PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	High blood pressure during pregnancy is associated with future cardiovascular disease: observational cohort study
AUTHORS	Lind, Joanne; Tooher, Jane; Chiu, Christine; Yeung, Kristen; Lupton, Samantha; Thornton, Charlene; Makris, Angela; O'Loughlin, Aiden; Hennessy, Annemarie

VERSION 1 - REVIEW

REVIEWER	Professor Dilly OC Anumba, MBBS FWACS FRCOG MD LL.M (Medical Law) Chair of Obstetrics and Gynaecology Honorary Consultant in Obstetrics & Gynaecology/Subspecialist in Fetomaternal Medicine Department of Human Metabolism Academic Unit of Reproductive and Developmental Medicine The University of Sheffield 4th Floor, Jessop Wing Tree Root Walk, Sheffield S10 2SF, UK Competing Interests: None
REVIEW RETURNED	21-Apr-2013

GENERAL COMMENTS	Excellent well written paper. Minor typos: P5 Line 2: Should be "return" not "returned" P9 Line 14 Should be "91.3" not "913" P11 Line 48 Sould be "causal" not "casual"

REVIEWER	Jodie Dodd The University of Adelaide, Australia
REVIEW RETURNED	22-Apr-2013

GENERAL COMMENTS	This study describes an observational/cross sectional analysis identifying an association between hypertensive disorders in pregnancy and subsequent risk of both hypertension and stroke in later adulthood. Importantly the authors have identified the major limitations of the study, including the nature in which the information was ascertained (ie questionnaire only). The most significant limitation of the study is the inability to evaluate the effect of different categories of hypertension in pregnancy, which in itself represents a considerably heterogeneous group of disorders. It would be valuable to have validated information about the timing and severity of hypertensive conditions in pregnancy, but this was not available in the current context of this study.

REVIEWER	Gloria Valdes MD Professor School of Medicine Pontificia Universidad Católica Santiago, Chile I have no competing interests.
REVIEW RETURNED	23-Apr-2013

GENERAL COMMENTS	**Major comments:** Comment to *Page 5: Lines 41-46: Women with HDP experience an abnormal response to the placenta with shallow vascular invasion of the placental trophoblasts which leads to an ischemic placenta.11"* The shallow vascular invasion described in this statement cannot be ascribed to gestational non-proteinuric hypertension. Women predisposed to hypertension may unmask their susceptibility in response to the characteristic increase of plasma volume, cardiac output, renin-angiotensin-aldosterone system. Comment to Pag 5 line 52 to page 6 line 10: "*The endothelial damage caused by HDP was thought to disappear immediately following birth as the mother's blood pressure returned to its normal value, and the endothelium appeared to returned to its prepregnancy state.12 There is now substantial evidence to show that the endothelial damage remains, and it is this damage that is thought to increase the risk of developing CVD in later life when compared to women who remain normotensive during pregnancy.13, 14"* It has to be taken into account that the endothelial dysfunction may represent an underlying preconceptional condition, as suggested by the finding that women with recurrent pregnancy loss – who did not present the second stage of preeclampsia characterised by deportation of placental factor/microparticles –had endothelial dysfunction 11 months after the index pregnancy (Hypertensión 2007;49:90-5). **Minor comment:** Please explain the following statement in Page 7 line 21: "*People aged 80 years and over, and residents of rural and remote areas were oversampled*

REVIEWER	Sandra Lowe VMO Obstetric Physician and Conjoint A/Prof, School of Women"s and Childrens Health Royal Hospital for Women and UNSW, Sydney.
REVIEW RETURNED	07-May-2013

GENERAL COMMENTS	Some questions and suggestions: "of which 7 706 (10.7%) reported having had HDP." Can the authors comment on this apparently relatively high incidence of HDP. "There was no significant difference in odds of having stroke in the other groups of women …. BMI < 25 & Yes HDP), compared to women of healthy weight who had remained normotensive during their pregnancy." ??explanation, Type 2 error?? Can you estimate the effect of parity or recurrent HDP ie as seen with risk of Type 2 diabetes and recurrent GDM ? "and CVD is more common in these women within one to two decades of the hypertensive in pregnancy event.20, 21" These references are incomplete as a number of other studies albeit case control studies have demonstrated this age effect eg Valdes G et al . Hypertension, 2009:53:733-38 Arnddottir GA et al BJOG 2005 :112:286 "may explain the increased odds of cardiovascular disease in women who had HDP, where the development of HDP was an early warning sign unmasking the genetic predisposition due tothe stress of pregnancy27" Need to offer the alternative hypothesis of HDP as a cause of these CVS complications "women who experience HDP should have their blood pressure closely monitored in the years following pregnancy." Good opportunity to stress monitoring and management of all modifiable CVS risk factors including smoking, hyperglycemia, hyperlipidemia In future research also need to stress there is no data demonstrating that such monitoring or intervention has been demonstrated to impact on outcome but biologically probable.

REVIEWER	Christoph Lees MD MRCOG Consultant in Obstetrics and Fetal-Maternal Medicine | Lead, Fetal Medicine | Rosie Maternity Addenbrookes Hospital | Cambridge University Hospitals NHS Foundation Trust Visiting Professor | Department of Development and Regeneration | Katholieke Universiteit Leuven | Belgium Editor in Chief | Fetal Maternal Medicine Reviews

	I have no competing interests, commercial interest nor other relevant disclosure in relation to my review of this manuscript.
REVIEW RETURNED	23-May-2013

GENERAL COMMENTS	This is an interesting and well written study that investigates, from questionnaire responses, the contribution of hypertensive disease in pregnancy to later cardiovascular disease and events and the timing of these. Further, the effect of BMI on cardiovascular events in later life is reported. Some of the findings are novel. The weaknesses of the study is that unlike several others (prospective cohorts or studies using linkage from pregnancy records) the presence of hypertension in pregnancy and subsequent events is based on patient recall. Further, as the authors state, those women with the most severe morbidities and death would likely be under-represented. And no distinction is made between gestational hypertension and pre-eclampsia. These points are made somewhat superficially in the discussion but some form of qualification or quantification of these biases on the results would strengthen the discussion. Following on from this point, even if gestational hypertension could not easily be differentiated from pre-eclampsia by asking patients in a questionnaire, it would have been very interesting had hypertensive disease in pregnancy been classified as that requiring treatment and that not requiring treatment. Further, with a sample of this size it would be possible to determine if hypertensive disease in pregnancy were associated with chronic renal disease. If this data is available it would strengthen the paper. It is not clear from the methods or figure 1 exactly how many women were approached and completed the questionnaire. The 45 and up study recruited 267,153 men and women. How many women, therefore, were potentially eligible? Is it 84,619? If 12,800 were excluded leaving 71,819, surely all did not satisfactorily complete the questionnaire. Or does 84,619 refer to the number of women that had completed the questionnaire, in which case this must be a subset of a larger number assessed for study inclusion.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Mr. Richard Sands
The abstract states 'A total of 84 619 women were eligible for this study of which 71 819 were included.' I can't find this information in the main manuscript. How/why were the other 13k women excluded?

Author response
The inclusion and exclusion criteria were included in the Methods section under Study Sample, and are also listed in Figure 1.
The authors have also revised the results section to include the following sentences.

"A total of 84 619 women were eligible for the study (Figure 1). These women had given birth between the ages of 18-45 years, had an intact uterus, and had not been diagnosed with high blood pressure prior to their first pregnancy. Of these women, 71 819 were included in the study (exclusion criteria

shown in Figure 1) of which 7 706 (10.7%) reported having had HDP."

Reviewer 2: Professor Dilly OC Anumba
P5 Line 2: Should be "return" not "returned"
P9 Line 14 Should be "91.3" not "913"
P11 Line 48 Sould be "causal" not "casual"

Author response
Typos P5 and P11 have been corrected. The P9 is not incorrect. There were 913 women who had reported having a stroke.

Reviewer 4: Professor Gloria Valdes
Comment to Page 5: Lines 41-46: Women with HDP experience an abnormal response to the placenta with shallow vascular invasion of the placental trophoblasts which leads to an ischemic placenta.11"
The shallow vascular invasion described in this statement cannot be ascribed to gestational non-proteinuric hypertension. Women predisposed to hypertension may unmask their susceptibility in response to the characteristic increase of plasma volume, cardiac output, renin-angiotensin-aldosterone system.

Author response
This hypothesis was mentioned in the discussion: "An inherited predisposition to endothelial dysfunction, obesity or insulin resistance may explain the increased odds of cardiovascular disease in women who had HDP, where the development of HDP was an early warning sign unmasking the genetic predisposition due to the stress of pregnancy"

Additionally, the following reference has been included in the introduction:
AM. Germain, MC Romanik, I Guerra, S Solari, M Soledad Reyes, RJ. Johnson, K Price, S. Ananth Karumanchi, G Valdés. Endothelial Dysfunction : A Link Among Preeclampsia, Recurrent Pregnancy Loss, and Future Cardiovascular Events? Hypertension 2007; 49:90-5.

Reviewer Comment
Page 5 line 52 to page 6 line 10: "The endothelial damage caused by HDP was thought to disappear immediately following birth as the mother's blood pressure returned to its normal value, and the endothelium appeared to returned to its prepregnancy state.12 There is now substantial evidence to show that the endothelial damage remains, and it is this damage that is thought to increase the risk of developing CVD in later life when compared to women who remain normotensive during pregnancy.13, 14"
It has to be taken into account that the endothelial dysfunction may represent an underlying preconceptional condition, as suggested by the finding that women with recurrent pregnancy loss – who did not present the second stage of preeclampsia characterised by deportation of placental factor/microparticles –had endothelial dysfunction 11 months after the index pregnancy (Hypertensión 2007;49:90-5).

Author response
The following sentence has also been included in the discussion: "Alternatively, pre-existing endothelial dysfunction prior to conception may be a triggering mechanism for the development of HDP, as well as increasing the risk for CVD later in life.15"

The following reference has been included in the manuscript.
AM. Germain, MC Romanik, I Guerra, S Solari, M Soledad Reyes, RJ. Johnson, K Price, S. Ananth Karumanchi, G Valdés. Endothelial Dysfunction : A Link Among Preeclampsia, Recurrent Pregnancy Loss, and Future Cardiovascular Events? Hypertension 2007; 49:90-5

Minor reviewer comment
Please explain the following statement in Page 7 line 21: "People aged 80 years and over, and residents of rural and remote areas were oversampled.

Author response
A greater number of people aged over 80 and from rural areas were invited to participate in this study

(compared with people under 80 years, or people living in urban areas). The decision to oversample was a component of the study design for the 45 and Up Study to enable studies which focused on these groups to be adequately powered.

Reviewer 5: Sandra Lowe
"of which 7 706 (10.7%) reported having had HDP." Can the authors comment on this apparently relatively high incidence of HDP.

Author response
The higher incidence of HDP in this population was addressed in the discussion, and attributed to bias in self reported data recall, or the systematic under-reporting of HDP: “In our study the prevalence of high blood pressure in pregnancy was 10.7% which is higher than what has previously been reported in the literature at 8.7%. This may be explained by self reported data recall bias or the systematic underreporting of HDP.”

Reviewer Comment
"There was no significant difference in odds of having stroke in the other groups of women …. BMI < 25 & Yes HDP), compared to women of healthy weight who had remained normotensive during their pregnancy."
??explanation, Type 2 error??

Author response
There were only a small number of women who had stroke in each category and therefore the lack of significant differences between the groups may be due to Type 2 error. Additionally, the discussion already included a sentence on the possible bias in the results: “Our data may have a selection bias with regard to the prevalence of stroke, as only women who survived their stroke were able to be surveyed.”

Reviewer Comment
Can you estimate the effect of parity or recurrent HDP ie as seen with risk of Type 2 diabetes and recurrent GDM ?

Author response
Data on whether a woman experienced HDP in more than one pregnancy was not available

Reveiwer Comment
"and CVD is more common in these women within one to two decades of the hypertensive in pregnancy event.20, 21"
These references are incomplete as a number of other studies albeit case control studies have demonstrated this age effect eg Valdes G et al . Hypertension, 2009:53:733-38 Arnddottir GA et al BJOG 2005 :112:286

Author response
The above references have been included in the manuscript.

Reviewer Comment
"may explain the increased odds of cardiovascular disease in women who had HDP, where the development of HDP was an early warning sign unmasking the genetic predisposition due to the stress of pregnancy27"
Need to offer the alternative hypothesis of HDP as a cause of these CVS complications

Author response
The hypothesis of HDP as a cause of future CVD was mentioned in the previous paragraph in the discussion: “Sustained endothelial dysfunction caused by damage to the endothelium during HDP may be responsible for the long-term consequences observed in these women.”

Reviewer Comment
"women who experience HDP should have their blood pressure closely monitored in the years following pregnancy." Good opportunity to stress monitoring and management of all modifiable CVS risk factors including smoking, hyperglycemia, hyperlipidemia

Author response
The following sentence has been added to the discussion: “Women who experience HDP should be closely monitored for cardiovascular risk factors, including blood pressure, hyperglycemia, and hyperlipidemia in the years following pregnancy.”

Reviewer Comment
In future research also need to stress there is no data demonstrating that such monitoring or intervention has been demonstrated to impact on outcome but biologically probable.

Author response
The last sentence of the paper has been modified as follows: "Future research within this field should focus on the association between the severity of HDP and future CVD, and whether different treatment strategies for HDP result in varied CVD health outcomes, and whether monitoring and early intervention (such as lifestyle modification) following pregnancy can help minimise the risk of future CVD in women who experienced HDP."

Reviewer 6: Christoph Lees
No distinction is made between gestational hypertension and pre-eclampsia. These points are made somewhat superficially in the discussion but some form of qualification or quantification of these biases on the results would strengthen the discussion. Following on from this point, even if gestational hypertension could not easily be differentiated from pre-eclampsia by asking patients in a questionnaire, it would have been very interesting had hypertensive disease in pregnancy been classified as that requiring treatment and that not requiring treatment. Further, with a sample of this size it would be possible to determine if hypertensive disease in pregnancy were associated with chronic renal disease. If this data is available it would strengthen the paper.

Author response
Data differentiating gestational hypertension from preeclampsia was not available. Data stratifying preeclampsia into treated and not treated was not available. Data on chronic renal disease was not available.

Reviewer Comment
It is not clear from the methods or figure 1 exactly how many women were approached and completed the questionnaire. The 45 and up study recruited 267,153 men and women. How many women, therefore, were potentially eligible? Is it 84,619? If 12,800 were excluded leaving 71,819, surely all did not satisfactorily complete the questionnaire. Or does 84,619 refer to the number of women that had completed the questionnaire, in which case this must be a subset of a larger number assessed for study inclusion.

Author response
The 45 and Up Study randomly sampled participants from the enrolment database of Medicare Australia. These individuals were sent a postal questionnaire to complete. A total of 267,153 men and women completed the baseline questionnaire, which represented a response rate of 18%. Women were only eligible for our study if they fulfilled the inclusion criteria (see inclusion criteria in methods and Figure 1) which totalled 84,619 women. Women were then excluded if they did not complete the questionnaire correctly, or if they had been told by a doctor that they had high blood pressure but were not being treated for it (see exclusion criteria in methods and Figure 1). Therefore there were 71,819 included in the analysis.