Review Article

A systematic review of the statistical methods in prospective cohort studies investigating the effect of medications on cognition in older people

Kris M. Jamsen, Ph.D.[a,b,*], Jenni Ilomäki, Ph.D.[a],
Sarah N. Hilmer, Ph.D.[b,c], Natali Jokanovic, B.Pharm.(Hons.)[a],
Edwin C.K. Tan, Ph.D.[a], J. Simon Bell, Ph.D.[a,b]

[a]*Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Australia*
[b]*Cognitive Decline Partnership Centre, Hornsby Ku-ring-gai Hospital, Hornsby, New South Wales, Australia*
[c]*Kolling Institute of Medical Research, Northern Clinical School, Sydney Medical School, University of Sydney, New South Wales, Australia*

Abstract

Background: There is increasing awareness that medications can contribute to cognitive decline. Prospective cohort studies are rich sources of clinical data. However, investigating the contribution of medications to cognitive decline is challenging because both medication exposure and cognitive impairment can be associated with attrition of study participants, and medication exposure status may change over time. The objective of this review was to investigate the statistical methods in prospective cohort studies assessing the effect of medications on cognition in older people.
Methods: A systematic literature search was conducted to identify prospective cohort studies of at least 12 months duration that investigated the effect of common medications or medication classes (anticholinergics, antihistamines, hypnotics, sedatives, opioids, statins, estrogens, testosterone, antipsychotics, anticonvulsants, antidepressants, anxiolytics, antiparkinson agents and bronchodilators) on cognition in people aged 65 years and older. Data extraction was performed independently by two investigators. A descriptive analysis of the statistical methods was performed.
Results: A total of 44 articles were included in the review. The most common statistical methods were logistic regression (24.6% of all reported methods), Cox proportional hazards regression (22.8%), linear mixed-effects models (21.1%) and multiple linear regression (14.0%). The use of advanced techniques, most notably linear mixed-effects models, increased over time. Only 6 articles (13.6%) reported methods for addressing missing data.
Conclusions: A variety of statistical methods have been used for investigating the effect of medications on cognition in older people. While advanced techniques that are appropriate for the analysis of longitudinal data, most notably linear mixed-effects models, have increasingly been employed in recent years, there is an opportunity to implement alternative techniques in future studies that could address key research questions.
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* Corresponding author. Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Australia.

E-mail address: kris.jamsen@monash.edu (K.M. Jamsen).

Introduction

Older people use a disproportionately large number of medications. It has been reported that ninety percent of people aged 65 years and older use one or more medications, of which nearly half use five or more medications.[1–4] There is increasing awareness that a range of commonly prescribed medications can contribute to cognitive impairment.[5] These mediations include anticholinergics, benzodiazepines, antihistamines, hypnotics and sedatives. Impaired cognition may arise due to the cumulative effect of taking multiple medications.[6] Older people may be particularly susceptible to medication-induced cognitive impairment due to accumulation resulting from renal impairment and increased permeability of the blood brain barrier.[7] Clinicians may mistakenly attribute impaired cognition to older age or underlying dementia.[5]

Prospective cohort studies provide a rich source of clinical data for investigating factors associated with cognitive decline. Examples of ongoing and completed prospective cohort studies which assess cognition include the ASPirin in Reducing Events in the Elderly (ASPREE) study[8] and the Cardiovascular Health Study.[9] Investigating the contribution of medications to cognitive decline in prospective cohort studies is challenging. For instance, both medication exposure and cognitive impairment can be associated with attrition of study participants. Also, medication exposure status may change over the duration of the follow-up, which can be due to either intentional or unintentional non-adherence, medication discontinuation, changes in dose or the prescribing of new medications that impair or enhance cognition. Fortunately, there are a range of statistical methods that can accommodate these (and other) challenges, such as multiple imputation, mixed-effects models and Generalized Estimating Equations (GEEs). However, this class of methods is generally more advanced than standard approaches used commonly in pharmacoepidemiology, such as linear and logistic regression. The complexity of these more advanced methods may tempt investigators to revert to standard approaches, which may not accommodate adequately the longitudinal nature of the data and/or limit the ability to address the research question of interest. Therefore, the choice of statistical methods used in these studies can greatly influence conclusions, and potentially, medication policies in older people. As such, it is important to

examine how statistical methodology has been applied to these studies, as this can provide insight into possible knowledge gaps and guidance for future analyses.

To date there has been no published review of the statistical methods in prospective cohort studies investigating the contribution of medications to cognitive impairment. The objective of this review was to investigate the statistical methods employed in prospective cohort studies investigating the effect of medications on cognition in older people. The specific objectives were to describe and comment on the statistical methods that have been used, examine whether the methods have changed over time and identify and discuss possible alternative methods for future studies.

Methods

Literature search strategy

A systematic search of the published literature was performed in PubMed from inception to May 2014. The list of medications and medication classes that can impair cognition was based on previously published reviews.[4,5] These included anticholinergics, antihistamines, hypnotics, sedatives, opioids, statins, estrogens, testosterone, antipsychotics, anticonvulsants, antidepressants, anxiolytics, antiparkinson agents and bronchodilators. Medical Subject Heading (MeSH) terms for these medications and medication classes included "cholinergic antagonists," "benzodiazepines," "histamine H1 antagonists," "hypnotics and sedatives," "psychotropic drugs," "analgesics, opioid," "opiate alkaloids," "hydroxymethylglutaryl-CoA reductase inhibitors," "estrogens," "testosterone," "GABA agonists," "antipsychotic agents," "anticonvulsants," "antidepressive agents," "anti-anxiety agents," "antiparkinson agents" and "bronchodilator agents". All of these MeSH terms were used with the "adverse effects," "pharmacology" and "therapeutic use" subheadings.

The MeSH terms for cognitive impairment included "amnesia," "cognition disorders," "dementia," "memory disorders," "cognition" and "memory." When possible, these MeSH terms were used with the following subheadings: "chemically induced," "drug effect," "etiology" and "epidemiology." The following plain text search terms for cognitive impairment were also used: "cognitive impairment," "cognitive dysfunction," "memory loss," "cognitive decline," "memory