Appendix 1: Search strategies of background papers for review article on risk factors and primary prevention of Alzheimer disease (part 1 of the series based on recommendations from the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia)

Articles on general risk factors

The identification and relative importance of risk factors is best addressed through longitudinal cohort studies. Although case–control studies can be used to explore risk factors for disease, significant differences have been observed when the results of case–control studies were compared with those of longitudinal studies. We asked "What modifiable risk factors are associated with all-cause dementia, Alzheimer disease or vascular dementia?"

We performed a comprehensive electronic search of the MEDLINE and EMBASE databases for articles published from 1966 to December 2005.* We identified 3424 articles. Of these, we excluded 1705 that were obviously irrelevant. One author reviewed the abstracts and references of the remaining 1719 articles to identify possibly relevant articles. We also included additional articles from personal files and those identified from the references of included and excluded articles. We used the following criteria to establish relevance: longitudinal cohort study; population broadly representative of Canadian demographics; dementia, Alzheimer disease or vascular dementia included as outcome; identification of "general" risk factors (e.g., hypertension, educational status, occupation, chemical exposure) included. Articles that addressed genetic risk factors were excluded (see section below on genetic risk factors).

Two of us independently assessed each full-length article for quality using the criteria of the Canadian Task Force on Preventive Health Care. Articles were classified as good (all criteria fulfilled), fair (minor flaws only, no fatal flaw) or poor (fatal flaw or multiple minor flaws).[1] After consulting several key references on appraisal of risk-factor literature, we chose the following criteria to determine whether an article was of good, fair or poor quality, or whether it should be excluded: population characteristics (inclusion criteria defined, including ages, locations, dates; exclusion of dementia at inception; population broadly representative of Canadian demographics); follow-up (all participants accounted for at end of follow-up, without excessive "preventable" losses; no differences in follow-up between those in whom dementia developed and those with no dementia); exposures or risk factors (list of risk factors considered; exposures measured in the same way for those with and without dementia); outcomes (dementia and subtypes defined by standardized criteria; ascertainment of outcome was independent of exposure status); and analysis (important confounders [age, sex, education at minimum] were included in analysis; statistical analysis was appropriate [e.g., multiple logistic regression]; specific measures of risk stated [e.g., relative risk]). A consensus was reached if disagreement occurred. Articles graded as good or fair were then submitted for data abstraction by 2 independent reviewers.

Articles on genetic risk factors

We performed a comprehensive electronic search of MEDLINE for articles published from 1966 to December 2005. We identified 1721 articles on genetic risk factors for Alzheimer disease and other dementias. After screening the abstracts, we retrieved 372 relevant articles for review. We also conducted a review of all the genes listed in the ALZGENE website

(accessed 2006 Feb 14), as well as articles from bibliographies of selected studies and from authors' personal files; this search yielded an additional 46 articles. We used the following criteria to establish relevance: large sample (> 300 each of cases and controls), well-defined clinical diagnostic criteria and findings consistently replicated in 4 or more independent samples. Because the apolipoprotein E genotype (*APOE*) is the only genetic risk factor that has been consistently replicated to date, we further examined studies on *APOE* and its interaction with other risk factors in relation to Alzheimer disease. We also looked at studies of single-gene mutations, because within specific families they are known to be causal and thus represent risk factors for unaffected biologic relatives of individuals with dementia carrying the specific mutation.

We independently assessed the full-length articles for quality using previously published recommendations.[2] We considered a genetic association study to be acceptable if (a) it had well-defined diagnostic criteria of the disease (for Alzheimer disease, it is diagnosed either clinically, by NINCDS-ADRDA criteria, or pathologically, by CERAD or Braak criteria); (b) the control subjects were well matched to cases with respect to age, sex and ethnicity; (c) the authors minimized potential population stratification by choosing a distinct population or ruling it out with proper analyses; (d) proper statistical methods were used, taking into account multiple comparisons; and (e) the sample size was adequate (> 300 each of cases and controls). A total of 62 articles on *APOE* that met our inclusion criteria were deemed to be of good or fair quality.

Articles on the primary prevention

We identified studies that addressed the prevention of dementia from 3 sources.* We idenitified articles from the original search for risk factors performed in December 2005 (total of 3424 articles with abstracts identified); from a targeted search for randomized controlled trials and systematic reviews performed in February 2006; and from bibliographies of retrieved articles and authors' personal files.

We assessed the quality of randomized controlled trials using the criteria of the Canadian Task Force on Preventive Health Care (see above).[1] We used the criteria described by Hunt and McKibbon[3] to assess the quality of the systematic reviews.

If there was conflicting evidence, we gave priority to studies that had higher levels of evidence and better quality ratings and that were the most recent. For example, several systematic reviews of epidemiologic and case–control trials suggested that the use of estrogens was protective against dementia (level 2 evidence); however, a large randomized trial showed an increased risk of dementia with the use of estrogen (level 1 evidence).[4] We found very few randomized controlled trials of interventions to prevent dementia on which to base firm conclusions. Maintaining our rigorous standard of evidence led to a large number of grade C recommendations (insufficient or contradictory evidence of efficacy).

*Details about the search strategies and keywords used are available in the original background papers, published in the October 2007 issue of *Alzheimer's and Dementia* (www.alzheimersanddementia.org). These articles are also freely available at www.cccdtd.ca (through agreement with Elsevier).

References

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