Reviewer's report

**Title:** Generalizability of guidelines and physicians' adherence. Case study on the JNC VI guidelines on hypertension

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**Reviewer:** Richard Thomson

**Level of interest:** A paper whose findings are important to those with closely related research interests

**Advice on publication:** Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Thank you for asking me to review this article which I read with interest.

There are some interesting observations here, but I think the paper is going to need major revision and re-writing before it could be published and indeed before I can fully and properly review it.

This study is cross-sectional, using patients from NHANES III to assess whether patients with identified hypertension have been appropriately treated with reference to JNC VI guidelines, and in relation to the generalisability of the trials that contributed to the development of these guidelines. The judgement of appropriateness is centred upon presence or absence of drug therapy. BP measures were taken at household interview.

The hypothesis underlying the work is that the limited generalisability of the evidence on which guidelines are based might reduce physicians' adherence to them. This study sought to "test the hypothesis that physicians adherence is lower in groups of people to whom guidelines are not generalisable".

I have a fundamental issue with the question and the methods subsequently used. The guidelines specify who should be considered for treatment; that is their purpose. They are derived from systematic review and meta-analysis of admittedly disparate randomised controlled trials which together cover a wide range of patients. It could be argued that one of the key functions of meta-analysis and systematic review is to produce more generalisable guidance.

The authors look differently at this. They assess the proportion of patients in the NHANES survey that would have been included or excluded in the individual trials that contributed to the JNC VI guidelines. Perhaps not surprisingly, this varied widely from trial to trial; only 52.5% of their population of hypertensives would potentially have been enrolled in at least two of the trials.

However, there are also some potential biases built into the study design, some of which the authors themselves acknowledge. Firstly, they have not been able to incorporate patients who are hypertensive but whose blood pressure is controlled. Furthermore, in categorising their patients into the treatment categories of the JNC VI risk stratification scheme (table 1), they have not been able to take account of the degree of control already experienced as a result of treatment. Hence, patients
already on anti-hypertensive therapy may well be mis-classified as a result of their blood pressure already having been reduced by treatment.

In some instances it is very difficult to interpret the data without the underlying numerator and denominator data. This needs to be rectified. For example, the final paragraph on page 10 has percentages without absolute numbers and it is not clear whether the statement that "23% of this population had a diagnosis of hypertension and 11% had hypertension requiring treatment ..." gives a total of 34% with hypertension or refers to 11% of the 23% who required treatment etc.

In table 3, it is not clear whether the first column includes the percentage of the total hypertensive population or does it exclude treated hypertensives with normal blood pressure?

There is an inconsistency between the categories stated in table 1 and those assigned in the text and in figure 1. Table 1 puts stage 1 and 2 together and stage 3 separately, whilst the text and figure 1 put stage 2 and 3 together and consider 1 separately. Which is correct?

Another possible source of bias is that the blood pressure used to categorise patients has been measured at a single point in time. There is likely to be a regression to the mean effect which would potentially reduce the absolute numbers of patients appropriate for the JNC VI guidelines.

As one would expect, the authors have had to make some judgements about data available in order to categorise people into JNC risk strata in table 1. Thus, they have used self-reported hypercholesterolemia as equivalent dyslipidemia. This will have under-estimated the levels of dyslipidemia. Equally, they have used family history in a relative under 50 (which does not appear to be included as a criterion in table 1) which differs from JNC VI. Again this will under-estimate the number of people eligible with any form of family history.

The conclusions on the types of drug treatment are also very difficult to interpret; the guidelines are about first line therapy at time of diagnosis whilst the study population used here is cross-sectional. Therefore any conclusions about use of particular drug therapies cannot take account of which drugs have previously been tested and tried (appropriately or inappropriately). Any conclusions on this basis are therefore limited.

I am confused by table 3. Eligibility for each trial was apparently assessed on the basis of age, gender and blood pressure levels, whilst exclusion criteria included MI, heart failure and renal impairment as appropriate. The marked variability and generalisability of the trials is therefore not surprising - in fact the VA I trial has a very low generalisability because it incorporated patients younger than the inclusion ages within this NHANES population!

From this approach the authors calculate that 57.5% would have potentially enrolled in at least one trial and 52.5% in at least two trials. It would also be very helpful for the reader (other than knowing the absolute numbers) to know what the main reasons for exclusion of those that would not have been included were.

The methods on page 9 could be more clearly stated. It is stated that the risk factors taken into account to assign people to each risk category were gender (male), age over 60 years, current smoking, parent with cardiovascular disease before the age of 50, self-reported diagnosis of hypercholesterolemia, and diabetes mellitus. If this is the case, then target organ disease has not been used (as it should have been) to classify patients according to table 1. I think part of the problem here is that some of the "exclusion" criteria for individual trials also represent "inclusion" criteria for considering drug therapy in the JNC VI recommendation and this in itself makes interpretation of the conclusions regarding generalisability quite difficult.

The authors state that the NHANES III study involved non-random sampling, but they haven't
described how and I think this is probably important in order to understand how representative the population is with which they are working here.

In terms of the presentation of the results, I think it is important that the statistical analyses are properly incorporated into the textual presentation and the conclusions. At the moment conclusions and summaries ignore the statistical findings. For example, on page 12 it is stated "we observed a lower prevalence of people that would have been enrolled in at least two trials in the group receiving drug treatment". However, when you look at the tabular data this is not significant.

Similarly, the findings presented in the third paragraph of page 12 also makes statements that seem at odds with the statistical analysis.

In conclusion, I think the data need to be more clearly presented, the authors need to be clearer about the potential biases within their study, and the implications of these for their findings, and they need to justify more clearly their definition of generalisability. For example, they state that "a substantial proportion of people (30%) with a diagnosis of hypertension ..." have not been prescribed any anti-hypertensive drug. Nonetheless, this figure would have been much smaller if the patients known to be hypertensive, but treated and controlled, had been included.

The authors conclude "the risk profile is much more important in influencing treatment than the actual blood pressure levels". This is not surprising as it is indeed in line with the JNC guidelines which are based upon absolute risk and not just blood pressure levels. To conclude that "the characteristics of the individual patient are driving the decision to treat more than the guidelines recommendations" is therefore difficult to justify since the guidelines themselves would promote treatment of people at higher risk and with higher prevalence of co-morbidities. Thus, the arguments on page 15 need re-thinking and re-stating (or at least justifying more clearly, although it is difficult to interpret all of these in the absence of the underlying data.)

I think any conclusions (e.g. top of page 16) about the type of medication use not mirroring JNC VI guidelines cannot be justified given the cross sectional nature of the data (see above).

Finally, the brief "conclusions" paragraph is open to challenge. The data do not "show a weak association between generalisability and adherence rate"; the association is not significant. The statement that the individual risk factor profile plays a major role in physicians' decisions to treat (with the implication that this is in some way different to the guidelines) is again not sustainable (see above).

**Competing interests:**

None declared.