

eText

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1 Amendments to the study protocol.

We made two amendments to the original study protocol (Walker et al, 2016):

- Exposure: ‘Centrally acting antihypertensives’ are primarily used for acute events, while ‘Loop diuretics’ are primarily used for heart failure, and so have been excluded from the analysis. We have also combined ‘Potassium-sparing diuretics and aldosterone antagonists’ and ‘Thiazides and related diuretics’ into a single category titled ‘Diuretics’ as prescriptions for the former in the data extract were rare.
- Control: We compared each drug classes against all other antihypertensive drug classes instead of using beta-adrenoceptor blocking drugs as the reference drug class.

2 Covariates in the multivariable logistic regression analysis.

Previous history of coronary heart disease, coronary-bypass surgery or cerebrovascular disease.

Presence of one or more relevant Read codes on record.

Chronic illness, including cancer and arthritis.

Charlson index implemented using Read code lists. (Charlson et al, 1987; Khan et al, 2010) Code lists based on those by Taylor et al. (Taylor et al, 2017)

Socioeconomic position.

2010 English Index of Multiple Deprivation (IMD) at the ‘twentile’ level, where 1 represents the least deprived and 20 the most deprived.

Consultation rate.

Calculated by dividing the total number of clinic visits by the length of the patient record prior to the index date to give an average annual rate.

Alcohol status.

Recorded value (current, former or never).

Smoking status.

Most recent of recorded value (current, former or never) or Read code indicating a recorded value. Code lists based on those by Wright et al. (Wright et al, 2017)

Bodt mass index.

Recorded value if available, or a calculated value using the last recorded height and weight measurements. Measurements taken before the age of 25 were excluded to ensure adult measurements were used.

3 Fullfillment of IV study reporting guidelines.

State which population target parameter the study aims to estimate (eg, local average treatment effect, effect of treatment on the treated) and the assumptions on which it depends (eg, monotonicity or no effect modification).

We make the following statement in the section ‘Statistical methods’: ‘To obtain a point estimate, we made a fourth instrument assumption of monotonicity. That is, we assumed all patients complied with their physicians’ preferred drug class. Consequently, the results were interpreted as the effect among patients whose prescription was affected by their physicians’ preference (known as the local average treatment effect).’

Report the association of instruments and exposure using a partial F-statistic.

The Cragg-Donald F statistic has been presented alongside the results for each of our analyses.

Report and test the association of observed potential confounding factors with both the exposure and the instrument.

See section ‘Assessment of bias’ in the article.

With multiple instruments report the test for overidentifying restrictions, ie, the Sargan or the Hansen test.

See section ‘Sensitivity analyses’ in the article.

For binary outcomes, exposures, and instruments, report a tabulation of the frequencies of each combination of instrument, exposure, and outcome, so readers can reconstruct basic results.

See eTable 3.

When using generalized linear models with binary outcomes, always use robust (sandwich estimators) or bootstrapped standard errors and take clustering of study participants into account where necessary.

The analysis used Stata’s ivreg2 command with ‘robust’ specified and clustering according to the physicians’ staff ID. The analysis was conducted in Stata version 15MP (StataCorp; College Station, TX).

4 Overlap with existing CPRD studies

Two existing studies have used the CPRD to assess whether antihypertensives can be repurposed for the prevention of dementia. However, to our knowledge, we are the first study to analyse this data using an instrumental variable analysis design to determine the effect of antihypertensives on dementia outcomes. The first existing study, by Davies et al, investigated the effects of angiotensin converting enzyme inhibitors and angiotensin-II receptor blockers, compared with other antihypertensives, on various dementia outcomes using logistic regression. There is a small overlap between the present study and Davies et al, which we have estimated to be 5.2% at most (48,363 new users of antihypertensives in Davies et al vs 849,378 new users of antihypertensives in the present study). The second, by Goh et al, compared the effects of angiotensin-II receptor blockers and angiotensin-converting enzyme inhibitors against each other in relation to dementia as a single outcome using Cox regression. As they did not consider other antihypertensive drug classes as an exclusion criterion, they had a much larger sample of 426,089 participants (as opposed to 221,421 participants) exposed to angiotensin-II receptor blockers and angiotensin-converting enzyme inhibitors. This made it difficult to calculate the overlap as many of these patients are likely to have been exposed to other antihypertensives. However, we do know

that there were 50,404 participants assigned to the drug classes angiotensin-II receptor blockers and angiotensin-converting enzyme inhibitors in our analysis that were not present in the Goh et al study. This is because they were prescribed after 2010, i.e. after the final data extract for the Goh et al study, so will not have been included in their analysis. Note that our study and the existing studies all used similar approaches for identifying patients who had been exposed to our drugs of interest – specifically using Medical codes and information from the British National Formulary. Despite the potential overlap of some of the data used in the present study with these studies in the literature, the study design and analysis differ considerably between them.

5 Conversion of relative risk estimates to additional cases per 1000 treated.

The Larsson et al meta-analysis reports a number of relative risk estimates that can be compared to the results from this study. However, our study presents the additional cases per 1000 treated so we must convert the relative risk estimates to be on the same scale before comparing them. The following derivation was based on the details provided at <https://bestpractice.bmj.com/info/toolkit/learn-ebm/how-to-calculate-risk/>.

To calculate the additional cases per 1000 treated, we first calculate the number needed to treat (NNT). Consider the following formula that uses absolute risk reduction (ARR):

$$NNT = \frac{1}{ARR}$$

Another way to express ARR uses the absolute risk of events in the control group (ARC) and the absolute risk of events in the treatment group (ART):

$$ARR = ARC - ART$$

Therefore:

$$NNT = \frac{1}{ARC - ART}$$

Relative risk can also be expressed in terms of ARC and ART by combining the following formulas concerning relative risk reduction (RRR):

$$RRR = 1 - RR$$

$$RRR = \frac{ARC - ART}{ARC}$$

Consequently:

$$\begin{aligned} 1 - RR &= \frac{ARC - ART}{ARC} \\ (1 - RR) ARC &= ARC - ART \end{aligned}$$

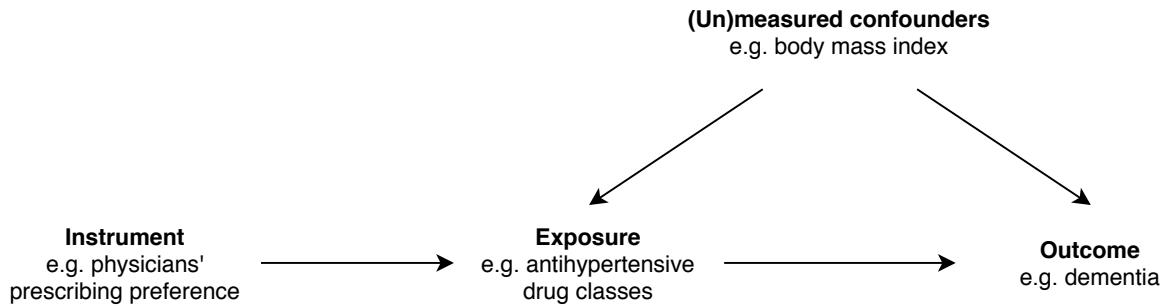
Ultimately, this means NNT can be expressed by RR as follows:

$$NNT = \frac{1}{(1 - RR) ARC}$$

Finally, once we have obtained NNT, we can then calculate the additional cases per 1000 treated according to the following equation:

$$\text{Additional cases per 1000 treated} = -1 \left(\frac{1000}{NNT} \right)$$

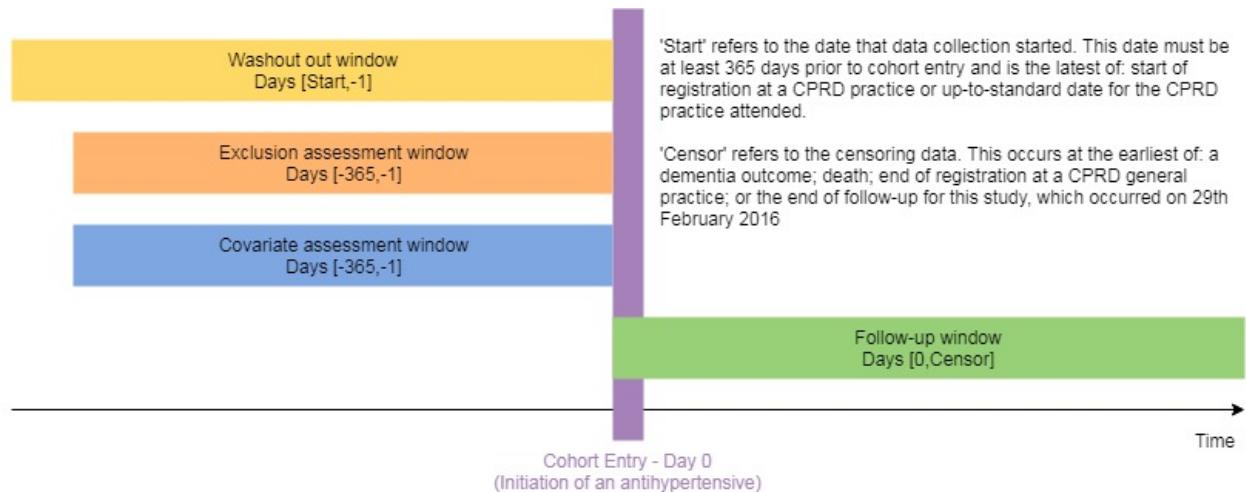
eFigure 1: Directed acyclic graph for the instrument variable model.



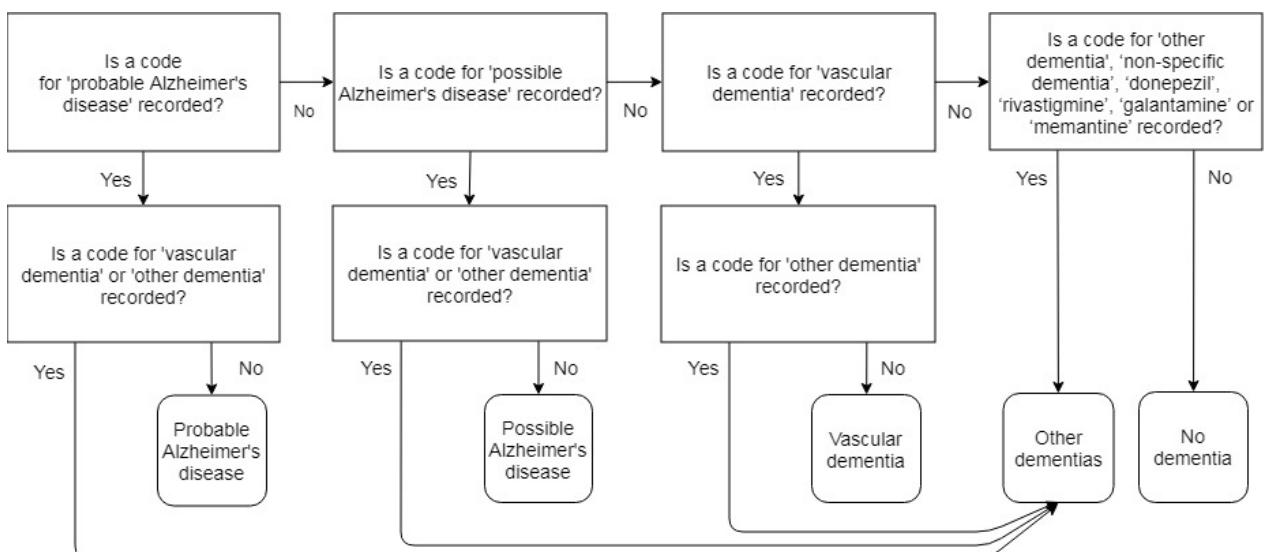
Instrumental variable analysis requires three assumptions:

- (i) Relevance – the instrument must associate with the exposure
- (ii) Independence – the instrument and the outcome must have no common causes
- (iii) Exclusion restriction – the instrument must only affect the outcome through the exposure

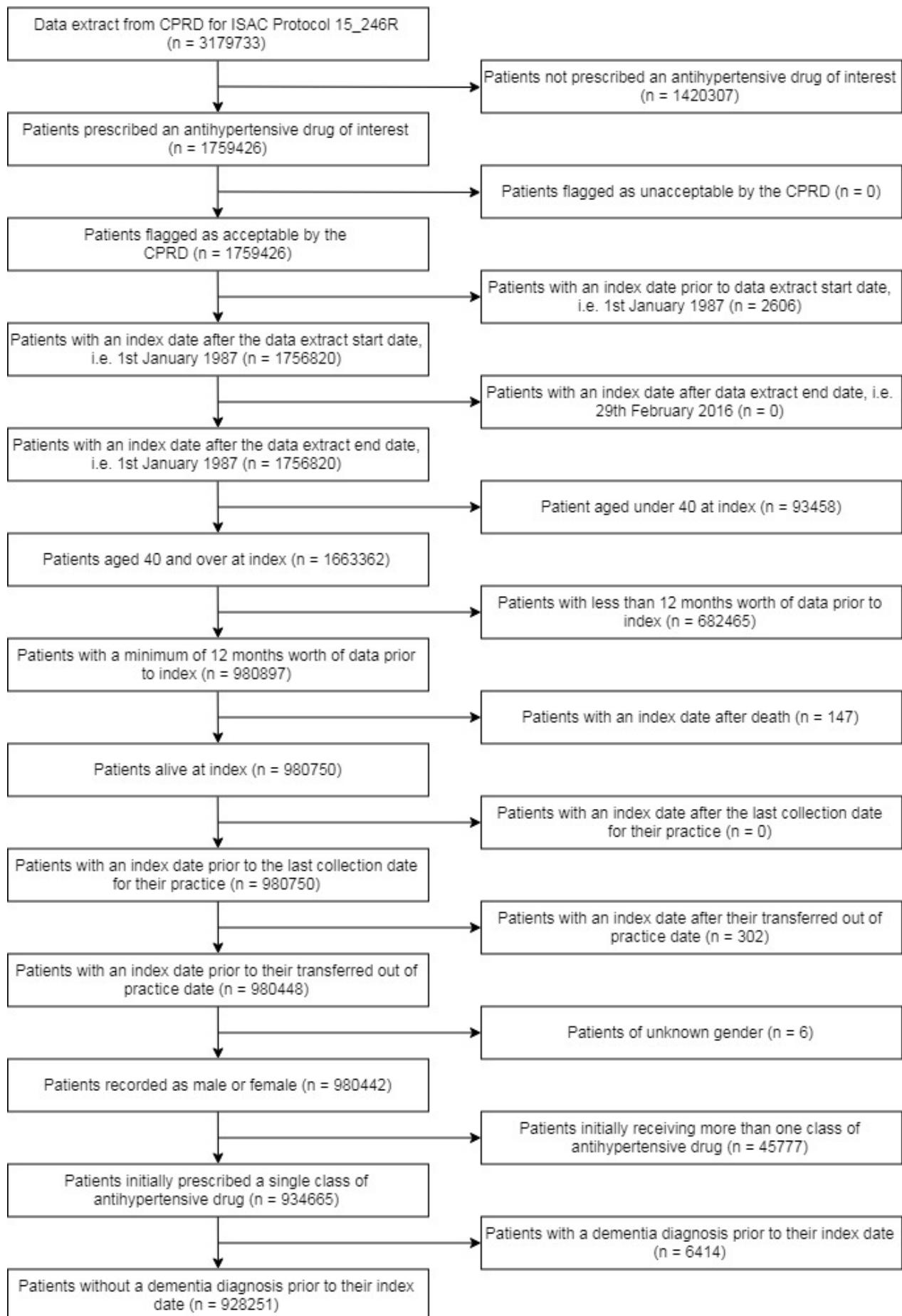
eFigure 2: Study design diagram.



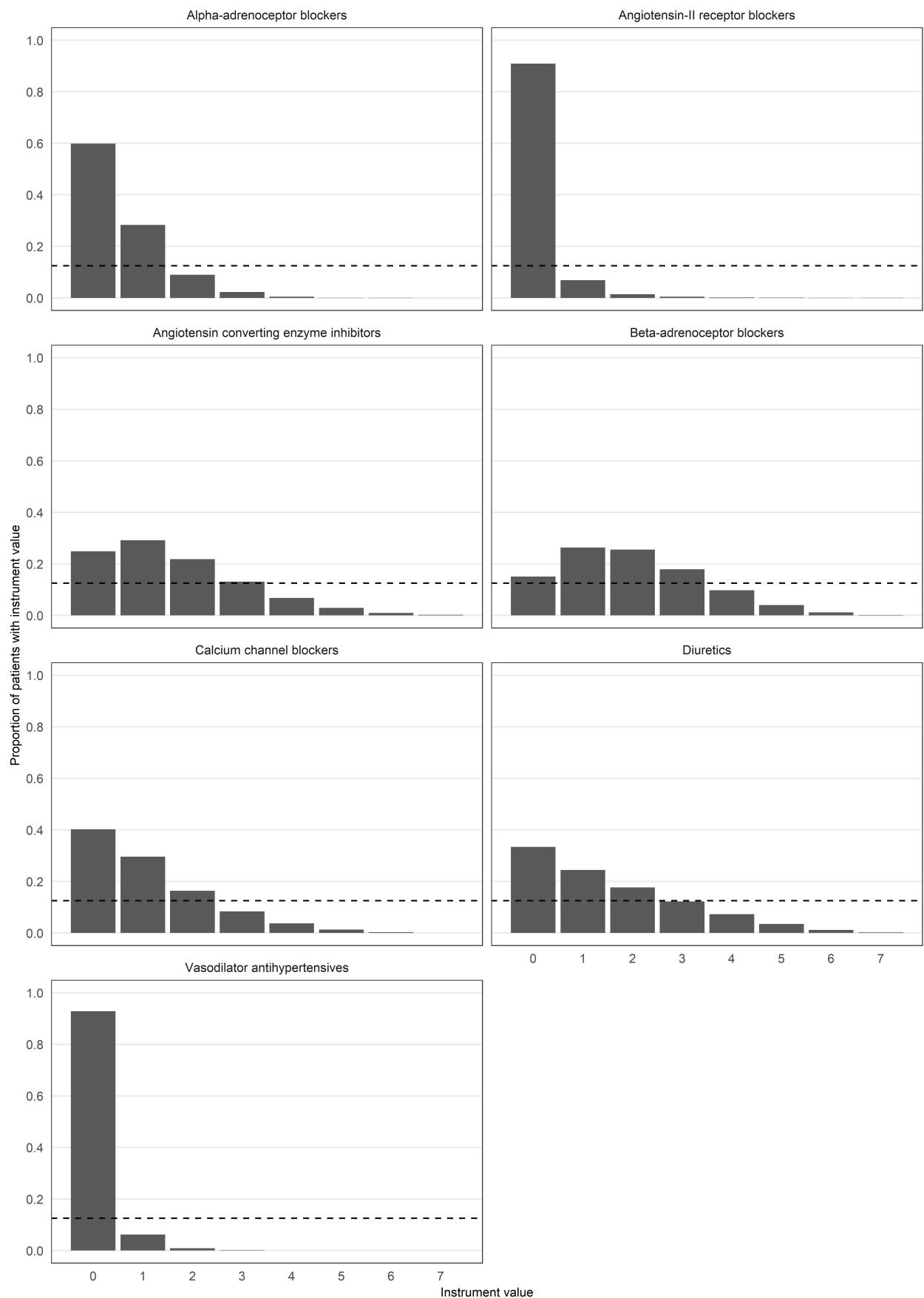
eFigure 3: Decision tree for outcome definitions.



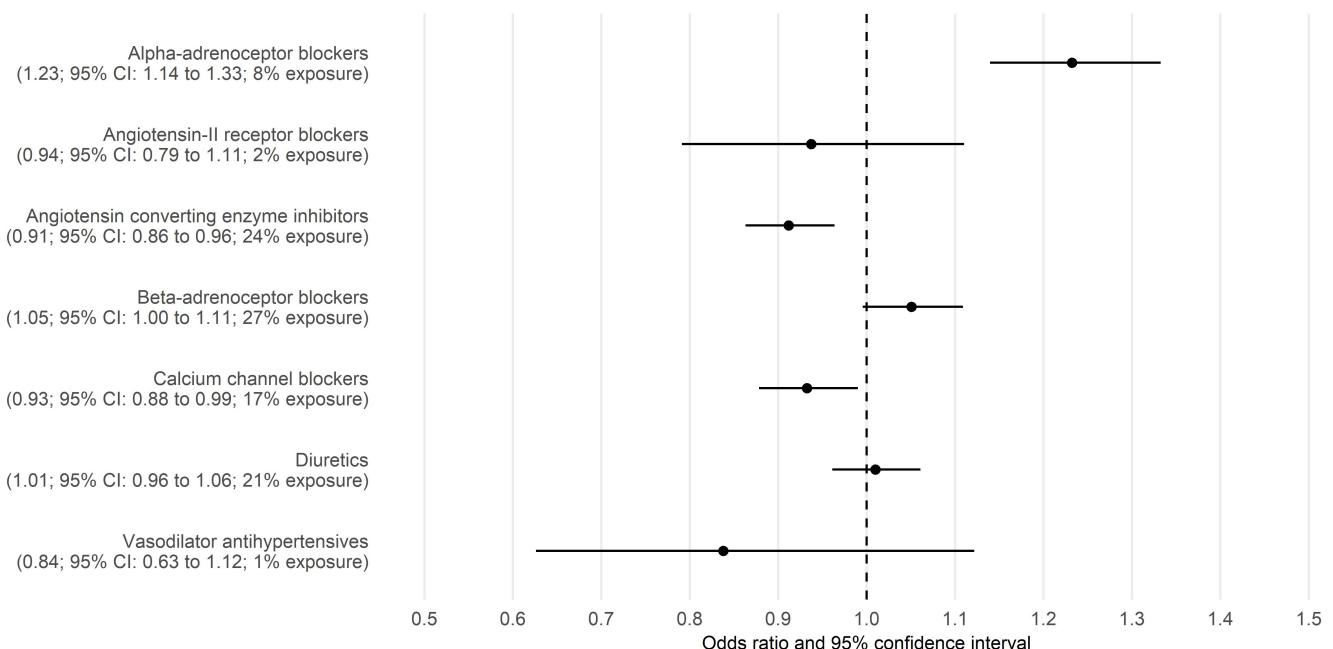
eFigure 4: Attrition of patients in the analysis cohort.



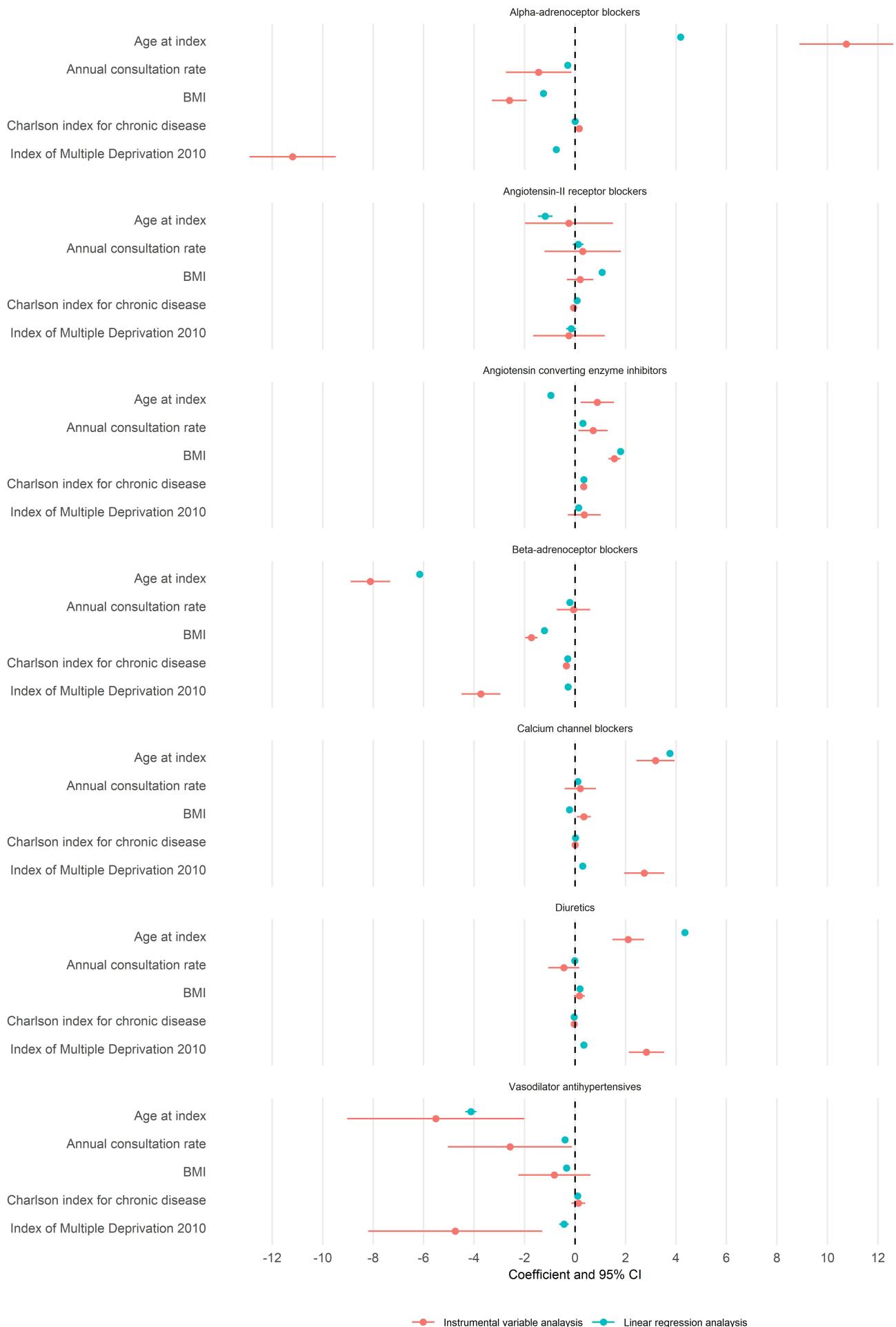
eFigure 5: Proportion of patients with each value of the instrument in the primary analysis.



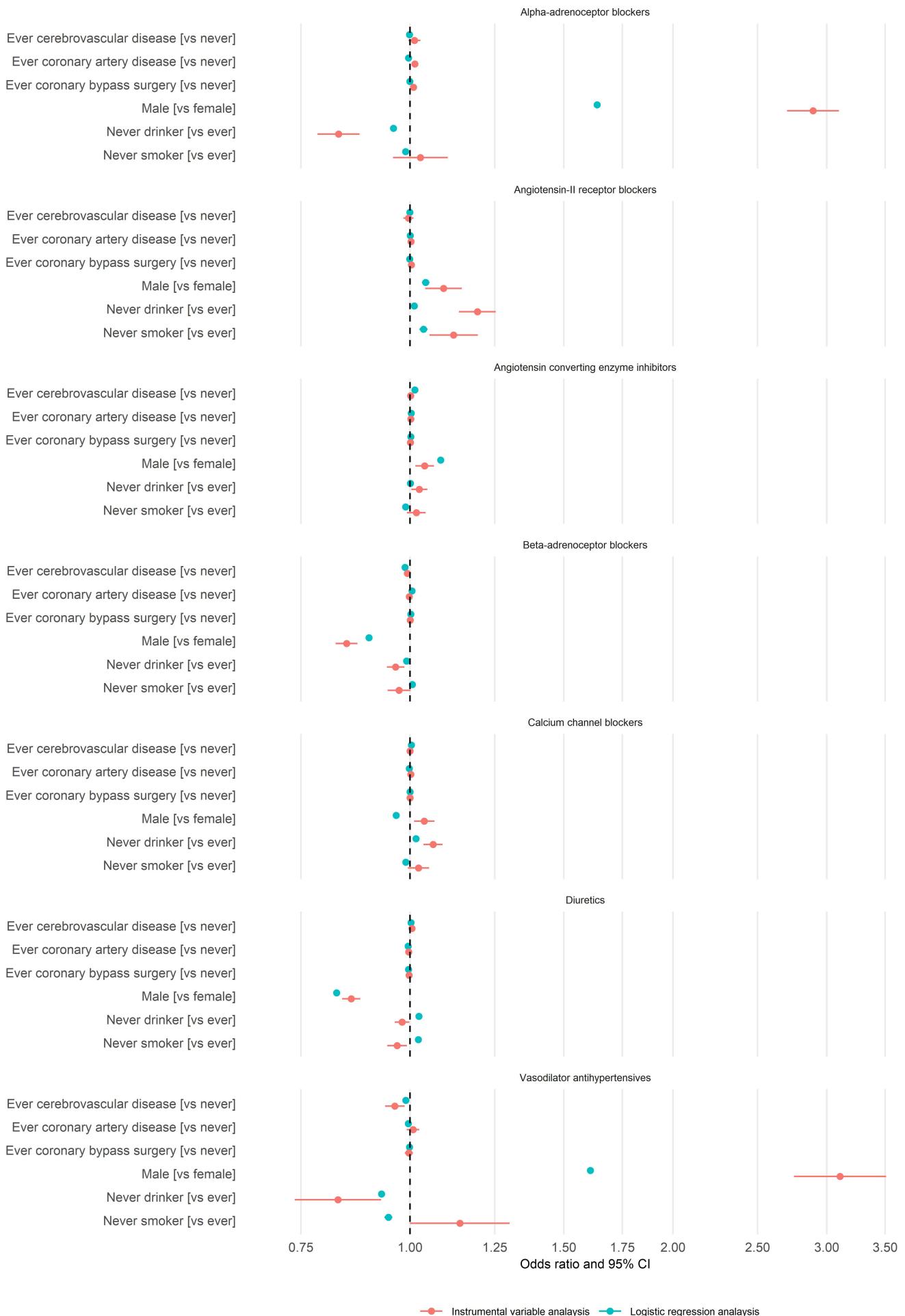
eFigure 6: Multivariable logistic regression results.



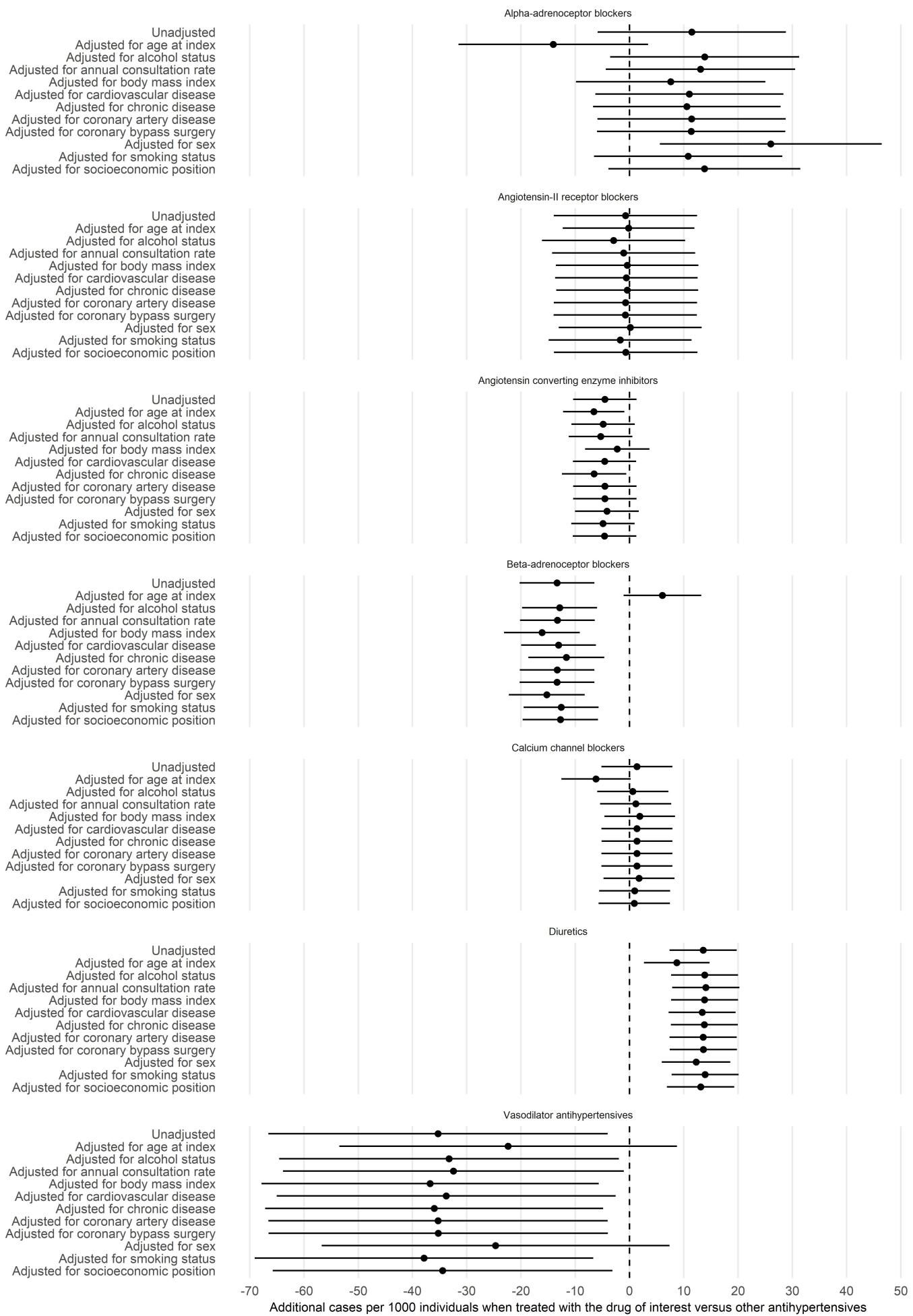
eFigure 7: Bias component plot for continuous covariates.



eFigure 8: Bias component plot for binary covariates.

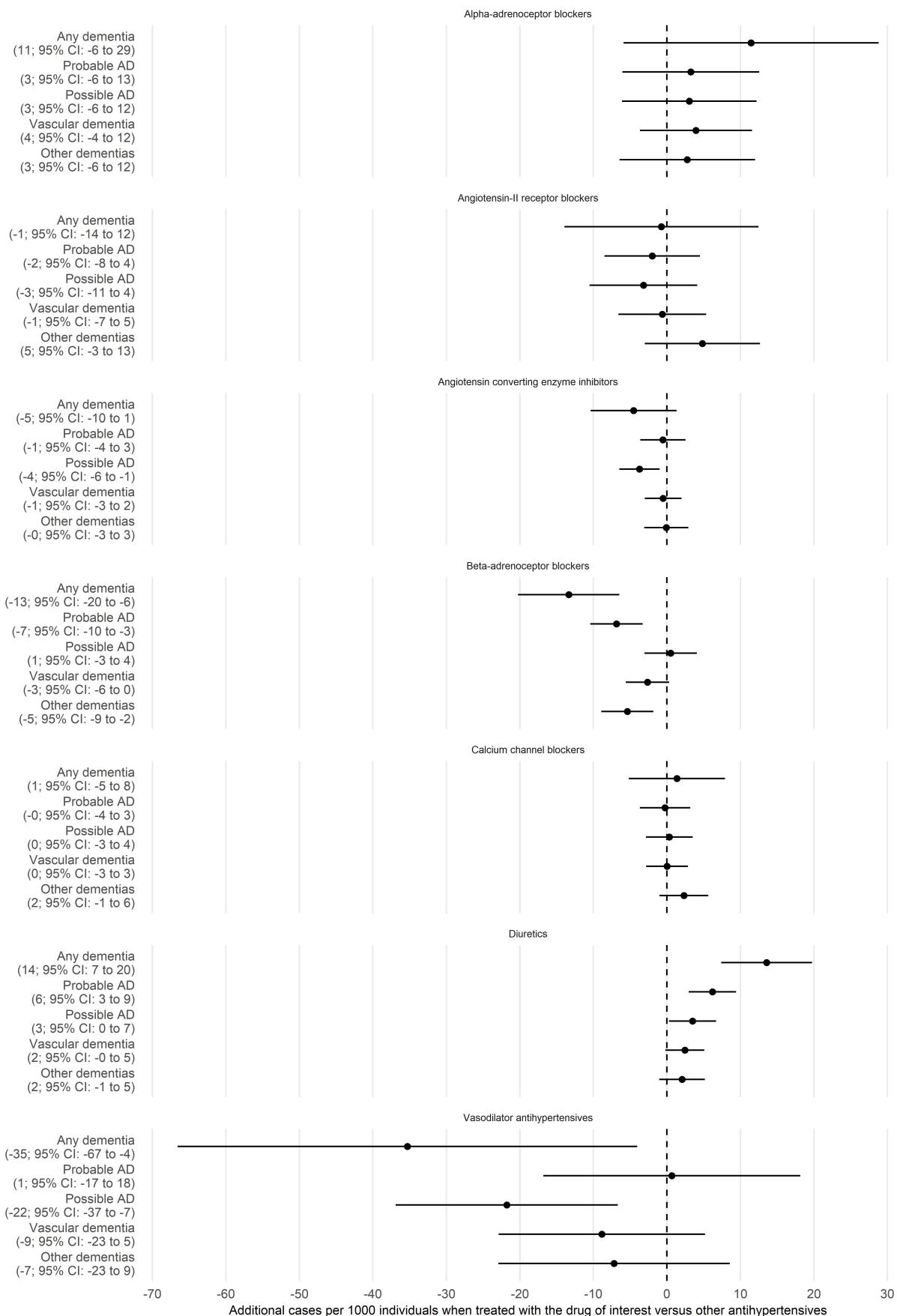


eFigure 9: Main analysis repeated with adjustment for each covariate in turn.



Note: IV regression was performed in each imputed dataset and estimates combined according to Rubin's rules to obtain the presented results.

eFigure 10: Main analysis repeated with dementia subtypes.



eFigure 11: Instrumental variable sensitivity analyses.

