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Cardiovascular risk factors and incident Alzheimer disease: A systematic review of the literature

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Abstract

Objective—The purpose of this study was to conduct a systematic review of the literature of cardiovascular factors pertaining to incident Alzheimer disease (AD).

Methods—A systematic literature review was conducted of all studies of cardiovascular risk factors for incident AD listed in PUBMED in English from 2000–2007. Risk factors included hypertension, diabetes, exercise, alcohol intake, smoking, B complex vitamins, homocysteine, stroke, atrial fibrillation, APOE, lipids, and diet. Inclusion criteria consisted of diagnoses of incident AD and longitudinal studies with cohorts of 500 or more.

Results—Individual clinically defined risk factors such as hypertension and diabetes were not significantly associated with increased risk for AD. The strength of the association for hypertension could be considerably strengthened by changing criteria such as midlife measurements or using higher cutoffs for systolic blood pressure. APOE ε4 was the most consistent risk factor. Interactions between risk factors modify risk particularly for hypertension and diabetes. Interactions modifying risk were also found for exercise and physical function, APOE ε4, diabetes and cholesterol.

Conclusions—In this review the evidence that single clinically defined cardiovascular risk factors are significantly associated with incident Alzheimer disease is inconsistent at best. The strength of the association of cardiovascular risk factors and AD can be influenced greatly by changing the parameters of measurement of risk factors and by identifying interactions between the factors.

Keywords

incident Alzheimer disease; cardiovascular risk factors; interactions

Introduction

There is now a great deal of interest in the prevention of Alzheimer Disease. Ideally prevention strategies should be driven by the results of large scale primary prevention trials. However, few if any of these trials are being conducted at present. Designing such a trial is not a simple issue and, even if initiated today, results might not be available for decades.

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Prevention strategies require the identification of a suitable intervention approach derived from systematic reviews of observational studies. The intervention must be considered together with potential modifiers such as subject characteristics. It also requires the identification of a target population based on risk factor characteristics and the risks and benefits of the prevention strategy.

Recent reviews of observational studies do not consistently focus on AD as the outcome of interest. Rather, investigators have reported on risk factors for multiple different cognitive outcomes including cognitive impairment, cognitive decline, and dementia as well as AD[1–3]. These studies have identified multiple potentially preventable risk factors. The most consistent finding in these prior reviews is the association of cognitive impairment with cardiovascular disease[4].

It has been suggested that researchers focusing on different cognitive outcomes may identify a different set of risk factors (or place different weights on known risk factors). Risk factors might logically differ across different cognitive outcomes because different cognitive outcomes may emanate from different pathophysiological processes[2]. This concern appears to be supported by the work of Bennett et al who have reported that many risk factors that have been identified using other clinical outcomes become non significant when AD pathology is used as the outcome[5].

At the last Alzheimer's Association conference on prevention, a symposium on potential primary prevention trials was held. In preparation for this symposium, we undertook a systematic review of the literature on all risk factors focusing only on incident AD. This paper reports on only the results pertaining to cardiovascular risk factors for incident AD.

Methods

We conducted a systematic literature search in PubMed of all published articles in the English language from 2000 to April of 2007 in order to capture the most recent publications. Search terms used included combinations of *Alzheimer disease*, *risk factors*, and words including and related to the following: hypertension, lipids, diabetes, metabolic syndrome, cerebrovascular, education, social networks, depression, APOE, exercise, diet, BMI, atrial fibrillation, smoking, and *alcohol*. We excluded all meta-analyses and reviews. We included longitudinal studies enrolling 500 or more subjects and reporting on incident Alzheimer disease. We selected studies with sample sizes of 500 or more because studies with these large sample sizes are more likely to have the power to detect meaningful relationships. Included papers also had to describe a formal clinical assessment procedure and use the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised Third Edition, or *Fourth Edition*, or the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's disease for diagnosis of AD.

The initial search returned 1926 articles. By applying the criteria described above and excluding for example imaging studies and in vitro studies, we selected 197 with potentially relevant citations for review of the abstracts; 76 articles met the criteria for data abstraction. This paper reports on the results of 61 papers from 23 studies, all observational, that pertain to the cardiovascular risk factors. We defined cardiovascular risk factors to include hypertension, diabetes, exercise, alcohol intake, smoking, B complex vitamins, stroke, atrial fibrillation, APOE, and lipids. APOE was included although it only has a modest effect on lipid regulation, because it also has a major effect on AD incidence. Hypertension was defined by self-reported diagnosis or treatment, observed participant medications, measurements, or a computerized inpatient register system. Diabetes was defined by self-

reported diagnosis or treatment, observed patient medication, documented use of insulin or an oral hypoglycemic drug, measured blood glucose, or health records. Exercise was determined by self-report from various questionnaires, as was alcohol intake and smoking status. A study participant's level of B complex vitamins were determined by blood samples or estimated from self-report of diet. The diagnosis of stroke was based on self-report, informant report, or medical records, and sometimes supplemented by a neurological examination. APOE genotype was determined using DNA from blood samples. Lipid levels were determined by using self-reported diagnosis or treatment, observed patient medication, venous blood specimen, or a laboratory database.

For each paper reviewed, we noted study cohort size, the number of incident AD cases, and the years of follow up. We extracted from the multivariate model reported in each paper the estimated Hazard Ratio (HR), Relative Risk (RR) or Odds Ratio (OR), respective 95% confidence intervals and p-values. We also extracted information regarding interactions of a risk factor with other factors. All studies included were from observational studies that varied considerably on exposure measures. In addition, a wide range of statistical models were used in these papers and covariates included in these models also differed substantially. To conduct a meta-analysis on these risk factors would require uniform criteria resulting in the exclusion of many studies. We chose to present a systematic review of all literature so that possible sources of heterogeneity could be examined instead of focusing on a statistical combination of data[6]. In presenting the results, we combined all effect estimates into one column without specifically noting whether they were HR, RR or OR estimates. For incident AD rates, the three measures of association (HR, RR, and OR) can be regarded as approximately the same[7].

Unlike the common approach in meta-analysis where one publication from a study is usually included, we allowed multiple papers from the same studies in order to show the wide variations in defining risk exposures even within the same study.

There were 12 articles from 8 studies reporting on dietary constituents and dietary supplements as a risk factor for incident AD[8–19]. The reported analyses included consideration of intake of vitamin B complex, niacin, vitamin C, vitamin E, combinations of B, C and E, multiple vitamins, antioxidants, fat including saturated and unsaturated, DHA and α-linolenic acid, carbohydrates, protein, tryptophan, tea and juice, and Mediterranean diet. Many studies reported an association between the particular dietary constituent and altered risk for AD. However, definitions and criteria for the constituents of diet varied considerably from paper to paper as did the statistical analytic models employed. This variability in the methodological approach precludes a simple summary of the evidence regarding AD risk and diet. For this reason, we include these papers in the reference list but do not further detail their results.

Results

Hypertension

Sixteen papers from ten studies reported on hypertension as a risk factor for AD. Nine papers from seven studies reported that hypertension was not a risk factor for AD[20–28]. According to two articles from the Kungsholmen Project, however, hypertension had the potential to become a risk factor depending on the parameters. The first article reported that a systolic blood pressure equal to or greater than 160 mm Hg did not affect risk significantly[29], while the second reported that a systolic blood pressure greater than 180 mm Hg significantly increased risk[30]. Additionally, the first paper reported that a low diastolic blood pressure (less than 70 mm Hg)[29] increased risk and the second reported that a very

low diastolic blood pressure (less than or equal to 65 mm Hg) also increased risk[30] (see Table 1).

Two articles from two studies reported on hypertension at midlife. One of these papers from the Cardiovascular Risk Factors, Aging, and Dementia study (CAIDE) reported that midlife systolic blood pressure in the range of 140–159 mm Hg did not affect risk significantly, while high midlife systolic blood pressure (equal to or greater than 160 mm Hg) significantly increased risk[21]. A paper from the Honolulu Heart Program/Honolulu-Asia Aging Study (HHP/HAAS) reported that low midlife diastolic blood pressure (below 80 mm Hg) increased risk[31]. These two papers from different studies reported inconsistent findings regarding midlife borderline high and midlife high diastolic blood pressure[21, 31] (see Table 1). An article from the East Boston Established Populations for Epidemiologic Studies of the Elderly (EPESE) reporting systolic blood pressure and diastolic blood pressure at various years before and after AD diagnosis was inconclusive[24].

Seven papers from four studies reported on the effect various interactions have on the risk for AD. One article from the Washington Heights-Inwood Columbia Aging Project (WHICAP) reported an interaction between hypertension and diabetes[28] and a second article from the same study reported an interaction between hypertension and stroke that increased risk[32]. Two additional papers from the Kungsholmen Project reported that the interaction between severe systolic hypertension (greater than or equal to 180 mm Hg) and borderline diabetes or diabetes both significantly increased risk[33, 34]. Three articles from three separate studies, the Kame Project, the Kungsholmen Project, and the CAIDE study, reported no interaction between systolic blood pressure and the APOE ε4 allele[21, 29, 35]. The article from the Kungsholmen Project also reported no significant interaction between systolic blood pressure of greater than or equal to 140 mm Hg and antihypertensive drug use or between a systolic blood pressure of greater than or equal to 140 mm Hg, APOE ε4, and antihypertensive drug use[29]. Regarding diastolic blood pressure, the same paper reported an interaction between a low diastolic blood pressure (less than 70 mm Hg) and the APOE ε4 carrier that increased risk, but reported no increased risk for low diastolic blood pressure in the APOE ε4 non-carrier[29]. No interactions were reported between diastolic blood pressure and antihypertensive drug use or between low diastolic blood pressure, an APOE ε4 carrier, and antihypertensive drug use[29] (see Table 1).

One paper reporting that hypertension increased risk in the Yoruba was discarded because the results were based on unreliable self report. The authors indicated that self report of hypertension was unreliable in this population because of their limited access to healthcare[25].

Synthesis of Hypertension

The results from this review of hypertension as a risk factor illustrate the problems in interpreting results from observational studies. All of the studies reporting significant associations in one way or another changed the criteria for defining hypertension in their models in order to obtain significance for incident AD. Presumably this was because using generally accepted clinical criteria did not, as was the case for the few studies that reported associations using them. The manipulations included altering the criteria levels for systolic (higher than 140) and diastolic (both lower and higher) or changing the length of the observation (mid life). Thus the often repeated simple statement that hypertension is a risk factor for incident AD does not capture the complexities of the association as described here and may have implications for both prevention strategies and prevention trials.

Diabetes

Seventeen articles from nine studies reported on diabetes as a risk factor for AD. Nine articles from seven studies reported that diabetes was not a significant risk factor[20, 23, 26, 27, 34–38]. Only one paper from the Religious Orders Study reported that diabetes increased risk[39]. A paper from the Kungsholmen Project reported that borderline diabetes increased risk[33], while an article from HHP/HAAS found that type 2 diabetes increased risk[40] (see Table 2).

Six papers from four studies reported on interactions that affected risk. One paper from WHICAP reported that the interaction between diabetes and stroke increased risk significantly[32]. A second paper from WHICAP reported an interaction between diabetes and hypertension[28]. Two articles from the Kungsholmen Project also reported interactions between borderline diabetes and severe systolic hypertension (greater than or equal to 180 mm Hg)[33] and diabetes and severe systolic hypertension that increased risk significantly[34].

Figure 1 illustrates the effect of diabetes/hypertension interactions on AD risk.

Only one paper reported significant interaction between diabetes and APOE ε4. This paper from the Kame Project reported that APOE ε4 non-carriers with diabetes had an increased risk for AD, while APOE ε4 carriers with diabetes had no significant change in risk[35]. The two articles from the Kungsholmen Project reported no interaction between borderline diabetes and APOE ε4[33] or between diabetes and APOE ε4 carriers[34]. A fourth article from the HHP/HAAS study found no interaction between type 2 diabetes and APOE ε4[40] (see Table 2).

Additionally, one paper from WHICAP reported on the related disorder of hyperinsulinemia and found that increasing insulin levels significantly increased risk[41]. Two papers, one from a study done in Kuopio, Finland and another from the HHP/HAAS, reporting on metabolic syndrome were inconsistent[42, 43].

Synthesis of Diabetes

The situation with regard to the association of diabetes with incident AD is similar in many respects to that described for hypertension. Most studies report no significant association between diabetes and incident AD and those few that do report only a modest effect.

It is only when diabetes is considered in association with other factors, particularly hypertension, that significant associations are reported. The magnitude of these interactions suggest a process which is not simply additive in nature, but an association beyond that expected from its component parts, hypertension and diabetes. (See table 2 and figure 1). This phenomenon has also been proposed for the association of the metabolic syndrome and heart disease risk but is not as yet uniformly accepted. The two papers reporting on the association of metabolic syndrome and incident AD produced inconsistent results however. Again, reporting simply that diabetes increases risk for AD does not fully describe the complexity of the relationship.

Lipids

Ten papers from eight studies reported on lipids as a risk factor for AD. Six papers from five studies reported on the effect high levels of cholesterol had on risk[20–22, 44–46]. Three papers from the Cache County, National Health and Nutrition Examination Survey I Epidemiologic Followup Study (NHEFS), and Adult Changes in Thought (ACT) studies reported that high cholesterol had no affect[20, 44, 45]. One article from the CAIDE study reported that high total cholesterol levels greater than 251 mg/dl increased risk significantly[22]. An additional paper

from this study also looked at high midlife cholesterol effects and reported that a high midlife total cholesterol of greater than or equal to 251 mg/dl increased risk significantly[21]. Alternatively, an article from WHICAP reported that a total cholesterol of greater than or equal to 229.01 mg/dl decreased risk[46].

Five articles from four studies reported on the affect interactions between cholesterol and other risk factors have on risk for AD. One paper from the NHEFS examined the interaction between high total cholesterol and high transferrin saturation and reported that the interaction between cholesterol greater than 261 mg/dl and transferrin saturation greater than 34.9% did not affect risk, while cholesterol greater than 268 mg/dl in combination with a transferrin saturation greater than 37% increased risk[45]. A paper from the CAIDE study reported an interaction between high midlife serum cholesterol greater than or equal to 251 mg/dl and high midlife systolic blood pressure (greater than or equal to 160 mm Hg) that significantly increased risk[47]. Two articles, from the CAIDE and ACT studies, reported no interaction between total cholesterol and APOE ε4[21, 44]. A fifth paper from the Indianapolis-Ibadan study reported that increasing levels of cholesterol in an APOE ε4 non-carrier increased risk in African Americans, whereas in those with APOE ε4 there was no affect[48].

Smoking

Four papers from four separate studies reported on the effect of smoking on incident AD. Three studies, the Chicago Health and Aging Project (CHAP), WHICAP, and a study from Chongqing City, reported that current smoking increased the risk of incident AD[28, 49, 50]. An additional article from the Canadian Study of Health and Aging (CSHA) recorded only smoking and found that it was not significant[23].

B Complex Vitamins and Stroke

Three articles from three studies reported on B complex vitamins as a risk factor for AD. Of these, one from the Conselice study reported that serum levels of folate below 8.9 nmol/L increased risk[51], while another from the Framingham study reported that low serum folate levels did not affect risk[52]. The third paper from WHICAP found that high levels of total folate intake (greater than or equal to 487.9 μg) significantly decreased risk[53]. All three articles reported that vitamins B6 and B12 had no effect on risk[51℃53]. These papers also looked at high levels of homocysteine, but the results were inconsistent.

Five papers, each from different studies, reported on stroke as a risk factor. Four of these reported that it did not increase risk[20, 23, 32, 54]. One of these papers from WHICAP, however, found that when stroke was combined with either hypertension or heart disease, the interactions significantly increased risk[32]. The fifth article from the Kame Project reported that a history of transient ischemic attack in an APOE ε4 non-carrier also increased risk[35].

Exercise

Five papers from four studies reported on exercise as a risk factor for AD. One paper from the CSHA reported that regular physical activity decreased risk[23]. Two articles from the CHAP and ACT studies reported that physical activity had no effect on AD risk[55, 56]. The article from the ACT study also reported that the interaction between exercise and a low performance based physical function score decreased risk[55]. The higher performance based physical function score combined with exercise had no affect on risk[55]. Additionally, a different paper from the CSHA looked at the interaction between a high level of physical activity and gender and reported that females with a high level of physical activity had a significantly decreased risk[57]. Males with a high level of physical activity had no significant change in risk[57]. A paper from the Cardiovascular Health Cognition Study (CHCS) reported

an interaction between leisure-time energy expenditure/activity index and APOE ε4[58]. Those without APOE ε4 had a decreased risk while those with APOE ε4 had no significant change in risk[58] (see Table 3). This paper and the previous paper also reported on the effect of varying levels of activity. Both found that at a lower level of activity the risk was not affected, but at higher levels of activity the risk decreased[57, 58]. The article from the CSHA also looked at various levels of activity combined with gender and reported that an increase in physical activity decreased risk significantly only in females[57]. The other article from the CHCS reported no correlation between increasing leisure-time energy expenditure and risk[58].

Alcohol

Six articles from five studies reported on alcohol intake as a risk factor for AD. Four papers, all from different studies, reported that alcohol intake had no significant effect on risk[8, 10, 59, 60]. An article from the Indianapolis-Ibadan study looked at regular alcohol consumption in an African American population and reported a decreased risk for AD[25]. A sixth article from WHICAP reported that light to moderate intake of wine was the only type of alcohol intake that significantly decreased risk[61]. Furthermore, this study found that light to moderate intake of wine only decreased the risk in ApoE ε4 non-carriers[61].

APOE ε4

Thirteen papers from eight studies analyzed APOE ε2 or APOE ε4 as risk factors for AD. Seven of these papers from five of the studies reported that APOE ε4 significantly increased risk[21, 23, 29, 54, 62–64]. One article from the Indianapolis-Ibadan Project reported that the presence of APOE ε4 in the Yoruba population in Nigeria had no affect on risk[65]. Two articles from two studies reported different results regarding the affect of APOE ε4 in African Americans. An article from the Indianapolis-Ibadan Project reported that APOE ε4 in African Americans increased the risk significantly[66], while an article from a study done in Chicago, Illinois reported that ApoE ε4 had no affect[67].

Three articles from two studies looked at APOE ε2 in three different populations. One article from the Indianapolis-Ibadan Project reported that APOE ε2 in African Americans significantly decreased risk[66] and another article from the same study reported it had no affect on risk in the Yoruba[65]. The third paper from the Kungsholmen Project reported that APOE ε2 also did not affect risk in a Swedish population except in females between the ages of 75 and 84[64]. In this segment of the population the presence of APOE ε2 decreased risk significantly.

Synthesis of Other Risk Factors

From this review the evidence of an association between single risk factors and incidence AD, with the exception of the possession of the ε4 allele of APOE and current smoking, is inconsistent at best. As is the case with hypertension and diabetes, attaining significance often involves varying the criteria or the measurements of the risk factors in question (for example lipids or the B complex) or the consideration of interactions (e.g. exercise and physical function, cholesterol levels and hypertension, stroke and hypertension). These results again highlight the complexities of the relationships between cardiovascular risk factors and AD.

Discussion

In this review of cardiovascular risk factors, with the exception of APOE ε4 and possibly current smoking, the evidence for a significant association between single risk factors and incidence AD is mostly negative or inconsistent at best. This includes risk factors such as

hypertension and diabetes when standard clinical criteria are employed. For example, in nine of nine papers, hypertension did not significantly increase AD risk, and diabetes did not significantly increase AD risk in 9 of 12 articles. This conclusion is at variance with other recent reviews of the association between risk factors and cognitive outcomes that reported a more consistent association[2, 3] but these incorporated broader outcomes, cognitive decline[2] or a mix of AD, dementia and cognitive decline[3]. It is possible that these outcomes included a wider range of pathological processes than those involved with incident AD.

However, the strength of the association between hypertension and AD risk could be modified considerably by changing the criteria for hypertension. This included either increasing or decreasing the cutoff point for systolic or diastolic blood pressure or by including observations at midlife. Thus the statement that hypertension is associated with incident AD does not capture the complexities of this relationship.

The results regarding the effect on AD risk of altering definitions of what constitutes hypercholesterolemia were more ambiguous. One reported that increasing cutoffs to greater than 251 mg/dl particularly when measured from midlife increased risk for AD but one other study reported that total cholesterol levels greater than or equal to 229 mg/dl actually decreased risk. The review indicates that the parameters in measuring the risk factors (both length and quantity of exposure) should be taken into consideration when considering risk for AD.

This review also points to the fact many clinically defined medical conditions such as hypertension may need further characterization to inform prevention strategy. For example, many studies measure blood pressure without further indicating whether subjects were already taking anti-hypertensive medication. The proportion of subjects on anti-hypertensive medicine may impact the strength of the association between blood pressure and AD risk.

A very striking feature of this review is the influence that interactions between risk factors have for modifying risk for AD. For example, although hypertension and diabetes individually were often reported as being non significant, the results from three papers indicated that there was an interaction between diabetes, hypertension and AD risk and this interaction dramatically increased the association between these risk factors and AD (Odds Ratios 2.6, 3.3, and 4.89 respectively)(Figure 1). The possession of APOE ε4 was reported to modify risk for diabetes and AD risk in one study. High cholesterol levels increased the risk for AD in one study of elderly African Americans but only for those individuals without APOE ε4. An interaction between cholesterol levels, transferrin saturation, and incident AD was reported in one study. While exercise was reported to have no effect in two of five reports a very intriguing interaction was reported by Larson et al. In their study on the effects of exercise on the risk for dementia and AD, they also directly measured performance based physical function. They reported an interaction between history of exercise and physical function. The association between exercise and dementia and AD risk was strongest in those participants with the lower performance based physical scores.

In particular this review highlights the sometimes highly significant effects of discovering interactions between individual risk factors and AD risk. The presence of a significant interaction between two risk factors may result in an altered risk for AD when both risk factors are present an order of magnitude greater than the risk associated with either risk factor alone or which could be explained by a simple additive effect. It strongly suggests that all analyses of risk factors from observational studies should include consideration of interactions.

Well designed prevention trials remain the most definitive method for identifying intervention strategies. Consideration of interactions might also play a significant role in

identifying a vulnerable population for these trials. It does suggest for example that individuals with both hypertension and diabetes may be at greater risk for incident AD than hypertension and diabetes alone and perhaps should be the target group for an intervention strategy. It suggests also that exercise intervention may have its greatest effect on individuals with low physical function.

The information regarding potential prevention strategies with the possible exception of exercise is suggestive but not comprehensive enough to propose a specific strategy. The protective effects of antihypertensive medication would appear to depend upon the targeted levels of both systolic and diastolic blood pressures and also possibly the APOE ε4 allele. Within the B complex vitamins, only folate was identified as modifying risk for AD in one study. Four of six papers reported no effect of mild to moderate alcohol consumption on AD risk. Current smokers appeared at greater risk in 3 of 4 studies.

There are a number of limitations in this review. This review was limited only to papers published from 2000 to 2007 in order to capture the most recent publications. Thus pertinent articles published before 2000 were not included.

Systematic review of observational studies is a difficult task because of the various definitions and categories used in reporting risk factors in different studies. We have attempted to compare reports involving similar measurements of risk factors. However this was not always possible. In the case of hypertension, for example, self-report, medication use and/or actual blood pressure measurements were used to define hypertension in different studies. A major finding of our review is the identification of interactions between risk factors. However many studies did not report whether interactions were examined, making it difficult to confirm whether significant interactions reported in other studies are consistent findings or whether they are the result of publication bias.

Publication bias is a major problem with all systematic reviews. Most large cohort observational studies measure multiple potential risk factors. It is likely that positive correlates would receive greater publication priority than negative findings from these studies. Thus the non-significant associations we identified in this review such as hypertension and diabetes may be even more frequent had all negative results received publication. Similarly many studies did not report whether or not interventions were evaluated. It is possible that this is also the result of non publication of negative findings thus making it difficult to confirm whether or not the reported significant associations are consistent findings.

Although this review was undertaken in part in an effort to minimize the heterogeneity of pathological pathways which may be present in studies involving broader cognitive outcomes such as cognitive decline and dementia, several reports suggest that the clinical manifestations of AD itself is the result of a combination of AD pathology and cerebrovascular pathology. The apparent association between cardiovascular risk and incident AD may be through the cerebrovascular pathway rather than a direct effect on AD pathology[68]. The biological explanation for the interactive effects of hypertension and diabetes on AD risk is unclear. It may be similar to the somewhat controversial reported synergistic effects of several components of the metabolic syndrome such as insulin resistance, obesity and hypertension on cardiovascular risk[69]. One common pathway proposed for this cluster effect is microvascular dysfunction[70].

In conclusion, there is limited evidence that single cardiovascular risk factors affect AD risk, but the strength of the association is influenced greatly by changing the parameters of the risk factors and in particular by identifying interactions between the factors. If the results of

these significant interactions are confirmed by more studies, they may help identify both potential prevention strategies and study populations for future prevention trials.

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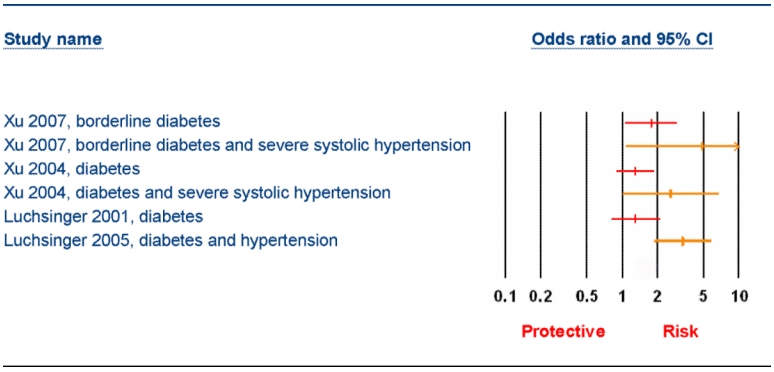

Figure 1.
Hypertension, Diabetes Interactions and Alzheimer Disease Risk

Table 1

Summary of results from the systematic review on the association between hypertension and incident AD. Interacting factors with hypertension are also included

Article	Study Name	Sample Size	Number of Incident AD Cases	Years of Follow Up	Risk Factor	Interaction	OR/RR/HR	95% Confidence Interval	P value
Blood Pressure Parameters									
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	SBP 140–159	not analyzed	1.3	0.8–2.0	n.s.
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	high SBP (≥ 160)	not analyzed	1.4	0.9–2.2	n.s.
Qiu/2003[30]	Kungsholmen Project	1270	256	Max: 6	very high SBP (above 180)	not analyzed	1.5	1.0–2.3	0.07
Qiu/200329	Kungsholmen Project	966	204	Max: 6	DBP ≥ 90	not analyzed	1.0	0.7–1.4	n.s.
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	low DBP (less than 70)	not analyzed	1.9	1.2–3.0	not given
Qiu/200330	Kungsholmen Project	1270	256	Max: 6	very low DBP (≤65)	not analyzed	1.7	1.1–2.4	not given
Midlife SBP									
Launer/200031	HHP/HAAS	3703	118	Max: 28	Midlife borderline high SBP (140–159)	not analyzed	1.23	0.63–2.43	n.s.
Kivipelto/2002[21]	CAIDE	1449	48	21	midlife SBP (140–159)	not analyzed	1.6	0.7–4.2	n.s.
Launer/2000[31]	HHP/HAAS	3703	118	Max: 28	high midlife SBP (≥ 160) high midlife	not analyzed	1.22	0.37–4.04	n.s.
Kivipelto/2002[21]	CAIDE	1449	48	21	SBP (≥160)	not analyzed	2.6	1.1–6.6	not given
Midlife DBP									
Launer/2000[31]	HHP/HAAS	3703	118	Max: 28	DBP (below 80)	not analyzed	1.86	1.01–3.46	not given
Kivipelto/2002[21]	CAIDE	1449	48	21	Midlife DBP (90–95)	not analyzed	1.2	0.4–3.3	n.s.
Launer/2000[31]	HHP/HAAS	3703	118	Max: 28	borderline high DBP (between 90–94	not analyzed	5.1	1.7–15.2	not given
Kivipelto/2002[21]	CAIDE	1449	48	21	high midlife DBP (≥95)	not analyzed	2.0	0.9–4.6	n.s.
Launer/2000[31]	HHP/HAAS	3703	118	Max: 28	DBP (≥95)	not analyzed	6.6	2.0–21.4	not given
Interactions									
Luchsinger/2005[28]	WHICAP	1138	176	5.5	hypertension	diabetes	3.3	1.9–5.9	0.03
Honig/2003[32]	WHICAP	1766	181	Max: 7	hypertension severe	stroke	2.14	1.40–3.27	not given
Xu/2007[33]	Kungsholmen Project	1173	307	Max: 9	systolic hypertension (≥180)	borderline diabetes	4.89	1.07–22.42	0.04

Article	Study Name	Sample Size	Number of Incident AD Cases	Years of Follow Up	Risk Factor	Interaction	OR/RR/HR	95% Confidence Interval	P value
Xu/2004[34]	Kungsholmen Project	1301	260	Max: 6	severe systolic hypertension (≥180)	diabetes	2.6	1.0–6.8	0.05
Borenstein/2005[35]	Kame Project	1859	90	Max: 9	high SBP (≥140)	APOE ε4 non carriers	1.79	0.82–3.89	0.15
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	SBP	APOE ε4	not given	no interaction	n.s.
Kivipelto/2002[21]	CAIDE	1449	48	21	SBP	APOE ε4	not given	no interaction	n.s.
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	SBP ≥140	antihypertensive drug use	0.5	0.2–1.1	0.09
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	SBP ≥140	APOE ε4 carrier and antihypertensive drug use	0.5	0.1–1.5	n.s.
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	low DBP (less than 70)	APOE ε4 carrier	4.5	2.6–8.0	not given
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	low DBP (less than 70)	APOE ε4 non carriers	1.3	0.7–2.5	n.s.
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	DBP	antihypertensive drug use	not given	no interaction	not given
Qiu/2003[29]	Kungsholmen Project	966	204	Max: 6	DBP (less than 70)	APOE ε4 carrier and antihypertensive drug use	3.2	0.9–11.6	0.07

AD-Alzheimer disease; OR-odds ratio; RR-relative risk; HR-hazard ratio; SBP-systolic blood pressure; DBP-diastolic blood pressure; HHP/HAAS-Honolulu Heart Program/Honolulu-Asia Aging Study; CAIDE-Cardiovascular Risk Factors, Aging, and Dementia; WHICAP-Washington Heights-Inwood Columbia Aging Project

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Table 2

Summary of results from the systematic review on the association between diabetes and incident AD. Interacting factors with diabetes are also included.

Article	Study Name	Sample Size	Number of Incident AD Cases	Years of Follow Up	Risk Factor	Interactions	OR/RR/HR	95% Confidence Interval	P value
Hayden/2006[20]	CCSMHA	3264	104	Max: 5	diabetes	not analyzed	1.33	0.66–2.46	n.s.
Akomolafe/2006[36]	Framingham	2210	237	12.7	diabetes	not analyzed	1.15	0.65–2.05	n.s.
Borenstein/2005[35]	Kame Project	1859	90	Max: 9	diabetes	not analyzed	not given	not given	0.35
Xu/2004[34]	Kungsholmen Project	1301	260	Max: 6	diabetes	not analyzed	1.3	0.9–2.1	n.s.
Lindsay/2002[23]	CSHA	4615	194	Max: 5	diabetes	not analyzed	1.03	0.58–1.84	n.s.
MacKnight/2002[38]	CSHA	5574	267	Max: 5	diabetes	not analyzed	1.3	0.83–2.03	n.s.
Posner/2002[26]	WHICAP	1259	157	Max: 7	diabetes	not analyzed	1.3	0.7–2.6	n.s.
Luchsinger/2001[37]	WHICAP	1262	157	4.3	diabetes	not analyzed	1.3	0.8–1.9	n.s.
Tyas/2001[27]	MSHA	694	36	Max: 5	diabetes	not analyzed	2.7	0.85–8.52	n.s.
Arvanitakis/2004[39]	Religious Orders Study	824	151	5.5	diabetes	not analyzed	1.65	1.10–2.47	not given
Xu/2007[33]	Kungsholmen Project	1173	307	Max: 9	borderline diabetes	not analyzed	1.77	1.06–2.97	not given
Peila/2002[40]	HHP/HAAS	2574	76	2.91	diabetes, type 2	not analyzed	1.9	1.1–3.2	not given
Honig/2003[32]	WHICAP	1766	181	Max: 7	diabetes	stroke	4.12	2.35–7.23	not given
Luchsinger/2005[28]	WHICAP	1138	176	5.5	diabetes	hypertension	3.3	1.9–5.9	0.03
Xu/2007[33]	Kungsholmen Project	1173	307	Max: 9	borderline diabetes	severe systolic hypertension (≥180 mm Hg)	4.89	1.07–22.42	0.04
Xu/2004[34]	Kungsholmen Project	1301	260	Max: 6	diabetes	severe systolic hypertension (≥180 mm Hg)	2.6	1.0–6.8	0.05
Borenstein/2005[35]	Kame Project	1859	90	Max: 9	diabetes	APOE ε4 non carriers	2.68	1.20–6.00	0.02
Borenstein/2005[35]	Kame Project	1859	90	Max: 9	diabetes	APOE ε4 carriers	0.45	0.11–1.96	0.29
Xu/2007[33]	Kungsholmen Project	1173	307	Max: 9	borderline diabetes	APOE-ε4	not given	not given	n.s.
Xu/2004[34]	Kungsholmen Project	1301	260	Max: 6	diabetes	APOE ε4 carriers	1	0.3–2.9	n.s.
Peila/2002[40]	HHP/HAAS	2574	76	2.91	diabetes, type 2	APOE ε4	not given	not given	p>0.2

AD-Alzheimer disease; OR-odds ratio; RR-relative risk; HR-hazard ratio; CCSMHA-Cache County Study of Memory, Health, and Aging; CSHA-Canadian Study of Health and Aging; WHICAP-Washington Heights-Inwood Columbia Aging Project; MSHA-Manitoba Study of Health and Aging; HHP/HAAS-Honolulu Heart Program/Honolulu- Asia Aging Study

Table 3

Summary of results from the systematic review on the association between exercise and incident AD. Interacting factors with exercise are also included.

Article	Study Name	Sample Size	Number of Incident AD Cases	Years of Follow Up	Risk Factor	Interaction	OR/RR/HR	95% Confidence Interval	P value
Lindsay/2002[23]	CSHA	4615	194	Max: 5	regular physical activity	not analyzed	0.69	0.50–0.96	not given
Wilson/2002[56]	CHAP	842	139	Max: 4	physical activity (measured in time spent)	not analyzed	1.04	0.98–1.10	n.s.
Larson/2006[55]	ACT	1740	107	6.2	exercise (3x/week)	not analyzed	0.69	0.45–1.05	0.081
Larson/2006[55]	ACT	1740	107	6.2	exercise	performance based physical function score of 10	0.58*	0.39–0.84*	0.004*
Larson/2006[55]	ACT	1740	107	6.2	exercise	performance based physical function score of 11	0.66*	0.46–0.94*	0.023*
Larson/2006[55]	ACT	1740	107	6.2	exercise	performance based physical function score of 12	0.75*	0.51–1.09*	0.126*
Laurin/2001[57]	CSHA	4615	194	Max: 5	high level of physical activity	female gender	0.27	0.08–0.90	0.05
Laurin/2001[57]	CSHA	4615	194	Max: 5	high level of physical activity	male gender	0.73	0.27–1.98	0.62
Podewils/2005[58]	CHCS	3375	245	5.4	leisure-time energy expenditure/activity index	APOE ε4 non carriers	0.44*	0.28–0.69*	p<0.001*
Podewils/2005[58]	CHCS	3375	245	5.4	leisure-time energy expenditure/activity index	APOE ε4 carriers	1.2*	0.63–2.29*	0.68*

AD-Alzheimer disease; OR-odds ratio; RR-relative risk; HR-hazard ratio; CSHA-Canadian Study of Health and Aging; CHAP-Chicago Health and Aging Project; ACT-Adult Changes in Thought; CHCS-Cardiovascular Health Cognition Study

*Data is from incident dementia, but authors reported observing the same pattern for incident AD.