

Dear Dr Lawson (Acting Editor),

Thank you for giving us the opportunity to respond to reviewers comments. We have edited our manuscript based on the feedback received and our specific responses to each point are detailed below. We hope that the manuscript will now be acceptable for publication in BJGP.

Kind regards,

Dr Sarah Lay-Flurrie

RESPONSE TO REVIEWERS

REVEIWER 1

COMMENT: This is a well-conducted study showing less hypertension-related workload for GPs following the 2011 NICE guideline. Results are clear. It remains speculative, though, whether it was truly the guideline or some other factor that caused the observed changes.

Is it possible to make an estimate of what this would mean in terms of cost reduction?

RESPONSE: Thank you. We acknowledge in the discussion that 'time-series cannot establish causality'. This was why we used negative controls to more fully understand the possibility that other factors were in part responsible for the changes in workload we observed. Estimates of potential cost reductions are best assessed through formal economic analyses, considering costs of diagnosis, treatment and reductions in future cardiovascular events. Recent formal economic analysis of the use of home or ambulatory monitoring for diagnosis has shown that it is cost-saving compared to clinic BP, with savings ranging from £7 per person for women over 70 to £186 for women under 40. We have added text to the discussion to reflect this point as follows:

"We have not provided cost estimates as part of this study, but recent formal economic analyses have shown that out-of-office monitoring is cost saving compared to clinic BP measurement, with savings of up to £186 per person.¹⁹"

COMMENT: The abbreviation CPRD should be written in full in the Methods section.

RESPONSE: We have now defined this in full at first use.

REVIEWER 2

COMMENT: I find this a well written manuscript, the aim is clear, the methods used seem sound. Blood pressure management is a relevant topic for general practice: the place where hypertension is daily bread and butter. With the aim of the study in mind and then looking at my own practice, hypertension management has different phases and elements: prevention of hypertension, detection or even screening for unknown hypertension in the population; diagnostic process once elevated BP is found, follow up of patients with low CVR but (mild) elevated BP, management of patients with hypertension and indication for treatment (non medical and medical), treating to target, evaluation of (pseudo) TRH, management of hypertensive urgency / emergency. Hypertension related workload in general practice and changes therein will depend on all these elements but in my experience most time is used in the diagnostic phase, in lifestyle

management/non-medical treatment and in treating to target. The NICE guideline radically changed practice to be (to my knowledge) the first hypertension guideline worldwide to advocate the use of ABPM/HBPM immediately after 1 office based BP > 140/90. This change is thus one in the diagnostic phase. Other international guidelines in that time advised to take 2-4 or “several” moments in “several weeks to months” time to measure OPBM 2-3 times per moment and then to establish or discard a diagnosis of HT. Data from before 2008 extracted from our research network showed that in the Netherlands a GP took on average 7 consultations before giving the code hypertension. One can imagine that these 7 consultations will become substantially less when consequently applying the NICE guideline recommendation. Now zooming in on the manuscript. I think it is worthwhile to understand how the workload of GP’s evolves over time and zooming in on hypertension makes sense, because it’s almost daily business for GP’s. Increased workload (actual and perceived) is a hot topic among GP’s and a source of frustration or even worse burn-out. I have doubts however if it is at all possible to come to a valid conclusion at least about the second aim of the study: the impact of the guideline on hypertension workload. Guidelines in HT tend to be revised every 5-10 years and with these revisions often come changes in all elements of HT management. Some changes may create extra work (eg more focus on prevention / early detection), some may reduce the workload (start with combination treatment, early use of ABPM). In this black box of changes there are also societal changes, , (primary care/health care) organisational changes, etc that indeed may affect HT related workload. If all other variables would stay the same I would expect less hypertension related work since 2011 because of less time used in the diagnostic phase and less unnecessary treatment of patients with white coat hypertension in the treatment phase of hypertension management. I would not expect relevant reductions in time/work in the treatment (non medical or medical) because of the guideline introduction. My general concern with this type of research / data is that results leave a lot of space for speculation / imagination but give too little firm ground to answer the research questions. For me the question then rises: what do we really learn from these data? Is it really true that GP practices put less time in HT management? I have my doubts about that (what may be gained in the diagnostic phase may be lost in more awareness about pseudoTRH for instance; less work in hypertension may have been substituted for more work in CVRM). However, assuming it is “true”, after reading the manuscript I still do not understand why.

RESPONSE: Thank you for the careful consideration of our paper. We agree that there are limitations of this type of research data and have further highlighted these in response to more specific comments below. We have also moderated the language we use to draw conclusions from our data, but would also argue that interrogating routine data is one of the few ways to assess the impact of guideline change at a national level after the fact and this is important for clinical practice. Though all research has various degrees of imprecision, being able to provide some objective evidence, with sufficient caveats, on this question is preferable to the all too frequent alternative in medicine of unsubstantiated personal opinions. During our study period, guidelines for hypertension were updated only once in 2011 and the shift to out-of-office measurement of blood pressure for the diagnosis of hypertension was the biggest single change within the guidance. We would therefore argue that observed changes in hypertension related workload, could plausibly be linked to guideline change, even when accounting for wider trends in consultation rates.

COMMENT: In an attempt to be able to draw conclusions after all, the authors try to “correct” for black box changes by comparing changes in HT workload over time with negative controls (asthma / all conditions). In my view this part is crucial for the interpretation of the results. Although the authors address the matter, I think these comparisons deserve more attention and elaboration in the core of the manuscript. I prefer to see figure 1 and 2 not only for hypertension but also for asthma and other chronic conditions (see my further comments). The control findings should be part of the summary at the start of the discussion section. In my view the summary is now to

strongly written in the interpretation/suggestion that the NICE guideline introduction seems to be the cause of the trend changes (or is at least associated with it). I fully agree with the statement in page 8 lines 51-52. In addition I would like to invite the authors to be more specific and focused about the finding that downward trends in asthma and all condition is similar to the trends in hypertension. (page 8 line 56 – page 9 line 12) After all isn't that a strong argument against the role of the NICE guideline as an explaining factor of the trends in hypertension consultations?

RESPONSE: Thank you. We agree with the reviewer that these negative control analyses are important to place our findings in context. We have now included time-series graphs for asthma-related and all-cause consultations, in addition to Table S4, to allow easier visual inspection of results (Supplementary Figures S2 and S3). Our view is that despite evidence of wider changes in consultation patterns, our analysis of hypertension related consultations as a proportion of all consultations demonstrates changes in hypertension management over and above these wider changes. We have however, edited the initial summary text and paragraph regarding asthma consultations as follows:

“The rate of hypertension related general practice consultation in England was stable between 2006 and 2010 and then fell between 2011 and 2017. This reduction was concurrent with similar changes in trend in the rate of asthma-related and all-cause consultations, suggesting that the new downward trend was driven in part by wider system or population level changes. However, changes in hypertension-related workload were relatively greater than changes in overall all-cause consultation rates and occurred primarily around the time of diagnosis, indicating that these changes may be plausibly associated with the guideline change in 2011. Similar patterns were observed for average consulting time.”

“Our analyses of hypertension and asthma related consultation, as well as all consultations, showed similar patterns, suggesting that system-wide changes were influencing all consultation rates during our study period. In this context, the impact of guideline changes will be limited and more difficult to discern in routine data. Our finding that the rate of consultation has fallen over recent years may be surprising given that GPs reported increased workload up to 2017,¹⁴ and media portrayals of a service in crisis.¹⁵”

COMMENT: Outcome variable: what is precisely meant by a clinical code for diagnosis or management of hypertension. How is this code given, is it a ICPC code in the evaluation part of consultation? Does this mean that only when hypertension is diagnosed patients are included or also in the process prior to that? Is part of patients in which the GP measures BP several times because in doubt of hypertension and decides that no further management is needed included or not? (What is coded in these instances?) Are codes used for preventive cardiovascular care in low risk patients? And for cardiovascular risk management? Hypertension management is part of cardiovascular risk management (CVRM). In The Netherlands from 2006 onwards hypertension guidelines even ceased to exist and were absorbed in the guideline on Cardiovascular Riskmanagement. Applying CVRM rather than hypertension management sec surely is not a unique Dutch feature. In my view it is important to put work related to hypertension in the context of work related to CVRM. Is it possible that time spent on hypertension management has become less over the years (whether or not due to NICE 2011) , but time spent on CVRM (including HT management) has increased. What is then the meaning/relevance of the findings presented in the current manuscript. Could the trend changes after 2011 be a result of stronger implementation of CVRM guidelines?

RESPONSE: Data in the CPRD is coded using Read codes. We have now included the list of codes used to define hypertension related activity (diagnosis, management or blood pressure measurement) in the supplementary material. These include general codes for blood pressure measurement applicable to patients with and without a diagnosis (e.g. 246..00 O/E - blood pressure reading) and codes relevant only to those with hypertension (e.g. 662d.00 Hypertension annual review). Other codes lists (e.g. for antihypertensive medication) are available from the authors on request but are overly long to include in the supplement. We included all adult patients without a prior history of hypertension in our analyses, but have edited the methods section to make the inclusion criteria clearer:

“The methods used for this study have been fully described previously.⁷ Briefly, this was a retrospective open cohort study of adults (aged 18 years and over) registered at English general practices contributing to the Clinical Practice Research Datalink (CPRD) between 1/4/2006 and 31/3/2017. Patients were included if their records were acceptable for research purposes and eligible for data linkage and they entered the study on the date they met all eligibility criteria. Patients were excluded if they had a history of hypertension prior to study entry, but were not excluded if they developed hypertension during follow-up”

We did not include codes for broader cardiovascular risk management in our definition of hypertension related activity. In England, guidance for cardiovascular disease prevention remains separate from that for hypertension. Hypertension continues to be managed as a separate condition in line with the Quality and Outcomes Framework, which incentivises activity specifically related to chronic conditions including hypertension. General practice coding related to this activity is therefore likely to be of high quality and the codes we used in our definition include those used under the framework.

Nevertheless, the reviewer is correct that broader cardiovascular risk assessments are relevant when considering treating patients with only moderately raised blood pressure. However, because our primary definition of hypertension related activity included any blood pressure recording, in patients with and without existing hypertension diagnosis, we are confident that consultations about cardiovascular risk more broadly would be captured by this definition. To clarify the issue, we have added further text to the discussion regarding as follows:

“Our definition of hypertension-related activity did not include codes specifically related to cardiovascular disease risk or prevention since, in England, guidelines for cardiovascular disease prevention (largely related to statin prescription in relation to CVD risk) are separate to those for hypertension.¹² Nevertheless our inclusion of codes for *any* BP measurement is likely to have captured many consultations considering cardiovascular risk more generally. Due to our inclusive definition, some consultations may have been misclassified (e.g. the use of calcium channel blockers in Raynaud’s phenomenon), but these would not have been expected to change with changes in hypertension guidance.¹³”

COMMENT: I can think of good reasons why the authors used asthma as negative control, but please explain in the manuscript why this condition was chosen. I would be interested also in some other chronic conditions as well: DM? Hyperlipidemia? COPD?

RESPONSE: We have added further text to the methods section to explain this choice:

“Asthma was chosen because it is primarily managed in primary care, similar to hypertension, but has a different pathophysiology and completely different diagnosis and treatment pathways. The

activities carried out to manage asthma are therefore unlikely to be affected by changes to hypertension guidelines.”

With respect to the specific conditions mentioned by the reviewer, our view was that at least some of the goals of hyperlipidemia and diabetes management fall under a broad umbrella of cardiovascular disease prevention. They therefore share commonalities with hypertension management, as raised by the reviewer in previous points, which may be influenced by guideline changes. Our view was that any negative control needed to be similar to hypertension in the following ways: managed in primary care, monitored regularly and well-recorded in the CPRD database. Conversely, the negative control needed to be different from hypertension in that we would not expect it to be influenced by a change in hypertension guidelines. Having ruled out hyperlipidemia, diabetes and chronic kidney disease for the reasons mentioned above, we decided we were left with asthma. We could add in other negative control analyses if the reviewer is able to suggest conditions that satisfy the criteria above, but also believe that such analyses are unlikely to provide further meaningful insight.

COMMENT: In the summary, one aim is mentioned. This aim is the second aim as written in the introduction section. This creates expectations for the reader. In my view the current manuscript is stronger in addressing the first rather than the second aim.

RESPONSE: We have reworded the summary (as detailed above) so that the first sentence speaks to our first aim more generally and a more new nuanced consideration of findings with respect to our second aim follows. We have discussed at length the limitations of these data to draw firm conclusions about our second aim and made changes on the basis of the other specific comments above. We hope that these satisfy the reviewers concerns about presenting a balanced picture.

COMMENT: I like table S1 and maybe it could have a more prominent part in the article. It shows time trends in a way that the average GP comprehends. It demonstrates a clear jump in the use of HBPM and ABPM after NICE 2011 and as such shows the impact of guidelines. (we did not see such impact of guidelines in Dutch hypertension care (van der wel et al . 2008). Hypertension diagnostic codes I expected to drop after 2011 because of less white coat hypertension coding. But increased awareness, better screening, more casefinding etc may have caused the absence of a drop. This column to me shows my struggle with the presented data as I mentioned earlier in the general comments part. It tickles the imagination, but it gives no clear answers.

RESPONSE: We included Table S1 in the supplement only as these data (covering trends in out-of-office BP measurement, diagnosis and treatment) are addressed in more detail in our previous publication from this project (referenced in the main text). We refer the reviewer to this paper for a full discussion of these findings as it would be inappropriate to duplicate these in the current manuscript and have included a comment in the discussion:

“We have not considered the clinical content of consultations in finer detail as this would overlap considerably with our previous work.”

COMMENT: Page 6 line 18, “before prior”

RESPONSE: Thank you. We have corrected this.

COMMENT: Table 1: median age of 36 ? is that correct or a typo? In The Netherlands the median age for newly diagnosed hypertension lies around 60.

RESPONSE: The median age of the cohort is 36. As stated in the methods, this cohort included all adults without a prior history of hypertension. It was also an open cohort so patients entered the study on the date they met all eligibility criteria including date of 18th birthday. We have edited the study population section to make this clearer:

“The methods used for this study have been fully described previously.⁷ Briefly, this was a retrospective open cohort study of adults (aged 18 years and over) registered at English general practices contributing to the Clinical Practice Research Datalink (CPRD) between 1/4/2006 and 31/3/2017. Patients were included if their records were acceptable for research purposes and eligible for data linkage and they entered the study on the date they met all eligibility criteria. Patients were excluded if they had a history of hypertension prior to study entry, but were not excluded if they developed hypertension during follow-up.”

COMMENT: Page 9 line 34-40. Somewhat confusing for me, I do not understand the first sentence. “unanticipated areas”? Where in the manuscript were anticipations addressed?

RESPONSE: This sentence relates to the previous literature and predictions made at the time of the introduction of the NICE guideline, which we reference in our introduction. We have, however, amended this sentence to make our point clearer:

“The introduction of the NICE hypertension guideline in 2011 was predicted to reduce workload by reducing the number of false diagnoses in people with white coat hypertension and workload related to subsequent management. We have shown that workload related to making a diagnosis more generally has reduced, rather than in the specific context predicted.”

COMMENT: Line 42-43. Too strong a formulation with the current data and interpretation.

RESPONSE: We have edited this sentence to better reflect the limitations of our findings:

“Whilst we cannot establish causality, our findings indicate that the implementation of out-of-office monitoring for diagnosis does not increase general practice workload and may deliver time savings.”