The association of pathology patterns and AD risk: with and without imputing pathology data

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Outline

• SMART (Statistical Modeling of Aging and Risk of Transition) study data sets
• Research question
• Brief explanation of Imputation methods used in this project
• Results
Statistical Modeling of Aging and Risk of Transition study (SMART)

• PIs: Fred Schmitt & Dick Kriscio (Kentucky)

• NIA R01AG386561 (2011-2016)

• A consortium of 11 different high-quality longitudinal studies of aging and cognition (N=11,541 participants)
MAPWU/Memory and Aging Project (Washington University)

OBAS/ Oregon Brain Aging Study I & II + AADAPt/African American Dementia and Aging Project + KEAP/Klamath Exceptional Aging Project (Oregon Health & Science University)

BRAiNS/Biologically Resilient Adults in Neurological Studies (Kentucky)

HAAS/Honolulu Asia Aging Study (Kuwakini Medical Center)

ROS/Religious Orders Study + MAPRU /Memory and Aging Project (Rush University)

Nun study (U. of Minnesota)

EAS/Einstein Aging Study (Yeshiva University)
Data: Statistical Modeling of Aging and Risk of Transition study (SMART)

- **Community samples**, not clinical samples (i.e., more representative of **mixed pathologies**, not limited to pure AD pathology). Ideal for characterizing risk and protective factors associated with subtypes of age-associated **mixed neuropathologies**
- **Over 6000 death**
- **Over 3000 autopsies** (but not all pathology variables available)

Research Question

Contribution of vascular factors on incidence of clinically diagnosed AD

How much additional risks are contributed by pathology-confirmed vascular factors, beyond definitive AD pathology, in developing clinically diagnosed AD
Background

- For a given level of AD pathology in the brain, the greater the number of cerebrovascular lesions, the greater the likelihood of clinically significant cognitive impairment / dementia
Population Attributable Risk (PAR): Risk of dementia could be reduced by 10.8% by eliminating overt cerebrovascular disease (stroke/TIA), and the risk of AD by 9.1%.
Objective

To examine the risk of incident AD associated with **pathology-confirmed presence** of vascular factors: lacunes (small artery infarcts) and one or more large artery cerebral infarct(s).

(Could also add, e.g., atherosclerotic vascular pathology (npavas), subcortical arteriosclerotic leukoencephalopathy (npart), hemorrhages (nphem) )
Inclusion Criteria in the Current Study

Due to the limitation in harmonization of some autopsy variables, the following 6 cohorts were used in the current analyses.

- MAPWU/Memory and Aging Project (Washington University)
- OBAS/ Oregon Brain Aging Study I & II + AADAPt/African American Dementia and Aging Project + KEAP/Klamath Exceptional Aging Project (Oregon Health & Science University)
- BRAiNS/Biologically Resilient Adults in Neurological Studies (Kentucky)
- ROS/Religious Orders Study + MAPRU /Memory and Aging Project (Rush University)

Inclusion criteria: normal cognition at baseline with Apoe4 information
AD definitive pathology (ADDP) was defined as having frequent or moderate neuritic plaques scores, or Braak& Braak neurofibrillary stage ≥ 5

6 pathology patterns:
1) ADDP only,
2) lacunes without ADDP,
3) ADDP and lacunes,
4) large infarcts without ADDP,
5) ADDP and large infarct(s) with or without lacunes,
6) no ADDP or vascular pathologies (control group). (LB pathology—controlled)
Approach
**MAR assumption?**
Among those with normal at baseline, apoe 4 information

<table>
<thead>
<tr>
<th>Mean (std)</th>
<th>With autopsy variables of our interests N=1054</th>
<th>Missing autopsy N=512</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at death</td>
<td>88.5 (7.26)</td>
<td>89.49 (7.31)</td>
<td>0.119</td>
</tr>
<tr>
<td>Women (%)</td>
<td>63.1</td>
<td>61.3</td>
<td>0.015</td>
</tr>
<tr>
<td>Years of Education</td>
<td>15.9 (3.43)</td>
<td>14.38 (3.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apoe*4 (at least one e4 allele, %)</td>
<td>22.1</td>
<td>22.8</td>
<td>0.523</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>7.84 (4.72)</td>
<td>6.92 (5.14)</td>
<td>0.017</td>
</tr>
<tr>
<td>Duration from the last assessment to death</td>
<td>0.95 (1.29)</td>
<td>1.82 (2.22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*: p-values are based on a logistic regression model (outcome=having autopsy data or not), including all variables in this table in the model
Why impute?

ADVANTAGE
• Increase power
• Reduce estimation bias
  e.g. 1: Autopsy cases—younger than general age of death → over-represent the pathology-cog association among younger group
  e.g. 2: Those who die with mixed pathologies might live longer → their death = less likely to be included in the autopsy sample → under-represent the pathology-cog association among those died with mixed pathologies
Why impute?

ALTERNATIVE APPROACHES

Use weights

✓ good for marginal representation, but not good for “associations”

✓ Wasting a lot of information available
MAR Assumption
Limitation

| X     | Y     | MAR: X is always observed and $\Pr(Y \text{ is observed}|X_{obs},Y_{obs},Y_{mis}) = \Pr(Y \text{ is observed}|X_{obs},Y_{obs})$ |
|-------|-------|-----------------------------------------------------------------------------------------------------------------------------------|
| observed | observed | $\Pr(Y_{mis}|X_{obs}) = \Pr(Y_{obs}|X_{obs})$                                                                                                                                 |

MAR assumption limitation suggests that the probability of observing $Y$ given $X$ is observed and $Y$ is observed is equal to the probability of observing $Y$ given $X$ is observed, even when $Y$ is missing.

**Explanation:**
- **X** and **Y** are variables in a study.
- **observed** indicates that the variable is observed.
- **?** indicates that the variable is missing.
- The MAR assumption states that the probability of observing $Y$ given $X$ is observed and $Y$ is observed is equal to the probability of observing $Y$ given $X$ is observed, even when $Y$ is missing.
Multiple Imputation (MI)

• MI analysis has many desirable advantages over other missing data analysis methods (e.g. weighting) for our data

• The assumption for missingness in our data is missing at random (MAR, Rubin 1976). We have evidence showing that the missing completely at random (MCAR) assumption is not satisfied.
## Data with Missing Values

<table>
<thead>
<tr>
<th>Pathology Variables from Autopsy</th>
<th>Clinical Diagnosis from Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully Observed Variables*</td>
<td></td>
</tr>
<tr>
<td>Large Infarct (Y/N?)</td>
<td>Age at MCI Onset</td>
</tr>
<tr>
<td>Lacunar Infarct (Y/N?)</td>
<td>Age at General Dementia Onset</td>
</tr>
<tr>
<td>ADDP (Y/N?)</td>
<td>“Dementia = AD?” at Dementia Onset</td>
</tr>
<tr>
<td>Lewy Body (Y/N?)</td>
<td>Age at AD Onset</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>observed</th>
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</tr>
</tbody>
</table>

* Fully observed variables: Gender, Education, Age at death, Clinical diagnosis at last available survey, Participants survey duration, Participants duration between end of survey and death, etc.
Challenges for MI Modeling

• Different types of variables: binary, continuous, or even survival variables

• Boundary restrictions: e.g., imputed age at dementia onsets must be later than last normal clinical diagnosis date, or normal dx does not come after observed or imputed AD onset age

• Logical restrictions: e.g., only those with dementia onset need additional imputed AD onset date (if participants were AD demented at that time, then AD onset date is equal to general dementia onset date)
Sequential Regression Multiple Imputation (SRMI)

- We adopt a sequential regression multiple imputation (SRMI, Raghunathan et al 2001) approach, also known as multivariate imputation by chained equations (MICE, van Buuren 2011), to impute the missing values.
- The SRMI approach uses an iterative algorithm with a sequence of fully conditionally specified models (similar to Gibbs samplers but with key differences).
- It’s particularly useful in our study as it can easily handle the challenging features.
- Algorithm convergence need to be closely monitored due to SRMI’s theoretical weakness (no joint distribution proposed).
The First Iteration
Fill missing values with initially imputed values

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</tr>
<tr>
<td>Lewy Body</td>
<td>Age at AD onset</td>
</tr>
</tbody>
</table>

* Fully observed variables: Gender, Education, Age at death, Last clinical diagnosis, Participants survey duration, Participants duration between end of survey and death, etc.
SRMI Model Specification for iteration \( t \geq 2 \)

- Pathology variables (4 binary variables)
  
  - \( m_1(\text{Large Infarct} \mid \text{Predictors}, \theta_1) \) -- logistic regression with covariates: Lacunar Infarct, ADDP, Lewy body, Apoe4, last available clinical diagnosis, gender, education, age at death, survey duration, survey end to death duration, age at MCI onset, age at dementia onset, age at AD onset
  
  - \( m_2(\text{Lacunar Infarct} \mid \text{Predictors}, \theta_2) \) -- logistic regression with covariates: Large Infarct, ADDP, Lewy body, Apoe4, last available clinical diagnosis, gender, education, age at death, survey duration, survey end to death duration, age at MCI onset, age at dementia onset, age at AD onset
  
  - \( m_3(\text{ADDP} \mid \text{Predictors}, \theta_3) \) -- logistic regression with covariates: Large Infarct, Lacunar Infarct, Lewy body, Apoe4, last available clinical diagnosis, gender, education, age at death, survey duration, survey end to death duration, age at MCI onset, age at dementia onset, age at AD onset
  
  - \( m_4(\text{Lewy Body} \mid \text{Predictors}, \theta_4) \) -- logistic regression with covariates: Large Infarct, Lacunar Infarct, ADDP, Apoe4, gender, education, age at death, survey duration, survey end to death duration, age at MCI onset, age at dementia onset, age at AD onset
SRMI Model Specification
for iteration $t \geq 2$

- Clinical variables (3 continuous and 1 binary)
  - $m_5(\text{MCI age of onset}|\text{Predictors}, \theta_5)$ – linear regression with covariates: Large Infarct, Lacunar Infarct, ADDP, Lewy body, Apoe4, gender, education, age at death, survey duration, survey end to death duration
  - $m_6(\text{General Dementia Onset}|\text{Predictors}, \theta_6)$ – linear regression with covariates: Large Infarct, Lacunar Infarct, ADDP, Lewy body, Apoe4, gender, education, age at death, survey duration, survey end to death duration
  - $m_7(\text{Dementia type=AD?}|\text{Predictors}, \theta_7)$ – logistic regression with covariates: Large Infarct, Lacunar Infarct, ADDP, Lewy body, Apoe4, gender, education, age at death, survey duration, survey end to death duration, age at MCI onset, age at dementia onset
  - $m_8(\text{AD age of onset}|\text{Predictors}, \theta_8)$ – linear regression with covariates: Large Infarct, Lacunar Infarct, ADDP, Lewy body, Apoe4, gender, education, age at death, survey duration, survey end to death duration
Imputing missing values for Large Infarct at the $t$th iteration

$m_1(\text{Large Infarct}|\text{updated predictors}, \theta_1)$ is fit, and $\theta_1(t)$ is drawn from its approximate posterior distribution.

<table>
<thead>
<tr>
<th>Large Infarct</th>
<th>Other Variables (updated at (t-1)th iteration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>observed</td>
<td>observed+Imputed(t-1)</td>
</tr>
<tr>
<td>?</td>
<td>observed+Imputed(t-1)</td>
</tr>
</tbody>
</table>

Missing values are drawn from $m_1(\text{Large Infarct}|\text{updated predictors}, \theta_1(t))$.
Imputing missing values for Lacunar Infarct at the $t$th iteration

$m2(\text{Lacunar Infarct} | \text{updated predictors}, \theta_2)$ is fit, and $\theta_2(t)$ is drawn from its approximate posterior distribution.

<table>
<thead>
<tr>
<th>Lacunar Infarct</th>
<th>Large Infarct (updated)</th>
<th>Other Variables (updated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>observed</td>
<td>observed+ Imputed(t)</td>
<td>observed+ Imputed(t-1)</td>
</tr>
<tr>
<td>?</td>
<td>observed+ Imputed(t)</td>
<td>observed+ Imputed(t-1)</td>
</tr>
</tbody>
</table>

Missing values are drawn from $m2(\text{Lacunar Infarct} | \text{updated predictors}, \theta_2(t))$.
Monitoring Algorithm Convergence

• Parameters from M=5 replicates should all reach the same convergence point
last_group: 1-normal, 2-MCI and 3-dementia; so two parameters 2vs1 and 3vs1 were estimated
100 iterations X 5 times Overlaid
NPLAC_reg=glm(high_NPLAC~last_group+female+Age_at_Death+LEWY+apoe4+survey_duration+end_death_duration+EDUC+MCI_onset2+dementia_onset+high_NPLINF+new_ad_path,data=imp1[m_high_NPLAC==0,],family=binomial(),x=TRUE)
ad_reg=glm(new_ad_path~last_group+female+Age_at_Death+LEWY+apoe4+survey_duration+end_death_duration+EDUC+MCI_onset2+dementia_onset+high_NPLINF+high_NPLAC,data=imp1[m_new_ad_path==0,],family=binomial(),x=TRUE)
LEWY_reg=glm(LEWY~high_NPLINF+high_NPLAC+new_ad_path+
last_group+female+Age_at_Death+apoe4+survey_duration+end_death_duration+EDUC+
MCI_onset2+dementia_onset,data=imp1[m_LEWY==0,],family=binomial(),x=TRUE)
MCI_onset2_reg = \text{lm}(\text{MCI_onset2} ~ \text{high_NPLINF} + \text{high_NPLAC} + \text{new_ad_path} + \text{female} + \text{Age_at_Death} + \text{LEWY} + \text{apoe4} + \text{survey_duration} + \text{end_death_duration} + \text{EDUC}, \text{data} = \text{imp1[m_MCI_onset2==0,]}, \text{x} = \text{TRUE})

Imputed MCI_onset2 is drawn from the approximate posterior distribution truncated above last_normal so that the imputed value is meaningful.
dementia_onset_reg = lm(dementia_onset ~
high_NPLINF + high_NPLAC + new_ad_path + female + Age_at_Death + LEWY + apoe4 + survey_duration + end_death_duration + EDUC, data = imp1[m_dementia_onset == 0, ], x = TRUE)

Imputed dementia_onset is drawn from the approximate posterior distribution truncated above MCI_onset2 so that the imputed value is meaningful.
ad_onset_reg = lm(ad_onset ~ high_NPLINF + high_NPLAC + new_ad_path + female + Age_at_Death + LEWY + apoe4 + survey_duration + end_death_duration + EDUC, data = imp1[m_ad_onset == 0, ], x = TRUE)
POSSPROB_AD_reg=glm(POSSPROB_AD~high_NPLINF+high_NPLAC+new_ad_path+LEWY+female+Age_at_Death+apoe4+survey_duration+end_death_duration+EDUC+MCI_onset2+dementia_onset,data=imp1[m_POSSPROB_AD==0,],family=binomial(),x=TRUE)
Results of cox proportional hazard models (outcome=prob/poss AD)

(1) using only observed autopsy data (2) using observed and imputed data. Models controls for sex, education, Apoe 4 and Lewy body pathology. **: p < 0.0001, *: p<0.01

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (1)</th>
<th>Hazard ratio (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1054</td>
<td>N=1566</td>
</tr>
<tr>
<td>No ADDP, no Lacunes, no Large Infarcts</td>
<td>Reference Group</td>
<td>Reference Group</td>
</tr>
<tr>
<td>AD Definitive Pathology (ADDP)</td>
<td>4.01**</td>
<td>3.60**</td>
</tr>
<tr>
<td>Lacunes without ADDP</td>
<td>2.24*</td>
<td>1.93*</td>
</tr>
<tr>
<td>ADDP + Lacunes</td>
<td>3.50**</td>
<td>3.01**</td>
</tr>
<tr>
<td>Large infarct(s) without ADDP</td>
<td>1.83*</td>
<td>1.81*</td>
</tr>
<tr>
<td>ADDP with large infarct(s)</td>
<td>4.93**</td>
<td>3.96**</td>
</tr>
</tbody>
</table>
Conclusions

• Strong association between missing pathology data and observed variables → MAR assumption (or informal dropout—this cannot be proved statistically)

• By using imputed pathology data, the association between pathology types and incidence of AD gets weaker for all pathology types (especially for ADDP)

• Possibly because those who go through autopsy are more likely to be those with diseases (AD or AD with other diseases)---using observed autopsy cases might be overestimating the risk of AD in relation with pathology types. (Some individuals who remained cognitively intact might be less likely to do autopsy, given the same pathology types)
Special Thanks to:

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