AIR POLLUTION & the AGING BRAIN

Jennifer Weuve, MPH, ScD
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)

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.

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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


Hebert LE, *Neurology* 2013

# persons in the US w/ AD, millions

Forecast

2000 2010 2020 2030 2040 2050

Year
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.

Hebert LE, *Neurology* 2013
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

Similar findings for cognition and cognitive decline.

Zhong G et al., PLoS ONE 2015
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

<table>
<thead>
<tr>
<th>Source/year</th>
<th>ES(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowen (2012)</td>
<td>1.00 (0.47, 2.14)</td>
</tr>
<tr>
<td>Rusanen (2011)</td>
<td>1.00 (0.94, 1.07)</td>
</tr>
<tr>
<td>Lin (2011)</td>
<td>1.01 (0.61, 1.67)</td>
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<tr>
<td>Kimm (Man) (2011)</td>
<td>1.00 (0.85, 1.17)</td>
</tr>
<tr>
<td>Kimm (Woman) (2011)</td>
<td>1.10 (0.92, 1.32)</td>
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<tr>
<td>Gao (2011)</td>
<td>0.93 (0.71, 1.21)</td>
</tr>
<tr>
<td>Chen (2011)</td>
<td>1.66 (0.53, 5.18)</td>
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<tr>
<td>Powe (2011)</td>
<td>1.05 (0.93, 1.19)</td>
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<tr>
<td>Rusanen (2010)</td>
<td>0.71 (0.26, 1.92)</td>
</tr>
<tr>
<td>Alonso (2009)</td>
<td>1.00 (0.73, 1.36)</td>
</tr>
<tr>
<td>Reitz (2007)</td>
<td>1.17 (0.92, 1.48)</td>
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<tr>
<td>Laurin (2007)</td>
<td>0.82 (0.64, 1.06)</td>
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<tr>
<td>Rosengren (2005)</td>
<td>1.07 (0.75, 1.52)</td>
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<tr>
<td>Cherubini (2005)</td>
<td>0.56 (0.30, 1.03)</td>
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<tr>
<td>Laurin (2004)</td>
<td>0.89 (0.67, 1.19)</td>
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<tr>
<td>Juan (2004)</td>
<td>1.52 (1.09, 2.12)</td>
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<tr>
<td>Tyas (2003)</td>
<td>0.80 (0.58, 1.10)</td>
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<tr>
<td>Launer (1999)</td>
<td>1.03 (0.79, 1.34)</td>
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<tr>
<td>Broe (1998)</td>
<td>1.08 (0.53, 2.20)</td>
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<tr>
<td>Overall (I-squared = 63%, p = 0.379)</td>
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</tbody>
</table>

1.01 (0.96, 1.06)

Zhong G et al., PLoS ONE 2015
By the time dementia emerges, many changes have been underway ... for years.
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.
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:
  - $\text{PM}_{2.5}$ (4)
  - Surrogates of traffic-related pollution (4)
  - $\text{PM}_{10}$ (3)
Most studies of cognition evaluated exposure in 1- to 2-year intervals before or “around” the cognitive assessment.

* Earlier and later exposure averages computed separately.
Studies of cognition: snapshot of associations with exposure

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

- **Adverse association**
- **Some adverse associations, but inconsistent**
- **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

Repeated cognitive assessments

interval over which exposure was averaged

Whitehall II

NHS
Studies of cognitive decline: snapshot of associations with exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>N</th>
<th>PM$_{10}$</th>
<th>Pm$_{co}$</th>
<th>PM$_{2.5}$</th>
<th>O$_3$</th>
<th>NO$_2$</th>
<th>CO</th>
<th>BC, traffic exhaust, DTR</th>
<th>API</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonne, 2014</td>
<td>Whitehall II (London)</td>
<td>13996</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weuve, 2012</td>
<td>NHS (women)</td>
<td>19409</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
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</tbody>
</table>

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

Adverse association

Some adverse associations, but inconsistent

Pollutant studied, but null association
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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>N</th>
<th>PM$_{10}$</th>
<th>PM$_{co}$</th>
<th>PM$_{2.5}$</th>
<th>O$_3$</th>
<th>NO$_2$</th>
<th>CO</th>
<th>BC, traffic exhaust, DTR</th>
<th>API</th>
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</thead>
<tbody>
<tr>
<td>Wilker, 2015</td>
<td>FOS</td>
<td>929</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

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 (NO₂, CO)**
  - Exposure averaged and updated thru event or censoring
  - Passive surveillance for dementia

- **NHIRD (PM_{2.5}, O₃)**
  - Exposure averaged over year 2000*
  - Passive surveillance for dementia

- **REGARDS**
  - Exposure averaged over yr before baseline
  - Annual MCI screening by phone

- *Also evaluated change in pollutant exposures from 2000 thru event or censoring.*
Studies of “mild cognitive impairment” (MCI) or dementia: snapshot of associations with exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>N</th>
<th>PM$_{10}$</th>
<th>PM$_{co}$</th>
<th>PM$_{2.5}$</th>
<th>O$_3$</th>
<th>NO$_2$</th>
<th>CO</th>
<th>BC, traffic exhaust, DTR</th>
<th>API</th>
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</thead>
<tbody>
<tr>
<td>Chang, 2014</td>
<td>NHIRD (Taiwan)</td>
<td>29947</td>
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<td>X</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Jung, 2014</td>
<td>NHIRD (Taiwan)</td>
<td>95960</td>
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</tr>
<tr>
<td>Loop, 2013</td>
<td>LA RCTs</td>
<td>20150</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- **Adverse association**
- Some adverse associations, but inconsistent
- Pollutant studied, but null association

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

<table>
<thead>
<tr>
<th>Pollutant</th>
<th># studies</th>
<th>Association of higher exposure with dementia risk, its precursors and correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{PM}_{2.5}$</td>
<td>9</td>
<td>Generally adverse</td>
</tr>
<tr>
<td>Traffic surrogates</td>
<td>6</td>
<td>Adverse but less consistent than $\text{PM}_{2.5}$</td>
</tr>
<tr>
<td>$\text{PM}_{10}$</td>
<td>5</td>
<td>Mixed, but adverse tendency</td>
</tr>
<tr>
<td>Ozone</td>
<td>3</td>
<td>Generally adverse (but only 3 studies)</td>
</tr>
</tbody>
</table>

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

Cognitively normal

amyloid $\beta$ deposits

tau-mediated neuronal injury + dysfunction

Mild cognitive impairment

brain structure

memory

clinical function

Dementia

advancing age (usually)

normal $\rightarrow$ abnormal
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

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)

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of active participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993-1996</td>
<td>3500</td>
</tr>
<tr>
<td>1997-1999</td>
<td>2500</td>
</tr>
<tr>
<td>2000-2002</td>
<td>1500</td>
</tr>
<tr>
<td>2003-2005</td>
<td>1000</td>
</tr>
<tr>
<td>2006-2008</td>
<td>500</td>
</tr>
</tbody>
</table>

80% lost (mainly because of death)
Unfortunately, cognition is often associated with attrition.

Example from the Chicago Health and Aging Project (continued)

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean global cognitive score in previous cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-1999</td>
<td>0.1</td>
</tr>
<tr>
<td>2000-2002</td>
<td>0.1</td>
</tr>
<tr>
<td>2003-2005</td>
<td>0.2</td>
</tr>
<tr>
<td>2006-2008</td>
<td>0.3</td>
</tr>
</tbody>
</table>

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

Difference* in cognitive score trajectory over 10 years: current vs never smokers

* Weighted to account for selective attrition

Weuve J et al., Epidemiology 2012
Pros + cons of researching specific outcomes

<table>
<thead>
<tr>
<th></th>
<th>COGNITION</th>
<th>DEMENTIA</th>
<th>COGNITIVE DECLINE</th>
<th>NEURO-IMAGING / CSF</th>
<th>AUTOPSY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiologic mechanisms</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td>++</td>
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<tr>
<td>Temporal clarity</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>--</td>
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<tr>
<td>Ease of participation</td>
<td>++</td>
<td></td>
<td>++</td>
<td>--</td>
<td>--</td>
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<tr>
<td>Efficient and inexpensive</td>
<td>++</td>
<td></td>
<td>-</td>
<td>+</td>
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<tr>
<td>Confounding</td>
<td>-</td>
<td></td>
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<td>+</td>
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<tr>
<td>Selection bias</td>
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</tbody>
</table>

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
  

- 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
RESO URC ES

- 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)

- **ALS**
  - Smoking appears to increase risk, but inconsistent by sex and age
    -- Ingre C *et al.*, *Clin Epidemiol.* 2015

Outdoor air pollution contains almost no nicotine
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
  - 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
ACKNOWLEDGEMENTS

- Melinda Power

- Joel Kaufman, Cynthia Curl, Adam Szpiro, Todd Beck, Denis Evans, Carlos Mendes de Leon
THANK YOU.