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Review

Diabetes and other vascular risk factors for dementia: Which factor matters most? A systematic review

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Abstract

Vascular risk factors, such as type 2 diabetes, hypertension, obesity and dyslipidaemia often co-occur. Each of these factors has been associated with an increased risk of dementia, but it is uncertain which factor imposes the greatest risk. Moreover, the effect of age at time of exposure may differ across factors. This paper systematically reviews the evidence for the association of each of these risk factors with dementia. Longitudinal population-based studies that assessed the incidence of dementia in relation to diabetes ($n=14$), hypertension ($n=13$), dyslipidaemia ($n=8$) or obesity ($n=9$) were included. All four risk factors were indeed associated with an increased risk of dementia, but the results of studies on diabetes and obesity were most consistent. The magnitude of the effects was comparable across the risk factors, with odds ratios for 'any dementia' around 1.5. For hypertension, obesity and dyslipidaemia age appeared to modulate the association: the risk of dementia was generally largest in studies that measured the risk factor in midlife (compared to late life) and had a long follow-up time. At midlife, the population attributable risk of dementia was highest for hypertension, up to 30% of cases of late life dementia. Later in life diabetes appears to convey the highest risk of dementia. This review shows that vascular risk factors should be regarded as a major target for preventive measures, but that timing of such measures appears to be critical.

Keywords: Dementia; Vascular risk factor; Diabetes; Hypertension; Dyslipidaemia; Obesity

Contents

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1. Introduction

Type 2 diabetes mellitus is a well-known risk factor for cardiovascular disease. Diabetes is also associated with cognitive decline and an increased risk of dementia in the elderly (Awad et al., 2004; Biessels et al., 2006). Type 2 diabetes develops in the context of insulin resistance and is often accompanied by other vascular risk factors such as hypertension, dyslipidaemia and obesity. The co-occurrence of these risk factors is generally referred to as 'the metabolic syndrome' (Reaven, 1988). There is evidence that each of the individual risk factors of the metabolic syndrome is associated with cognitive decline and dementia. As these risk factors are potential targets for therapeutic intervention it is important to examine the contribution of each of these risk factors to the risk of dementia. In this context it is also important to assess whether the effects of the individual risk factors are independent from each other.

Several studies suggest that the association between dementia and vascular risk factors varies with age. High blood pressure in middle-age, for example, is a clear risk factor for dementia in old age (Whitmer et al., 2005b). In old age, however, *low* blood pressure may be associated with an increased risk of dementia (Verghese et al., 2003).

In this paper we systematically reviewed studies on the risk of dementia associated with type 2 diabetes mellitus, hypertension, obesity and dyslipidaemia. We aimed to quantify and compare the association with dementia for these four risk factors, and to address the potential modifying role of age at the time of exposure.

2. Materials and methods

2.1. Identification of studies

This systematic review aimed to include all published studies that provide an estimate of the incidence of dementia associated with type 2 diabetes mellitus or impaired glucose metabolism, hypertension, dyslipidaemia or obesity and that met the following inclusion criteria: (1) the study population was recruited at the population level; (2) the study had a longitudinal design; (3) the results were adjusted for the basic confounders age, sex as well as educational level; and (4) adjusted odds ratios, relative risks or hazard ratios could be calculated or extracted from the paper. Studies on the prevalence of vascular risk factors in patients with established dementia were excluded.

Medline 1966 to June 2007 and bibliographies from included papers were used to identify relevant papers. The search was limited to papers that were written in English and concerned humans. We used the search terms ("diabetes", "hyperglycaemia" or "glucose tolerance"), ("hypertension" or "blood pressure"), ("dyslipidaemia", "hypercholesterolaemia", "cholesterol", "high-density lipoprotein", "low-density lipoprotein" or "triglycerides"), ("waist circumference", "obesity", "overweight", "abdominal fat" or "body-mass index") in combination with ("dementia" or "Alzheimer's disease") in full or truncated versions. Titles and abstracts were scanned and potentially eligible papers were collected in full-text versions. RPK and EvdB independently judged eligible papers according to the inclusion criteria. In case of disagreement a consensus judgment was made, together with GJB.

2.2. Included papers

For diabetes/impaired glucose metabolism the search yielded 1423 papers, 14 of which met our inclusion criteria for diabetes and two for impaired glucose metabolism. The search yielded 1597 hits for hypertension (13 studies were included), 1291 hits for dyslipidaemia (eight studies were included) and 274 hits for obesity (nine studies were included). Papers that addressed more than one vascular risk factor were included in multiple risk factor sections in this review (Whitmer et al., 2005b; Yamada et al., 2003; Yoshitake et al., 1995; Kalmijn et al., 2000). When more than one paper reported on the same population (e.g. Honolulu-Asia Aging Study, Kungsholmen project), the paper with the largest sample size and/or the most detailed information on that risk factor and/or dementia was included.

2.3. Data extraction and analysis

Odds ratios, relative risks and hazard ratios were extracted from the included studies and are presented in Table 1a–d. Age, sex and education-adjusted analyses are presented. When available, analyses that additionally adjusted for other factors are also presented. Information on baseline and follow-up sample size, follow-up time and age at baseline was recorded. To obtain insight in the potential modifying role of age at the time of exposure the studies are listed according to age at baseline. Risk factors in the included studies were either dichotomized (e.g. diabetes yes/no) or analysed as continuous variables in statistical analyses. To increase the clarity of this review, these different ways of expressing the risk of dementia are presented separately in Table 1a–d. Since only population-based studies were included in this review the majority of the study populations included both participants who were and were not treated for a particular risk factor. When data on untreated participants were available (i.e. Qiu et al., 2003; Launer et al., 2000) these were included in the tables. We did not perform a formal meta-analysis because of the heterogeneity of risk factor and dementia assessment, study design (e.g. age at