Patient Preferences and Benefit-Risk Tradeoffs in Interception of Alzheimer's Disease

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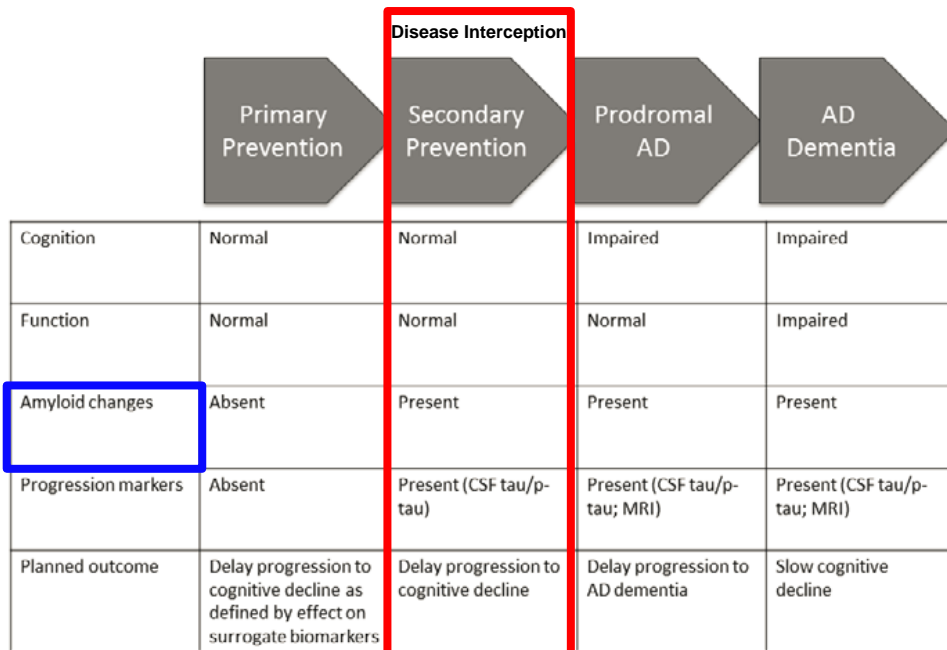
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- **The statements made in this presentation are those of the authors and not necessarily those of the company or institution that employ them.**

Alzheimer's Disease Stages & Intervention Points

Goal: Disease Modifying Therapies

Biomarkers inform risk and progression

	Primary Prevention	Secondary Prevention	Prodromal AD	AD Dementia
		Disease Interception		
Cognition	Normal	Normal	Impaired	Impaired
Function	Normal	Normal	Normal	Impaired
Amyloid changes	Absent	Present	Present	Present
Progression markers	Absent	Present (CSF tau/p-tau)	Present (CSF tau/p-tau; MRI)	Present (CSF tau/p-tau; MRI)
Planned outcome	Delay progression to cognitive decline as defined by effect on surrogate biomarkers	Delay progression to cognitive decline	Delay progression to AD dementia	Slow cognitive decline

Adapted from Cummings, *JPAD, Vol 4(2), 2017*

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Benefit-risk in Alzheimer's Disease Interception

- **Suppose a brain test shows that you will get Alzheimer's disease in 5-10 years. You are healthy now and have intact memory.**

- **A novel treatment can delay the onset of the disease by a few years, but there are side effects**

- **How tolerant are you to these side effects – to delay a disease that you may not live long enough to have?**

➔ **Patient preference study needed to assess this tradeoff**

Objectives

- **To quantify benefit-risk tradeoffs of interception therapy for Alzheimer's Disease (AD) among older adults**

- **To investigate heterogeneity of these expressed preferences**

Study and Survey Designs

- **US adults (n=1004) aged between 60 and 85, no current memory problems or diagnoses**
- **Discrete-choice experiment**
- **10 trade-off questions**
  ‣ Participants are told to assume they <u>will</u> develop Alzheimer's Disease based on a biomarker
  ‣ Choice between treatment or no treatment
  ‣ Remaining lifespan shown

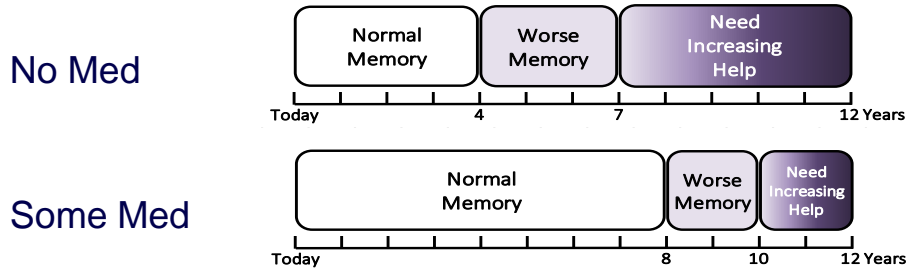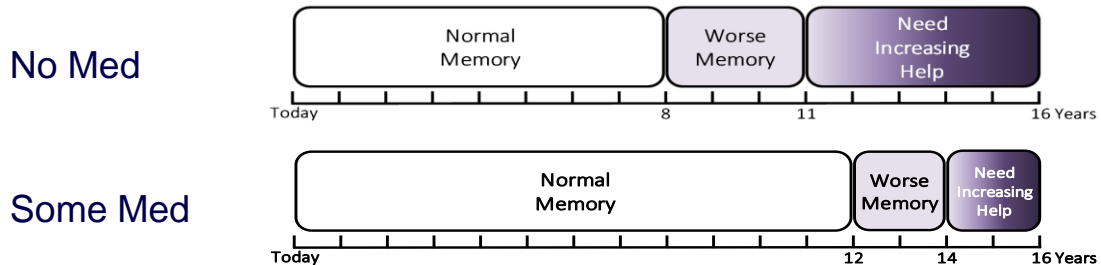# Status Quo: Remaining Life and AD

12-year Version

No Med

Normal Memory | Worse Memory | Need Increasing Help

Today — 4 — 7 — 12 Years
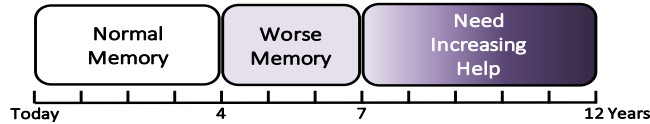
16-year Version

No Med

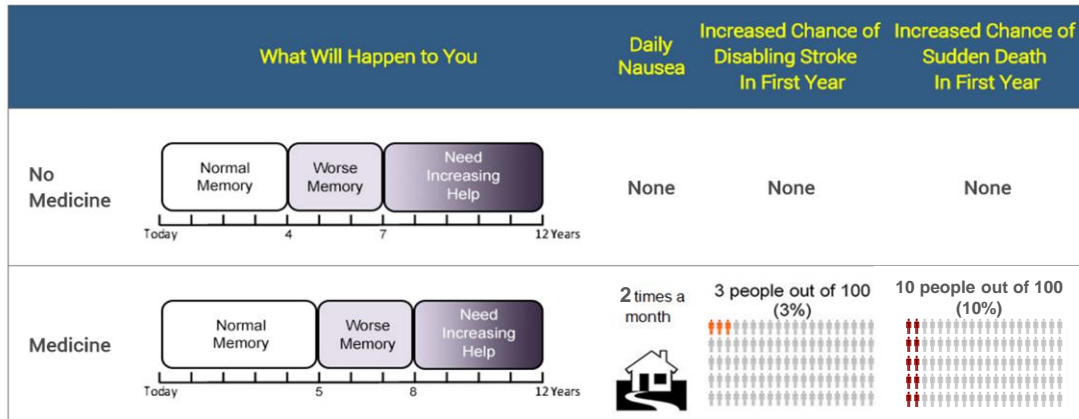Normal Memory | Worse Memory | Need Increasing Help

Today — 8 — 11 — 16 Years
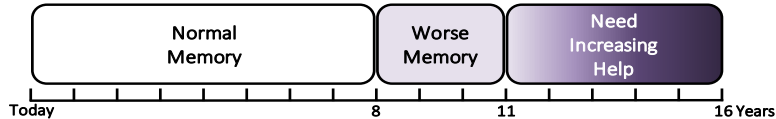
Trade-off Task Example 1: Alzheimer's Disease Preference Study

Please think about the following two options, No Medicine and Medicine.

If you need to see the description for a medicine effect, place your cursor on the yellow text.

What Will Happen to You	Daily Nausea	Increased Chance of Disabling Stroke In First Year	Increased Chance of Sudden Death In First Year
No Medicine — Normal Memory, Worse Memory, Need Increasing Help — Today, 4, 7, 12 Years	None	None	None
Medicine — Normal Memory, Worse Memory, Need Increasing Help — Today, 5, 8, 12 Years	2 times a month	3 people out of 100 (3%)	10 people out of 100 (10%)

Which would you choose if these were your only options?
- ○ No medicine
- ○ Medicine

Trade-off Task Example 2: Alzheimer's Disease Preference Study

Please think about the following two options, No Medicine and Medicine.

If you need to see the description for a medicine effect, place your cursor on the yellow text.
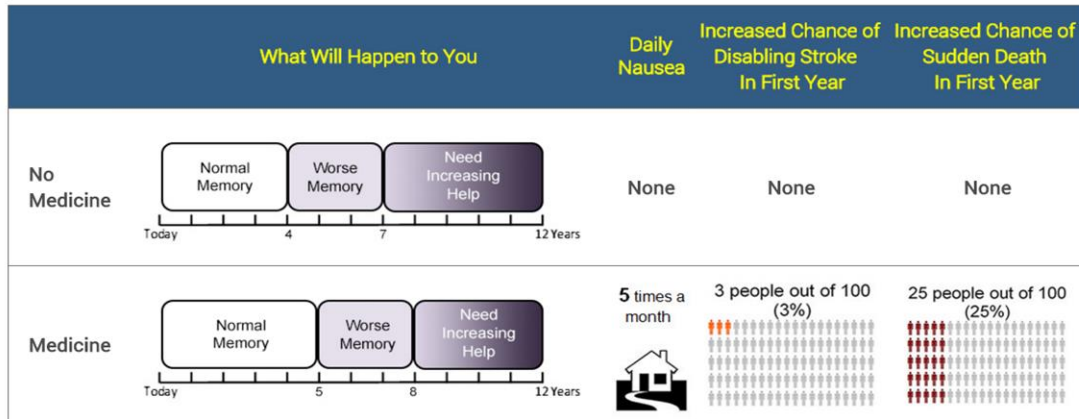
Which would you choose if these were your only options?

○ No medicine

○ Medicine

Regression Analysis: Alternative Choice-Models Studied

- **Taste heterogeneity**
  - ▸ Random-parameters logit (RPL) using Stata: taste heterogeneity modeled as normal distributions
  - ▸ Scale-adjusted latent-class analysis (LCA) using LatentGOLD: taste heterogeneity modeled as discrete classes with similar preferences adjusted for different variances
- **RPL**
  - ▸ Linear variables for each attribute, indicated by Box-Cox specification tests
  - ▸ Interaction term for nonlinearity in _time with MCI_ and _time with dementia_ combinations
  - ▸ An opt-out dummy representing _No Med_
 - ▸ Rescaled log-odds parameter estimates to facilitate comparisons

Sample Characteristics

	Overall (N = 1004)	Age 60 to 74 (n = 670)	Age 75 to 85 (n = 334)
Mean Age	70	66	78
Female	50%	50%	49%
White race	92%	90%	96%
4-year college degree or more	41%	41%	41%
Have had a test for memory problems or AD	5%	4%	7%
Have known one or more family members or friends with AD or other serious memory problem	64%	62%	68%

RPL: 12-Year Version, Age 75-85
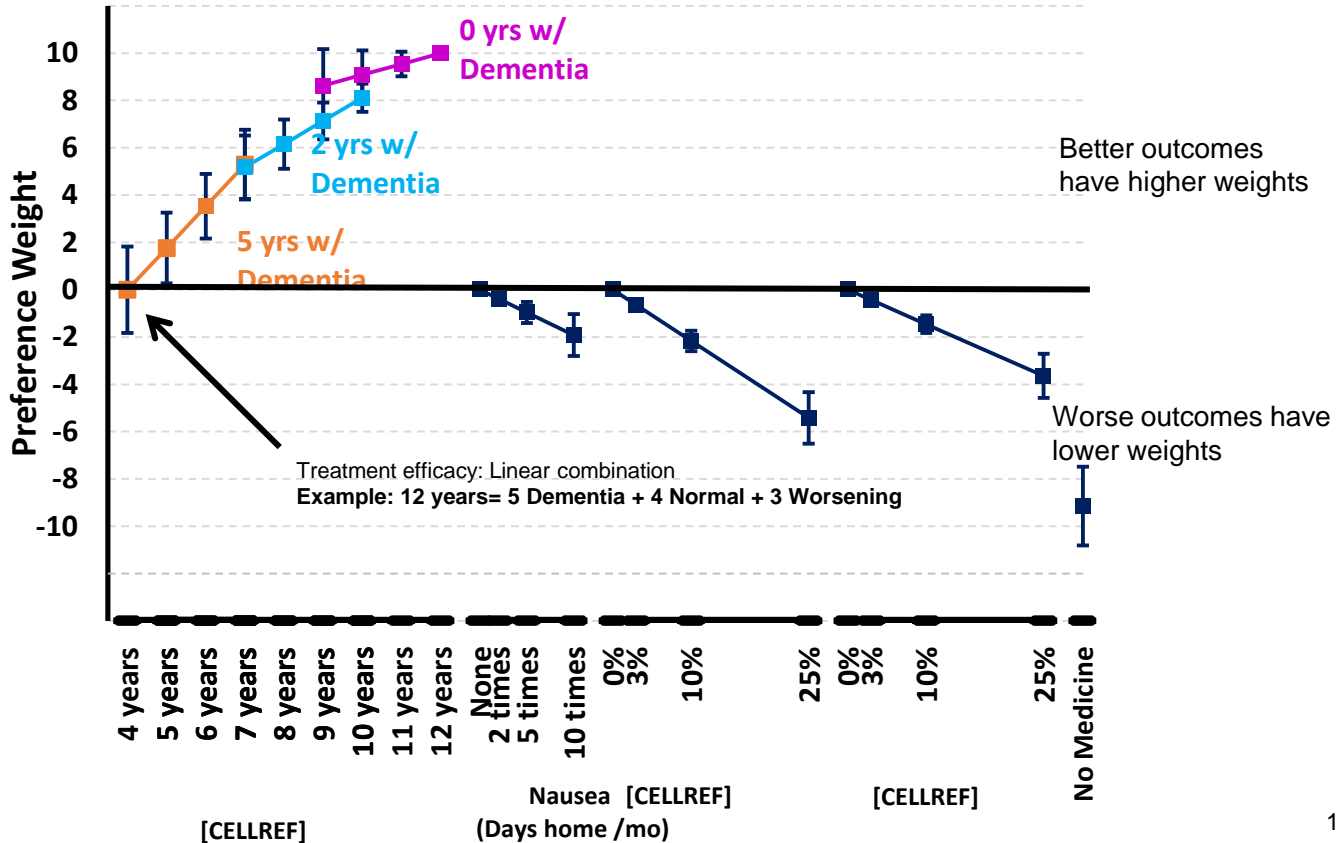
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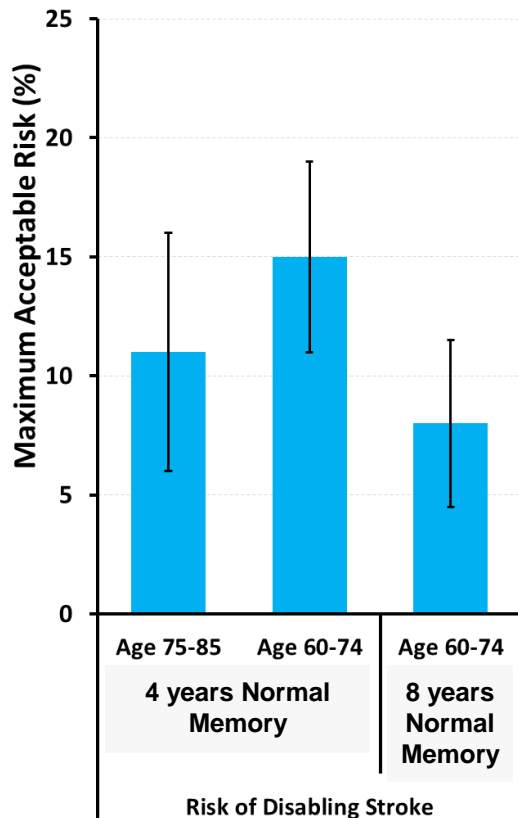
RPL: Maximum Acceptable Risk (MAR) in exchange for 2 more years of normal memory (1 MCI, 1 AD year avoided)
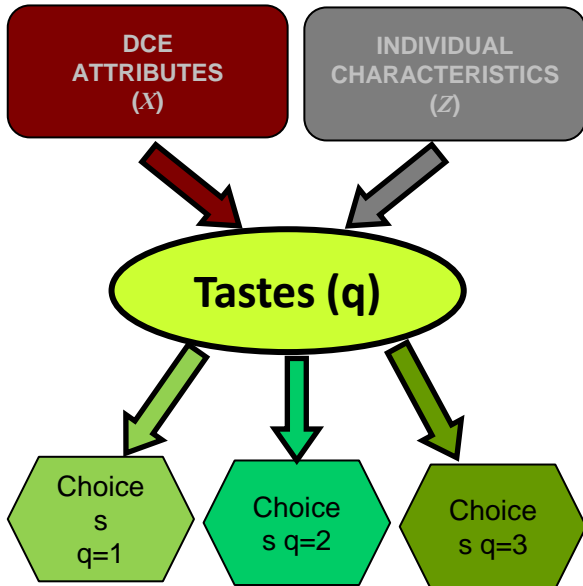
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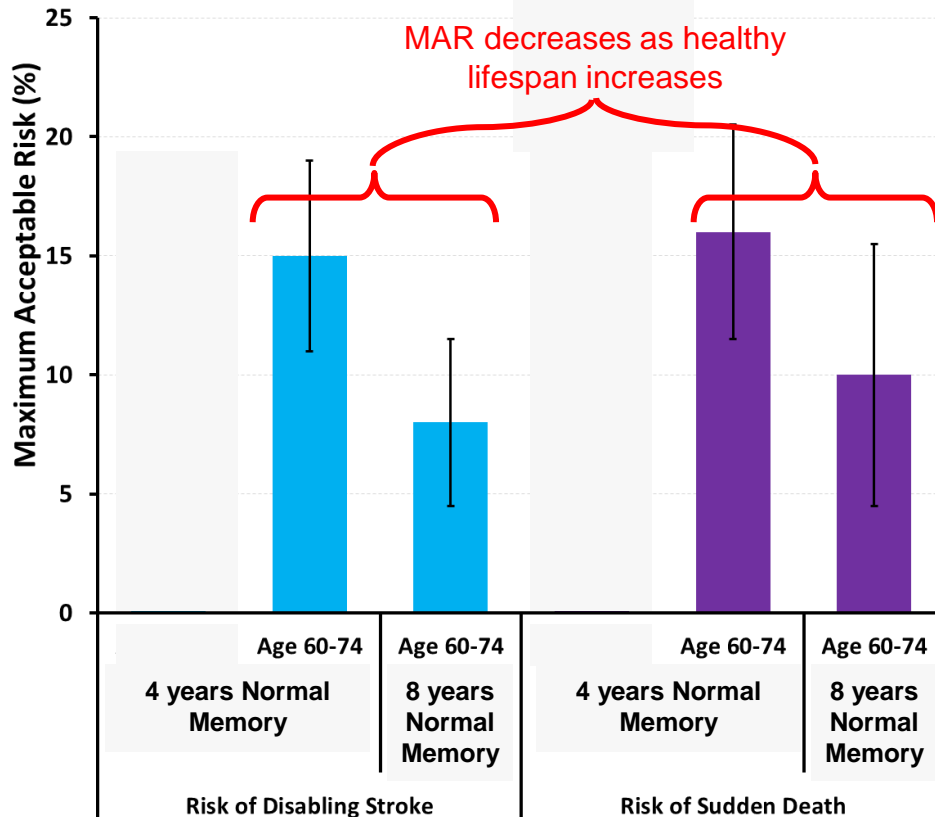
Latent-Class Analysis (LCA)

CLASS-MEMBERSHIP PROBABILITY

$$Pr[Class = q(Z)]$$

Individual has tastes q that depend on individual characteristics Z

CLASS-SPECIFIC CHOICE PROBABILITY

$$Pr(Choices \,| Class = q, X)$$

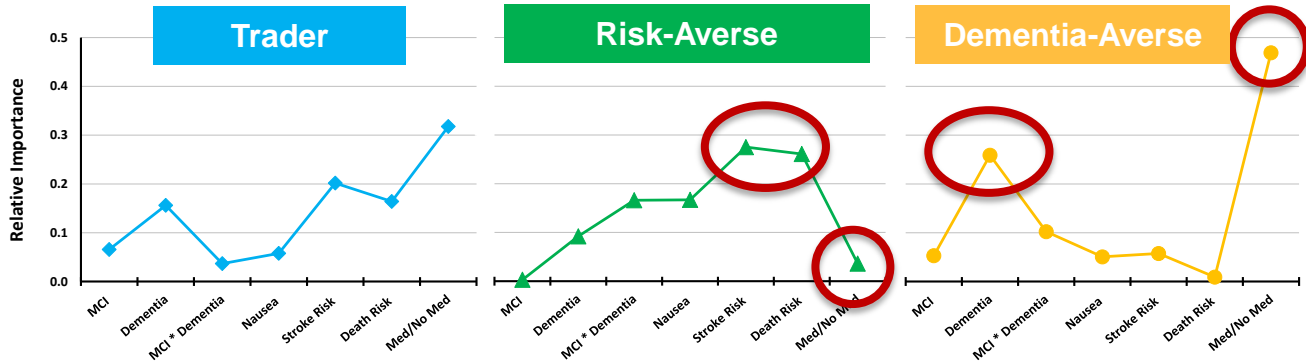**Individual makes choices given tastes q and attributes X**

UNCONDITIONAL CHOICE PROBABILITY

$$Pr(Choices) =$$

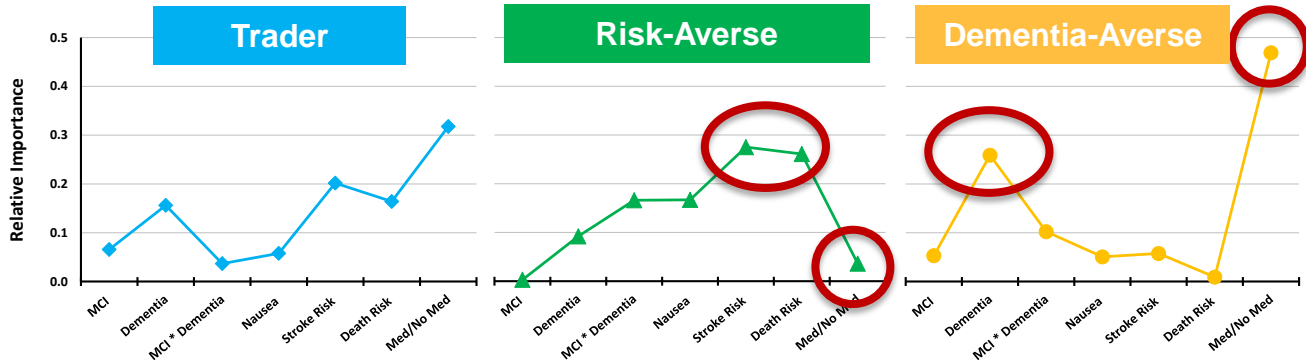$$\sum_{q=1}^{3} Pr(Choices \,| Class = q, X) \cdot Pr[Class = q(Z)]$$

Individual makes choices unconditional on class membership

LCA: 3 Classes of Benefit-Risk Tradeoffs

Proportion of sample	40%	33%	27%
Primary concerns	• Prefer medication • Trade off among all attributes	• Prefer no medication • More concerned about risks	• Strongly prefer medication • More concerned about efficacy

LCA: 3 Classes of Benefit-Risk Tradeoffs

Proportion of sample	40%	33%	27%
Primary concerns	• Prefer medication • Trade off among all attributes	• Prefer no medication • More concerned about risks	• Strongly prefer medication • More concerned about efficacy
Statistically significant participant-level covariates	• Younger • More likely to report health problems • Less likely to have AD caregiving experience	• Less likely to report health problems • Least likely to have AD caregiving experience • More likely to be assigned to 16-year version	• Older • Most likely to have AD caregiving experience • More likely to be assigned to 12-year version

Conclusions

- **Patients would accept 8 – 16% change disabling stroke or sudden death for 2 additional years normal memory**
  - ‣ Dependent on age and years of normal memory remaining

- **Identified 3 distinct subgroups of patients**
  - ‣ Traders
  - ‣ Treatment side effect averse
  - ‣ Dementia averse

  Groups differed by age, general health, AD caregiving experience, and time frame assigned

- **2 in 3 were willing to accept treatment risks to delay AD 1 in 3 were risk averse with strong preference for no Tx**

Methodological Take-Away Messages

- **RPL results**
  - Describe preferences for "average" respondents
  - Can be useful for strategy, B-R and policymaking

- **LCA results**
  - Avoid ecological fallacies
  - Describe heterogeneity, identifying groups with similar preferences
  - Help guide regulatory and clinical decision making