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# Risk factors associated with the onset and progression of Alzheimer's disease: A systematic review of the evidence

Mona Hersi[a,b,*], Brittany Irvine[a], Pallavi Gupta[a], James Gomes[a,c,d], Nicholas Birkett[a,b], Daniel Krewski[a,b,e]

[a] McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada
[b] School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[c] Environmental Health Research Unit, University of Ottawa, ON, Canada
[d] Interdisciplinary School of Health Sciences, Faculty of Health Sciences, University of Ottawa, ON, Canada
[e] Risk Sciences International, Ottawa, Ontario Canada

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ABSTRACT

A systematic review was conducted to identify risk factors associated with the onset and progression of Alzheimer's disease (AD). Moderate and high quality systematic reviews were eligible for inclusion. Primary studies reporting on non-genetic risk factors associated with neuropathologically or clinically confirmed AD were considered. Eighty one systematic reviews reporting on AD onset and 12 reporting on progression satisfied the eligibility criteria. Four hundred and thirty-two relevant primary studies reporting on onset were identified; however, only those published between 2010 and 2012 (n = 65) were included in the qualitative synthesis. Several factors including statins, light-to-moderate alcohol consumption, compliance with a Mediterranean diet, higher educational attainment, physically and cognitively stimulating activities, and APOE ε2 appeared to be associated with a decreased risk of AD onset. The evidence was suggestive of an increased risk of AD associated with head injury in males, age, diabetes mellitus, conjugated equine estrogen use with medroxyprogesterone acetate, current smoking, and lower social engagement. With respect to genetic factors, APOE ε4 remained the strongest predictor of AD. Physical and cognitive activities were associated with a beneficial effect on cognitive function and other indicators of dementia progression while higher educational attainment was associated with faster cognitive decline. Although suggestive of an association, the current evidence for a majority of the identified putative factors for AD onset and progression was weak, at best due to conflicting findings across studies or inadequate evidence. Further research is required to confirm the etiological or protective role of a number of risk factors.



## 1. Introduction

Alzheimer's disease (AD) is the most common form of dementia (Lindsay and Anderson, 2003). Dementia is characteristic of a number of conditions including, but not limited to, AD (Public Health Agency of Canada, 2010; National Advisory Council on Aging, 2004). AD involves irreparable neuronal degeneration which gives rise to a myriad of clinically detectable neurological impairments (Parihar and Hemnani, 2004; Gauthier et al., 2005). Short- and long-term memory loss represent the most pronounced cognitive marker of AD, with non-cognitive indicators encompassing declining physical capacity and alterations in behaviour (Gauthier et al., 2005; Aglukkaq, 2011). Characterized by debilitating symptoms which can dramatically impact quality of life, AD usually results in death within a decade post- diagnosis (Aglukkaq, 2011). Data suggests that one in ten elderly Canadians had dementia in 2011 with 60–70% of these cases attributed to AD (Aglukkaq, 2011). Compared to AD occurrence in 2008, a more than two-fold increase in AD incidence and prevalence is anticipated by 2038 (Alzheimer Society, 2010).

Despite the abundance of AD research, the etiology of this neurological disease is not yet understood (National Advisory Council on Aging, 2004). The objective of the study was to

* Corresponding author. Present address: Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, ON, Canada.
*E-mail address:* mhersi@ohri.ca (M. Hersi).

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systematically search the current scientific literature to identify risk factors associated with the onset and progression of AD.

## 2. Methods

This review was conducted in accordance to the methodological details outlined in the accompanying methods paper (Hersi et al., 2016). The systematic review of risk factors associated with disease onset involved two phases: (1) an umbrella review of systematic reviews (i.e., a systematic search of the literature to identify existing systematic reviews); (2) a systematic search of the literature to identify primary studies. For the systematic review of factors associated with disease progression, only an umbrella review of systematic reviews was conducted.

### 2.1. Search methods

Separate search strategies were designed to identify: (1) systematic reviews reporting on risk factors for disease onset; (2) systematic reviews reporting on risk factors for disease progression; and (3) primary studies reporting on risk factors for disease onset.

Systematic reviews reporting on onset-related factors were identified through a search of electronic databases and grey literature sources including MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations, PubMed, EMBASE, CINAHL, HuGE-NET, PsychINFO, TOXNET Toxicology Data Network, AARP Ageline, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), AlzGene, ProQuest Digital Dissertations and Theses database, Google and GoogleScholar. Disease-specific journals including the American Journal of Alzheimer's Disease and Other Dementias (1986-December 31, 2011) and the International Journal of Alzheimer's Disease (2009-December 31, 2011) were also searched. Where possible, database specific search filters, such as those developed by InterTASC Information Specialists' Sub-Group and McMaster University's Health Information Research Unit, were also applied to identify systematic reviews and citations reporting on risk factors associated with onset or progression. The reference lists of a sample of retrieved articles were reviewed for potentially missed studies. The initial search was conducted in September 2011. The OVID AutoAlerts feature was enabled to ensure that newly indexed relevant articles were identified. The AutoAlerts feature was disabled on December 31, 2011. Databases without an alerts feature were re-searched until the end of December 2011. The search for systematic reviews on AD progression was restricted to MEDLINE and EMBASE and was conducted in March 2013.

Primary studies reporting on risk factors associated with AD onset were identified through a search of electronic databases including MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, CINAHL and AgeLine. The search was conducted in July 2012. The search for risk factors for AD progression was limited to systematic reviews. All search strategies are provided in Supplementary material I.

### 2.2. Eligibility criteria

For the first phase of the review, systematic reviews reporting on risk factors associated with AD onset or progression were eligible for inclusion. French and English language reviews were eligible if a computerized database search was conducted and the eligibility criteria of the review were explicitly stated. Reviews which failed to distinguish AD from all-cause dementia or dementia subtypes were excluded for the systematic review of disease onset. An exception was made for reviews reporting on progression. Systematic reviews examining non-pharmacological factors impacting cognitive and non-cognitive (such as behaviour, physical function, quality of life, mortality) indicators of AD progression were considered.

Primary studies were eligible for inclusion if they reported on non-genetic risk factors associated with the development of AD. Only studies which diagnosed AD using neuropathologic examination or according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), the Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA), or the International Classification of Diseases (ICD) criteria were considered. Studies reporting solely on non-AD dementias as well as those failing to distinguish AD from all-cause dementia or dementia subtypes were excluded. Studies reporting on the effect of psychological stress were excluded from the present report and have been reviewed elsewhere (Hersi, 2015).

### 2.3. Study screening and data extraction

Studies were screened according to the process described by Hersi et al. (2016). For systematic reviews reporting on disease onset, data were extracted by one reviewer. A second reviewer independently extracted data from a randomly selected 10% sample of reviews. Disagreements were addressed through consensus. Due to limited resources, data from primary studies and systematic reviews reporting on AD progression was extracted by a single reviewer only.

### 2.4. Quality appraisal

The quality of systematic reviews was assessed according to the AMSTAR criteria (Shea et al., 2009). For systematic reviews reporting on AD onset, quality assessment was conducted by one reviewer. A second reviewer independently assessed the quality of a randomly selected 10% sample of reviews. Quality assessment of reviews reporting on AD progression was conducted entirely by a single reviewer. Low quality reviews with an AMSTAR score of 3 or less were excluded from the qualitative synthesis. The quality of primary studies was not evaluated.

### 2.5. Literature search results

The study selection process is outlined in Figs. 1–3 . A total of 136 systematic reviews reporting on risk factors associated with disease onset (n = 121) and progression (n = 15) were identified. Of these, 93 were deemed to be of high quality and were included in the qualitative syntheses for disease onset (n = 81) and progression (n = 12). A list of excluded systematic reviews on onset and progression, along with reasons for exclusion, can be found in Supplementary material I. One moderate quality review (Daviglus et al., 2011) was later excluded from the overview of AD onset as it was a manuscript version of an identified Health Technology Assessment (HTA) (Williams et al., 2010). Two reviews were also later excluded from the overview of AD progression (Isaac et al., 2008; Aguirre et al., 2013). The review by Isaac et al. (2008) was excluded because an updated version (Farina et al., 2012) of the review was identified. The review by Aguirre et al. (2013) was excluded as it was a duplicate of a Cochrane review (Woods et al., 2012). Details regarding the quality appraisal of each systematic review on onset and progression are also provided in Supplementary material I.

A total of 432 relevant primary studies reporting on disease onset were identified. The breadth of the primary study literature precluded inclusion of all 432 studies. As such, only the most recent studies (those published from 2010 to 2012) were selected for inclusion in the qualitative synthesis (n = 65). A list of included primary studies is provided in Supplementary material I. Five