Ankle-Brachial Index as a Marker of Cognitive Impairment and Dementia in General Population. A systematic review.

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Review

Key-words: cognitive impairment, ankle-brachial index, peripheral artery disease, dementia

Abstract (181 words)

Objective: To investigate the association between a low Ankle-Brachial Index (ABI) and several grades of cognitive disorders: cognitive impairment, dementia and Alzheimer's disease (AD), in the general population.

Methods: We performed a systematic review of the literature, including all prospective, longitudinal or cross-sectional studies assessing both peripheral artery disease (PAD), defined by a low ABI, and cognitive function.

Results: 12 publications were included in this review, of whom 6 reported cross-sectional analysis and 6 reported longitudinal analysis. All except one reported a significant association between a low ankle-brachial index and cognitive impairment, dementia or AD. Beyond cognitive impairment, patients with PAD are at an increased risk to develop dementia or Alzheimer's disease.

Conclusion: In this review, we confirm that a low (<0.90) ABI can be considered as a marker of cognitive impairment and dementia. ABI provides independent and supplemental information on subject's susceptibility to develop cognitive disorders, along its usefulness to predict cardiovascular diseases (CVD). Given its availability, easiness, safety to patients and low cost, the ABI could be useful in clinical practice and research in the field of cognitive diseases.

Cognitive disorders and cardiovascular diseases (CVDs) are both highly prevalent within the older population worldwide. From a public health perspective, the screening of both conditions at an early stage for appropriate intervention is of paramount importance. Among cardiovascular diseases, lower-extremities peripheral artery disease (PAD) is easily detectable by the measurement of the ankle-brachial index (ABI). Using the common criteria of ABI <0.90 to define PAD (Aboyans & Criqui, 2009), several epidemiological studies showed an increasing prevalence of this condition in the elderly, estimated around 10% by the age of 65, as high as 25% after the age of 85 (Aboyans & Criqui, 2009). Concomitantly, the global prevalence of dementia is estimated respectively at 3.9% after 60, and closed to 25.0% for those aged 85 and older (Ferri et al, 2005). Thus, PAD and cognitive disorders, especially dementia and Alzheimer's disease, coexist with increasing age.

The implication of cardiovascular risk factors in the development of cognitive impairment, even dementia, at an older age is now clearly established. Hypertension (Slooter et al, 1997; Launer et al, 1995; Starr et al, 1993; Qiu et al, 2005), diabetes (Messier et al, 1996; Ott et al, 1996), obesity (Naderali et al, 2009), and hypercholesterolemia (Goldstein et al, 2008) are associated with cognitive disorders in the elderly. These conditions are also prevalent in PAD patients (Kannel et al, 1994). Atherosclerosis is believed to be involved in the development of dementia and its two major subtypes: vascular dementia and Alzheimer's disease (AD) (de la Torre et al, 2004). Given these, it is reasonable to suspect these patients to suffer from cognitive disorders due to concomitant cardiovascular diseases.

While the poor cardiovascular prognosis of patients with asymptomatic or symptomatic PAD is now widely evidenced (Criqui et al, 1992), data on cognitive prognosis of patients with this condition are scarce. The influence of cardiovascular diseases and risk factors on cognition in the elderly is of importance in search of predictors and pathways for prevention of dementia (Haan et al, 1999). Moreover, a prompt diagnosis of cognitive dysfunction in PAD patients may lead to specific therapeutic strategies to limit its progression (Price et al, 2006; Johnson et al, 2010).

The association between clinical or subclinical PAD and cognitive function has been recently highlighted (Rafnsson et al, 2009). Patients with PAD are at increased risk for cognitive decline, independently of previous cerebrovascular disease and cardiovascular risk factors. First developed to aid the diagnosis of PAD, the ABI has

also been shown as a simple, harmless and accurate, measure of generalized atherosclerosis (Fowkes et al, 1988).

In this systematic review, we focused on the association between a low ABI and several grades of cognitive disorders: cognitive impairment, dementia and Alzheimer's disease, in general population. We hypothesized that beyond its prognostic value for mortality and CVD events, ABI could also identify subjects at risk of cognitive disorders.

Methods

Search strategy and selection criteria

A systematic search of literature was performed using Pubmed (Medline, 1966-2010), Scopus (1823-2010), ScienceDirect (Elsevier, 1823-2010), IngentaConnect and RefDoc (from INIST/CNRS, 1847-2010) databases.

The search strategy included the following keywords in various combinations: "cognitive impairment", "dementia", "Alzheimer's disease", "atherosclerosis", "peripheral arterial disease", "peripheral artery disease", "peripheral vascular disease" or "ankle brachial index". The systematic search was performed up to June 2010. Abstracts from conferences proceedings were also identified during this search.

The titles and abstracts of all results identified during the initial search were evaluated by the authors (MG and VA) to identify potentially relevant articles, using the inclusion criteria. In addition, we manually searched the reference lists of relevant articles to identify those missed by electronic researches. The full text of reports fulfilling all inclusion criteria was retrieved for further analysis. Authors were contacted if full-text article was not available. When duplicate publications on the same cohort were identified, only the most recent or the most informative was kept, whereas congress communications were excluded.

Data extraction

Two investigators (MG, VA) independently extracted data from selected articles: first author, year of publication, country and type of the study, type of population included, number of patients, cognitive outcome and tests used, criteria used, vascular comorbidities investigated, ABI cut-point, and main results.

Studies were first selected according to the selection criteria: (1) language (English or French), (2) population-based study, (3) prospective or cross-sectional, assessing

both PAD and cognitive function (4) sample size: at least 100 participants and (5) studies not including participants with history of stroke.

Quality assessment

Five quality criteria were evaluated: (1) the study had a clearly formulated aim, (2) the assessment of cognitive impairment, dementia or Alzheimer's Disease (AD) has to be clearly described, (3) neuropsychological tests and thresholds if used has to be mentioned for any cognitive impairment outcome, (4) diagnostic criteria used during the study have to be specified when the cognitive outcome was dementia and/or Alzheimer's Disease and (5) peripheral artery disease has to be defined by a low ABI.

Results

Study selection

The literature search flow-chart is presented in Figure 1. The combined search in the 5 electronic databases identified 2934 potentially eligible references, of which 2911 were excluded based on the title and abstracts. Twenty-three references were selected for further investigation. Full articles were collected and evaluated. Twelve articles met our criteria and were included in the systematic review. Among the 11 excluded references, 5 investigated PAD including ABI measures but the results were presented as atherosclerosis sum scores or ABI measures were not detailed, 4 were case-control studies, one was an abstract and the last a duplicate publication.
Considering the 12 publications included in the review, 10 investigated specifically the association between low ABI and cognitive impairment, dementia or AD (Haan et al, 1999; Woo et al, 2006; Price et al, 2006; Breteler et al, 1994; van Oijen et al, 2007; Laurin et al, 2007; Hofman et al, 1997; Newman et al, 2005; Johnson et al, 2010; Sugawara et al, 2010). In the 2 remaining articles (Vupputuri et al, 2008; Bruce et al, 2008), ABI and cognitive function were both assessed, although their association was not the primary goal. Complete description of the studies is presented in Table 1.

Cross-sectional analysis

The association between a low ABI and cognitive impairment has been studied in cross-sectional analysis (Table 2).

In a Chinese population-based study, ABI was on average lower in subjects with cognitive impairment (Mini Mental State Examination (MMSE)<24): 1.02 ± 0.13 for cognitively impaired subjects versus 1.08 ± 0.12 for those without cognitive impairment ($p<0.001$). In multivariate analysis, adjusted for age, gender, diabetes, hypertension, smoking, history of coronary artery disease, alcohol and vitamin C consumption, and minimum time to walk 6m, a significant association between low (<0.90) ABI and cognitive impairment was found (Woo et al, 2006).

The MMSE was also used in the Rotterdam Study to determine cognitive impairment. In this population-based study with participants aged >65 years, the proportion of patients below the MMSE threshold were compared in multiple regression analysis. The proportion of subjects with MMSE<24 was significantly higher among participants with an ABI <0.90 (10.4% vs. 5.0% in the absence of PAD, $p<0.0001$). Similar findings were reported when the MMSE threshold was fixed to 26: 17.5% vs. 11.1%, $p<0.0001$) (Breteler et al, 1994).

In another cross-sectional report from the Rotterdam Study, low ABI (<0.90) was significantly associated to all dementia, and vascular dementia (VaD) but not with AD or non-vascular dementia (Table 3). Odds ratios for all dementia, AD and VaD increased with the increasing number of markers of atherosclerosis (PAD, plaques in common carotid arteries, and intima-media thickness). This study also indicated that participants with peripheral atherosclerosis and APOE ε4 genotype had an increased risk for all dementia, AD and VaD (Hofman et al, 1997).

In the Fremantle Diabetes Study (Australia), cognition in diabetics aged ≥70 was assessed by the MMSE and the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE). Compared to diabetics with normal cognitive function, those with cognitive impairment or dementia were more likely to present concomitantly an ABI≤0.90 (37.8% in normal subjects, 45.0% in cognitively impaired and 75.0% in diabetics with dementia, $p=0.002$) (table 2). Dementia was independently associated with older age, male sex, diabetes and PAD (Table 3).

A study from Japan showed that even after adjustments for confounding factors, a low ABI (1^{st} quartile, below 1.08) was an independent risk factor for cognitive impairment (Table 2). Low ABI and education were the only significant risk factors of poor cognition in this study (Sugawara et al, 2010).

In the US National Health and Nutrition Examination Survey (1999-2002), subjects with PAD (ABI<0.90) tended to have lower scores at the Digit Symbol Substitution Test (DSS) compared to PAD-free counterparts (Vupputuri et al, 2008).

Several cognitive functions (praxia, memory and language) were assessed in the Edinburg Artery Study, ten years after the measurement of ABI. Adjusted for age and sex, subjects with an ABI<0.90 at baseline were significantly at higher risk of impaired nonverbal reasoning, verbal fluency and processing speed 10 years later (Table 2). In contrast, the immediate and delayed verbal declarative memory did not differ according to the ABI. Similar findings were reported with an ABI<0.95 (Price et al, 2006).

Longitudinal analysis

Five years after the initial cognitive testing, i.e. 15 years after the Edinburg Artery Study's inception, the same cognitive tests were repeated in order to refine and extend initial observations. These analyses showed that ABI was significantly associated with the level of cognitive function (correlation coefficient=0.15, p=0.001), still significant but attenuated when considering anxiety, depression and other covariates (correlation coefficient=0.07, p=0.03). Conversely the authors did not find any significant association between ABI decrease (between years 5 and 12) and cognitive performances change (Johnson et al, 2010).

After a follow-up of 7.6 years of Australians elder diabetics, multiple logistic regressions identified ABI <0.90 as an independent predictor of cognitive impairment and dementia (Table 3) (Bruce et al, 2008).

The association between atherosclerosis and dementia has also been prospectively investigated in the Rotterdam study (Table 3). After a mean follow-up of 9 years, this study did not find any significant association between neither ABI at baseline nor ABI at the third survey and the onset of dementia, AD or VaD (van Oijen et al, 2007).

A low ABI (both continuous and dichotomized classes) was associated with greater decline in cognition measured with DSS (p<0.0001) and MMSE in the Cardiovascular Health Study. A subject with a low (<0.90) ABI had an average DSS score decline of 2.73 points over 7 years, and of 4.62 points for the MMSE score, compared to 0.39 and 0.66 respectively, for subjects with an ABI ≥0.90 (Haan et al, 1999). During this study, the incidence of dementia was higher in those with an ABI

<0.90 (60.5 per 1000 person-year) than those with a normal ABI (26.4 per 1000 person-year). The corresponding unadjusted Hazard Ratio (HR) for dementia in those with prevalent PAD was 2.3 (95%CI 1.4-3.9). After adjustment for age, sex, race, education, income, presence of APOE ε4 allele and MMSE score, the HR for dementia in elderly with ABI<0.90 was 2.5. The association between AD and an ABI <0.8 was significant and rates of AD increased at lower levels of ABI. The same patterns were observed for overall dementia, AD or mixed AD, and AD excluding VaD (Newman et al, 2005).

In the population-based Honolulu-Asia Aging Study, low ABI (<0.90) was significantly associated with the risk of incident total dementia after adjustments for age and education (Table 3). In a multivariate model accounting for several confounders, subjects with an ABI<0.90 were at increased (66%) risk of incident dementia and a >2 fold increase risk of VaD compared to those with ABI>0.90. Low ABI was associated with the risk of incident AD when adjusted for age and education (Table 3). Moreover, low ABI was related to an increased risk of total dementia and VaD, and with AD if subjects were ApoE ε4 carriers (Laurin et al, 2007).

Discussion

This systematic review highlights that cognitive testing scores were poorer in subjects with a low ABI in all cross-sectional studies. The cognitive impairment affected predominantly memory, praxias (non-verbal reasoning, executive function) and language. Beyond cognitive impairment, patients with a low ABI are at increased risk to develop dementia or Alzheimer's disease. While the cross-sectional studies are not able to provide information about the sequence between PAD and cognitive impairment or dementia, they indicated that a low ABI is often associated with the presence of cognitive impairment or dementia.

The association between a low ABI and cognitive disorders was found in all cross-sectional studies and confirmed by longitudinal studies for incident cases of cognitive impairment, Alzheimer disease and dementia (especially of vascular dementia). Cohort studies evidenced that patients with a low ABI are at increased risk for cognitive decline and incident dementia or AD. A low ABI appears as a marker for cognitive performance in clinically stroke-free patients (Mangiafico et al, 2006). Nevertheless, the 15-year follow-up of the Edinburg Artery Study failed to show any association between ABI decline and cognitive function aggravation

(Johnson et al, 2010). Only the longitudinal data of the Rotterdam Study (van Oijen et al, 2007) lacked to confirm an association between ABI and risk for dementia, although the cross-sectional analyses were positive.

Quality assessment

This review results from an extensive search in international databases of studies assessing the association between low ABI and cognitive disorders. Publications identified have been evaluated considering their main features.

Both cross-sectional and longitudinal analyses were included in this review. While the longitudinal studies provide higher level of evidence, the scarcity of prospective studies led us to also include good quality cross-sectional analysis, corresponding sometimes as the baseline data of longitudinal studies (Breteler et al, 1994; Hofman et al, 1997; Price et al, 2006; Bruce et al, 2008). Case-control studies were excluded from our review in order to focus on general population. Indeed, in most of case-control studies identified, participants were recruited in hospitals. Moreover, these studies included insufficient number of participants in each group.

Neuropsychological tests used during the assessment of cognitive impairment in the different studies were analysed with scrutiny. These tests had to be priorily validated. Manuscripts also had to clearly mention the threshold used to determine the cognitive impairment and the domains examined or affected in such case. When the study focused on a dementia or AD outcome, criteria followed for the diagnosis has to be respectively DSM or NINCDS-ADRDA, which are the most applied in epidemiological researches. Even if two different versions of DSM criteria are used in the studies, the difference between DSM-III-R and DSM-IV criteria is not substantial enough to lead to a bias in the quality of this review.

Cognitive impairment and PAD share putative risk factors, such as age and CVD, but depression is also evoked to be linked to both affections. The prevalence of clinically significant depressive symptoms is high in men and women with PAD (Mc Dermott et al, 2003). Because of functional impairment, patients with PAD may have an increased prevalence of depressive symptoms. Besides, the Rotterdam study reported that atherosclerosis and depression are associated in the elderly (Tiemeier et al, 2004), but causal inferences are unknown. As depressive symptoms are also associated to poor cognitive functioning (Dufouil et al, 1996; Yaffe et al, 1999) and

depression is regarded as a risk factor for dementia and AD (Jorm et al, 2000; Geerlings et al, 2000), this condition should be considered when studying the association between PAD and cognitive impairment. Only in one report, Johnson et al (2010) suggested that the depression may explain the association between cognitive function and PAD, but further studies are necessary.

All the studies were population-based, although the Rotterdam study (Breteler et al, 1994; van Oijen et al, 2007; Hofman et al, 1997) also included institutionalized subjects. Generally, authors highlighted that the selection of subjects who agreed a health survey, probably healthier, and the exclusion of deceased subjects and non-responders may have underestimated the strength of the association between a low ABI and cognitive impairment (Haan et al, 1999; Woo et al, 2006; Price et al, 2006; Breteler et al, 1994; Bruce et al, 2008; van Oijen et al, 2007). As pointed out by Breteler et al. (1994) in the Rotterdam study, survival bias may have distorted the results and underestimated the risks because subjects with severe PAD may have died from cardiovascular disease before developing dementia.

The presented studies mostly included age as an adjustment variable in the statistical models in order to avoid ageing effects in these associations. Indeed, age is clearly associated to cognitive impairment and is the only established risk factor for dementia and AD (Prince et al, 2009).

Other probable confounding variables were taken into account in several studies, mostly cardiovascular disease risk factors. It has been shown that patients who experienced TIA or stroke have significantly worst performances during cognitive testing (Rao et al, 1999), as well as older patients with intermittent claudication (Waldstein et al, 2003; Singh-Manoux et al, 2003). In the Rotterdam Study, exclusion of stroke patients and censoring individuals at the time of incident stroke did not affect the estimates, so that the association with dementia is not explained by clinical stroke (van Oijen et al, 2007). Further adjustments for cardiovascular comorbidities and risk factors, as potential confounders (stroke, trans-ischemic attack, diabetes, hypertension, myocardial infarction etc…), were made in several studies (Haan et al, 1999; Kuo et al, 2007; van Oijen et al, 2007; Laurin et al, 2007). Yet, the ABI may provide additional prognostic information to that obtained by the enumeration of CVD risk factors and comorbidities.

The association between a low ABI and vascular dementia was generally the strongest (Hofman et al, 2007; Laurin et al, 2007). This supports the hypothesis that

ABI can be used as a marker of atherosclerosis when the etiology of dementia (vascular vs. non-vascular) should be determined. However, low ABI is also associated with incident AD (Laurin et al, 2007; Newman et al, 2005), so that it should be considered as a marker of all types of dementia in general population.

Beyond PAD, other localisations of atherosclerosis have been investigated for their association to cognitive impairment and dementia. Carotid intima-media thickness (C-IMT) and pulse wave velocity (PWV), as measures of sub-clinical CVD, are frequently associated to ABI in order to determine the relative contribution of atherosclerosis to cognitive impairment or dementia/AD. Increased C-IMT and PWV were associated with lower scores on memory performance, processing capacity and executive functioning in middle-aged and elderly men (Muller et al, 2007). Plaques in carotid arteries and increased C-IMT were found to be significantly associated to AD, VaD and all dementia in the Rotterdam Study (Hofman et al, 1997; Breteler et al, 1994). Overall, atherosclerosis is associated to poorer cognitive function and increased risk for dementia (Muller et al, 2007; van Oijen et al, 2007). Honig et al. (2005) suggested that atherosclerotic cerebrovascular disease may be part of the pathogenesis of AD because of strong association with neuritic plaques. However, in contrast to these markers of atherosclerosis, the ABI is easier, with low-cost material, feasible with some training by any physician or nurse, and from this standpoint, the ABI is the most useful marker of atheroclerosis in a patient suspect of cognitive disorders.

Other factors have been considered in some studies. CRP and D-dimers levels were also independent negative predictors of cognitive performance in patients with asymptomatic PAD (Mangiafico et al, 2006). Three studies (Haan et al, 1999, Laurin et al, 2007; Hofman et al, 1997) showed that the presence of the ApoE ε4 allele tended to increase the rate of cognitive decline or the risk to develop dementia, but artery diseases have a role independent of the ApoE ε allele (Haan et al, 1999). As both PAD and cognitive impairment are reported to be related to a spectrum of asymptomatic brain changes (Bots et al, 1993; Swan et al, 2000), Mangiafico et al. (2006) suggest that vascular brain damage is the most probable mediator linking PAD to cognitive impairment, and highlight the need of studies combining neuroimaging with PAD and cognitive assessment.

In this general review, we confirm that despite the use of several criteria to assess different dimensions of cognitive function, a low (<0.90) ABI can be considered as a marker of cognitive impairment and dementia. Similar to its usefulness to predict CVD, ABI provides independent and incremental information on subject's susceptibility to develop cognitive disorders, compared to that provided by the presence of risk factors. Given its ease of use, safety to patients and low cost, this review highlights the interest of this marker of atherosclerosis to identify elder populations at higher risk of cognitive impairment or dementia. We advocate further research in this topic in order to ascertain its benefits in clinical practice in the field of cognitive diseases.

Acknowledgements

The authors would like to thank Mrs Elisabeth Grelier for her technical help in literature searching and Dr Benoît Marin for his helpful advices during this work.

We also thank the Fondation pour la Recherche Médicale (FRM) for supporting our researches and the French National Agency for Research (ANR).

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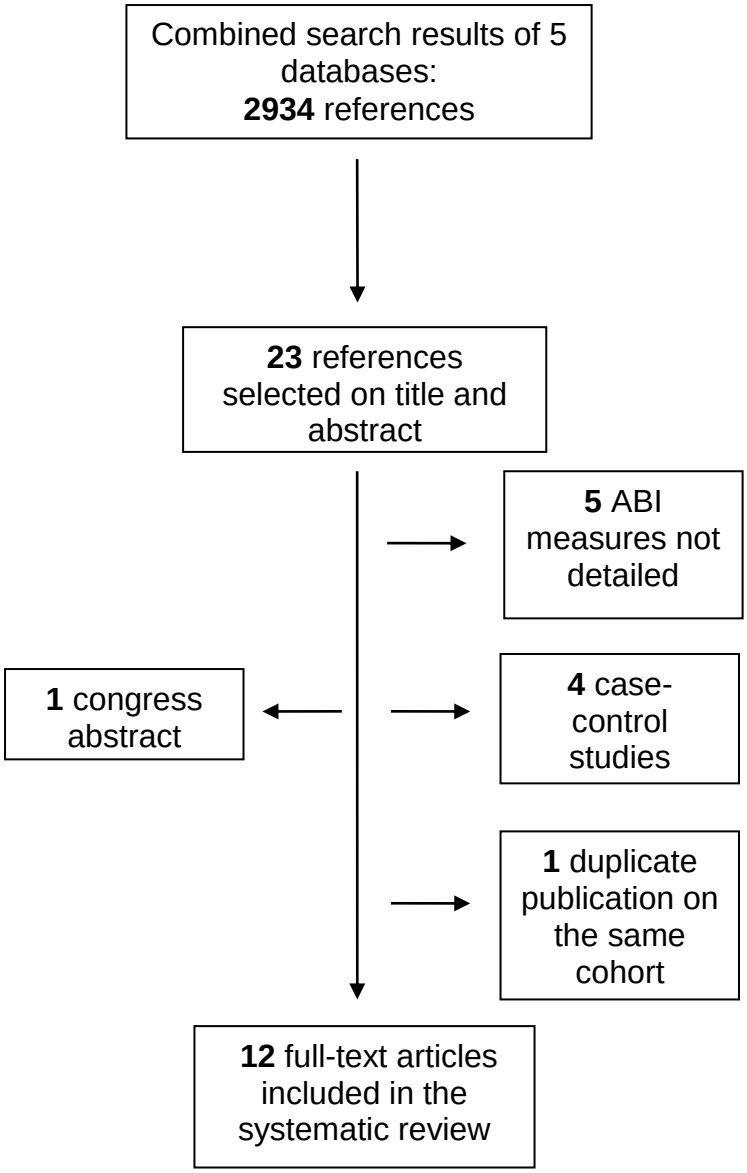


Figure 1: Literature review flow-chart.

Table 1: Main characteristics of the studies included in the systematic review.

Author	Country (Study name)	N (men/women)	Mean age (years)	ABI threshold	Cognitive outcome
Cross-sectional analysis					
Breteler et al., 1994	Netherlands (Rotterdam study)	4971 (NA)	>55.0	<0.90	Cognitive Impairment
Hofman et al., 1997	Netherlands (Rotterdam study)	1982 (36%/64%)	66.0	<0.90	Dementia / AD
Woo et al., 2006	China	3998 (50%/50%)	72.5	<0.90	Cognitive Impairment
Price et al., 2006	Scotland (Edinburgh Artery Study)	717 (50%/50%)	64.9	<0.90 and <0.95	Cognitive Impairment
Vupputuri et al., 2008	USA (NHANES)	2386 (44%/56%)	71.0	<0.90	Cognitive Impairment
Sugawara et al., 2010	Japan (Iwaki Health Promotion Project)	388 (36%/64%)	68.5	1st ABI tertile (1.08)	Cognitive Impairment
Longitudinal analysis					
Haan et al., 1999	USA (Cardiovascular Health Study)	5888 (NA)	>65.0	<0.90	Cognitive Impairment / Dementia
Newman et al., 2005	USA (Cardiovascular Health Study)	2539 (40%/60%)	74.0	<0.90	Dementia / AD
van Oijen et al., 2007	Netherlands (Rotterdam study)	3962 (41%/59%)	65.7	<0.90	Dementia / AD
Laurin et al., 2007	Honolulu & Japan (Honolulu-Asia Aging Study)	2588 (NA)	76.9	<1.0 and <0.9	Dementia / AD
Bruce et al., 2008 *	Australia (Fremantle Diabetes Study)	302 (48%/52%)	76.0	≤0.9	Dementia / AD
Johnson et al., 2010	Scotland (Edinburg Artery Study)	452 (NA)	64.9	<0.90 and <0.95	Cognitive Impairment

NA = Not Available, * publication also presenting cross-sectional analysis

PAD = Peripheral Artery Disease; ABI = Ankle-Brachial Index; AD = Alzheimer's Disease

NHANES = Nutritional Health and Nutrition Examination Survey

Table 2: The association between low ABI and cognitive impairment.

Author	Cognitive assessment	Threshold	OR / HR (95% CI)	Adjusted for	Affected dimension
Cross-sectional analysis					
Breteler et al., 1994	MMSE	24 or 36	-	Age, sex, education	
Woo et al., 2006	MMSE	24	1.75 (1.33-2.30) 1.58 (1.19-2.09)	Age, sex All factors	
Price et al., 2006 §	Logical Memory Subtest (WMS)	*	-	-	Memory
	Raven's Progressive Matrices	*	1.2 (0.6-2.2) °	Age, sex	Praxia (non-verbal reasoning)
	Verbal Fluency Test	*	1.7 (1.0-3.1) °	Age, sex	Language
	DSS	*	3.1 (1.5-6.1) °	Age, sex	Praxia (executive function)
Vupputuri et al., 2008	DSS	32	-	-	Praxia (executive function)
Bruce et al., 2008	MMSE IQCODE	28 3.1	2.0 (1.1-3.7)		
Sugawara et al., 2010	MMSE	24	3.19 (1.30-7.82)	Age, sex, education, smoking status, alcohol intake, BMI, LDL-cholesterol, triglyceride,HbA1c, systolic blood pressure, pulse pressure	
Longitudinal analysis					
Bruce et al., 2008	MMSE IQCODE	28 3.1	2.2 (1.2-4.0)	-	

DSS = Digit Symbol Substitution Test; MMSE = Mini-Mental State Examination; NART = National Adult Reading Test; WMS = Weschler Memory Scale

§ (Price et al., 2006): only results for ABI<0,9 are presented

* = scores analysed as continuous variables

° = top tertiles compared to bottom tertiles

OR = Odds Ratio, 95% CI = 95% Confidence Interval

Table 3: The association between low ABI and dementia or Alzheimer's disease.

Author	Cognitive assessment	Diagnosis	Criteria	Mesure of Association (95% CI)	Adjusted for
Cross-sectional analysis					
Hofman et al., 2007	MMSE, GMS	Dementia	DSM-III-R	OR = 1.5 (1.1-2.0)	Age, sex
		AD	NINCDS-ADRDA	OR = 1.3 (0.9-1.8)	
		VaD	DSM-III-R	OR = 2.5 (1.3-4.8)	
Bruce et al., 2008	MMSE, IQCODE	Dementia	DSM-IV	OR = 4.5 (1.4-14.8)	
Longitudinal analysis					
Bruce et al., 2008	MMSE, IQCODE	Dementia	DSM-IV	HR = 5.3 (2.1-13.7)	
van Oijen et al., 2007	MMSE , GMS, CAMDEX	Dementia	DSM-III-R	HR = 1.2 (0.9-1.7)	Age, sex
		AD	NINCDS-ADRDA	HR = 1.3 (0.9-1.8)	
		VaD	NINDS-AIREN	HR = 0.7 (0.2-2.6)	
Laurin et al., 2007	CASI	Dementia	DSM-III-R	HR = 1.8 (1.3-2.5)	Age, education
		AD	NINCDS-ADRDA	HR = 1.6 (1.0-2.5)	
		VaD	CADDTC	HR = 2.8 (1.4-5.6)	
Newman et al., 2005	MMSE, DSS	Dementia	-	HR = 2.4 (1.4-4.0)	Age, ethnicity, education, income, ApoEε4 allele
		AD	NINCDS-ADRDA	HR = 2.2 (1.1-4.5)	

MMSE = Mini-Mental State Examination; GMS-A = Geriatric Mental State Examination; IQCODE = Informant Questionnaire for Cognitive Decline in the Elderly; CAMDEX = Cambridge Mental Disorders of the Elderly Examination; CASI = Cognitive Abilities Screening Instrument, DSS = Digit Symbol Substitution Test

AD = Alzheimer's disease; VaD = Vascular Dementia; CI= cognitive Impairment

DSM-III-R = Diagnostic and Statistical Manual 3rd Revision; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; CADDTC = California Alzheimer's Disease Diagnostic and Treatment Centers

OR = Odds Ratio, HR = Hazard Ratio, 95% CI = 95% Confidence Interval

Haan et al, 1999 and Johnson et al, 2010 did not measure the association with Hazard Ratio, full results are in the text.