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Featured Article

Interarm differences in systolic blood pressure and the risk of dementia and subclinical brain injury

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Abstract

Introduction: This study examined whether interarm differences in systolic blood pressure (IDSBP) ≥10 mm Hg were associated with the risk of incident dementia and subclinical brain injury.
Methods: Between 1992 and 1998, 2063 participants of the Framingham Heart Study underwent assessment of IDSBP with results related to the 10-year risk of incident dementia including clinically characterized Alzheimer's disease. Secondary outcomes included markers of subclinical brain injury on magnetic resonance imaging.
Results: High IDSBP were associated with a greater risk of incident dementia (hazard ratio [HR] 1.92; 95% confidence interval [CI], 1.09–3.40) and Alzheimer's disease (HR, 2.32; 95% CI, 1.29–4.18), but only in those who carried an apolipoprotein E (*APOE*) ε4 allele. IDSBP also predicted lower total brain volumes and more prevalent silent brain infarcts in those who were *APOE* ε4 positive.
Discussion: High IDSBP were associated with an increased risk of dementia, including clinical Alzheimer's disease, and subclinical brain injury in those who were *APOE* ε4 positive.

Keywords: Dementia; Alzheimer's disease; Blood pressure; Interarm differences in systolic blood pressure; Cerebrovascular disease; Atherosclerosis; Peripheral vascular disease; Ankle-brachial index; ABI; Magnetic resonance imaging; Framingham Heart Study

1. Introduction

Dementia is a devastating illness associated with the progressive deterioration of brain volume and cognitive ability, eventually leading to a complete loss of independence and mortality. Exposure to vascular risk factors increases to the risk of stroke, white matter lesions, silent brain infarcts, and cortical atrophy [1–5], thereby increasing the likelihood of dementia, including its most common form, Alzheimer's disease [6–8]. Although considerable interest surrounds the role of vascular risk in the development of cerebrovascular disease [7,9], numerous vascular risk factors are yet to be examined with respect to dementia or markers of brain aging on magnetic resonance imaging (MRI), such as brain volume and white matter integrity.

Approximately 20% of adults have a difference in systolic blood pressure (BP) between the arms of at least 10 mm Hg [10]; a sign of possible vascular pathology [11]. Large interarm differences in systolic blood pressure (IDSBP) may suggest peripheral vascular disease, including upper limb ischemia associated with atherosclerosis and subclavian artery stenosis [11]. IDSBP may, thus, be associated with poorer blood flow and perfusion to the upper extremities, including the brain [12]. In support of this assertion, IDSBP of ≥15 mm Hg are associated with preexisting cerebrovascular disease [11]. In patients with acute

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ischemic stroke, those with an IDSBP of ≥10 mm Hg have an increased risk of all-cause and cardiovascular mortality [13]. However, to our knowledge, the association of IDSBP with incident dementia has not been investigated prospectively. As IDSBP can be easily measured in primary care, it may be a useful tool to identify those at an increased risk of dementia.

Recently, the Framingham Heart Study showed that IDSBP ≥10 mm Hg were associated with an increased risk of cardiovascular events over 13.3 years of surveillance [14]. Given that cardiovascular disease is often associated with cerebrovascular disease and cerebrovascular disease is known to increase risk for dementia, the aim of this study was to determine the association between IDSBP and the risk of incident dementia and markers of brain injury on MRI among participants of the Framingham Heart Study. IDSBP were calculated at baseline and related to the 10-year risks of incident dementia and clinically apparent Alzheimer's disease. We also examined the association between IDSBP and total brain volume (TBV), white matter hyperintensity volume (WMHV), and silent cerebral infarcts; biological markers of subclinical brain vascular injury also associated with an increased risk of dementia [8].

2. Methods

2.1. Study population

The sample included participants of the Framingham Heart Study Original [15] and Offspring study [16] cohorts. The Original cohort was established in 1948, with follow-up examination cycles occurring approximately every 2 years. In 1971, offspring of the Original cohort and their spouses were invited to the study and the Offspring cohort was formed. Follow-up examinations have occurred approximately every 4–6 years for the Offspring cohort.

Participants included in this study had a valid IDSBP measurement, which was completed during examination 23 (1991–1994) for the Original cohort and examination 6 (1995–1998) for the Offspring cohort. IDSBP measurements were related to the 10-year risk of incident dementia and MRI outcomes measured at examination cycle 25 (1997–1999) for the Original Cohort and 7 (1998-2001) for the Offspring cohort, an average of 3.8 years after IDSBP were measured. The selection of study participants, including numbers available for analysis, can be seen in Fig. 1. For the sample with available MRI, we only included participants that were free from stroke and dementia at the time IDSBP were measured. For the sample that were followed for incident dementia, we only examined participants who were both aged ≥60 years and free from prevalent dementia at the time IDSBP were measured. The study was approved by the Institutional Review Board at Boston University Medical Center, and written informed consent was obtained from all participants.

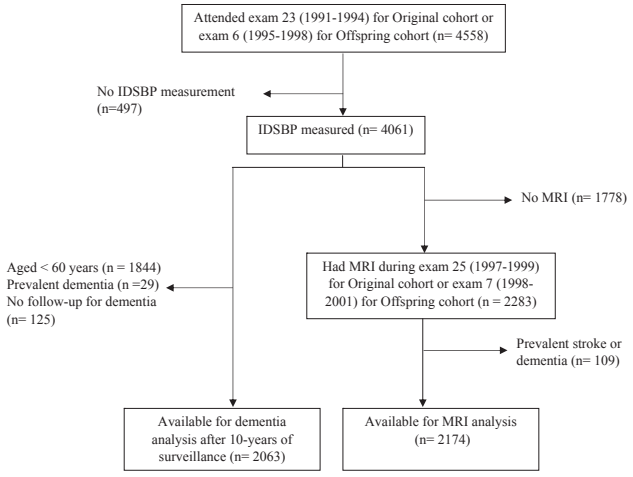

Fig. 1. Selection of study participants. MRI was performed an average of 3.8 years after IDSBP were measured. The risk of incident dementia was calculated as the 10-year risk, starting from the time of IDSBP measurement. Abbreviations: IDSBP, interarm differences in systolic blood pressure; MRI = magnetic resonance imaging.

2.2. Assessment of IDSBP and the ankle-brachial index

For the original purpose of calculating the ankle-brachial index (ABI), brachial systolic BPs were taken from each arm and ankle by trained technicians following a standardized protocol. Before BP measurements, participants lay supine for ≥5 minutes. The sequence of measurement was right arm, left arm, right ankle, and then left ankle. Participants were classified as having an IDSBP <10 mm Hg or ≥10 mm Hg, a categorization used in previous publications [14,17]. For the purpose of comparison, we also calculated the ABI, which is a marker of peripheral artery disease calculated as the ratio between the BP in ankle relative to the arm. The arm with the highest systolic BP was used to calculate the ABI separately for the left and right ankles. A low ABI was defined as <0.9 in either leg [18].

2.3. Assessment of incident dementia

We calculated the 10-year risk of incident dementia beginning from the time IDSBP measurements were assessed. Dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [19]. Alzheimer's disease was diagnosed based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for definite, probable, or possible Alzheimer's disease [20].

Participants underwent cognitive screening (using the mini-mental state examination [MMSE] [21]) at each examination cycle and comprehensive neuropsychological testing at selected examination cycles. To complement routine cognitive assessment, screening for dementia also occurred in response to referrals from the participant, their family, primary care provider, or other health care professionals.