RESEARCH ARTICLE

Blood Pressure, Antihypertensive Use, and Late-Life Alzheimer and Non-Alzheimer Dementia Risk

An Individual Participant Data Meta-Analysis

Matthew J. Lennon, MD, Darren M. Lipnicki, PhD, Ben Chun Pan Lam, PhD, John D. Crawford, BSc, MEngSc, PhD, Aletta E. Schutte, PhD, Ruth Peters, PhD, Therese Rydberg-Sterner, PhD, Jenna Najar, MD, PhD, Ingmar Skoog, MD, PhD, Steffi G. Riedel-Heller, MD, MPH, Susanne Röhr, PhD, Alexander Pabst, PhD, Antonio Lobo, MD, Concepción De-la-Cámara, MD, Elena Lobo, PhD, Richard B. Lipton, MD, Mindy J. Katz, MD, Carol A. Derby, PhD, Ki Woong Kim, MD, PhD, Ji Won Han, MD, PhD, Dae Jong Oh, MD, PhD, Elena Rolandi, MSc, Annalisa Davin, MSc, Michele Rossi, BS, Nikolaos Scarmeas, MD, MSc, PhD, Mary Yannakoulia, MSc, PhD, Themis Dardiotis, PhD, Hugh C. Hendrie, MBChB, DSc, Sujuan Gao, PhD, Isabelle Carriere, PhD, Karen Ritchie, PhD, Kaarin J. Anstey, Nicolas Cherbuin, PhD, Shifu Xiao, MD, PhD, Ling Yue, MD, Wei Li, MD, Maëlenn Guerchet, PhD, Pierre-Marie Preux, PhD, Victor Aboyans, MD, PhD, Mary N. Haan, DrPH, MPH, Allison Aiello, PhD, Marcia Scazufca, PhD, and Perminder S. Sachdev, MD, PhD, as the Cohort Studies of Memory in an International Consortium (COSMIC) Group

Correspondence
Dr. Lennon
matthew.lennon@unsw.edu.au

Neurology® 2024;103:e209715. doi:10.1212/WNL.0000000000209715

Abstract

Background and Objectives

Previous randomized controlled trials and longitudinal studies have indicated that ongoing antihypertensive use in late life reduces all-cause dementia risk, but the specific impact on Alzheimer dementia (AD) and non-AD risk remains unclear. This study investigates whether previous hypertension or antihypertensive use modifies AD or non-AD risk in late life and the ideal blood pressure (BP) for risk reduction in a diverse consortium of cohort studies.

Methods

This individual participant data meta-analysis included community-based longitudinal studies of aging from a preexisting consortium. The main outcomes were risk of developing AD and non-AD. The main exposures were hypertension history/antihypertensive use and baseline systolic BP/diastolic BP. Mixed-effects Cox proportional hazards models were used to assess

RELATED ARTICLE

Editorial
Hypertension, Antihypertensive Medications, and Dementia Risk in Old Age: A Complicated Relationship
Page e209788

MORE ONLINE

CME Course
NPub.org/cmelist

From the Faculty of Medicine and Health (M.J.L., D.M.L., B.C.P.L., J.D.C., P.S.S.), and Centre for Healthy Brain Aging (CHeBA) (M.J.L., D.M.L., B.C.P.L., J.D.C., P.S.S.), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, University of New South Wales, Sydney; School of Psychology and Public Health (B.C.P.L.), La Trobe University, Melbourne; The George Institute for Global Health (A.E.S., R.P.), Barangaroo; School of Biomedical Sciences (R.P.), University of New South Wales, Sydney, Australia; School of Public Health (R.P.), Imperial College London, United Kingdom; School of Population Health (A.E.S.), University of New South Wales, Sydney, Australia; Neuropsychiatric Epidemiology Unit (T.R.-S., J.N., I.S.), Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy, Centre for Ageing and Health (AGECAP) at the University of Gothenburg; Aging Research Center (T.R.-S.), Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University; Region Västra Götaland (J.N., I.S.), Sahlgrenska University Hospital, Psychiatry, Cognition and Old Age Psychiatry Clinic, Gothenburg, Sweden; Section Genomics of Neurodegenerative Diseases and Aging (J.N.), Department of Clinical Genetics, Vrije Universiteit Amsterdam, Amsterdam UMC, the Netherlands; Institute of Social Medicine (S.G.R.-H., S.R., A.P.), Occupational Health and Public Health (ISAP), Medical Faculty, University of Leipzig, Germany; School of Psychology (S.R.), Massey University, Albany Campus, Auckland, New Zealand; Global Brain Health Institute (GBHI) (S.R.), Trinity College Dublin, Ireland; Department of Medicine and Psychiatry (A.L., C.D.-l-C.), Universidad de Zaragoza; Instituto de Investigación Sanitaria Aragón (IIS Aragón) (A.L., C.D.-l-C., E.L.), Zaragoza; CIBERSAM (A.L., C.D.-l-C., E.L.), Madrid, Spain; Department of Preventive Medicine and Public Health (E.L.), Universidad de Zaragoza, Spain; Department of Neurology (R.B.L., M.J.K., C.A.D.), and Department of Epidemiology and Population Health (R.B.L., C.A.D.), Albert Einstein College of Medicine, Bronx, NY; Department of Neuropsychiatry (K.W.K., J.W.H.), Seoul National University Bundang Hospital, Seongnam; Department of Psychiatry (K.W.K., J.W.H.), Seoul National University College of Medicine; Department of Brain and Cognitive Sciences (K.W.K.), Seoul National University College of Natural Sciences; Workplace Mental Health Institute (D.J.O.), Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea; Golgi Cenci Foundation (E.R., A.D., M.R.), Abbiategrasso, Milan; Department of Brain and Behavioural Sciences (E.R.), University of Pavia, Italy; 1st Department of Neurology (N.S.), Aiginition Hospital, National and Kapodistrian University of Athens, Greece; Department of Neurology (N.S.), Columbia University, New York, NY; School of Health Sciences and Education (M.Y.), Department of Nutrition and Dietetics, Harokopio University; Department of Neurology (T.D.), University Hospital of Larissa; Faculty of Medicine (T.D.), School of Health Sciences, University of Thessaly, Larissa, Greece; Department of Psychiatry (H.C.H.), Indiana University School of Medicine; Indiana Alzheimer Disease Research Center (H.C.H., S.G.), Indiana Alzheimer Disease Research Center; Department of Biostatistics and Health Data Science (S.G.), Indiana University School of Medicine, Indianapolis; Institut for Neurosciences of Montpellier INM (I.C., K.R.), University Montpellier, INSERM; Institut du Cerveau Trocadéro (K.R.), Paris, France; School of Psychology (K.J.A.), and Ageing Futures Institute (K.J.A.), University of New South Wales; Neuroscience Research Australia (K.J.A.), Sydney; National Centre for Epidemiology and Population Health (N.C.), Australian National University, Canberra, Australia; Department of Geriatric Psychiatry (S.X., L.Y., W.L.), Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine; Alzheimer's Disease and Related Disorders Center (S.X., L.Y., W.L.), Shanghai Jiao Tong University, China; Inserm U1094 (M.G., P.-M.P., V.A.), IRD UMR270, Univ. Limoges, CHU Limoges, EpiMaCT-Epidemiology of Chronic Diseases in Tropical Zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth, France; Laboratory of Chronic and Neurological Diseases Epidemiology (LEMACEN) (M.G.), Faculty of Health Sciences, University of Abomey-Calavi, Cotonou, Benin; Department of Cardiology (V.A.), Dupuytren 2 University Hospital, Limoges, France; School of Medicine (M.N.H.), University of California, San Francisco; Robert N. Butler Columbia Aging Center (A.A.), Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; Departamento de Psiquiatria (M.S.), Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Brazil; and Neuropsychiatric Institute (P.S.S.), Prince of Wales Hospital, Sydney, Australia.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = Alzheimer dementia; **ADRDA** = Alzheimer's Disease and Related Disorders Association; **BMI** = body mass index; **BP** = blood pressure; **COSMIC** = Cohort Studies of Memory in an International Consortium; **DBP** = diastolic BP; ***DSM-III-R*** = *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; **HR** = hazard ratio; **HTN/AHT** = hypertension history and antihypertensive use; **IPD** = individual participant data; **MMSE** = Mini-Mental State Examination; **NINCDS** = National Institute of Neurological and Communicative Diseases; **RCT** = randomized controlled trial; **RR** = relative risk; **SBP** = systolic BP; **VaD** = vascular dementia.

risk and natural splines were applied to model the relationship between BP and the dementia outcomes. The main model controlled for age, age^2, sex, education, ethnoracial group, and study cohort. Supplementary analyses included a fully adjusted model, an analysis restricting to those with >5 years of follow-up and models that examined the moderating effect of age, sex, and ethnoracial group.

Results

There were 31,250 participants from 14 nations in the analysis (41% male) with a mean baseline age of 72 (SD 7.5, range 60–110) years. Participants with untreated hypertension had a 36% (hazard ratio [HR] 1.36, 95% CI 1.01–1.83, $p = 0.0406$) and 42% (HR 1.42, 95% CI 1.08–1.87, $p = 0.0135$) increased risk of AD compared with "healthy controls" and those with treated hypertension, respectively. Compared with "healthy controls" both those with treated (HR 1.29, 95% CI 1.03–1.60, $p = 0.0267$) and untreated hypertension (HR 1.69, 95% CI 1.19–2.40, $p = 0.0032$) had greater non-AD risk, but there was no difference between the treated and untreated groups. Baseline diastolic BP had a significant U-shaped relationship ($p = 0.0227$) with non-AD risk in an analysis restricted to those with 5-year follow-up, but otherwise there was no significant relationship between baseline BP and either AD or non-AD risk.

Discussion

Antihypertensive use was associated with decreased AD but not non-AD risk throughout late life. This suggests that treating hypertension throughout late life continues to be crucial in AD risk mitigation. A single measure of BP was not associated with AD risk, but DBP may have a U-shaped relationship with non-AD risk over longer periods in late life.

Introduction

Hypertension, a disorder that affects an estimated 1.3 billion persons worldwide,[1] is the leading cause of strokes and cerebrovascular disease.[2] There is good evidence that mid-life hypertension, but not late-life, increases the risk of vascular dementia (VaD).[3] For Alzheimer dementia (AD), 2 meta-analyses[4,5] found no association between late-life or mid-life hypertension and AD, whereas a third found that mid-life hypertension increased AD risk by 18%–25%.[6] More recently, Ou et al.,[7] in the largest meta-analysis to date, found that mid-life hypertension was associated with a 19% increased risk of late life AD, whereas late-life hypertension (>65 years) had no significant link to AD.

The consistent meta-analytic findings of no relationship between either categorical or linear late-life blood pressure (BP) and either AD or VaD may mask nonlinear effects of BP seen in late life. Van Dalen et al.[8] ran an individual participant data (IPD) meta-analysis (n = 17,286, mean age [SD] = 74.5 [7.3], age range = 55+) to assess the U-shaped relationship between systolic BP (SBP), diastolic BP (DBP), and dementia outcomes. They found that the low point of risk for dementia was approximately SBP 185 mm Hg and DBP 139 mm Hg, although this estimate was significantly lower at older ages. As well as changing effects with increasing age, studies have also indicated that the association between BP and AD may be modified by sex[9,10] and ethnicity.[11] A study of late-life (>65 years) US Medicare data[12] (n_{White} = 3,121,553, n_{Black} = 320,720) demonstrated that hypertension was linked to a higher risk of AD in Black populations compared with White.

Antihypertensives and AD Prevention

Antihypertensives have been associated with a 13% reduced risk of all-cause dementia in a meta-analysis of 7 randomized controlled trials (RCTs) of late-life participants.[13] However, few RCTs of antihypertensive use have examined AD specifically as an outcome, and the majority of the longitudinal studies focus on all-cause dementia. The Syst-Eur Study[14] (n = 2,902, mean follow-up = 3.9 years) found a 40% reduction in AD risk for an antihypertensive treatment group, in a population of those aged 60 years and older. By contrast, the HYVET-COG Study[15] (n = 3,336, mean follow-up = 2 years) in those aged 80 years and older found no effect of antihypertensive treatment on AD risk. Although RCTs are the gold standard when it comes to assessing the effectiveness of interventions, they often have key limitations of short follow-up periods, insufficient power to detect rare events, and highly curated participant populations from developed countries that limit generalizability.

A 2020 IPD meta-analysis[16] (n = 31,090, age >55 years) found that antihypertensive use reduced all-cause dementia and AD risk by 12% and 16%, respectively, in those with elevated baseline BP. More recently a case-control study of 215,547 Italian persons older than 65 years found that those with intermediate and high exposure to antihypertensives had an 18% and 29% reduction in AD risk, respectively.[17] Our group recently published an IPD meta-analysis of 17 studies from 15 countries from around the world (n = 34,519).[18] We found that individuals aged 60 years or older with untreated hypertension had a 42% increased risk of all-cause dementia compared with those without hypertension and a 26% increased risk compared with those with treated hypertension. In addition, there was no association between baseline BP and dementia risk and no significant interaction between baseline BP and antihypertensive use. AD has distinct familial, genetic, and environmental risk factors[19] compared with other dementias, as well as specific symptomatic and disease-modifying treatments.[20] As such, risk mitigation strategies for AD may need to be different to other dementias, and it is important that the particular effect of BP and antihypertensive use on AD risk, in addition to all-cause dementia, be understood. In this study, we use international data from 14 longitudinal cohorts including studies from the Republic of Congo, Brazil, China, and Nigeria. We use an IPD approach to investigate how antihypertensive medication use is associated with the risk of both AD and non-AD, and we explore ideal BP for dementia risk using a flexible, nonlinear model.

Methods

Contributing Studies

This analysis incorporated 14 community-based longitudinal studies of aging (n = 31,250) that were participants of the Cohort Studies of Memory in an International Consortium (COSMIC) group, a collaborative that has been described in previous studies.[18,21] The COSMIC consortium includes longitudinal studies that examine cognitive change and dementia diagnosis over time. To be included in this study, studies at a minimum had collected basic demographic, AD diagnosis, and BP/hypertension history data. Participants were from 14 countries (the United States, Brazil, Australia, China, Japan, Korea, Republic of Congo, Nigeria, Germany, Spain, Italy, France, Sweden and Greece). The follow-up durations varied between 2 and 15 years. Participants younger than 60 years were excluded for not being in "late life." Participants with a dementia diagnosis at baseline were excluded from the analyses. Demographic and follow-up information for the individual studies are shown in Table 1. This study is presented according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses-IPD guidelines (eTable 1).

Standard Protocol Approvals, Registrations, and Patient Consents

Approval was given by the University of New South Wales Human Research Ethics Committee (HC 12446 and HC 17292). Each participating study had their own participant consent and independent ethics approval from their regional ethics board (eTable 2).

BP Measures, History of Hypertension, Antihypertensive Medication Use, and Covariates

All studies included information on self-reported prior, physician diagnosis of hypertension, and the majority had data for antihypertensive use at baseline (12 studies). The studies had up to 3 measures of BP at baseline, taken while seated, and baseline BP was taken to be the average of the multiple measures. Information on BP measurement methods for the studies is provided in eTable 3. Individuals with BP ±3 SDs from the grand mean (across studies) were excluded as outliers (i.e., SBP <73.1 and >204.1 mm Hg, and DBP <45.1 and >114.4 mm Hg) (see eTable 4). The covariates used in the analyses were age, sex, years of education, ethnoracial group, body mass index (BMI), diabetes mellitus status, hypercholesterolemia, and smoking status (for details see eTables 5–7).

Dementia Outcomes

The 2 main outcome variables for this study were AD and non-AD dementia. These diagnoses were made within each study rather than centrally adjudicated. Three studies included in our previous paper did not have AD diagnosis data and were therefore excluded. Across cohorts, the diagnostic criteria used were *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) or *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM-III-R*) for all-cause dementia and National Institute of Neurological and Communicative Diseases (NINCDS)-Alzheimer's Disease and Related Disorders Association (ADRDA) for AD (eTable 8). Individuals diagnosed with all-cause dementia and not AD were defined as non-AD. A subset of those with non-AD were diagnosed with VaD, based on National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria, and sensitivity analyses were performed examining specific risk for this outcome. Dementia onset was assigned a date half-way between the assessment date when dementia was first diagnosed and the previous assessment date.

Categorization of Covariates

Education level was provided either as years of education or in a categorical form that was converted to number of years (eTable 6) and treated as a continuous variable. Ethnoracial group was treated as a 4-level categorical variable (0—White, 1—Asian, 2—Black, 3—others). Other covariates included BMI (continuous variable), diabetes mellitus status (categorical variable; 0—no diabetes, 1—diabetes), hypercholesterolemia (categorical variable; 0—no hypercholesterolemia, 1—hypercholesterolemia), and smoking status (categorical variable; 0—never smoker, 1—previous smoker, 2—current smoker).

Statistical Analysis

The statistical analyses were prespecified on Open Science Framework.[22] For the main analyses, a 1-step IPD approach was applied (i.e., models were run for all participants in a combined data set with a random-effect term for study). This

Table 1 Summary of Study and Total Participant Characteristics

Study	Study name (abbreviation)	Main ethnoracial groups	Age, y, mean (SD)	Sex, male, %	Education, y, mean (SD)	Maximum no. of waves	Maximum follow-up, y	Follow-up, y, mean (SD)	SBP, mm Hg, mean (SD)	DBP, mm Hg, mean (SD)	HTN/AHT status, n (%)[a]	AD, n (%)[a]	Time to AD diagnosis, y, mean (SD)	Non-AD, n (%)[a]	Time to non-AD diagnosis, y, mean (SD)
Xiao et al. (2016)[38]	Chinese Longitudinal Aging Study (CLAS)	Asian, Chinese	71.1 (7.8)	45.50	7.7 (5.3)	3	7.2	1.1 (1.6)	129.6 (15.2)	77.9 (8.7)	1: 1,049 (50.5) 2: 9 (0.4) 3: 913 (44) 4: 105 (5.1)	33 (1.6)	0.5 (0.1)	23 (1.1)	0.5 (0.1)
Guerchet et al. (2014)[39]	Epidemiology of dementia in Central Africa (EPIDEMCA)	Black, African	73.1 (6.6)	41.10	2 (3.7)	4	2.9	0.8 (1.1)	142.1 (26.7)	80.9 (13.4)	1: 0 (0) 2: 0 (0) 3: 33 (41.2) 4: 47 (58.8)	12 (3.7)	1.8 (0.7)	7 (2.2)	0.9 (0.6)
Dardiotis et al. (2014)[40]	The Hellenic Longitudinal Investigation of Aging and Diet (HELIAD)	White, Greek	72.8 (5.5)	40.10	8.1 (5)	2	7.3	1.7 (1.7)	131.7 (17.7)	77.4 (9.9)	1: 478 (25.9) 2: 165 (8.9) 3: 1,113 (60.3) 4: 89 (4.8)	53 (2.8)	1.6 (0.4)	9 (0.5)	1.5 (0.4)
Hendrie et al. (2001)[41]	Indianapolis-Ibadan Study (Ibadan)	Black, African	73.6 (5.9)	27.80	1.2 (3.2)	7	17.7	7.5 (5)	155.3 (32.7)	85.9 (16)	—	258 (15.6)	4.8 (3.3)	36 (2.2)	5.3 (3.7)
	Indianapolis-Ibadan Study (Indianapolis)	Black, African American	75.7 (6)	33.40	11 (3.1)	7	17.4	6.5 (4.6)	146.9 (22.2)	80.3 (11.8)	—	241 (16.6)	5 (3.7)	54 (3.7)	4.6 (3.5)
Katz et al. (2011)[42]	Einstein Aging Study (EAS)	White/Black, North American	78.1 (5.3)	38.20	13.2 (3.6)	16	19.6	2.8 (3.4)	134.1 (15.9)	77.4 (8.5)	1: 591 (29.7) 2: 207 (10.4) 3: 1,018 (51.2) 4: 172 (8.7)	98 (4.8)	3.8 (3.3)	55 (2.7)	3.8 (3.4)
Ritchie et al. (2010)[43]	Etude Santé Psychologique Prévalence Risques et Traitement (ESPRIT)	White, French	73.1 (5.5)	41.60	10.2 (3.8)	4	9	9.3 (5.6)	140.9 (17.4)	79.7 (9.9)	1: 1,191 (54.8) 2: 182 (8.4) 3: 765 (35.2) 4: 35 (1.6)	126 (5.8)	6.7 (4.5)	83 (3.8)	7.3 (4.4)
Rydberg Sterner et al. (2019)[44]	Gothenburg H70 Birth Cohort Studies (GothenburgH70)	White, Swedish	73.3 (4.9)	28.90	9.7 (3.7)	3	10.7	5.9 (4.1)	155.6 (21.8)	84.5 (11.3)	1: 453 (57.7) 2: 79 (10.1) 3: 229 (29.2) 4: 24 (3.1)	72 (9.2)	6.2 (2.9)	52 (6.6)	5.5 (2.7)
Guaita et al. (2013)[45]	Brain Ageing in Abbiategrasso (Invece.Ab)	White, Italian	72.2 (1.3)	46	6.8 (3.3)	2	3.3	3.4 (1.4)	141.7 (17.5)	78.9 (8.4)	1: 443 (34.9) 2: 63 (5) 3: 729 (57.4) 4: 34 (2.7)	22 (1.7)	2.3 (1.1)	37 (2.9)	2.5 (1)
Han et al. (2018)[46]	Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD)	Asian, Korean	69.9 (6.6)	43.60	8.2 (5.3)	4	7.1	4 (2.3)	126.2 (14.8)	77.9 (9.2)	1: 1,137 (29.5) 2: 161 (4.2) 3: 2,233 (58) 4: 320 (8.3)	175 (2.8)	2.7 (1.5)	51 (0.8)	2.3 (1.5)
Reidel-Heller et al. (2001)[47]	Leipzig Longitudinal Study of the Aged (LEILA)	White, German	81.5 (4.9)	25.90	11.9 (1.7)	7	16	4.8 (3.4)	158.6 (24.3)	86.1 (16.2)	—	135 (13.7)	3.4 (2.2)	94 (9.5)	4.2 (3.2)

Continued

Table 1 Summary of Study and Total Participant Characteristics *(continued)*

Study	Study name (abbreviation)	Main ethnoracial groups	Age, y, mean (SD)	Sex, male, %	Education, y, mean (SD)	Maximum no. of waves	Maximum follow-up, y	Follow-up, y, mean (SD)	SBP, mm Hg, mean (SD)	DBP, mm Hg, mean (SD)	HTN/AHT status, n (%)[a]	AD, n (%)[a]	Time to AD diagnosis, y, mean (SD)	Non-AD, n (%)[a]	Time to non-AD diagnosis, y, mean (SD)
Anstey et al. (2012)[48]	Personality and Total Health Through Life Study (PATH)	White, Australian	62.5 (1.5)	51.50	13.7 (2.8)	4	13.9	9.7 (4.5)	139.8 (19.5)	83 (10.7)	1: 1,455 (58.7) 2: 0 (0) 3: 820 (33.1) 4: 202 (8.2)	34 (1.3)	9.5 (1.8)	46 (1.8)	8.4 (3)
Haan et al. (2003)[49]	Sacramento Area Latino Study on Aging (SALSA)	Mixed, Mexican	70.4 (6.8)	41.60	7.3 (5.3)	7	9.4	5.5 (3.2)	138.5 (19.3)	75.9 (10.6)	1: 548 (32.3) 2: 0 (0) 3: 719 (42.4) 4: 429 (25.3)	69 (4.1)	3.9 (1.6)	47 (2.8)	1 (0)
Scazufca et al. (2008)[50]	São Paulo Ageing & Health Study (SPAH)	Mixed, Brazilian	72.1 (6.2)	39.20	2.5 (3)	2	4.1	1.8 (0.9)	146 (25.9)	85.9 (13.6)	1: 355 (19.9) 2: 0 (0) 3: 1,074 (60.2) 4: 356 (19.9)	0 (0)	0 (0)	37 (2.1)	2 (0)
Lobo et al. (2005)[51]	Zaragoza Dementia Depression Project (ZARADEMP)	White, Spanish	73.9 (9.3)	42.90	7.1 (3.8)	3	6.7	2.9 (2.1)	141.3 (18.7)	79.1 (11.2)	1: 122 (6.9) 2: 0 (0) 3: 1,397 (79.2) 4: 245 (13.9)	87 (2)	2.2 (1.2)	50 (1.1)	2.1 (1.2)
	Total		72.1 (7.5)	41	8.3 (5.3)			4.2 (3.9)	137.8 (21)	79.9 (11.2)	1: 7,822 (35.9) 2: 866 (4) 3: 11,043 (50.7) 4: 2,058 (9.4)	1,415 (4.5)	4.2 (3.3)	681 (2.2)	4.1 (3.6)

Abbreviations: AD = Alzheimer dementia; COSMIC = Cohort Studies of Memory in an International Consortium; DBP = diastolic blood pressure; HTN/AHT = hypertension history-antihypertensive use; SBP = systolic blood pressure.

Summary table of ethnoracial groups, demographics at baseline, and dementia rates of the 14 studies included in COSMIC after exclusions. The Indianapolis-Ibadan Study consisted of 2 separate cohorts (1 in Africa and 1 in the United States); hence, they are classified as separate studies.

[a] Classes for HTN/AHT status 1—no history of hypertension and not taking antihypertensives ("healthy controls"); 2—no history of hypertension but taking antihypertensives ("uncertain hypertension"); 3—history of hypertension and taking antihypertensives ("treated hypertension"); 4—history of hypertension and not taking antihypertensives ("untreated hypertension").

approach, rather than the traditional 2-step, random-effects meta-analysis, was used because our meta-analyses incorporated small studies with low event rates, where investigating interactions effects has limited power in 2-step approaches.[23] Hypertension history, as a dichotomous variable, was examined, but because its effect was significantly modified by treatment status (eTable 10), the main analysis focused on a categorical variable based on both hypertension history and antihypertensive use (HTN/AHT) status. This variable had 4 possible groups:

1. No hypertension history, no baseline antihypertensive use ("healthy control" participants)
2. No hypertension history, baseline antihypertensive use ("uncertain hypertension")
3. Hypertension history, baseline antihypertensive use ("treated hypertension")
4. Hypertension history, no baseline antihypertensive use ("untreated hypertension")

Individuals in the second group, with uncertain hypertension, were excluded from this part of the analysis (n = 866, 4% of participants). They were removed because they may have been taking an antihypertensive but not been aware or failed to recall that they had been diagnosed with hypertension previously or they may have been taking an antihypertensive for a reason other than hypertension (e.g., heart failure, palpitations, arrhythmias, kidney disease).

This classification was a critical constituent of the analysis and consequently a between-group comparison of characteristics was run, including covariates and baseline Mini-Mental State Examinations (MMSE) (eTable 9). We had BP measures from a single point in time (baseline) and thus did not consider BP in the classification of hypertension given that diagnosis of hypertension requires at least 2 BP measures taken at least 1 month apart.[24]

In assessing baseline BP, SBP and DBP, the measures were centered (SBP at 140 mm Hg and DBP at 80 mm Hg) and divided by 5 (i.e., measured in units of 5 mm Hg) to generate comparable effect sizes with other covariates. Previous publications[8,25] have indicated that BP has a U-shaped or parabolic association with AD. Thus, these putative nonlinear associations were assessed using natural splines terms for SBP and DBP, with 2–4 degrees of freedom according to best fit (using Akaike Information Criteria and Bayesian Information Criteria). Studies have similarly found that dementia risk increases quadratically rather than linearly with age.[26] Consequently, age was grand-mean centered (at 73 years) and linear and quadratic age terms (age and age^2) were incorporated into every analysis.

Mixed-effects Cox proportional hazards survival models were used to examine the association between the independent variables and progression to both AD and non-AD. Separate cause-specific hazards models were used rather than Fine-Gray models as for the purposes of this study, the outcomes were mutually exclusive.[27] The first analysis assessed the risk of AD and non-AD associated with HTN/AHT status. The second examined the associations of baseline SBP/DBP to AD and non-AD, utilizing the aforementioned natural splines to model the association. Models comprised both continuous BP parameters and HTN/AHT status were attempted but were excluded because of poor model fit, number of excluded participants, and a lack of interaction significance.

The main, partially adjusted analysis incorporated covariates of age, age^2, sex, education, ethnoracial group, and a random intercept term for study. This parsimonious model was used as the main one to minimize participant exclusion, particularly from lower socioeconomic regions, where studies frequently lacked covariates used in the fully adjusted model. Additional analyses were performed to test the robustness of results as follows: First, a fully adjusted analysis was performed, controlling for additional covariates of hypercholesterolemia, BMI, smoking status, and diabetes mellitus. Second, a restricted analysis, excluding those with less than 5-year follow-up was run. This approach was needed as dementia progressively develops over years and thus occurrence of dementia within several years of baseline is probably caused by factors substantially before study baseline. Third, to assess contributions of individual studies, the main model was run within each study, and the results were examined for outliers and heterogeneity. Fourth, to assess the putative moderating effects of age, sex and ethnoracial group, interactions between the main predictors (HTN/AHT status and baseline BP) with these variables were included in separate models. These models assessing the interaction effects were adjusted for age, age^2, sex, education, ethnoracial group, and a random intercept term for study. Fifth, to assess the impact of effectiveness of BP control in those with treatment, the main analyses were re-run with the treated hypertension group divided into those with BP <140/90 mm Hg (controlled) and those with BP either >140 mm Hg SBP or >90 mm Hg DBP (uncontrolled). Finally, to assess the contributions of VaD to the non-AD results, the partially adjusted model, fully adjusted model, and >5-year model were repeated with VaD as the main outcome.

The Sydney COSMIC team harmonized the data across studies and performed the mixed-effects Cox regressions using the coxme and splines packages in R 4.3.1. A significance threshold of $p < 0.05$ was used.

Data Availability

Researchers can apply to use COSMIC data by completing a COSMIC Research Proposal Form available from cheba.unsw.edu.au/consortia/cosmic/research-proposals.

Results

Participant Characteristics

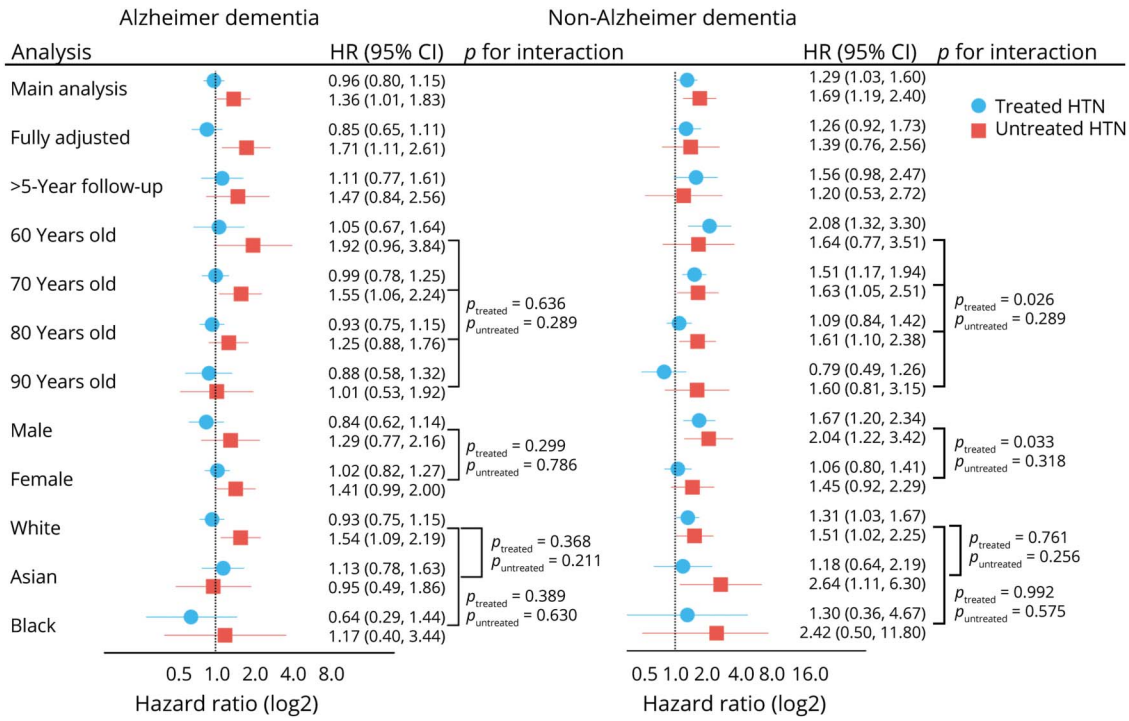
There were 56,821 total participants in the studies, 2,884 (5.1%) were excluded for dementia at baseline and 31,250

dementia-free participants (55%) had sufficient data to be included in the analysis. The mean baseline age was 72.1 (SD = 7.5) years, and 41% were male (Table 1). The mean follow-up was 4.2 years (SD = 3.9), and the mean years of education was 8.3 years (SD = 5.3). The mean baseline SBP and DBP were 137.8 (SD = 21) mm Hg and 79.9 (SD = 11.2) mm Hg, respectively. Of the hypertensive/antihypertensive groups, 35.9% were "healthy controls," 4% were excluded as "uncertain hypertension," 50.7% were treated hypertension, and 9.4% were untreated hypertension. Those with untreated hypertension (compared with healthy controls) were significantly more likely have fewer years of education, be current smokers, less likely to be Asian, and have poorer baseline MMSE scores (eTable 9). The mean time to AD and non-AD diagnosis was 4.2 (SD = 3.3) and 4.1 years (SD = 3.6), respectively, although these measures varied significantly by study (Table 1). Of the 12 studies that included VaD diagnosis data, 35.6% of dementia cases were non-AD, and among them 45.2% were VaD (16.1% of all cases).

History of Hypertension and Antihypertensive Use

In the main analysis, participants with untreated hypertension had significantly higher risk of AD (HR 1.363, 95% CI 1.013–1.832, $p = 0.0406$) compared with "healthy controls" (Figure 1 and Table 2), whereas those with treated hypertension had no elevated AD risk. However, considering the non-AD outcome, those with either treated hypertension (HR 1.285, 95% CI 1.029–1.604, $p = 0.0267$) or untreated hypertension (HR 1.693, 95% CI 1.193–2.403, $p = 0.0032$) had significantly greater non-AD risk than "healthy controls." The untreated hypertension group had significantly higher risk of AD (HR 1.418, 95% CI 1.075–1.872, $p = 0.0135$) than the treated hypertension group, but the risk of non-AD did not differ significantly. In the supplementary analysis (eTable 10), hypertension history, without stratifying for treatment status, was associated with greater risk of non-AD (HR 1.366, 95% CI 1.154–1.616, $p = 0.0003$) but was not associated with AD risk. In the fully adjusted analysis, controlling for other vascular covariates ($N_{studies} = 7$), the associations with AD remained significant but associations with non-AD did not. In the analysis restricted to those with >5 years of follow-up ($N_{studies} = 9$), none of the associations remained significant. In the 2-step random-effects meta-analysis, comparisons between treated and untreated hypertension groups for AD and non-AD risk showed low heterogeneity ($I^2 = 0\%$ and 7.7%). By contrast, heterogeneity was substantially higher when comparing those with untreated

Figure 1 Association of HTN/AHT Status With AD and Non-AD Risk



The association of HTN/AHT status with the risk of AD and non-AD dementia (x-axis in log2 scale). The main analysis (partially adjusted) included covariates of age, age^2, sex, education, ethnoracial group, and a random effect for study. The fully adjusted analysis included additional covariates of BMI, smoking status, history of hypercholesterolemia, and diabetes mellitus. Each of the other analyses applied the partially adjusted model. The *p*-values show the size of the interaction effect for age, sex, and ethnoracial group with treated hypertension (compared with "healthy controls") and untreated hypertension (compared with "healthy controls"). Age was treated as a continuous variable, sex as a categorical variable, and ethnoracial group as a categorical variable with 3 major groups (White, Asian, and Black). The numbers and brackets on the right are the hazard ratios and 95% confidence intervals. The *p*-values show the significance of the interaction term. The interaction *p*-values used White participants as the main comparison group in the ethnoracial analysis (as this was the largest group included). AD = Alzheimer dementia; BMI = body mass index; HTN/AHT = hypertension history-antihypertensive use.

Table 2 Summary of Cox Proportional Hazards Mixed-Effects Models Examining Relationship Between HTN/AHT Status, Baseline BP, and Both AD and Non-AD Risk

HTN/AHT status and dementia risk						
	Main analysis (n = 19,251, n [event] = 615)		Fully adjusted analysis (n = 7,610, n [event] = 295)		Restricting to >5 y follow-up (n = 4,707, n [event] = 151)	
AD	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
Treated hypertension (comp "healthy controls")	0.961 (0.801–1.152)	0.6644	0.853 (0.653–1.113)	0.2411	1.115 (0.771–1.612)	0.5618
Untreated hypertension (comp "healthy controls")	1.363 (1.013–1.832)	0.0406	1.705 (1.114–2.609)	0.014	1.467 (0.841–2.56)	0.1768
Untreated hypertension (comp treated hypertension)	1.418 (1.075–1.872)	0.0135	1.999 (1.318–3.032)	0.0011	1.316 (0.779–2.223)	0.3051
Non-AD	**Main analysis (n = 18,975, n [event] = 414)**		**Fully adjusted analysis (n = 7,645, n [event] = 200)**		**Restricting to >5 y follow-up (n = 4,704, n [event] = 89)**	
Treated hypertension (comp "healthy controls")	1.285 (1.029–1.604)	0.0267	1.256 (0.915–1.724)	0.158	1.561 (0.984–2.477)	0.0588
Untreated hypertension (comp "healthy controls")	1.693 (1.193–2.403)	0.0032	1.389 (0.755–2.558)	0.2909	1.202 (0.53–2.724)	0.6594
Untreated hypertension (comp treated hypertension)	1.318 (0.953–1.822)	0.0949	1.106 (0.608–2.013)	0.741	0.77 (0.347–1.706)	0.5197

Baseline BP and dementia risk			
AD	**Main analysis (n = 25,457, n [event] = 905)**	**Fully adjusted (n = 9,251, n [event] = 333)**	**Restricting to >5 y follow-up (n = 7,182, n [event] = 294)**
SBP, mm Hg	0.4234	0.8655	0.7029
100	1.007 (0.752–1.35)	1.09 (0.697–1.704)	0.997 (0.703–1.416)
120	1.073 (0.947–1.214)	0.981 (0.854–1.127)	0.981 (0.904–1.064)
140	0.986 (0.924–1.052)	1.023 (0.943–1.111)	1.047 (0.976–1.124)
160	0.912 (0.777–1.07)	1.012 (0.809–1.265)	1.021 (0.899–1.16)
180	0.921 (0.81–1.048)	0.863 (0.627–1.189)	0.862 (0.722–1.029)
DBP, mm Hg	0.2217	0.9985	0.8592
60	1.001 (0.809–1.239)	0.979 (0.688–1.394)	1.098 (0.799–1.51)
70	1.095 (1–1.2)	0.989 (0.879–1.113)	1.004 (0.901–1.12)
80	0.99 (0.956–1.024)	1.005 (0.931–1.084)	1.007 (0.967–1.049)
90	0.907 (0.823–0.999)	1.012 (0.884–1.159)	1.003 (0.888–1.133)
100	0.975 (0.819–1.16)	1.003 (0.549–1.831)	0.906 (0.635–1.291)
Non-AD	**Main analysis (n = 25,531, n [event] = 531)**	**Fully adjusted (n = 9,310, n [event] = 272)**	**Restricting to >5 y follow-up (n = 7,181, n [event] = 143)**
SBP, mm Hg	0.3136	0.6522	0.3293
100	1.114 (0.798–1.555)	1.232 (0.772–1.968)	1.079 (0.488–2.384)
120	0.908 (0.838–0.985)	0.994 (0.878–1.125)	0.899 (0.783–1.033)
140	1.004 (0.941–1.072)	0.949 (0.861–1.046)	0.989 (0.83–1.18)
160	1.137 (1.024–1.262)	1.024 (0.847–1.239)	1.176 (0.96–1.441)
180	1.12 (0.969–1.295)	1.172 (0.952–1.442)	1.344 (1.149–1.572)
DBP, mm Hg	0.1922	0.4589	0.0227
60	1.045 (0.789–1.385)	1.044 (0.686–1.588)	1.813 (1.159–2.838)
70	0.965 (0.866–1.076)	0.969 (0.833–1.128)	0.98 (0.826–1.162)
80	0.954 (0.89–1.022)	0.954 (0.855–1.063)	0.86 (0.75–0.985)

Continued

Table 2 Summary of Cox Proportional Hazards Mixed-Effects Models Examining Relationship Between HTN/AHT Status, Baseline BP, and Both AD and Non-AD Risk *(continued)*

Non-AD	Main analysis (n = 25,531, n [event] = 531)	Fully adjusted (n = 9,310, n [event] = 272)	Restricting to >5 y follow-up (n = 7,181, n [event] = 143)
90	1.038 (0.923–1.166)	1.049 (0.893–1.232)	1.045 (0.863–1.266)
100	1.229 (0.968–1.561)	1.295 (0.962–1.743)	1.348 (1.01–1.8)

Abbreviations: AD = Alzheimer dementia; BP = blood pressure; DBP = diastolic BP; HR = hazard ratio; HTN/AHT = hypertension history-antihypertensive use; SBP = systolic BP.
Summary of Cox proportional hazards mixed-effects models examining relationship between HTN/AHT status, baseline BP, and both AD and non-AD risk. n indicates the total number of participants included in each analysis. n (event) indicates the total number of incident dementia cases. The models were all adjusted for age, age^2, sex, education, and ethnoracial group and a random-effect term for study. There were 12 studies included in the main analysis for HTN/AHT status (CLAS, EAS, EPIDEMCA, ESPRIT, H70, HELIAD, Invece.Ab, KLOSCAD, PATH, SALSA, SPAH, and ZARADEMP). There were 7 studies included in the fully adjusted analysis for HTN/AHT status (EAS, EPIDEMCA, ESPRIT, Invece.Ab, KLOSCAD, PATH, and SALSA). The fully adjusted analysis included additional covariates of BMI, smoking status, history of hypercholesterolemia and diabetes mellitus. There were 9 studies included in the restricted >5 year follow-up analysis for HTN/AHT status (CLAS, EAS, ESPRIT, H70, HELIAD, KLOSCAD, PATH, SALSA, and ZARADEMP). For the main analysis of the measures of baseline BP, there were 14 studies included (CLAS, EAS, EPIDEMCA, ESPRIT, H70, HELIAD, Indianapolis-Ibadan, Invece.Ab, KLOSCAD, LEILA, PATH, SALSA, SPAH, and ZARADEMP). There were 7 studies included in the fully adjusted model for baseline BP (EAS, EPIDEMCA, ESPRIT, Invece.Ab, KLOSCAD, PATH, and SALSA). There were 11 studies included in the >5 year follow-up analysis for baseline BP (CLAS, EAS, ESPRIT, H70, HELIAD, Indianapolis-Ibadan, KLOSCAD, LEILA, PATH, SALSA, and ZARADEMP). *p* Values for the baseline BP natural splines were computed by comparing the model fit of the model with and without the natural splines terms.

hypertension and "healthy controls" (I^2 = 32.4% and 63.5%) or those with treated hypertension and "healthy controls" (I^2 = 11.9% and 78.3%) (eTable 11). The results for the VaD analysis were largely similar to that of non-AD with 3 key differences. First, in the main, partially adjusted analysis those with treated hypertension had no elevated risk of VaD compared with "healthy controls." Second, those with untreated hypertension had significantly greater risk of VaD compared with those with treated hypertension (HR 1.714, 95% CI 1.034–2.841, p = 0.0366). Third, when restricting to those with more than 5-year follow-up baseline SBP was associated with a positive, approximately linear association with VaD risk (p = 0.0092) (eTable 12 and eFigure 1).

Interaction analyses revealed that the difference in non-AD risk between the treated hypertension group and "healthy controls" significantly diminished with increasing age (p = 0.026) (eTable 13 and Figure 1). Furthermore, the difference in risk between those with treated hypertension and "healthy controls" was significant in men but not in women (p = 0.0327). There were no significant moderating factors for the AD analysis. No moderating effect of race was observed for either AD or non-AD risk.

Baseline BP

In the main, partially adjusted analysis there was no significant linear or nonlinear association between baseline SBP or DBP and either AD or non-AD risk (Table 2 and Figure 2, A and B). This finding was supported by the null associations seen in the fully adjusted analysis. However, in the analysis restricted to those with >5 years of follow-up, there was a significant U-shaped association between baseline DBP and non-AD risk (p = 0.0227) (Table 2 and Figure 3, A and B). Heterogeneity of the estimates across studies ranged from very small to moderate (I^2 = 0.1%–58.7%) (eTable 10).

The associations between DBP and AD risk as well as SBP and non-AD risk were significantly moderated by age (p = 0.0132 and 0.0313, respectively) (Figure 4 and eTable 1). Figure 4A suggests that the association between DBP and AD risk inverts with increasing age, with low DBP associated with increased AD risk at 60 and decreased risk by 90. Figure 4B indicates that while the association between SBP and non-AD risk at 60 years of age is U-shaped, it flattens with age. However, in both analyses the main effects were nonsignificant irrespective of the point at which age was centered (i.e., assessing the effect at 60, 70, 80, or 90), indicating that the interaction may not be meaningful. There were no other significant interactions between age, sex, or ethnoracial group for the SBP or DBP natural splines terms (eTable 14).

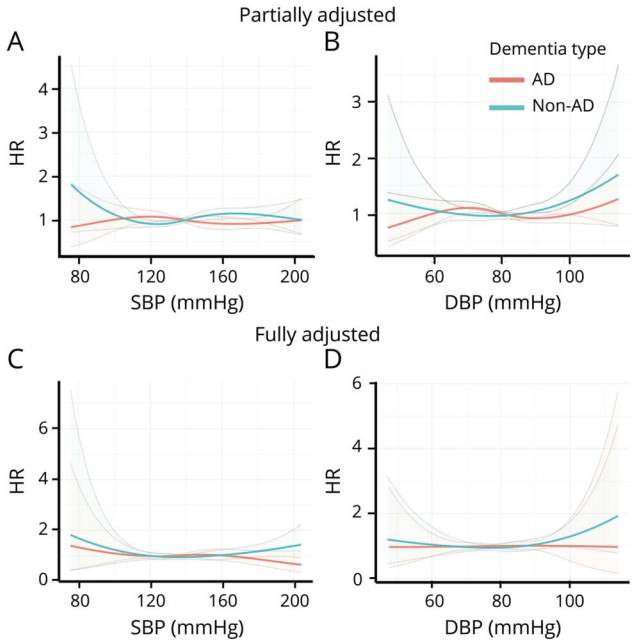
Interaction Between Baseline BP and HTN/AHT Status

There were no significant interactions between either SBP or DBP and the HTN/AHT status of participants for either AD or non-AD (eTable 15). However, when baseline BP was considered as a binary variable (controlled <140/90 mm Hg or uncontrolled >140 mm Hg SBP or >90 mm Hg DBP), those who had treated hypertension that was uncontrolled had substantially elevated risk of non-AD (HR 1.331, 95% CI 1.04–1.704, p = 0.0233), whereas those with treated, controlled hypertension had no increased risk (eTable 16). This result was consistent in those participants restricted to 5-year follow-up but was no longer significant in the fully adjusted analysis. There was no difference in AD risk between those with controlled or uncontrolled treated hypertension.

Discussion

In this study, there were a number of key insights into the association of late-life hypertension and AD risk. We found that those with untreated hypertension had significantly higher risk of AD than "healthy controls" (main model: +36%, fully adjusted: +70%) and those with treated hypertension

Figure 2 Association Between Continuous SBP/DBP and Both AD and Non-AD Risk Using Nonlinear Natural Splines



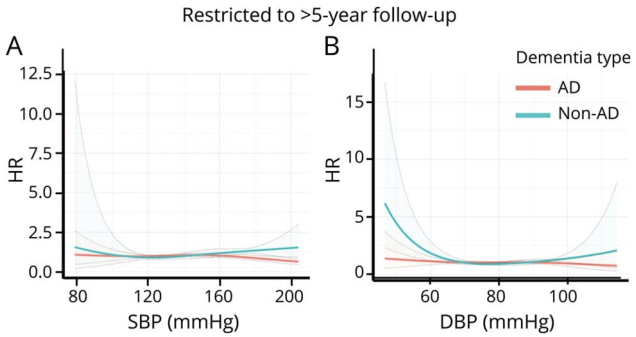
The relationship between SBP, DBP, and AD/non-AD risk with 95% CIs (shaded areas). In all models, SBP and DBP was grand-mean centered (at 140 mm Hg and 80 mm Hg, respectively) and all HRs represent within-group risk relative to this grand-mean. A restricted cubic splines model was applied. (A and B) The main analysis (partially adjusted) which included the covariates of age, age^2, sex, education, ethnoracial group and a random effect for study. (C and D) The fully adjusted analysis which included additional covariates of BMI, smoking status, history of hypercholesterolemia, and diabetes mellitus. AD = Alzheimer dementia; BMI = body mass index; DBP = diastolic blood pressure; HR = hazard ratio; SBP = systolic blood pressure.

(main model: +42%, fully adjusted: +100%). Within those with treated hypertension, there was no difference in AD risk between those with and without effective BP control at baseline. This estimate is similar to the 40% greater risk of AD in those with untreated vs treated hypertension found in the Syst-Eur Clinical Trial.[14] However, it differs considerably from the 6% estimate from a 2022 meta-analysis[28] of 3 observational studies. The studies in that meta-analysis used insurance data and included participants from both mid-life and late-life, whereas this meta-analysis used data for individuals age 60 years or older from longitudinal studies of aging. The incidence of dementia is low before late life and thus including participants younger than 60 years may underestimate the risk of dementia.

In this study, diagnosed hypertension, both treated and untreated, was associated with considerably greater risk of non-AD in late life compared with "healthy controls" in the partially but not fully adjusted analysis. There was no difference in overall non-AD risk between the treated and untreated hypertension groups. However, untreated hypertension was associated with a higher risk of VaD. The non-AD and VaD results should be considered with caution because the results of the partially adjusted analysis were not replicated in the fully adjusted analysis or when restricted to more than 5 years of follow-up, indicating that the differences may be better explained by vascular covariates. Nevertheless, our VaD finding is corroborated by the Ou et al. meta-analysis that found a similar association between VaD and hypertension (relative risk [RR] 2.12, 95% CI 1.50–2.99). The results for VaD are also consistent with the few published clinical trials that have found that the risk of poststroke dementia, a subtype of VaD, is significantly modified by antihypertensive use, reducing the risk by up to 34%.[29] A challenge to interpreting the differing results of AD, non-AD, and VaD is that the delineation of AD from VaD is somewhat arbitrary, and postmortem studies indicate that coexistence of Alzheimer and vascular pathology is the norm (up to 80% of AD cases).[30]

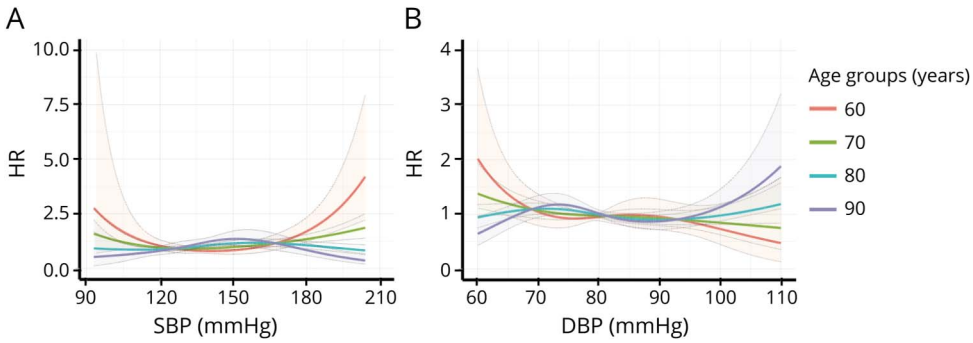
The subgroup analyses found that men with treated hypertension were at greater risk of non-AD than women (HR_{male} 1.67, HR_{female} 1.06, $p_{interaction}$ = 0.033). This finding is consistent with previous research indicating that men are more susceptible to poststroke dementia than women (RR_{male} 2.7 vs RR_{female} 1.7).[31] In addition, we found that the increased non-AD risk associated with treated hypertension diminished with advancing age, whereas untreated hypertension was associated with elevated non-AD risk throughout late life.[32] Regarding ethnoracial groups, this study, like others,[33] found that there were higher rates of hypertension among Black individuals. However, the associations of treated and untreated hypertension with AD and non-AD were not significantly different between ethnoracial groups, suggesting that antihypertensives are likely to be similarly effective in dementia prevention in different ethnoracial groups.

Figure 3 Association Between Continuous SBP/DBP and Both AD and Non-AD Risk Restricted to Participants With Over 5-Year Follow-Up



The relationship between SBP, DBP, and AD/non-AD risk with 95% CIs (shaded areas) in participants with over 5 years of follow-up. In all models SBP and DBP was grand-mean centered (at 140 mm Hg and 80 mm Hg, respectively), and all HRs represent within-group risk relative to this grand-mean. A restricted cubic splines model was applied. (A and B) SBP and DBP, respectively, are shown. AD = Alzheimer dementia; BMI = body mass index; DBP = diastolic blood pressure; HR = hazard ratio; SBP = systolic blood pressure.

Figure 4 Moderating Effect of Age on the Association Between Continuous SBP/DBP and Both AD and Non-AD Risk



The relationship between SBP, DBP, and AD/non-AD risk with 95% CIs (shaded areas) showing the changing relationship with increasing age. In all models SBP and DBP was grand-mean centered (at 140 mm Hg and 80 mm Hg, respectively), and all HRs represent within-group risk relative to this grand-mean. These models were partially adjusted and included covariates of age, age^2, sex, education, ethnoracial group, and a random effect for study. A restricted cubic splines model was applied. (A) The significant moderating effect of age on the relationship between baseline SBP and non-AD risk. (B) The significant moderating effect of age on the relationship between baseline DBP and AD risk. AD = Alzheimer dementia; BMI = body mass index; DBP = diastolic blood pressure; HR = hazard ratio; SBP = systolic blood pressure.

There were no significant associations between baseline SBP or DBP in late life with AD or non-AD. This is broadly in keeping with numerous previous analyses[4,5,7] showing no association between late-life BP and all-cause dementia or AD. However, when restricting analyses to more than 5 years of follow-up, there was a significant positive and approximately linear association between SBP and VaD and nonlinear associations between DBP and both non-AD and VaD risk. For non-AD, low DBP conferred greater risk than high DBP with lowest risk at around 80 mm Hg. For VaD, high DBP conferred greater risk than low DBP and lowest risk was at around 67 mm Hg. Two meta-analyses[7,34] have previously reported low DBP in late life as a risk factor of all-cause dementia. Furthermore, a meta-analysis by Van Dalen et al.[8] found a U-shaped association between DBP and all-cause dementia, with lowest risk around DBP 139 mm Hg. The Chicago Health and Ageing Project (n = 2,137) also found a U-shaped association, but the lowest risk for dementia was suggested to be a SBP of 138 mm Hg and a DBP of 77 mm Hg.[25] The fact that this finding was only significant in those with more than 5 years of follow-up is consistent with the years elapsed over which BP causes vascular disease, cognitive impairment, and eventual dementia. However, given that other vascular risk factors were not controlled for this result should be interpreted with caution. Animal studies have shown that low DBP, partially caused by vascular disease and diminished vascular elasticity, contributes to poorer cerebral perfusion pressures, likely ischemia and neurodegeneration.[35] In the future, trials for specific treatments of diastolic hypotension will help to clarify this association in humans and provide insight into best practice management of this condition.

We found that baseline BP (SBP and DBP) did not moderate the association between hypertension/antihypertensive use status for AD risk. This finding is consistent with our previous study[18] and with the Peters et al.[13] meta-analysis of clinical trials, both finding the treatment effect is not modified by baseline BP. This finding indicates that a single measure of baseline BP, being a cross-sectional snapshot of a highly variable[36] biomarker, is of limited practical use when deciding to continue antihypertensive treatment for AD risk reduction. However, those with treated hypertension who had poorly controlled BP had significantly higher non-AD risk than those with well-controlled BP. This result should be interpreted with caution as when we controlled for other vascular risk factors in the fully adjusted model the association was no longer significant indicating that the relationship is potentially confounded.

All included studies used *DSM-IV* or *DSM-III-R* criteria with 3 studies additionally using NINCDS-ADRDA criteria. Even when using the NINCDS criteria, validation studies[37] found only a sensitivity of 81% and specificity of 71% in diagnosing "probable" and it cannot discriminate accurately between AD and VaD. Longitudinal studies initiated in more recent times more frequently include biomarkers of AD, which the cohort studies within our consortium lacked. The variability in dementia diagnostic criteria is part of the larger limitation of cohort study variability. Hypertension definitions varied by location leading to possible discrepancies in diagnosis. Many of the studies report dementia onset shortly after study baseline, and given its long prodromal phase, this indicates there may have been substantial baseline cognitive impairment. Most of the studies also did not report mortality data and thus our analysis did not account for the competing risks of dementia and death. Many of the participants with baseline hypertension probably had this condition since mid-life, and the results are thus not likely reflective of late-life onset hypertension. Owing to study heterogeneity, multiple waves of BP measures were not able to be used and given the

considerable variability in BP, the single baseline measure may not accurately capture those with consistently high or low BP. There are likely to be nonrandom differences between those who do and do not take antihypertensives that we could not control for, including socioeconomic status, health literacy, access to medications, poorly managed comorbidities, and depression and other mental illnesses that may confound the association between hypertension status and dementia risk. Stroke/TIA and heart disease were other potential confounders that were not controlled for because they may act as mediators rather than covariates and including them would have excluded many participants from developing countries missing those data. Similarly, the partially adjusted model was used as the main model to limit exclusion of participants, but these results may be confounded and should be interpreted with caution. Finally, some studies have indicated that certain classes of antihypertensives[28] may be more effective at reducing AD risk than others and this study lacked data on antihypertensive classes to investigate this putative moderating effect.

To conclude, this IPD meta-analysis, with data from 14 nations, including studies from developing countries, illustrates that throughout late life those with treated hypertension had a lower risk of AD compared with those with untreated hypertension, suggesting that antihypertensive use should be part of any AD prevention strategy even in late life. By contrast, both treated and untreated hypertension were associated with elevated non-AD risk, and there were no significant differences in risk between the 2 groups, although the elevated risk of non-AD in the treated group was largely attributable to those with poorly controlled BP. This study suggests that a single measure of SBP or DBP does not predict AD risk, and it is likely that more than 1 measure is required to guide treatment. DBP may have a U-shaped relationship with non-AD risk over longer time periods.

Acknowledgment

The head of the Cohort Studies of Memory in an International Consortium (COSMIC) Group is Perminder S. Sachdev, and the study coordinator is Darren M. Lipnicki. The research scientific committee leads the scientific agenda of COSMIC and provides ongoing support and governance; it comprises member study leaders. The COSMIC research scientific committee and additional principal investigators include Juan J. Llibre-Rodriguez (Research Scientific Committee [RSC] member; 10/66 Cuba [Cuban Health and Alzheimer Study]), Daisy Acosta (RSC member; 10/66 Dominican Republic), Ana Luisa Sosa (RSC member; 10/66 Mexico), Mariella Guerra Arteaga (RSC member; 10/66 Peru), Ivonne Z. Jimenez-Velazquez (RSC member; 10/66 Puerto Rico), Aquiles Salas (RSC member; 10/66 Venezuela), Yuda Turana (RSC member; Atma Jaya Cognitive & Aging Research [ACtive Aging Research]), Oscar H. Del Brutto (RSC member; The Atahualpa Project), Erico Costa (RSC member; Bambui Cohort Study of Aging), Sabrina Noel (RSC member; Boston Puerto Rican Health Study), Bagher Larijani (RSC member; Bushehr Elderly Health [BEH] Program), Iraj Nabipour (additional study leader; Bushehr Elderly Health [BEH] Program), Kenneth Rockwood (RSC member; Canadian Study of Health & Aging [CSHA]), Xiao Shifu (RSC member; Chinese Longitudinal Aging Study [CLAS]), Carol Brayne (RSC member; Cognitive Function and Ageing Studies [CFAS]), Richard Lipton (RSC member and NIH Grant Investigator; Einstein Aging Study [EAS] and the Albert Einstein College of Medicine), Mindy J. Katz (additional study leader and NIH Grant Investigator; Einstein Aging Study [EAS] and The Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, New York, NY), Maëlenn Guerchet (RSC member and NIH Grant Investigator; Epidemiology of Dementia in Central Africa [EPIDEMCA]), Pierre-Marie Preux (additional study leader; Epidemiology of Dementia in Central Africa [EPIDEMCA]), Eleonora d'Orsi (RSC member; EpiFloripa Aging Study), Karen Ritchie (RSC member; Etude Santé Psychologique Prévalence Risques et Traitement [ESPRIT]), Marie-Laure Ancelin (additional study leader; Etude Santé Psychologique Prévalence Risques et Traitement [ESPRIT]), Maria Skaalum Petersen (RSC member; Faroese Septuagenarian Cohort), Rhoda Au (RSC member; Framingham Heart Study [FHS]), Ingmar Skoog (RSC member; Gothenburg H70 Birth Cohort Studies), Nikolaos Scarmeas (RSC member; Hellenic Longitudinal Investigation of Aging and Diet [HELIAD]), Toshiharu Ninimiya (RSC member; Hisayama Study), Linda Lam (RSC member; Hong Kong Memory and Ageing Prospective Study [HK-MAPS]), Oye Gureje (RSC member; Ibadan Study of Ageing [ISA]), Stella-Maria Paddick (RSC member; Identification and Intervention for Dementia in Elderly Africans [IDEA] Study), Richard Walker (additional study leader; Identification and Intervention for Dementia in Elderly Africans [IDEA] Study), Liang-Kung Chen (RSC member; I-Lan Longitudinal Aging Study [ILAS]), Mohammad Auais (RSC member; IMIAS [International Mobility in Aging Study]), Ricardo Oliveira Guerra (additional study leader; IMIAS [International Mobility in Aging Study]), Hugh Hendrie (RSC member; Indianapolis Ibadan Dementia Project), Elena Rolandi (RSC member; Invecchiamento Cerebrale in Abbiategrasso [Invece.Ab]), Ann Hever (RSC member; The Irish Longitudinal Study on Ageing [TILDA]), Rose Anne Kenny (additional study leader; The Irish Longitudinal Study on Ageing [TILDA]), Ki-Woong Kim (RSC member; KLOSCAD [Korean Longitudinal Study on Cognitive Aging and Dementia]), Kenichi Meguro (RSC member; Kurihara Project), Jacobijn Gussekloo (RSC member; Leiden 85-plus study), Steffi G. Riedel-Heller (RSC member; Leipzig Longitudinal Study of the Aged [LEILA75+]), Suzana Shahar (RSC member; LRGS TUA: Neuroprotective Model for Healthy Longevity among Malaysian Older Adults), Sebastian Koehler (RSC member; Maastricht Aging Study [MAAS]), Kay Deckers (additional study leader; Maastricht Aging Study [MAAS]), Jacqueline

Dominguez (RSC member; Marikina Memory and Aging Project [MMAP]), Mary Ganguli (RSC member and NIH Grant Investigator; Monongahela-Youghiogheny Healthy Aging Team [MYHAT] and University of Pittsburgh, PA), Murali Krishna (RSC member and NIH Grant Investigator; MYNAH [MYsore studies of Natal effects on Ageing and Health] and Centre for Mental Health and Society, University of Bangor, India), Nilton Custodio (RSC member; Neuroepidemiology of cognitive impairment in adults from marginal urban areas: a door-to-door population study in the Puente Piedra district, Lima, Perú), Bernadette McGuinness (RSC member; Northern Ireland Cohort for the Longitudinal Study of Ageing [NICOLA]), Frank Kee (additional study leader; Northern Ireland Cohort for the Longitudinal Study of Ageing [NICOLA]), Kaarin J. Anstey (RSC member; Personality & Total Health [PATH] Through Life project), Michael Crowe (RSC member; Puerto Rican Elderly: Health Conditions Study [PREHCO]), Allison Aiello (RSC member; Sacramento Area Latino Study on Aging [SALSA]), Kenji Narazaki (RSC member; Sasaguri Genkimon Study), Ding Ding (RSC member; Shanghai Aging Study [SAS]), Roger Ho (RSC member; Singapore Longitudinal Ageing Studies [SLAS I & II]), Marcia Scazufca (RSC member; São Paulo Ageing & Health Study [SPAH]), Henry Brodaty (RSC member and NIH Grant Investigator; Sydney Memory & Ageing Study [MAS] and Centre for Healthy Brain Ageing [CHeBA], UNSW Sydney, Australia), Perminder S. Sachdev (additional study leader and NIH Grant Investigator; Sydney Memory & Ageing Study [MAS], Centre for Healthy Brain Ageing [CHeBA], UNSW Sydney, and Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia), Yen-Ching Chen (RSC member; Taiwan Initiative for Geriatric Epidemiological Research [TIGER]), Jen-Hau Chen (additional study leader; Taiwan Initiative for Geriatric Epidemiological Research [TIGER]), Kenichi Meguro (RSC member; Tajiri Project), Vincent Mubangizi (RSC member; Ugandan study), Pascual Sanchez-Juan (RSC member; Vallecas Project), Richard Mayeux (RSC member; Washington Heights Inwood and Columbia Aging Project [WHICAP]), Nicole Schupf (additional study leader; Washington Heights Inwood and Columbia Aging Project [WHICAP]), Mika Kivimaki (RSC member; Whitehall II), Antonio Lobo (RSC member; ZARADEMP Project), Louisa Jorm (NIH Grant Investigator; Centre for Big Data Research in Health and Professor, UNSW Sydney, Australia), Sarah Bauermeister (NIH Grant Investigator; Department of Psychiatry, University of Oxford, and Dementias Platform UK), Henrik Zetterberg (NIH Grant Investigator; Psychiatry and Neurochemistry, University of Gothenburg, Sweden), Ester Cerin (NIH Grant Investigator; Behaviour, Environment and Cognition Research Program, Australian Catholic University Limited, Australia), Jaime Miranda (NIH Grant Investigator; Department of Medicine, School of Medicine, Universidad Peruana Cayetano Heredia, Peru), Wei Wen (NIH Grant Investigator; Centre for Healthy Brain Ageing [CHeBA], UNSW Sydney, Australia), Vibeke Catts (NIH Grant Investigator; Centre for Healthy Brain Ageing [CHeBA], UNSW Sydney, Australia), John D. Crawford (NIH Grant Investigator; Centre for Healthy Brain Ageing [CHeBA], UNSW Sydney, Australia), Nicole Kochan (NIH Grant Investigator; Centre for Healthy Brain Ageing [CHeBA], UNSW Sydney, Australia), Louise Mewton (NIH Grant Investigator; Matilda Centre, University of Sydney, Australia), Thomas Karikari (NIH Grant Investigator; University of Pittsburgh, PA), Anbupalam Thalamuthu (NIH Grant Investigator; Centre for Healthy Brain Ageing [CHeBA], UNSW Sydney, Australia), and Karen Mather (NIH Grant Investigator; Centre for Healthy Brain Ageing [CHeBA], UNSW Sydney, Australia). We thank the participants and their informants for their time and generosity in contributing to this research. We also thank the research teams for the contributing cohort studies. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Study Funding

In Australia, the project is funded by a National Health and Medical Research Council grant (grant number APP1169489). Research reported in this publication was supported by the National Institute on Aging of the NIH under Award Number R01AG057531. The EPIDEMCA study was funded by the French National Research Agency (ANR-09-MNPS-009–01), the AXA Research Fund (grant 2012–Project Public Health Institute [Inserm]–PREUX Pierre-Marie), and the Limoges University Hospital through its Appel à Projet des Equipes Émergentes et Labellisées scheme The HELIAD cohort was funded by the Alzheimer's Association, European Social Fund, and Greek Ministry of Health. Alzheimer's Association under grant IIRG-09-133014; National Strategic Reference Framework (NSRF)-EU program Excellence Grant (ARISTEIA), which is cofunded by the European Social Fund and Greek financial resources under grant 189 10276/8/9/2011; and the Greek Ministry for Health and Social Solidarity under grant DY2b/oik.51657/14.4.2009. The LEILA75+ study was funded by the Interdisciplinary Centre for Clinical Research at the University of Leipzig (grant 01KS9504). The MAS study was funded by the National Health and Medical Research Council (grant numbers APP350833, APP568969, and APP1093083) in Australia. Funding for the CLAS study was from the Ministry of Science and Technology, National Pillar Program 2009BAI77B03 and the National Key Clinical Disciplines at Shanghai Mental Health Center (Office of Medical Affairs, Ministry of Health, 2011-873). The H70 study was supported by AgeCap-Center for Aging and Health, Riksbankens Jubileumsfond, FORTE, and the Swedish Brain Power. The H70 study data collection was supported by The Swedish Research Council, Swedish Research Council for Health, Working Life and Welfare, Epilife, Swedish Brain Power, The Alzheimer's Association Zenith Award, The Alzheimer's Association Stephanie B Overstreet Scholars, The Bank of Sweden Tercentenary Foundation, Stiftelsen

Söderström-Königska Sjukhemmet, Stiftelsen för Gamla Tjänarinnor, Handlanden Hjalmar Svenssons Forskningsfond, and Stiftelsen Professor Bror Gadelius' Minnesfond. KLOSCAD was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health and Welfare, South Korea (grant number HI09C1379 [A092077]). PATH is funded by NHMRC Grants 973302, 179805, 418039, 1002160. SLAS was supported by a research grant (number 03/1/21/17/214) from the Biomedical Research Council, Agency for Science, Technology and Research, Singapore. ZARADEMP Study was supported by grants from the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, Madrid, Spain (grants 94/1562, 97/1321E, 98/0103, 01/0255, 03/0815, 06/0617, G03/128, 12/02254, 16/00896, 19/01874), and the Fondo Europeo de Desarrollo Regional (FEDER) of the European Union and Gobierno de Aragón (grant B15_17R). The ESPRIT project is financed by the regional government of Languedoc-Roussillon, the Agence National de Recherche (ANR) Project 07 LVIE 004, and an unconditional grant from Novartis. The Einstein Aging Study (EAS) is supported by the NIA (P01AG03949), the Czap Foundation, and the Max and Sylvia Marx Foundation. SPAH was funded by the Wellcome Trust (GR066133MA), UK and FAPESP (grant number 1998/12727-0), São Paulo, Brazil; Marcia Scazufca is supported by CNPq-Brazil (307579/2019-0). Funding for COSMIC comes from the NIA–NIH (award number 1RF1AG057531–01). The funder approved the initial plan for the consortium but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclosure

A.E. Schutte is funded by an Investigator Grant of the National Health and Medical Research Council of Australia (GNT2017504), and received speaker honoraria from Servier, Novartis, Abbott, Medtronic, Omron, and Aktiia. J. Najar was funded by Alzheimersfonden (AF-967865), the ALF-agreement (72660), and Stiftelsens Hjalmar Svenssons forskningsfond (HJSV2022059, HJSV2023023). A. Lobo had a consultancy with Janssen and received financial support to attend scientific meetings from Eli Lilly, Bial, and Janssen. C. De-la-Cámara received financial support to attend scientific meetings from Janssen, Almirall, Lilly, Lundbeck, Rovi, Esteve, Novartis, AstraZeneca, Pfizer, and Casen Recordati. E. Lobo has received an honorarium from the University of Granada. K.J. Anstey is supported by ARC Laureate Fellowship FL190100011, and received a speaker honoraria from Roche. The other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* April 18, 2024. Accepted in final form June 27, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Matthew J. Lennon, MD	Faculty of Medicine and Health, and Centre for Healthy Brain Aging (CHeBA), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, University of New South Wales, Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Darren Lipnicki, PhD	Faculty of Medicine and Health, and Centre for Healthy Brain Aging (CHeBA), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, University of New South Wales, Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Ben Chun Pan Lam, PhD	Faculty of Medicine and Health, and Centre for Healthy Brain Aging (CHeBA), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, University of New South Wales, Sydney; School of Psychology and Public Health, La Trobe University, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
John D. Crawford, BSc, MEngSc, PhD	Faculty of Medicine and Health, and Centre for Healthy Brain Aging (CHeBA), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, University of New South Wales, Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Aletta E. Schutte, PhD	The George Institute for Global Health, Barangaroo; School of Population Health, University of New South Wales, Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Ruth Peters, PhD	The George Institute for Global Health, Barangaroo; School of Biomedical Sciences, University of New South Wales, Sydney, Australia; School of Public Health, Imperial College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Therese Rydberg-Sterner, PhD	Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy, Centre for Ageing and Health (AGECAP) at the University of Gothenburg; Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Jenna Najar, MD, PhD	Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy, Centre for Ageing and Health (AGECAP) at the University of Gothenburg; Region Västra Götaland, Sahlgrenska University Hospital, Psychiatry, Cognition and Old Age Psychiatry Clinic, Gothenburg, Sweden; Section Genomics of Neurodegenerative Diseases and Aging, Department of Clinical Genetics, Vrije Universiteit Amsterdam, Amsterdam UMC, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ingmar Skoog, MD, PhD	Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy, Centre for Ageing and Health (AGECAP) at the University of Gothenburg; Region Västra Götaland, Sahlgrenska University Hospital, Psychiatry, Cognition and Old Age Psychiatry Clinic, Gothenburg, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Steffi G. Riedel-Heller, MD, MPH	Institute of Social Medicine, Occupational Health and Public Health (ISAP), Medical Faculty, University of Leipzig, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Susanne Röhr, PhD	Institute of Social Medicine, Occupational Health and Public Health (ISAP), Medical Faculty, University of Leipzig, Germany; School of Psychology, Massey University, Albany Campus, Auckland, New Zealand; Global Brain Health Institute (GBHI), Trinity College Dublin, Ireland	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Alexander Pabst, PhD	Institute of Social Medicine, Occupational Health and Public Health (ISAP), Medical Faculty, University of Leipzig, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Antonio Lobo, MD	Department of Medicine and Psychiatry, Universidad de Zaragoza; Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza; CIBERSAM, Madrid, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Concepción De-la-Cámara, MD	Department of Medicine and Psychiatry, Universidad de Zaragoza; Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza; CIBERSAM, Madrid, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Elena Lobo, PhD	Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza; CIBERSAM, Madrid; Department of Preventive Medicine and Public Health, Universidad de Zaragoza, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Richard B. Lipton, MD	Department of Neurology, and Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mindy J. Katz, MD	Department of Neurology, Albert Einstein College of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Carol A. Derby, PhD	Department of Neurology, and Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ki Woong Kim, MD, PhD	Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam; Department of Psychiatry, Seoul National University College of Medicine; Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ji Won Han, MD, PhD	Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam; Department of Psychiatry, Seoul National University College of Medicine, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Dae Jong Oh, MD, PhD	Workplace Mental Health Institute, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Elena Rolandi, MSc	Golgi Cenci Foundation, Abbiategrasso, Milan; Department of Brain and Behavioural Sciences, University of Pavia, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Annalisa Davin, MSc	Golgi Cenci Foundation, Abbiategrasso, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Michele Rossi, BS	Golgi Cenci Foundation, Abbiategrasso, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Nikolaos Scarmeas, MD, MSc, PhD	1st Department of Neurology, Aiginition Hospital, National and Kapodistrian University of Athens, Greece; Department of Neurology, Columbia University, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mary Yannakoulia, MSc, PhD	School of Health Sciences and Education, Department of Nutrition and Dietetics, Harokopio University, Greece	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Themis Dardiotis, PhD	Department of Neurology, University Hospital of Larissa; Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Hugh C. Hendrie, MBChB, DSc	Department of Psychiatry, Indiana University School of Medicine; Indiana Alzheimer Disease Research Center, Indiana Alzheimer Disease Research Center, Indianapolis	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Sujuan Gao, PhD	Indiana Alzheimer Disease Research Center, Indiana Alzheimer Disease Research Center; Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indianapolis	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Isabelle Carriere, PhD	Institut for Neurosciences of Montpellier INM, University Montpellier, INSERM, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Karen Ritchie, PhD	Institut for Neurosciences of Montpellier INM, University Montpellier, INSERM; Institut du Cerveau Trocadéro, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Kaarin J. Anstey	School of Psychology, University of New South Wales; Ageing Futures Institute, University of New South Wales; Neuroscience Research Australia, Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Nicolas Cherbuin, PhD	National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Appendix *(continued)*

Name	Location	Contribution
Shifu Xiao, MD, PhD	Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine; Alzheimer's Disease and Related Disorders Center, Shanghai Jiao Tong University, China	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ling Yue, MD	Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine; Alzheimer's Disease and Related Disorders Center, Shanghai Jiao Tong University, China	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Wei Li, MD	Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine; Alzheimer's Disease and Related Disorders Center, Shanghai Jiao Tong University, China	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Maëlenn Guerchet, PhD	Inserm U1094, IRD UMR270, Univ. Limoges, CHU Limoges, EpiMaCT-Epidemiology of Chronic Diseases in Tropical Zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth, France; Laboratory of Chronic and Neurological Diseases Epidemiology (LEMACEN), Faculty of Health Sciences, University of Abomey-Calavi, Cotonou, Benin	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Pierre-Marie Preux, PhD	Inserm U1094, IRD UMR270, Univ. Limoges, CHU Limoges, EpiMaCT-Epidemiology of Chronic Diseases in Tropical Zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Victor Aboyans, MD, PhD	Inserm U1094, IRD UMR270, Univ. Limoges, CHU Limoges, EpiMaCT-Epidemiology of Chronic Diseases in Tropical Zone, Institute of Epidemiology and Tropical Neurology, OmegaHealth; Department of Cardiology, Dupuytren 2 University Hospital, Limoges, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mary N. Haan, DrPH, MPH	School of Medicine, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Allison Aiello, PhD	Robert N. Butler Columbia Aging Center, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Marcia Scazufca, PhD	Departamento de Psiquiatria, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Brazil	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Perminder S. Sachdev, MD, PhD	Faculty of Medicine and Health, and Centre for Healthy Brain Aging (CHeBA), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, University of New South Wales; Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

References

1. World Health Organization. *Global Report on Hypertension*. WHO; 2023.
2. Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1223-1249. doi:10.1016/s0140-6736(20)30752-2
3. Emdin CA, Rothwell PM, Salimi-Khorshidi G, et al. Blood pressure and risk of vascular dementia: evidence from a primary care registry and a cohort study of transient ischemic attack and stroke. *Stroke*. 2016;47(6):1429-1435. doi:10.1161/STROKEAHA.116.012658
4. Guan JW, Huang CQ, Li YH, et al. No association between hypertension and risk for Alzheimer's disease: a meta-analysis of longitudinal studies. *J Alzheimers Dis*. 2011;27(4):799-807. doi:10.3233/JAD-2011-111160
5. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology*. 2011;22(5):646-659. doi:10.1097/EDE.0b013e31822708b5
6. Lennon MJ, Makkar SR, Crawford JD, Sachdev PS. Midlife hypertension and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis*. 2019;71(1):307-316. doi:10.3233/JAD-190474
7. Ou YN, Tan CC, Shen XN, et al. Blood pressure and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 209 prospective studies. *Hypertension*. 2020;76(1):217-225. doi:10.1161/HYPERTENSIONAHA.120.14993
8. van Dalen JW, Brayne C, Crane PK, et al. Association of systolic blood pressure with dementia risk and the role of age, U-shaped associations, and mortality. *JAMA Intern Med*. 2022;182(2):142-152. doi:10.1001/jamainternmed.2021.7009
9. Blanken AE, Nation DA. Does gender influence the relationship between high blood pressure and dementia? Highlighting areas for further investigation. *J Alzheimers Dis*. 2020;78(1):23-48. doi:10.3233/JAD-200245
10. Qiu C, von Strauss E, Winblad B, Fratiglioni L. Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. *Stroke*. 2004;35(8):1810-1815. doi:10.1161/01.STR.0000133128.42462.ef
11. Levine DA, Gross AL, Briceño EM, et al. Association between blood pressure and later-life cognition among black and white individuals. *JAMA Neurol*. 2020;77(7):810-819. doi:10.1001/jamaneurol.2020.0568
12. Akushevich I, Kolpakov S, Yashkin AP, Kravchenko J. Vulnerability to hypertension is a major determinant of racial disparities in Alzheimer's disease risk. *Am J Hypertens*. 2022;35(8):745-751. doi:10.1093/ajh/hpac063
13. Peters R, Xu Y, Fitzgerald O, et al. Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis. *Eur Heart J*. 2022;43(48):4980-4990. doi:10.1093/eurheartj/ehac584
14. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet*. 1998;352(9137):1347-1351. doi:10.1016/s0140-6736(98)03086-4
15. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7(8):683-689. doi:10.1016/S1474-4422(08)70143-1
16. Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol*. 2020;19(1):61-70. doi:10.1016/S1474-4422(19)30393-X
17. Rea F, Corrao G, Mancia G. Risk of dementia during antihypertensive drug therapy in the elderly. *J Am Coll Cardiol*. 2024;83(13):1194-1203. doi:10.1016/j.jacc.2024.01.030
18. Lennon MJ, Lam BCP, Lipnicki DM, et al. Use of antihypertensives, blood pressure, and estimated risk of dementia in late life: an individual participant data meta-analysis. *JAMA Netw Open*. 2023;6(9):e2333353. doi:10.1001/jamanetworkopen.2023.33353
19. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6
20. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512-527. doi:10.1001/jama.2023.13239
21. Sachdev PS, Lipnicki DM, Kochan NA, et al. COSMIC (Cohort Studies of Memory in an International Consortium): an international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups. *BMC Neurol*. 2013;13:165. doi:10.1186/1471-2377-13-165
22. Lennon M. Blood pressure, antihypertensive use and Alzheimers dementia risk: an IPD meta-analysis of 14 cohort studies in an international consortium [online]. *Open Sci. Framew*. 2023. Accessed January 3, 2024. osf.io/rkx79/
23. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med*. 2017;36(5):855-875. doi:10.1002/sim.7141
24. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13-e115. doi:10.1161/HYP.0000000000000065
25. Rajan KB, Barnes LL, Wilson RS, Weuve J, McAninch EA, Evans DA. Blood pressure and risk of incident Alzheimer's disease dementia by antihypertensive medications and APOE ε4 allele. *Ann Neurol*. 2018;83(5):935-944. doi:10.1002/ana.25228
26. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry*. 1998;55(9):809-815. doi:10.1001/archpsyc.55.9.809
27. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med*. 2017;36(27):4391-4400. doi:10.1002/sim.7501
28. Adesuyan M, Jani YH, Alsugeir D, et al. Antihypertensive agents and incident Alzheimer's disease: a systematic review and meta-analysis of observational studies. *J Prev Alzheimers Dis*. 2022;9(4):715-724. doi:10.14283/jpad.2022.77
29. Pearce LA, McClure LA, Anderson DC, et al. Effects of long-term blood pressure lowering and dual antiplatelet treatment on cognitive function in patients with recent lacunar stroke: a secondary analysis from the SPS3 randomised trial. *Lancet Neurol*. 2014;13(12):1177-1185. doi:10.1016/S1474-4422(14)70224-8
30. Toledo JB, Arnold SE, Raible K, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*. 2013;136(pt 9):2697-2706. doi:10.1093/brain/awt188
31. Ivan CS, Seshadri S, Beiser A, et al. Dementia after stroke: the Framingham Study. *Stroke*. 2004;35(6):1264-1268. doi:10.1161/01.STR.0000127810.92616.78
32. Peng M, Chen G, Tang KL, et al. Blood pressure at age 60-65 versus age 70-75 and vascular dementia: a population based observational study. *BMC Geriatr*. 2017;17(1):252. doi:10.1186/s12877-017-0649-3
33. Mital R, Bayne J, Rodriguez F, Ovbiagele B, Bhatt DL, Albert MA. Race and ethnicity considerations in patients with coronary artery disease and stroke: JACC focus seminar 3/9. *J Am Coll Cardiol*. 2021;78(24):2483-2492. doi:10.1016/j.jacc.2021.05.051
34. Xu W, Tan L, Wang H-F, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2015;86(12):1299-1306. doi:10.1136/jnnp-2015-310548
35. Varsos GV, Richards HK, Kasprowicz M, et al. Cessation of diastolic cerebral blood flow velocity: the role of critical closing pressure. *Neurocrit Care*. 2014;20(1):40-48. doi:10.1007/s12028-013-9913-3
36. Bo M, Massaia M, Merlo C, Sona A, Canade A, Fonte G. White-coat effect among older patients with suspected cognitive impairment: prevalence and clinical implications. *Int J Geriatr Psychiatry*. 2009;24(5):509-517. doi:10.1002/gps.2145
37. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944. doi:10.1212/wnl.34.7.939
38. Xiao S, Lewis M, Mellor D, et al. The China longitudinal ageing study: overview of the demographic, psychosocial and cognitive data of the Shanghai sample. *J Ment Health*. 2016;25(2):131-136. doi:10.3109/09638237.2015.1124385
39. Guerchet M, Mbelesso P, Ndamba-bandzouzi B, et al. Epidemiology of dementia in Central Africa (EPIDEMCA): protocol for a multicentre population-based study in rural and urban areas of the Central African Republic and the Republic of Congo. *Springerplus*. 2014;3:1044. doi:10.1186/2193-1801-3-338
40. Dardiotis E, Kosmidis MH, Yannakoulia M, Hadjigeorgiou GM, Scarmeas N. The hellenic longitudinal investigation of aging and diet (HELIAD): rationale, study design, and cohort description. *Neuroepidemiology*. 2014;43(1):9-14. doi:10.1159/000362723
41. Hendrie HC, Ogunniyi A, Hall KS, et al. Incidence of dementia and Alzheimer disease in 2 communities Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. *JAMA*. 2001;285(6):739-747. doi:10.1001/jama.285.6.739
42. Katz MJ, Lipton RB, Hall CB, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites A report from the Einstein Aging Study. *Alzheimer Dis Assoc Disord*. 2012;26(4):335-343. doi:10.1097/WAD.0b013e31823dbcfc

43. Ritchie K, Carrière I, Ritchie CW, Berr C, Artero S, Ancelin M-L. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. *BMJ*. 2010;341:c3885. doi:10.1136/bmj.c3885
44. Rydberg Sterner T, Ahlner F, Blennow K, et al. The Gothenburg H70 Birth cohort study 2014-16: design, methods and study population. *Eur J Epidemiol*. 2019;34(2):191-209. doi:10.1007/s10654-018-0459-8
45. Guaita A, Colombo M, Vaccaro R, et al. Brain aging and dementia during the transition from late adulthood to old age: design and methodology of the "invece.Ab" population-based study. *BMC Geriatr*. 2013;13:98. doi:10.1186/1471-2318-13-98
46. Han JW, Kim TH, Kwak KP, et al. Overview of the Korean longitudinal study on cognitive aging and dementia. *Psychiatry Investig*. 2018;15(8):767-774. doi:10.30773/pi.2018.06.02
47. Riedel-Heller SG, Busse A, Aurich C, Matschinger H, Angermeyer MC. Incidence of dementia according to DSM-III-R and ICD-10: results of the Leipzig Longitudinal Study of the Aged (LEILA75+), Part 2. *Br J Psychiatry*. 2001;179:255-260. doi:10.1192/bjp.179.3.255
48. Anstey KJ, Christensen H, Butterworth P, et al. Cohort profile: the PATH through life project. *Int J Epidemiol*. 2012;41(4):951-960. doi:10.1093/ije/dyr025
49. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older latinos: the influence of type 2 diabetes mellitus, stroke and genetic factors. *J Am Geriatr Soc*. 2003;51:169-177. doi:10.1046/j.1532-5415.2003.51054.x
50. Scazufca M, Menezes PR, Araya R, et al. Risk factors across the life course and dementia in a Brazilian population: results from the Sao Paulo Ageing & Health Study (SPAH). *Int J Epidemiol*. 2008;37(4):879-890. doi:10.1093/ije/dyn125
51. Lobo A, Saz P, Marcos G, et al. The ZARADEMP Project on the incidence, prevalence and risk factors of dementia (and depression) in the elderly community: I. The context and the objectives. *Eur J Psychiatry*. 2005;19(1):31-39. doi:10.4321/s0213-61632005000100003