 2008
- Sister studies collect additional related measures in the human brain, blood, and muscle

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Select results on diabetes, cognition, and neuropathology

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Diabetes, cognitive impairment, cognitive decline, and incident dementia

Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function	Archives Neurol 2004
Diabetes and Function in Different Cognitive Systems in Older Individuals Without Dementia	Diabetes Care 2006
Diabetes and Cognitive Systems in Older Black and White Persons	ADAD 2010
Cognitive Decline Following Incident and Pre-Existing Diabetes Mellitus in a Biracial Population Study	Neurology 2016
Is Midlife Metabolic Syndrome Associated With Cognitive Function Change? The Study of Women's Health Across the Nation	J Clin Endocrinol Metab 2020

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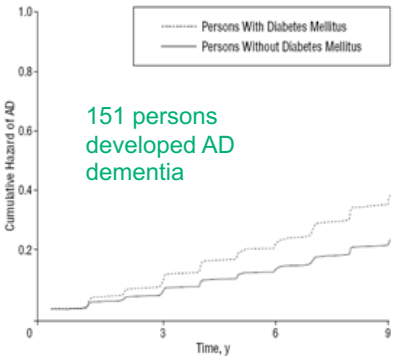
Diabetes, dementia risk, cognitive decline

Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function

Archives Neurol 2004
Subjects from ROS



151 persons developed AD dementia

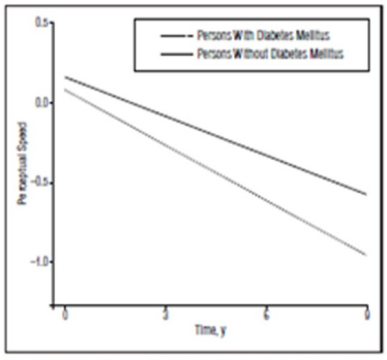


Figure 2. Predicted 9-year paths of change in perceptual speed in typical participants with and without diabetes mellitus.

Proportional hazards model adjusted for age, sex, and educational level, those with diabetes mellitus had a 65% increase in the risk of developing AD compared with those without diabetes mellitus
HR = 1.65; 95% CI: 1.10-2.47

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Diabetes and neuropathology

Diabetes is related to cerebral infarction but not to AD pathology in older persons	Neurology 2006
Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology	Alz&Dem 2016
Diabetes, Hemoglobin A1c, and Regional Alzheimer's Disease and Infarct Pathology	ADAD 2017
Diabetes is Not Associated with Alzheimer's Disease Neuropathology	JAD 2017
Association of Hemoglobin A1C With TDP-43 Pathology in Community-Based Elders	Neurology 2021

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Brain insulin signaling, Alzheimer's disease pathology, and cognitive function

R01 NS084965 (BIRA)

Ann Neurol 2020
Subjects from ROS

Table 1. Characteristics of subjects by diabetes status*

	Total n =150	Diabetes n =75	No Diabetes n =75
DEMOGRAPHIC			
Age-at-death, years (SD)	86.6 (6.1)	86.6 (5.9)	86.7 (6.3)
Women, n (%)	72 (48%)	36 (48%)	36 (48%)
Education, years (SD)	18.1 (3.3)	18.2 (3.1)	18.1 (3.4)
COGNITIVE SCORE**			
Global cognitive function score	-0.871 (1.203)	-0.920 (1.183)	-0.822 (1.229)
Perceptual speed	-1.229 (1.202)	-1.341 (1.186)	-1.117 (1.215)
Working memory	-0.607 (1.028)	-0.650 (1.047)	-0.564 (1.015)
Episodic memory	-0.828 (1.465)	-0.876 (1.459)	-0.781 (1.48)
Semantic memory	-0.792 (1.367)	-0.779 (1.268)	-0.804 (1.468)
Visuospatial ability	-0.668 (0.940)	-0.640 (0.914)	-0.697 (0.97)
NEUROPATHOLOGIC			
Alzheimer's disease pathology			
Global score, median (SD)	0.6 (0.6)	0.7 (0.6)	0.6 (0.5)
Amyloid score, median (SD)	1.6 (0.2,4.5)	2 (0.3,5.3)	1.4 (0.2,4.1)
Tangles score, median (SD)	3.2 (1.2,7.4)	3.5 (1.1,7.8)	2.7 (1.2,7)

*Mean (SD), unless otherwise specified
**Cognitive data proximate-to-death

RESULTS

While no other molecular measures were significant, brain pT^{308} AKT1/total AKT1 (by ELISA) was associated with

More AD pathology:
- Global measure
- Amyloid burden
- Tangle density

Lower cognition:
- Global cognition (proximate to death)

Subjects with and without diabetes were matched by age and sex (n= 150)

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Overall

LIMITATIONS

- Diabetes not well characterized
- Conditions are complex (metabolic syndrome)
- Pathophysiologic mechanisms linking diabetes to dementia needs further elucidation, including mediation effects
- Observational study with cross-sectional design does not establish causation

STRENGTHS

- Prospective design with up to 29 years of annual follow-up in large cohorts of community-dwelling older persons
- High follow-up rates (90-95% range)
- Detailed neuropsychologial test data with summary measures of global cognition/domains, and dementia classification
- High autopsy rates (85-90% range), with systematically-collected neuropathologic data

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Works in Progress

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Peripheral and central (brain) insulin signaling

RF1 AG059621 (PABIR) (data collection ongoing)

- Overall goal:
  - to examine associations of peripheral (serum, muscle) with central (brain) insulin resistance, and
  - the associations of peripheral and central insulin resistance with AD neuropathology and cognitive function
- Design: Using MAP biospecimens and data, collect ELISA measures and untargeted proteomics and phosphoproteomics, and other measures

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Metformin, cognitive function, and brain pathology

R01 NS084965 (BIRA) and RF1 AG059621 (PABIR)

(Sood A. et al., manuscript in preparation)
Subjects from ROSMAPMARS

	Total		Non metformin users		Metformin users	
	All	Autopsy	All	Autopsy	All	Autopsy
CHARACTERISTIC	n=4126	n=1715	n=3637	n=1574	n= 489	n=141
Demographics						
Age at bl, years	77.36	80.13	77.82	80.38	73.96	77.31
(+/- SD)	(7.74)	(7.03)	(7.71)	(6.93)	(7.09)	(7.50)
Men, n	1084	544	923	483	161	61
(%)	(26%)	(32%)	(25%)	(31%)	(33%)	(43%)
Education, years	16.15	16.30	16.23	16.36	15.55	15.54
(+/- SD)	(3.71)	(3.59)	(3.63)	(3.57)	(4.21)	(3.81)
Clinical variables at baseline						
Diabetes, n	638	213	282	126	356	87
(%)	(15%)	(12%)	(8%)	(8%)	(73%)	(62%)
History of hypertension, n	2232	815	1892	730	340	85
(%)	(54%)	(48%)	(52%)	(46%)	(70%)	(60%)
Medications use at baseline						
Insulin, n	116	49	73	36	43	13
(%)	(3%)	(3%)	(2%)	(2%)	(9%)	(9%)
Oral hypoglycemic, n	370	112	96	49	274	63
(%)	(9%)	(7%)	(3%)	(3%)	(56%)	(45%)

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Metformin, cognitive function, and brain pathology

(Sood A. et al., manuscript in preparation)
Subjects from ROSMAPMARS

RESULTS

In total samples of 4126 older persons followed annually for a mean of 8.2 years, metformin users had (compared to non-users):

- a lower baseline level of global cognition (estimate= -0.067, SE=0.028, p=0.018)
- improving cognition over time (estimate= 0.0114, SE=0.0055, p=0.0401)

Autopsy subset of 1715 deceased persons (average age at death 89.6 years), we found in metformin users vs not:

- no difference in AD pathology
- for CVD pathology: less atherosclerosis (estimate= -0.505, SE= 0.165, p=0.002) and increased subcortical infarcts (estimate 0.484, SE= 0.171, p=0.005)

CONCLUSIONS: Complex relation of metformin with brain health (cognition and pathology)

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Epigenetic marker

RF1 AG074549 (REVA)

- Overall goal: to elucidate epigenetic mechanisms linking vascular risk factors (DM, BP, and BMI) to AD/ADRD clinical and pathological phenotypes, in older Whites and Blacks
- Design: discovery and validation of 5hmC scores in serum and brain, elucidation of biologic pathways and racial differences in DM and dementia (using MAP and MARS cohorts)

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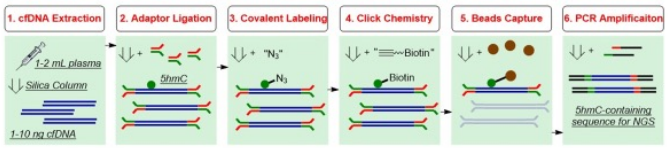
Feasibility study: Genome-wide Mapping Implicates 5-Hydroxymethylcytosine (5hmC) in Diabetes Mellitus (DM) and Alzheimer's Disease (AD)

(Beadell A. et al., manuscript in preparation)
Subjects from MAPMARS

METHODS:

- **80 deceased MAP individuals across four groups: AD-only (neuropathologically defined), DM-only (clinically defined), AD with DM (AD+DM), and non-AD/non-DM controls**
- **5hmC-Seal: a highly sensitive chemical labeling technique we developed, which pulls down 5hmC containing DNA fragments, and uses NGS to capture the t5hmC signals on the genome**
- **Genome-wide profiling of 5hmC in circulating cell-free DNA (cfDNA) from antemortem serum samples and brain tissue genomic DNA (gDNA) from postmortem prefrontal cortex tissue**
- **Differential analysis and machine learning (elastic net regularization and multivariate logistic regression) to explore whether 5hmC might be implicated in DM-associated AD, and which biological pathways are involved**

Summary of nano-hmC-Seal steps to measure 5hmC in cfDNA



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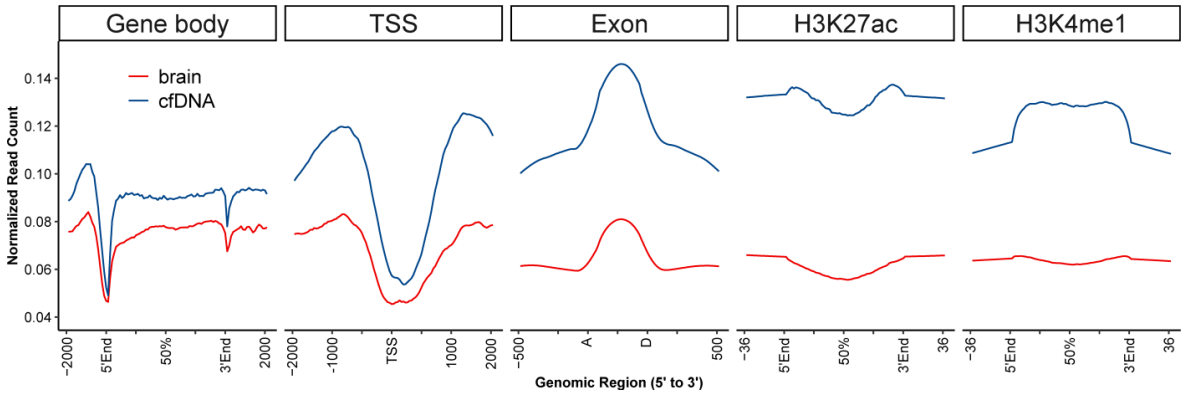
Overview of the capture of 5hmC



5hmC in both serum (cfDNA) and brain (gDNA) has gene regulatory relevance:
-most captured 5hmC fragments are enriched in the gene bodies, relative to the flanking regions
-the captured 5hmC fragments are co-localized with two histone modification (enhancer) marks

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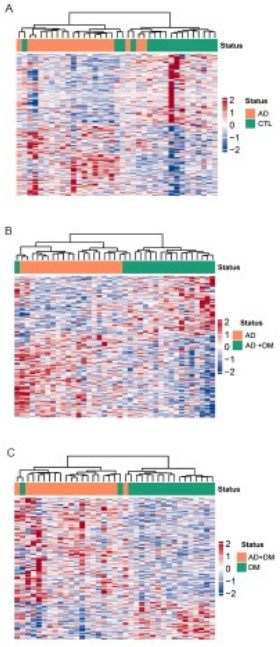
Differential analysis

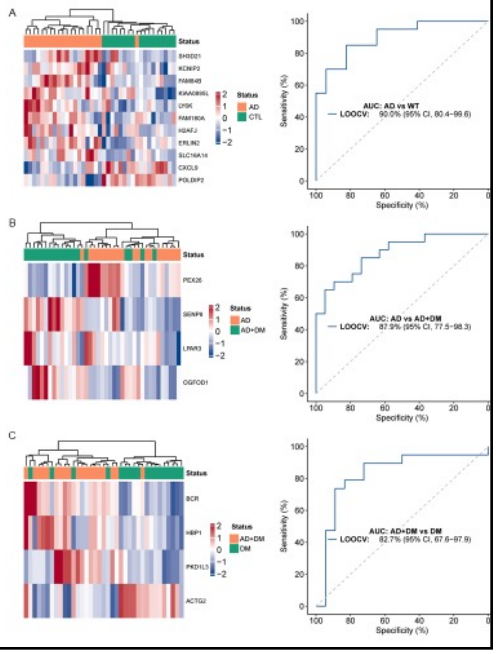
RESULTS
cfDNA

Modeling



Machine learning

Elastic net regularization and multivariable logistic regression with the LOOCV (leave-one-out cross-validation) approach



5%FDR

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Conclusions

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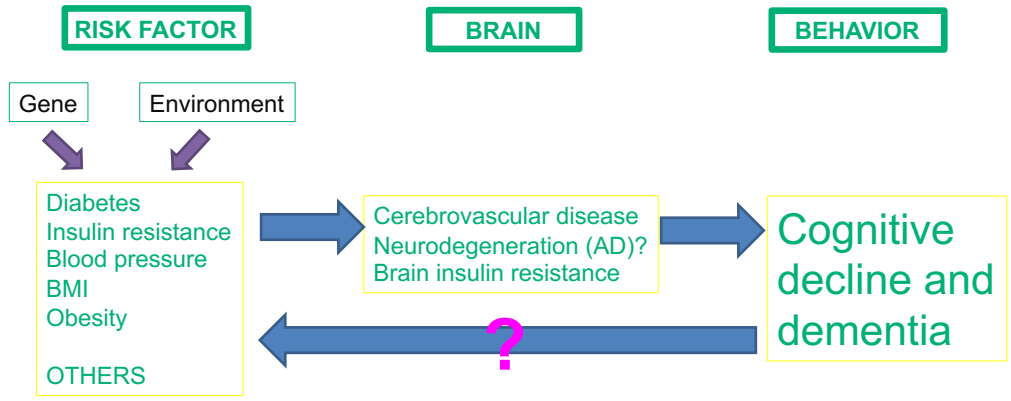
Overly simplified conceptual framework



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Future directions

- Disentangle underlying mechanisms of dementia using these and other techniques, including
  - genetic, epigenetic, -omics, and other state of the science methods
  - environmental (exposome), social determinants of health, racioethnic and other factors with qualitative and quantitative methods
- Identify therapeutic targets and test treatments and prevention approaches (clinical trials)
- Need integrative approaches

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Question for the audience:

Looking for a position to work with human biospecimens and data?

Postdoc, Research Scientist, and other positions available

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https://www.radc.rush.edu/

The Rush Alzheimer's Disease Center (RADC), one of 29 Alzheimer's disease (AD) Research Centers across the country designated and funded by the National Institute on Aging (NIA), is dedicated to supporting research about the cause, treatment, and prevention of AD, other dementias, and a range of other common chronic conditions of aging. The many RADC studies generate an enormous variety of unique data and biospecimens to support this effort. RADC faculty and staff are committed to sharing these resources with the wider aging and AD research community to accelerate the pace at which new knowledge is created for the treatment and prevention of dementia and other age-related chronic neurologic conditions, and have distributed data across the United States and the world.

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