Research using NACC Data

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Overview

- Research to date
- Recently published examples
  - ADC and non-ADC investigators
  - NACC researchers
- Lilah Besser's work using NACC data
  - "Mild cognitive impairment among Parkinson's disease subjects in the Uniform Data Set"
  - "Late life systolic blood pressure, body mass index, and heart rate, and Alzheimer's neuropathology among those without dementia before autopsy"

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Research to Date

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Frequency of NACC data requests

Number of requests by request type	Year					
	2009	2010	2011	2012	2013	2014
Proposals	26	30	73	54	58	59
All data files*	55	85	217	174	204	162
Table requests*	39	106	133	85	51	32

*Includes updating files with most recent data, adding variables, other adjustments, etc.

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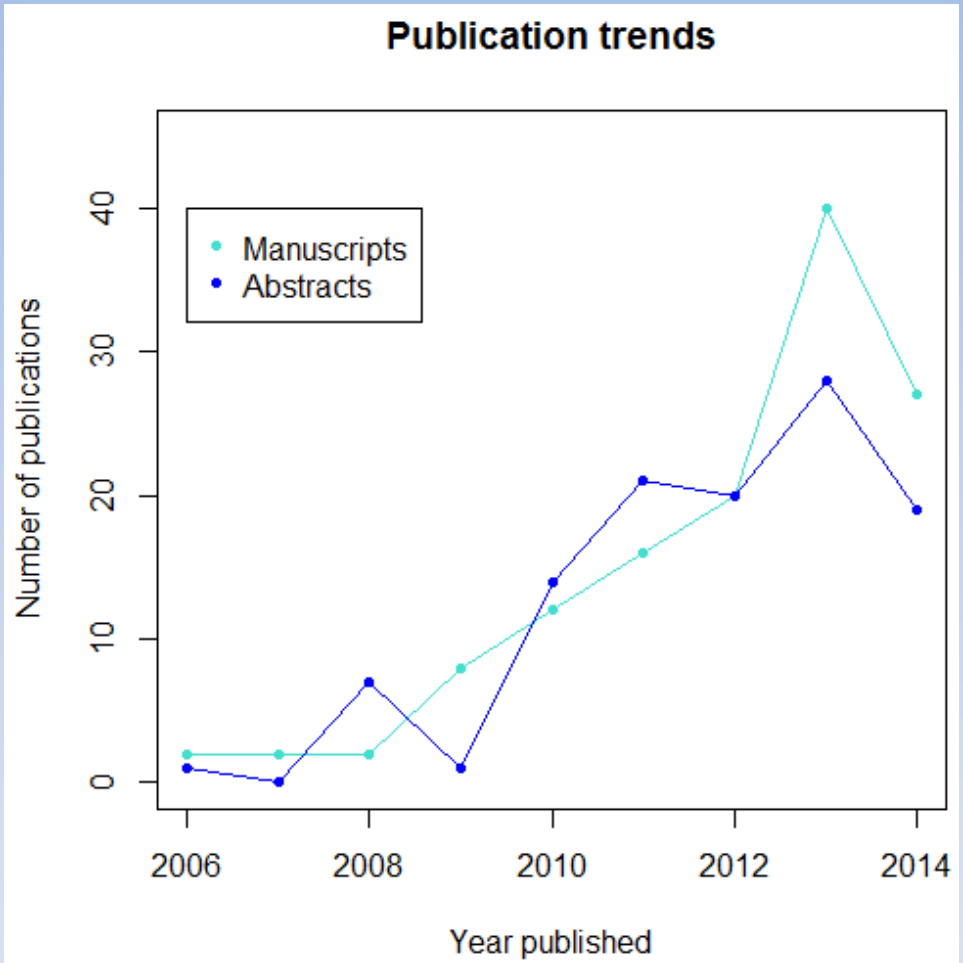
Manuscripts and abstracts



NOTE: Publications initiated by NACC staff (a NACC staff member is the first author) have been excluded.

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Research proposals using NACC data

Past trends

- rate of clinical progression and cognitive decline
- assessment of clinical criteria and guidelines
- neuropsychological test norms
- neuropsychiatric symptoms
- cross-sectional analyses
- dementia

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Research proposals using NACC data

Recent topics

- GWAS and genetic studies
- neuropsychological test composite scores
- vascular risk factors and pathology
- FTD syndromes
- longitudinal clinical-pathological correlation studies
- feasibility studies and sample size estimations
- preclinical Alzheimer's disease and MCI

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Recent examples using NACC data

ADC and non-ADC researchers

Toledo et al. (2013). *Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Center.* Brain 136(9): 2697-2706.

- CVD is a common co-pathology
- It more frequently occurs with AD than other neuropathologies
- Presence of CVD decreases threshold needed to have dementia symptoms
- Treating CVD can help delay onset of dementia

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Recent examples using NACC data

ADC and non-ADC researchers

Altmann et al. (2014). *Sex Modifies the APOE-Related Risk of Developing Alzheimer's Disease.* Ann Neurol 75(4): 563-573.

- NACC data: replicated findings that APOE e4 confers greater risk for AD for women than for men.
- ADNI data : In MCI, women with APOE e4 had higher levels of CSF total tau than men.

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Recent examples using NACC data
ADC and non-ADC researchers

Nelson et al (2014). *ABCC9 gene polymorphism is associated with hippocampal sclerosis of aging pathology.* Acta Neuropathol 127(6): 825-843.

- ABCC9 gene associated with hippocampal sclerosis
- NACC subjects using type of diabetes drug (sulfonylureas) known to modify ABCC9 protein function, were more likely to develop hippocampal sclerosis.

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Recent examples using NACC data

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- Gill et al, Alzheimers Dement. 2013; 9(5 Suppl); S63-71.
  - "Differences in rate of functional decline across three dementia types"
- Besser et al, ADAD 2014; 28(1): 36-43.
  - "Body Mass Index, Weight Change, and Clinical Progression in Mild Cognitive Impairment and Alzheimer Disease"
- Monsell et al, Neurology, 2014; 83(5):434-40.
  - "Neuropsychological changes in asymptomatic persons with Alzheimer disease neuropathology"

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Lilah Besser's Project #1:

MCI among Parkinson's disease subjects in the UDS

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MCI among Parkinson's disease subjects in the UDS

Besser, L; Monsell, S; Heller, K; Hawes, S; Mock, C; Zhou, A; Weintraub, S; Litvan, I; Kukull, W.

Aim 1: To compare demographics, clinical characteristics, and neuropsychological test scores between MCI-PD subjects and those with the most common MCI subtype, MCI due to Alzheimer's disease (MCI-AD).

Diagnosis groups	Mild cognitive impairment (MCI) definition
MCI-PD (PD with MCI by Petersen criteria)	MCI met Petersen criteria — initial UDS visit PD diagnosis — initial UDS visit Motor decline was first symptom No Alzheimer's disease (AD) — initial UDS visit
MCI-AD (MCI due to AD)	MCI met Petersen criteria — initial UDS visit Primary, probable AD dementia — UDS follow-up No PD/dementia with Lewy bodies (DLB) – any visit

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Aim 1 Methods

- UDS data from 16 Centers with MCI-PD subjects
- Unadjusted analysis comparing demographic and clinical characteristics
- Difference in mean neuropsychological test scores
  - 11 linear and logistic regression models
  - Bonferroni correction for multiple comparison, $p<.0045$
  - Covariates: age, sex, education, years since cognitive decline onset, and depression

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MCI-PD subjects in the UDS

- n = 136
- 54% amnestic
- 84% affected in multiple domains

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Demographic and clinical differences in MCI-PD and MCI-AD

Characteristic	MCI-PD (n=136)	MCI-AD (n=627)
Mean age at initial UDS visit (years)	69.9	75.4
Male	75%	47%
Depression	46%	30%
Visual or auditory hallucinations	23%	1%
REM sleep behavior disorder	19%	<1%
Anticholinergics	4%	1%
Amantadine	16%	<1%
Other dopaminergics	91%	1%
Antipsychotics	10%	<1%
Depression medication	46%	23%

All characteristics reported above were significantly different ($p<.05$) between the MCI-PD and MCI-AD group; Education, race, and CDR sum of boxes score were not significantly different between the two groups.

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Adjusted differences in test scores comparing MCI-PD and MCI-AD

Neuropsychological test	Score range	Estimate	95% CI
MMSE pentagon correct	0, 1	OR: 0.50	0.26, 0.93
Logical Memory Immediate	0-25	**Beta: 2.76***	1.79, 3.73
Logical Memory Delayed	0-25	**Beta: 4.10***	3.33, 4.86
Digit Span Forward length	0-8	Beta: 0.24	-0.01, 0.49
Digit Span Backward length	0-7	Beta: 0.06	-0.38, 0.49
Animals	0-77	Beta: 0.84	-0.51, 2.18
Vegetables	0-77	**Beta: 1.16***	0.51, 1.80
Boston Naming Test	0-30	Beta: 0.63	0.06, 1.21
Trail Making Test A	0-150	**Beta: 11.18***	5.02, 17.34
Trail Making Test B	0-300	**Beta: 37.49***	20.12, 54.87
WAIS-R Digit Symbol	0-93	Beta: -2.41	-4.53, -0.29

OR = odds ratio; 11 separate logistic or linear regression models (using GEE), all models adjusted for age at initial visit, sex, education, years since cognitive decline onset, and depression. * $p < 0.0045$ (Bonferroni correction)

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Aim 2

- To estimate and describe PD subjects in UDS who meet/do not meet Level 1 PD-MCI criteria proposed by the Movement Disorders Society (MDS, 2012).

Diagnosis groups	Mild cognitive impairment (MCI) definition
MCI-PD (PD with MCI by Petersen criteria)	**MCI met Petersen criteria — initial UDS visit** PD diagnosis at initial UDS visit Motor decline was first symptom No AD at initial UDS visit
PD-MCI (PD with MCI by MDS criteria)	**MCI met MDS Level 1 criteria (≥2 neuropsychological tests 1SD below norm) — initial UDS visit** PD diagnosis at initial UDS visit Motor decline was first symptom No AD at initial UDS visit

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Subjects meeting MDS PD-MCI Criteria

- 82% of MCI-PD subjects would be classified as PD-MCI according to new MDS Level 1 criteria
- Subjects who did NOT meet Level 1 criteria:
  - Better scores on many neuropsych tests (9%)
  - No neuropsychological test battery (9%)

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Next steps

- Consider ways of addressing how motor symptoms may have affected our findings.
- Compare longitudinal change in neuropsychological test scores in MCI-PD and MCI-AD subjects.

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Lilah Besser's Project #2:

Blood pressure, body mass index, and heart rate, and AD neuropathology among those without dementia

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Blood pressure, body mass index, and heart rate, and AD neuropathology among those without dementia

Besser; Ramirez-Gomez; Heller; Hawes; Zhou; Chui; Schneider; Kukull

- Aim: To examine, among subjects without dementia before death, whether average late-life body mass index (BMI), systolic blood pressure (SBP), and heart rate (HR) are associated with AD neuropathology at autopsy.

Diagnosis groups	Definition
Normal cognition (NC) N=204	Clinician diagnosis of NC at last UDS visit before death
Mild cognitive impairment (MCI) N=168	Clinician diagnosis of MCI at last UDS visit before death

Eligibility criteria

- Restricted to:
  - UDS subjects with autopsy data
  - 60 years or older at time of death
  - Two or more UDS visits before death
  - At least one visit within 3 years of death
  - No missing data on exposures (BMI, SBP, HR)

Exposures and Outcome

- Exposures: calculated over two or more UDS visits
  - Average systolic blood pressure (mmHg)
  - Average body mass index (kg/m^2)
  - Average heart rate (bpm)
- Outcome: AD neuropathology at autopsy
  - AD neuropath+
    - Braak stage III-IV, and
    - Moderate to frequent neuritic plaques
  - AD neuropath-
    - Braak stage 0-II, and
    - No or sparse neuritic plaques

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Methods

- Compare demographic, clinical, neuropathology characteristics in the AD neuropath+ and AD neuropath- groups
  - Separately by diagnosis group (NC, MCI)
- Unadjusted and adjusted logistic regression models (GEE accounting for Center clustering)
  - Examined association between continuous independent variables (SBP, BMI, and HR) and AD neuropath

Characteristics of NC subjects

Characteristic of Normal Cognition subjects	AD neuropath+	AD neuropath-
Sample size	N = 36	N = 168
Mean age	89 years	87 years
Mean number of UDS visits	3.6 visits	3.9 visits
Mean time between last UDS visit and autopsy	1.0 years	0.9 years
Global CDR **% with CDR = 0.0** **% with CDR = 0.5**	 **80.6%** **19.4%**	 **94.0%** **6.0%**
% reported smoking	**33.3%**	**53.6%**
% APOE e4 carrier	**28.1%**	**11.1%**
% with cerebral amyloid angiopathy NP	**35.3%**	**8.4%**

Characteristics that are bolded were significantly different ($p<.05$); Other characteristics that were examined and were not significantly different in AD neuropath + and - groups: education; race; sex; history of hypertension, diabetes, cardiovascular disease, stroke, hypercholesterolemia, thyroid disease, atrial fibrillation, pacemaker; antihypertensive and anti-lipid medication use; cerebrovascular, FTLD, Lewy body disease, and hippocampal sclerosis neuropathology at autopsy

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Characteristics of MCI subjects

Characteristic of MCI subjects	AD neuropath+	AD neuropath-
Sample size	n = 65	n = 103
Mean age (years)	88 years	88 years
Mean number of UDS visits	3.8 visits	4.0 visits
Mean time between last UDS visit and autopsy	**1.0 years**	**0.7 years**
% reporting cardiovascular disease	**38.5%**	**58.3%**
% APOE e4 carrier	**34.5%**	**16.3%**
% with cerebral amyloid angiopathy NP	**29.0%**	**7.8%**

Bolded characteristics were significantly different ($p<.05$); Other characteristics that were not significantly different in AD neuropath + and - groups: education; race; sex; history of hypertension, diabetes, stroke, hypercholesterolemia, thyroid disease, atrial fibrillation, pacemaker, smoking; antihypertensive and anti-lipid medication use; cerebrovascular, FTLD, Lewy body disease, and hippocampal sclerosis neuropathology at autopsy

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Vitals among NC and MCI subjects

Characteristic (averaged over ≥2 UDS visits)	NC AD neuropath+	NC AD neuropath-
Mean (SD) systolic BP (mmHg)	133.3 (18.9)	131.3 (17.3)
Mean (SD) body mass index (kg/m^2)	**24.3 (4.1)***	**26.8 (5.7)***
Mean (SD) heart rate (bpm)	69.3 (7.4)	71.3 (9.8)

Characteristic (averaged over ≥2 UDS visits)	MCI AD neuropath+	MCI AD neuropath-
Mean (SD) systolic BP (mmHg)	131.5 (13.7)	132.7 (14.3)
Mean (SD) body mass index (kg/m^2)	25.2 (4.4)	25.5 (4.2)
Mean (SD) heart rate (bpm)	**73.7 (9.5)***	**69.4 (7.3)***

BP: blood pressure; NC: Normal cognition

* $P < 0.05$

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Final multivariable model results

Characteristic	Model 1: NC OR (95% CI)	Model 2: MCI OR (95% CI)
Systolic BP (mmHg)	1.01 (0.98-1.03)	0.99 (0.97-1.02)
Body mass index (kg/m^2)	**0.90 (0.82-0.99)**	0.98 (0.89-1.09)
Heart rate (bpm)	0.97 (0.93-1.02)	**1.07 (1.04-1.11)**

BP=blood pressure; NC=Normal cognition; Covariates: death age, sex, education, number of UDS visits, reported diabetes, hypercholesterolemia, or atrial fibrillation; past/present anti-hypertensive use, time between last UDS visit and autopsy

Compared to NC subjects with BMI of 18.5, those with BMI of 24.9 have 50% decreased odds of AD neuropath (OR: 0.50, 95% CI: 0.27-0.93).

Compared to MCI subjects with a heart rate of 70, those with heart rate of 75 have 42% increased odds of AD neuropath (OR: 1.42, 95% CI: 1.19-1.70).

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Main findings

- Systolic blood pressure:
  - No association with AD neuropath in NC or MCI
- Lower body mass index:
  - Seems to be a clinical indicator for underlying AD neuropath in NC but not MCI
  - Published research consistent with our findings, but no known studies focused on those with NC or MCI
- Higher heart rate:
  - Potentially a novel indicator of underlying AD neuropath in MCI but not NC

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Conclusions

- NACC data:
  - Increased use by ADC and non-ADC investigators
  - Requested by investigators in 17 countries
  - Focus of the requests parallel dementia research trends
    - High profile studies using NACC data
  - NACC research scientists heavily use the data
    - We are able to advise others about the strengths and pitfalls of the data
- Lilah Besser's research:
  - Work-in-progress
  - Welcome feedback

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