Supplementary Material File 2: Instrumental variable analysis

Instrumental variables (IV) offer an approach to address unmeasured confounding. The approach lies in the ability to identify a valid instrument that acts to assign treatment, but is unrelated to the confounders and only affects the outcomes through its direct effect on the treatment. 1 Instrumental variables such as the prescribing preferences of the GP or GP practice, have been successfully used in previous studies using routinely collected primary care data. 2-4 The three assumptions of IV are: relevance (the IV causes a change in the treatment received), exclusion (the IV affects the outcome only through the treatment received) and exchangeability (the IV does not share common causes with the outcome).5 Concerns using a GP’s preference for prescribing as an IV are that the GP’s choice of treatment may well reflect other aspects of their care that will influence patient outcomes, may influence their recording of outcomes and patients who seek out particular GPs who prescribe certain treatments may have different characteristics and baseline risks of the outcomes. 1 We describe the feasibility of using instrumental variables in our study here.

### Methods

We created three potential instruments estimated as the proportion of previous patients with dementia who were prescribed a Z-drug initially on presenting with a sleep disturbance (i) among the previous 5 eligible cases, (ii) for the previous case only, or (iii) across the whole practice. The IV was coded as binary, such that when the proportion of patients previously prescribed Z-drugs was greater than 0.5, the IV indicated a Z-drug prescription for the current patient. We restricted our analysis to those patients with a dementia diagnosis presenting for the first time with either a recorded diagnosis/symptom of sleep disturbance or who were prescribed a Z-drug. We also restricted to practices with more than 5 eligible patients.

We investigated the validity of the relevance assumption, by testing the strength of association between prior Z-drug prescriptions and the actual Z-drug prescription using a partial F-test, from a regression of the actual prescription on the IV adjusted for covariates. A partial F-statistic test of less than 10 indicates an insufficient association between the IV and actual treatment assignment. 6 As other indicators of weak instruments, we estimated the proportion of compliers (i.e. the proportion of patients whose prescription of a Z-drug is dependent on the type of GP), and the partial r2 when adding the IV to a regression model of treatment assignment that includes the covariates. The exchangeability assumption was tested by examining covariate balance across the IV. We estimated standardized differences in covariates across the IV and considered values above 0.2 to indicate imbalance. 7 We also estimated the bias ratio, as the ratio of the mean difference in covariates across the IV divided by the proportion of compliers, to the mean difference in covariates across actual treatment assignment. Bias ratios less than 1 indicate that the IV has resulted in greater covariate balance than in the main analysis.8

### Results

##### IV strength

A Z-drug prescription was predicted by the IV for 3,050, 3,405 and 3,203 patients when examining the Z-drug prescription of the previous case only, the previous 5 eligible cases, and across the whole practice, respectively. Of these patients, 2,128 (70%), 2,316 (68%) and 2,360 (74%) went on to be prescribed a Z-drug (Table 1). The proportion of compliers for each IV was estimated as 27%, 33% and 46%. The difference in partial r2 after adding the IVs to the first-stage model for treatment including the confounders, was 3%, 4% and 10%, respectively. The F-statistic from the regression models were 8%, 9% and 15%. Hence the variables of the Z-drug prescription of the previous case and average of the previous 5 eligible cases were not considered sufficient strong to act as IVs. The IV based on the average proportion of Z-drugs across the whole practice was considered sufficiently strong to satisfy the first assumption of relevance and was explored further.

Table 1. Statistical characteristics of the instrumental variables based on the GP practice’s prescribing preferences

|  |  |
| --- | --- |
|  | Instrumental variable (number of GP practice patients used to estimate next Z-drug prescription) |
|   | Last patient | Last 5 patients | All patients |
| Prob(Z-drug | IV=0) | 43% | 35% | 27% |
| Prob(Z-drug | IV=1) | 70% | 68% | 74% |
| Compliers | 27% | 33% | 46% |
| r2 with confounders | 9% | 9% | 9% |
| r2 plus IV | 12% | 14% | 20% |
| Increase in pseudo r2 | 3% | 4% | 10% |
| F statistic | 8.3 | 9.1 | 14.5 |

##### Exchangeability assumption

Most potential measured confounders were similar across the IV of the GP practice’s preference for prescribing Z-drugs to people with dementia with sleep disturbance (Table 2 and Table 3). GP practices with a preference for Z-drug prescribing were more likely to be from the South/London, be in less deprived areas, have patients with more frequent GP and hospital visits, and less patients with urinary incontinence or a history of sleep disturbance. Unsurprisingly patients from GP practices with a preference for Z-drug prescribing, had a greater history of Z-drug or benzodiazepine prescriptions. However, the bias ratio is >1 for most covariates, showing that the imbalance is greater when using IV rather than actual treatment.

### Summary

Although we identified an IV that was sufficiently strongly associated with current Z-drug prescription, i.e. that of the tendency of the GP practice to prescribe Z-drugs to people living with dementia, it was considered too weak to be useful for informative analysis. As the majority of covariates had been well balanced in the main analysis, i.e. patient characteristics could not well predict who was prescribed a Z-drug, and as the identified IV was not particularly strong, then performing IV analyses would have led to wide effect estimates for the adverse events and potentially introduce more bias than in the main analyses. 8 Hence, we did not proceed with an IV analysis.

Table 2. Imbalance of measured covariates between patients with Z-drugs commonly prescribed at their practice versus commonly not prescribed

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Proportion** | **Standardised difference** |  |
| **Characteristic**  | **IV=Z-drug** | **IV=no Z-drug** | **Bias ratio** |
| Women | 60% | 60% | 0.00 | -0.1 |
| Age, years | 83.1 | 82.9 | 0.03 | 1.4 |
| White ethnicity | 92% | 91% | 0.01 | 1.7 |
| Care home | 36% | 33% | 0.05 | 6.1 |
| Index date | 21/02/2009 | 05/11/2008 | 0.07 | 0.7 |
| GP practice - South/London | 49% | 38% | 0.20 | 5.4 |
| GP practice area IMD quintile | 3.2 | 3.4 | -0.13 | 11.8 |
| **Health behaviours** |  |  |  |  |
| Current smoker | 9% | 9% | -0.02 | -1.3 |
| Alcohol user | 23% | 27% | -0.08 | 2.2 |
| Body mass index | 24.7 | 24.5 | 0.04 | -6.2 |
| Systolic blood pressure | 134.0 | 134.1 | -0.01 | 1.2 |
| **Dementia** |  |  |  |  |
| Months since dementia diagnosis | 18.2 | 17.7 | 0.03 | 3.0 |
| Alzheimer's disease | 1.2 | 1.2 | -0.08 | 5.1 |
| Anticholinesterase Rx in last 90 days | 21% | 18% | 0.08 | 16.9 |
| Memantine Rx in last 90 days | 2% | 1% | 0.04 | 2.6 |
| Antipsychotic Rx in last 90 days | 19% | 15% | 0.08 | 1.7 |
| Agitation/psychosis history  | 18% | 21% | -0.06 | 1.9 |
| End of life care | 5% | 5% | 0.01 | 1.1 |
| **Sleep disturbance** |  |  |  |  |
| Sleep disturbance diagnosis pre dementia | 22% | 34% | -0.28 | 11.1 |
| History of benzodiazepine use  | 24% | 20% | 0.09 | 3.9 |
| History of z-drug use  | 9% | 5% | 0.15 | 2.7 |
| **Medical history in past year** |  |  |  |  |
| Falls | 27% | 30% | -0.07 | -3.3 |
| Fractures | 10% | 8% | 0.08 | 1.9 |
| Dizziness/unsteadiness | 5% | 7% | -0.06 | 5.6 |
| Faints/syncope | 6% | 7% | -0.05 | 6.5 |
| UTI/acute LRTI | 25% | 23% | 0.04 | 1.4 |
| Influenza vaccination | 69% | 73% | -0.08 | 2.0 |
| Pneumonia vaccination  | 5% | 6% | -0.04 | 16.0 |
| Physician consultations | 8.4 | 7.6 | 0.11 | 12.0 |
| Hospital admissions | 1.2 | 0.9 | 0.14 | 0.7 |

Table 3. Imbalance of measured comorbidities and co-medication between patients with Z-drugs commonly prescribed at their practice versus commonly not prescribed

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Proportion** | **Standardised difference** |  |
| **Characteristic**  | **IV=Z-drug** | **IV=no Z-drug** | **Bias ratio** |
| **Comorbidities** |  |  |  |  |
| Depression | 27% | 24% | 0.07 | -3.5 |
| Depression symptoms | 18% | 20% | -0.06 | 2.0 |
| Anxiety | 16% | 16% | -0.01 | 0.7 |
| Anxiety symptoms | 11% | 14% | -0.09 | 2.9 |
| Parkinson's disease | 5% | 7% | -0.07 | -5.6 |
| Urinary incontinence | 15% | 25% | -0.26 | 3.1 |
| Benign prostatic hyperplasia | 10% | 11% | -0.03 | -1.9 |
| Asthma | 9% | 10% | -0.02 | -89.8 |
| Cancer  | 20% | 20% | 0.01 | 0.4 |
| COPD | 7% | 8% | -0.02 | 1.5 |
| Osteoporosis | 12% | 11% | 0.02 | -0.8 |
| Other muscleroskeletal conditions | 13% | 13% | -0.02 | 1.2 |
| Osteoarthritis/RA | 39% | 42% | -0.06 | 2.2 |
| Other joint conditions | 82% | 84% | -0.04 | 2.2 |
| Headache/migraine | 19% | 21% | -0.07 | 2.3 |
| Back/neck pain | 53% | 54% | -0.01 | 0.3 |
| ARMD | 6% | 6% | -0.01 | 0.4 |
| Cataract | 28% | 31% | -0.07 | 4.1 |
| Glaucoma | 10% | 10% | -0.01 | 1.0 |
| Retinal disorder | 8% | 9% | -0.05 | 60.7 |
| Diabetes  | 14% | 15% | -0.05 | -318.8 |
| Hyperlipidemia | 12% | 15% | -0.09 | 2.8 |
| Hypertension | 51% | 56% | -0.11 | 3.0 |
| Stroke/TIA | 22% | 22% | -0.01 | -1.8 |
| Myocardial infarction | 8% | 10% | -0.04 | 4.5 |
| Heart failure | 9% | 10% | -0.02 | 35.6 |
| Atrial fibrillation | 15% | 15% | -0.01 | -0.8 |
| Angina | 15% | 17% | -0.05 | 4.6 |
| Venous thromboembolism | 7% | 6% | 0.01 | -1.5 |
| **Prescriptions in last 90 days** |  |  |  |  |
| SSRI | 19% | 19% | 0.00 | 0.0 |
| Other antidepressant | 24% | 25% | -0.03 | -6.4 |
| Antiepileptic | 24% | 25% | -0.05 | 2.6 |
| Parkinson's disease drug | 24% | 26% | -0.08 | -14.9 |
| Analgesic | 40% | 40% | -0.01 | 0.3 |
| Inhaled corticosteroid | 4% | 5% | -0.03 | 1.6 |
| Lipid regulating medication | 32% | 33% | -0.02 | 1.7 |
| Diuretic | 31% | 30% | 0.03 | 22.4 |
| Beta blocker | 17% | 17% | 0.00 | -0.2 |
| ACE inhibitor | 19% | 20% | -0.01 | 0.4 |
| Angiotensin II receptor antagonist  | 25% | 25% | 0.00 | 0.3 |
| Calcium channel blocker | 17% | 19% | -0.05 | 4.8 |
| Anticoagulant | 5% | 5% | 0.01 | -0.4 |
| Antiplatelet | 44% | 45% | -0.03 | -20.4 |
| Cardiac glycoside | 8% | 7% | 0.02 | 1.5 |
| NSAID | 7% | 7% | -0.02 | 0.6 |
| Bisphosphonate | 9% | 9% | 0.02 | -0.8 |
| Calcium/Vitamin D | 17% | 18% | -0.02 | 1.4 |
| Diabetes medications | 10% | 12% | -0.05 | -196.7 |
| Antibiotic (in last 30 days) | 20% | 19% | 0.04 | 1.5 |

References

1. Ertefaie A, Small DS, Flory JH, Hennessy S. A tutorial on the use of instrumental variables in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2017;**26**:357-67. <http://dx.doi.org/10.1002/pds.4158>

2. Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. *Epidemiology* 2006;**17**:268-75. <http://dx.doi.org/10.1097/01.ede.0000193606.58671.c5>

3. Uddin MJ, Groenwold RH, de Boer A, Gardarsdottir H, Martin E, Candore G*, et al.* Instrumental variables analysis using multiple databases: an example of antidepressant use and risk of hip fracture. *Pharmacoepidemiol Drug Saf* 2016;**25 Suppl 1**:122-31. <http://dx.doi.org/10.1002/pds.3863>

4. Davies NM, Gunnell D, Thomas KH, Metcalfe C, Windmeijer F, Martin RM. Physicians' prescribing preferences were a potential instrument for patients' actual prescriptions of antidepressants. *J Clin Epidemiol* 2013;**66**:1386-96. <http://dx.doi.org/10.1016/j.jclinepi.2013.06.008>

5. Lousdal ML. An introduction to instrumental variable assumptions, validation and estimation. *Emerg Themes Epidemiol* 2018;**15**:1. <http://dx.doi.org/10.1186/s12982-018-0069-7>

6. Stock JH, Wright JH, Yogo M. A survey of weak instruments and weak identification in generalized method of moments. *Journal of Business & Economic Statistics* 2002;**20**:518-29. <http://dx.doi.org/10.1198/073500102288618658>

7. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. *Communications in Statistics-Simulation and Computation* 2009;**38**:1228-34. <http://dx.doi.org/Pii> 910355371

10.1080/03610910902859574

8. Baiocchi M, Cheng J, Small D. Instrumental variable methods for causal inference (vol 33, pg 2297, 2014). *Statistics in Medicine* 2014;**33**:4859-60. <http://dx.doi.org/10.1002/sim.6254>