DEMENTIA

What it is

deficits in **memory**, language, problem-solving and other **cognitive skills** that affects a person's **ability to perform everyday activities**.
Dementia is not part of “normal aging,” but it is strikingly common.

Prevalent cases among US adults, aged 65 and older:

- Amyotrophic lateral sclerosis (ALS)
- Parkinson’s disease
- Stroke
- Alzheimer’s disease dementia (AD)
Alzheimer’s disease is the most common cause of dementia

Pathologically characterized by:

- amyloid beta *plaques* between neurons
- Abnormal form of tau (a protein that organizes the neuron’s microtubules) → *neurofibrillary tangles*
- neuronal death
Although AD dementia is common, most AD pathology occurs with other pathologies.

AD dementia prevalence expected to triple

# persons in the US w/ AD, millions

Year

Forecast

Hebert LE, Neurology 2013
No relief in sight

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

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

- Effective **treatment does not exist**
Broadly based interventions—e.g., cutting widespread exposures to a causal agent—could reduce population burden of dementia

Forecast with intervention that delays AD onset by 2 years

Hebert LE, Neurology 2013
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 process that reflects progression toward dementia (or beyond).
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

Elevates risk of cardiovascular disease, stroke, and vascular risk factors (e.g., hypertension)
A systematic review of published epidemiologic research evaluating the relation of air pollution exposure with dementia, cognitive decline and associated outcomes.

Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential contributor to cognitive decline. *NeuroToxicology* (in press).
Goals of the review

Catalogue the results of existing epidemiologic studies

Describe how these results were obtained

Interpret the results in light of how the studies were conducted
Epidemiologic studies identified

10 studies of cognition
2 studies of cognitive decline
2 studies of brain imaging
4 studies of incident cognitive impairment or dementia
1 study of hospital admissions for dementia
Epidemiologic studies identified

- 10 studies of cognition
- 2 studies of cognitive decline
- 2 studies of brain imaging
- 4 studies of incident cognitive impairment or dementia
- 1 study of hospital admissions for dementia

Dementia  Cognitive decline  Associated outcomes
The 10 studies of cognition

- Conducted in US, UK, Germany and China

- Most common exposures evaluated:
  - Surrogates of *traffic-related pollution* (5)
  - Fine PM \((\text{PM}_{2.5})\) (5)
  - Fine + thoracic PM \((\text{PM}_{10})\) (4)
Many studies of cognition evaluated exposure in 1- to 2-year intervals before or “around” the cognitive assessment interval over which exposure was averaged.
### Snapshot of associations between exposure and cognition

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>N</th>
<th>PM&lt;sub&gt;10&lt;/sub&gt;</th>
<th>PM&lt;sub&gt;co&lt;/sub&gt;</th>
<th>PM&lt;sub&gt;2.5&lt;/sub&gt;</th>
<th>O&lt;sub&gt;3&lt;/sub&gt;</th>
<th>NO&lt;sub&gt;2&lt;/sub&gt;</th>
<th>CO</th>
<th>Traffic-related pollutants, DTR</th>
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<td>Ailshire, 2014</td>
<td>HRS</td>
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<td>Chen, 2009</td>
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<td>Power, 2011</td>
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<td>Ranft, 2009</td>
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<td>Wellenius, 2012</td>
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<td>Zeng, 2010</td>
<td>CLHSL (China)</td>
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</table>

- **Adverse association**
- **Some adverse associations, but inconsistent**
- **Pollutant studied, but null association**
The 2 studies of brain imaging

- Conducted in the US

- Both evaluated $\text{PM}_{2.5}$

- Used magnetic resonance imaging (MRI) measures of
  - total brain volume
  - regional volumes (e.g., hippocampal volume)
  - white and grey matter volumes
  - cerebral ischemic injury, and infarctions
The brain imaging study measured exposures around the time of imaging.
### Snapshot of associations between exposure and MRI measures

<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>Traffic-related pollutants, DTR</th>
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<td>Chen, 2015</td>
<td>WHIMS-MRI</td>
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<td>Wilker, 2015</td>
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<td>X</td>
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</tbody>
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- **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 $\text{PM}_{2.5}$ and $\text{PM}_{10}$, 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.
Snapshot of associations between exposure and cognitive decline

<table>
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<tr>
<th>Study</th>
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<th>N</th>
<th>PM$_{10}$</th>
<th>PM$_{co}$</th>
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<th>O$_3$</th>
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<td>Tonne, 2014</td>
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<tr>
<td>Weuve, 2012</td>
<td>NHS (women)</td>
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- **Adverse association**
- **Some adverse associations, but inconsistent**
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The 4 studies of incident “cognitive impairment” or dementia

- Conducted in Taiwan, Sweden and the US

- Most common pollutant evaluated: PM$_{2.5}$ (2)
Some studies of CI and dementia measured exposures before, some after, and some around the time of the outcome assessments.
## Snapshot of associations between exposure and cognitive impairment or dementia

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<tr>
<th>Study</th>
<th>Cohort</th>
<th>N</th>
<th>PM$_{10}$</th>
<th>PM$_{\text{co}}$</th>
<th>PM$_{2.5}$</th>
<th>O$_3$</th>
<th>NO$_2$</th>
<th>CO</th>
<th>Traffic-related pollutants, DTR</th>
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<td>Jung, 2014</td>
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<td>Loop, 2013</td>
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<td>Oudin, 2015</td>
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- **Adverse association**
- **Some adverse associations, but inconsistent**
- **Pollutant studied, but null association**
# Summary of findings

<table>
<thead>
<tr>
<th>Pollutant</th>
<th># studies</th>
<th>Association of higher exposure with cognitive decline, dementia risk, and related outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$PM_{2.5}$</td>
<td>11</td>
<td>Generally adverse</td>
</tr>
<tr>
<td>Traffic surrogates</td>
<td>8</td>
<td>Adverse but less consistent than $PM_{2.5}$</td>
</tr>
<tr>
<td>$PM_{10}$</td>
<td>6</td>
<td>Mixed, but adverse tendency</td>
</tr>
<tr>
<td>$NO_2$ and ozone</td>
<td>3 each</td>
<td>Generally adverse (but only 3 studies)</td>
</tr>
</tbody>
</table>

Too few studies of other pollutants to meaningfully summarize.
Strengths of the research

- Many studies used "long-term" exposure metrics

- Many studies extensively accounted for socioeconomic factors
  - Major source of bias
  - Especially in studies of cognition, dementia
Could some other factor explain the adverse associations?

From sensitivity analyses of 2 studies, such a confounding factor would have to be:

Unmeasured confounding factor
e.g.,
—socioeconomic disadvantage
—another exposure

Air pollution exposure

Dementia
Could some other factor explain the adverse associations?

From sensitivity analyses of 2 studies, such a confounding factor would have to be:

**Unmeasured confounding factor**
e.g.,
— socioeconomic disadvantage
— another exposure

*strongly related to exposure* AND *dementia outcome*

Air pollution exposure

Dementia

- Amyloid plaques
- Neurofibrillary tangles
- Disintegrating microtubules
- Tau protein clumps
Limitations of the research

- Many studies **adjusted for putative intermediate factors**
  - Stroke, cardiovascular factors, diabetes, mood
  → **results might not reflect total effect of air pollution** on dementia outcome (among other problems)

- **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
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
    - Death certificates can be 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

  Likely to result in underestimates of adverse effects on aging brain
Unfortunately, cognition is often associated with attrition. Example from the Chicago Health and Aging Project.
POLICY IMPLICATIONS

- The aging brain has not been part of policy deliberations.

- **Is it time to bring it into the discussion? Probably:**
  - Quality, consistency, volume and plausibility of evidence
  - Associations observed at low levels
  - Wide-spread exposures
  - Oncoming dementia epidemic

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Forecast with intervention that delays AD onset by 2 years

**potential for substantial public health impact**
FUTURE NEEDS

- More studies of **cognitive decline**
- Studies of dementia that incorporate **systematic diagnostic assessments**
- More studies of **specific pollutants** + particle speciation
- Studies of **dose, timing** (duration, critical windows)
- Joint consideration of **noise**
- Evaluations of **intervention effects** (e.g., real or hypothesized effects of regulatory changes on the dementia epidemic)
ACKNOWLEDGMENTS

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Melinda Power, Sara Adar, Jeff Yanosky

CHICAGO HEALTH and AGING PROJECT
Todd Beck, Denis Evans
Thank you.