Do Anticholinergic Drugs Cause Dementia?

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Advances in the treatment of dementia

- There aren’t any
- Right now, the best intervention for dementia is PREVENTION
- We definitely don’t want to INCREASE our patients’ risk of developing dementia

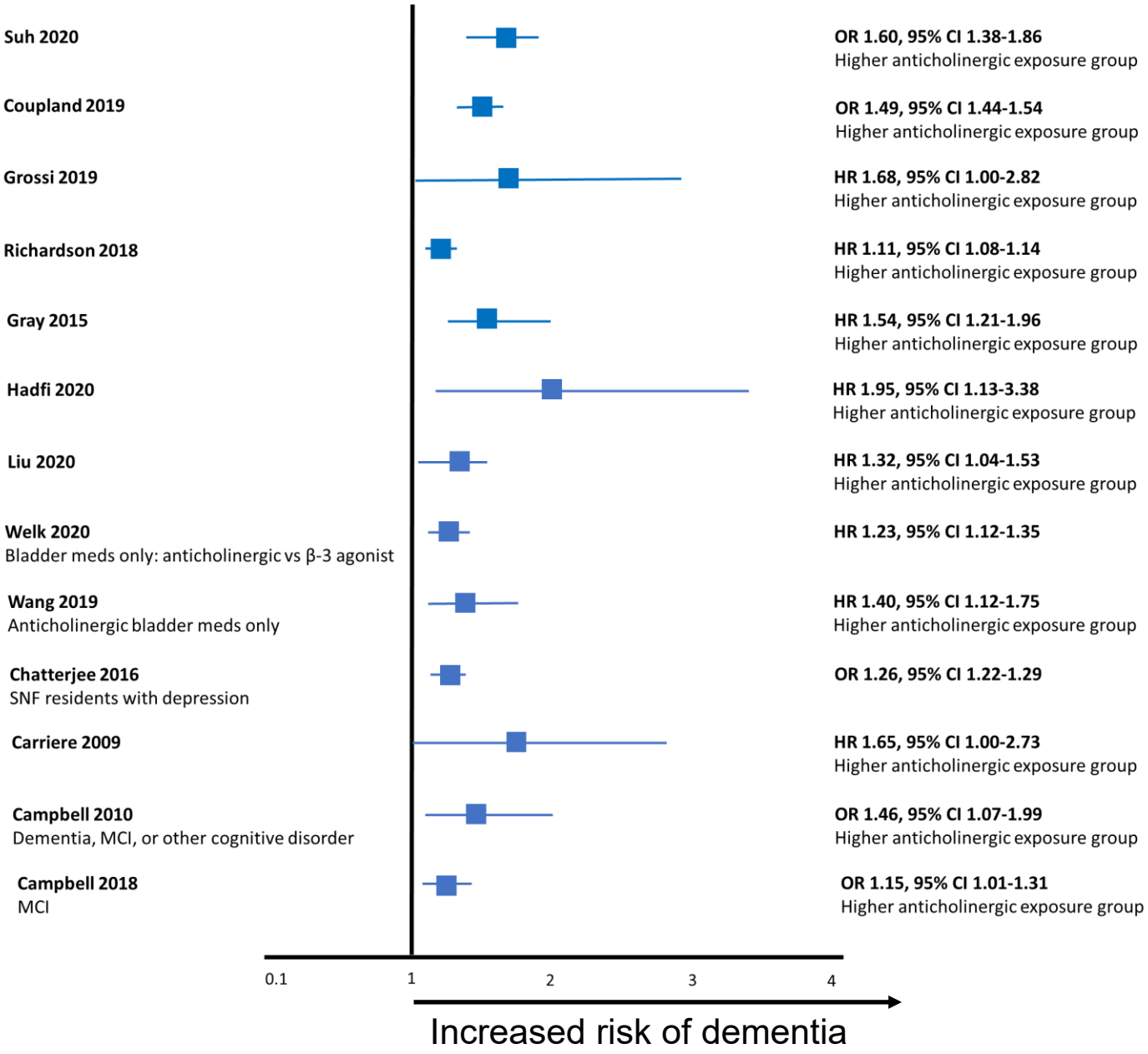
Prevention of dementia—what can we directly control?

- Can counsel our patients on lifestyle interventions and offer treatment—but often very hard to make these changes
  - Ambivalence
  - Socioeconomic barriers
  - Psychosocial barriers
  - Difficult to make/sustain behavior change
    - Exercise
    - Smoking cessation
    - Social isolation
    - Hearing aids
- Factors which require large-scale social change
  - Air pollution
  - Lack of access to education

We have a great deal of control over which medications we prescribe

- IF there are medications that can cause dementia, AND we stop prescribing them, THEN we have a way to help prevent dementia in our patients that is:
  - Easy
  - Almost fully within our control
- So, are there commonly used medications that can cause dementia?
  - Can these medications be replaced by other interventions that are cognitively safe and equally/more effective at treating the underlying conditions?
- Hypothesis: anticholinergic drugs can directly cause dementia, and safe/effective alternatives exist
  - Let’s examine the evidence

Anticholinergic drug use and dementia



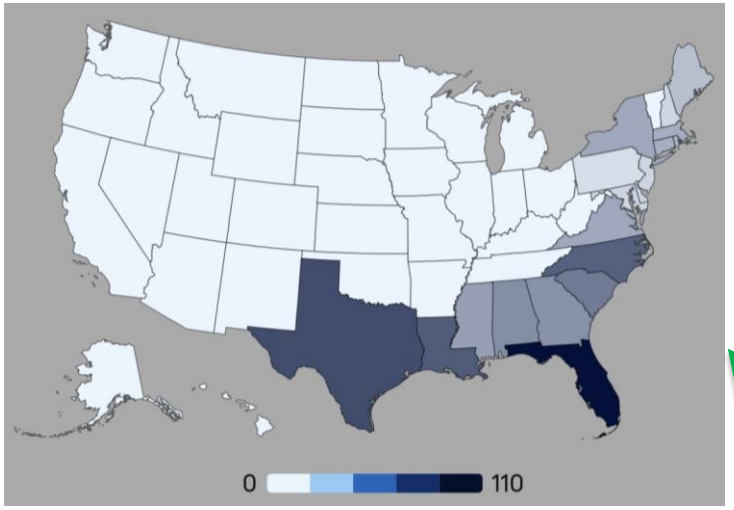
Link between anticholinergic drug use and dementia

- A large and growing body of evidence shows that individuals who take anticholinergic drugs have a higher risk of later developing irreversible dementia
  - NOT just short-term cognitive side effects
- Do the anticholinergic drugs actually CAUSE the dementia?

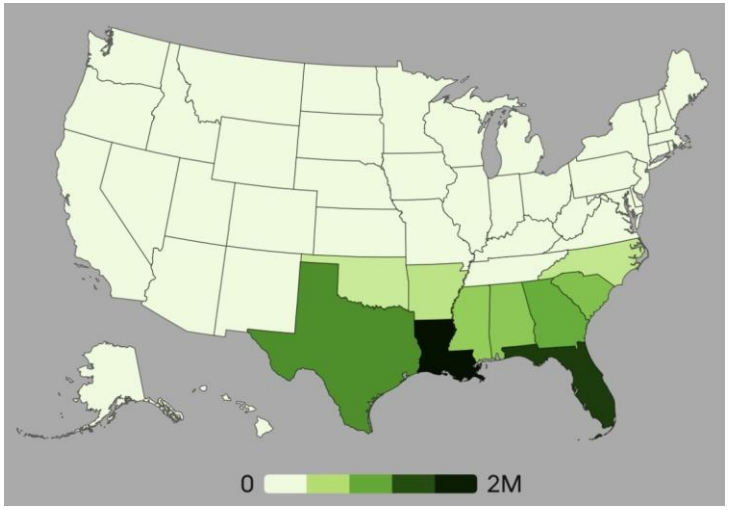
Establishing causality

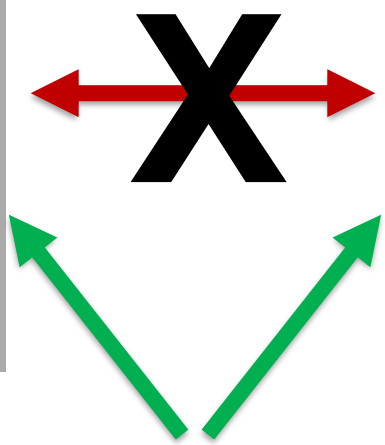
- Correlation ≠ causation
  - Do alligators attract hurricanes? Do hurricanes deposit alligators?

Hurricane landfalls



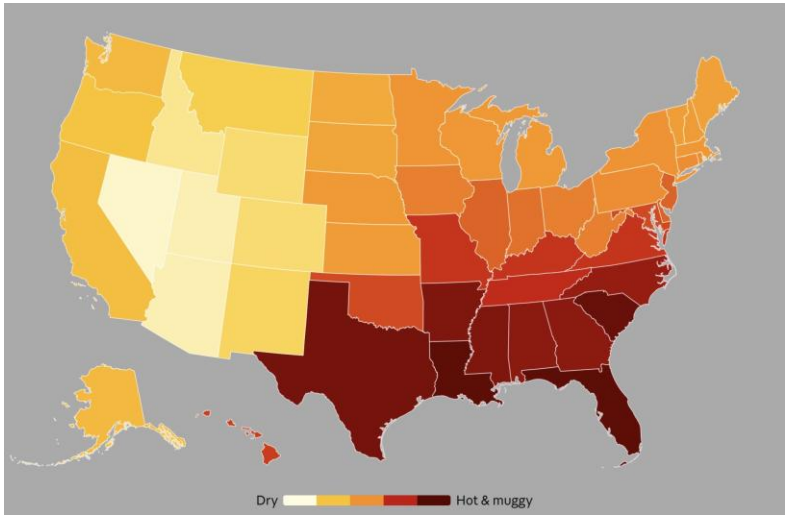
Alligator population





High dew point

- Warm, humid air fuels sea surface temps → hurricane formation and landfall
- Warm coastal wetlands → ideal alligator habitat (alligators live in wet areas need sustained warmth year-round)



Average summer dew point (measure of heat & humidity)

Exposure to X is associated with outcome Y: 4 possible explanations

- Exposure to X causes outcome Y
- Outcome Y causes exposure to X
- Condition Z causes both exposure to X and outcome Y
- Relationship between X and Y is random chance / statistical noise

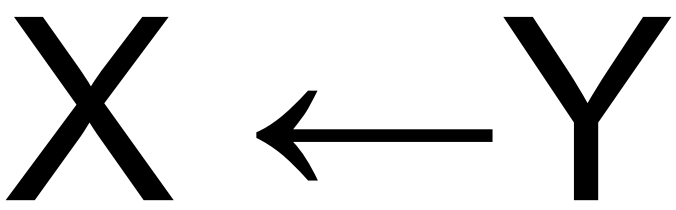
Exposure to X causes outcome Y

- Individuals who take clozapine have higher rates of agranulocytosis than individuals not taking clozapine
  - Clozapine causes the agranulocytosis

$$X \rightarrow Y$$

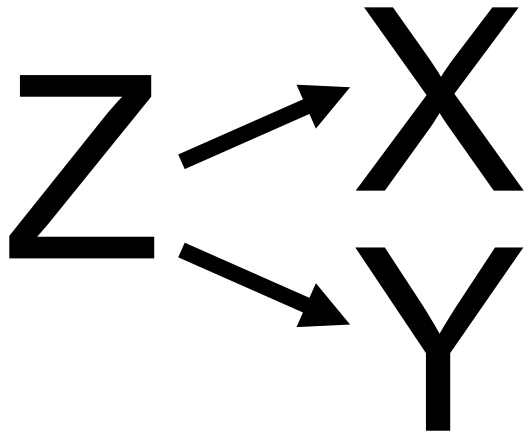
Outcome Y causes exposure to X

- Individuals who take clozapine have higher rates of schizophrenia than individuals not taking clozapine
  - Schizophrenia causes the clozapine use



Condition Z causes both exposure to X and outcome Y

- In the placebo arms of RCTs of cardiovascular drugs, individuals who had better placebo adherence lived longer than those with worse placebo adherence
  - Overall good health habits likely caused both good adherence and decreased mortality
- At an elementary school, children who read chapter books were taller than children who read picture books
  - Fifth graders are generally both taller and more advanced readers than kindergarteners
  - Older age caused both the increased height and better reading skills



Relationship between X and Y is random chance / statistical noise

- Florida has more alligators and manatees than Pennsylvania, and also had an earlier COVID-19 peak at the beginning of the pandemic
  - ????

$$Z \rightarrow X$$

$$W \rightarrow Y$$

Establishing causality

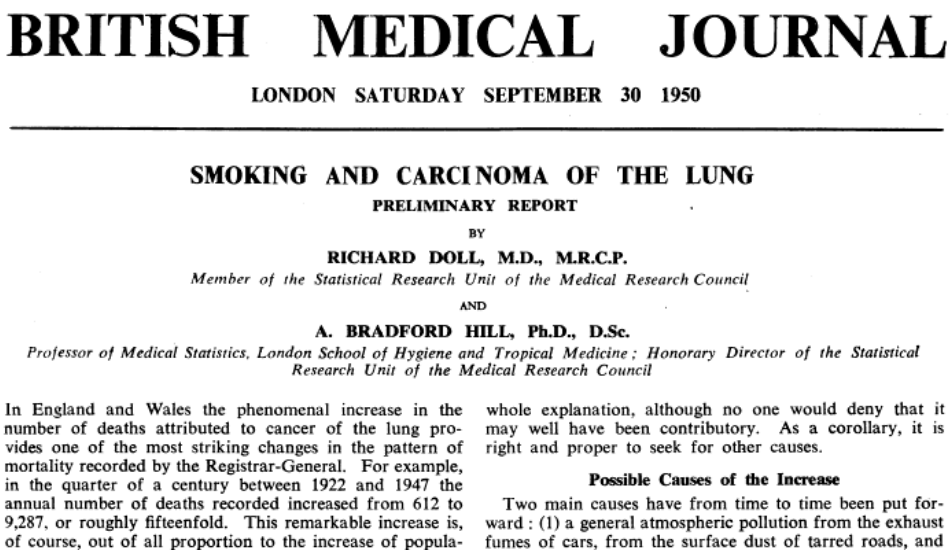
- RCTs can definitively answer the question of whether a medication causes a particular disease
  - Randomization removes other factors like patient characteristics that could influence both medication use and disease development
- No one is ever going to do a RCTs of anticholinergic drugs (or anything else) that starts when participants are in early adulthood and follows them until old age to see who develops dementia
  - Even if you had unlimited funds and study personnel, and even if you didn't mind waiting 50 years for an answer, who would volunteer for a trial in which you'd have to spend your entire life taking a specific drug or taking a placebo???

Establishing causality

- Not just a problem for studies of medications linked to dementia
  - Can’t randomize people to start smoking or not, to see who gets lung cancer
  - Can’t randomize people to drop out of high school or complete a PhD to see if higher levels of education causatively reduce dementia risk
    - Rather than being a function of better baseline cognitive resilience/reserve, or of less exposure to adverse childhood experiences/harms of low SES

How do we establish causality in the absence of RCTs?

- Epidemiologists have developed a set of criteria to help determine whether a specific drug/exposure caused a particular disease
  - Bradford Hill criteria
    - Most famous application: established that smoking directly causes lung cancer



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SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

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In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is, of course, out of all proportion to the increase of population...

whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and

Criteria for causality

- Temporality
- Consistency
- Biological gradient
- Strength of association
- Reversibility
- Plausibility / coherence
- Specificity
- Analogy
- Experimental evidence

- You DON’T have to have all of them to establish a causal association
  - But, the more criteria which are met, the stronger the evidence for causality

Temporality

- To be causative, the exposure must PRECEDE the outcome
  - Temporal association MUST be in the right direction
  - Only MANDATORY criteria for causality
    - If someone only took a drug after a disease developed, the drug could not possibly have caused the disease

Temporality

- If the drug causes the disease, the patient has to take the drug BEFORE the disease occurs
  - In the case of clozapine and schizophrenia, history-taking shows that the patient FIRST developed schizophrenia and THEN took clozapine
    - So obviously, the clozapine did NOT cause the schizophrenia
- However, just showing the drug exposure came first doesn't—by itself—prove the drug caused the disease
  - Need the other criteria to help strengthen the case for causality

Temporality: not always obvious

- In the case of dementia, how do you determine whether the drug or the disease came first?
  - Most dementias develop slowly over years
  - Hard to pinpoint true onset
  - Most people have years of decline before a formal diagnosis of dementia is made
- Psychiatric manifestations of dementia—like depression, anxiety, and insomnia—frequently precede cognitive symptoms, sometimes by years
  - May cause individuals with prodromal dementia to be prescribed psychiatric medications more often than their cognitively intact peers

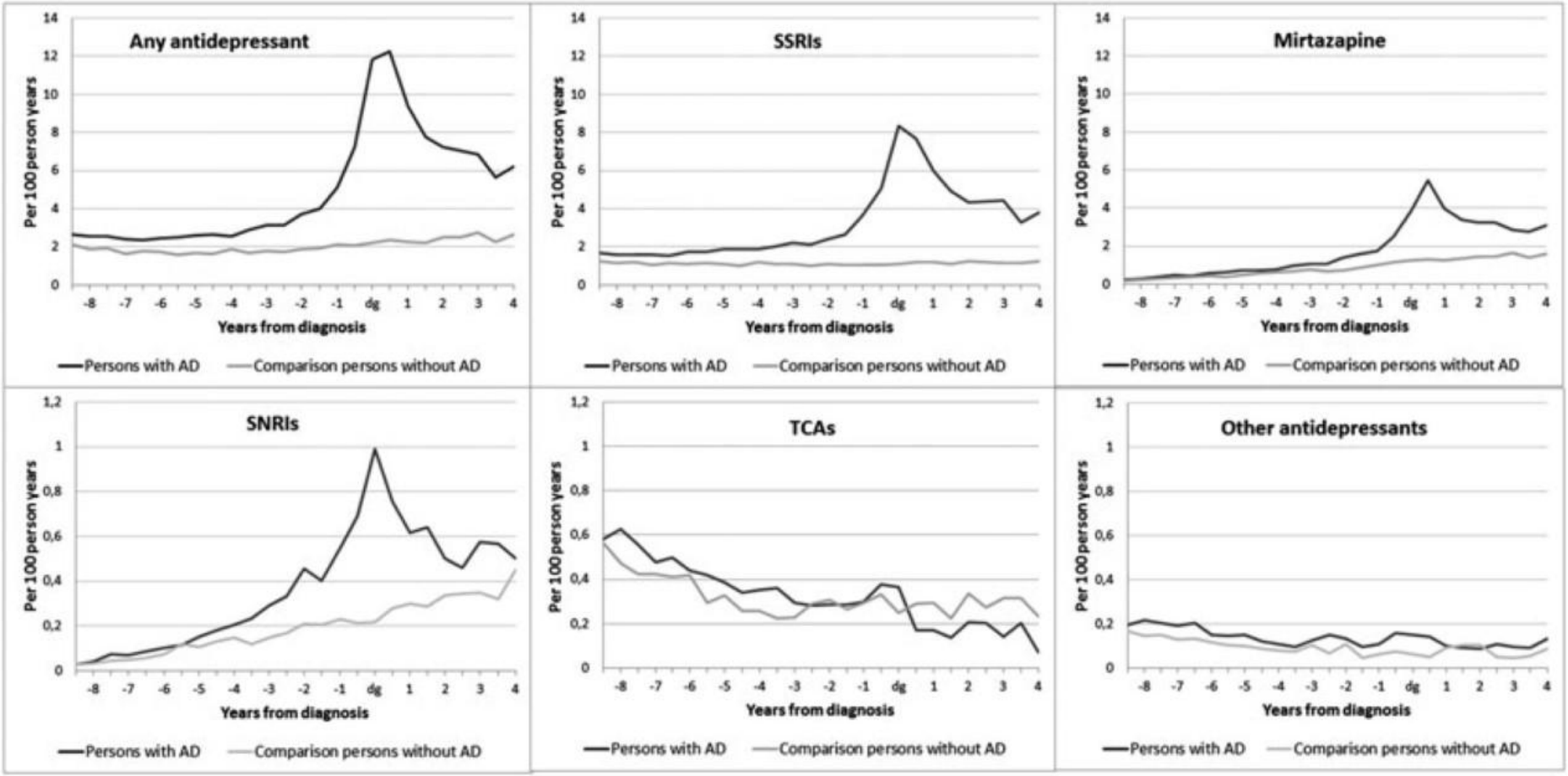
Insidious onset of dementia onset can bias results

- Difficulty determining the true date of dementia onset can give rise to two types of biases that can lead to false conclusions about causality
  - Reverse causality
  - Selective prescribing bias

Reverse causality

- The association between use of a particular medication and higher rates of subsequent dementia is due to patients in the earliest stages of dementia preferentially receiving the medication
  - The medication use may have preceded the FORMAL DIAGNOSIS of dementia, but in fact the underlying disease process was already underway before starting the medication
- Reverse causality can give rise to the FALSE conclusion that the medication caused the disease, when in fact it was the other way around

Reverse causality



Antidepressant use quadruples shortly before formal diagnosis of Alzheimer disease: example of reverse causality

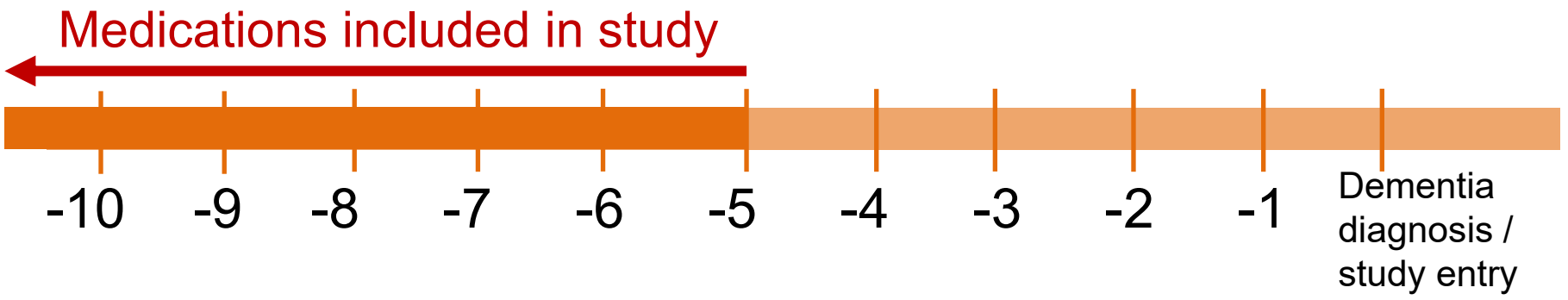
- Drug is used to treat early symptoms of what will turn out to be AD

Selective prescribing bias

- Healthiest / lowest-risk individuals preferentially receive the drug
- If an older adults presents with early cognitive complaints, clinicians might stop medications known to cause at least short-term cognitive impairment, like anticholinergic drugs
  - Thus, certain medications may end up being avoided in patients with early dementia, with the result that only the cognitively healthiest individuals take them
- Selective prescribing bias can give rise to the FALSE conclusion that the medication DOES NOT cause the disease (or even protects against it!) when in fact it was the other way around
- Very hard to put a number on how often reverse causality and selective prescribing bias occur
  - Definitely CAN'T assume they cancel each other out!

Which came first: the drug or the dementia?

- How to resolve the problem of temporality: require a lag time between medication initiation and diagnosis of dementia (or study entry, for healthy controls)
  - For example, researchers designing a study could:
    - Assume that whatever process ultimately produced dementia was already underway during the five years prior to diagnosis
    - Therefore, the study will ignore any new medications initiated in that period, and only look at medicines started more than 5 years before diagnosis



How long should the lag time be?

- Lag time approach reduces reverse causality and selective prescribing biases
  - But how much lag time do we need?
    - Dementia onset is usually insidious process
    - Dementia generally progresses slowly
- Hard to determine exactly how long a lag time is needed
  - 1-2 years is probably BARE MINIMUM
  - Longer periods such as 5+ years probably preferable

How do you know if lag time is long enough?

- One method: check whether the strength of the association changes with different lag periods
  - If the association is very strong with a 1-year lag period, but disappears with a 5-year lag period:
    - Suggests that use of the drug markedly increases as the time of dementia onset grows closer
    - Therefore may represent reverse causality
  - If association is equally strong with a 1-year lag period and a 5-year lag period:
    - Suggests that early dementia symptoms do NOT account for increased use of the drug
    - Therefore the drug may actually CAUSE the dementia

Lag time is essential in interpeting dementia causality

- If study doesn't require any lag time between medication initiation and dementia diagnosis:
  - Patients prescribed a drug on Monday and diagnosed with dementia on Tuesday count as drug-associated dementia cases
- Without lag time, it's hard to ensure the REQUIRED criteria of temporality is met:
  - ie, can't make sure the drug use came BEFORE the dementia

Match the study design to the problem

- Lag time isn't always necessary for problems other than dementia, when onset of the outcome is very clear and occurs acutely
  - Alcohol use and MVAs
    - Individuals who drink heavily are more likely to have a MVA one hour later
    - The alcohol very likely caused/contributed to the MVA
    - 2-year lag time would likely obscure the causative relationship

Cross-sectional designs not appropriate for dementia causation studies

- Because can't satisfy temporality
- Cross-sectional study of ER patients looking at BAL and rates of traumatic injury
    - Concludes higher BALs are a risk factor for traumatic injuries
        - Probably reasonable (if patients not drinking in the ER)
- Cross-sectional study of patients in Psychiatry clinic
    - Produces misleading conclusions that:
        - SSRIs cause depression
            - Reverse causality
        - Benzodiazepines prevent opioid use disorder
            - Selective prescribing bias

Consistency

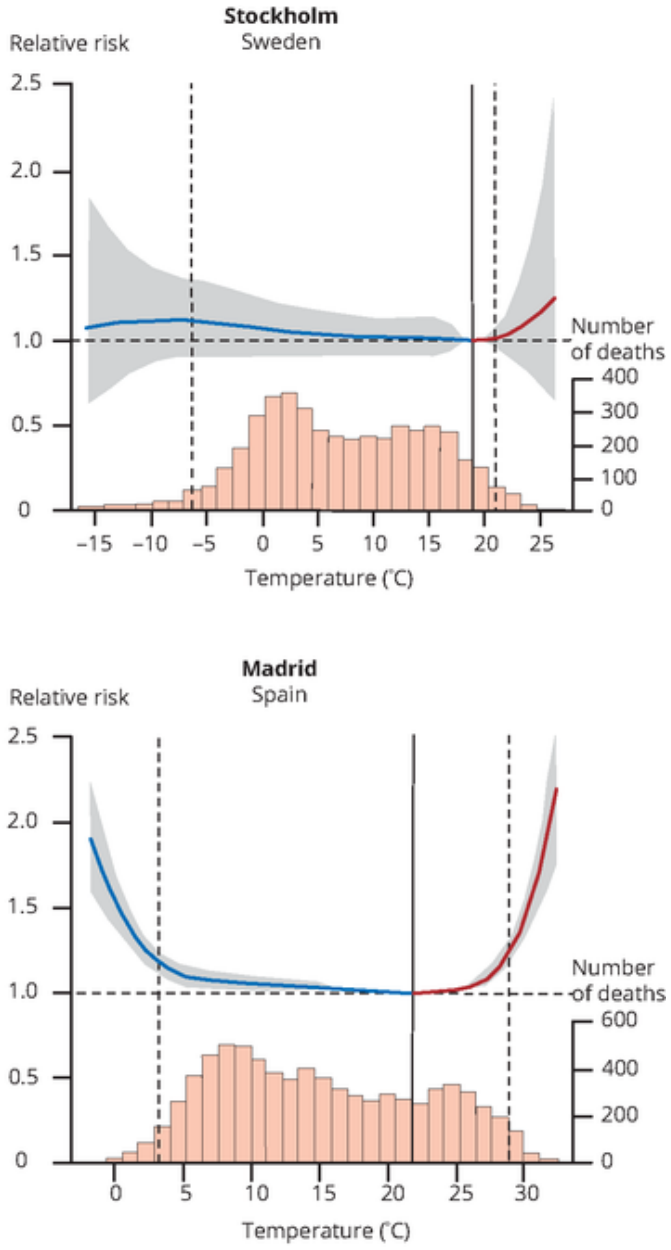
- Link between drug exposure and disease development should occur CONSISTENTLY
- If the exposure really causes the disease, then multiple studies by different researchers in different settings with different valid methodologies should all find the link
  - A properly designed retrospective case-control study in the US, and a properly designed prospective cohort study in Kenya, should both find that smoking increases the risk of lung cancer
    - Benzodiazepines and dementia:
      - Link found in some studies, not in others (even with similar methodologies)
        - Finding is not CONSISTENT
          - Do benzodiazepines cause dementia? Who knows???

Biological gradient

- If the exposure causes the outcome, then exposure to higher doses or longer time periods of use of the drug should be more likely to produce the outcome than lower exposures
  - Individuals who smoke large amounts of cigarettes for many years have a higher lung cancer risk than those who smoke smaller amounts for only a few years
- This type of dose-response relationship is OFTEN true for causal associations, but not ALWAYS true
  - Clozapine-induced agranulocytosis
    - NOT dose-dependent
    - Actually more likely to happen in patients new to the drug than those who have been on it a long time
- A biological gradient strengthens the case for causality
  - But absence of a biological gradient doesn't disprove causality

Biological gradient

- Sometimes need to look for biological gradient in order to identify an association
  - Considering all degrees of exposure together can obscure a causative relationship
    - Threshold effects: ie, causality only occurs with higher levels of exposure
    - Nonlinear effects



Strength of association

- The stronger an association between an exposure and an outcome, the more likely that association is causative.
  - If people who take a particular drug are 1% more likely to have a particular outcome:
    - May well be due to statistical noise or to other differences between the groups
  - If people who take the drug are 500% more likely to have a particular outcome:
    - It's much more likely that the drug caused the outcome
      - In the absence of other explanations for the relationship

Plausibility / coherence

- Given our currently available scientific knowledge, is there a plausible and coherent biological mechanism by which the drug/exposure could cause the outcome?
  - If so, strengthens the case for causation
    - Antipsychotics and tardive dyskinesia
      - Antipsychotics act on dopamine receptors
      - Dopaminergic pathways are involved in motor function
      - So plausible/coherent mechanism by which antipsychotics could cause movement disorders
    - If a study found that people who took ARBs were more likely to develop TD, we'd want to see very compelling evidence in other areas before concluding that ARBs cause TD
      - Because no currently known mechanism
- However, potentially some mechanism could exist, and we just don't know about it yet

Plausibility / coherence

- Some causative theories so implausible / incoherent that can almost certainly be ruled out on this criteria alone
    - Everything we know about meteorology says no way alligators could steer the course of hurricanes
  - But the whole, this is rare
    - There's a lot we don't know!
- Just because we can describe a plausible and coherent mechanism by which an exposure could cause an outcome, doesn't mean the exposure really does cause the outcome!
  - Hormone replacement therapy and cardiovascular outcomes
    - Premenopausal women have the lowest rates of CVD
    - Plausible that postmenopausal HRT could reduce CVD in older women
    - However, RCTs showed that HRT actually increases cardiovascular risk in older postmenopausal women
    - Relationship turns out to be very complicated, possibly different in older vs younger postmenopausal women

Even if a plausible mechanism exists, is it the BEST explanation?

- At pandemic start, FL had earlier COVID-19 peak than PA
- FL has more alligators and manatees than PA
- Hypothesis: Exposure to alligators and manatees caused COVID-19 in humans
- Plausible / coherent?
  - Maybe! COVID-19 has zoonotic transmission
    - Within the realm of possibility that alligators and manatees served as a vector for spread to humans
- But a much better explanation exists for why FL had earlier peak of COVID-19 than PA
  - FL reopened earlier

Reversibility

- Does removing the exposure lower the chances of the outcome?
  - If so, this reversibility supports the case for causation
- This only works if the exposure is removed before an irreversible outcome occurs
  - Quitting smoking doesn’t cure lung cancer
  - But people who quit smoking before that happens have a lower risk of lung cancer than people who continue to smoke

Criteria that don't apply for dementia causation

- Specificity
  - Outcome almost never occurs without a specific exposure
    - Mesothelioma and asbestos
  - Hard to apply for any single exposure in a common multifactorial disease like dementia
- Analogy
  - If one specific exposure is known to cause the outcome, then perhaps other similar exposures can too
    - If personally smoking causes lung cancer, logical that secondhand smoke can too
  - We don't know what causes (neurodegenerative) dementia
- Experimental evidence
  - Outcome decreases after non-RCT intervention to reduce the exposure
    - SIDS rate fell 50% after back-to-sleep campaign
  - No similar public health interventions for dementia

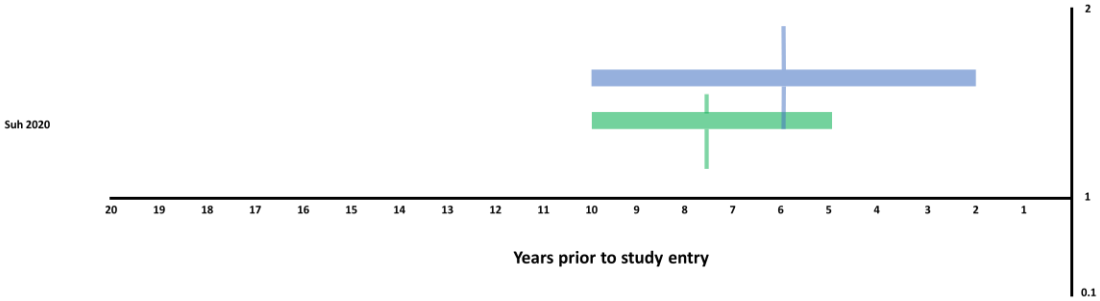
Do anticholinergic drugs directly cause dementia?

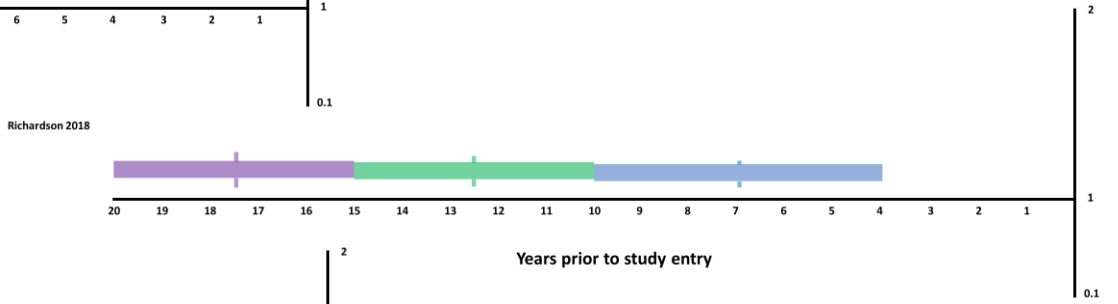
- Multiple studies show that individuals who take anticholinergic drugs are more likely to go onto subsequently develop dementia
- Do anticholinergic drugs play a role in directly causing dementia?
  - That is, are there people who, were it not for their use of anticholinergic drugs, would never have developed dementia?
    - In the same way that there are people, who if they'd never smoked, would never have gotten lung cancer
- We can use the epidemiologic criteria for causation to decide

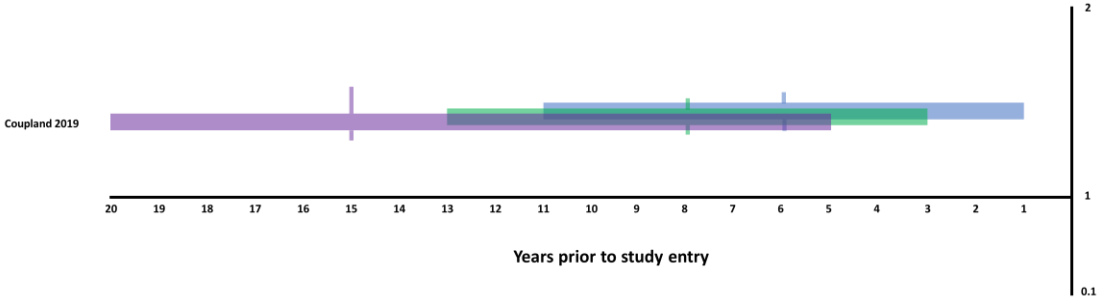
Anticholinergic drugs and dementia: temporality

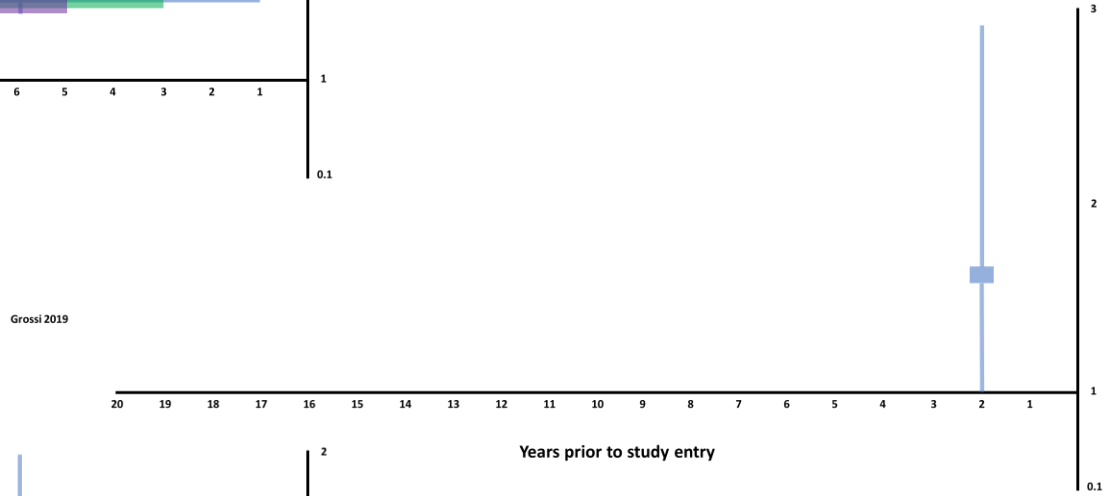
- Can we be sure the anticholinergic drug use truly preceded the dementia?
  - Look at studies with lag periods
    - Reduce the risk of reverse causation and healthy user effect
    - Exclude participants in the early stages of dementia
  - To make sure the drug use really came before the dementia

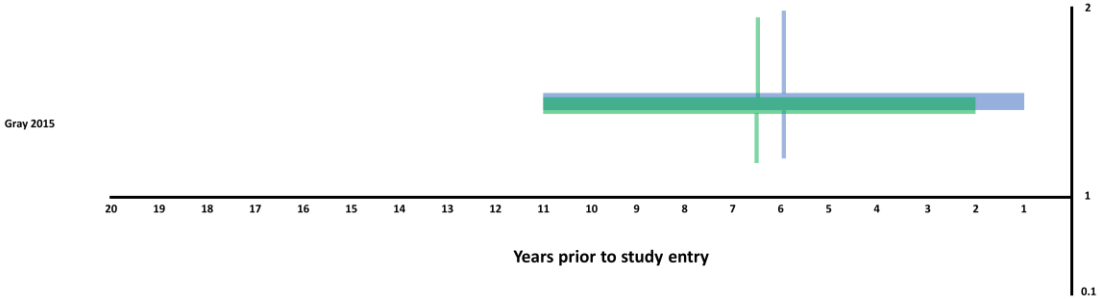
Anticholinergic drugs and dementia: temporality







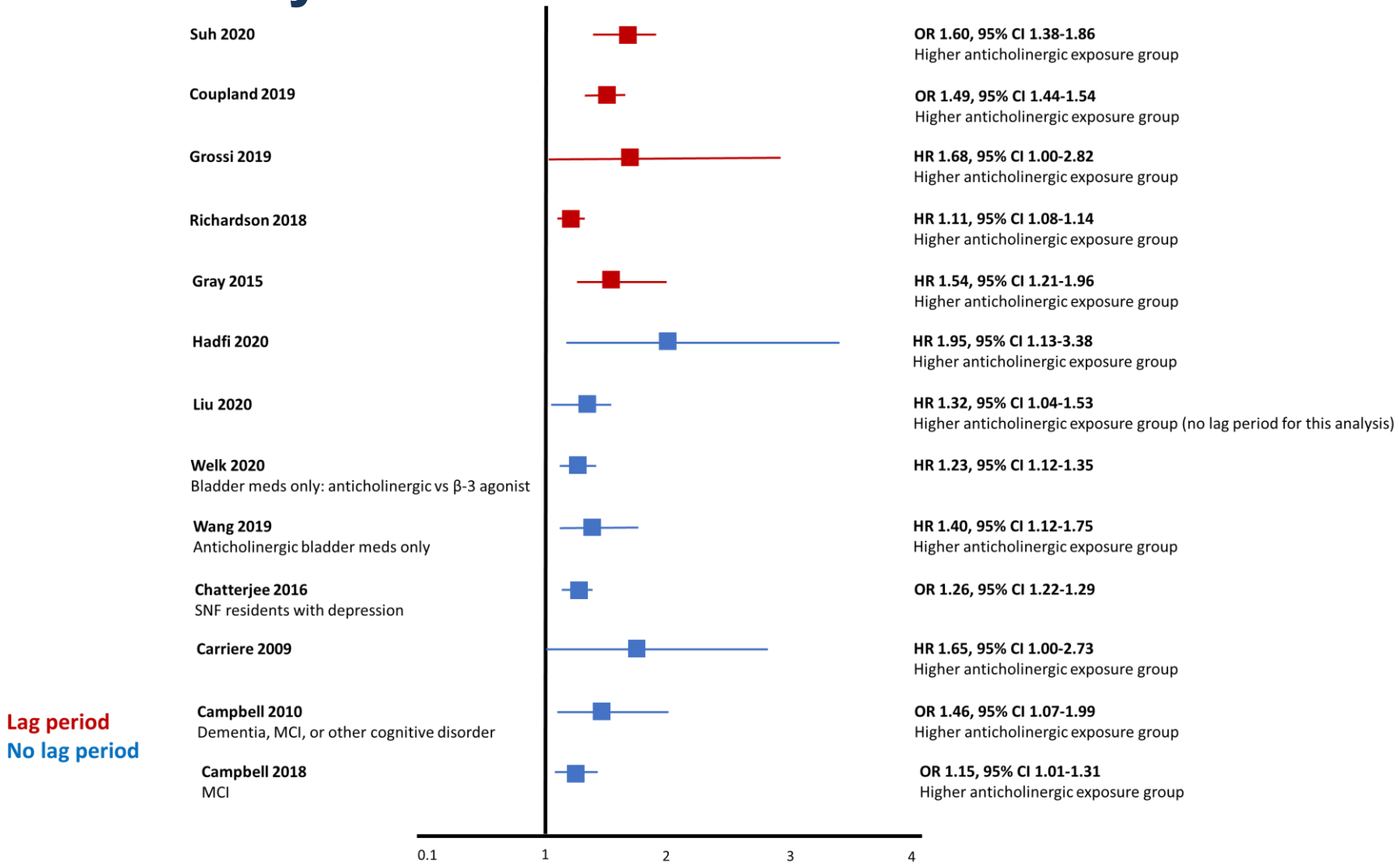




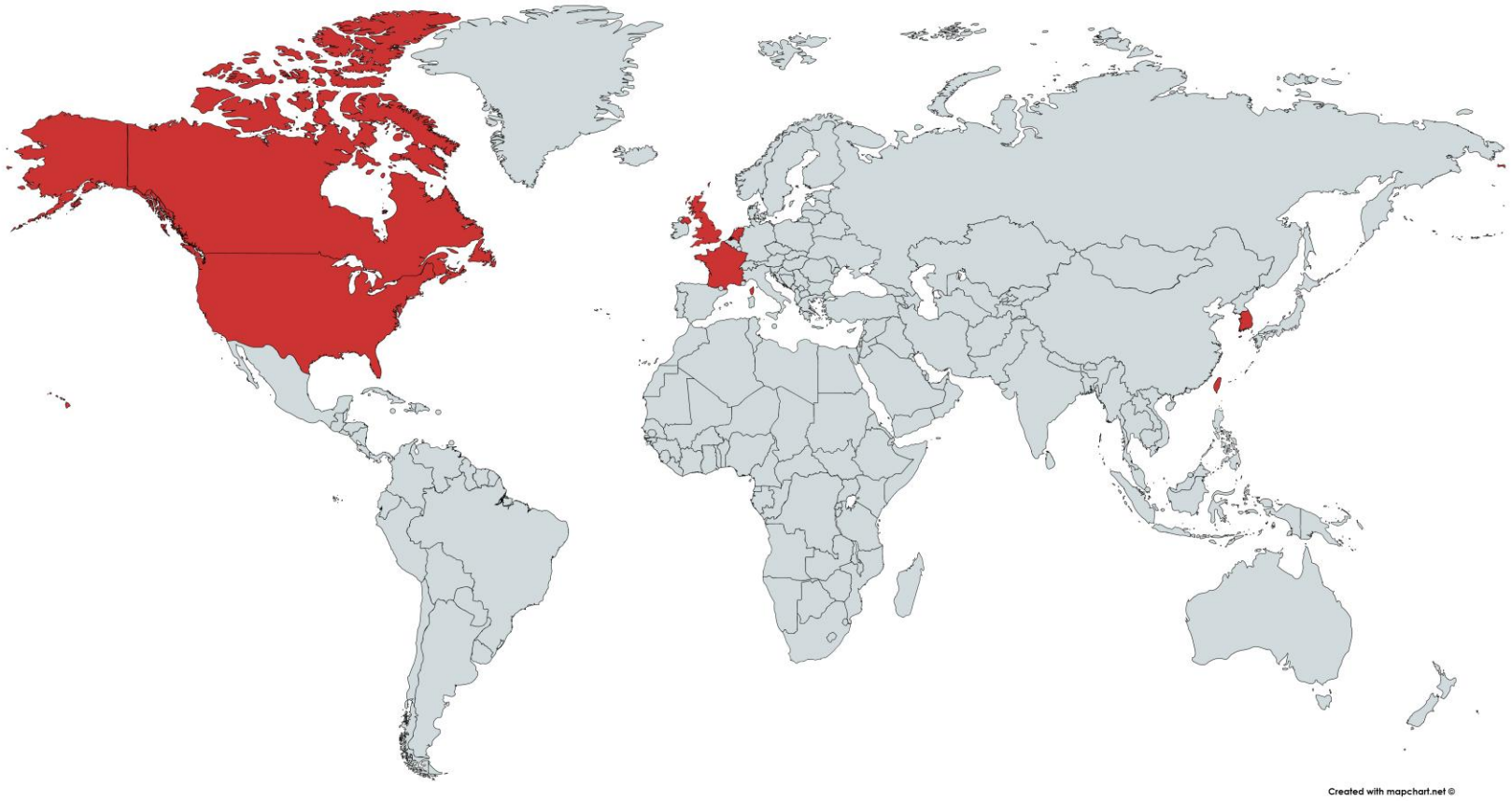
Anticholinergic drugs and dementia: consistency

- Almost all studies of long-term cognitive effects of anticholinergic drug use have found increased rates of subsequent dementia
  - For individuals who use strongly anticholinergic drugs for at least 3-4 years
    - In many studies, lower levels of exposure not associated with increased rates (biological gradient/threshold effect)
  - Using different valid methodologies
  - Conducted in different populations

Anticholinergic drugs and dementia: consistency



Anticholinergic drugs and dementia: consistency



Higher rates of dementia with anticholinergic use: study locations

Anticholinergic drugs and dementia: consistency

- Methodologies that found higher rates of dementia with anticholinergic use:
  - Database case-control
  - Prospective longitudinal
  - Prospective cohort
  - Retrospective cohort
- Ascertainment methods in studies that found higher rates of dementia with anticholinergic use:
  - New dementia diagnosis in medical records
  - New dementia diagnosis in Medicare claims database
  - Clinical dementia evaluation by study clinicians / expert panel

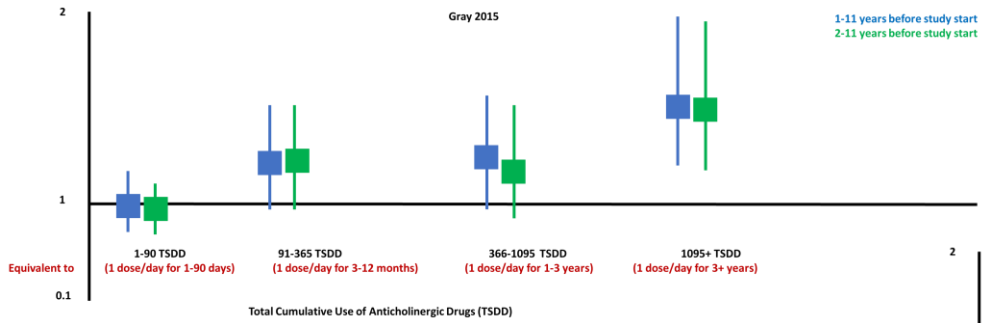
Anticholinergic drugs and dementia: biological gradient

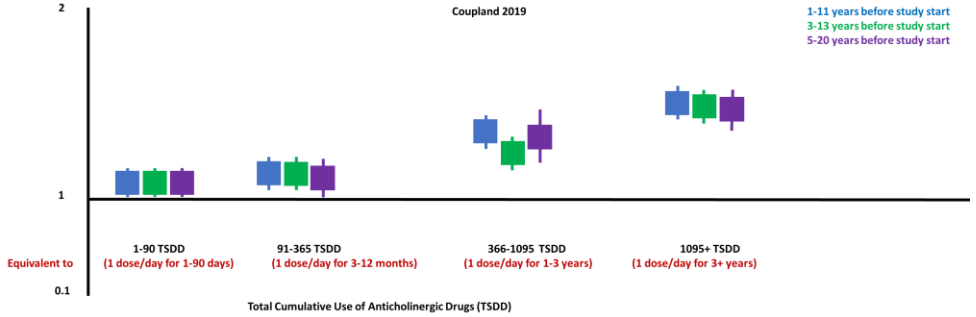
- Does the relationship between anticholinergic drug use and dementia show a biological gradient?
  - Yes!
- Factors associated with higher rates of dementia:
  - Longer duration of anticholinergic use
  - Use of multiple anticholinergic drugs
  - Higher doses of anticholinergic drugs
  - Use of strongly anticholinergic drugs
- Short-term use of anticholinergic drugs, or use of only weakly anticholinergic drugs:
  - Generally NOT associated with increased dementia risk

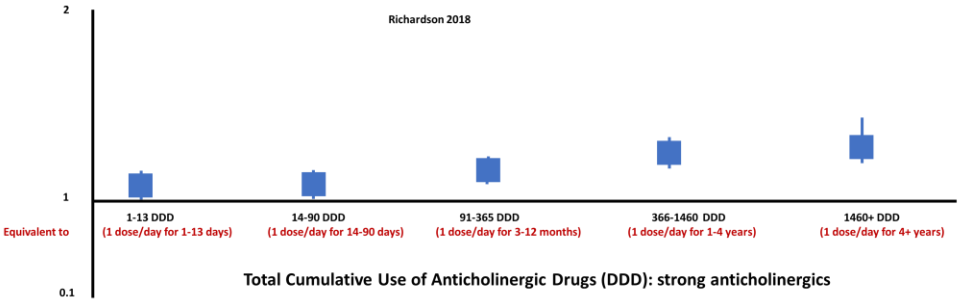
Anticholinergic drugs and dementia: biological gradient

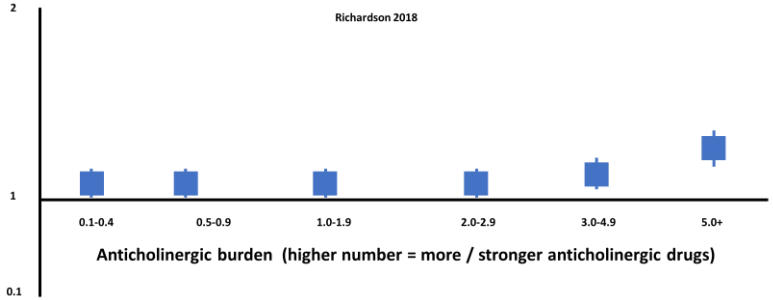
- Methods of assessing biological gradient
  - Total standardized daily doses (TSDD) and defined daily doses (DDD)
    - Dose of medication (scaled) x duration of use
    - Anticholinergic equivalent of pack-years of smoking
  - Anticholinergic burden
    - Whether medication is weakly or strongly anticholinergic
  - Duration of use

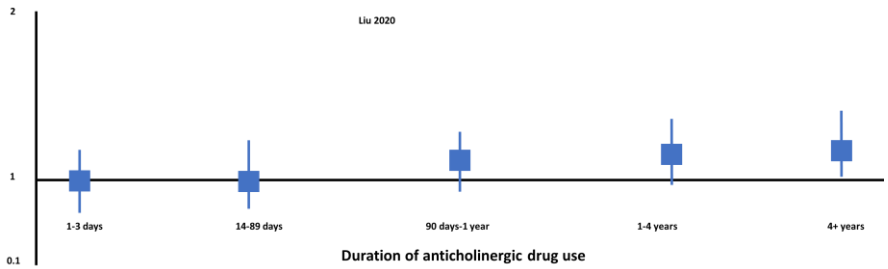
Anticholinergic drugs and dementia: biological gradient

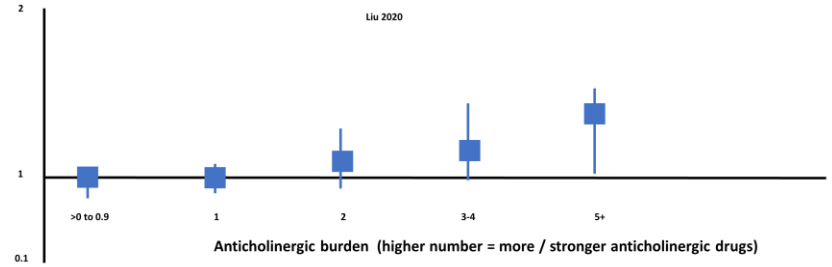








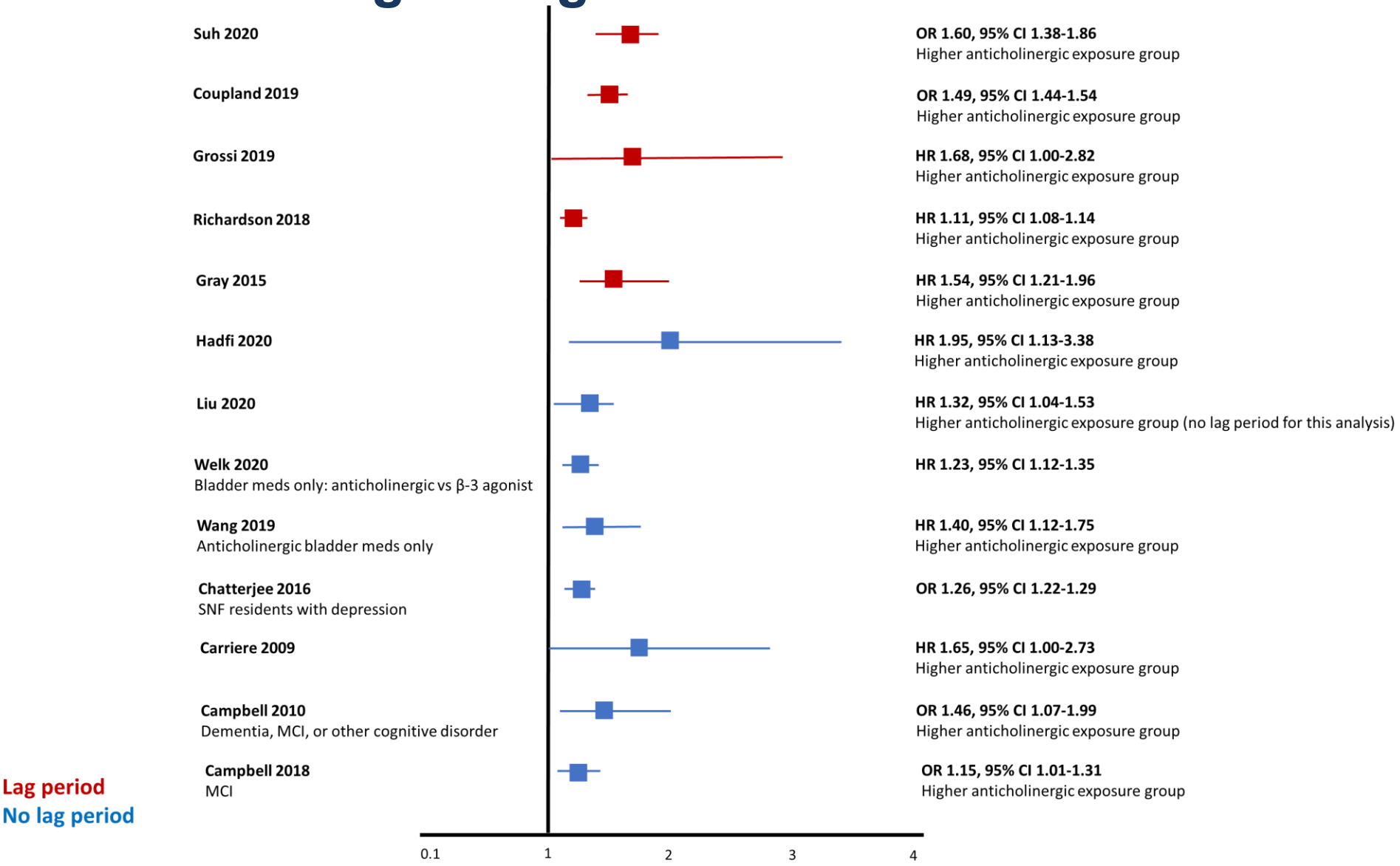




Anticholinergic drugs and dementia: biological gradient

- Even in the studies where the headline is “no link between anticholinergic drugs and dementia”:
  - They ALL found higher rates of dementia in people who had longer periods of anticholinergic use and/or who used more/stronger anticholinergic drugs
    - ie, appear to show a threshold effect
  - Overall negative findings due to most of anticholinergic exposure group having only brief/weak anticholinergic exposures
    - A study of smoking and lung cancer, in which 90% of the smoking group only had ever smoked for 1 month before quitting, might well not find that smoking increases cancer risk

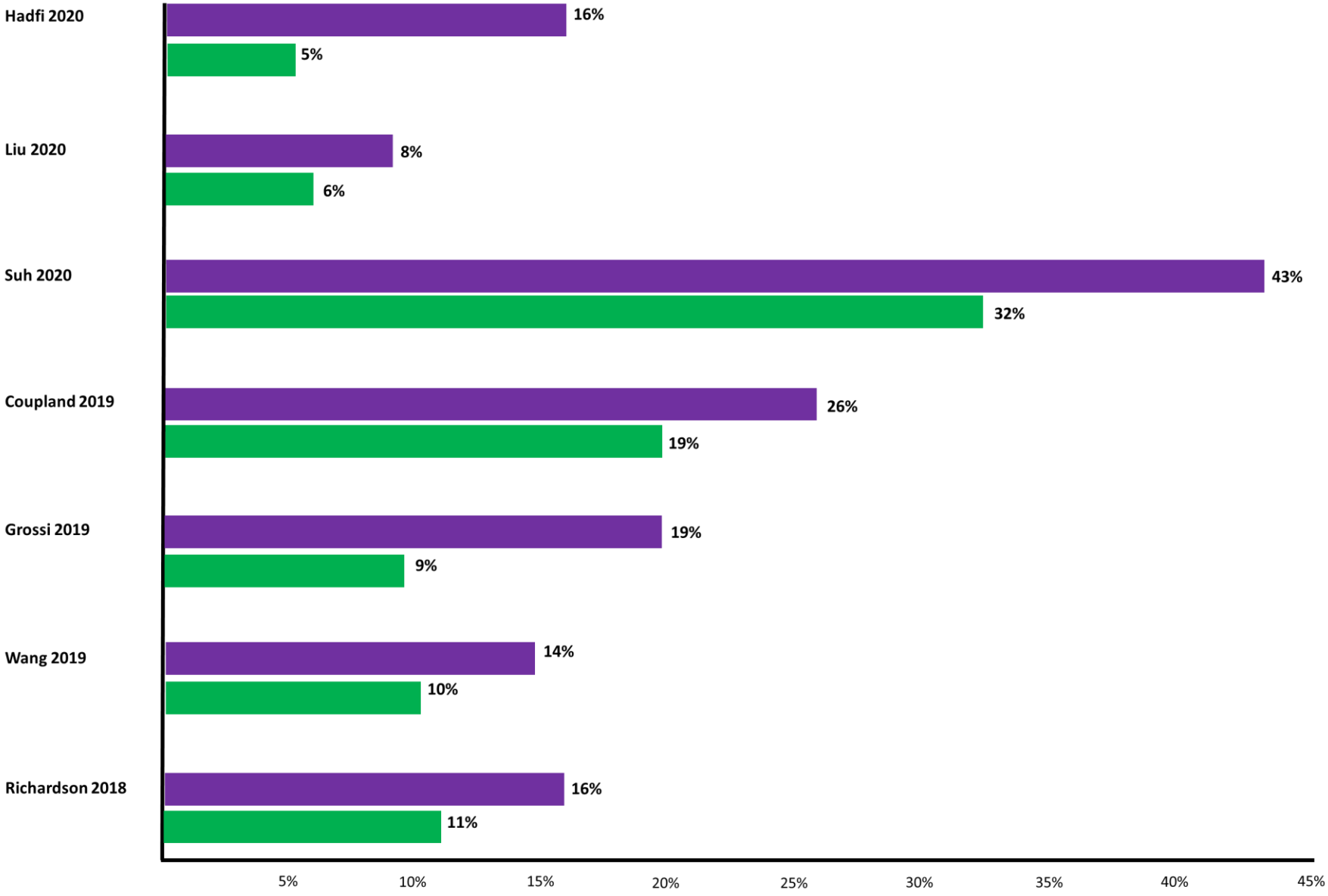
Anticholinergic drugs and dementia: effect size



Individuals who use anticholinergic drugs for years are 11% to 65% more likely to develop dementia than nonusers

- Use = strongly anticholinergic drugs for ≥ 3-4 years

Anticholinergic drugs and dementia: effect size



Absolute risk increase: 2-11 percentage points

- Strongly anticholinergic drugs taken for ≥ 3-4 years

Anticholinergic drugs and dementia: effect size

- Range of effect sizes is likely due to differences sample size, duration of follow-up, population baseline dementia rates, case ascertainment, etc
- Dementia causation is generally multifactorial
  - Effect size of anticholinergic drugs is similar to that of other dementia risk and protective factors

Anticholinergic drugs and dementia: plausibility / coherence

- Is there a known biological mechanism by which anticholinergic drugs could cause dementia?

- Acetylcholine's role in memory
  - Acetylcholine is the key neurotransmitter in memory
  - RCTs in humans show that one-time administration of anticholinergic drugs creates short-term amnesia in healthy humans
    - Anticholinergic drugs often used as probe to experimentally induce amnesia in studies of memory

Anticholinergic drugs and dementia: plausibility / coherence

- Data from animal RCTs show that anticholinergic drugs:
  - Kill cholinergic neurons
  - Increase the formation of neurofibrillary tangles
    - The neuropathology of Alzheimer disease
  - Cause proinflammatory effects
    - May play a role in increase neurodegeneration and cerebrovascular disease

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Anticholinergic drugs and dementia: plausibility / coherence

- Human imaging studies:
  - Individuals who chronically use anticholinergic drugs show decreased cortical volume, particularly in the temporal lobes
    - The pattern seen in Alzheimer disease
- Human autopsy studies:
  - Some autopsy studies have found that individuals who used anticholinergic drugs have more dementia neuropathology
    - However, other studies haven't

Anticholinergic drugs and dementia: plausibility / coherence

- Are there better explanations for the relationship between anticholinergic drug use and dementia?
  - Could the association be due to baseline differences that drive both dementia and anticholinergic use?
    - Depression, schizophrenia, neurologic disease, etc
  - So far, does NOT appear to be the case

Anticholinergic drugs and dementia: plausibility / coherence

- Association between anticholinergic use and dementia persists even after controlling for depression, anxiety, insomnia, neurologic disease, urinary incontinence, and other health-related variables
  - Shown in multiple studies, using propensity-score matching
    - Statistical method of making case group/control group as alike as possible except for the exposure of interest

Anticholinergic drugs and dementia: plausibility / coherence

- Studies restricted to specific groups ("like compared to like") also show elevated dementia risk with anticholinergic drug use
  - Individuals with bladder disorders (2 studies):
    - Examining ONLY use of anticholinergic bladder medications
    - Both found higher rates of subsequent dementia in anticholinergic group
  - Individuals with depression: Higher rates of subsequent dementia in anticholinergic group
  - Individuals with Parkinson disease (2 studies):
    - Both found higher rates of subsequent dementia in anticholinergic group

Anticholinergic drugs and dementia: plausibility / coherence

- The authors of one study found that the elevated risk of dementia with use of strongly anticholinergic drugs disappeared when anticholinergic antidepressants and anticholinergic antipsychotics were excluded
  - They speculated that underlying conditions therefore may have caused the elevated risk
- However, in this study, over 1/2 the anticholinergic drugs used were antidepressants/antipsychotics
  - Likely just wasn't enough statistical power remaining to detect any association between other classes of anticholinergic drugs and dementia

Anticholinergic drugs and dementia: plausibility / coherence

- Overall, the evidence argues AGAINST the alternate hypothesis that other underlying conditions, like depression/psychiatric disorders or neurologic conditions, increase rates of both anticholinergic use and dementia

- There is plausible and coherent case that anticholinergic drugs can directly increase the risk of dementia
  - Supported by multiple lines of evidence
  - Relationship not better explained by other factors

Anticholinergic drugs and dementia: reversibility

- What about reversibility?
- If you stop taking anticholinergic drugs BEFORE developing irreversible dementia, will you have a lower risk of dementia than people who continue to take anticholinergic drugs?
  - Not a lot of data on this question
- One study found that individuals who stopped using anticholinergic drugs were less likely to subsequently develop dementia, than those who continued using them
  - Overall, not well-studied

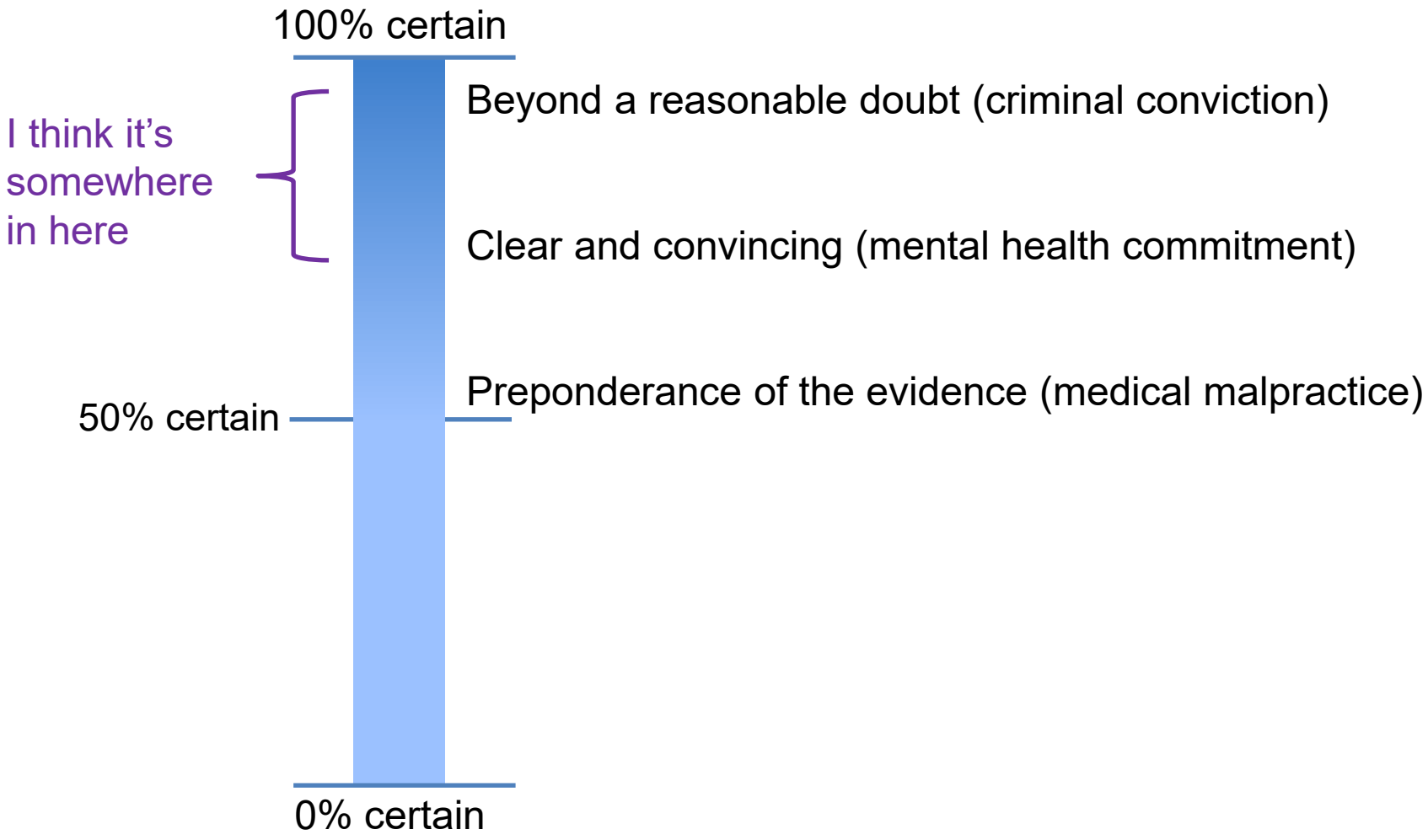
Anticholinergic drugs probably directly cause irreversible dementia

- Temporality: use of anticholinergic drugs precedes the dementia by years
- Consistently: association occurs consistently in multiple studies, conducted using different methodologies, in different populations
- Biological gradient: longer use / higher anticholinergic burden increase dementia risk more than shorter use/lower burden
- Strength of association: effect size similar to other known dementia risk/protective factors
- Plausible/coherent: evidence from neurobiology of memory, animal studies, and neuroimaging studies supports a mechanism by which anticholinergic drugs could cause dementia. Autopsy findings inconsistent so far.
- Reversibility: people who stop taking anticholinergic drugs may have less dementia risk than those who continue taking them (but need more studies)

Anticholinergic drugs can probably directly cause irreversible dementia

- Based on the epidemiologic criteria for causation:
  - Appears probable that anticholinergic drugs do indeed cause increased risk for dementia
  - Patients who take anticholinergic drugs may get dementia when they otherwise wouldn’t have

How strong is the case against anticholinergic drugs?



What do we do with this information?

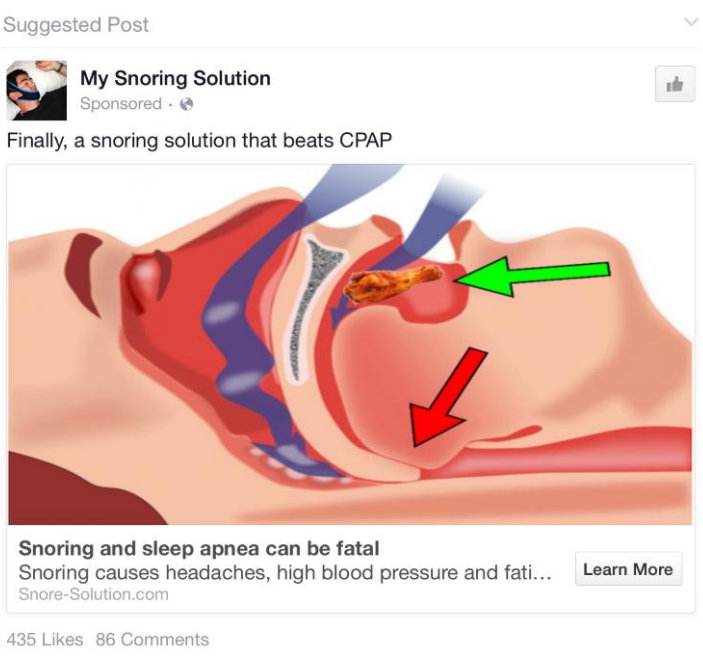
- If we accept that the evidence shows anticholinergic drugs probably do directly cause irreversible dementia, what does this mean for practice?
  - Is this a significant enough risk to worry about?
  - Can we treat target conditions effectively without anticholinergic drugs?

Number Needed to Harm (NNH)

- How many people must have the exposure, for 1 additional person to develop the bad outcome?
  - NNH of 10: For every 10 people who have the exposure, 1 person will have the bad outcome who otherwise wouldn't have
  - Same concept as NNT, but in the opposite direction

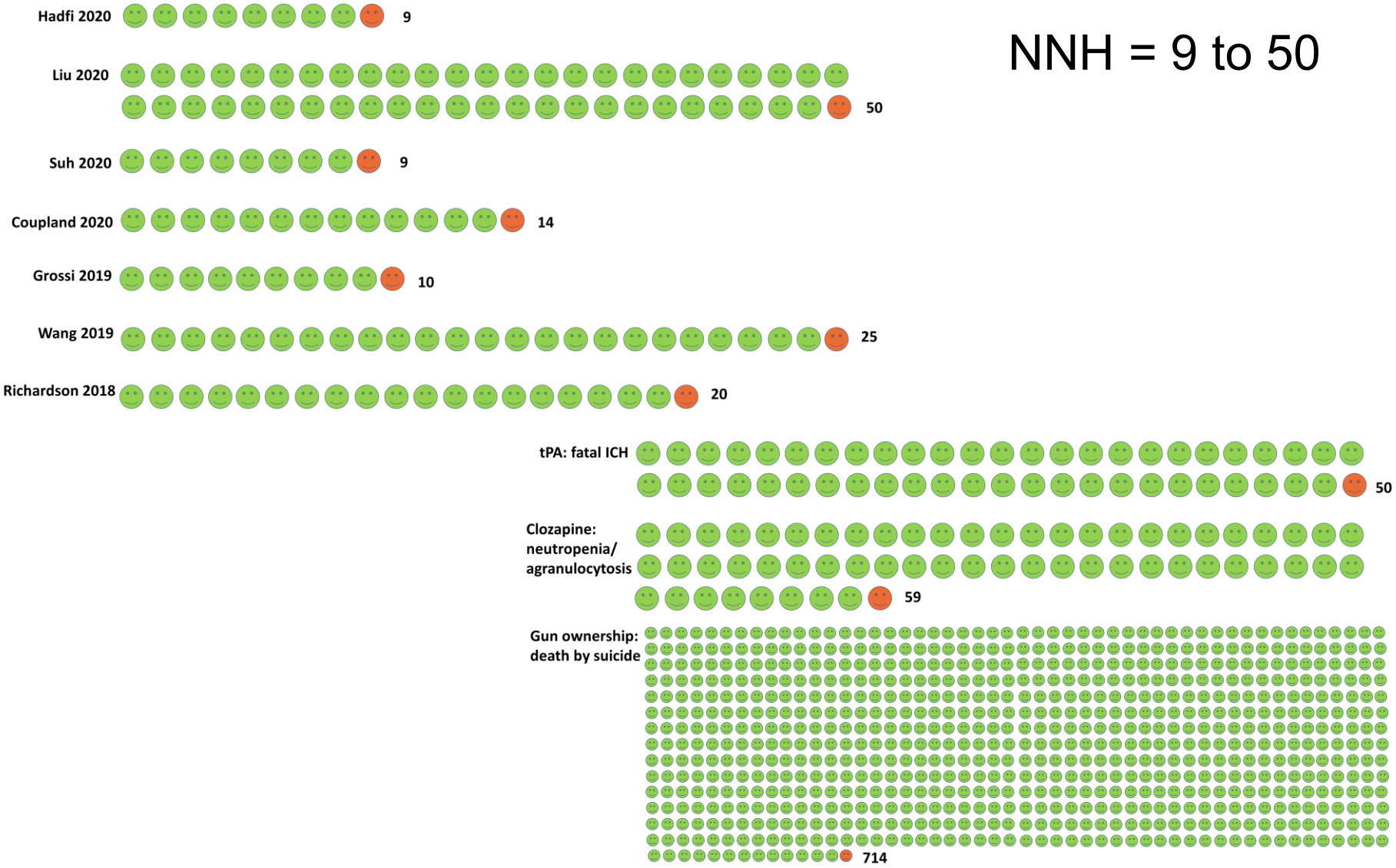
What's an acceptable NNH?

- Depends on how bad the harm is, alternate treatment options, and how much potential benefit there is
- Effective antidepressant
  - NNH of 2-3 likely acceptable for the outcome of transient mild nausea at treatment initiation
  - NNH of 100 for liver failure probably unacceptable
  - NNH of 10,000 for ICH probably acceptable
- Experimental surgery that may cure an otherwise uniformly fatal condition
  - NNH of 2-3 for death may be ok
    - What do you have to lose?
- Airway occlusion by chicken wing for treatment of OSA
  - NNH ≈ 1 for the outcome of death
  - Risk/benefit ratio unacceptable



NNH for anticholinergic drugs: dementia

- How many people have to take anticholinergic drugs, to cause one case of dementia that wouldn't have happened otherwise?



NNH = 9 to 50

What do we do about it?

- Anticholinergic drugs probably do directly increase the risk of dementia
  - Risk is not trivial—NNH less favorable than other things we often worry more about
- For most conditions, other effective and cognitively safe alternatives exist
  - So it makes sense to avoid anticholinergic drugs whenever possible

What about symptom control / disease treatment?

- Several studies show that discontinuing anticholinergic drugs actually IMPROVES overall quality of life
- Choice is NOT between suffering with symptoms or getting dementia
- Most patients can have EFFECTIVE and COGNITIVELY SAFE treatment with non-anticholinergic interventions

What about younger patients?

- For logistical reasons, thus far all published studies of anticholinergic drugs and dementia have looked at late-middle-aged or older patients
  - Dementia before age 60 is quite rare
  - Practical difficulties in following prospective study participants from their 20s to late life
  - Medical records/insurance claims generated 40-50 years ago not easily searchable
- So do these findings generalize to younger patients?
  - We don't necessarily know
  - BUT: we do know that longer anticholinergic exposure is associated with higher dementia risk
    - So if you start using hydroxyzine when you're 20, and stay on it for the next 40 years, that's a lot of time for the drug to work whatever harm it may be doing…

“But it’s just short-term”

- Many patients actually remain on anticholinergic drugs (including “short-term” PRNs) for many years
- Examples:
  - Patient started on diphenhydramine PRN for sleep as part of a standard psychiatric hospital admission set
    - After discharge, patient continues to take it because “it must be safe—after all, they gave it to me in the hospital”
  - Psychiatrist has a clear plan to stop hydroxyzine once the SSRI kicks in
    - Patient never goes back to the psychiatrist and the PCP just keeps refilling the medications because “the psychiatrist started it—it must be a good plan”

Reducing anticholinergic burden

- Anticholinergic drugs appear in multiple therapeutic categories
- How to know what's anticholinergic:
  - Anticholinergic Cognitive Burden Scale identifies risky anticholinergic drugs
    - Available online
- Many patients end up on multiple anticholinergic drugs to treat multiple problems
  - Often prescribed by PCPs or non-psychiatry/neurology specialists who haven't heard yet about these drugs' potential to cause dementia
- Higher anticholinergic burden = higher risk of dementia, so this is a worrisome situation

Reducing anticholinergic burden

- As psychiatric clinicians, we are brain specialists
- In addition to minimizing our own use of anticholinergic drugs as far as possible, we can also respectfully collaborate with other providers to reduce our mutual patients' anticholinergic burden and preserve brain health
  - In my experience, most PCPs/other specialists, once informed of the dementia risks, are very open to exploring other alternatives

Anticholinergic drugs in Psychiatry

- TCAs
- Paroxetine (only SSRI/SNRI with any significant anticholinergic activity)
  - Paroxetine linked to increased dementia risk in some studies, but not others
- Low/medium-potency typical antipsychotics (eg, chlorpromazine, perphenazine
- Some atypical antipsychotics:
  - Clozapine
  - Olanzapine
  - Quetiapine
- Antiparkinson/anti-EPS agents (benztropine, trihexyphenidyl)
- Hydroxyzine, diphenhydramine, other anticholinergic antihistamines
  - Out of all the above, these drugs likely have the WORST risk/benefit ratio

Reducing the use of anticholinergic drugs in Psychiatry

- Hydroxyzine, diphenhydramine, and other anticholinergic antihistamines
  - Often used for anxiety and sleep
- Don't have much evidence for efficacy
  - Diphenhydramine only improves sleep by 8 minutes/night
  - If a medication's going to give you dementia, it should at least fix your other problems!
- Need to SPECIFICALLY ASK about over-the-counter diphenhydramine or other anticholinergic sleep aids, including PRNs
  - Many patients on their own initiative take OTC sleep medications (which—except for melatonin—are almost all anticholinergic), and never think to mention it to us
- Counsel patients: most patients are VERY receptive to exploring non-anticholinergic options once informed of the dementia risks

Non-anticholinergic alternatives for anxiety/sleep

(Other than benzodiazepines / z-drugs, which have their own set of risks)

- SSRIs/SNRIs, buspirone for anxiety
  - MUCH stronger evidence base for efficacy than anticholinergic drugs
- Other medications with RCT evidence:
  - Melatonin for sleep
  - Trazodone for sleep
  - Mirtazapine for sleep (though may cause weight gain)
  - Propranolol for some types of anxiety
- Evidence-based psychotherapies
  - CBT for insomnia (CBT-I): may be the most effective long-term option for sleep overall
  - Many evidence-based psychotherapies for anxiety

Do some patients truly need certain types of anticholinergic drugs (TCAs, certain antipsychotics)?

- More complicated risk/benefit calculation
- Not first-line choices, but some patients don't respond to other options, and appear to truly need them
  - Certain patients with depression may truly respond preferentially/only to TCAs
  - Otherwise treatment-refractory schizophrenia that only responds to certain antipsychotics
- In these circumstances, the need to effectively treat current serious symptoms may reasonably outweigh future concerns about dementia
  - But can still try to mitigate risk as far as possible
    - Use less anticholinergic TCAs
      - Nortriptyline and desipramine are the LEAST anticholinergic TCAs

What about EPS?

- If patients DEVELOP antipsychotic-induced EPS:
  - May be preferable to lower dose / switch to a different antipsychotic. rather than adding an anticholinergic antiparkinson agent like benztropine or trihexyphenidyl
    - Unless there's reason to think antipsychotic changes would cause a relapse
- Antiparkinson drugs DO NOT prevent TD
  - Only treat currently existing EPS
  - Many patients tolerate high-potency typical antipsychotics without any motor symptoms
  - If never had trial off anticholinergic antiparkinson drugs, reasonable to at least try
- DON'T give antiparkinson drugs prophylactically to individuals on ATYPICAL antipsychotics with little risk of causing parkinsonism

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Akathisia

- Cognitively safe alternatives for akathisia:
  - Propranolol
    - Probably best first-line treatment overall
  - Vitamin B6
  - Mirtazapine

Safe and effective evidence-based alternatives to anticholinergic drugs for general medical conditions

- Urinary incontinence:
  - Instead of anticholinergics like oxybutynin or solifenacin, use:
    - Mirabegron (beta-3 agonist)
    - Bladder training
    - Pelvic floor exercises
    - Physical therapy

Safe and effective evidence-based alternatives to anticholinergic drugs for general medical conditions

- Migraine prophylaxis:
  - Instead of amitriptyline/TCAs, use:
    - Venlafaxine (225 mg/day or higher)
      - Venlafaxine and amitriptyline EQUALLY EFFECTIVE in head-to-head RCT
    - Propranolol
    - Magnesium oxide 400-600 mg qday

Safe and effective evidence-based alternatives to anticholinergic drugs for general medical conditions

- For back/neck pain:
  - Instead of anticholinergic muscle relaxers like cyclobenzaprine and methocarbamol, use:
    - Duloxetine
    - Physical therapy
    - Yoga
    - Aquacize
    - Massage
    - Stretching
    - Heat
  - Anticholinergic muscle relaxers are only minimally effective anyway (for most chronic pain)
    - If a medication's going to give you dementia, it should at least fix your other problems!

Safe and effective evidence-based alternatives to anticholinergic drugs for general medical conditions

- For benign paroxysmal positional vertigo:
  - Instead of anticholinergic drugs like meclizine or scopolamine, use:
    - Canalith repositioning maneuvers
    - Vestibular physical therapy
  - Not only are canalith repositioning maneuvers and vestibular PT cognitively safe, they're also much more likely to resolve the vertigo!

Safe and effective evidence-based alternatives to anticholinergic drugs for general medical conditions

- For allergic rhinitis:
  - Instead of strongly anticholinergic antihistamines, use:
    - Nasal saline irrigation
    - Locally acting nasal sprays
    - Nonsedating antihistamines

But what if you're not convinced?

- Everyone has different levels of risk tolerance
- Even if you think all of this is nonsense, in the end it's up to our patients to decide how much risk they want to accept

Autonomy

- One of the 4 key principles of medical ethics
  - Part of autonomy is INFORMED consent
    - Obligation to inform patients about information THEY would likely find relevant, before they make a decision about accepting a treatment
    - In my experience, most patients are VERY interested to know that certain medications may cause dementia
      - Often say:
        - “No one ever told me that before”
        - “I would never have taken it if I’d known there was even a chance”

Informed consent for anticholinergic drugs

- Even if you don't believe there's a proven causative link between anticholinergic drugs and dementia, patients may want to know that:
  - Multiple well-designed studies, conducted by respected experts in the field, show an increased risk of dementia
  - Many epidemiologists, behavioral neurologists, neuroscientists, etc believe that anticholinergic drugs can directly cause irreversible dementia
- We routinely warn patients about risks with far less evidence for causality than anticholinergics and dementia
  - Antipsychotics and death in dementia
  - SSRIs and suicidality in young people
- **Patients have a right to know the risks**