The effects of blood pressure reduction on cognitive function: a review of effects based on pooled data from clinical trials

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CRD summary
The authors concluded that blood-pressure reduction may have a variable effect on different aspects of cognitive function, with improvements in dementia and memory tasks but impairment in perceptual processing and learning capacity tasks. In view of the methodological weaknesses of the review, including a lack of information about the included studies and failure to adequately address the variation between them, these conclusions may not be reliable.

Authors' objectives
To evaluate the effects of blood-pressure (BP) reduction on cognitive function.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from January 1980 to March 2005 to identify eligible studies published in any language; the search terms were reported. Reference lists of previous reviews and retrieved articles were also examined.

Study selection

Study designs of evaluations included in the review
Published randomised controlled trials (RCTs) were eligible for inclusion. Studies with small sample sizes that contributed to heterogeneity in preliminary meta-analyses of cognitive outcomes were excluded.

Specific interventions included in the review
Studies of antihypertensive drugs compared with each other or placebo were eligible for inclusion. The review did not specify which antihypertensive drugs were used in the included studies. Where studies compared antihypertensive drugs against each other, the treatment with greater antihypertensive effect was considered the intervention arm of the trial. Studies of antihypertensives known to have detrimental cognitive effects were excluded after preliminary data analysis showed significant heterogeneity.

Participants included in the review
Inclusion criteria were not specified with respect to the participants. The participants in the included studies were aged from 46 to 76 years, with a mean baseline systolic BP of 138 to 191 mmHg and diastolic BP of 77 to 101 mmHg.

Outcomes assessed in the review
Studies that measured the effect of systolic and diastolic BP reduction on any measure of cognitive performance were eligible for inclusion. The cognitive outcomes assessed in the included studies comprised dementia (including the Mini Mental State Examination, MMSE), memory, perceptual processing, executive function and learning capacity. Systolic and diastolic reductions in BP were reported. The duration of follow-up ranged from 0.5 to 60 months (mean 18; median 5).

How were decisions on the relevance of primary studies made?
Two reviewers working independently selected articles for inclusion, with decisions reached by consensus.

Assessment of study quality
The following quality criteria were considered: quality of randomisation, blinding, reporting of withdrawals, generation of random numbers and concealment of allocation. One point was allocated for each area addressed. Two reviewers working independently assessed study quality.

Data extraction
Two reviewers working independently extracted data for the review. For each outcome measure, the reviewers...
extracted mean values and standard deviations of systolic and diastolic BP and cognitive measures at baseline and trial completion. Study authors were contacted for missing data.

Methods of synthesis
How were the studies combined?
Studies that reported sufficient information (11 of the 16) were pooled statistically, using a fixed-effect model to generate weighted mean differences (WMDs). Meta-analyses were stratified according to the type of outcome assessed.

How were differences between studies investigated?
Statistical heterogeneity was evaluated by means of the chi-squared and I-squared statistics. Studies were excluded from meta-analyses of cognitive outcomes in order to create homogeneous samples.

Results of the review
Sixteen RCTs (n=19,501) were included.

The median quality score of the included studies was 4 (range: 3 to 5). The studies were clinically heterogeneous with respect to interventions, follow-up times, patient age, and degree or duration of hypertension. There was highly significant heterogeneity between the studies in most (5 out of 6) meta-analyses for the outcome of BP reduction (I-squared 97.0 to 98.6%).

Four RCTS (n=13,212) assessed the effect of BP pressure reduction on MMSE after a mean of 17.7 months’ treatment. Three studies were pooled and showed a WMD in BP of -4.8/-2.6 mmHg between the two study arms, which was associated with a statistically significant improvement in the intervention arm in mean MMSE score (WMD 0.19, 95% CI: 0.19, 0.19). The fourth study (n=69) was excluded from analysis because of heterogeneity.

Five RCTs (n=717) assessed the effect of BP reduction on logical memory after a mean of 5.2 months’ treatment. The pooled studies showed a WMD in BP of -3.2/-1.5 mmHg between the two study arms, which was associated with a statistically significant improvement in the intervention arm in immediate (WMD 0.62, 95% CI: 0.21, 1.02) and delayed (WMD 0.67, 95% CI: 0.23, 1.11) scores for logical memory tasks.

Four RCTs (n=2,396) assessed the effect of BP reduction on perceptual processing and sequencing, using the trail making test (TMT)-A after a mean of 18.3 months’ treatment. The pooled studies showed a WMD in BP of -17.1/-7.0 mmHg between the two study arms, which was associated with a significant decline in trail making performance in the intervention arm (WMD -1.12 seconds, 95% CI: -1.22, -1.02).

Three RCTs (n=2,184) assessed the effect of BP reduction on paired associate learning. The pooled studies showed a WMD in BP of -17.1/-7.0 mmHg between the two study arms, which was associated with a significant decline in performance in the intervention arm (WMD -0.04 seconds, 95% CI: -0.04, -0.04).

One RCT (n=351) investigated digit span, symbol digit substitution and the TMT-B, but there was no significant reduction in BP in the intervention group and no change in cognitive performance.

Authors’ conclusions
BP reduction may have a heterogeneous effect on different aspects of cognitive function: improvements in dementia and memory tasks, but impairment in perceptual processing and learning capacity tasks.

CRD commentary
The review question was clear and a variety of relevant sources were searched, although the restriction to published studies may mean that some studies were missed. The inclusion criteria were wide and there were few details about the included participants, interventions and study settings. The study selection, validity assessment and data extraction processes were carried out in duplicate, which helps minimise error and bias. It is unclear whether the data synthesis was appropriate, as heterogeneous studies were excluded from the meta-analysis of cognitive outcomes without consideration of possible reasons and without providing any detailed information about these studies. However, the authors commented that the exclusion of these studies did not change the overall findings of the review. Marked
heterogeneity in the meta-analysis of BP outcomes was not addressed. As the authors stated in their discussion, different studies were used in analyses of MMSE/memory impairments and perceptual/learning measures and this also weakens the evidence. In view of the methodological weaknesses, including the lack of details provided about the included studies and the failure to adequately address heterogeneity, these conclusions may not be reliable.

**Implications of the review for practice and research**

Practice: The authors stated that treatment with antihypertensive drugs reduces decline in global cortical function and memory, but may not have similar effects on subcortical executive function and learning capacity.

Research: The authors stated that more research is needed to assess the effect of BP reduction in individuals whose cerebrovascular disease status is well characterised; such research should use assessments sensitive to changes in specific cognitive functions.

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