High blood pressure (BP) has been associated with an increased risk of cerebrovascular disease, stroke, and Alzheimer disease pathology. Epidemiologic studies are consistent in showing that high BP, particularly in midlife, is a risk factor for the development of dementia in late life. However, supporting randomized evidence of the inference that BP-lowering therapy can prevent dementia has been slow in coming over the last 30 years. The most recent randomized trial, the Systolic Blood Pressure Intervention Trial—Memory and Cognition in Decreased Hypertension (SPRINT-MIND), therefore, makes a pivotal contribution to the field, reemphasizing broader public health benefits of BP lowering and directing future research.1

With SPRINT-MIND, there are now 8 completed randomized controlled trials that have evaluated different approaches to BP lowering (and levels of achieved systolic BP [SBP]) on dementia outcomes.2-7 While none of the trials has shown a clear treatment effect, the data collectively are more persuasive in showing a significantly lower risk of dementia in a random-effects meta-analysis of published results (relative risk reduction [RR] 0.93, 95% confidence interval [CI] 0.86 to 1.00, p = 0.07; I² 0%, Egger test of publication bias p = 0.10) (table e-1 and figure e-1, doi.org/10.5061/dryad.qr266nv).

However, there is more to the story. The baseline level of SBP varied across trials, with earlier trials recruiting patients with higher BP than more recent trials, and the difference in achieved SBP between randomized arms ranging from 24 to 17 mm Hg.2 If we hypothesize that higher SBP is associated with greater risk, we might expect those trials with the greatest difference in achieved BP between randomized groups would have the largest reduction in risk of dementia. Our meta-regression, albeit with inevitably few data points, shows a slope of a −0.009 (−0.026 to 0.007) reduction in the risk of dementia per mm Hg SBP difference between groups (figure e-2, doi.org/10.5061/dryad.qr266nv). Further exploration of a potential dose response in those trials that achieved a large (≥10 mm Hg) SBP difference showed a stronger point estimate consistent across trials (RR 0.88, 95% CI 0.78 to 0.98, p = 0.03; I² 0%, Egger test of publication bias p = 0.59; figure). It is also important to note that these data have arisen from trial populations with variable sociodemographic and clinical characteristics in participants of predominantly early old age and rates of dementia have been low and complicated by premature death and comorbidity. Furthermore, the primary focus of the majority of these trials has been on assessing serious cardiovascular events over just a few years of follow-up, and sophisticated evaluation of cerebrovascular pathology has been infrequent. Future studies in this area would benefit from modern methods allowing greater identification of the contributing etiology for incident dementias, in particular where vascular disease is present without amyloid deposition and vice versa.

Can we conclude that BP lowering to levels of at least 10 mm Hg systolic are needed to reduce risk of dementia? The totality of the clinical trial data is now moderately strong, and there is no evidence of important harms from the treatment. Yet, although SPRINT-MIND is congruent with prior trials, it shares the same limitation of not being designed to primarily determine effects on dementia.
Despite broad acceptance of hypertension as a risk factor for cognitive decline and dementia, there is still a gap in there being no single trial that has taken account of prior limitations and has been designed primarily to examine the role of BP lowering for the prevention of dementia. With a global aging population, high prevalence of hypertension, and simple low-dose combination BP-lowering treatment approaches gaining in acceptability, resolving this uncertainty is timely, feasible, and urgent.

Author contributions
R. Peters: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval.
J. Warwick: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval.
K. Anstey: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.
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Figure
Meta-analysis of trials of blood pressure (BP) lowering on dementia outcomes, according to having ≥10 mm Hg systolic BP difference between randomized groups.

| Group                  | Relative Risk (95% Confidence Interval) |
|------------------------|-----------------------------------------|
| SPRINT-MIND RR (1)     | 0.85 (0.68, 1.05)                        |
| SHEP RR (5)            | 0.84 (0.55, 1.30)                        |
| PROGRESS RR (3)        | 0.89 (0.74, 1.07)                        |
| HYVET RR (2)           | 0.90 (0.71, 1.13)                        |
| Combined (random)      | 0.88 (0.78, 0.98)                        |

HYVET = Hypertension in the Very Elderly Trial; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SHEP = Systolic Hypertension in the Elderly Program; SPRINT-MIND = Systolic Blood Pressure Intervention Trial—Memory and Cognition in Decreased Hypertension.