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Featured Article

Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses

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Abstract

Introduction: Dementia is a heterogeneous neurodegenerative disease, whose etiology results from a complex interplay between environmental and genetic factors.

Methods: We searched PubMed to identify meta-analyses of observational studies that examined associations between nongenetic factors and dementia. We estimated the summary effect size using random-effects and fixed-effects model, the 95% CI, and the 95% prediction interval. We assessed the between-study heterogeneity (I-square), evidence of small-study effects, and excess significance.

Results: A total of 76 unique associations were examined. By applying standardized criteria, seven associations presented convincing evidence. These associations pertained to benzodiazepines use, depression at any age, late-life depression, and frequency of social contacts for all types of dementia; late-life depression for Alzheimer's disease; and type 2 diabetes mellitus for vascular dementia and Alzheimer's disease.

Discussion: Several risk factors present substantial evidence for association with dementia and should be assessed as potential targets for interventions, but these associations may not necessarily be causal.

Keywords: Alzheimer's disease; Dementia; Epidemiology; Risk factors; Umbrella review

1. Introduction

Over 46 million people live with dementia in 2016 world wide, and the number is expected to exceed 130 million by 2050 [1]. This unprecedented increase of the number of patients is mainly due to the considerable rise in life expectancy and population aging world wide. The annual cost of dementia care was estimated at $818 billion, world wide, in 2014; and it is expected to exceed $1 trillion by 2018. No therapies are currently available to delay or arrest the disease onset and progression, and drug development has been problematic compared with other disease areas [2]. Moreover, there are considerable gaps in our understanding of the nosology and etiologic complexity of the disease.

Aimed at delaying disease onset by modulating modifiable risk factors, primary prevention has been proposed as a potentially effective and feasible tool to address the global challenge

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posed by dementia [3]. It has been suggested that a third of Alzheimer's disease (AD) cases might be attributable to modifiable factors such as diabetes mellitus, midlife hypertension and obesity, physical activity, depression, smoking, and low educational attainment [4,5]. An observed decline in the incidence and prevalence of AD in western European countries and United States has been ascribed to better management of cardiovascular and metabolic risk factors [4,6–9]. Unfortunately, it is difficult to validate these speculations in randomized trials because primary preventive trials with clinical dementia outcomes would require large sample sizes and prolonged follow-up. Owing to the chronic and slowly progressive nature of this disease, both pharmacologic and nonpharmacologic randomized clinical trials for dementia mostly evaluate surrogate cognitive decline outcomes rather than clinical disease outcomes.

We performed an umbrella review of the evidence across existing systematic reviews and meta-analyses of observational studies to systematically map the evidence on environmental risk factors for dementia. Our aim was to provide an overview of the range and validity of the reported associations of diverse, potentially modifiable (nongenetic) risk factors by evaluating whether there is evidence for biases in this literature, and finally, pinpoint the number of previously studied associations that have been synthesized with meta-analyses and have shown the strongest evidence for association.

2. Methods

2.1. Search strategy and eligibility criteria

We conducted an umbrella review, that is, a comprehensive and systematic collection and evaluation of systematic reviews and meta-analyses performed on a specific research topic [10]. The methods of the umbrella review are standardized and follow the same principles as previous umbrella reviews for other neurological disorders [11–13].

We systematically searched PubMed up to January 16, 2016, to identify systematic reviews and meta-analyses of observational studies examining associations of potentially modifiable (environmental and other nongenetic) factors with all types of dementia (Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia). Relevant keywords for the search strategy were (dementia OR Alzheimer*) AND ("systematic review" OR meta-analysis). Two independent investigators (V.B. and L.B.) retrieved and abstracted the full text of potentially eligible articles. We excluded meta-analyses that investigated the association between genetic markers and risk for dementia as these factors have been examined extensively elsewhere [14,15], and they are not modifiable. We also did not consider fluid biomarkers as they are not directly modifiable, and the literature on fluid biomarkers is being reviewed systematically elsewhere (http://www.alzforum.org/alzbiomarker). Meta-analyses with an outcome related to cognitive decline or impairment, progression of dementia, or severity of symptoms were excluded. We further excluded meta-analyses including less than three component studies. When an association was covered by more than one meta-analyses, we kept the meta-analysis with the largest number of component studies with available data on individual studies. We did not apply any language restrictions in our search strategy.

2.2. Data extraction

Two independent investigators (V.B. and L.B.) extracted the data, and in case of discrepancies, consensus was reached. From each eligible article, we abstracted information on the first author, journal and year of publication, the examined risk factors and the number of studies considered. We also extracted the study-specific risk estimates (i.e., risk ratio, odds ratio, hazard ratio) along with their corresponding confidence interval (CI) and the number of cases and controls in each study. If a risk factor was examined in more than one levels of comparison, we extracted the data for the comparison having the largest number of component studies. Also, when a meta-analysis combined effect estimates for incidence of dementia and score in a cognitive test, we considered the former. Furthermore, we recorded whether the eligible articles applied any criteria to assess the quality of component studies.

2.3. Statistical analysis

We applied standardized methods for the umbrella review and state-of-the-art approaches to evaluate findings on putative risk factors for dementia, that have been applied to assess the epidemiologic credibility for environmental risk factors of other neurodegenerative diseases [11–13], whereas similar assessments have been successfully applied in genetic studies [16,17]. Specifically, for each meta-analysis, we estimated the summary effect size and its 95% CI using both fixed-effects and random-effects models [18,19]. We also estimated the 95% prediction interval (PI), which accounts for the between-study heterogeneity and evaluates the uncertainty for the effect that would be expected in a new study addressing that same association [20,21]. For the largest study of each meta-analysis, we estimated the standard error (SE) of the effect size and we examined whether the SE was less than 0.10. In a study with SE <0.10, the difference between the effect estimate and the upper or lower 95% CI <0.20 (i.e. this uncertainty is less than what is considered a small effect size).

Between-study heterogeneity was quantified using the I^2 metric [22]. I^2 ranges between 0% and 100% and quantifies the variability in effect estimates that is due to heterogeneity rather than sampling error [23]. Values exceeding 50% or 75% are considered to represent large or very large heterogeneity, respectively.

We assessed small-study effects (i.e., whether smaller studies tend to give substantially larger estimates of effect