Risk Factors for Age of Onset of AD in the Cache County Study

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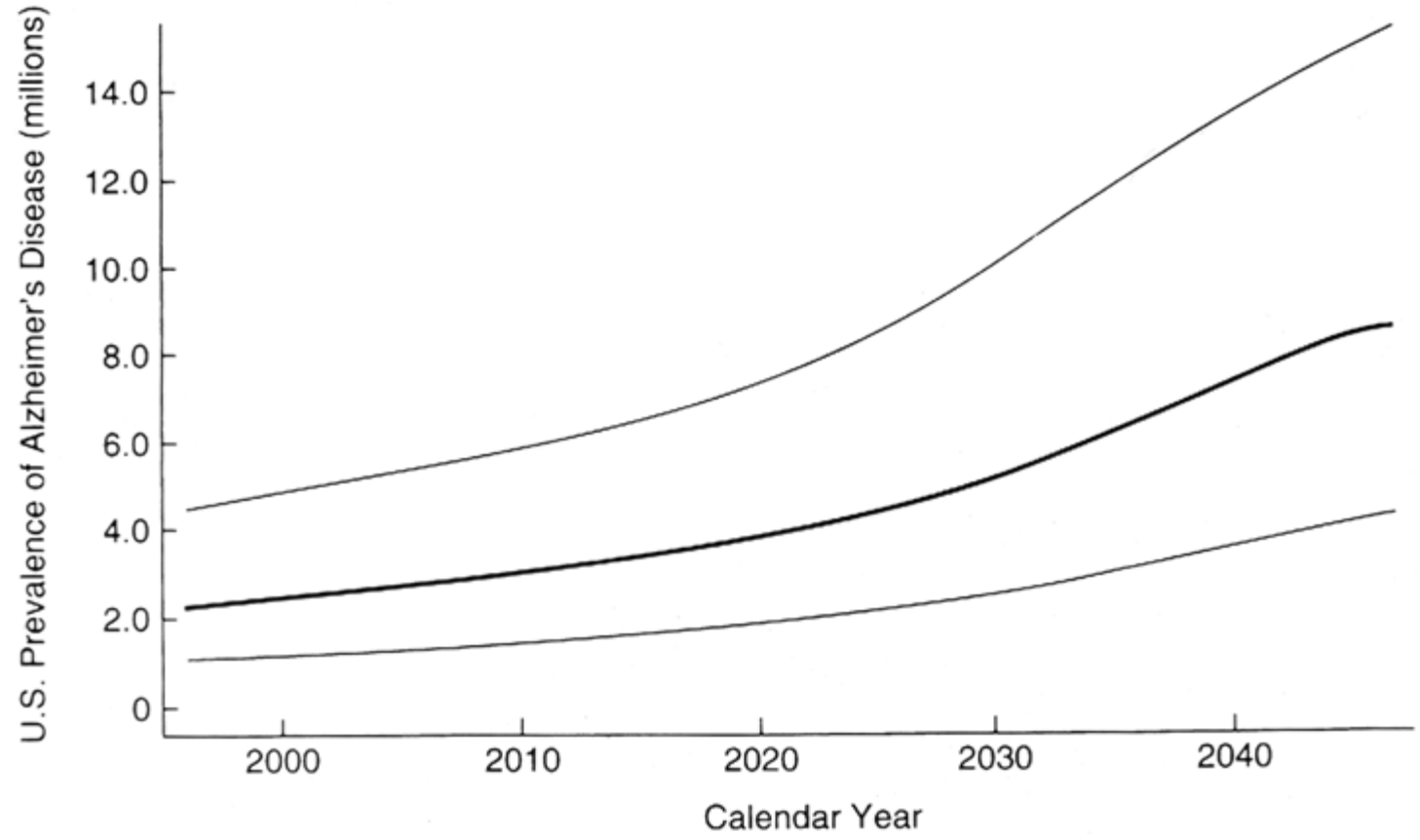
Disclosures

- None



Note. Estimates and ranges are based on the mean, minimum, and maximum age-specific incidence rates shown in Table 1.

Projections of Alzheimer's disease prevalence in the United States: 1997-2047

Brookmeyer, 1998

The projected effect of risk factor reduction on Alzheimer's disease prevalence

Deborah E Barnes, Kristine Yaffe

At present, about 33·9 million people worldwide have Alzheimer's disease (AD), and prevalence is expected to triple over the next 40 years. The aim of this Review was to summarise the evidence regarding seven potentially modifiable risk factors for AD: diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity. Additionally, we projected the effect of risk factor reduction on AD prevalence by calculating population attributable risks (the percent of cases attributable to a given factor) and the number of AD cases that might be prevented by risk factor reductions of 10% and 25% worldwide and in the USA. Together, up to half of AD cases worldwide (17·2 million) and in the USA (2·9 million) are potentially attributable to these factors. A 10–25% reduction in all seven risk factors could potentially prevent as many as 1·1–3·0 million AD cases worldwide and 184 000–492 000 cases in the USA.

Lancert Neurology 2011 10:819-28

	Population prevalence	Relative risk (95% CI)	PAR (confidence range)	Number of cases attributable (thousands; confidence range)
Worldwide				
Diabetes mellitus	6·4%	1·39 (1·17–1·66)	2·4% (1·1–4·1)	826 (365–1374)
Midlife hypertension	8·9%	1·61 (1·16–2·24)	5·1% (1·4–9·9)	1746 (476–3369)
Midlife obesity	3·4%	1·60 (1·34–1·92)	2·0% (1·1–3·0)	678 (387–1028)
Depression	13·2%	1·90 (1·55–2·33)	10·6% (6·8–14·9)	3600 (2295–5063)
Physical inactivity	17·7%	1·82 (1·19–2·78)	12·7% (3·3–24·0)	4297 (1103–8122)
Smoking	27·4%	1·59 (1·15–2·20)	13·9% (3·9–24·7)	4718 (1338–8388)
Low education	40·0%	1·59 (1·35–1·86)	19·1% (12·3–25·6)	6473 (4163–8677)
Combined (maximum)	..	..	50·7%	17 187 028*
USA				
Diabetes mellitus	8·7%	1·39 (1·17–1·66)	3·3% (1·5–5·4)	174 (77–288)
Midlife hypertension	14·3%	1·61 (1·16–2·24)	8·0% (2·2–15·1)	425 (119–798)
Midlife obesity	13·1%	1·60 (1·34–1·92)	7·3% (4·3–10·8)	386 (226–570)
Depression	19·2%	1·90 (1·55–2·33)	14·7% (9·6–20·3)	781 (506–1078)
Physical inactivity	32·5%	1·82 (1·19–2·78)	21·0% (5·8–36·6)	1115 (308–1942)
Smoking	20·6%	1·59 (1·15–2·20)	10·8% (3·0–19·8)	574 (159–1050)
Low education	13·3%	1·59 (1·35–1·86)	7·3% (4·4–10·3)	386 (236–544)
Combined (maximum)	..	..	54·1%	2 866 951*

PAR=population attributable risk. *Absolute number.

Table: **Alzheimer's disease cases attributable to potentially modifiable risk factors worldwide and in the USA**

Barnes, 2011

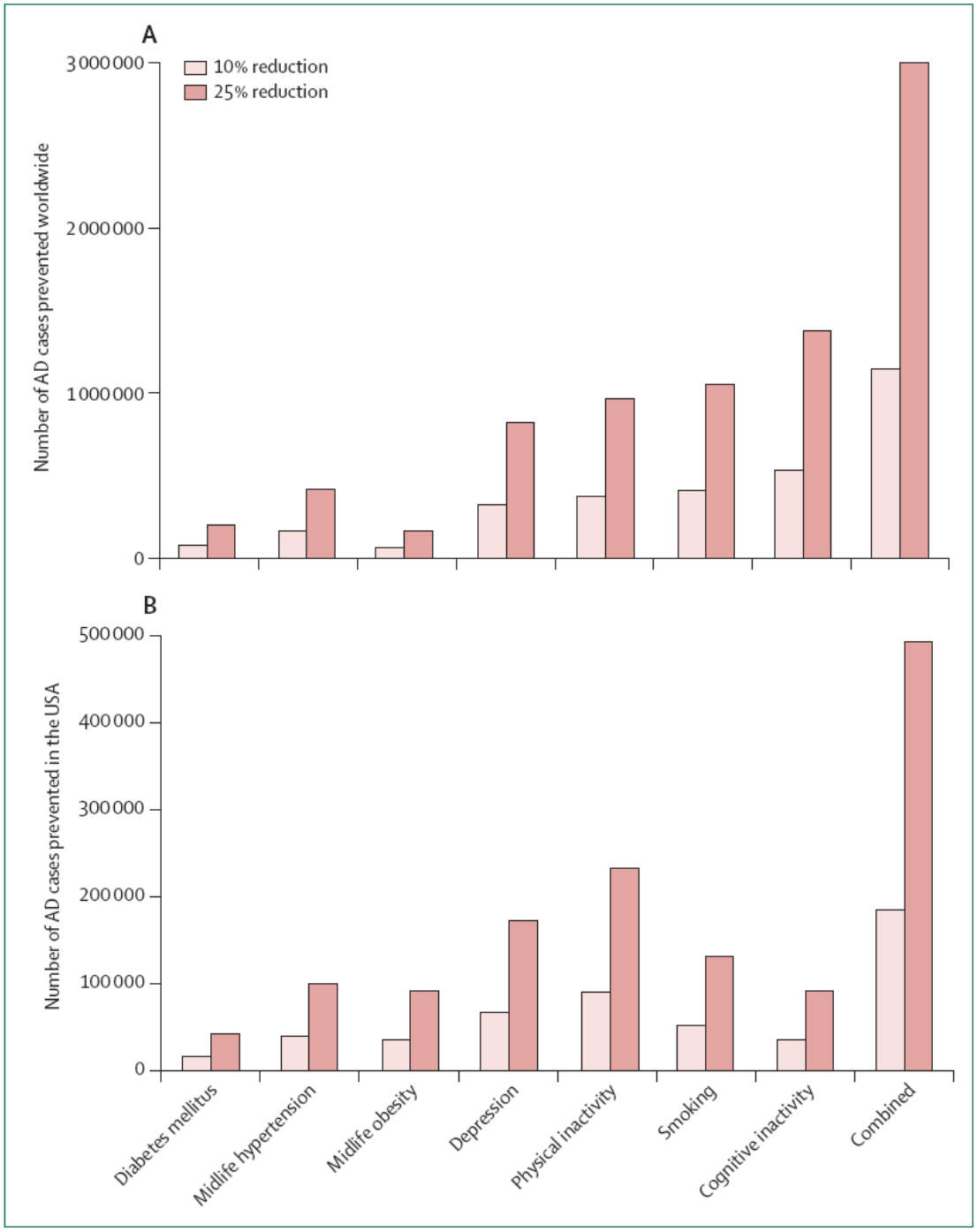


Figure: Potential number of AD cases that could be prevented through risk factor reduction

Barnes, 2011

Alzheimer disease pathology and longitudinal cognitive performance in the oldest-old with no dementia

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ABSTRACT

Objective: It has been hypothesized that individuals without dementia with Alzheimer disease (AD) neuropathology may be in the preclinical stages of dementia and could be experiencing subtle cognitive decline. The purpose of this study was to compare longitudinal cognitive performance in oldest-old individuals without dementia with and without AD neuropathology.

DISCUSSION Individuals who died with high AD neuropathology had a similar trajectory of global cognition and memory performance before death when compared to individuals with low AD neuropathology. We found evidence of learning effects in these participants; however, these learning effects were greater in individuals with lower AD neuropathology.

Neurology 2012 79:915-21

AHQR Review: Risk Factors for AD

Daviglus et al. Arch Neurol 2011, 68:1185-90

- Diabetes mellitus
- Midlife Hyperlipidemia
- Current tobacco use

- "Currently, insufficient evidence exists to draw firm conclusions on the association of any modifiable factors with risk of AD."

Age and rate of Cognitive Decline in AD: Implications for Clinical Trials

Bernick, Arch Neurol 2012, 69:901-5

- 3 cohorts in drug trials
- Age at entry into study (cross-sectional comparison)

- "Older age at baseline associated with slower rate of decline on ADAS-Cog 11 and MMSE"

CERAD plaque score	
Low (none, sparse)	30 (52)
High (moderate, frequent)	28 (48)
Braak and Braak tangle stage	
Low (I–III)	35 (60)
High (IV–VI)	23 (40)
CERAD plaque with Braak and Braak tangle	
Low plaque and low tangle	24 (41)
Low plaque and high tangle	6 (10)
High plaque and low tangle	11 (19)
High plaque and high tangle	17 (29)

Subramanian, 2012

Table 3 Fit statistics for AD neuropathology and cognitive performance[a]

Pathology and cognitive measure	−2ln(L)	No. of parameters	LRT	Difference in number parameters	*p* Value
Plaques					
3MS					
Model 1	620.8	10	5.9	7	0.55
Model 2	614.9	17			
CVLT					
Model 1	531.1	10	3.1	7	0.88
Model 2	528.0	17			
Tangles					
3MS					
Model 1	620.8	10	5.5	7	0.60
Model 2	615.3	17			
CVLT					
Model 1	531.1	10	5.3	7	0.62
Model 2	525.8	17			

Subramanian, 2012

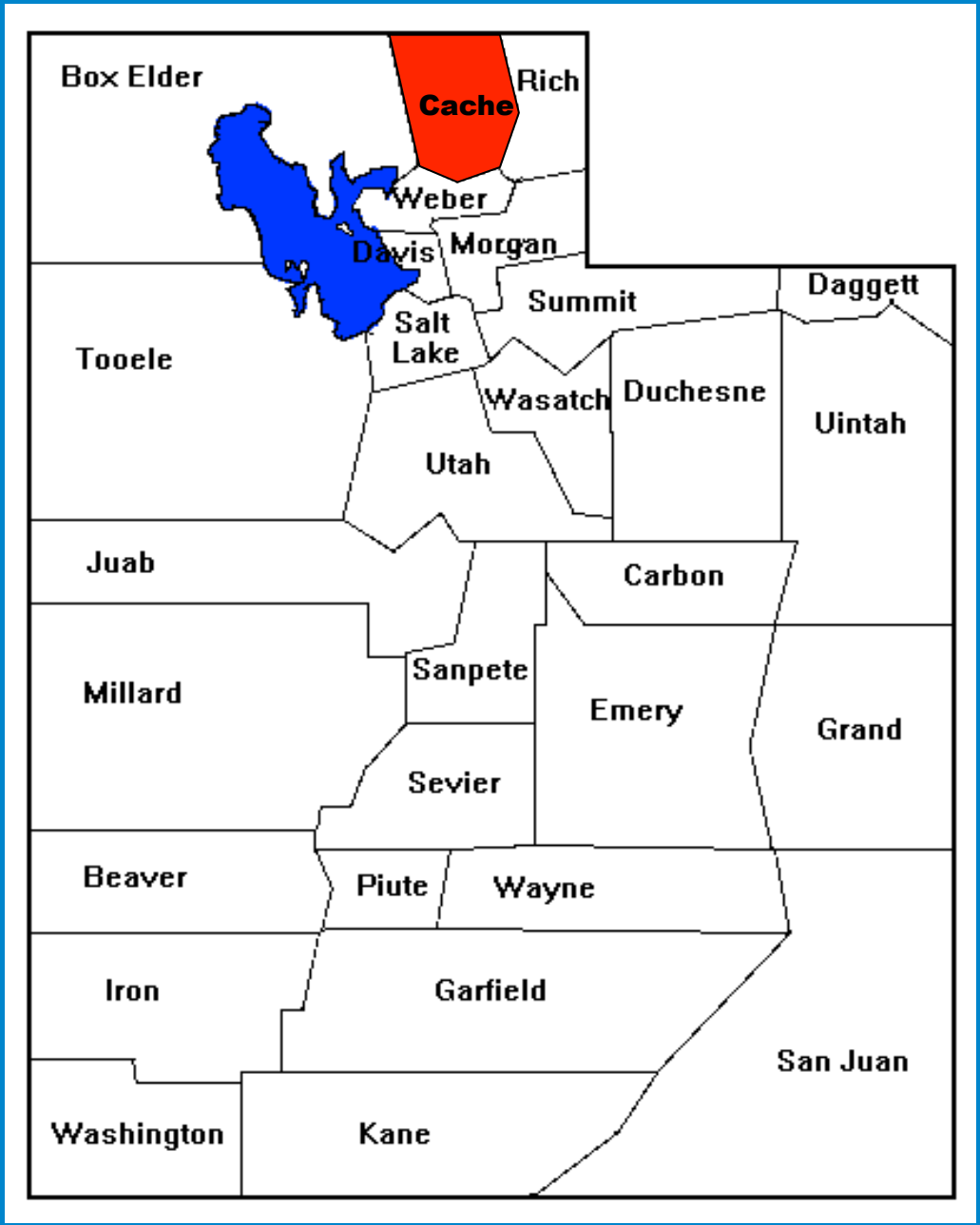
Plausible Hypotheses

1. *Pre-symptomatic recognition* and intervention will be a successful primary preventive strategy
   a. risk factor reduction
   b. prevention of cell death by biologically active compounds

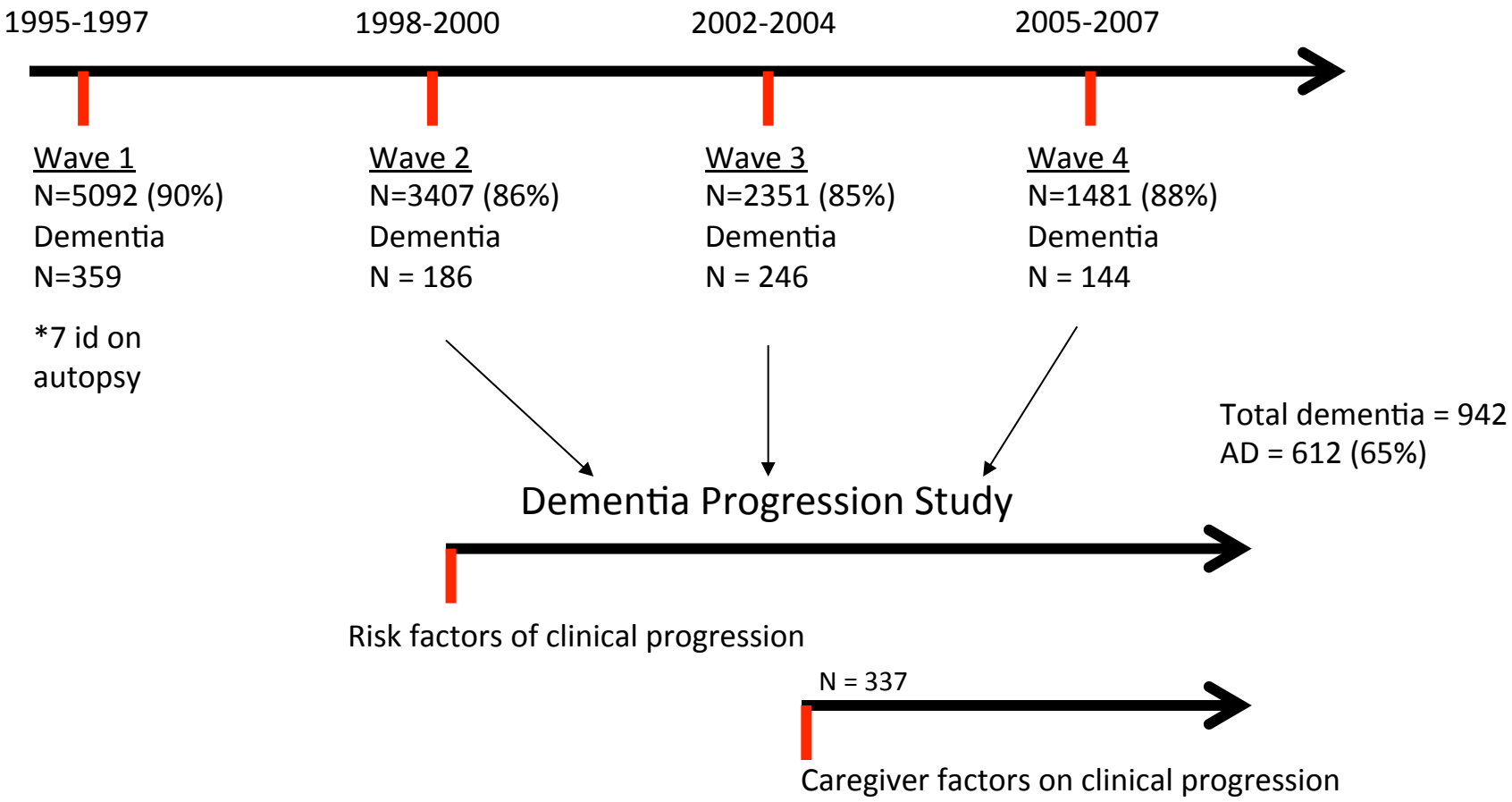
2. *Recognition of very early symptoms* will lead to successful secondary prevention by
   a. risk factor reduction
   b. prevention of cell death by biologically active compounds

3. *Delaying age of onset* will result in both primary prevention and secondary prevention by competing mortality and slower progression at late age

Cache County, Utah



Cache County Study

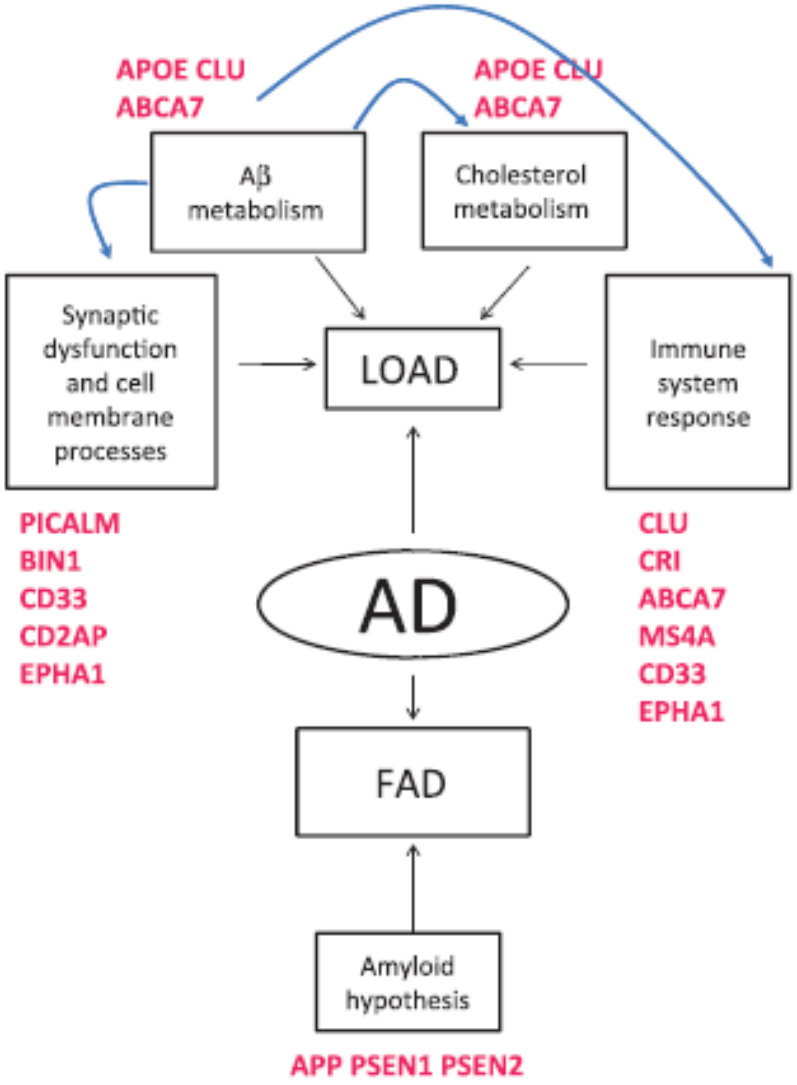


Model Predicting Age of Onset: Potentially Modifiable Risk Factors

VARIABLES	STD β	t	sig
Constant		28.79	.000
Elevated Baseline Cholesterol	-.189	-2.782	.006
BMI at Diagnosis	-.182	-2.679	.008
Hypertension Before Age 60	-.015	-.213	.832
Hypertension After Age 60	.163	2.298	.023
Some Activity	-.292	-2.410	.017
Moderate Activity	-.373	-2.737	.007
Vigorous Activity	.362	-2.338	.020

The 3 new pathways leading to Alzheimer's disease

Morgan *Neuropath and Appl Neurobiol* 2011; 37:353-7



3 Implicated Pathways

- **Immune System Function**
- ***-CLU***
- ***-CR1***
- ***-ABCA7***
- ***-MS4A***
- ***-CD33***
- ***EPHA1***
- **Cholesterol Metabolism**
- ***-APOE***
- ***-CLU***
- ***-ABCA7***
- **Synaptic Dysfunction/Cell Membrane Processes**
- **-PICALM**
- ***-BIN1***
- ***-CD33***
- ***-CD2AP***
- ***-EPHA1***