BJGP British Journal of General Practice

Systolic inter-arm blood pressure difference and risk of cognitive decline in the elderly: cohort study

Journal:	*British Journal of General Practice*
Manuscript ID	BJGP-2019-0677.R1
Manuscript Type:	Article {quantitative - not RCT}
Date Submitted by the Author:	n/a
Complete List of Authors:	Clark, Christopher; University of Exeter Medical School, Primary Care Research Group, Institute of Health Research Thomas, Daniel; University of Exeter Medical School, Primary Care Research Group, Institute of Health Research Lewellyn, David; University of Exeter Medical School, . Mental Health Research Group, Institute of Health Research; The Alan Turing Institute Ferrucci, Luigi; National Institutes of Health Bandinelli, Stefania; Local Health Unit Tuscany Centre, Geriatric Unit Campbell, John; University of Exeter Medical School, General Practice and Primary Care
Keywords:	Cognitive Dysfunction, Blood Pressure, Cohort Studies

Systolic inter-arm blood pressure difference and risk of cognitive decline in the elderly: cohort study

Christopher E Clark[1], Daniel Thomas[1], David J. Llewellyn[2,3], Luigi Ferrucci[4], Stefania Bandinelli[5], John L Campbell[1]

1. Primary Care Research Group
Institute of Health Research
University of Exeter Medical School
Smeall Building, St Luke's Campus
Magdalen Rd, Exeter, Devon, England EX1 2LU

2. Mental Health Research Group
Institute of Health Research
University of Exeter Medical School
College House, St Luke's Campus
Magdalen Rd, Exeter, Devon, England EX1 2LU

3. The Alan Turing Institute
British Library
96 Euston Road
London, England NW1 2DB

4. National Institute on Aging
251 Bayview Blvd. Room 04C228
Baltimore, MD 21224 – USA

5. Geriatric Unit, Local Health Unit Tuscany Centre,
Florence, Italy.

Abstract: 250 words
Text: 2548 words
Tables: 5
Figures: 2

Address for correspondence: c.e.clark@exeter.ac.uk

Abstract

Background

Systolic inter-arm difference in blood pressure (IAD) and cognitive decline are both associated with cardiovascular disease. We hypothesised that IAD may, therefore, be predictive of cognitive decline.

Aim

To examine associations of IAD with cognitive decline in a community population.

Design and Setting

Prospective study of older Italian adults enrolled in the InCHIANTI study.

Method

We explored univariable and multivariable associations of IAD with declines in Mini Mental State Examination (MMSE) scores, Trail Making Test A and B scores, and a composite outcome representing substantial decline in any of these scores. We used backward stepwise regression to adjust observed associations of IAD with cognitive decline.

Results

The rate of decline for MMSE scores in 1133 participants was greater with systolic IAD ≥ 5mmHg or ≥ 10mmHg. On univariable analyses continuous IAD was associated with the composite outcome (Odds ratio (OR) 1.16 per 5 mmHg of IAD (95%CI 1.02 to 1.31)). Substantial decline in MMSE score was seen with IAD ≥5mmHg (OR 1.41 (1.03 to 1.93)), and in the composite outcome with IAD ≥5mmHg (OR 1.44 (1.10 to 1.89)) or ≥10mmHg (OR 1.39 (1.03 to 1.88)). After multivariable adjustment an IAD ≥5mmHg remained associated with reductions in the composite outcome, reflecting declining cognitive performance (OR 1.46 (1.05 to 2.03).

Conclusion

A systolic IAD ≥5mmHg is associated with cognitive decline in a representative older population. Given that inter-arm differences in blood pressure are easily measured, confirmation of these findings could inform individualised treatment for the prevention of cognitive decline and dementia.

250 words

Keywords

Cognitive Dysfunction; Blood Pressure; Aged; Aged, 80 & over; Cohort Studies

How this fits in

- Inter-arm blood pressure differences are associated with increased cardiovascular and all-cause mortality.
- Cognitive decline is associated with hypertension and cerebrovascular disease, and may be mitigated by aggressive blood pressure lowering in those most at risk.

- Detection of an inter-arm difference in blood pressure may identify individuals at excess risk of cognitive decline.
- Recognition of IAD as a risk marker for cognitive decline may help to inform personalised discussion of blood pressure lowering, and other preventative strategies, in reducing the risk of cognitive decline.

Introduction

Hypertension and dementia are both associated with older age and with each other.[1] Globally the numbers living with dementia are predicted to rise, representing substantial and increasing costs and care burdens for society.[2 3] Risks of developing dementia are associated with known risk markers for cardiovascular disease such as mid-life hypertension,[4 5] diabetes,[6] and a widening pulse pressure.[7]

A difference in systolic blood pressures between arms (inter-arm difference; IAD) has also been shown to be associated with increased risk of cardiovascular morbidity and mortality, and is associated with increasing pulse pressure and arterial stiffness.[8 9] A systolic IAD ≥ 10mmHg is found in 11% of people with hypertension and 7% of those with diabetes.[10] The precise aetiology of an IAD is incompletely established, however arterial changes seem to be a common contributor.[11] A body of evidence now exists to support recognition of IAD as an early marker for subsequent vascular disease, and to quantify that risk for cardiovascular events.[12 13]

Pre-clinical vascular damage can be observed early in the course of hypertension,[14] whereas measurable cognitive decline or a diagnosis of dementia are later consequences of exposure to raised blood pressure.[5 15] White matter lesions predict onset of dementia;[16] their progression is slowed when hypertension is controlled, and antihypertensive treatment is associated with reduced risk of subsequent Alzheimer's disease.[17 18] Recent evidence suggests that intensive blood pressure lowering may prevent progression of cognitive impairment.[19] Prediction of those most at risk of future progression of white matter lesions and cognitive decline is, therefore, desirable in order to target or intensify treatment for them appropriately.[20]

Given the above, we considered that IAD may also have a prognostic association with future cognitive decline. To our knowledge this association has only to date been reported for a sub-group of the Framingham cohort who possess the apolipoprotein E (APOE) ε4 allele, and not observed for the overall study population.[21] If adults with an IAD are shown to be at risk of greater cognitive decline than those without, then IAD measurement in clinical practice could help to differentiate those people with most to gain from early interventions and intensive blood pressure lowering. We undertook the analyses presented here, using data from the InCHIANTI study, a well-documented prospective cohort study of older community living adults, to explore the associations of IAD with cognitive decline.[22]

Methods

Population and setting

The Invecchiare in Chianti (InCHIANTI) study is a population-based cohort study of older adults based in Greve in Chianti and Bagno a Ripoli in Italy. In total, 1270 participants over the age of 65 were recruited from a random sample of city registers between August 1998 and March 2000. Recruitment was designed to be representative of the older Chianti population, with oversampling of those aged over 90 to ensure representation of the oldest old within the cohort. Finally, 30 men and women for each decade of age from 20 years upwards were also recruited to achieve a total of 1,453. Follow-up has been carried out every 3 years for up to 13 years. Ethical approval for the InCHIANTI study was provided by the Italian National Research Council on Aging Ethical Committee, and participants gave informed consent.[22]

Outcome measures

At recruitment and at each three-yearly follow up, cognitive function was assessed by administration of the 30-point Mini Mental State Examination (MMSE); executive functioning was assessed using Trail-Making Tests A and B with a 300 second time limit.[23 24] We used the latest follow up data before censorship to examine changes in cognitive measures from baseline, adjusting for length of follow up.

We defined *substantial cognitive decline* for each test as follows: a reduction in MMSE score of 5 points or more from baseline, being in the worst 10% of decliners from baseline in Trails A or Trails B, or failure to complete these tests in the time allowed.[25-27] We also examined a composite outcome, based on the method of Espeland et al, whereby cognitive decline was defined by any one of the substantial cognitive decline criteria for the MMSE, Trails A or Trails B described above.[28]

During the recruitment medical examination blood pressure was measured with subjects resting supine using a standard mercury sphygmomanometer. The sequence of measurements was right arm first then, after a two minute pause, the left arm. Two further measurements subsequently took place on the higher reading arm. Inter-arm difference was calculated as right minus left from the paired first measurements. Systolic and diastolic blood pressures were defined as the mean of the second and third measurements. All blood pressure measurements were taken from the initial baseline recruitment examinations.

Statistical analysis

We planned a priori to adjust analyses for covariates known to be associated with vascular disease, IAD or cognitive decline. Specifically, these were: age, sex, baseline MMSE score, years of education, systolic and diastolic blood pressure, hypercholesterolemia (defined as total cholesterol 5.0 or greater), current smoking status, diabetes (defined as any of: recorded medical history of diabetes, use of medication for diabetes, or fasting glucose of 7.0mmol/l at baseline), established vascular disease (defined as medical history of myocardial infarction, angina or peripheral arterial disease at baseline; ankle-brachial pressure index <0.9, or carotid artery stenosis of greater than 40% on clinical assessment), cerebrovascular disease (defined as medical history or clinical examination suggestive of previous stroke or transient ischaemic attack), body mass index (BMI) and length of time in

study.

Continuous and discrete variables were compared according to IAD using t-tests and chi-square tests as appropriate. Non-normally distributed continuous data were compared using Mann-Whitney U tests. We compared changes of cognitive test scores, and (to adjust for varied follow up lengths) rates of change of cognitive scores by dichotomous systolic IAD cut-offs. We then explored univariable and multivariable associations of absolute systolic IAD as both a continuous variable, and as a dichotomous variable, with substantial cognitive decline using logistic regression modelling. For dichotomous IAD we adopted IAD cut-offs of ≥5 and ≥10 mmHg throughout for consistency with existing literature.[29] Examination of the commonly quoted IAD ≥15mmHg threshold was planned a priori but is not presented due to a low prevalence of participants meeting this magnitude of IAD.

We calculated unadjusted odds ratios (OR) of substantial cognitive decline for each cognitive test separately and for the composite measure according to IAD. We explored multivariable associations of systolic IAD, adjusting for the covariates listed above with cognitive measures that showed significant univariable association with systolic IAD using backwards stepwise regression. The threshold for inclusion of covariates in multivariable modelling was set at $P < 0.2$. The final adjusted model was used to derive adjusted ORs for cognitive decline according to IAD. Terms for age, sex and systolic blood pressure were retained, irrespective of p-value, on aetiological grounds.

P-values were two-sided throughout. All analyses were performed using Stata Version 14 (StataCorp, College Station, Texas, USA).

Results

There are 1453 participants in the InCHIANTI study cohort. After excluding participants missing blood pressure measurements, and those with a pre-existing diagnosis of dementia, there were 1251 eligible for analysis. Of these 118 lacked any follow-up data for cognitive tests, therefore all analyses were based on the remaining 1,133 participants (Figure 1). Median follow up was 9.0 years (inter-quartile range 8.2 to 9.2 years). Within the cohort follow up measurements existed for MMSE in 1,118 (98.7%), Trails A in 933 (82.3%) and Trails B in 657 (58.0%) participants. Those without follow up records, in comparison to those contributing to the analyses were older, had higher rates of vascular and cerebrovascular disease, and had lower baseline MMSE scores and years of completed education than participants included in the analyses (Table 1).

Mean systolic blood pressure at recruitment was 145.6mmHg (SD 21.4) with evidence of rounding to zero (Figure 2). Within this population there were 277 (24.5%) people with a systolic IAD ≥ 5mmHg, 212 (18.7 %) with an IAD ≥ 10mmHg and 30 (2.7%) with an IAD ≥ 15mmHg. Compared to those with an IAD < 10mmHg, those above the threshold had lower baseline scores for MMSE and longer Trails A and B times; they were older and completed shorter years of follow up. Blood pressures and the rate of hypertension were higher in association with an IAD (Table 2).

MMSE scores declined at a greater rate for participants with a systolic IAD ≥ 5mmHg and ≥ 10mmHg compared to those without. No differences were seen for the Trail Making Tests (Table 3).

On univariable analysis systolic IAD, as a continuous variable, was associated with the composite outcome (OR 1.16 per 5 mmHg of IAD (95%CI 1.02 to 1.31); *P* = 0.021). Using dichotomised terms for systolic IAD the odds of substantial decline in the MMSE score were greater with a systolic IAD ≥5mmHg (1.41 (95%CI 1.03 to 1.93); *P* = 0.032), and in the composite score with a systolic IAD ≥5mmHg or IAD ≥10mmHg (1.44 (95%CI 1.10 to 1.89); *P* = 0.009 and 1.39 (95%CI 1.03 to 1.88); *P* = 0.030). No difference was evident for Trail Making Tests (Table 4).

Given no findings of univariable associations between Trail Making Tests and IAD, multivariable modelling was only undertaken to explore substantial decline in MMSE scores and in the composite scores. We derived multivariable models, to which IAD was added to calculate adjusted ORs for associations of IAD with cognitive measures. Variables retaining significance in either model were age, sex, baseline MMSE, years in education, diabetes, previous cerebrovascular event and duration of follow up (Table 5). These models, with inclusion of systolic blood pressure as planned, were used to adjust univariable associations of IAD for all variables (Table 4). After adjustment, continuous IAD was no longer associated with any of the outcomes. For dichotomous IAD cut-offs only an IAD ≥5mmHg remained associated with increased odds of decline in the composite outcome (OR 1.5 (1.1 to 2.0); *P* = 0.03).

Discussion

Summary

In this cohort, representative of the older Italian population, a systolic inter-arm difference ≥5mmHg was observed to be associated with a decline of 5 or more points in the Mini Mental State Examination score over a median nine year follow up period. When a composite score also taking account of a decline in Trail Making Tests is considered, this association is also observed for an inter-arm difference ≥10mmHg, and as a continuous variable. After adjustment in a multivariable model, the composite outcome remains more likely to be achieved with an inter-arm difference ≥5mmHg.

Strengths and limitations

This study achieved high retention and follow up rates over almost a decade, allowing longitudinal study of clinically meaningful changes. The availability of a large number of baseline variables permitted robust adjustment of findings, although completion rates for follow up Trail testing were lower than the MMSE so may have constrained the ability to demonstrate changes in these outcomes. The MMSE examination also has limitations as a screening tool for cognitive impairment and dementia, therefore we used an accepted definition of significant change in scores.[30] A sequential blood pressure measurement method can over-estimate IAD in comparison to a simultaneous method, and the pause between measurements may have augmented differences due to white coat effects.[10 31] There was also evidence of rounding of blood pressure readings, which can contribute to measurement error through digit preference.[32] Nevertheless these limitations make the blood pressure readings analogous to routine clinical measurements, and the prognostic value of IAD derived from sequential measurements in other studies has not differed significantly from that of simultaneous measurements.[8 13] To minimise the impact of test to test variability in cognitive assessments we adopted valid criteria for a substantial reduction in cognition over time, and adjusted outcomes for duration of follow up.[25-27] The composite measure for cognitive decline has been reported from cross-sectional work,[28] but to our knowledge, it has not previously been reported in prospective analyses such as presented here.

The InCHIANTI cohort is representative of an older Italian population (excepting those aged over 90).[33] Ethnic differences in the aetiology and prognostic importance of systolic IAD may exist,[13 34] but this is uncertain.[31] Consequently we are cautious of extrapolating these findings to other ethnic groups. We did not observe rising risks of cognitive decline with increasing magnitude of IAD. Previous individual studies and study-level meta-analyses have also failed to show a positive correlation between size of hazard ratios for prospective mortality outcomes and magnitude of IAD,[8 12] although this has recently become evident in our current large (>57,000 records) individual participant data meta-analysis.[13] The current study had few people (<3%) with a systolic IAD ≥ 15mmHg; it lacked power to explore IADs above the ≥ 10 mmHg threshold and the sample size available for this study was too small to demonstrate trends in risk according to level of IAD. The limitations in measurement technique discussed above could also have contributed to the differences in associations seen between 5mmHg and 10mmHg IAD cut-offs.

In presenting analyses of four cognitive outcomes we recognise the risk of spurious associations being observed by chance alone. A conservative approach to interpretation, taking account of a Bonferroni correction, would apply a *P*-value of 0.0125 as an appropriate threshold for significance testing. Whilst none of our adjusted findings met this level of significance, all of the odds ratios presented are consistent in direction (i.e. > 1.0) suggesting that IAD may be associated with cognitive decline, but that this study was limited in power (as evidenced by the wide confidence intervals observed) to demonstrate such associations. Due to limitations of the data we could take account of introduction of drugs for dementia during the study, however only 1% of the cohort reported use of such drugs at follow up, indicating a low likelihood of impact on our findings.

Comparison with existing literature

Systolic IADs have been observed to be associated in both cross-sectional and prospective studies with higher incidences of all-cause mortality, stroke and cerebral arterial stenoses.[8 35-37] An increasing pulse pressure is also associated with both magnitude of IAD and magnetic resonance imaging evidence of markers for dementia risk.[9 34 38] Therefore an association of IAD with cognitive decline is plausible given these vascular associations, due to vascular stiffening.[4 39] However, to our knowledge, only one previous longitudinal cohort study has examined this. Using data from the Framingham Heart Study, investigators found an association of IAD with cognitive decline restricted to the subgroup of participants possessing the APOE ε4 allele.[21] One other study has reported an association between differences in ankle artery pressures and greater decline in a composite cognitive score in people with diabetes.[28] Consequently, we believe that this study presents the first data to associate an IAD in blood pressure with cognitive decline in a general cohort representative of an older age community population.

Given the absence of effective treatments to date for established dementia, current emphasis is on prevention and reduction of cognitive decline.[19] Intensive blood pressure lowering may be effective but is not risk free strategy, therefore recognition of novel cardiovascular risk markers to refine risk prediction and stratify treatment priorities is important.[40] IAD is one such easily measured risk marker, associated with arterial stiffening and elevated pulse wave velocity thus indicating increased risk of target organ damage at an early stage.[41] Addition of non-invasive assessments of target organ damage can reclassify individuals with such risk markers present into higher risk groups.[42] Our findings require confirmation in other populations but, if reproducible, then IAD measurement may offer an opportunity to identify, at a pre-clinical stage, those most likely to benefit from aggressive preventative strategies.[20]

Implications for research and/or practice

Recommendations to initially check blood pressure in both arms are included in international hypertension guidelines.[43 44] Uptake of bilateral measurement may be increasing, and this can be facilitated by providing clinicians with evidence about the implications of an IAD.[45 46] The new National Institute for Health and Care Excellence hypertension guidelines have reduced their suggested threshold for a significant IAD from 20mmHg to 15mmHg.[44] More recent evidence suggests that a systolic IAD below 5mmHg can be considered a normal finding, whilst excess cardiovascular events and deaths start to be observed above this threshold.[13 47-49] Our current findings provide initial evidence to add

cognitive decline to these outcomes at the same threshold, whilst evidence suggests that people with an IAD below 5 mmHg can be reassured. Awareness of the evidence around IAD can inform discussion of individual interventions to address modifiable risk factors and improve primary prevention of cardiovascular diseases. An inter-arm difference is easily checked without additional equipment or skills. Whilst simultaneous measurement might be preferred by guidelines, there is substantial evidence to demonstrate the prognostic associations of sequentially measured IADs obtained in practice.[13 43]

Intensive blood pressure lowering may reduce progression of cognitive impairment, but it is not without risk.[19] Such regimes are consistently associated with more frequent adverse events such as acute kidney injury, hypotension, falls and fractures.[50-53] Thus there is a trade-off between reducing risks of events and increasing risks of adverse events; this implies the need to personalise treatments by addressing risk markers for individuals.[54] Confirmation of IAD as a risk marker for future cognitive decline could help to target intensification of treatment to those most at risk of events.

Conclusions

Among older adults, our findings suggest that a systolic inter-arm difference may be associated with global cognitive decline. Adjustment for cardiovascular risk markers attenuates but does not abolish this association. The current findings lacked power due to sample size limitations, but suggest that further study in bigger populations is warranted. Given that inter-arm differences in blood pressure are easily measured, confirmation of the findings reported here could, in future, inform individualised treatment to reduce the risk of cognitive decline and dementia.

Acknowledgements

Contributors

CEC proposed this study and undertook analyses. DT undertook the study and initial analyses for his MPH Dissertation (Manchester 2015). DJL offered advice on analysis and interpretation of cognitive impairment indices. LF & SB supported the study on behalf of the InCHIANTI investigators. CEC & JLC supervised conduct of DT's MPH Dissertation. CEC drafted the manuscript, all authors revised and edited the manuscript and all authors have read, reviewed and approved the final manuscript.

Funding

CEC was supported by an NIHR Clinical Lectureship award.

DJL is supported by the James Tudor Foundation, the Mary Kinross Charitable Trust, the Halpin Trust, the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care for the South West Peninsula (PenCLAHRC), the National Institute on Aging/National Institutes of Health (NIA/NIH) under award number RF1AG055654, and the Alan Turing Institute under the Engineering and Physical Sciences Research Council (EPSRC) grant EP/N510129/1.

This work was supported in part by the Intramural Research Program of the National Institute on Aging, National Institute of Health, Baltimore, MD 21224, USA.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NIHR, the NHS or the Department of Health.

Competing interests

None declared

Ethical approval

The Italian National Research Council on Aging Ethical Committee approved the InCHIANTI study.

Prior publication

Interim findings from DT's MPH Dissertation were presented in at the European Society for Hypertension, Paris, and awarded the Alberto Ferrari Poster Prize (*J Hypertens* 2016; 34, e-Supplement 2: e224)

Data sharing statement

The InCHIANTI datasets are available on application with a research proposal to the InCHIANTI investigators at http://inchiantistudy.net/wp/

References

1. Emdin CA, Anderson SG, Callender T, et al. Usual blood pressure, peripheral arterial disease, and vascular risk: cohort study of 4.2 million adults. *BMJ* 2015;351:h4865. doi: 10.1136/bmj.h4865
2. Naghavi M, Wang HD, Lozano R, et al. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385(9963):117-71.
3. World Health Organization. Dementia: a public health priority. *Dementia* 2012:112-12. doi: 978 92 4 156445 8
4. 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):1429-35. doi: 10.1161/strokeaha.116.012658 [published Online First: 2016/05/12]
5. Rouch L, Cestac P, Hanon O, et al. Blood pressure and cognitive performances in middle-aged adults: the Aging, Health and Work longitudinal study. *J Hypertens* 2019;37(6):1244-53. doi: 10.1097/HJH.0000000000002013 [published Online First: 2019/01/10]
6. Xu W, Qiu C, Gatz M, et al. Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. *Diabetes* 2009;58(1):71-7. doi: 10.2337/db08-0586 [published Online First: 2008/10/28]
7. Qiu C, Winblad B, Viitanen M, et al. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. *Stroke* 2003;34(3):594-9. doi: 10.1161/01.STR.0000060127.96986.F4 [published Online First: 2003/03/08]
8. Clark CE, Taylor RS, Shore AC, et al. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. *Lancet* 2012;379:905-14.
9. Canepa M, Milaneschi Y, Ameri P, et al. Relationship between inter-arm difference in systolic blood pressure and arterial stiffness in community-dwelling older adults. *J ClinHypertens (Greenwich)* 2013;15(12):880-87.
10. Clark C, Taylor R, Shore A, et al. Prevalence of systolic inter-arm differences in blood pressure varies for different primary care populations: systematic review and meta-analysis. *Br J Gen Pract* 2016;66(11):652.
11. Giles TD. Inter-Arm Difference in Systolic Blood Pressure-"The Plot Stiffens". *Journal of Clinical Hypertension* 2013;15(12):878-79.
12. Cao K, Xu J, Shangguan Q, et al. Association of an inter-arm systolic blood pressure difference with all-cause and cardiovascular mortality: An updated meta-analysis of cohort studies. *International journal of cardiology* 2015;189(0):211-19.
13. Clark C, Boddy K, Warren F, et al. Inter-arm differences in blood pressure and mortality: individual patient data meta-analysis and development of a prognostic algorithm (INTERPRESS-IPD COLLABORATION). *Canadian Journal of Cardiology* 2018;34(10):S131. doi: 10.1016/j.cjca.2018.07.212

14. Williams B. Hypertension in the Young: Preventing the Evolution of Disease Versus Prevention of Clinical Events. *Journal of the American College of Cardiology* 2007;50(9):840-42.
15. de Roos A, van der Grond J, Mitchell G, et al. Magnetic Resonance Imaging of Cardiovascular Function and the Brain: Is Dementia a Cardiovascular-Driven Disease? *Circulation* 2017;135(22):2178-95. doi: 10.1161/CIRCULATIONAHA.116.021978 [published Online First: 2017/06/01]
16. Benedictus MR, van Harten AC, Leeuwis AE, et al. White Matter Hyperintensities Relate to Clinical Progression in Subjective Cognitive Decline. *Stroke* 2015;46(9):2661-4. doi: 10.1161/STROKEAHA.115.009475 [published Online First: 2015/07/16]
17. Yasar S, Xia J, Yao W, et al. Antihypertensive drugs decrease risk of Alzheimer disease: Ginkgo Evaluation of Memory Study. *Neurology* 2013;81(10):896-903. doi: 10.1212/WNL.0b013e3182a35228 [published Online First: 2013/08/06]
18. Verhaaren BF, Vernooij MW, de Boer R, et al. High blood pressure and cerebral white matter lesion progression in the general population. *Hypertension* 2013;61(6):1354-9. doi: 10.1161/HYPERTENSIONAHA.111.00430 [published Online First: 2013/03/27]
19. Sprint Mind Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA* 2019;321(6):553-61. doi: 10.1001/jama.2018.21442 [published Online First: 2019/01/29]
20. Solomon A, Soininen H. Dementia: Risk prediction models in dementia prevention. *Nature Reviews Neurology* 2015;11(7):375-77. doi: 10.1038/nrneurol.2015.81
21. Pase MP, Beiser A, Aparicio H, et al. Interarm differences in systolic blood pressure and the risk of dementia and subclinical brain injury. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 2016;12(4):438-45. doi: 10.1016/j.jalz.2015.09.006
22. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J AmGeriatrSoc* 2000;48(12):1618-25.
23. Reitan RM. Validity of the Trail Making Test as an Indicator or Organic Brain Damage. *Perceptual and Motor Skills* 1958;8(3):271-76. doi: 10.2466
24. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12(3):189-98. doi: 10.1016/0022-3956(75)90026-6
25. Schmand B, Lindeboom J, Launer L, et al. What is a significant score change on the mini-mental state examination? *International Journal of Geriatric Psychiatry* 1995;10(5):411-14. doi: 10.1002/gps.930100510
26. Littlejohns TJ, Kos K, Henley WE, et al. Serum leptin and risk of cognitive decline in elderly italians. *Journal of Alzheimer's Disease* 2015;44(4):1231-39. doi: 10.3233/JAD-141836
27. Llewellyn DJ, Lang IA, Langa KM, et al. Vitamin D and risk of cognitive decline in elderly persons. *ArchInternMed* 2010;170(1538-3679 (Electronic)):1135-41. doi: 10.1001/archinternmed.2010.173
28. Espeland MA, Beavers KM, Gibbs BB, et al. Ankle-brachial index and inter-artery blood pressure differences as predictors of cognitive function in overweight and obese older adults with diabetes: Results from the Action for Health in Diabetes movement

and memory study. *International Journal of Geriatric Psychiatry* 2015;30(10):999-1007.

29. Clark CE, Boddy K, Warren FC, et al. Associations between interarm differences in blood pressure and cardiovascular disease outcomes: protocol for an individual patient data meta-analysis and development of a prognostic algorithm. *BMJ Open* 2017;7:e016844. doi: 10.1136/bmjopen-2017-016844
30. Tombaugh TN. Test-retest reliable coefficients and 5-year change scores for the MMSE and 3MS. *Archives of Clinical Neuropsychology* 2005;20(4):485-503. doi: 10.1016/j.acn.2004.11.004
31. Schwartz CL, Clark C, Koshiaris C, et al. Interarm Difference in Systolic Blood Pressure in Different Ethnic Groups and Relationship to the "White Coat Effect": A Cross-Sectional Study. *Am J Hypertens* 2017 doi: 10.1093/ajh/hpx073
32. Kallioinen N, Hill A, Horswill MS, et al. Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: a systematic review. *Journal of Hypertension* 2017;35(3):421-41. doi: 10.1097/HJH.0000000000001197
33. Clark CE, Thomas D, Warren F, et al. Detecting Risks Of Postural Hypotension (DROP): derivation and validation of a prediction score for primary care. *BMJ Open* 2018;8 doi: http://dx.doi.org/10.1136/bmjopen-2017-020740
34. Clark C, Warren F, Boddy K, et al. Inter-arm blood pressure difference: Insights into aetiology from the INTERPRESS-IPD collaboration. *Journal of Hypertension* 2019;37:e34. doi: 10.1097/01.hjh.0000570704.05992.fa
35. Kim JY, Kim EJ, Namgung J, et al. Between-visit reproducibility of inter-arm systolic blood pressure differences in treated hypertensive patients: the coconet study. *Hypertens Res* 2016 doi: 10.1038/hr.2016.173 [published Online First: 2016/12/23]
36. Wang Y, Zhang J, Qian Y, et al. Association of Inter-arm Blood Pressure Difference with Asymptomatic Intracranial and Extracranial Arterial Stenosis in Hypertension Patients. *Sci Rep* 2016;6:29894. doi: 10.1038/srep29894
37. Kranenburg G, Spiering W, de Jong PA, et al. Inter-arm systolic blood pressure differences, relations with future vascular events and mortality in patients with and without manifest vascular disease. *International journal of cardiology* 2017;244:271-76. doi: 10.1016/j.ijcard.2017.06.044
38. Cox SR, Lyall DM, Ritchie SJ, et al. Associations between vascular risk factors and brain MRI indices in UK Biobank. *European Heart Journal* 2019;40(28):2290-300. doi: 10.1093/eurheartj/ehz100
39. Mitchell GF, van Buchem MA, Sigurdsson S, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain : a journal of neurology* 2011;134(Pt 11):3398-407. doi: 10.1093/brain/awr253 [published Online First: 2011/11/15]
40. Simon A, Levenson J. May subclinical arterial disease help to better detect and treat high-risk asymptomatic individuals? *J Hypertens* 2005;23(11):1939-45.
41. Tomiyama H, Inoguchi T, Munakata M, et al. Simultaneously Measured Interarm Blood Pressure Difference and Stroke: An Individual Participants Data Meta-Analysis. *Hypertension* 2018;71(6):1030-38.
42. Abellan-Huerta J, Montoro-Garcia S, Soria-Arcos F. Most advisable strategy in search of asymptomatic target organ damage in hypertensive patients. *Hipertension y Riesgo Vascular* 2017;34(4):149-56.

43. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European Heart Journal* 2018;39(33):3021-104. doi: 10.1093/eurheartj/ehy339
44. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. 28/8/19 ed. London, 2019.
45. Mejzner N, Clark CE, Smith LF, et al. Trends in the diagnosis and management of hypertension: repeated primary care survey in South West England. *British Journal of General Practice* 2017 doi: 10.3399/bjgp17X690461
46. Parker E, Glasziou P. Use of evidence in hypertension guidelines: should we measure in both arms? *British Journal of General Practice* 2009;59:e87-e92. doi: 10.3399/bjgp09X395012
47. Clark CE, Taylor RS, Butcher I, et al. Inter-arm blood pressure difference and mortality: a cohort study in an asymptomatic primary care population at elevated cardiovascular risk. *British Journal of General Practice* 2016;66(5):241-2. doi: 10.3399/bjgp16X684949
48. Hirono A, Kusunose K, Kageyama N, et al. Development and validation of optimal cut-off value in inter-arm systolic blood pressure difference for prediction of cardiovascular events. *Journal of Cardiology* 2018;71(1):24-30. doi: 10.1016/j.jjcc.2017.06.010
49. White J, Mortensen LH, Kivimaki M, et al. Interarm differences in systolic blood pressure and mortality among US army veterans: aetiological associations and risk prediction in the Vietnam experience study. *EurJPrevCardiol* 2014;21(11):1394-400.
50. The SPRINT Research Group: A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *New England Journal of Medicine* 2015;373(22):2103-16. doi: 10.1056/NEJMoa1511939
51. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *New England Journal of Medicine* 2010;362(17):1575-85. doi: doi:10.1056/NEJMoa1001286
52. Clark C, McManus R. The use of highly structured care to achieve blood pressure targets. *BMJ* 2012;345:10.1136/bmj.e7777.
53. Butt DA, Mamdani M, Austin PC, et al. THe risk of hip fracture after initiating antihypertensive drugs in the elderly. *Archives of Internal Medicine* 2012;172(22):1739-44. doi: 10.1001/2013.jamainternmed.469
54. Patel KK, Arnold SV, Chan PS, et al. Personalizing the Intensity of Blood Pressure Control: Modeling the Heterogeneity of Risks and Benefits From SPRINT (Systolic Blood Pressure Intervention Trial). *Circulation Cardiovascular quality and outcomes* 2017;10(4) doi: 10.1161/circoutcomes.117.003624 [published Online First: 2017/04/05]

Legends of tables & figure

Table 1. Differences between eligible participants with and without follow-up data

Table 2. Characteristics of participants according to systolic inter-arm difference by IAD status ≥ 10 or < 10 mmHg

Table 3. Changes in cognitive scores according to systolic inter-arm difference

Table 4. Unadjusted and adjusted odds ratios for substantial cognitive decline for all participants according to systolic inter-arm difference

Table 5. Multivariable models for measures of cognitive decline associated with inter-arm difference

Figure 1 – Identification of participants eligible for study

	Included (1133)	Excluded (118)	p-value
Age (years)	66.4 (15.3)	78.2 (11.7)	<0.001
Female - n (%)	621 (54.8)	64 (52.2)	0.905
Current smokers – n (%)	218 (19.2)	17 (14.4)	0.201
Body mass index	27.2 (4.1)	27.5 (4.3)	0.478
Baseline MMSE score*	26.3 (2.9)	23.2 (4.2)	<0.001
Years in education*	6.8 (4.2)	5.0 (3.3)	<0.001
Years of follow up	8.1 (1.5)	2.9 (2.5)	<0.001
Systolic blood pressure	145.6 (21.4)	152.2 (23.7)	0.002
Diastolic blood pressure	83.1 (9.5)	83.9 (9.3)	0.345
Systolic IAD ≥ 10 mmHg	2.4 (4.8)	2.7 (7.8)	0.564
Hypertension - n (%)	834 (73.6)	94 (79.7)	0.153
Diabetes – n (%)	143 (12.6)	15 (12.7)	0.978
Vascular disease - n (%)	177 (15.6)	36 (31.0)	<0.001
Cerebrovascular disease - n (%)	49 (4.3)	18 (15.3)	<0.001

Continuous data reported as mean (standard deviation), except when *non-normally distributed where median (interquartile range given)
MMSE = Mini mental state examination
IAD = inter-arm blood pressure difference

Table 1. Differences between eligible participants with and without follow-up data

	IAD ≥ 10 mmHg (212)	IAD < 10 mmHg (921)	p-value
Age (years)	69.3 (12.9)	65.7 (15.7)	0.003
Female - n (%)	117 (55.2)	95 (44.8)	0.902
Current smokers – n (%)	38 (17.9)	180 (19.5)	0.590
Body mass index	26.8 (16.2)	27.2 (27.0)	0.210
Baseline MMSE score*	26 (24 to 28)	27 (25 to 29)	0.025
Baseline Trails A score*	76 (46 to 118)	65 (41 to 102)	0.003
Baseline Trails B score*	157 (98 to 246)	138 (84 to 227)	0.026
Years in education*	5 (4 to 8)	5 (5 to 8)	0.167
Years of follow up	7.8 (7.6)	8.2 (8.1)	0.006
Systolic blood pressure	158.2 (20.9)	142.6 (20.5)	<0.001
Diastolic blood pressure	87.0 (9.0)	82.1 (9.3)	<0.001
Hypertension - n (%)	187 (88.2)	647 (70.3)	<0.001
Diabetes – n (%)	31 (14.6)	112 (12.2)	0.330
Vascular disease - n (%)	30 (14.2)	147 (16.0)	0.513
Cerebrovascular disease - n (%)	11 (5.2)	38 (4.1)	0.493

Continuous data reported as mean (standard deviation), except when *non-normally distributed where median (interquartile range given)
MMSE = Mini mental state examination; IAD = systolic inter-arm difference

Table 2. Characteristics of participants according to systolic inter-arm difference by IAD status ≥ 10 or < 10 mmHg

	sIAD < 5mmHg	sIAD ≥ 5mmHg	p	sIAD < 10mmHg	sIAD ≥ 10mmHg	p
Change in MMSE score (units)	2.17 (1.78 to 2.56)	2.91 (2.08 to 3.73)	0.084	2.25 (1.86 to 2.63)	2.80 (1.89 to 3.72)	0.237
Rate of change MMSE score*	0.29 (0.24 to 0.35)	0.45 (0.32 to 0.58)	0.012	0.31 (0.25 to 0.36)	0.44 (0.29 to 0.59)	0.052
Change in Trails A score (seconds)	5.55 (2.47 to 8.63)	5.68 (-1.35 to 12.70)	0.970	5.77 (2.74 to 8.79)	4.68 (-3.53 to 12.90)	0.779
Rate of change Trails A score*	0.75 (0.36 to 1.13)	0.62 (-0.28 to 1.52)	0.780	0.79 (0.39 to 1.16)	0.42 (-0.61 to 1.45)	0.463
Change in Trails B score (seconds)	10.92 (6.03 to 15.80)	2.96 (-6.46 to 12.38)	0.130	10.66 (5.93 to 15.38)	1.43 (-9.47 to 12.38)	0.117
Rate of change Trails B score*	1.26 (0.68 to 1.84)	0.18 (-0.97 to 1.32)	0.084	1.22 (0.66 to 1.78)	-0.0097 (-1.39 to 1.32)	0.081

MMSE = Mini Mental State Examination; Trails = trail making score; IAD = systolic inter-arm difference
*change in unit score per year of follow up

Table 3. Changes in cognitive scores according to systolic inter-arm difference

Cognitive Measure	IAD ≥ 5mmHg				IAD ≥ 10mmHg			
	Unadjusted	p	Adjusted*	p	Unadjusted	p	Adjusted*	p
MMSE	1.41 (1.03 to 1.93)	0.032	1.31 (0.91 to 1.88)	0.140	1.30 (0.92 to 1.83)	0.142	1.07 (0.72 to 1.60)	0.740
Trails A	1.17 (0.80 to 1.70)	0.415	1.10 (0.71 to 1.73)	0.663	1.24 (0.82 to 1.86)	0.305	1.05 (0.64 to 1.74)	0.833
Trails B	1.30 (0.94 to 1.79)	0.112	1.23 (0.80 to 1.89)	0.344	1.27 (0.89 to 1.83)	0.192	1.06 (0.66 to 1.73)	0.800
Composite outcome	1.44 (1.10 to 1.89)	0.009	1.46 (1.05 to 2.03)	0.026	1.39 (1.03 to 1.88)	0.030	1.23 (0.85 to 1.78)	0.265

MMSE = Mini Mental State Examination; Trails = trail making score; IAD = systolic inter-arm difference

*adjusted for age, sex, baseline MMSE score, years in education, systolic blood pressure, ankle-brachial index, presence of diabetes, previous cerebrovascular event and duration of follow up

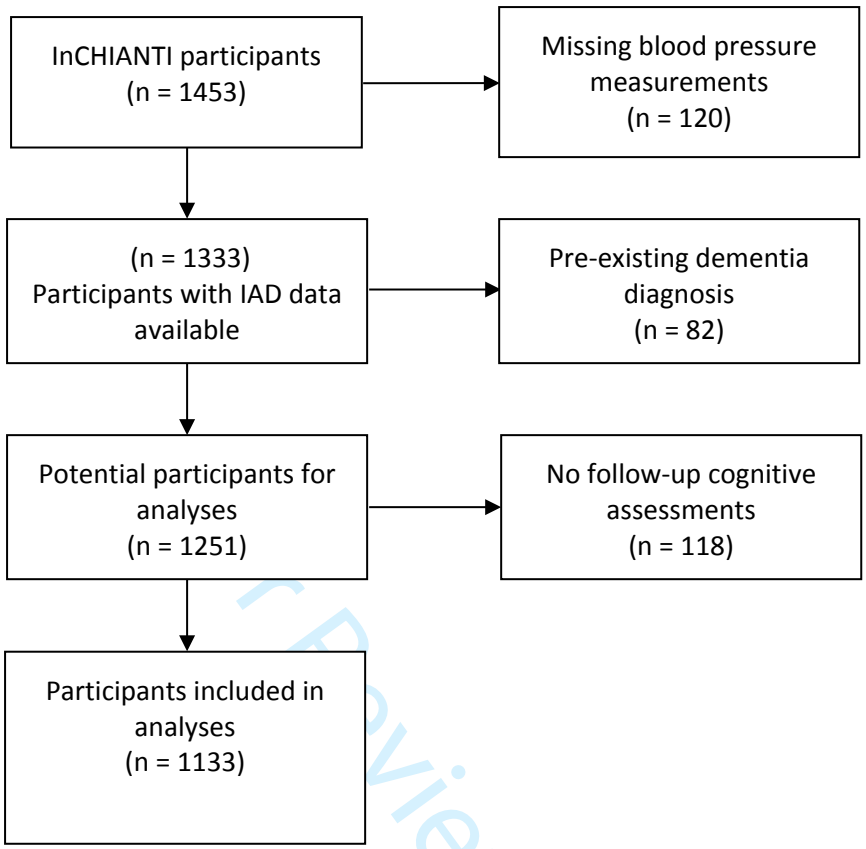
Table 4. Unadjusted and adjusted odds ratios for substantial cognitive decline for all participants according to systolic inter-arm difference

Variable	Decline in MMSE score ≥5		Composite outcome	
	OR	P	OR	p
Age	1.09	<0.001	1.07	<0.001
Sex	1.20	0.267	1.35	0.037
Baseline MMSE	1.02	0.617	0.94	0.050
Years in education	0.91	0.003	0.90	<0.001
Systolic blood pressure	1.01	0.235	1.00	0.980
Ankle-brachial index	1.58	0.397	0.52	0.184
Diabetes	1.49	0.068	1.96	0.002
Previous cerebrovascular event	2.22	0.020	1.53	0.231
Duration of follow up	1.02	<0.001	1.02	<0.001

MMSE = Mini Mental State Examination

Variables dropped from models on backwards stepwise regression:
baseline cardiovascular disease; baseline diastolic blood pressure; hypercholesterolaemia smoking status; body mass index; carotid stenosis ≥40%

Table 5. Multivariable models used to adjust associations of cognitive decline measures with inter-arm difference.



IAD = systolic inter-arm blood pressure difference

Figure 1 – Identification of participants eligible for study

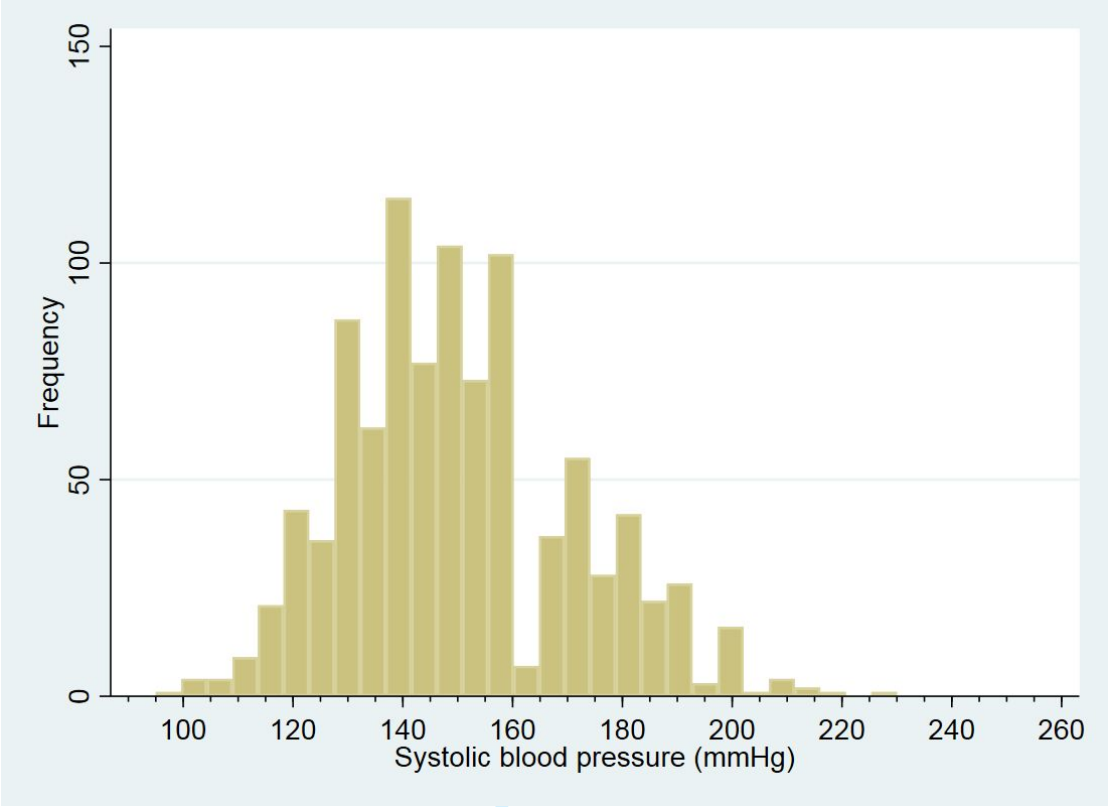


Figure 2 – distribution of systolic blood pressure at recruitment