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Review

# The influence of vascular risk factors on cognitive decline in patients with dementia: A systematic review

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ABSTRACT

*Background and objective:* Vascular risk factors (VRF) are associated with a higher incidence of dementia. However, the relationship with disease progression is unclear. This review examined the association of VRF (hypertension, hypercholesterolemia, diabetes mellitus, overweight, smoking or multiple VRF) and cognitive decline in patients suffering from dementia.
*Methods:* Literature was searched in four databases (Pubmed, Embase, Cochrane, PsychInfo) and 1779 articles were identified. This resulted in a total of 20 articles which were included.
*Results:* Twelve studies on hypertension (HT) were inconsistent about the association with cognitive decline. For hypercholesterolemia (HC) 2 (out of 7) studies were associated with increased cognitive decline, as were both (2/2) studies which researched LDL-cholesterol. Articles were inconclusive about the effect of diabetes mellitus (DM): five (out of 13) found less cognitive decline, 2 found more cognitive decline, and 6 found no significant effect of DM. Overweight (BMI > 25 kg/m$^2$) was associated in 2/4 studies with a slower rate of cognitive decline, while the other 2 studies found no effect. All studies (5/5) that researched smoking did not find a significant effect. Four studies (out of 7) that looked at multiple VRF found faster cognitive decline, and 3/7 found no effect.
*Discussion:* The results of this review suggest an association between LDL-cholesterol and the progression of dementia, while inconsistent results were found for other VRF. Additional prospective cohort studies and experimental studies should be performed to better understand the causal contribution of VRF on cognitive decline in dementia.



**Contents**



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## 1. Introduction

Dementia is a growing problem. Every four seconds there is a new case of dementia and in 2040, there are expected to be over 90 million patients worldwide [1]. As more people suffer from this disease it will also create a growing burden for caregivers and for health care costs [2,3]. More people will be affected by dementia due to aging of the population [1]. Next to aging, vascular risk factors (VRF) are known to enhance the risk of dementia.

Hypertension (HT) earlier in life raises the risk of Alzheimer's Disease (AD). Hypothesized underlying pathology is that hypertension leads to hyalinization of vessel walls, thereby causing hypoperfusion and ischemia of white matter in the brain [4]. In addition, hypercholesterolemia has been linked to cognitive decline due to its not yet completely unraffeled interaction with the amyloid-β protein [5]. The use of statins seems to substantially lower the prospect of developing dementia, although this effect has not been seen with other drugs for the treatment of high levels of cholesterol [6]. Furthermore, alterated levels of glucose, insuline or amyloid in patients with diabetes mellitus (DM) are also associated with an increased risk of dementia [7]. Next to these risk factors, cigarette smoking and its effects on inflammation, cholesterol and thrombosis can also boost the incidence of dementia [8,9]. In contradiction to the risk factors mentioned above, being overweight, defined as a body mass index (BMI) greater than 25 kg/m$^2$, is stated to have a protective effect, while loss of BMI might be a marker of beginning dementia [10].

The effects of VRF on the incidence of dementia have been well researched. However, the influence of these risk factors on the progression of dementia is not so clear. As different individual studies showed inconsistent results and as studies which systematically reviewed the aforementioned VRF are lacking, this systematic review might be able to give an overview. This is of great clinical importance as most VRF are preventable or can be well treated, which would possibly slow down cognitive decline in patients with dementia. If so, it might help control health care costs and prevent the burden for caregivers to grow even more.

The aim of this study was to evaluate whether VRF (HT, hypercholesterolemia, DM, overweight, smoking, multiple VRF) are associated with the progression of dementia.

## 2. Methods

On June 25, 2012, a search without time span limitation was performed in four databases: Pubmed, Embase, Psychinfo and Cochrane database. The search strategy was based on a PICO (Patient, Intervention/Control, Outcome) with the key words: 'dementia', 'vascular risk factors' (e.g. 'hypertension', 'diabetes', 'hypercholesterolemia', 'overweight', 'smoking') and different cognitive tests as 'Mini mental state exam' and 'ADAS Cog'. The complete search syntax for Pubmed can be found in supplement 1 (S1).

Search results were imported to Refworks and duplicates were deleted. Both exact and close duplicates were first screened on being correctly selected as duplication.

Titles left were subjected to screening on relevance, followed by the potentially relevant abstract. Articles had to meet the following six inclusion criteria: (a) original study; (b) study population included patients diagnosed with dementia; (c) addressed cognition, cognitive decline, course or progression of dementia; (d) evaluates any number of vascular risk factors: either hypertension, hypercholesterolemia, diabetes mellitus, weight/body mass index and/or smoking; (e) used one or more cognitive tests as outcome measurements; and (f) were published in either English or Dutch. If the abstract was unavailable or no certain decision on inclusion could be made based on its abstract, the original paper was retrieved unless it was stated as being a dissertation, comment or review. Articles excluded did not meet the inclusion criteria, researched primarily the effect of medication or were unavailable in full-text. Of the online unavailable articles, two were retrieved on paper and for three others, the authors were contacted by email and requested to email their article. If they did not provide their article, it was excluded from this review.

After inclusion was completed, data were obtained from the articles that were relevant. Data extracted included study design, type of dementia, number of patients in the study, mean age of the patients, the researched vascular risk factors, the outcome measurement and the statistic test used. We also documented information about study selection and validation. In the few cases that a study provided both univariate and multivariate analysis, only the latter was included as that is the model which corrects for possible confounders. Also, if tests were available with and without considering the effect of time, the result with time was acquired. Furthermore, the effect or use of medication was not taken into account.

## 3. Results

A total of 3392 potentially relevant articles were retrieved with the search strategy aforementioned. Duplicate studies ($n = 1613$) were deleted, and based on title and abstract screening 41 articles were selected for full text evaluation. Of these, another 24 were excluded due to the following reasons: no full text available ($n = 8$), not an original study ($n = 3$), or not addressing the PICO ($n = 13$). A flowchart of the search is shown in Fig. 1.

Twenty articles were retrieved for this review. Of these, sixteen (84%) had a longitudinal design and four (16%) had a cross-sectional design. All papers were published between 2004 and 2012. Most studies used the diagnostic NINCDS-ADRA criteria for the diagnosis of AD, some used the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The 2 studies which also looked at vascular dementia (VaD) used the NINDS-AIREN criteria.

The study populations can be summarized as follows: mean age at entry was >60 years, and mostly >70 years; many of the studies had >50% women; number of participants ranged from 20 to 719 subjects.

All included longitudinal studies are shown in Table 1 (supplementary data; S2) with their characteristics and outcomes of interest to this review. The cross-sectional studies can be found in Table 2 (S3).

### 3.1. Hypertension

Ten studies researched hypertension as a categorical variable [11–20]. The definition of HT varied across studies, using (combinations of) systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, HT reported in medical history, use of relevant medication and/or self-reported HT.

Of these studies, eight solely looked at HT as a categorical variable. Four of these studies found more cognitive decline [11,12,14,17] and four did not find an association between HT and cognitive decline [13,15,16,18]. Mielke et al. [19] and Van Bruchem-Visser et al. [20] researched HT both categorical and as a continuous variable. They found inconsistent results. Two studies researched DBP as a continuous variable. Razay et al. [21] and Van Bruchem-Visser et al. [20] found more cognitive decline and no significant effect, respectively. Three studies investigated SBP as a continous variable, which were inconsistent [19,20,22].

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