AIR POLLUTION
& the AGING BRAIN

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Institute for Healthy Aging
**RUSH UNIVERSITY
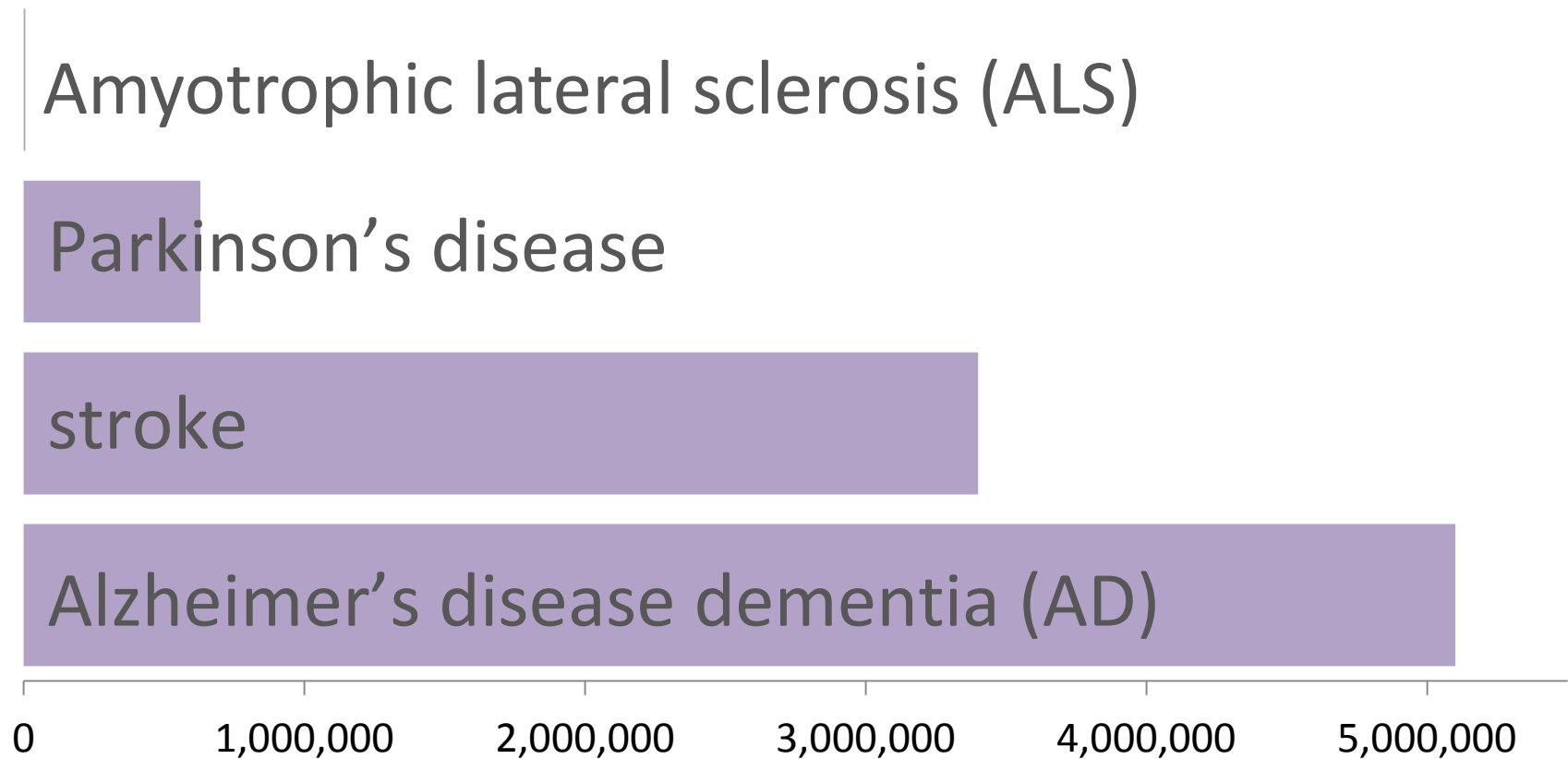MEDICAL CENTER**

FOCUS: DEMENTIA

What it is

decline in **memory**, language, problem-solving and other **cognitive skills** that affects a person's **ability to perform everyday activities**.

Why it is a focus

Dementia, its precursors and correlates are the **focus of most epidemiologic research to date** on air pollution and neurodegenerative disease.

Dementia is not part of "normal aging," but it *is* strikingly common

Amyotrophic lateral sclerosis (ALS)

Parkinson's disease

stroke

Alzheimer's disease dementia (AD)

| 0 | 1,000,000 | 2,000,000 | 3,000,000 | 4,000,000 | 5,000,000 |

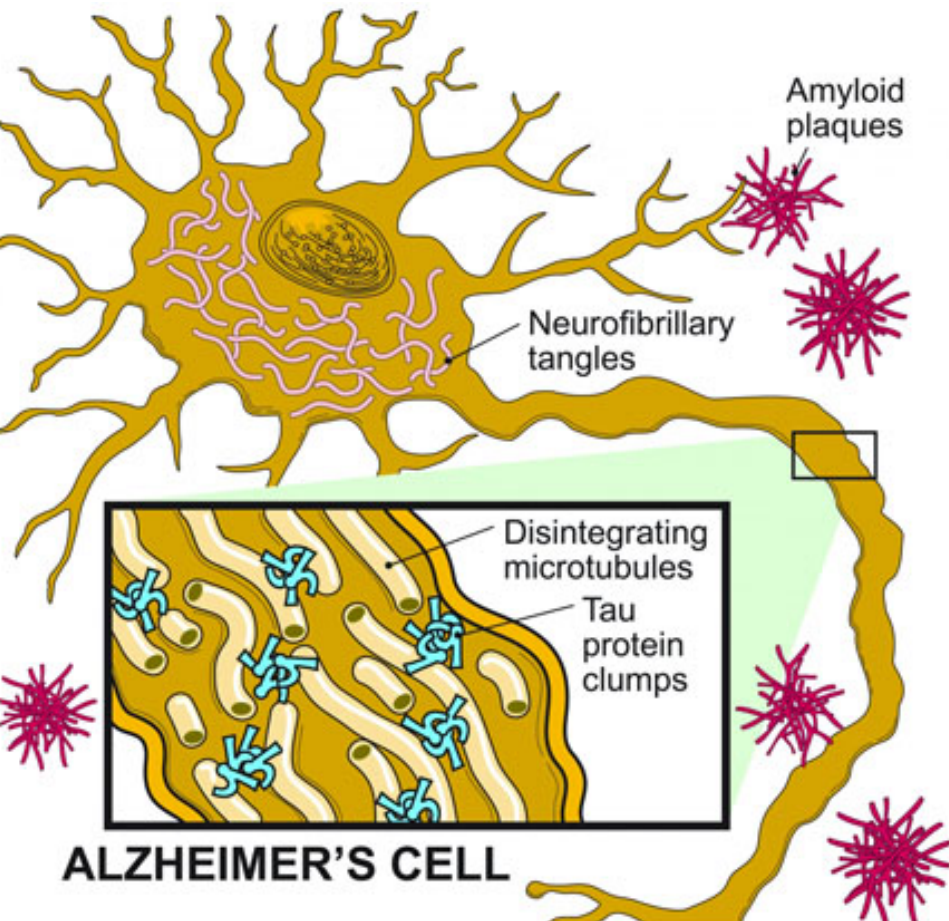Prevalent cases among US adults, aged 65 and older

Alzheimer's disease is the most common cause of dementia
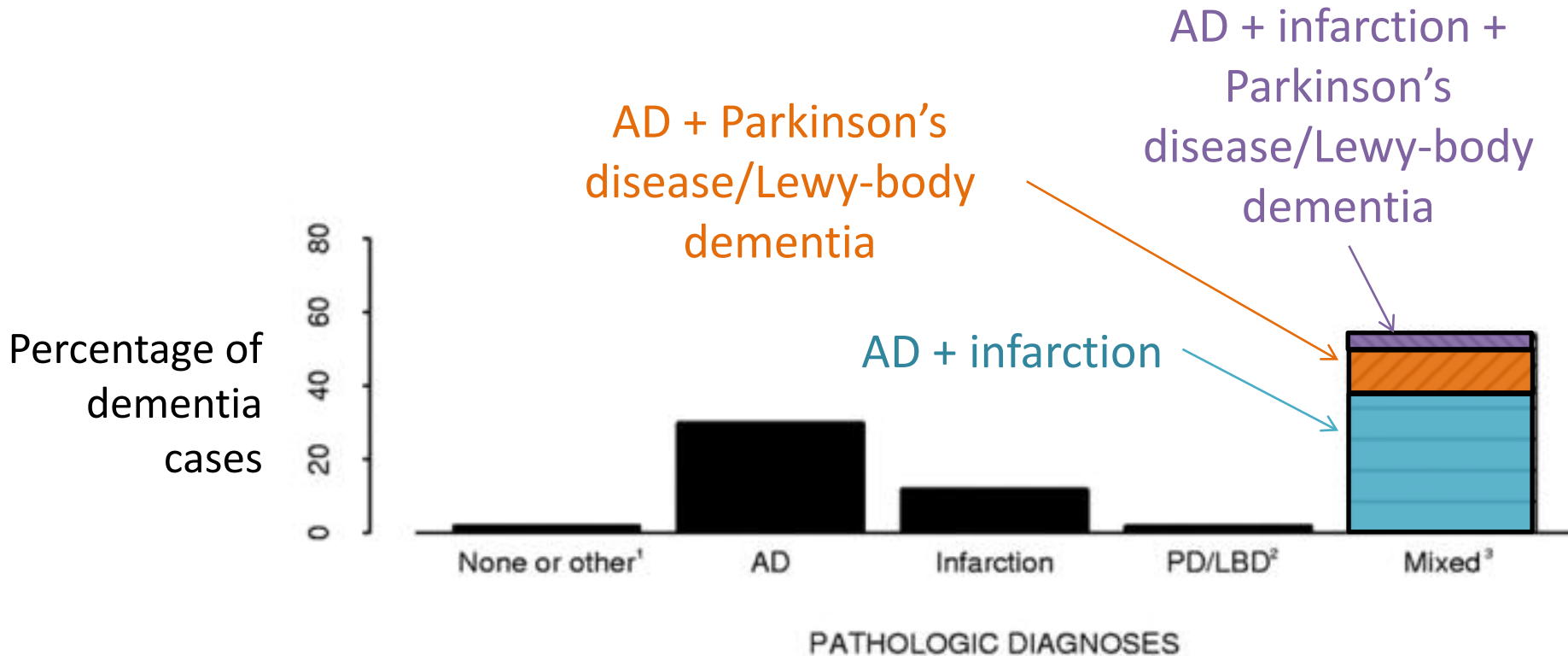

Pathologically characterized by:

amyloid beta **plaques** between neurons

hyperphosphorylated tau (a protein associated with neuron's microtubules) → **neurofibrillary tangles**

neuronal death

Although AD dementia is common, most AD pathology occurs with other pathologies

AD + infarction + Parkinson's disease/Lewy-body dementia

AD + Parkinson's disease/Lewy-body dementia

AD + infarction

Percentage of dementia cases

PATHOLOGIC DIAGNOSES

None or other[1]   AD   Infarction   PD/LBD[2]   Mixed[3]

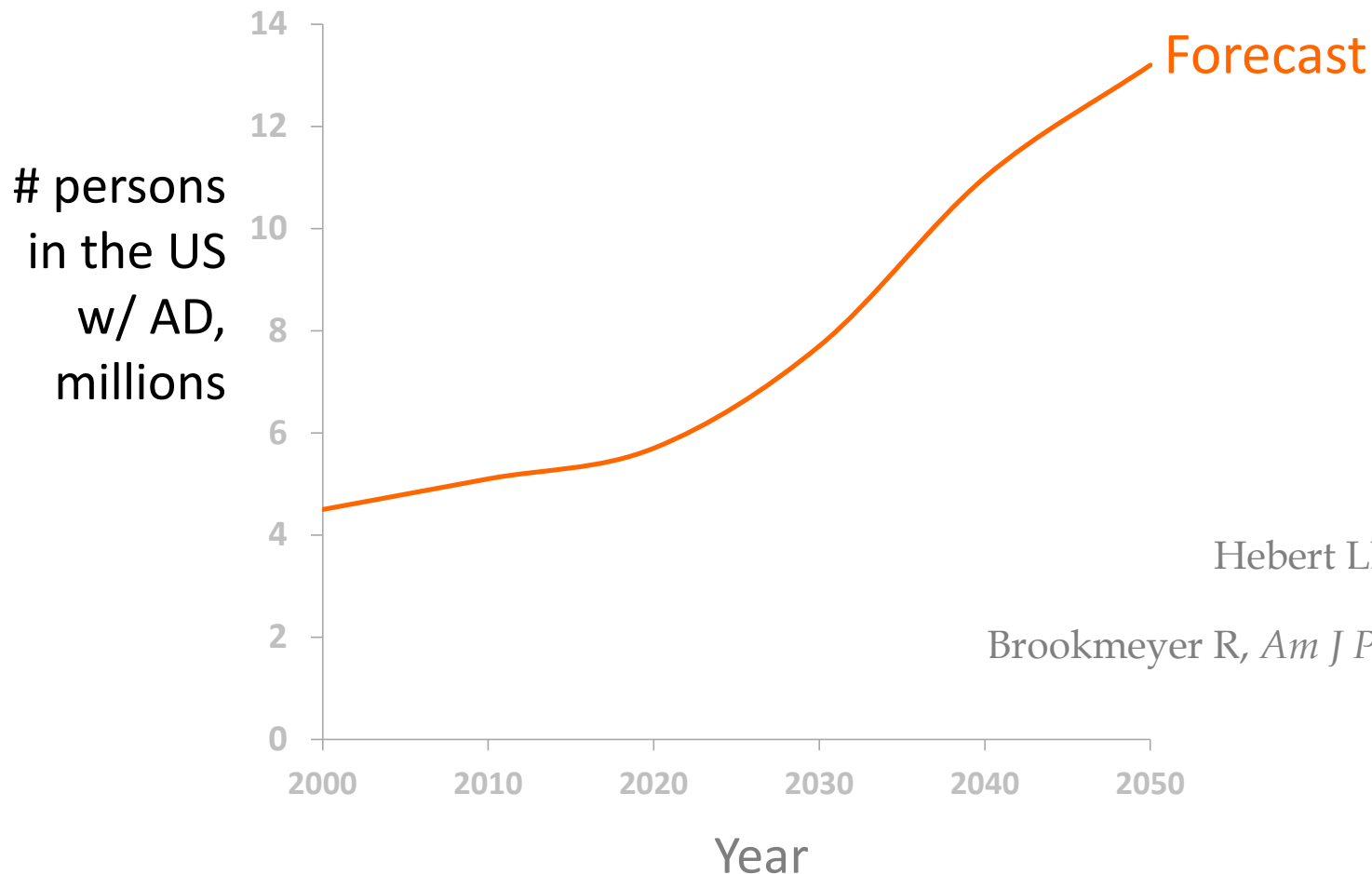Schneider J, *et al. Neurology* 2007; 69(24):2197-2204

IMPLICATION:

It is difficult and possibly misleading to distinguish clinically diagnosed AD dementia from other dementia phenotypes without additional information.

Instead of "pure AD," think "AD and AD-plus."

AD dementia prevalence expected to triple
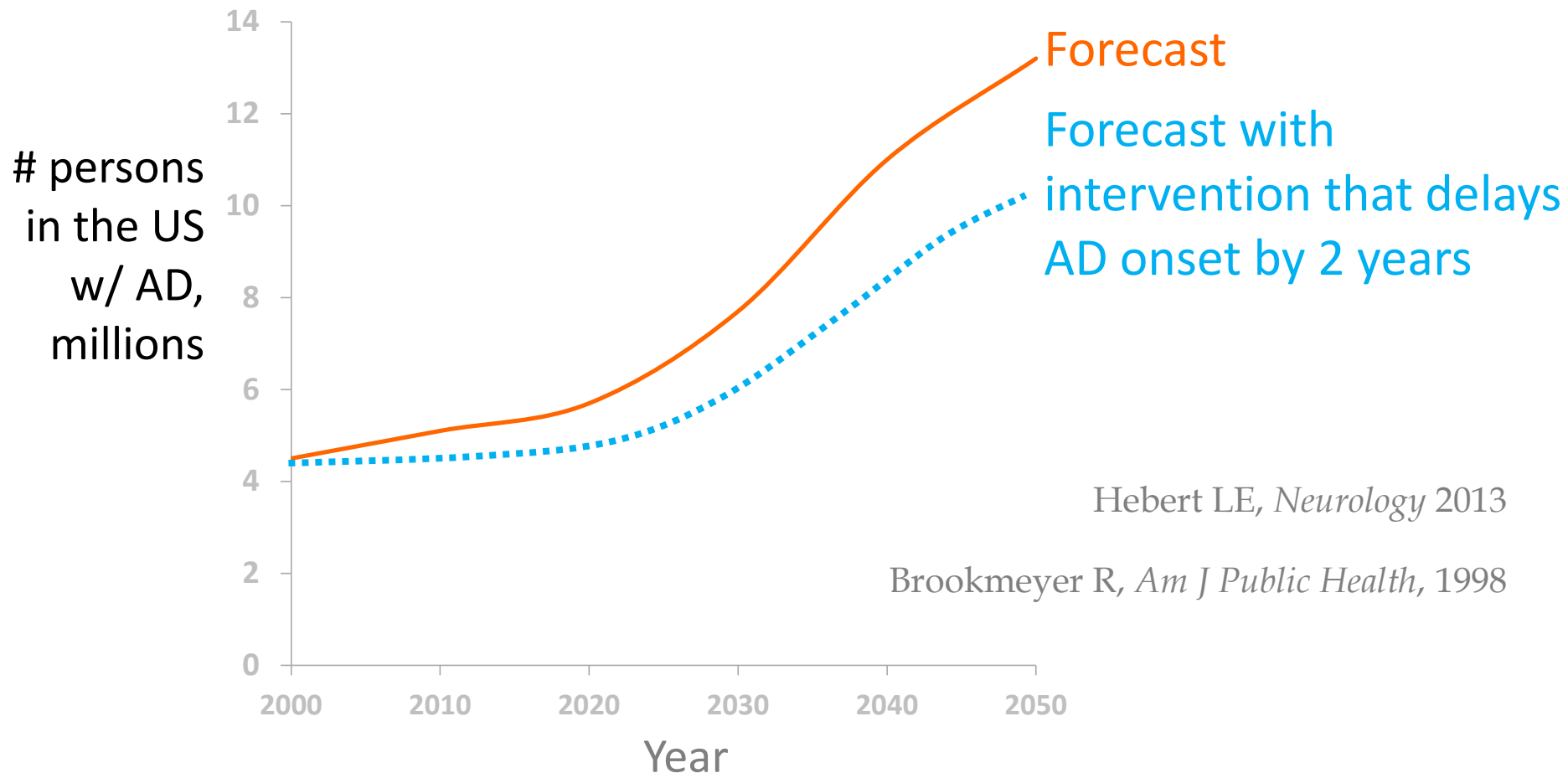

persons in the US w/ AD, millions

Forecast

Year

Hebert LE, *Neurology* 2013

Brookmeyer R, *Am J Public Health*, 1998

No relief in sight

- Enormous costs *Alz & Dement 2015;11:332-384*

- Huge end-of-life burden Weuve, *Alz & Dement,* 2014

- Incidence is not waning Hebert, *Neurology*, 2010

- Effective treatment does not exist

Broadly based interventions—e.g., *cutting widespread exposures to a causal agent*— could reduce population burden of dementia

persons in the US w/ AD, millions

Year

Forecast

Forecast with intervention that delays AD onset by 2 years

Hebert LE, *Neurology* 2013

Brookmeyer R, *Am J Public Health*, 1998

How might air pollution wreak havoc on the aging brain?

Ambient particulate matter (PM) can access the brain via circulation + intranasal route
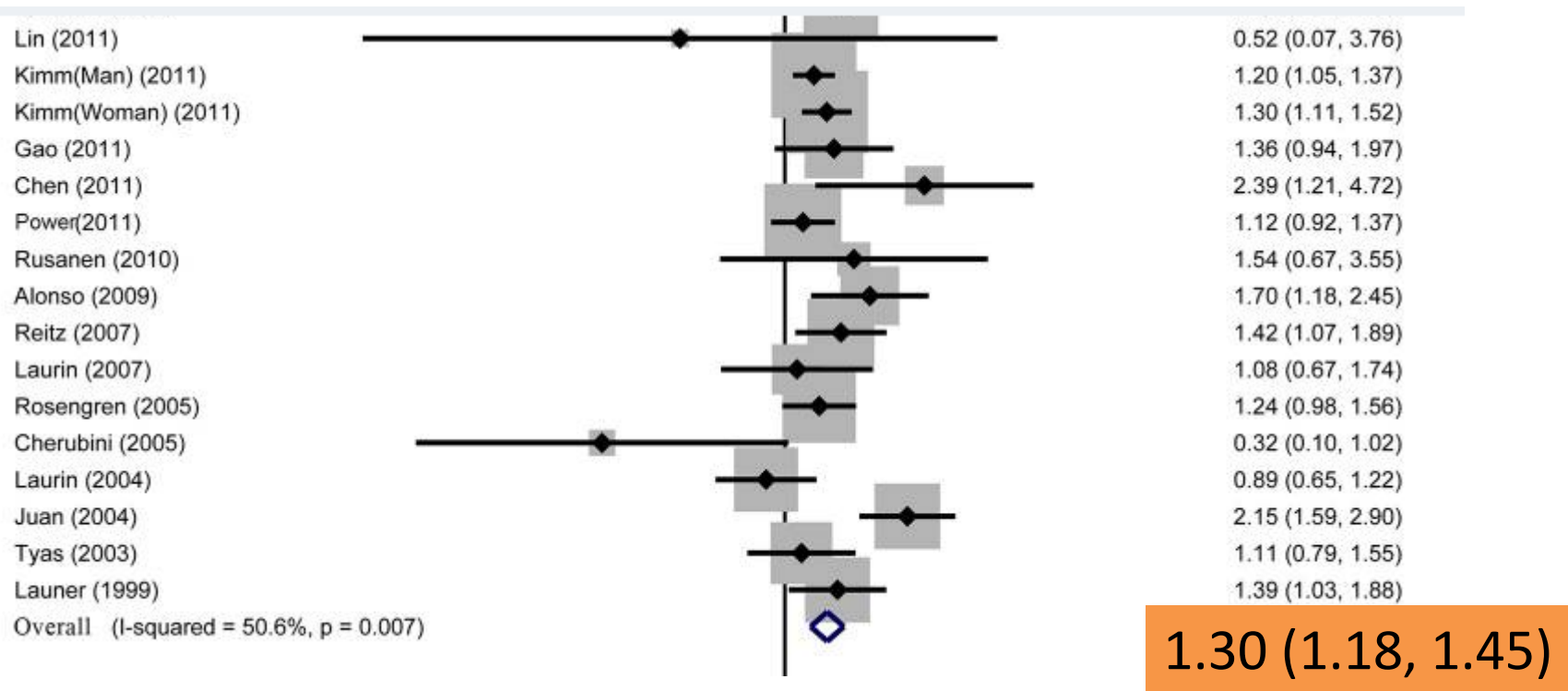
→ inflammatory response, injure BBB, increase amyloid-beta

Associations with cardiovascular disease, stroke, and vascular risk factors

Possible combination of acute and chronic effects

Clues from research on smoking

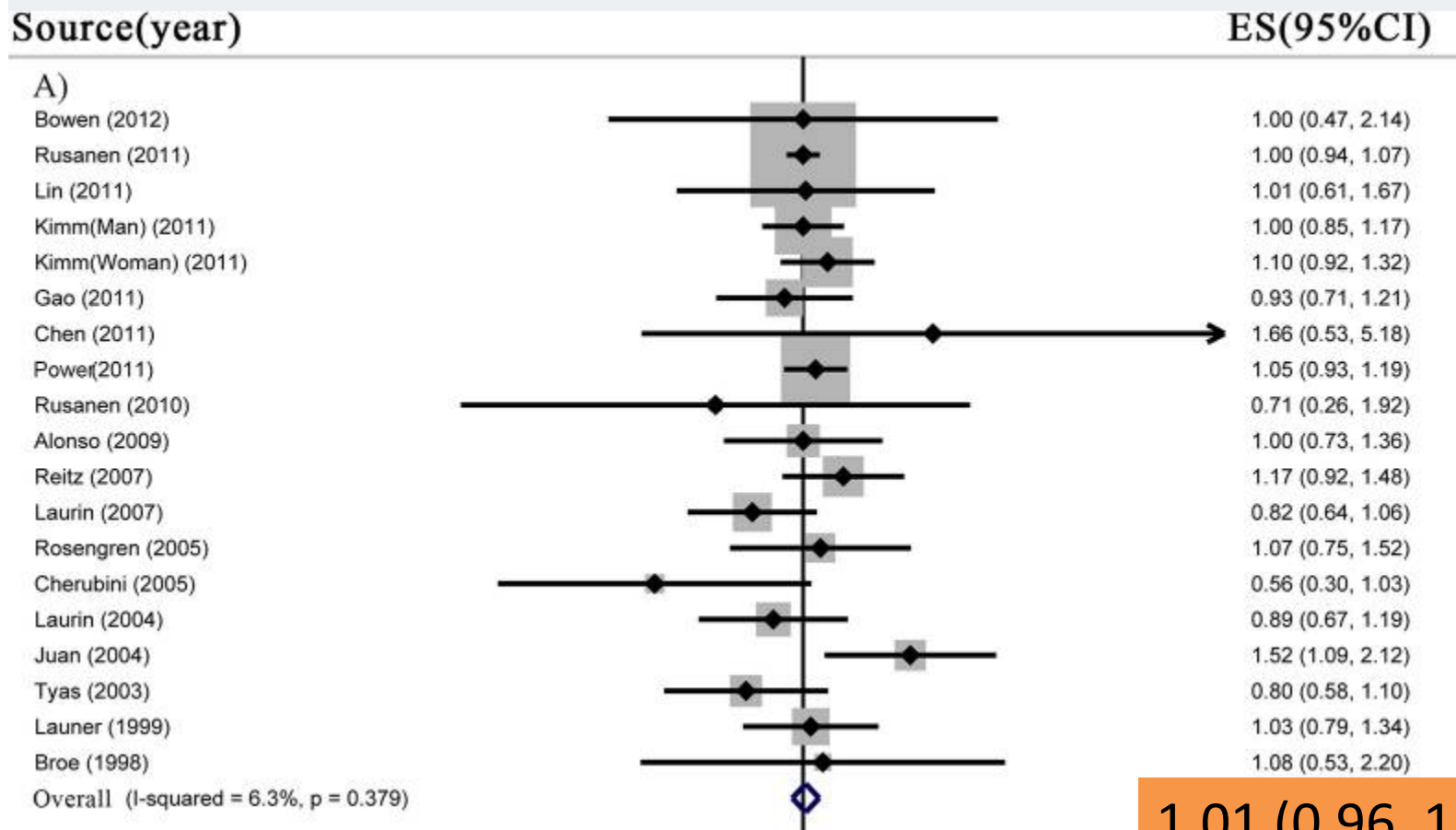Meta-analysis of current smoking and risk of all-cause dementia

Lin (2011)	0.52 (0.07, 3.76)
Kimm(Man) (2011)	1.20 (1.05, 1.37)
Kimm(Woman) (2011)	1.30 (1.11, 1.52)
Gao (2011)	1.36 (0.94, 1.97)
Chen (2011)	2.39 (1.21, 4.72)
Power(2011)	1.12 (0.92, 1.37)
Rusanen (2010)	1.54 (0.67, 3.55)
Alonso (2009)	1.70 (1.18, 2.45)
Reitz (2007)	1.42 (1.07, 1.89)
Laurin (2007)	1.08 (0.67, 1.74)
Rosengren (2005)	1.24 (0.98, 1.56)
Cherubini (2005)	0.32 (0.10, 1.02)
Laurin (2004)	0.89 (0.65, 1.22)
Juan (2004)	2.15 (1.59, 2.90)
Tyas (2003)	1.11 (0.79, 1.55)
Launer (1999)	1.39 (1.03, 1.88)
Overall (I-squared = 50.6%, p = 0.007)	

1.30 (1.18, 1.45)

Zhong G et al., PLoS ONE 2015

Similar findings for cognition and cognitive decline.

Deckers K et al. Int J Geriatr Psychiatry 2015
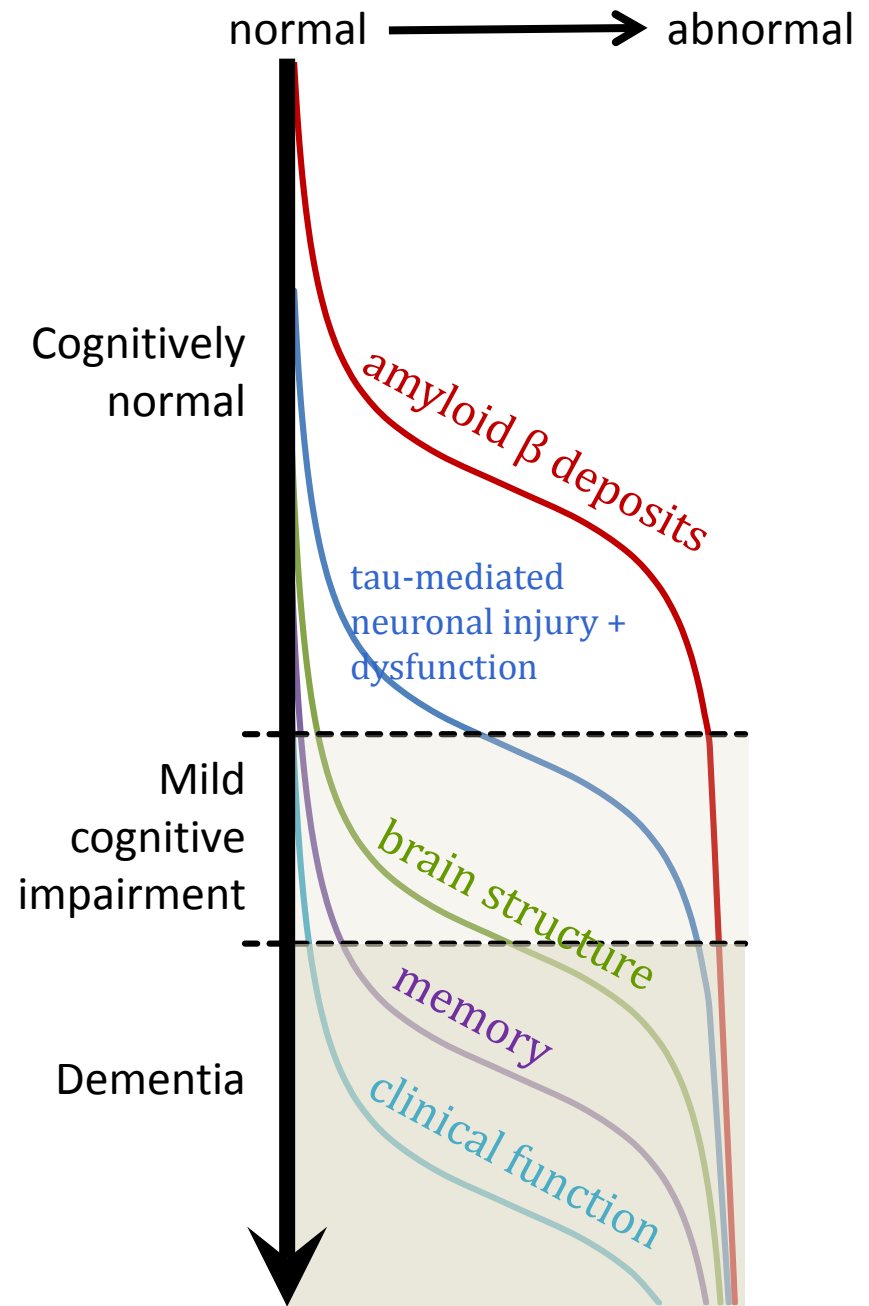*Beydoun MA et al. BMC Public Health 2014*

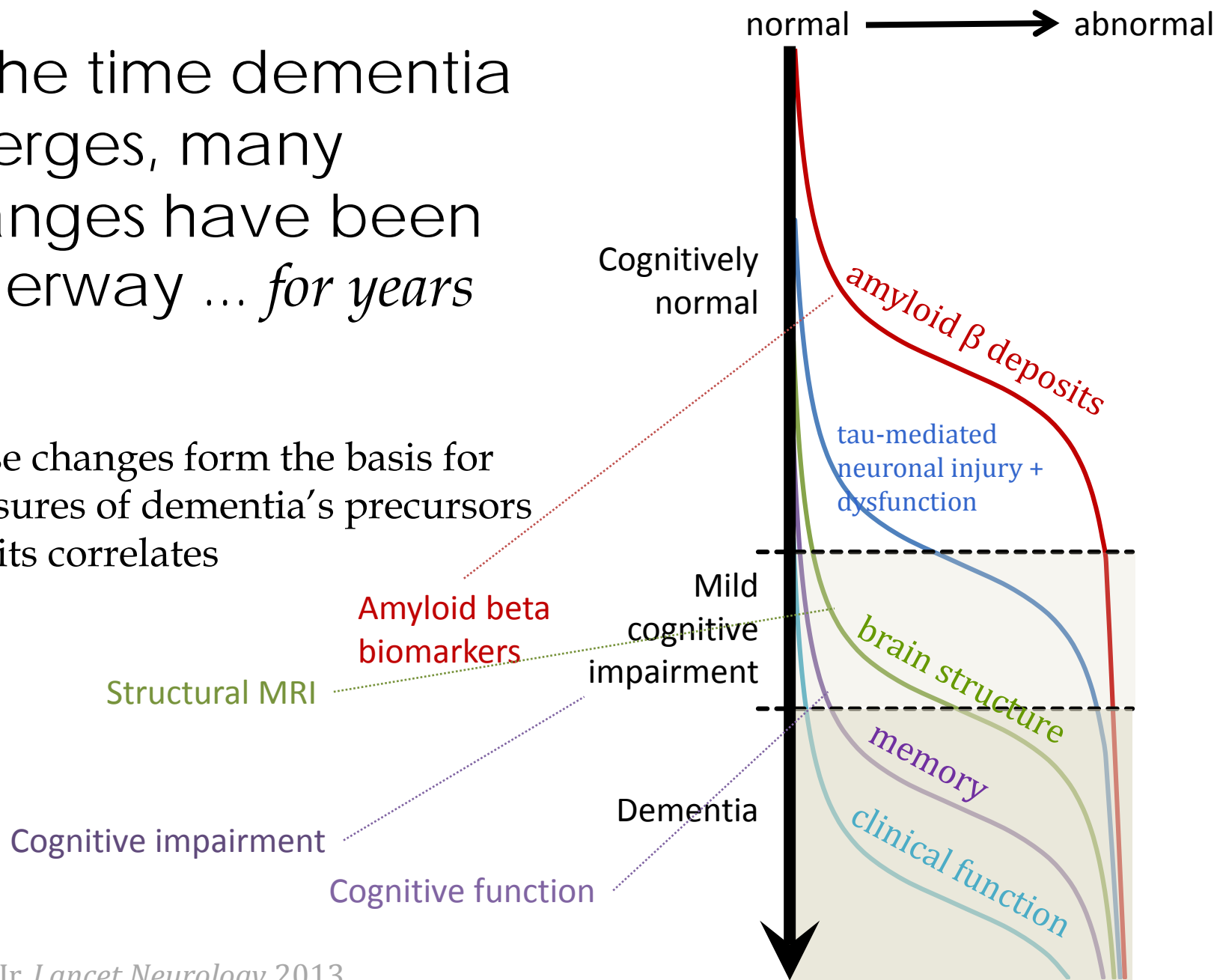# Meta-analysis of former smoking and risk of all-cause dementia

Source(year)	ES(95%CI)
A)	
Bowen (2012)	1.00 (0.47, 2.14)
Rusanen (2011)	1.00 (0.94, 1.07)
Lin (2011)	1.01 (0.61, 1.67)
Kimm(Man) (2011)	1.00 (0.85, 1.17)
Kimm(Woman) (2011)	1.10 (0.92, 1.32)
Gao (2011)	0.93 (0.71, 1.21)
Chen (2011)	1.66 (0.53, 5.18)
Power(2011)	1.05 (0.93, 1.19)
Rusanen (2010)	0.71 (0.26, 1.92)
Alonso (2009)	1.00 (0.73, 1.36)
Reitz (2007)	1.17 (0.92, 1.48)
Laurin (2007)	0.82 (0.64, 1.06)
Rosengren (2005)	1.07 (0.75, 1.52)
Cherubini (2005)	0.56 (0.30, 1.03)
Laurin (2004)	0.89 (0.67, 1.19)
Juan (2004)	1.52 (1.09, 2.12)
Tyas (2003)	0.80 (0.58, 1.10)
Launer (1999)	1.03 (0.79, 1.34)
Broe (1998)	1.08 (0.53, 2.20)
Overall (I-squared = 6.3%, p = 0.379)	

1.01 (0.96, 1.06)

By the time dementia emerges, many changes have been underway ... *for years*

normal → abnormal

Cognitively normal

amyloid β deposits

tau-mediated neuronal injury + dysfunction

Mild cognitive impairment

brain structure

Dementia

memory

clinical function

By the time dementia emerges, many changes have been underway ... *for years*

These changes form the basis for measures of dementia's precursors and its correlates

Amyloid beta biomarkers

Structural MRI

Cognitive impairment

Cognitive function

normal → abnormal

Cognitively normal

amyloid β deposits

tau-mediated neuronal injury + dysfunction

Mild cognitive impairment

brain structure

Dementia

memory

clinical function

Cognitive decline is a dynamic outcome that captures progression toward dementia (or beyond)
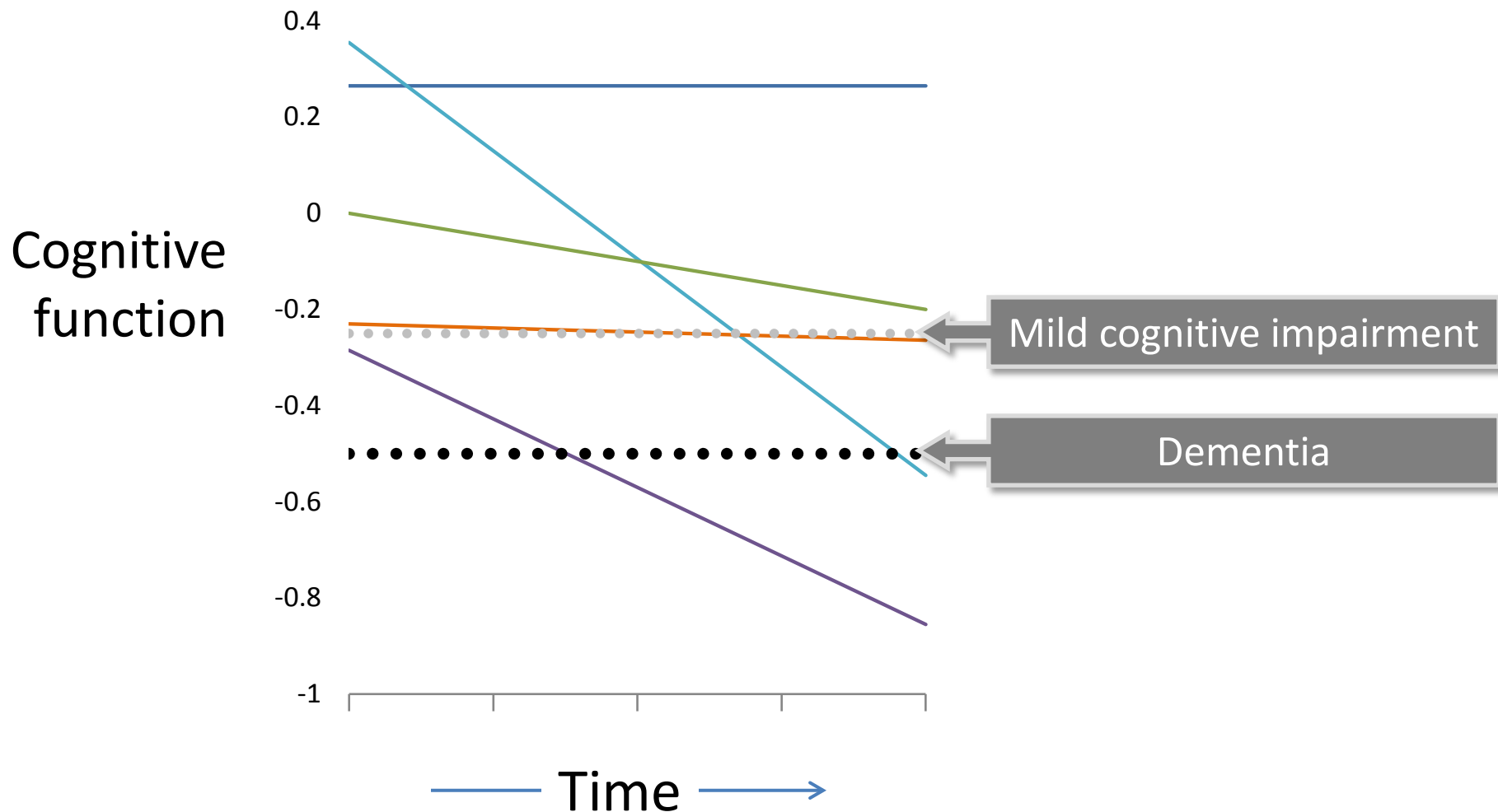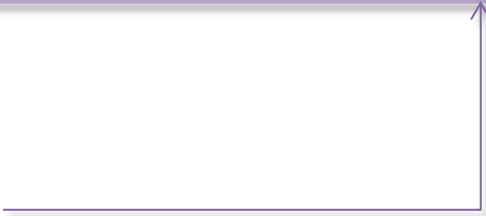
A systematic review

of published epidemiologic research

on the relation of air pollution exposure with dementia, its precursors and its correlates

Epidemiologic studies identified

9 studies of **cognition**

2 studies of **cognitive decline**

1 study of **brain imaging**

3 studies of **incident mild cognitive impairment (MCI) or dementia**

Dementia, its precursors and its correlates

The 9 studies of cognition

- Conducted in US, UK, Germany and China

- Most common exposures evaluated:
  - $PM_{2.5}$ (4)
  - Surrogates of traffic-related pollution (4)
  - PM_{10} (3)

Most studies of cognition evaluated exposure in 1- to 2-year intervals before or "around" the cognitive assessment

cognitive assessment

interval over which exposure was averaged

HRS
ACL
NHANES
LA RCTs
NAS
SALIA*
Whitehall II
MOBILIZE Boston
CLHLS
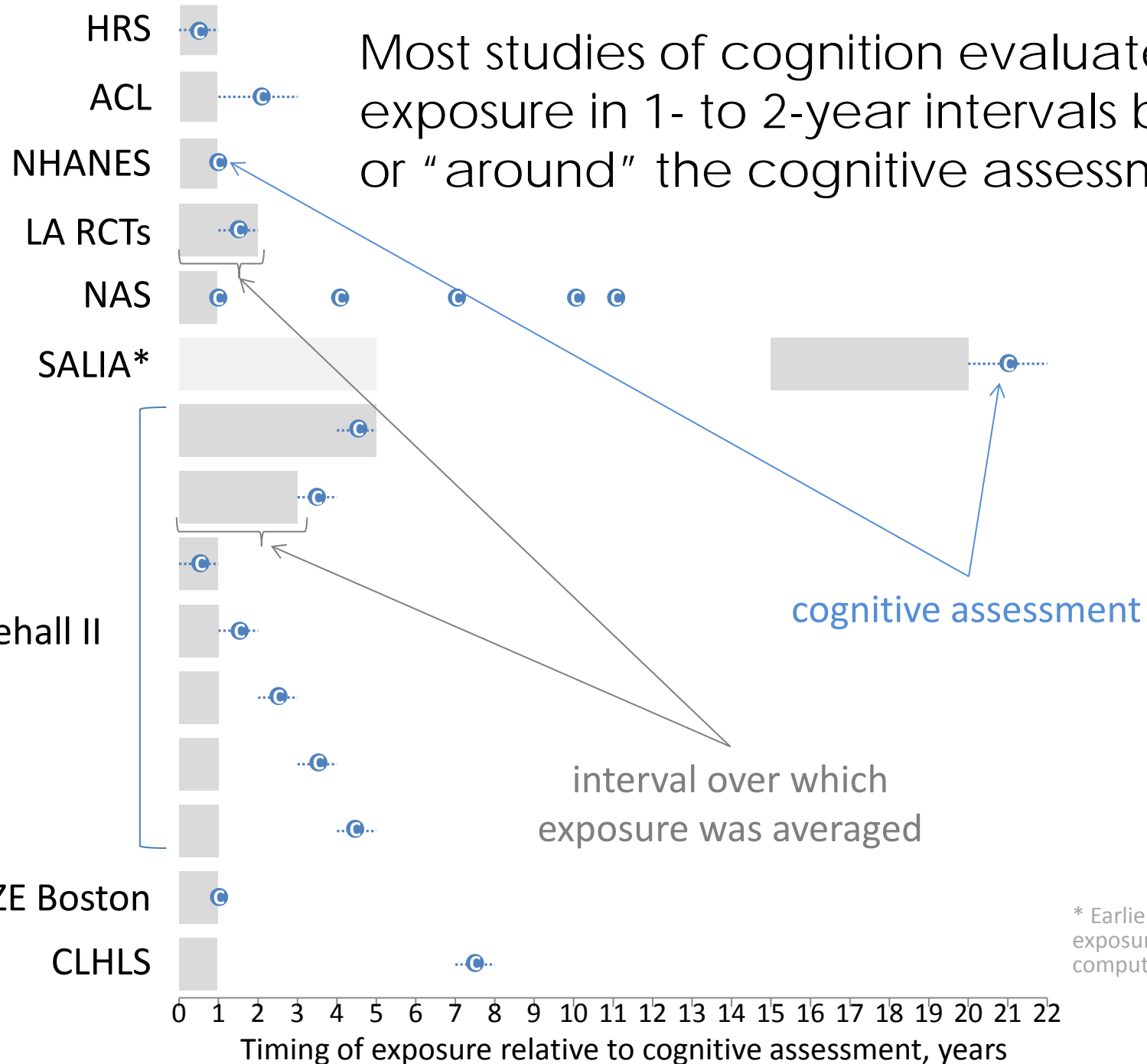
* Earlier and later exposure averages computed separately.

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

Timing of exposure relative to cognitive assessment, years

Studies of cognition: snapshot of associations with exposure

Study	Cohort	N	PM$_{10}$	PM coarse	PM$_{2.5}$	O$_3$	NO$_2$	CO	BC, traffic exhaust, DTR	API
Ailshire, 2014	HRS	13996			●					
Ailshire, 2014	ACL	780			●					
Chen, 2009	NHANES III	1764	X			●				
Gatto, 2014	LA RCTs	1496			▲	X	X			
Power, 2011	NAS (men)	680							●	
Ranft, 2009	SALIA (Germany)	399	X						▲	
Tonne, 2014	Whitehall II (London)	2867	▲		▲				X	
Wellenius, 2012	MOBILIZE Boston	765							●	
Zeng, 2010	CLHSL (China)	15973								●

● Adverse association   ▲ Some adverse associations, but inconsistent   X Pollutant studied, but null association

The 2 studies of cognitive decline

- Conducted in US and UK

- Both evaluated $PM_{2.5}$ and PM_{10}, along with other pollutants unique to each study.

The studies of cognitive decline evaluated decline over 4-5 years, but differed in how their exposure intervals were related temporally to the cognitive assessments

Timing of exposure interval relative to cognitive assessment, years
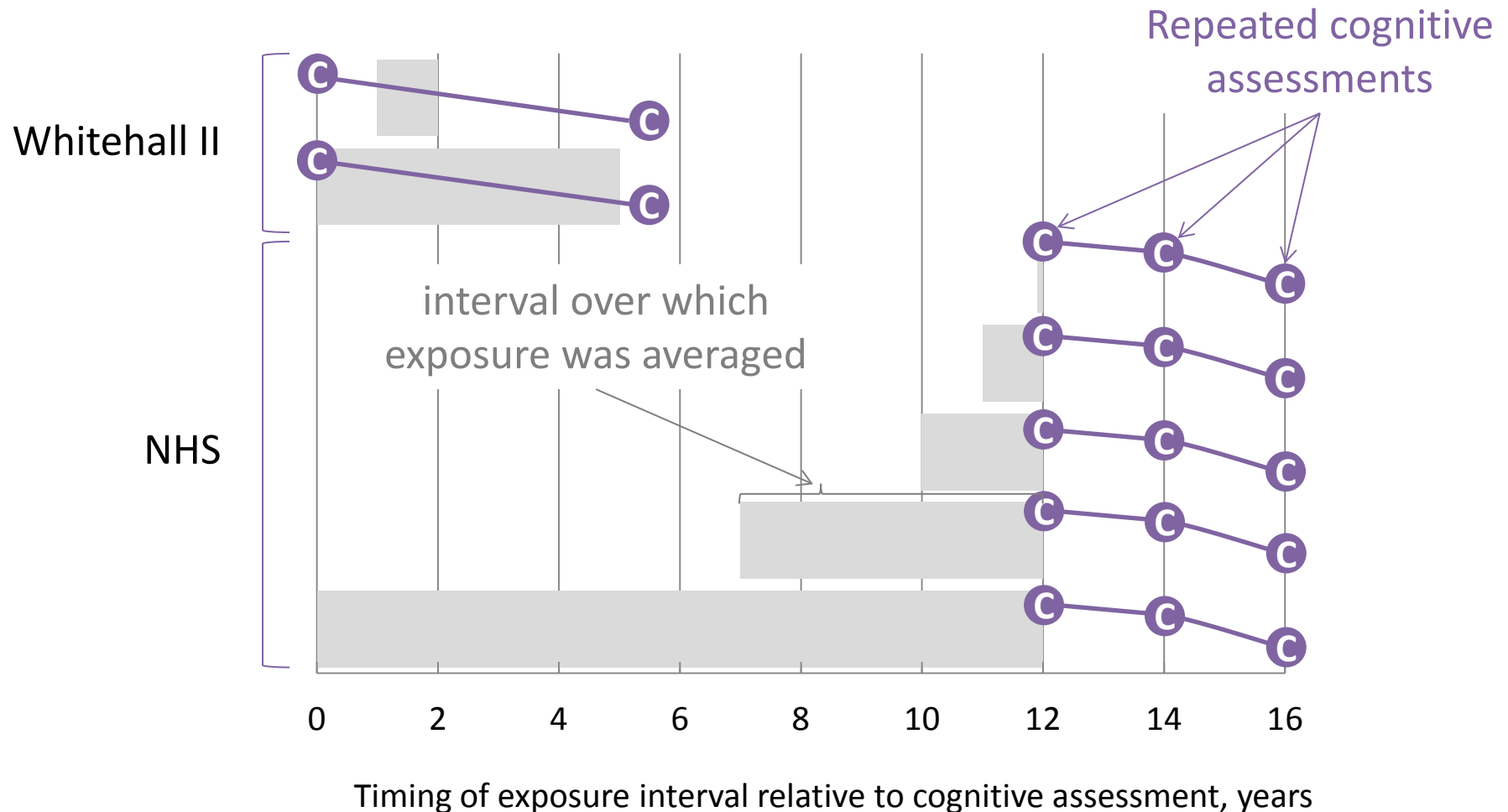
Studies of cognitive *decline*: snapshot of associations with exposure

Study	Cohort	N	PM_{10}	Pm_{co}	$PM_{2.5}$	O_3	NO_2	CO	BC, traffic exhaust, DTR	API
Tonne, 2014	Whitehall II (London)	13996	▲		▲				X	
Weuve, 2012	NHS (women)	19409	●	●	●					

● Adverse association   ▲ Some adverse associations, but inconsistent   X Pollutant studied, but null association

PM_{co} = coarse PM; DTR = distance to road; API = air pollution index

The study of brain imaging

- Conducted in US (New England)

- Evaluated $PM_{2.5}$ and surrogate of traffic-related air pollution.

- Used magnetic resonance imaging (MRI) measures of total brain volume, hippocampal volume, cerebral ischemic injury, and infarctions

The brain imaging study measured exposures around the time of imaging

FOS

Exposure averaged over 2001

Brain MRI

1998   1999   2000   2001   2002

Year
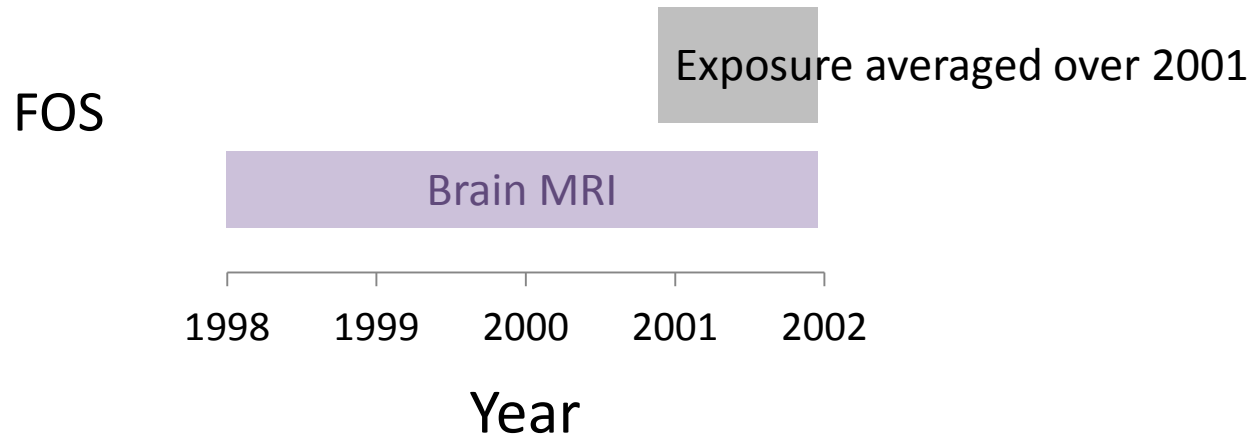
Study	Cohort	N	PM$_{10}$	PM$_{co}$	PM$_{2.5}$	O$_3$	NO$_2$	CO	BC, traffic exhaust, DTR	API
Wilker, 2015	FOS	929			⬤				X	

⬤ Adverse association   ▲ Some adverse associations, but inconsistent   X Pollutant studied, but null association

PM$_{co}$ = coarse PM; DTR = distance to road; API = air pollution index

The 3 studies of incident "mild cognitive impairment" (MCI) or dementia

- Conducted in US and Taiwan (2 studies in Taiwanese cohort)

- Two studies evaluated $PM_{2.5}$; other pollutants were unique to each study

The studies of MCI and dementia measured exposures before and around the time of outcome assessments

NHIRD (NO$_2$, CO)

Exposure averaged and updated thru event or censoring

Passive surveillance for dementia

NHIRD (PM$_{2.5}$, O$_3$)

Exposure averaged over year 2000*

Passive surveillance for dementia

REGARDS

Exposure averaged over yr before baseline

Annual MCI screening by phone

1998   2000   2002   2004   2006   2008   2010
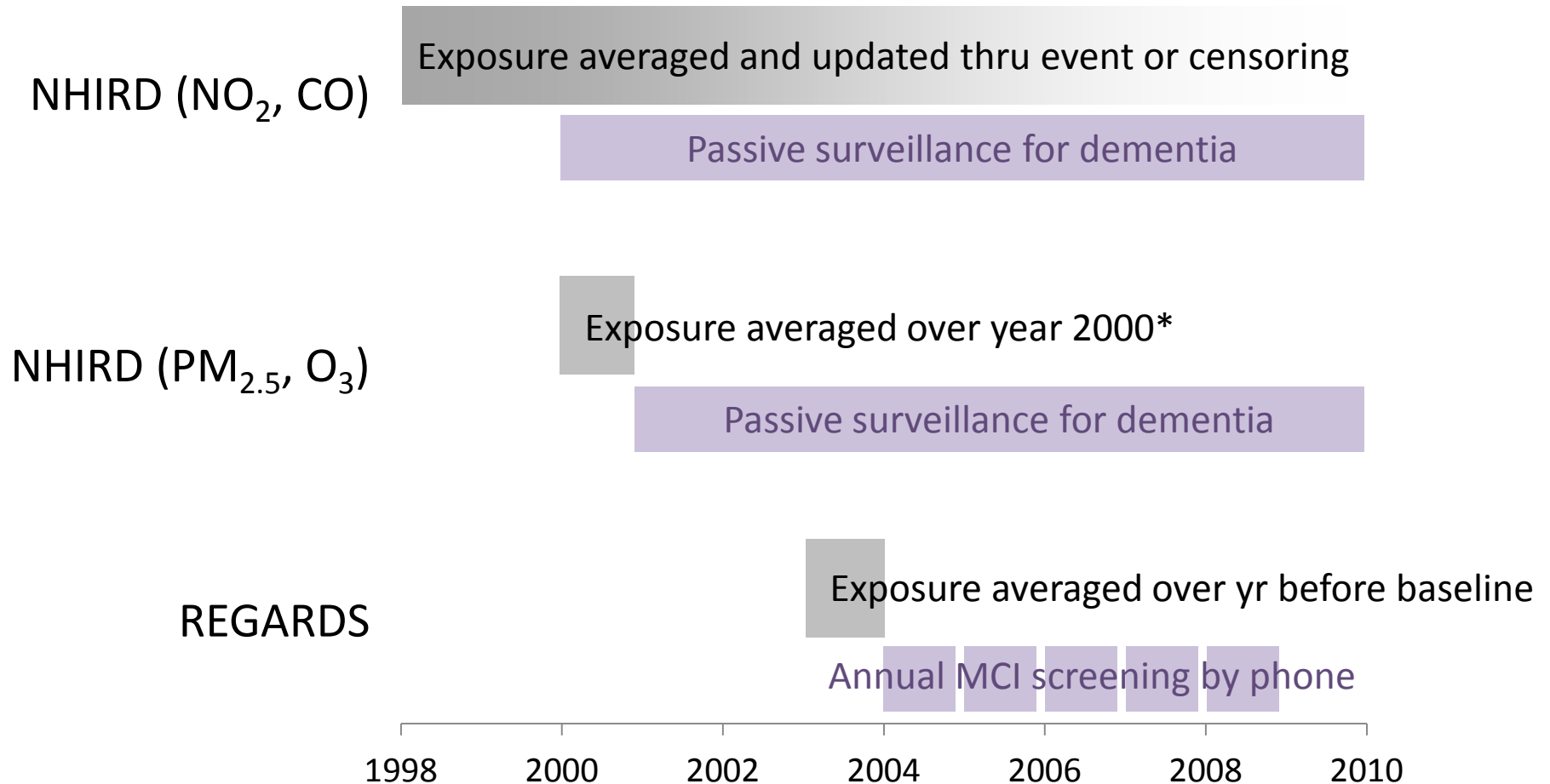
* Also evaluated change in pollutant exposures from 2000 thru event or censoring.

Year

Studies of "mild cognitive impairment" (MCI) or dementia: snapshot of associations with exposure

Study	Cohort	N	PM$_{10}$	PM$_{co}$	PM$_{2.5}$	O$_3$	NO$_2$	CO	BC, traffic exhaust, DTR	API
Chang, 2014	NHIRD (Taiwan)	29947					●	●		
Jung, 2014	NHIRD (Taiwan)	95960			X	●				
Loop, 2013	LA RCTs	20150			X					

● Adverse association   ▲ Some adverse associations, but inconsistent   X Pollutant studied, but null association

PM$_{co}$ = coarse PM; DTR = distance to road; API = air pollution index

Summary of findings

Pollutant	# studies	Association of higher exposure with dementia risk, its precursors and correlates
$PM_{2.5}$	9	Generally adverse
Traffic surrogates	6	Adverse but less consistent than $PM_{2.5}$
PM_{10}	5	Mixed, but adverse tendency
Ozone	3	Generally adverse (but only 3 studies)

Too few studies of other pollutants to adequately summarize.
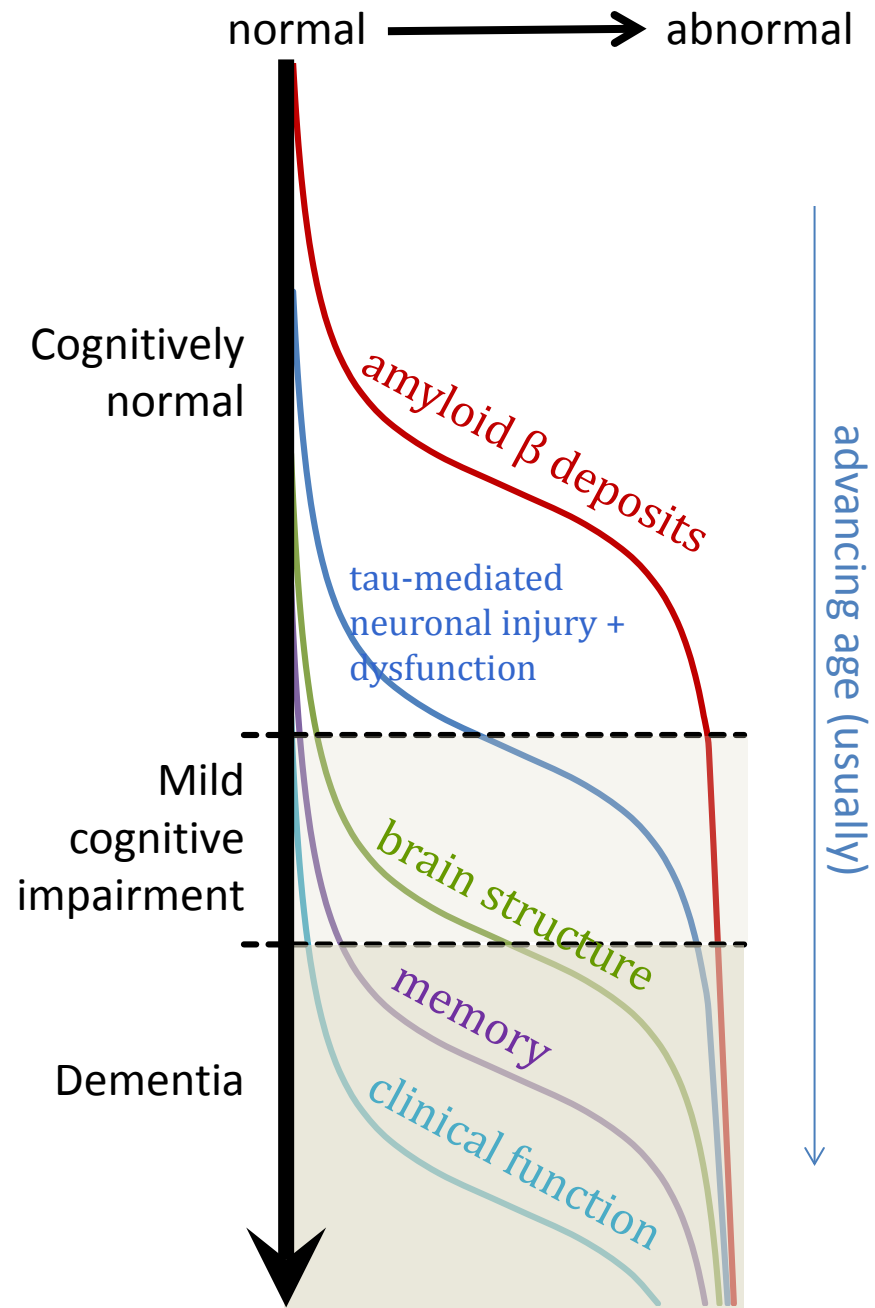
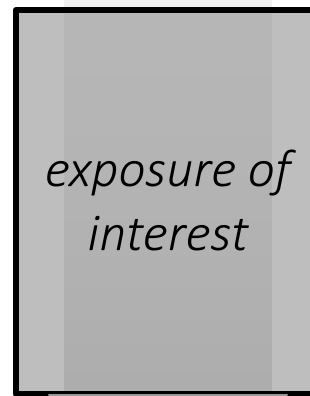# Strengths of this research

- Many studies extensively adjusted for socioeconomic factors
  - Major source of confounding
  - Especially in studies of cognition, dementia

- Many studies used "long-term" exposure metrics

Limitations of this research

- Many studies adjusted for putative intermediate factors
  - Stroke, cardiovascular factors, diabetes
  - Mood

- Temporal incoherence
  - Developing dementia is not an acute event
  - Some etiologic windows are likely to be long or distant
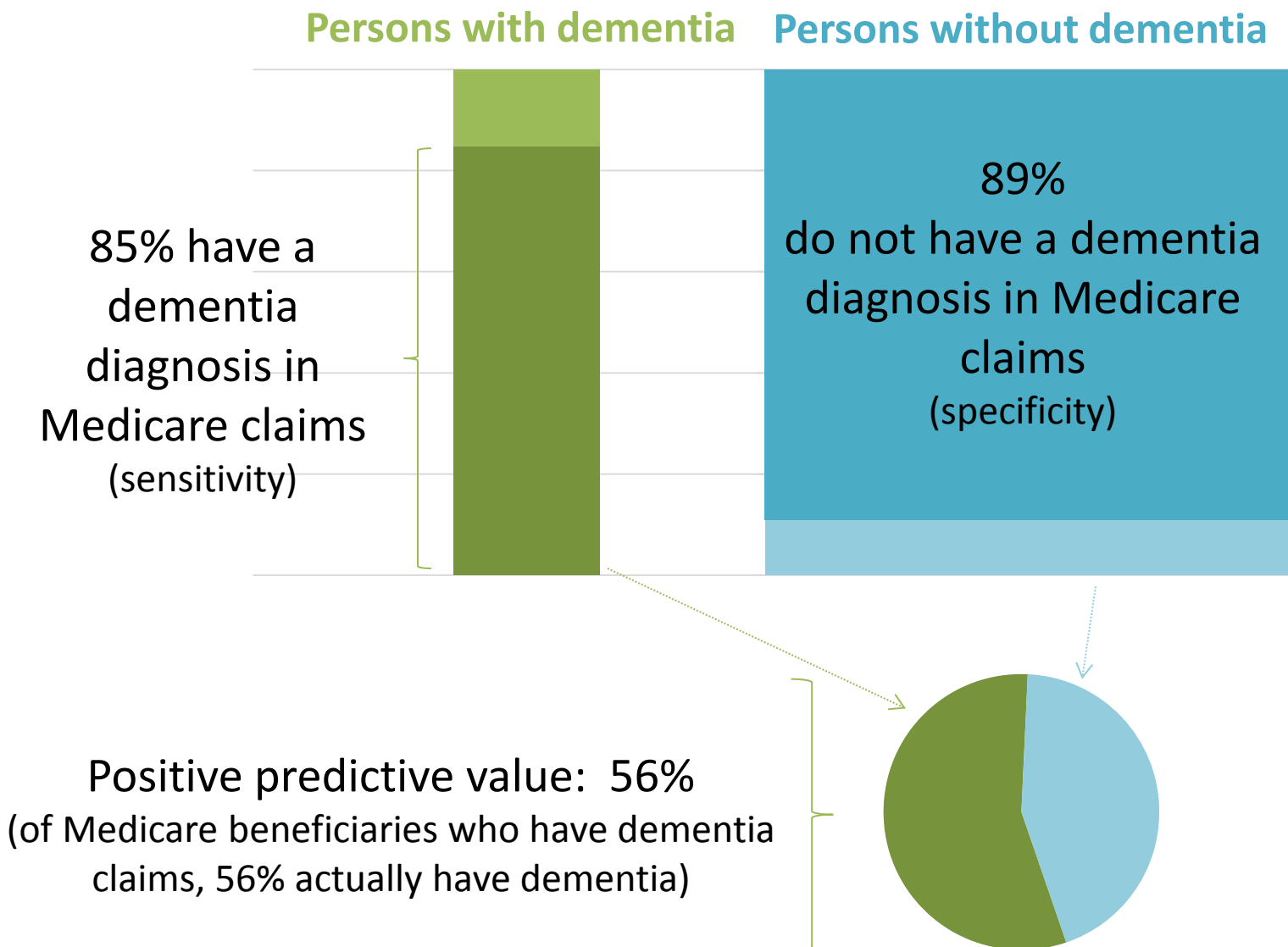
Late-life measures of exposure may miss the mark

- Measurement error

- Misspecified etiologic window

- Reverse causation

exposure of interest

measured exposure

normal → abnormal

Cognitively normal

Mild cognitive impairment

Dementia

amyloid β deposits

tau-mediated neuronal injury + dysfunction

brain structure

memory

clinical function

advancing age (usually)

Limitations of this research (2)

- Problematic outcome assessments
  - Mismatch of instrument to population's ability and possible disease state
  - Reliance on clinical data (passive surveillance)
    - Huge proportion of people with dementia are not diagnosed
    - Getting better, but still not optimal
    - Death certificates are even worse, likely missing 80-90% of AD cases

Example: Dementia diagnoses in Medicare claims

Persons with dementia   **Persons without dementia**

85% have a dementia diagnosis in Medicare claims
(sensitivity)

89% do not have a dementia diagnosis in Medicare claims
(specificity)

Positive predictive value: 56%
(of Medicare beneficiaries who have dementia claims, 56% actually have dementia)

Taylor *et al. J Alzheimers Dis.* 2009

Limitations of this research (3)

- Selection
  - Survival to study enrollment
  - Ability/willingness to participate
    - Often hinges on being unimpaired, mobile, and not too ill
    - Neuroimaging and lumbar puncture are often impractical
    - Home visits and telephone interviews can facilitate participation
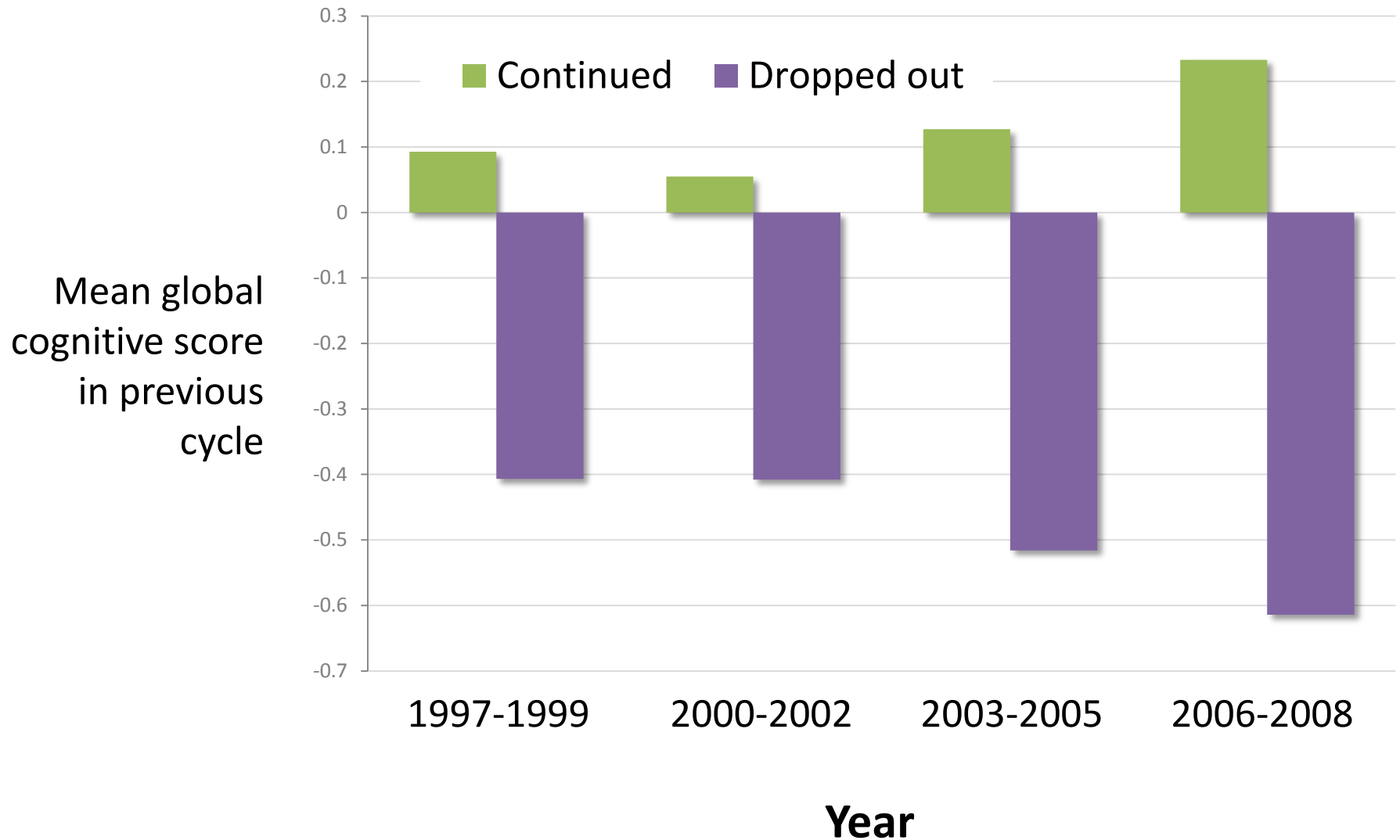 - Attrition after enrollment

Selection: attrition
An example from the Chicago Health and Aging Project

Number of active participants
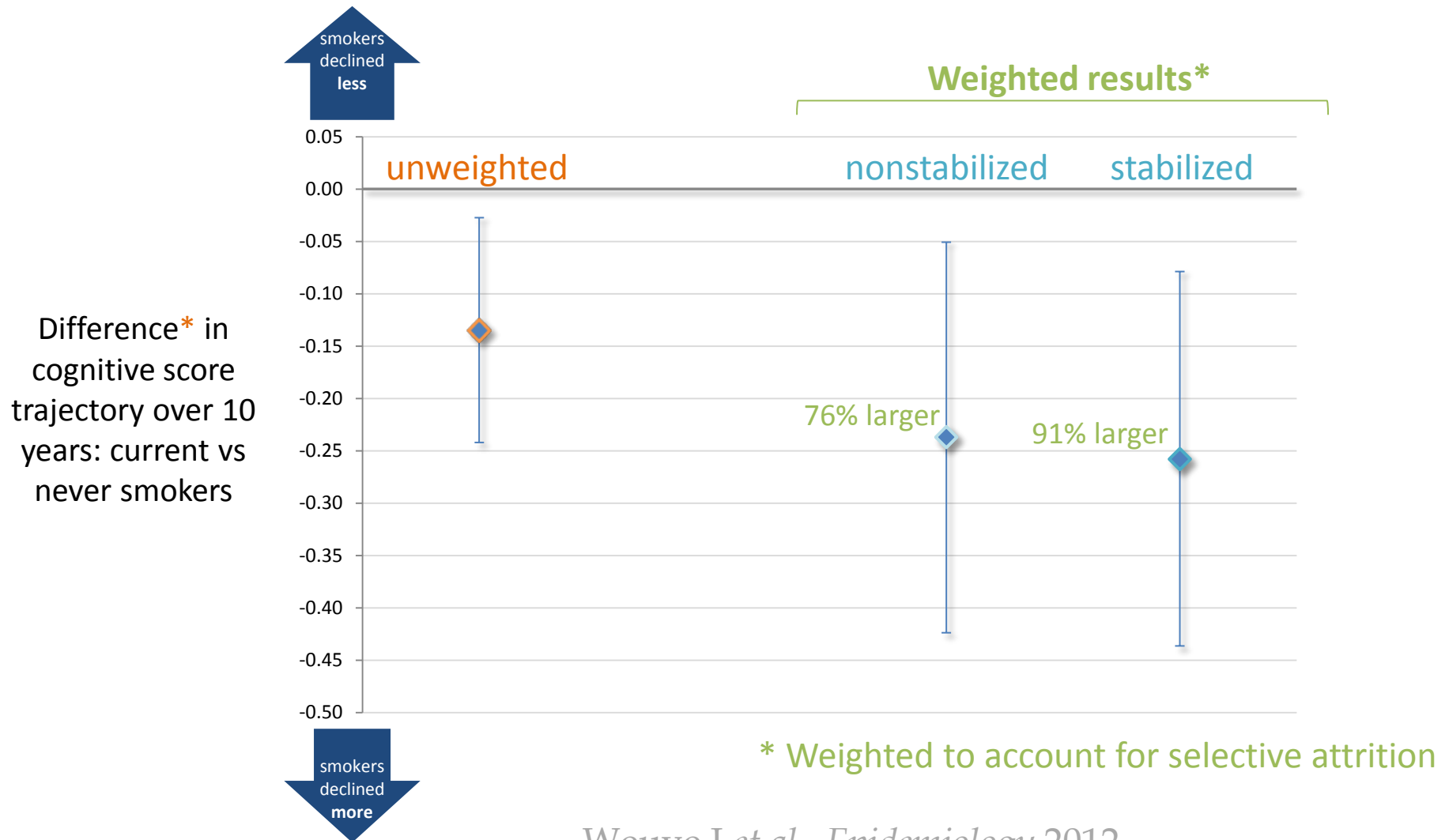
80% lost
(mainly because of death)
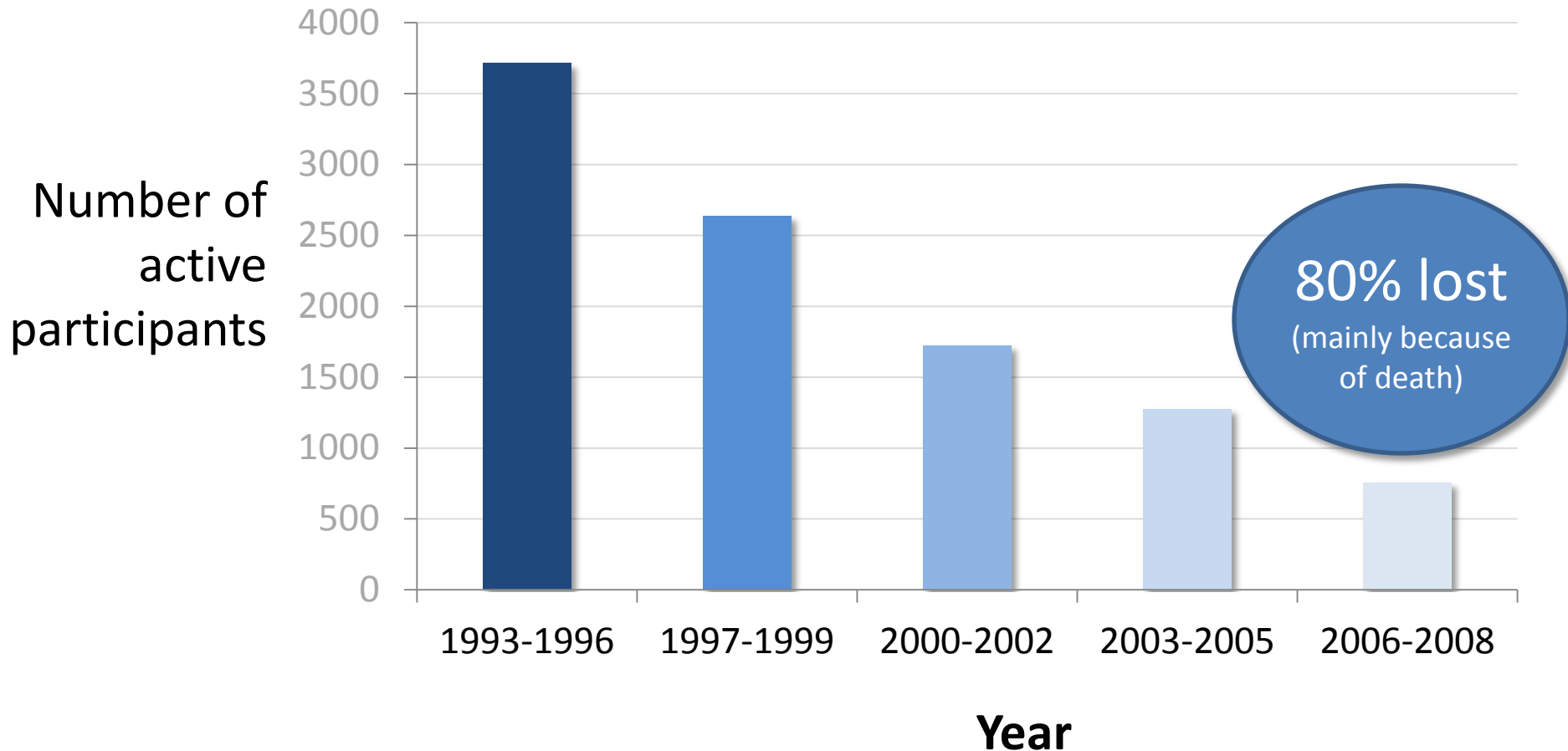
Unfortunately, cognition is often associated with attrition
Example from the Chicago Health and Aging Project (continued)

Example of difference in findings from analyses that account for vs ignore attrition:
current smoking and rate of cognitive decline

Weuve J *et al.*, *Epidemiology* 2012

Pros + cons
of researching specific outcomes

	COGNITION	DEMENTIA	COGNITIVE DECLINE	NEURO-IMAGING / CSF	AUTOPSY
Pathophysiologic mechanisms				++	++
Temporal clarity		-			--
Ease of participation	++		++	--	--
Efficient and inexpensive	++	-	+	---	--
Confounding	-	-	+		
Selection bias		-		--	--

Used and interpreted carefully, research on ALL of these outcomes can serve the evidence base.

FUTURE NEEDS

Although there are now 14 published epidemiologic papers, many gaps remain that have implications for our understanding and for intervening. Needs:

- More cross-disciplinary collaboration

<div align="right">--Weuve, Am J Epidemiol. 2014</div>

- More studies of cognitive *decline*

- Studies of dementia that incorporate systematic diagnostic assessments

The count is 14 instead of 15, because Tonne reported on cognitive function and cog decline, thus the paper contributed to 2 sets of results here.

FUTURE NEEDS (continued)

- More studies of specific pollutants + speciation studies/NPACT equivalent for the aging brain

- Consideration of noise

- Evaluations of intervention effects (e.g., real or hypothesized effects of regulatory changes on the dementia epidemic)

- Studies of dose, timing (duration, critical windows)

- Mediation studies (e.g., how exposure affects brain via cerebrovascular damage)

--Valeri & Vanderweele, *Psychol Methods*. 2012

RESOURCES

- Your friendly neighborhood dementia epidemiologist

- The MEthods for Longitudinal studies in DEMentia (MELODEM) initiative

- The AlzRisk Project

- Integrative Analysis of Longitudinal Studies of Aging (IALSA)

- IOM Report on Cognitive Aging

Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS): Clues from research on smoking

- PD
  - Consistent finding of *inverse* association of smoking with risk
  - Indication that nicotine may inhibit key pathogenic pathway in PD (formation of α-synuclein fibrils)

    --Wirdefeldt K *et al., Eur J Epidemiol.* 2011

    Outdoor air pollution contains almost no nicotine

- ALS
  - Smoking appears to increase risk, but inconsistent by sex and age

    --Ingre C *et al., Clin Epidemiol.* 2015

Little epidemiologic research has been conducted on air pollution exposure in relation to PD and ALS

- 3 studies of PD

  - No association with PM_{10}, $PM_{2.5}$ or coarse fraction ($PM_{10-2.5}$)

    --Palacios N *et al.*, *Environ. Health* 2014

  - Higher risk with higher ambient Mn

    --Finkelstein MM & Jerrett M, *Environ Health* 2007

  - Higher risk with proximity to industrial Cu and Mn emissions

    --Willis AW *et al.*, *Am J Epidemiol* 2010

- No studies of ALS

- Yet *toxicologic and ecologic evidence are suggestive*

ACKNOWLEDGMENTS