

## **Benzodiazepine use and risk of cognitive decline and dementia - systematic review and meta-analysis**

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**Introduction** We aimed to synthesise published evidence on the association between long-term use of benzodiazepines and risk of cognitive decline and dementia.

**Methods** We searched MEDLINE and EMBASE (1996-2016) for observational studies of the association between benzodiazepine use and cognitive decline/dementia in participants aged >50 years. We used ROBINS-I to assess study validity, and we evaluated ascertainment of cognitive decline/dementia, nature of drug use and confounding. We conducted random effects inverse variance meta-analyses, and assessed heterogeneity using the  $I^2$  statistic. We screened 1667 titles and abstracts and included 16 studies in the systematic review. Most of the studies were considered to have serious risk of bias.

**Results** For dementia outcomes, meta-analysis of adjusted data from 8 studies demonstrated a pooled odds ratio (OR) of 1.45 (95% Confidence Interval [CI] 1.11, 1.90, substantial heterogeneity,  $I^2=98%$ ) associated with benzodiazepine use. For cognitive change, meta-analysis of 3 studies showed that benzodiazepines were associated with decline in cognitive scores, pooled OR of 1.43 (95% CI 1.02, 1.99 with  $I^2=0%$ ). Limitations are substantial heterogeneity in the meta-analysis, and considerable variation in methods in ascertaining dementia or change in cognitive function. We also identified evidence of publication bias where quantitative results were not fully reported for non-significant findings; the omission of these data means that the meta-analysis may have yielded inflated estimates of risk.

**Conclusions** We found substantial inconsistencies in the evidence of cognitive change and dementia associated with benzodiazepine use. Nevertheless, in practice, clinicians are conscious that benzodiazepines are linked to other serious adverse effects in older people (for example, falls) and it is important to follow guidelines on minimizing potentially inappropriate use of long-term benzodiazepines. Interestingly, the findings of this systematic review conflict with a recent nested case-control study. This research was supported by funding from Alzheimer's Society (AS-PG-2013-017).