University of Basel

Case study of studying the association between benzodiazepines and Alzheimer's disease

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Background (Press)

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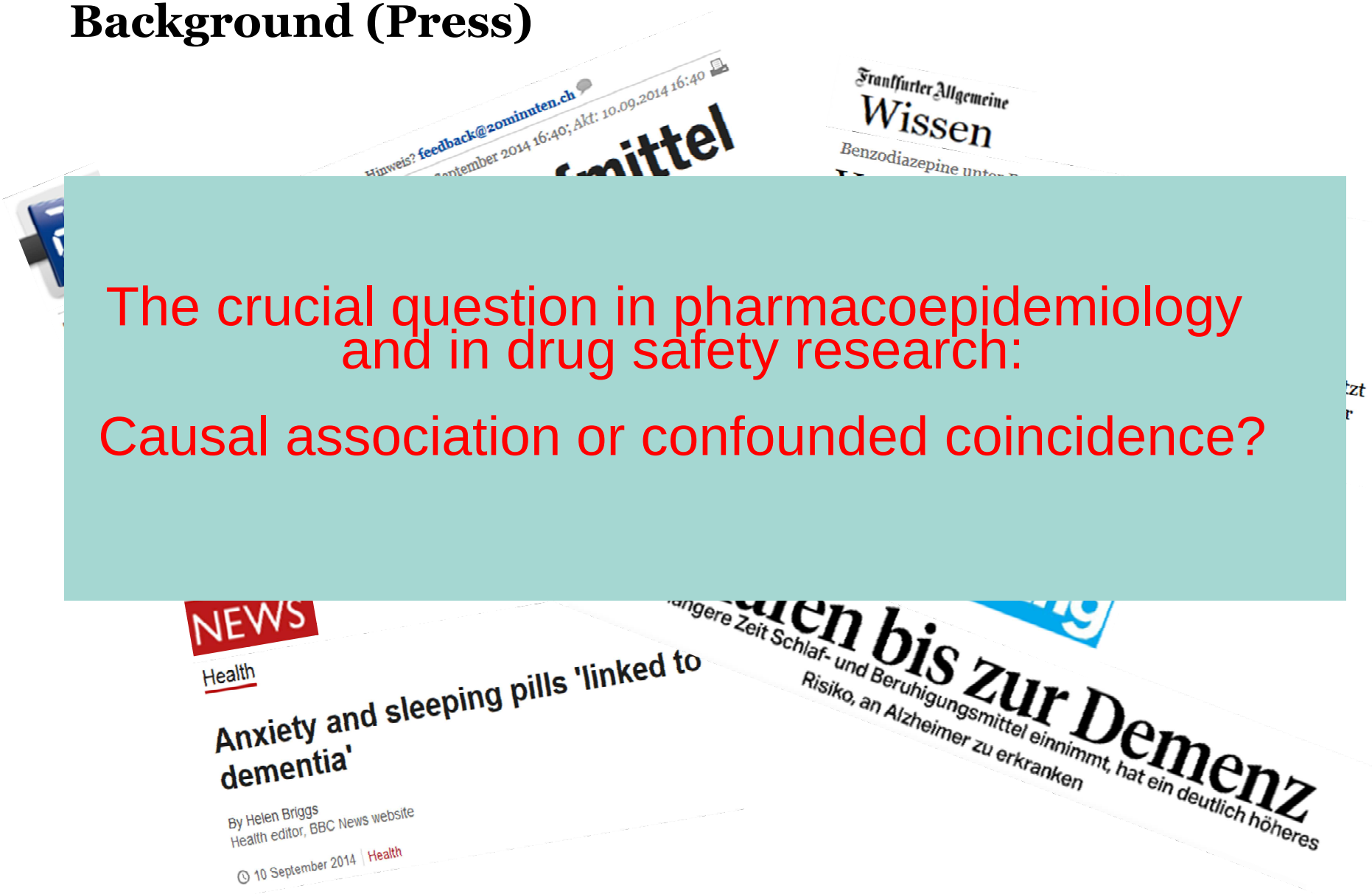

The crucial question in pharmacoepidemiology and in drug safety research:

Causal association or confounded coincidence?

Background (Scientific)

Risk of incident stroke in patients with Alzheimer disease or vascular dementia

Neurology 2013

Patrick Imfeld, PhD
Michael Bodmer, MD
Markus Schuerch, PhD
Susan S. Jick, DSc
Christoph R. Meier, PhD

ABSTRACT

Objective: To explore the risk of ischemic stroke, hemorrhagic stroke, or TIA in patients with Alzheimer disease (AD) or vascular dementia (VD).

Methods: We conducted a follow-up study with a nested case-control analysis using the UK-based General Practice Research Database. We included patients aged 65 years and older with an inci-

Epidemiology, Co-Morbidities, and Medication Use of Patients with Alzheimer's Disease or Vascular Dementia in the UK

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[c]*Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA*

J Alzheimer Dis 2013

Background (Scientific)

Seizures in patients with Alzheimer's disease or vascular dementia: A population-based nested case–control analysis

Epilepsia 2012

*†Patrick Imfeld, *Michael Bodmer, ‡Markus Schuerch, §Susan S. Jick, and *†§Christoph R. Meier

Metformin, Other Antidiabetic Drugs, and Risk of Alzheimer's Disease: A Population-Based Case–Control Study

Patrick Imfeld, MSc,† Michael Bodmer, MD,* Susan S. Jick, DSc,‡ and Christoph R. Meier, PhD*†‡*

J Am Geriatr Soc 2012

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Full-length Article

Influenza infections and risk of Alzheimer's disease

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What is the ‘correct’ index date of a disease?

- Alzheimer’s disease
- Cancer
- Parkinson’s Disease
- Diabetes
- Hypertension
- Rosacea
- …

Vs.

- Fracture
- Myocardial infarction
- Hemorrhagic stroke
- Sudden hearing loss
- Epileptic fit
- Death
- …

Background (Scientific)

– Benzodiazepines are widely used for the treatment of insomnia and anxiety

– Due to concerns based on well-known short-term side-effects on memory and cognition (such as drowsiness, confusion, difficulties in focusing and concentration, anterograde amnesia, etc.), several (observational) studies addressed the question whether use of benzodiazepines is associated with an increased risk of dementia

– Most of these studies found more benzodiazepine use in patients with dementia compared to controls

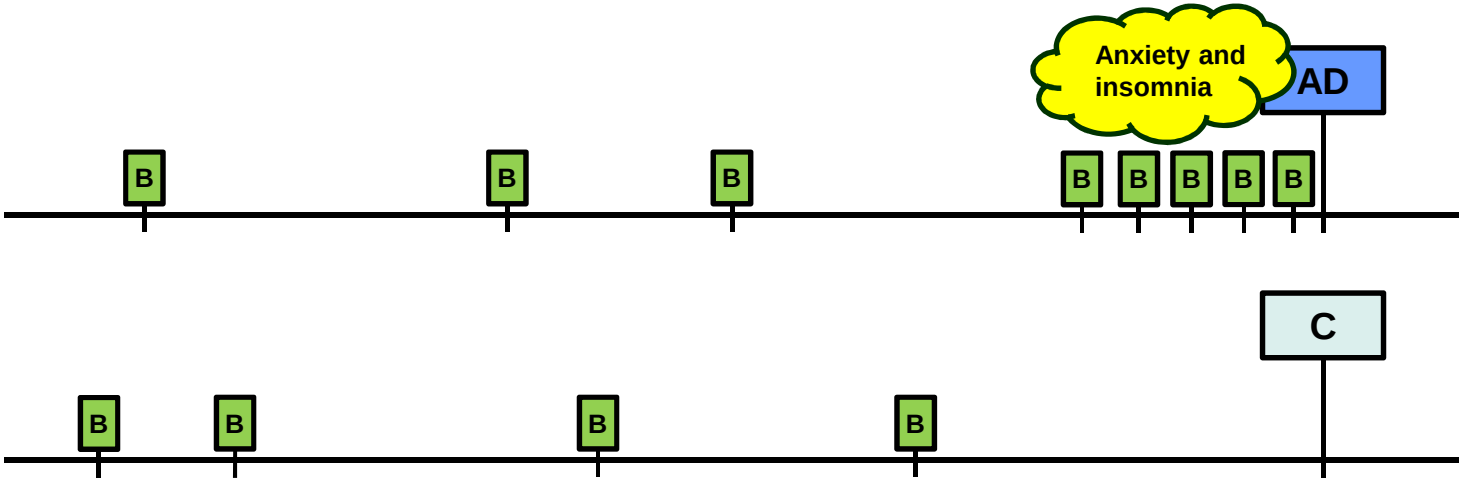
– To date a mechanistic hypothesis linking benzodiazepine use with an increased risk of dementia is lacking

– **CAVE:** benzodiazepines are often prescribed to treat prodromal symptoms of dementia (such as anxiety and insomnia): **protopathic bias**

Protopathic bias

Protopathic (or reverse causation) bias occurs when a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected. When the disease is later discovered, a causal relationship may be incorrectly inferred between the pharmaceutical agent and the disease.[1]

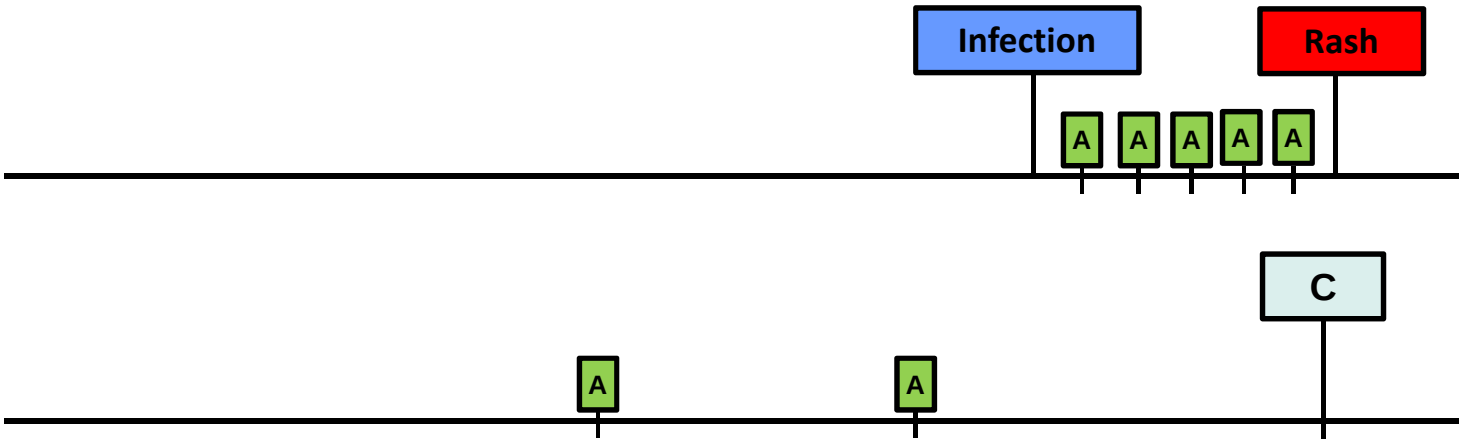
[1]Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. Am J Med. 1980;68:255–8



Protopathic bias vs. confounding by indication

Confounding by indication represents a constellation in pharmacoepidemiology / drug safety research in which an association between drug exposure and an outcome of interest is not causal, but reflects a characteristic of the underlying disease for which a drug has been prescribed.

Example: use of an antibiotic is associated with skin rash; however, the underlying infection may be responsible for the skin rash.



The BMJ Study

BMJ 2014;349:g5205 doi: 10.1136/bmj.g5205 (Published 9 September 2014)

RESEARCH

Benzodiazepine use and risk of Alzheimer's disease: case-control study

OPEN ACCESS

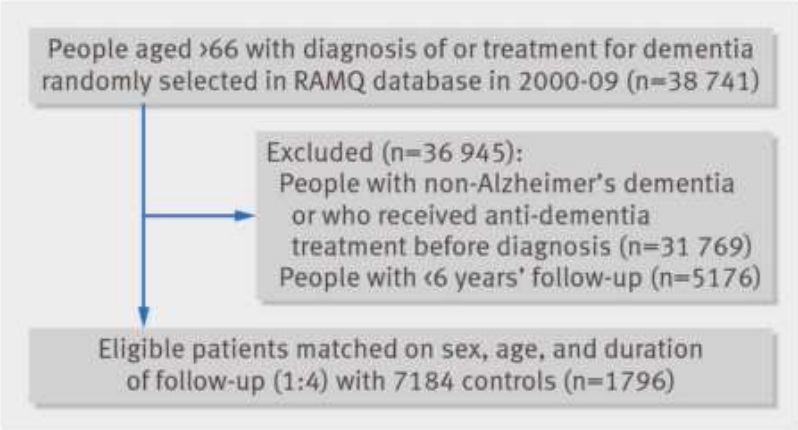
Sophie Billioti de Gage *PhD student*[1], Yola Moride *professor*[2 3], Thierry Ducruet *researcher*[2], Tobias Kurth *director of research*[4 5], Hélène Verdoux *professor*[1 6], Marie Tournier *associate professor*[1 6], Antoine Pariente *associate professor*[1], Bernard Bégaud *professor*[1]

Methods

– **Study design:** case-control study

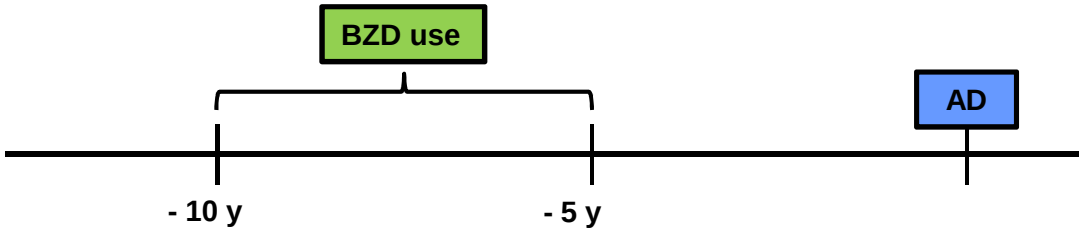
– **Datasource/setting:** Canadian administrative claims database (RAMQ), containing information about prescriptions and medical services

– **Study population: 1796** patients aged >66 y (living in the community) with an **incident** diagnosis of Alzheimers's disease (AD) between 2000 and 2009 (index date) and **at least 6 years of history** before the index date, matched to **7184** controls on sex, age, and duration of previous history before the index date (1:4 matching)



Methods

– **Exposure:** Benzodiazepine (BZD) use in a time window ranging from 5-10 years (maximum duration of follow-up) before the AD diagnosis (index date)



– **Three levels of exposure:**

  – **Ever use:** at least one BZD prescription during the above defined time window

  – **Cumulative dose**: calculated as number of prescribed daily doses (PDDs) and categorized as 1-90 PDDs, 91-180 PDDs, or >180 PDDs (90 PDDs ≡ cumulative exposure of 3 months)

  – **Drug elimination half life**: users of short-acting (<20 h) BZDs or long-acting (≥20 h) BZDs

Results

	No (%) of cases (n=1796)	No (%) of controls (n=7184)	Univariable odds ratio (95% CI)*	Multivariable odds ratio (95% CI)	
				Model 1*†	Model 2*‡
Benzodiazepine ever use:					
Non-users	902 (50.2)	4311 (60.0)	1.00	1.00	1.00
Users	894 (49.8)	2873 (40.0)	1.52 (1.37 to 1.69)	1.51 (1.36 to 1.69)	1.43 (1.28 to 1.60)
Benzodiazepine density exposure (No of prescribed daily doses):					
Non-users	902 (50.2)	4311 (60.0)	1.00	1.00	1.00
1-90	234 (13.0)	1051 (14.6)	1.08 (0.92 to 1.27)	1.09 (0.92 to 1.28)	1.05 (0.89 to 1.24)
91-180	70 (3.9)	257 (3.6)	1.33 (1.01 to 1.75)	1.32 (1.01 to 1.74)	1.28 (0.97 to 1.69)
>180	590 (32.9)	1565 (21.8)	1.85 (1.63 to 2.09)	1.84 (1.62 to 2.08)	1.74 (1.53 to 1.98)
Benzodiazepine elimination half life:					
Non-users	902 (50.2)	4311 (60.0)	1.00	1.00	1.00
Short half life (<20 h)	585 (32.6)	1996 (27.8)	1.43 (1.27 to 1.61)	1.43 (1.27 to 1.61)	1.37 (1.21 to 1.55)
Long half life (≥20 h)	309 (17.2)	877 (12.2)	1.72 (1.48 to 1.99)	1.70 (1.46 to 1.98)	1.59 (1.36 to 1.85)

*Matched for age, sex, and follow-up length.

†Adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).

‡Further adjusted for anxiety, depression, and insomnia diagnosis.

Our study

Drug Saf (2015) 38:909–919
DOI 10.1007/s40264-015-0319-3

ORIGINAL RESEARCH ARTICLE

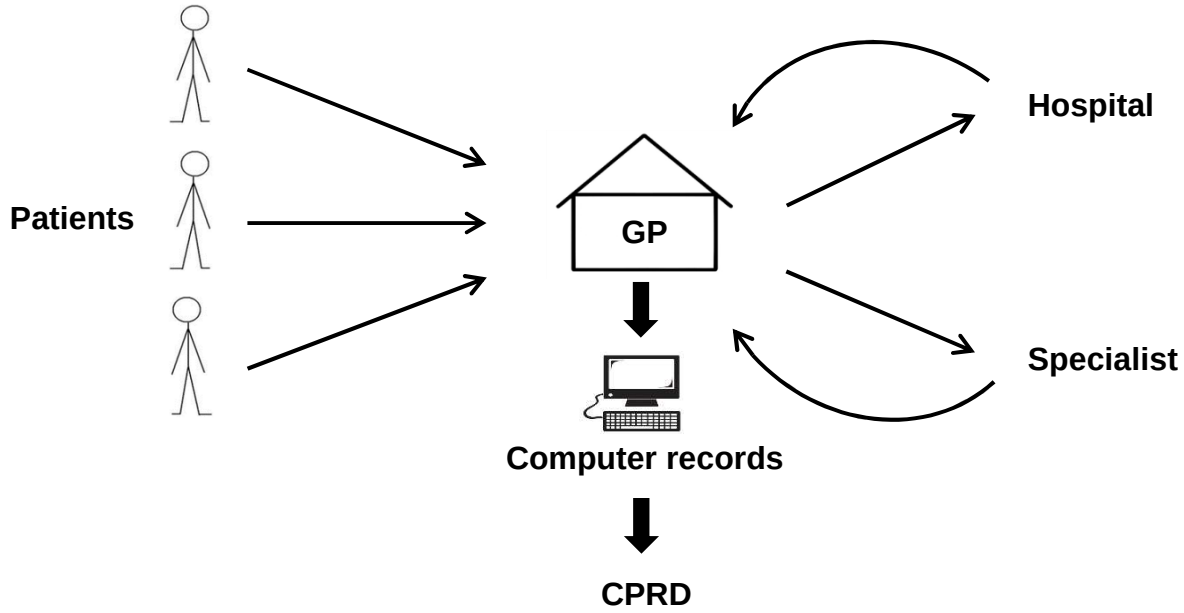
Benzodiazepine Use and Risk of Developing Alzheimer's Disease or Vascular Dementia: A Case–Control Analysis

Patrick Imfeld[1,2] · Michael Bodmer[1] · Susan S. Jick[3] · Christoph R. Meier[1,2,3]

Methods

– **Study design/setting:** Case-control analysis

– **Data source:** The Clinical Practice Research Datalink (CPRD), a primary care database from the UK.

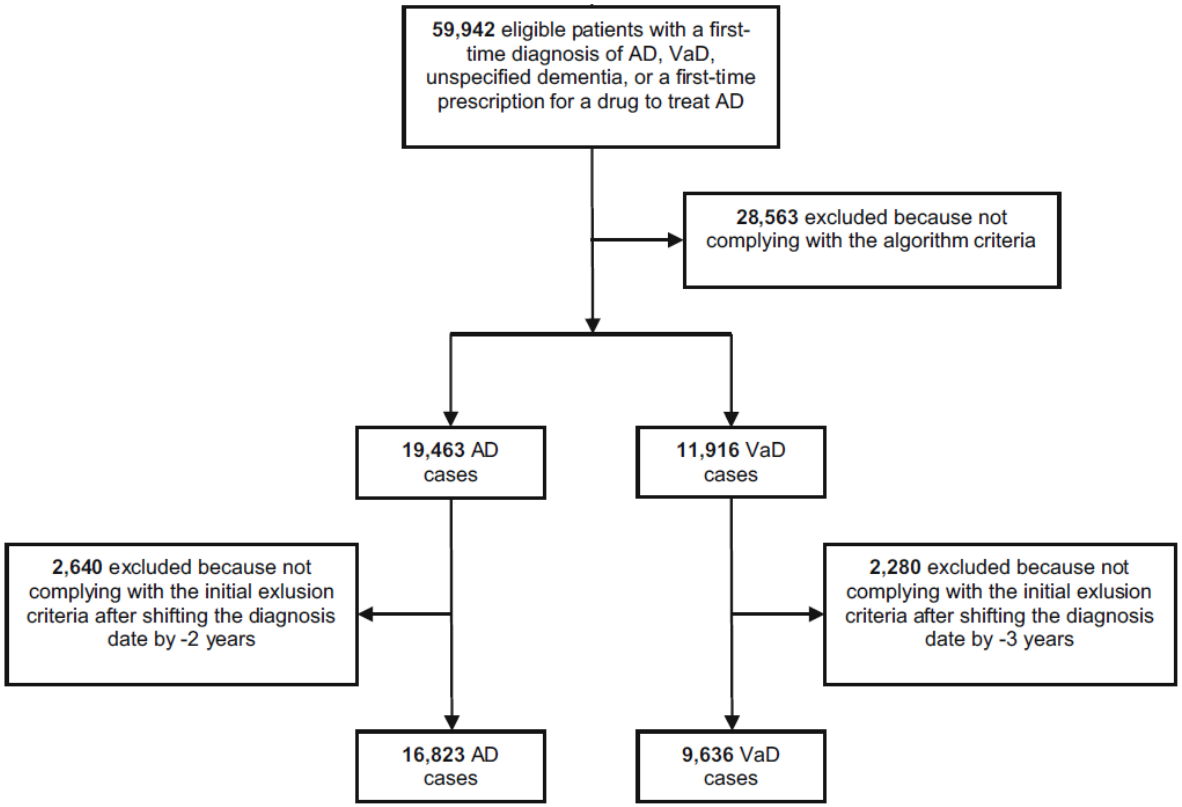


CPRD

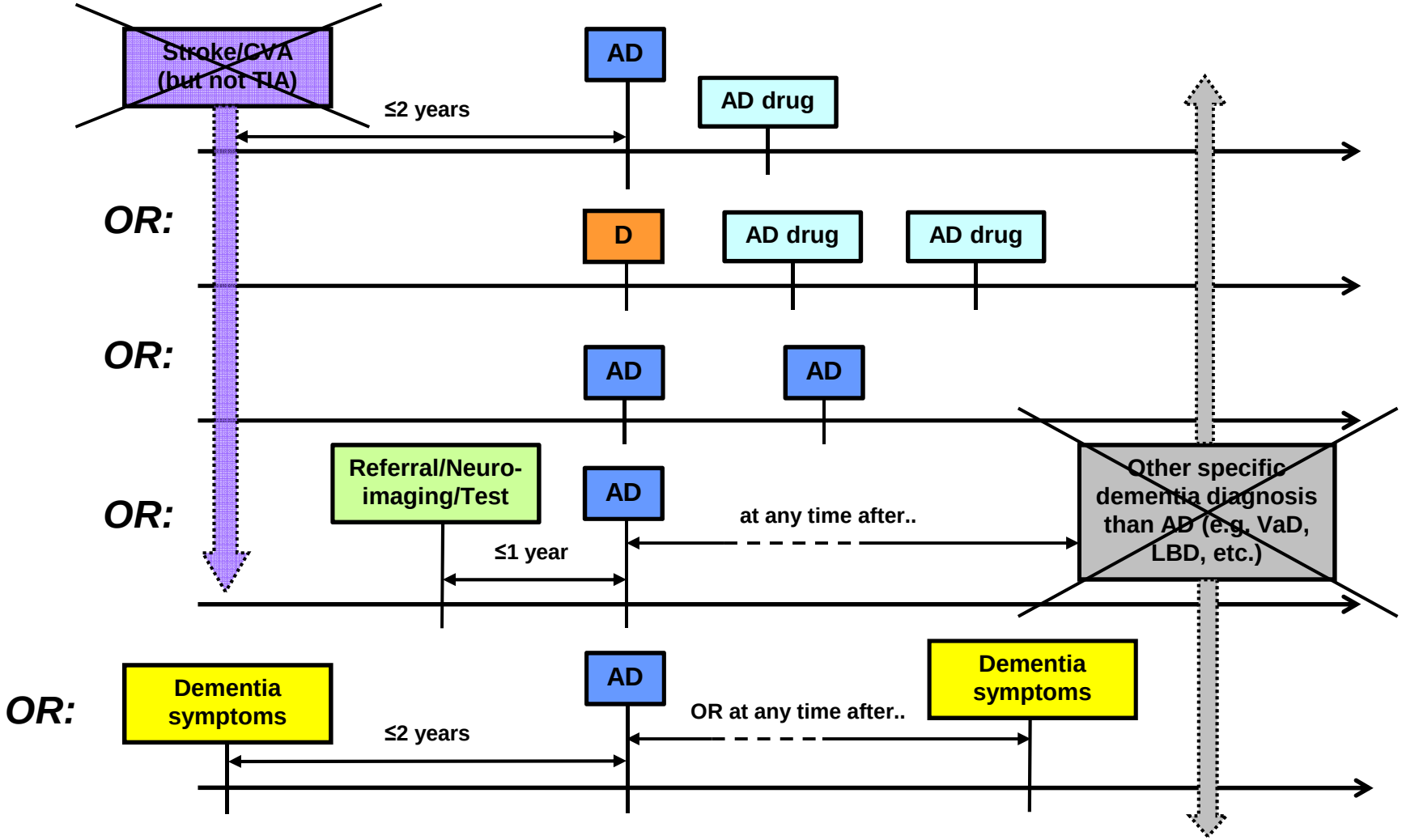
- Contains approx. 11 million active patients from some 600 GPs (as of January 2016)
- Start of data collection in 1987 (ongoing until now)
- Data is representative of the UK population in terms of age, sex, geographic distribution, and annual turnover rate
- Contains information about:
  - **Demographics:** age, sex, general practice, ZIP-code/region
  - **Life-style factors:** BMI, alcohol consumption, smoking status
  - **Diagnoses:** from GPs and specialists, **referrals and hospitalisations**
  - **Drug prescriptions:** exact product descriptions (i.e. strength, package size, sometimes dosage instructions)
  - **Laboratory values** (not all validated yet)
  - **Procedures:** examinations, tests, imaging

Methods

– **Study population: 26, 459** patients aged ≥65 years with newly diagnosed (index date) Alzheimer's disease (AD) or vascular dementia (VaD) between 1998 and 2013, **identified through a specific algorithm,** matched 1:1 to dementia-free controls on age, sex, index date, general practice, and number of years of recorded history in the database

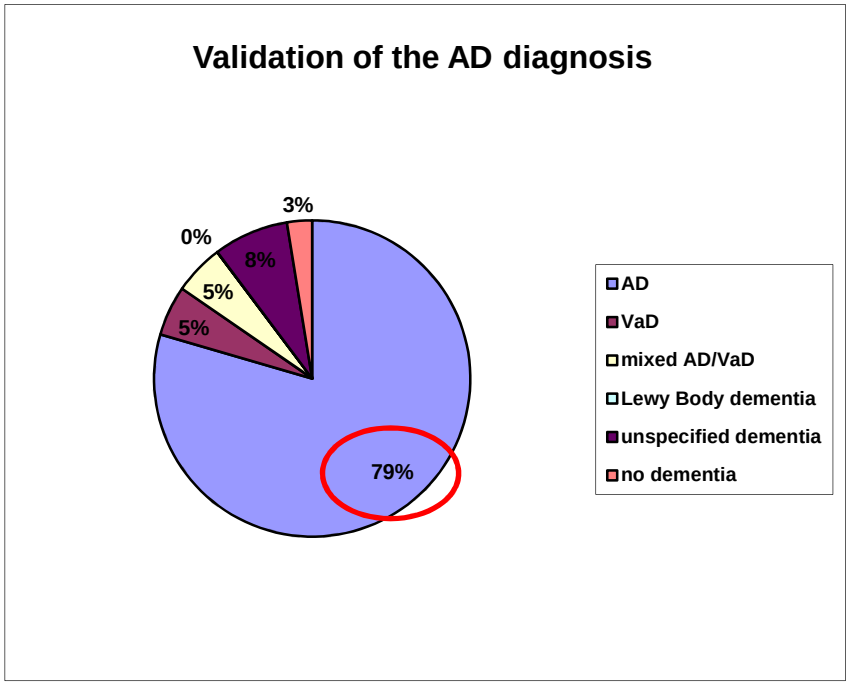


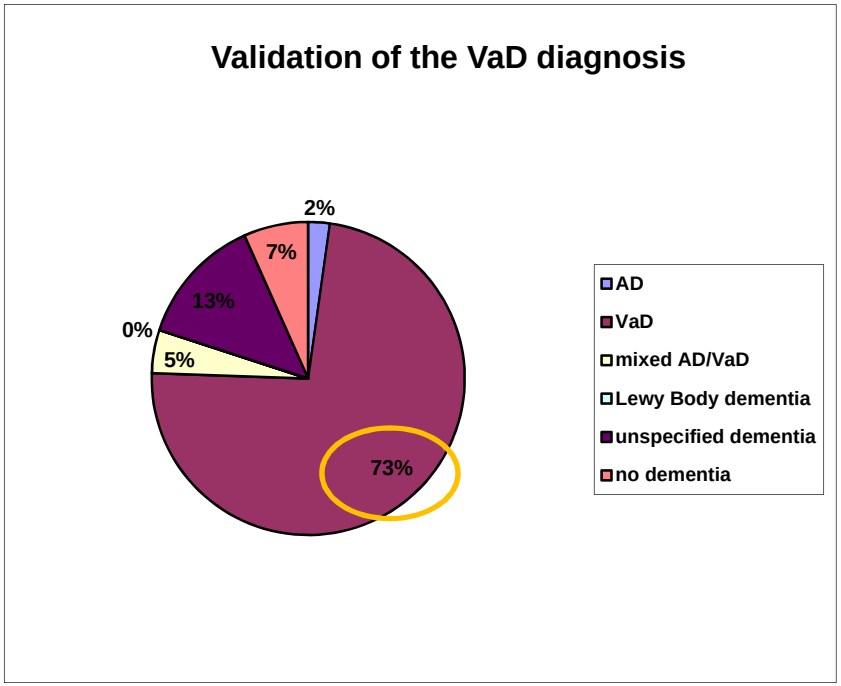
Algorithm
Example of AD



Validation of the algorithm

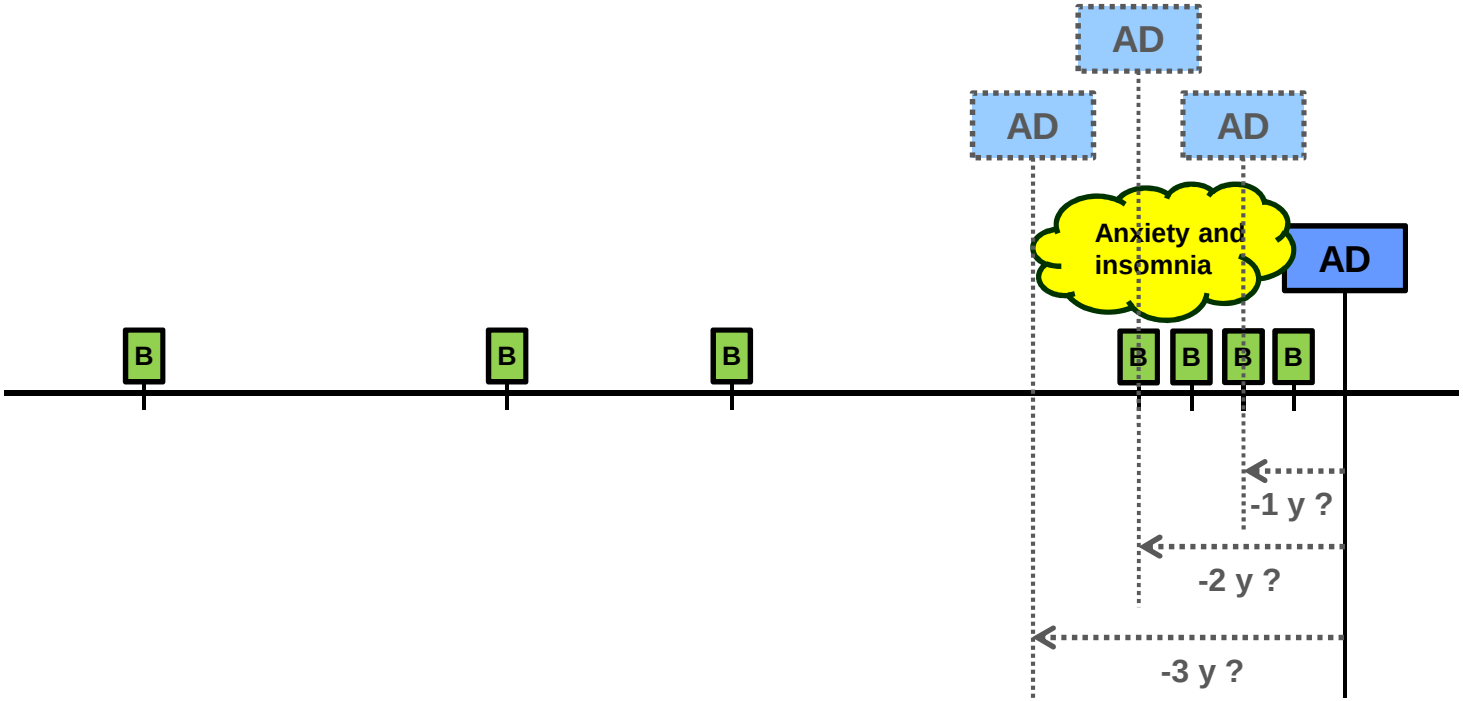
- Questionnaire sent to GPs
- In 79% of the AD cases, the GPs confirmed the recorded AD diagnosis
- For VaD, the corresponding confirmation rate was 73%



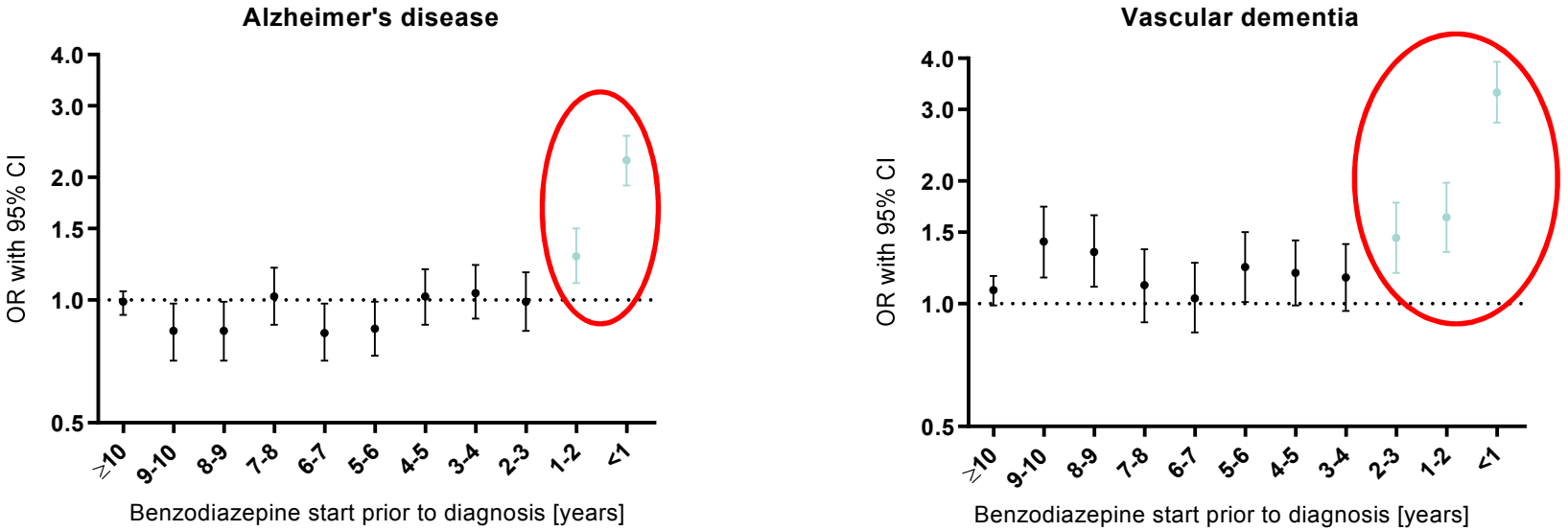


Methods

– **Induction time:** determination of an optimal induction time to control for benzodiazepine prescribing during the prodromal phase of dementia by systematically exploring the risk of AD or VaD in relation to the first benzodiazepine prescription prior to the diagnosis date and by shifting the diagnosis date backwards accordingly



Results:
Determination of Induction Time

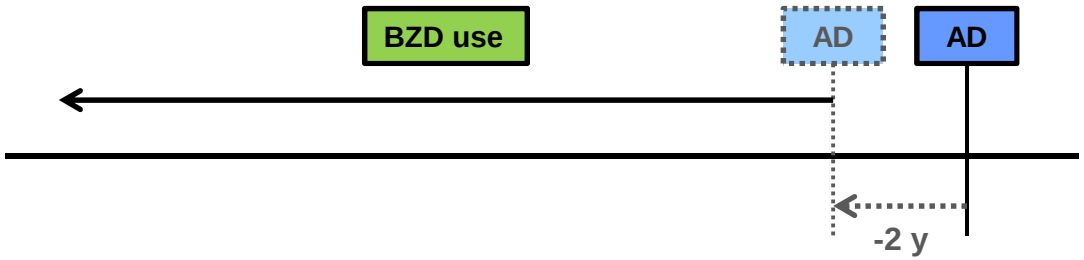


Determination of induction time. Adjusted ORs with 95 % CIs of Alzheimer's disease or vascular dementia in relation to benzodiazepine start presented as *whisker plots. Colored whisker plots* are those presumably subject to protopathic bias. *OR* odds ratio, *CI* confidence interval

– The appropriate induction time was determined as **2 years prior to the AD** diagnosis date and **3 years prior to the VaD** diagnosis date and the diagnosis date shifted backwards accordingly

Methods

- **Exposure:** benzodiazepine use [including the benzodiazepine receptor agonists (BzRAs) zolpidem, zopiclon, and zaleplon] prior to the shifted index date



- **Two levels of exposure:**
  - **Ever use:** at least one BZD prescription during the observation period
  - **Duration of use**: approximated by number of previous BZDs prescriptions and categorized as 1-9, 10-29, 30-59, 60-99, 100-149, or ≥150 prescriptions (1 prescription ≡ 28 days)

- **Two stratified analyses:**
  - **By benzodiazepine type:** users of only classical BZDs or BzRAs
  - **By drug elimination half-life:** users of only ultrashort-, short to intermediate-, or long-acting BZDs

Results: Risk of Alzheimer's Disease

	Alzheimer's disease			
	Cases [*n* (%)] (*n* = 16,823)	Controls [*n* (%)] (*N* = 16,823)	Unadjusted [OR (95 % CI)]	Adjusted[a] [OR (95 % CI)]
Benzodiazepine use				
No use	11,945 (71.0)	12,029 (71.5)	1.00 (Reference)	1.00 (Reference)
Ever use	4878 (29.0)	4794 (28.5)	1.03 (0.98–1.08)	0.95 (0.90–1.00)
Benzodiazepine use by number of prescriptions				
No use	11,945 (71.0)	12,029 (71.5)	1.00 (Reference)	1.00 (Reference)
1–9	3063 (18.2)	2914 (17.3)	1.06 (1.00–1.13)	0.99 (0.94–1.06)
10–29	607 (3.6)	621 (3.7)	0.99 (0.88–1.11)	0.90 (0.80–1.01)
30–59	412 (2.5)	421 (2.5)	0.98 (0.85–1.13)	0.90 (0.78–1.04)
60–99	380 (2.3)	331 (2.0)	1.16 (1.00–1.35)	1.06 (0.91–1.23)
100–149	239 (1.4)	274 (1.6)	0.88 (0.74–1.05)	0.79 (0.66–0.94)
≥150	177 (1.1)	233 (1.4)	0.77 (0.63–0.94)	0.69 (0.57–0.85)

OR odds ratio, *CI* confidence interval

[a] Adjusted for body mass index, smoking status, and depression

– There was no substantial difference in the risk of AD for classical benzodiazepines only or users of BzRAs only; however, the number of exclusive long-term users of BzRAs was low (data not shown)

Results: Risk of Vascular Dementia

	Vascular dementia			
	Cases [*n* (%)] (*n* = 9636)	Controls [*n* (%)] (*n* = 9636)	Unadjusted [OR (95 % CI)]	Adjusted[a] [OR (95 % CI)]
Benzodiazepine use				
No use	6764 (70.2)	7060 (73.3)	1.00 (Reference)	1.00 (Reference)
Ever use	2872 (29.8)	2576 (26.7)	1.17 (1.10–1.25)	1.08 (1.01–1.15)
Benzodiazepine use by number of prescriptions				
No use	6764 (70.2)	7060 (73.3)	1.00 (Reference)	1.00 (Reference)
1–9	1708 (17.7)	1598 (16.6)	1.12 (1.04–1.21)	1.04 (0.96–1.13)
10–29	387 (4.0)	305 (3.2)	1.34 (1.15–1.57)	1.21 (1.04–1.42)
30–59	275 (2.9)	224 (2.3)	1.30 (1.08–1.56)	1.19 (0.99–1.43)
60–99	234 (2.4)	198 (2.1)	1.24 (1.02–1.51)	1.13 (0.93–1.38)
100–149	138 (1.4)	141 (1.5)	1.04 (0.82–1.32)	0.92 (0.72–1.17)
≥150	130 (1.4)	110 (1.1)	1.26 (0.97–1.63)	1.11 (0.85–1.45)

[a] *adjusted for BMI, smoking and depression*

– Similar results were observed for users of classical benzodiazepines only, whereas the number of long-term users of BzRAs only was too low for a meaningful interpretation (data not shown)

Conclusions

- This large analysis provides evidence that benzodiazepines are not a risk factor for AD; we would expect increasing ORs with increasing exposure duration, if causal.
- Whenever there is a certain likelihood that drug use may be associated with symptoms of a so far undetected disease, there is a risk of protopathic bias, particularly for current and short-term use, particularly when the onset of the disease of interest is unknown, and particularly when it is slowly developing.
- When a disease is slowly developing, and when it is to be expected that a given drug of interest may cause cumulative toxicity, current use and short-term use is somewhat irrelevant and actually potentially misleading; cumulative / long-term use is crucial.
- Two possible techniques to address the issue of 'late diagnoses' and 'vague index dates' are:

  - shifting the index date by an *a priori* estimated time span

  - analysing the 'real' results and shifting the index date based on data

- The ultimate answer would come from a RCT, which will never take place…

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