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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002964
Article Type:	Research
Date Submitted by the Author:	28-Mar-2013
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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Hypertension < CARDIOLOGY, Stroke < NEUROLOGY, Maternal medicine < OBSTETRICS

High blood pressure during pregnancy is associated with future cardiovascular disease: observational cohort study

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ABSTRACT

Objectives The study aimed to determine if having a hypertensive disorder of pregnancy (HDP) is risk factor for future cardiovascular disease (CVD), independent of age and BMI.

Design Data were sourced from the baseline questionnaire of the *45 and Up Study*, Australia, an observational cohort study.

Setting Participants were randomly selected from the Australian Medicare Database within New South Wales.

Participants A total of 84 619 women were eligible for this study of which 71 819 were included. These women had given birth between the ages of 18 and 45 years, had an intact uterus and ovaries, and had not been diagnosed with high blood pressure prior to their first pregnancy.

Results HDP was associated with higher odds of having high blood pressure (<58 years: adjusted odds ratio 3.79, 99% confidence interval 3.38 to 4.24, P<0.001; ≥58 years: 2.83, 2.58 to 3.12, P<0.001) and stroke (<58 years: 1.69, 1.02 to 2.82, P=0.008; ≥58 years: 1.46, 1.13 to 1.88, P<0.001) in later life. Women with HDP had a younger age of onset of high blood pressure (45.6 years versus 54.8 years, p<0.001) and stroke (58.0 years versus 62.5 years, p<0.001). Women who had HDP and whose present day BMI was <25 had significantly higher odds of having high blood pressure, compared to women who were normotensive during pregnancy (<58 years: 4.55, 3.63 to 5.71, P<0.001; ≥58 years, 2.94, 2.49 to 3.47, P<0.001). Women who had HDP and a present day BMI ≥ 25 had significantly increased odds of high blood pressure (<58 years: 12.48, 10.63 to 14.66, P<0.001; ≥58 years, 5.16, 4.54 to 5.86, P<0.001), compared with healthy weight women with a normotensive pregnancy.

Conclusions HDP is an independent risk factor for future CVD and this risk is further exacerbated by the presence of overweight or obesity in later life.

ARTICLE SUMMARY

Article Focus

- Hypertensive disorders of pregnancy have been associated with an increased risk of maternal cardiovascular disease in later life.
- It remains unclear whether high blood pressure during pregnancy is an independent risk factor for future cardiovascular disease or whether it is confounded by traditional risk factors such as age and BMI.

Key Messages

- Our study shows that a history of hypertensive disorders of pregnancy (HDP) is significantly associated with having high blood pressure and stroke in later life.
- HDP is an independent risk factor for future cardiovascular disease and the risk of CVD is further exacerbated by the presence of overweight or obesity in later life, particularly in women <58 years of age.

Strengths and Limitations

- This is a large observational cohort study which included 71 819 women.
- These data are unable to differentiate between the different categories of HDP and the timing of onset of the disease in the pregnancy.

INTRODUCTION

Cardiovascular disease (CVD) is a major contributor to worldwide morbidity and mortality and is the leading cause of death in the USA in individuals aged 65 years and over.[1] In Australia, approximately 2 million women are affected by CVD and the three leading causes of death in women are coronary heart disease, stroke and other heart diseases (including heart failure).[2] Age is a powerful predictor of cardiovascular disease, with increasing age associated with increasing arterial stiffness[3] and endothelial dysfunction[4] which predisposes the individual to high blood pressure and premature aging of the vascular system.[5] Excess body fat is also a known risk factor for both arterial stiffening endothelial dysfunction and subsequent cardiovascular disease.[6, 7]

Recent evidence has demonstrated that women with hypertensive disorders of pregnancy (HDP) have increased arterial stiffness,[8] and these women may be at a greater risk of future cardiovascular disease when compared to women who experience a normotensive pregnancy.[9] HDP, which include gestational hypertension, preeclampsia/eclampsia, chronic hypertension and superimposed preeclampsia on chronic hypertension, occur in 5-10% of all pregnancies within Australia.[10] 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] This causes the placenta to release antiangiogenic proteins which result in endothelial dysfunction. The clinical features of the maternal response to this abnormality include hypertension, renal impairment, liver impairment, pulmonary oedema, thrombocytopenia, coagulopathy and neurological disturbances. It can exacerbate existing endothelial dysfunction in women with chronic high blood pressure. 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 pre-pregnancy 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]

The aim of this study was to determine whether women who reported to have had a HDP were at an increased likelihood of having high blood pressure or stroke in later life, using observational data from the *45 and Up Study*, Australia. We also aimed to determine how this association was modified by a woman's age and BMI and whether the age of onset of high blood pressure or stroke in later life, differed between women who had HDP and those who remained normotensive.

METHODS

Study Sample

This study obtained data from women participating in the *45 and Up Study*, a large scale cohort study of 267 153 men and women aged 45 and over in New South Wales, Australia. Participants were randomly selected from the Australian Medicare Database which provides near complete coverage of the population. The participants were enrolled into the study by consenting to and completing a baseline questionnaire (available at www.45andUp.org.au) and giving consent for long term follow up through data linkage and repeat data collection. People aged 80 years and over, and residents of rural and remote areas were oversampled. Study recruitment commenced in January 2006 and was completed in April 2009. The methods for the *45 and Up Study* have been described elsewhere.[15] The *45 and Up Study* received ethics approval from the University of NSW Human Ethics Committee and the current study was approved by the UWS Human Research Ethics Committee. Exposure-outcome relationships estimated from the *45 and Up Study* data have been shown to be consistent with another large study of the same population, regardless of the underlying response rate or mode of questionnaire administration.[16]

All of the data used in this study were acquired from the *45 and Up Study* baseline questionnaire. Women were included in this study if: they were age 45 years or more; had given birth between 18 years of age and 45 years of age; had not had a hysterectomy or both ovaries removed and were not diagnosed with high blood pressure prior to their first pregnancy (Figure 1).

Women were identified as having had HDP by responding "Yes" to the question "Has a doctor ever told you that you have: high blood pressure - when pregnant". Where the age of

"high blood pressure - when pregnant" was within 1 year of the women's age when she first gave birth, the HDP was identified as occurring during her first pregnancy. Where the age of "high blood pressure - when pregnant" was greater than 1 year from the women's age when she first gave birth, the HDP was identified as occurring during a subsequent pregnancy.

Women were identified as having high blood pressure when not pregnant if they answered "Yes" to the question "In the last month have you been treated for: high blood pressure". Women were identified as having a stroke if they answered "Yes" to the question "Has a doctor ever told you that you have: stroke". Women were excluded if: they reported having high blood pressure prior to having their first child; answered "Yes" to "Has a doctor ever told you that you have: high blood pressure – when not pregnant" but were not being treated for high blood pressure; they failed to provide an age of onset for high blood pressure or stroke; they provided invalid data for family history; or they provided invalid data for the number of children they had given birth to in their specified age range (Figure 1). Classification of demographic and lifestyle characteristics have been described elsewhere.[17]

Statistics

Odds ratios and 99% confidence intervals for the association between (i) demographic and lifestyle characteristics and HDP, (ii) HDP and high blood pressure in later life, and (iii) HDP and stroke in later life, were estimated using logistic regression. Analyses were repeated for (ii) and (iii) combining HDP status (yes or no) and BMI (<25 or ≥25) into a single variable with four categories. Both crude and adjusted odds ratios were calculated and descriptions refer to adjusted odds ratios unless otherwise specified. Due to the known association between high blood pressure and ageing, women were stratified according to age using the median age as the cut point (<58 years, ≥58 years) when testing the association between HDP

and both high blood pressure and stroke in later life. Odds ratios were adjusted for country of origin, income level, BMI, smoking status, alcohol consumption, physical activity, family history of high blood pressure (for high blood pressure analysis), family history of stroke (for stroke analysis), history of oral contraceptive use, history of menopausal hormone therapy, and number of children. Categories for each covariate have been previously described.[17] An additional category for missing values was included for variables with missing data. Linear regression was used to study the association between age of onset of both high blood pressure and stroke, with HDP. All statistical tests were two-sided, using a significance level of $p<0.01$ to partially account for multiple testing issues.[18] All statistical analyses were carried out using SPSS software version 20 (IBM Corp New York USA).

RESULTS

A total of 71 819 women were included in the study (Figure 1) of which 7 706 (10.7%) reported having had HDP. Of these, 3 237 (42.0%) reported current treatment for high blood pressure and 165 (2.1%) reported having had a stroke. In comparison, of the 64 113 women who did not report HDP, 10 668 (16.6%) reported current treatment for high blood pressure and 913 (1.4%) reported having had a stroke. There was no significant difference in odds for having high blood pressure (OR 1.02, 99% CI 0.88 to 1.16, p=0.77) or stroke (OR 0.99, 99% CI 0.64 to 1.54, p=0.97) between HDP during first pregnancy compared with HDP in a subsequent pregnancy. As a result, analysis grouped all women who reported HDP, irrespective of which pregnancy it had occurred.

The association between socio-demographic factors and whether a woman had HDP are shown in Table 1. A positive family history of high blood pressure, a positive family history of stroke, oral contraceptive use, and having three or more children were associated with significantly higher odds of having had HDP. Current smoking status was associated with reduced odds of having had HDP compared to women who had never smoked.

HDP was associated with increased odds of having high blood pressure in later life (women <58 years: OR 3.79, 99% CI 3.38 to 4.24, p<0.001) compared to women who remained normotensive during pregnancy (Table 2). The average age of onset of high blood pressure in later life was 45.6 years for women who had HDP compared to 54.8 years for women who remained normotensive in their pregnancy (adjusted β = -8.30, 99% CI -8.89 to -7.71, p<0.001).

Stratifying women according to HDP status and BMI found that women who had HDP and whose current BMI was ≥25, had significantly increased odds of having high blood pressure (women <58 years: OR 12.48, 99% CI 10.63 to 14.66, p<0.001; women ≥58 years: OR 5.15, 99% CI 4.54 to 5.86, p<0.001) compared to women who did not have HDP and whose present day BMI was <25 (Figure 2). Women who had HDP and whose present day BMI was <25 had significantly higher odds of having high blood pressure, compared to women who did not have HDP and whose present day BMI was ≥25 (women <58 years: OR 1.33, 99% CI 1.08 to 1.64, p<0.001; women ≥58 years: OR 1.56, 99% CI 1.33 to 1.83, p<0.001).

HDP was also associated with increased odds of having stroke in later life (women <58 years: OR 1.69, 99% CI 1.02 to 2.82, p<0.001; women ≥58 years: OR 1.46, 99% CI 1.13 to 1.88, p<0.001) compared to women who remained normotensive in their pregnancy (Table 2). The average age of onset of stroke in later life was 58.0 years for women who had HDP compared to 62.5 years for women who remained normotensive in their pregnancy (adjusted β = -4.01, 99% CI -6.87 to -1.16, p<0.001).

Stratifying women according to HDP status and BMI found that women who had HDP and whose current BMI was ≥25, had significantly increased odds of having stroke (women <58 years: OR 2.24, 99% CI 1.14 to 4.42, p=0.002; women ≥58 years: OR 1.46, 99% CI 1.05 to 2.04, p=0.003) compared to women who did not have HDP and whose present day BMI was <25 (Figure 3). There was no significant difference in odds of having stroke in the other groups of women (BMI ≥ 25 & No HDP, and BMI < 25 & Yes HDP), compared to women of healthy weight who had remained normotensive during their pregnancy.

DISCUSSION

The *45 and Up Study* is the largest self-reported cohort of Australian women ever examined. Our results show that having a hypertensive disorder of pregnancy (HDP) is associated with significantly increased odds of having high blood pressure in later life, compared to women that remained normotensive, and this was exacerbated in women with a BMI $\geq$ 25 kg/m^2. Women who reported having HDP were 9.2 years younger at the age of onset of high blood pressure, compared to women who experienced healthy pregnancies. Similarly, women who suffered HDP had significantly higher odds of having stroke compared to women who remained normotensive in their pregnancy and the age of onset of stroke was significantly earlier in women with HDP. Women within the healthy weight range in our study, and who had experienced HDP, had significantly higher odds of having present day high blood pressure compared to similar aged women who were overweight or obese, but who had been normotensive during pregnancy. Women who had both risk factors, namely BMI $\geq$ 25 kg/m^2 and a HDP, had up to 12.48 increased odds of having high blood pressure and up to 2.24 increased odds of stroke, compared to women within the healthy weight range with normotensive pregnancies. This shows that HDP is an independent risk factor for future high blood pressure and when combined with traditional risk factors such as BMI, a history of HDP can significantly increase the odds of future CVD.

This study analysed cross-sectional and observational data from the baseline questionnaire from the *45 and Up Study*. As a result, the casual nature of associations could not be assessed. 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. These data are unable to differentiate between the different categories of HDP, the severity of the disease, duration of the pregnancy, the timing of onset of the disease in the pregnancy, and the relationship between

the timing of high blood pressure and the timing of delivery. Other studies have shown that the more severe the high blood pressure and the earlier its onset during pregnancy, the greater the risk of future high blood pressure compared to women who suffer a milder or more moderate form of the disease.[28, 29] 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%.[10] This may be explained by self reported data recall bias or the systematic underreporting of HDP.[30]

Our results support existing evidence of a link between HDP and subsequent cardiovascular risk. Studies have shown that women who had HDP have a greater risk of cardiovascular morbidity including an increased risk of hypertension, stroke and coronary heart disease,[14, 19] and CVD is more common in these women within one to two decades of the hypertensive in pregnancy event.[20, 21] Our study extends these findings by showing that women with HDP have a significantly younger age of onset of both high blood pressure and stroke. HDP was significantly associated with increased odds of future CVD in all age groups analysed, but the odds reduced with increasing age demonstrating age as an independent predictor of future CVD.

HDP shares many of the aetiologies of CVD such as inflammation and endothelial changes, as well as having overlapping risk factors such as obesity, insulin resistance and dyslipidemia. Sustained endothelial dysfunction caused by damage to the endothelium during HDP may be responsible for the long-term consequences observed in these women. Studies have shown that endothelial dysfunction persists in women following HDP, namely preeclampsia.[13, 22, 23] Additionally, studies have found a strong link between preeclampsia and higher circulating concentrations of fasting insulin,[24] lipid, and coagulation factors[25] post

partum. High BMI is also known to adversely influence the endothelium,[7] and endothelial dysfunction is an early risk factor for future catastrophic CVD events in obese adults.[26] 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[27]. This increased risk of CVD is further exacerbated by the presence of overweight or obesity in later life, particularly in women <58 years of age.

HDP are associated with higher odds of having cardiovascular disease in later life and HDP are an independent risk factor for future CVD. Women who are overweight or obese and have HDP have significantly higher odds of having both high blood pressure and stroke in later life. This study adds to the evidence[31] that a woman's pregnancy history is important when assessing her future risk of CVD and women who experience HDP should have their blood pressure closely monitored in the years following pregnancy. Women should be encouraged to maintain a healthy weight, particularly if they experience HDP. 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.

DECLARATION OF COMPETING INTERESTS

The authors of this work have no competing interests to declare.

FUNDING STATEMENT

The *45 and Up Study* is managed by the Sax Institute in collaboration with major partner Cancer Council New South Wales; and partners the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; *beyondblue: the national depression initiative*; Ageing, Disability and Home Care, NSW Family and Community Services; Australian Red Cross Blood Service and UnitingCare Ageing. JML is supported by a National Health and Medical Research Council - Australian Biomedical Fellowship. JT is supported by a PEARLS (Preeclampsia Research Laboratories) PhD scholarship. SJL is the recipient of a University of Western Sydney Postgraduate Research Award and an Ingham Health Research Institute scholarship. The sponsors were not involved in the analysis, or interpretation of the data; and preparation, review, or approval of the manuscript for the study reported here.

DATA SHARING

There is no additional data available.

ETHICS

The *45 and Up Study* received ethics approval from the University of NSW Human Research Ethics Committee (HREC 10186) and the current study was approved by the University of Western Sydney Human Research Ethics Committee (H8561).

CONTRIBUTORSHIP

All authors included on a paper fulfil the criteria of authorship and there are no other individuals that meet the criteria for authorship. JML had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and is guarantor. JT, CLC, KY, SJL, CT, AM, AO, AH and JML conceived and designed the study. JT, CLC, KY and JML drafted the manuscript. JML supervised the study and was responsible for the statistical analysis. All authors participated in interpreting the data and critically revising the manuscript.

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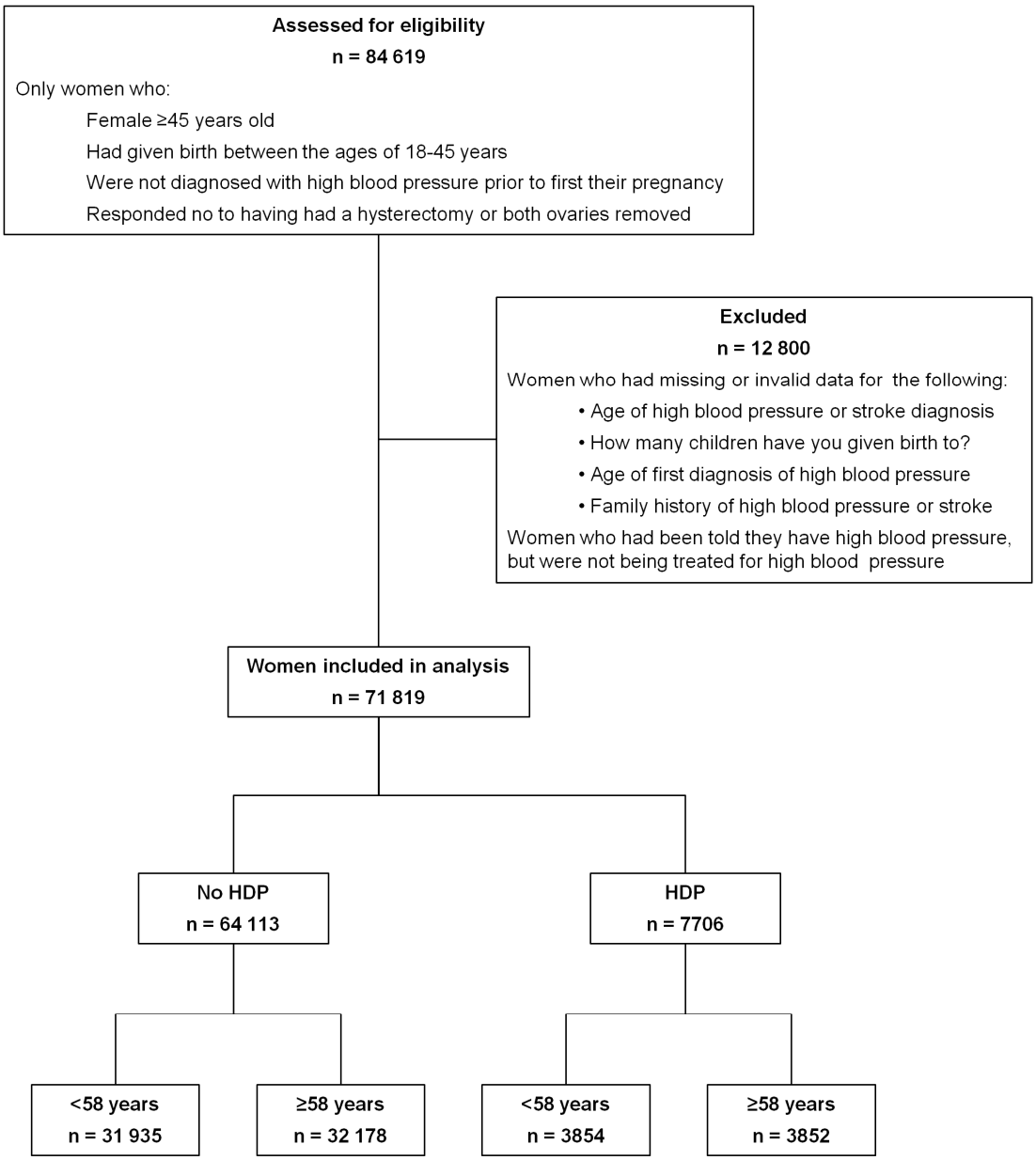

Figure 1. Participants included in the study.

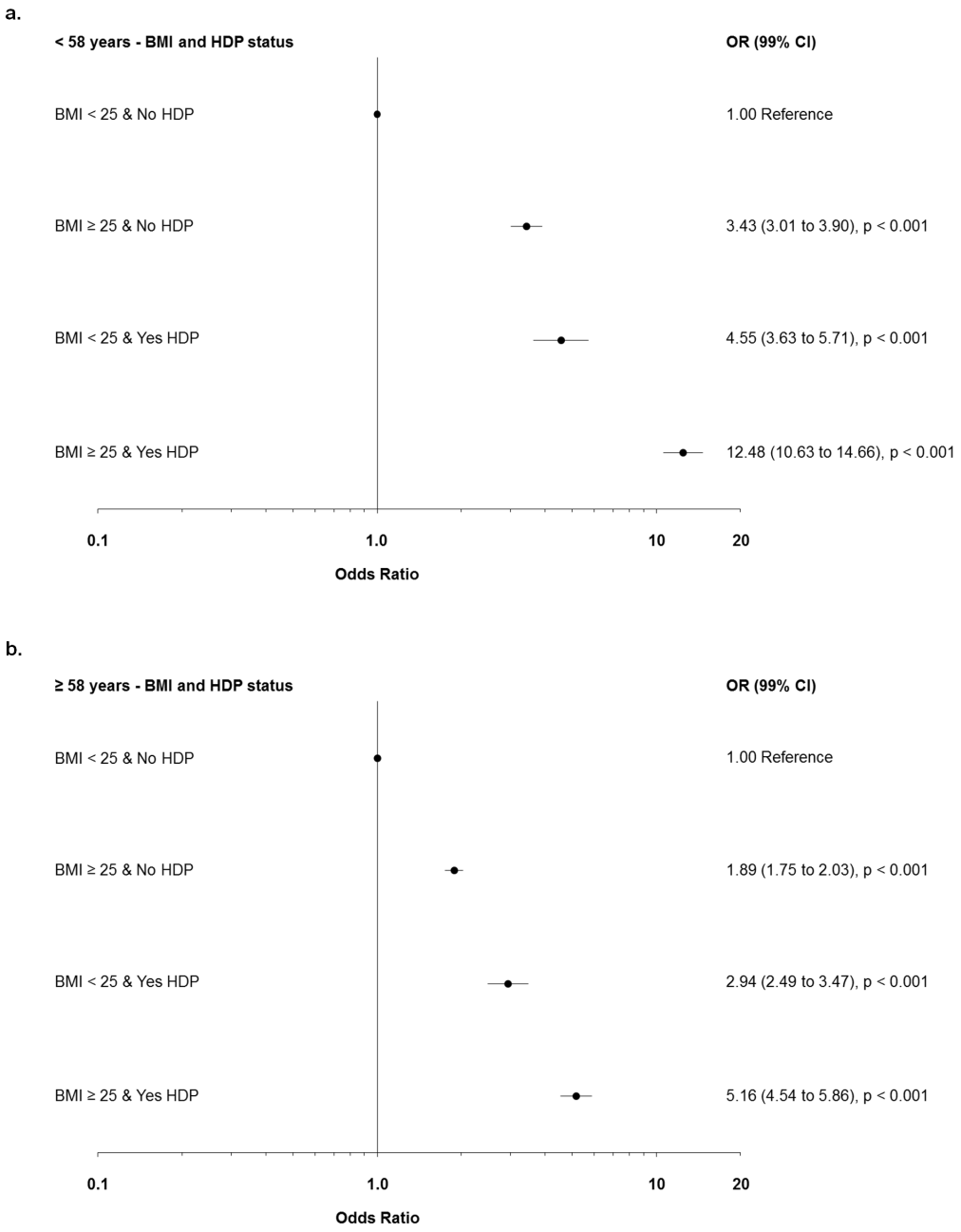

Figure 2. The odds of having high blood pressure depending on a woman's BMI and whether she had a hypertensive disorder of pregnancy (HDP), compared to women with present day BMI < 25 who were normotensive during pregnancy, stratified by current age.

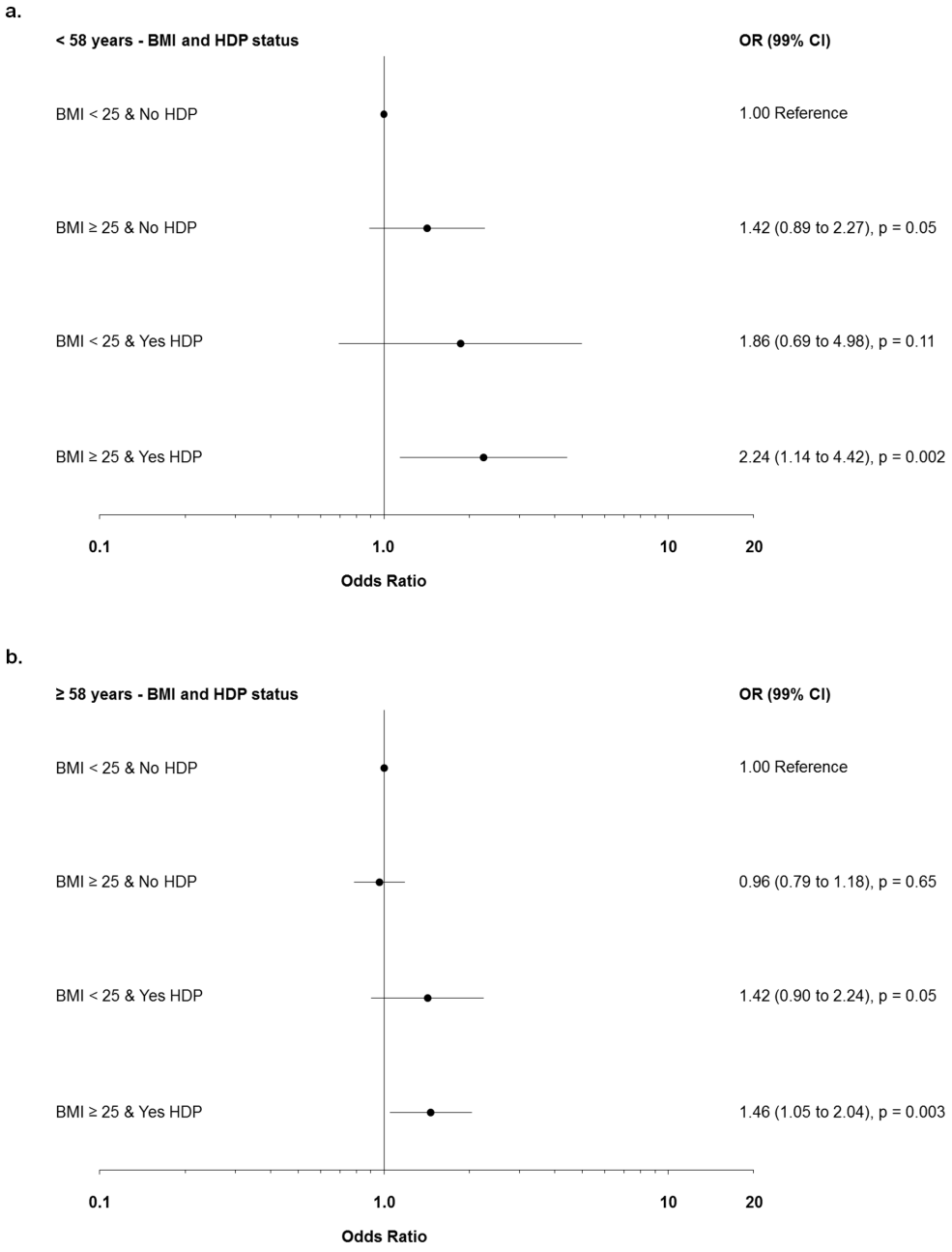

Figure 3. The odds of having stroke depending on a woman's BMI and whether she had a hypertensive disorder of pregnancy (HDP), compared to women with present day BMI < 25 who were normotensive during pregnancy, stratified by current age.

Table 1. Socio-demographic factors and health risk factors associated with hypertensive disorders of pregnancy

Characteristics	Status	N (% column)	% HDP	Odds ratio (99% CI)†
Family history of High BP	No	33 349 (46)	7	1.00
	Yes	38 470 (54)	14	2.14 (2.00 to 2.30)‡
Family history of Stroke	No	53 416 (74)	10	1.00
	Yes	18 403 (26)	13	1.13 (1.05 to 1.21)‡
Smoking status	Never	46 832 (65)	11	1.00
	Past	19 996 (28)	11	0.95 (0.89 to 1.02)
	Current	4 669 (7)	9	0.79 (0.69 to 0.91)‡
Past oral contraceptive use	No	12 339 (17)	9	1.00
	Yes	58 440 (81)	11	1.28 (1.17 to 1.40)‡
Number of Children	1	7 581 (11)	9	1.00
	2	29 298 (41)	10	1.10 (0.98 to 1.23)
	3	21 441 (30)	11	1.23 (1.09 to 1.38)‡
	4 or more	13 499 (19)	12	1.46 (1.29 to 1.65)‡

% HDP - the percentage of women who responded yes to having had high blood pressure when pregnany. Percentages do not consistently total to 100% due to missing values.

†Adjusted for family history of high blood pressure, family history of stroke, smoking status, history of oral contraceptive use, and number of children.

‡ $p < 0.01$

Table 2. Association between high blood pressure when pregnant and maternal cardiovascular disease in later life

CVD	Current Age	HDP	Cases (n)	Crude Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)†
High blood pressure	<58	No	31 935	1·00 reference	
		Yes	3 854	4.89 (4.40 to 5.43)	3.79 (3.38 to 4.24)‡
	≥58	No	32 178	1.00 reference	
		Yes	3 852	3.51 (3.21 to 3.84)	2.83 (2.58 to 3.12)‡
Stroke	<58	No	35 613	1·00 reference	
		Yes	176	1.92 (1.17 to 3.16)	1.69 (1.02 to 2.82)‡
	≥58	No	35 128	1·00 reference	
		Yes	902	1.45 (1.13 to 1.85)	1.46 (1.13 to 1.88)‡

†analysis adjusted for country of origin, income level, BMI, smoking status, alcohol consumption, physical activity, family history of high blood pressure (for high blood pressure analysis), family history of stroke (for stroke analysis), history of oral contraceptive use, history of menopausal hormone therapy, and number of children.

‡ $p < 0.01$

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

High blood pressure during pregnancy is associated with future cardiovascular disease: observational cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002964.R1
Article Type:	Research
Date Submitted by the Author:	17-Jun-2013
Complete List of Authors:	Tooher, Jane; Royal Prince Alfred Hospital, Chiu, Christine; University of Western Sydney, School of Medicine Yeung, Kristen; University of Western Sydney, School of Medicine Lupton, Samantha; University of Western Sydney, School of Medicine Thornton, Charlene; University of Western Sydney, School of Medicine Makris, Angela; University of Western Sydney, School of Medicine; Liverpool Hospital, Renal Medicine O'Loughlin, Aiden; University of Western Sydney, School of Medicine Hennessy, Annemarie; University of Western Sydney, School of Medicine Lind, Joanne; University of Western Sydney, School of Medicine
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Hypertension < CARDIOLOGY, Stroke < NEUROLOGY, Maternal medicine < OBSTETRICS

High blood pressure during pregnancy is associated with future cardiovascular disease: observational cohort study

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ABSTRACT

Objectives The study aimed to determine if having a hypertensive disorder of pregnancy (HDP) is risk factor for future cardiovascular disease (CVD), independent of age and BMI.

Design Data were sourced from the baseline questionnaire of the *45 and Up Study*, Australia, an observational cohort study.

Setting Participants were randomly selected from the Australian Medicare Database within New South Wales.

Participants A total of 84 619 women were eligible for this study of which 71 819 were included. These women had given birth between the ages of 18 and 45 years, had an intact uterus and ovaries, and had not been diagnosed with high blood pressure prior to their first pregnancy.

Results HDP was associated with higher odds of having high blood pressure (<58 years: adjusted odds ratio 3.79, 99% confidence interval 3.38 to 4.24, P<0.001; ≥58 years: 2.83, 2.58 to 3.12, P<0.001) and stroke (<58 years: 1.69, 1.02 to 2.82, P=0.008; ≥58 years: 1.46, 1.13 to 1.88, P<0.001) in later life. Women with HDP had a younger age of onset of high blood pressure (45.6 years versus 54.8 years, p<0.001) and stroke (58.0 years versus 62.5 years, p<0.001). Women who had HDP and whose present day BMI was <25 had significantly higher odds of having high blood pressure, compared to women who were normotensive during pregnancy (<58 years: 4.55, 3.63 to 5.71, P<0.001; ≥58 years, 2.94, 2.49 to 3.47, P<0.001). Women who had HDP and a present day BMI ≥ 25 had significantly increased odds of high blood pressure (<58 years: 12.48, 10.63 to 14.66, P<0.001; ≥58 years, 5.16, 4.54 to 5.86, P<0.001), compared with healthy weight women with a normotensive pregnancy.

Conclusions HDP is an independent risk factor for future CVD and this risk is further exacerbated by the presence of overweight or obesity in later life.

ARTICLE SUMMARY

Article Focus

- Hypertensive disorders of pregnancy have been associated with an increased risk of maternal cardiovascular disease in later life.
- It remains unclear whether high blood pressure during pregnancy is an independent risk factor for future cardiovascular disease or whether it is confounded by traditional risk factors such as age and BMI.

Key Messages

- Our study shows that a history of hypertensive disorders of pregnancy (HDP) is significantly associated with having high blood pressure and stroke in later life.
- HDP is an independent risk factor for future cardiovascular disease and the risk of CVD is further exacerbated by the presence of overweight or obesity in later life, particularly in women <58 years of age.

Strengths and Limitations

- This is a large observational cohort study which included 71 819 women.
- These data are unable to differentiate between the different categories of HDP and the timing of onset of the disease in the pregnancy.

INTRODUCTION

Cardiovascular disease (CVD) is a major contributor to worldwide morbidity and mortality and is the leading cause of death in the USA in individuals aged 65 years and over.[1] In Australia, approximately 2 million women are affected by CVD and the three leading causes of death in women are coronary heart disease, stroke and other heart diseases (including heart failure).[2] Age is a powerful predictor of cardiovascular disease, with increasing age associated with increasing arterial stiffness[3] and endothelial dysfunction[4] which predisposes the individual to high blood pressure and premature aging of the vascular system.[5] Excess body fat is also a known risk factor for both arterial stiffening endothelial dysfunction and subsequent cardiovascular disease.[6 7]

Recent evidence has demonstrated that women with hypertensive disorders of pregnancy (HDP) have increased arterial stiffness,[8] and these women may be at a greater risk of future cardiovascular disease when compared to women who experience a normotensive pregnancy.[9] HDP, which include gestational hypertension, preeclampsia/eclampsia, chronic hypertension and superimposed preeclampsia on chronic hypertension, occur in 5-10% of all pregnancies within Australia.[10] 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] This causes the placenta to release antiangiogenic proteins which result in endothelial dysfunction. The clinical features of the maternal response to this abnormality include hypertension, renal impairment, liver impairment, pulmonary oedema, thrombocytopenia, coagulopathy and neurological disturbances. It can exacerbate existing endothelial dysfunction in women with chronic high blood pressure. 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 return to its pre-

pregnancy 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.[13-15]

The aim of this study was to determine whether women who reported to have had a HDP were at an increased likelihood of having high blood pressure or stroke in later life, using observational data from the *45 and Up Study*, Australia. We also aimed to determine how this association was modified by a woman's age and BMI and whether the age of onset of high blood pressure or stroke in later life, differed between women who had HDP and those who remained normotensive.

METHODS

Study Sample

This study obtained data from women participating in the *45 and Up Study*, a large scale cohort study of 267 153 men and women aged 45 and over in New South Wales, Australia. Participants were randomly selected from the Australian Medicare Database which provides near complete coverage of the population. The participants were enrolled into the study by consenting to and completing a baseline questionnaire (available at www.45andUp.org.au) and giving consent for long term follow up through data linkage and repeat data collection. People aged 80 years and over, and residents of rural and remote areas were oversampled. Study recruitment commenced in January 2006 and was completed in April 2009. The methods for the *45 and Up Study* have been described elsewhere.[16] The *45 and Up Study* received ethics approval from the University of NSW Human Ethics Committee and the current study was approved by the UWS Human Research Ethics Committee. Exposure-outcome relationships estimated from the *45 and Up Study* data have been shown to be consistent with another large study of the same population, regardless of the underlying response rate or mode of questionnaire administration.[17]

All of the data used in this study were acquired from the *45 and Up Study* baseline questionnaire. Women were included in this study if: they were age 45 years or more; had given birth between 18 years of age and 45 years of age; had not had a hysterectomy or both ovaries removed and were not diagnosed with high blood pressure prior to their first pregnancy (Figure 1).

Women were identified as having had HDP by responding "Yes" to the question "Has a doctor ever told you that you have: high blood pressure - when pregnant". Where the age of

"high blood pressure - when pregnant" was within 1 year of the women's age when she first gave birth, the HDP was identified as occurring during her first pregnancy. Where the age of "high blood pressure - when pregnant" was greater than 1 year from the women's age when she first gave birth, the HDP was identified as occurring during a subsequent pregnancy.

Women were identified as having high blood pressure when not pregnant if they answered "Yes" to the question "In the last month have you been treated for: high blood pressure". Women were identified as having a stroke if they answered "Yes" to the question "Has a doctor ever told you that you have: stroke". Women were excluded if: they reported having high blood pressure prior to having their first child; answered "Yes" to "Has a doctor ever told you that you have: high blood pressure – when not pregnant" but were not being treated for high blood pressure; they failed to provide an age of onset for high blood pressure or stroke; they provided invalid data for family history; or they provided invalid data for the number of children they had given birth to in their specified age range (Figure 1). Classification of demographic and lifestyle characteristics have been described elsewhere.[18]

Statistics

Odds ratios and 99% confidence intervals for the association between (i) demographic and lifestyle characteristics and HDP, (ii) HDP and high blood pressure in later life, and (iii) HDP and stroke in later life, were estimated using logistic regression. Analyses were repeated for (ii) and (iii) combining HDP status (yes or no) and BMI (<25 or ≥25) into a single variable with four categories. Both crude and adjusted odds ratios were calculated and descriptions refer to adjusted odds ratios unless otherwise specified. Due to the known association between high blood pressure and ageing, women were stratified according to age using the median age as the cut point (<58 years, ≥58 years) when testing the association between HDP

and both high blood pressure and stroke in later life. Odds ratios were adjusted for country of origin, income level, BMI, smoking status, alcohol consumption, physical activity, family history of high blood pressure (for high blood pressure analysis), family history of stroke (for stroke analysis), history of oral contraceptive use, history of menopausal hormone therapy, and number of children. Categories for each covariate have been previously described.[18] An additional category for missing values was included for variables with missing data. Linear regression was used to study the association between age of onset of both high blood pressure and stroke, with HDP. All statistical tests were two-sided, using a significance level of $p<0.01$ to partially account for multiple testing issues.[19] All statistical analyses were carried out using SPSS software version 20 (IBM Corp New York USA).

RESULTS

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. Of these, 3 237 (42.0%) reported current treatment for high blood pressure and 165 (2.1%) reported having had a stroke. In comparison, of the 64 113 women who did not report HDP, 10 668 (16.6%) reported current treatment for high blood pressure and 913 (1.4%) reported having had a stroke. There was no significant difference in odds for having high blood pressure (OR 1.02, 99% CI 0.88 to 1.16, p=0.77) or stroke (OR 0.99, 99% CI 0.64 to 1.54, p=0.97) between HDP during first pregnancy compared with HDP in a subsequent pregnancy. As a result, analysis grouped all women who reported HDP, irrespective of which pregnancy it had occurred.

The association between socio-demographic factors and whether a woman had HDP are shown in Table 1. A positive family history of high blood pressure, a positive family history of stroke, oral contraceptive use, and having three or more children were associated with significantly higher odds of having had HDP. Current smoking status was associated with reduced odds of having had HDP compared to women who had never smoked.

HDP was associated with increased odds of having high blood pressure in later life (women <58 years: OR 3.79, 99% CI 3.38 to 4.24, p<0.001) compared to women who remained normotensive during pregnancy (Table 2). The average age of onset of high blood pressure in later life was 45.6 years for women who had HDP compared to 54.8 years for women who

remained normotensive in their pregnancy (adjusted β = -8.30, 99% CI -8.89 to -7.71, p<0.001).

Stratifying women according to HDP status and BMI found that women who had HDP and whose current BMI was ≥25, had significantly increased odds of having high blood pressure (women <58 years: OR 12.48, 99% CI 10.63 to 14.66, p<0.001; women ≥58 years: OR 5.15, 99% CI 4.54 to 5.86, p<0.001) compared to women who did not have HDP and whose present day BMI was <25 (Figure 2). Women who had HDP and whose present day BMI was <25 had significantly higher odds of having high blood pressure, compared to women who did not have HDP and whose present day BMI was ≥25 (women <58 years: OR 1.33, 99% CI 1.08 to 1.64, p<0.001; women ≥58 years: OR 1.56, 99% CI 1.33 to 1.83, p<0.001).

HDP was also associated with increased odds of having stroke in later life (women <58 years: OR 1.69, 99% CI 1.02 to 2.82, p<0.001; women ≥58 years: OR 1.46, 99% CI 1.13 to 1.88, p<0.001) compared to women who remained normotensive in their pregnancy (Table 2). The average age of onset of stroke in later life was 58.0 years for women who had HDP compared to 62.5 years for women who remained normotensive in their pregnancy (adjusted β = -4.01, 99% CI -6.87 to -1.16, p<0.001).

Stratifying women according to HDP status and BMI found that women who had HDP and whose current BMI was ≥25, had significantly increased odds of having stroke (women <58 years: OR 2.24, 99% CI 1.14 to 4.42, p=0.002; women ≥58 years: OR 1.46, 99% CI 1.05 to 2.04, p=0.003) compared to women who did not have HDP and whose present day BMI was <25 (Figure 3). There was no significant difference in odds of having stroke in the other

groups of women (BMI ≥ 25 & No HDP, and BMI < 25 & Yes HDP), compared to women of healthy weight who had remained normotensive during their pregnancy.

DISCUSSION

The *45 and Up Study* is the largest self-reported cohort of Australian women ever examined. Our results show that having a hypertensive disorder of pregnancy (HDP) is associated with significantly increased odds of having high blood pressure in later life, compared to women that remained normotensive, and this was exacerbated in women with a BMI $\geq$ 25 kg/m^2. Women who reported having HDP were 9.2 years younger at the age of onset of high blood pressure, compared to women who experienced healthy pregnancies. Similarly, women who suffered HDP had significantly higher odds of having stroke compared to women who remained normotensive in their pregnancy and the age of onset of stroke was significantly earlier in women with HDP. Women within the healthy weight range in our study, and who had experienced HDP, had significantly higher odds of having present day high blood pressure compared to similar aged women who were overweight or obese, but who had been normotensive during pregnancy. Women who had both risk factors, namely BMI $\geq$ 25 kg/m^2 and a HDP, had up to 12.48 increased odds of having high blood pressure and up to 2.24 increased odds of stroke, compared to women within the healthy weight range with normotensive pregnancies. This shows that HDP is an independent risk factor for future high blood pressure and when combined with traditional risk factors such as BMI, a history of HDP can significantly increase the odds of future CVD.

This study analysed cross-sectional and observational data from the baseline questionnaire from the *45 and Up Study*. As a result, the causal nature of associations could not be assessed. 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. These data are unable to differentiate between the different categories of HDP, the severity of the disease, duration of the pregnancy, the timing of onset of the disease in the pregnancy, and the relationship between

the timing of high blood pressure and the timing of delivery. Other studies have shown that the more severe the high blood pressure and the earlier its onset during pregnancy, the greater the risk of future high blood pressure compared to women who suffer a milder or more moderate form of the disease.[20 21] 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%.[10] This may be explained by self reported data recall bias or the systematic underreporting of HDP.[22]

Our results support existing evidence of a link between HDP and subsequent cardiovascular risk. Studies have shown that women who had HDP have a greater risk of cardiovascular morbidity including an increased risk of hypertension, stroke and coronary heart disease,[14 23] and CVD is more common in these women within one to two decades of the hypertensive in pregnancy event.[24-27] Our study extends these findings by showing that women with HDP have a significantly younger age of onset of both high blood pressure and stroke. HDP was significantly associated with increased odds of future CVD in all age groups analysed, but the odds reduced with increasing age demonstrating age as an independent predictor of future CVD.

HDP shares many of the aetiologies of CVD such as inflammation and endothelial changes, as well as having overlapping risk factors such as obesity, insulin resistance and dyslipidemia. Sustained endothelial dysfunction caused by damage to the endothelium during HDP may be responsible for the long-term consequences observed in these women. Alternatively, pre-existing endothelial dysfunction prior to conception may be a triggering mechanism for HDP as well as increasing the risk for CVD later in life.[15] Studies have shown that endothelial dysfunction persists in women following HDP, namely preeclampsia.[13 15 28 29]

Additionally, studies have found a strong link between preeclampsia and higher circulating concentrations of fasting insulin,[30] lipid, and coagulation factors[31] post partum. High BMI is also known to adversely influence the endothelium,[7] and endothelial dysfunction is an early risk factor for future catastrophic CVD events in obese adults.[32] 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[33]. This increased risk of CVD is further exacerbated by the presence of overweight or obesity in later life, particularly in women <58 years of age.

HDP are associated with higher odds of having cardiovascular disease in later life and HDP are an independent risk factor for future CVD. Women who are overweight or obese and have HDP have significantly higher odds of having both high blood pressure and stroke in later life. This study adds to the evidence[34] that a woman's pregnancy history is important when assessing her future risk of CVD. Women who experience HDP should be closely monitored for cardiovascular risk factors, including blood pressure, hyperglycemia, and hyperlipidemia in the years following pregnancy. Women should be encouraged to maintain a healthy weight, particularly if they experience HDP. Future research within this field should focus on the association between the severity of HDP and future CVD, 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.

DECLARATION OF COMPETING INTERESTS

The authors of this work have no competing interests to declare.

FUNDING STATEMENT

The *45 and Up Study* is managed by the Sax Institute in collaboration with major partner Cancer Council New South Wales; and partners the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; *beyondblue: the national depression initiative*; Ageing, Disability and Home Care, NSW Family and Community Services; Australian Red Cross Blood Service and UnitingCare Ageing. JML is supported by a National Health and Medical Research Council - Australian Biomedical Fellowship. JT is supported by a PEARLS (Preeclampsia Research Laboratories) PhD scholarship. SJL is the recipient of a University of Western Sydney Postgraduate Research Award and an Ingham Health Research Institute scholarship. The sponsors were not involved in the analysis, or interpretation of the data; and preparation, review, or approval of the manuscript for the study reported here.

DATA SHARING

There is no additional data available.

ETHICS

The *45 and Up Study* received ethics approval from the University of NSW Human Research Ethics Committee (HREC 10186) and the current study was approved by the University of Western Sydney Human Research Ethics Committee (H8561).

CONTRIBUTORSHIP

All authors included on a paper fulfil the criteria of authorship and there are no other individuals that meet the criteria for authorship. JML had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and is guarantor. JT, CLC, KY, SJL, CT, AM, AO, AH and JML conceived and designed the study. JT, CLC, KY and JML drafted the manuscript. JML supervised the study and was responsible for the statistical analysis. All authors participated in interpreting the data and critically revising the manuscript.

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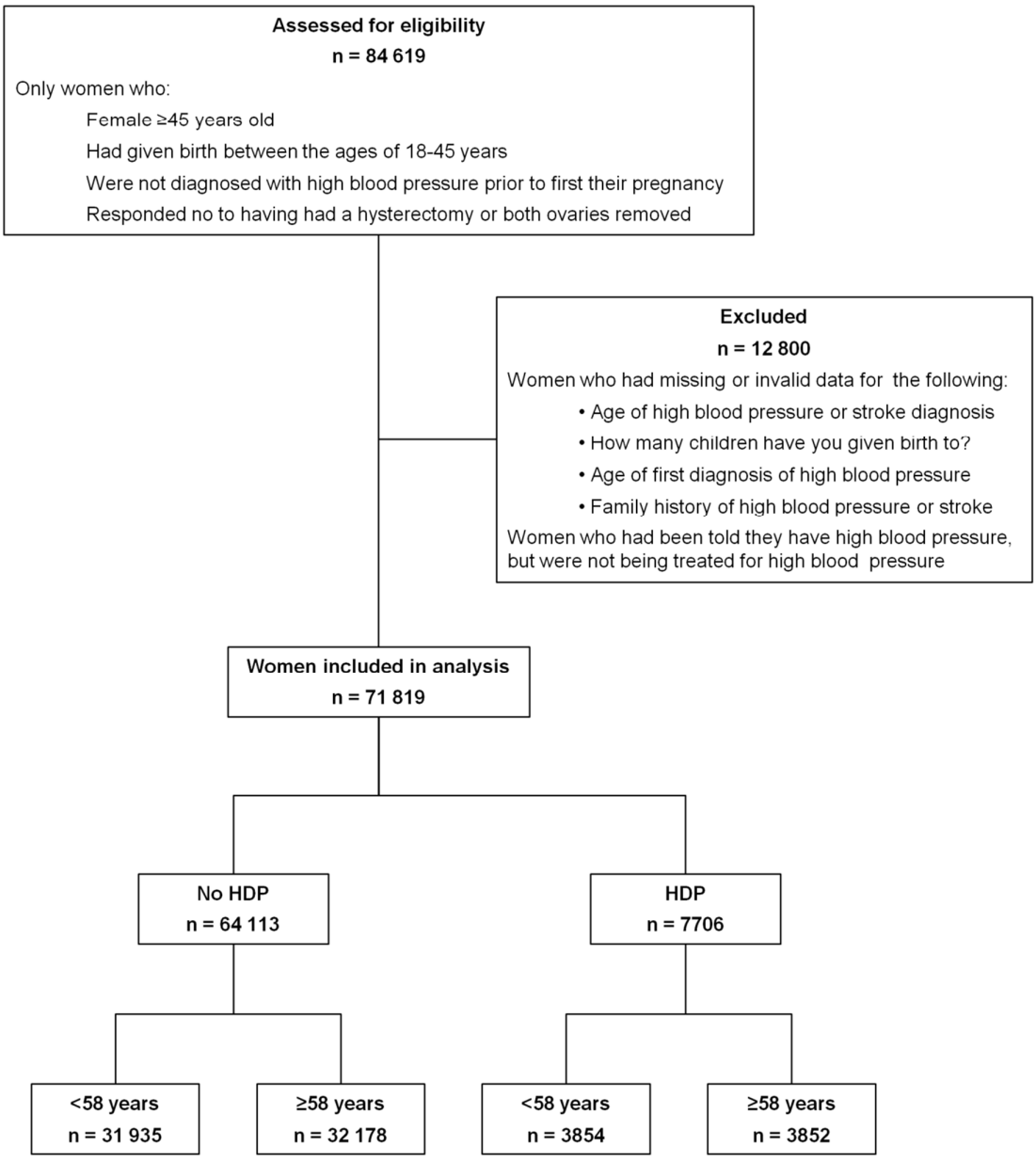

Figure 1. Participants included in the study.

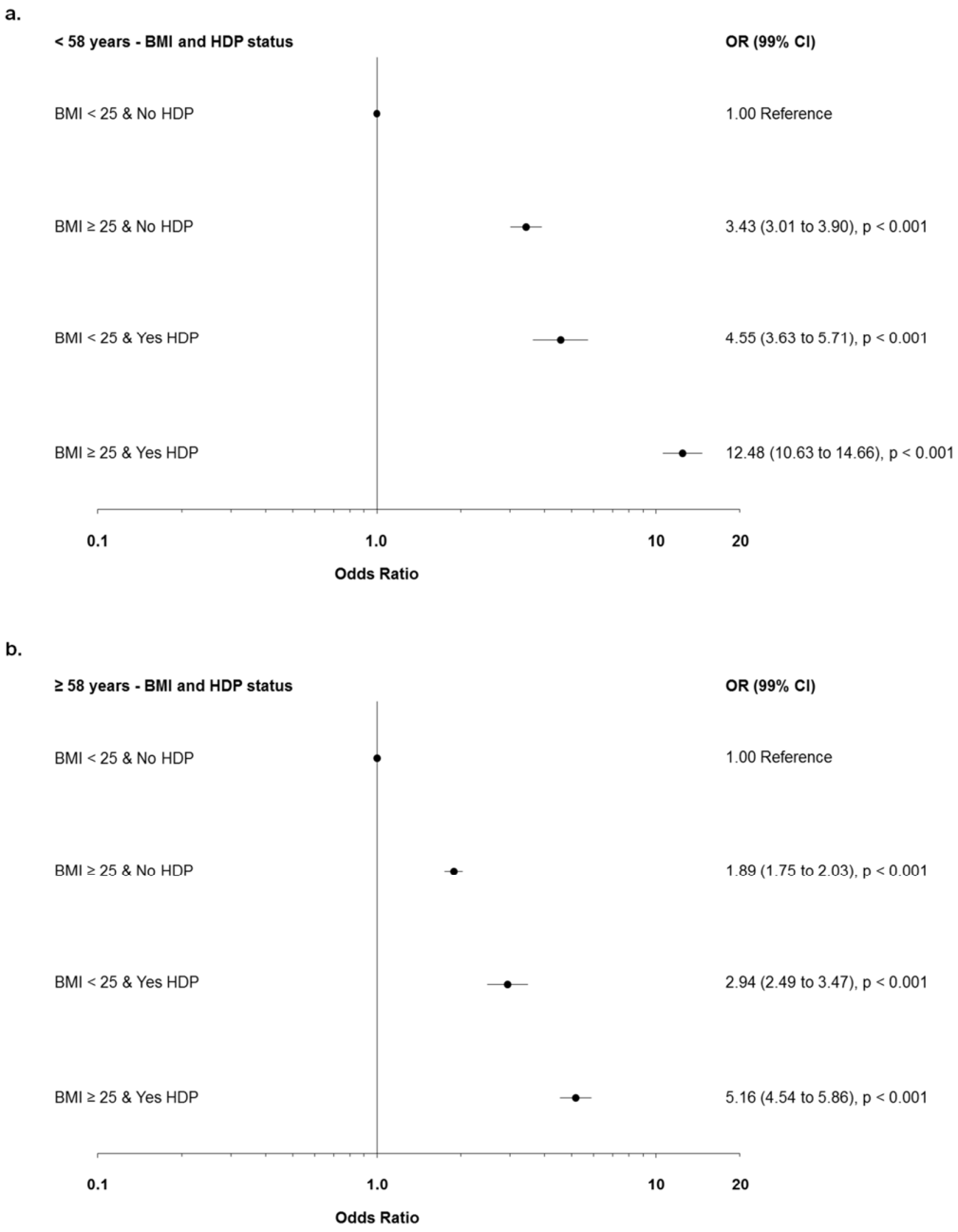

Figure 2. The odds of having high blood pressure depending on a woman's BMI and whether she had a hypertensive disorder of pregnancy (HDP), compared to women with present day BMI < 25 who were normotensive during pregnancy, stratified by current age.

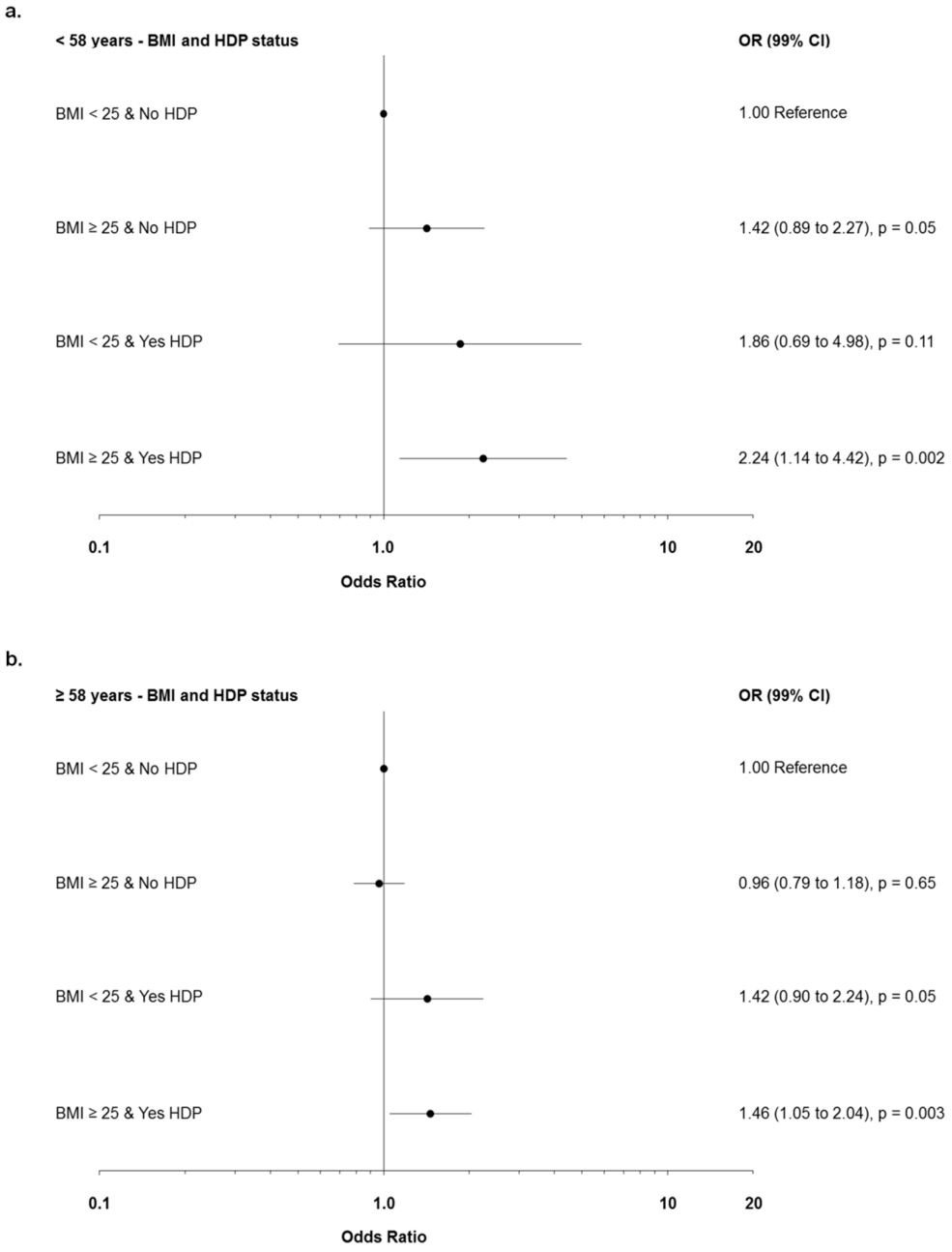

Figure 3. The odds of having stroke depending on a woman's BMI and whether she had a hypertensive disorder of pregnancy (HDP), compared to women with present day BMI < 25 who were normotensive during pregnancy, stratified by current age.

Table 1. Socio-demographic factors and health risk factors associated with hypertensive disorders of pregnancy

Characteristics	Status	N (% column)	% HDP	Odds ratio (99% CI)†
Family history of High BP	No	33 349 (46)	7	1.00
	Yes	38 470 (54)	14	2.14 (2.00 to 2.30)‡
Family history of Stroke	No	53 416 (74)	10	1.00
	Yes	18 403 (26)	13	1.13 (1.05 to 1.21)‡
Smoking status	Never	46 832 (65)	11	1.00
	Past	19 996 (28)	11	0.95 (0.89 to 1.02)
	Current	4 669 (7)	9	0.79 (0.69 to 0.91)‡
Past oral contraceptive use	No	12 339 (17)	9	1.00
	Yes	58 440 (81)	11	1.28 (1.17 to 1.40)‡
Number of Children	1	7 581 (11)	9	1.00
	2	29 298 (41)	10	1.10 (0.98 to 1.23)
	3	21 441 (30)	11	1.23 (1.09 to 1.38)‡
	4 or more	13 499 (19)	12	1.46 (1.29 to 1.65)‡

% HDP - the percentage of women who responded yes to having had high blood pressure when pregnany. Percentages do not consistently total to 100% due to missing values.

†Adjusted for family history of high blood pressure, family history of stroke, smoking status, history of oral contraceptive use, and number of children.

‡ $p < 0.01$

Table 2. Association between high blood pressure when pregnant and maternal cardiovascular disease in later life

CVD	Current Age	HDP	Cases (n)	Crude Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)†
High blood pressure	<58	No	31 935	1·00 reference	
		Yes	3 854	4.89 (4.40 to 5.43)	3.79 (3.38 to 4.24)‡
	≥58	No	32 178	1.00 reference	
		Yes	3 852	3.51 (3.21 to 3.84)	2.83 (2.58 to 3.12)‡
Stroke	<58	No	35 613	1·00 reference	
		Yes	176	1.92 (1.17 to 3.16)	1.69 (1.02 to 2.82)‡
	≥58	No	35 128	1·00 reference	
		Yes	902	1.45 (1.13 to 1.85)	1.46 (1.13 to 1.88)‡

†analysis adjusted for country of origin, income level, BMI, smoking status, alcohol consumption, physical activity, family history of high blood pressure (for high blood pressure analysis), family history of stroke (for stroke analysis), history of oral contraceptive use, history of menopausal hormone therapy, and number of children.

‡ $p < 0.01$

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

High blood pressure during pregnancy is associated with future cardiovascular disease: observational cohort study

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ABSTRACT

Objectives The study aimed to determine if having a hypertensive disorder of pregnancy (HDP) is risk factor for future cardiovascular disease (CVD), independent of age and BMI.

Design Data were sourced from the baseline questionnaire of the *45 and Up Study*, Australia, an observational cohort study.

Setting Participants were randomly selected from the Australian Medicare Database within New South Wales.

Participants A total of 84 619 women were eligible for this study of which 71 819 were included. These women had given birth between the ages of 18 and 45 years, had an intact uterus and ovaries, and had not been diagnosed with high blood pressure prior to their first pregnancy.

Results HDP was associated with higher odds of having high blood pressure (<58 years: adjusted odds ratio 3.79, 99% confidence interval 3.38 to 4.24, P<0.001; ≥58 years: 2.83, 2.58 to 3.12, P<0.001) and stroke (<58 years: 1.69, 1.02 to 2.82, P=0.008; ≥58 years: 1.46, 1.13 to 1.88, P<0.001) in later life. Women with HDP had a younger age of onset of high blood pressure (45.6 years versus 54.8 years, p<0.001) and stroke (58.0 years versus 62.5 years, p<0.001). Women who had HDP and whose present day BMI was <25 had significantly higher odds of having high blood pressure, compared to women who were normotensive during pregnancy (<58 years: 4.55, 3.63 to 5.71, P<0.001; ≥58 years, 2.94, 2.49 to 3.47, P<0.001). Women who had HDP and a present day BMI ≥ 25 had significantly increased odds of high blood pressure (<58 years: 12.48, 10.63 to 14.66, P<0.001; ≥58 years, 5.16, 4.54 to 5.86, P<0.001), compared with healthy weight women with a normotensive pregnancy.

Conclusions HDP is an independent risk factor for future CVD and this risk is further exacerbated by the presence of overweight or obesity in later life.

ARTICLE SUMMARY

Article Focus

- Hypertensive disorders of pregnancy have been associated with an increased risk of maternal cardiovascular disease in later life.
- It remains unclear whether high blood pressure during pregnancy is an independent risk factor for future cardiovascular disease or whether it is confounded by traditional risk factors such as age and BMI.

Key Messages

- Our study shows that a history of hypertensive disorders of pregnancy (HDP) is significantly associated with having high blood pressure and stroke in later life.
- HDP is an independent risk factor for future cardiovascular disease and the risk of CVD is further exacerbated by the presence of overweight or obesity in later life, particularly in women <58 years of age.

Strengths and Limitations

- This is a large observational cohort study which included 71 819 women.
- These data are unable to differentiate between the different categories of HDP and the timing of onset of the disease in the pregnancy.

INTRODUCTION

Cardiovascular disease (CVD) is a major contributor to worldwide morbidity and mortality and is the leading cause of death in the USA in individuals aged 65 years and over.[1] In Australia, approximately 2 million women are affected by CVD and the three leading causes of death in women are coronary heart disease, stroke and other heart diseases (including heart failure).[2] Age is a powerful predictor of cardiovascular disease, with increasing age associated with increasing arterial stiffness[3] and endothelial dysfunction[4] which predisposes the individual to high blood pressure and premature aging of the vascular system.[5] Excess body fat is also a known risk factor for both arterial stiffening endothelial dysfunction and subsequent cardiovascular disease.[6 7]

Recent evidence has demonstrated that women with hypertensive disorders of pregnancy (HDP) have increased arterial stiffness,[8] and these women may be at a greater risk of future cardiovascular disease when compared to women who experience a normotensive pregnancy.[9] HDP, which include gestational hypertension, preeclampsia/eclampsia, chronic hypertension and superimposed preeclampsia on chronic hypertension, occur in 5-10% of all pregnancies within Australia.[10] 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] This causes the placenta to release antiangiogenic proteins which result in endothelial dysfunction. The clinical features of the maternal response to this abnormality include hypertension, renal impairment, liver impairment, pulmonary oedema, thrombocytopenia, coagulopathy and neurological disturbances. It can exacerbate existing endothelial dysfunction in women with chronic high blood pressure. 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 return~~ed~~ to its pre-

pregnancy 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.[13-15]

The aim of this study was to determine whether women who reported to have had a HDP were at an increased likelihood of having high blood pressure or stroke in later life, using observational data from the *45 and Up Study*, Australia. We also aimed to determine how this association was modified by a woman's age and BMI and whether the age of onset of high blood pressure or stroke in later life, differed between women who had HDP and those who remained normotensive.

METHODS

Study Sample

This study obtained data from women participating in the *45 and Up Study*, a large scale cohort study of 267 153 men and women aged 45 and over in New South Wales, Australia. Participants were randomly selected from the Australian Medicare Database which provides near complete coverage of the population. The participants were enrolled into the study by consenting to and completing a baseline questionnaire (available at www.45andUp.org.au) and giving consent for long term follow up through data linkage and repeat data collection. People aged 80 years and over, and residents of rural and remote areas were oversampled. Study recruitment commenced in January 2006 and was completed in April 2009. The methods for the *45 and Up Study* have been described elsewhere.[16] The *45 and Up Study* received ethics approval from the University of NSW Human Ethics Committee and the current study was approved by the UWS Human Research Ethics Committee. Exposure-outcome relationships estimated from the *45 and Up Study* data have been shown to be consistent with another large study of the same population, regardless of the underlying response rate or mode of questionnaire administration.[17]

All of the data used in this study were acquired from the *45 and Up Study* baseline questionnaire. Women were included in this study if: they were age 45 years or more; had given birth between 18 years of age and 45 years of age; had not had a hysterectomy or both ovaries removed and were not diagnosed with high blood pressure prior to their first pregnancy (Figure 1).

Women were identified as having had HDP by responding "Yes" to the question "Has a doctor ever told you that you have: high blood pressure - when pregnant". Where the age of

"high blood pressure - when pregnant" was within 1 year of the women's age when she first gave birth, the HDP was identified as occurring during her first pregnancy. Where the age of "high blood pressure - when pregnant" was greater than 1 year from the women's age when she first gave birth, the HDP was identified as occurring during a subsequent pregnancy.

Women were identified as having high blood pressure when not pregnant if they answered "Yes" to the question "In the last month have you been treated for: high blood pressure". Women were identified as having a stroke if they answered "Yes" to the question "Has a doctor ever told you that you have: stroke". Women were excluded if: they reported having high blood pressure prior to having their first child; answered "Yes" to "Has a doctor ever told you that you have: high blood pressure – when not pregnant" but were not being treated for high blood pressure; they failed to provide an age of onset for high blood pressure or stroke; they provided invalid data for family history; or they provided invalid data for the number of children they had given birth to in their specified age range (Figure 1). Classification of demographic and lifestyle characteristics have been described elsewhere.[18]

Statistics

Odds ratios and 99% confidence intervals for the association between (i) demographic and lifestyle characteristics and HDP, (ii) HDP and high blood pressure in later life, and (iii) HDP and stroke in later life, were estimated using logistic regression. Analyses were repeated for (ii) and (iii) combining HDP status (yes or no) and BMI (<25 or ≥25) into a single variable with four categories. Both crude and adjusted odds ratios were calculated and descriptions refer to adjusted odds ratios unless otherwise specified. Due to the known association between high blood pressure and ageing, women were stratified according to age using the median age as the cut point (<58 years, ≥58 years) when testing the association between HDP

and both high blood pressure and stroke in later life. Odds ratios were adjusted for country of origin, income level, BMI, smoking status, alcohol consumption, physical activity, family history of high blood pressure (for high blood pressure analysis), family history of stroke (for stroke analysis), history of oral contraceptive use, history of menopausal hormone therapy, and number of children. Categories for each covariate have been previously described.[18] An additional category for missing values was included for variables with missing data. Linear regression was used to study the association between age of onset of both high blood pressure and stroke, with HDP. All statistical tests were two-sided, using a significance level of $p<0.01$ to partially account for multiple testing issues.[19] All statistical analyses were carried out using SPSS software version 20 (IBM Corp New York USA).

RESULTS

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, ~~A total of~~ 71 819 ~~women~~ were included in the study (exclusion criteria shown in Figure 1) of which 7 706 (10.7%) reported having had HDP. Of these, 3 237 (42.0%) reported current treatment for high blood pressure and 165 (2.1%) reported having had a stroke. In comparison, of the 64 113 women who did not report HDP, 10 668 (16.6%) reported current treatment for high blood pressure and 913 (1.4%) reported having had a stroke. There was no significant difference in odds for having high blood pressure (OR 1.02, 99% CI 0.88 to 1.16, p=0.77) or stroke (OR 0.99, 99% CI 0.64 to 1.54, p=0.97) between HDP during first pregnancy compared with HDP in a subsequent pregnancy. As a result, analysis grouped all women who reported HDP, irrespective of which pregnancy it had occurred.

The association between socio-demographic factors and whether a woman had HDP are shown in Table 1. A positive family history of high blood pressure, a positive family history of stroke, oral contraceptive use, and having three or more children were associated with significantly higher odds of having had HDP. Current smoking status was associated with reduced odds of having had HDP compared to women who had never smoked.

HDP was associated with increased odds of having high blood pressure in later life (women <58 years: OR 3.79, 99% CI 3.38 to 4.24, p<0.001) compared to women who remained normotensive during pregnancy (Table 2). The average age of onset of high blood pressure in later life was 45.6 years for women who had HDP compared to 54.8 years for women who

remained normotensive in their pregnancy (adjusted β = -8.30, 99% CI -8.89 to -7.71, p<0.001).

Stratifying women according to HDP status and BMI found that women who had HDP and whose current BMI was ≥25, had significantly increased odds of having high blood pressure (women <58 years: OR 12.48, 99% CI 10.63 to 14.66, p<0.001; women ≥58 years: OR 5.15, 99% CI 4.54 to 5.86, p<0.001) compared to women who did not have HDP and whose present day BMI was <25 (Figure 2). Women who had HDP and whose present day BMI was <25 had significantly higher odds of having high blood pressure, compared to women who did not have HDP and whose present day BMI was ≥25 (women <58 years: OR 1.33, 99% CI 1.08 to 1.64, p<0.001; women ≥58 years: OR 1.56, 99% CI 1.33 to 1.83, p<0.001).

HDP was also associated with increased odds of having stroke in later life (women <58 years: OR 1.69, 99% CI 1.02 to 2.82, p<0.001; women ≥58 years: OR 1.46, 99% CI 1.13 to 1.88, p<0.001) compared to women who remained normotensive in their pregnancy (Table 2). The average age of onset of stroke in later life was 58.0 years for women who had HDP compared to 62.5 years for women who remained normotensive in their pregnancy (adjusted β = -4.01, 99% CI -6.87 to -1.16, p<0.001).

Stratifying women according to HDP status and BMI found that women who had HDP and whose current BMI was ≥25, had significantly increased odds of having stroke (women <58 years: OR 2.24, 99% CI 1.14 to 4.42, p=0.002; women ≥58 years: OR 1.46, 99% CI 1.05 to 2.04, p=0.003) compared to women who did not have HDP and whose present day BMI was <25 (Figure 3). There was no significant difference in odds of having stroke in the other

groups of women (BMI ≥ 25 & No HDP, and BMI < 25 & Yes HDP), compared to women of healthy weight who had remained normotensive during their pregnancy.

DISCUSSION

The *45 and Up Study* is the largest self-reported cohort of Australian women ever examined. Our results show that having a hypertensive disorder of pregnancy (HDP) is associated with significantly increased odds of having high blood pressure in later life, compared to women that remained normotensive, and this was exacerbated in women with a BMI $\geq$ 25 kg/m^2. Women who reported having HDP were 9.2 years younger at the age of onset of high blood pressure, compared to women who experienced healthy pregnancies. Similarly, women who suffered HDP had significantly higher odds of having stroke compared to women who remained normotensive in their pregnancy and the age of onset of stroke was significantly earlier in women with HDP. Women within the healthy weight range in our study, and who had experienced HDP, had significantly higher odds of having present day high blood pressure compared to similar aged women who were overweight or obese, but who had been normotensive during pregnancy. Women who had both risk factors, namely BMI $\geq$ 25 kg/m^2 and a HDP, had up to 12.48 increased odds of having high blood pressure and up to 2.24 increased odds of stroke, compared to women within the healthy weight range with normotensive pregnancies. This shows that HDP is an independent risk factor for future high blood pressure and when combined with traditional risk factors such as BMI, a history of HDP can significantly increase the odds of future CVD.

This study analysed cross-sectional and observational data from the baseline questionnaire from the *45 and Up Study*. As a result, the ~~casual~~causal nature of associations could not be assessed. 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. These data are unable to differentiate between the different categories of HDP, the severity of the disease, duration of the pregnancy, the timing of onset of the disease in the pregnancy, and the relationship

between the timing of high blood pressure and the timing of delivery. Other studies have shown that the more severe the high blood pressure and the earlier its onset during pregnancy, the greater the risk of future high blood pressure compared to women who suffer a milder or more moderate form of the disease.[20 21] 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%.[10] This may be explained by self reported data recall bias or the systematic underreporting of HDP.[22]

Our results support existing evidence of a link between HDP and subsequent cardiovascular risk. Studies have shown that women who had HDP have a greater risk of cardiovascular morbidity including an increased risk of hypertension, stroke and coronary heart disease,[14 23] and CVD is more common in these women within one to two decades of the hypertensive in pregnancy event.[24-27] Our study extends these findings by showing that women with HDP have a significantly younger age of onset of both high blood pressure and stroke. HDP was significantly associated with increased odds of future CVD in all age groups analysed, but the odds reduced with increasing age demonstrating age as an independent predictor of future CVD.

HDP shares many of the aetiologies of CVD such as inflammation and endothelial changes, as well as having overlapping risk factors such as obesity, insulin resistance and dyslipidemia. Sustained endothelial dysfunction caused by damage to the endothelium during HDP may be responsible for the long-term consequences observed in these women. Alternatively, pre-existing endothelial dysfunction prior to conception may be a triggering mechanism for HDP as well as increasing the risk for CVD later in life.[15] Studies have shown that endothelial dysfunction persists in women following HDP, namely preeclampsia.[13 15 28 29]

Additionally, studies have found a strong link between preeclampsia and higher circulating concentrations of fasting insulin,[30] lipid, and coagulation factors[31] -post partum. High BMI is also known to adversely influence the endothelium,[7] and endothelial dysfunction is an early risk factor for future catastrophic CVD events in obese adults.[32] 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[33]. This increased risk of CVD is further exacerbated by the presence of overweight or obesity in later life, particularly in women <58 years of age.

HDP are associated with higher odds of having cardiovascular disease in later life and HDP are an independent risk factor for future CVD. Women who are overweight or obese and have HDP have significantly higher odds of having both high blood pressure and stroke in later life. This study adds to the evidence[34] that a woman's pregnancy history is important when assessing her future risk of CVD. ~~and w~~Women who experience HDP should be closely monitored for cardiovascular risk factors, including blood pressure, hyperglycemia, and hyperlipidemia ~~have their blood pressure closely monitored~~ in the years following pregnancy. Women should be encouraged to maintain a healthy weight, particularly if they experience HDP. 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.

DECLARATION OF COMPETING INTERESTS

The authors of this work have no competing interests to declare.

FUNDING STATEMENT

The *45 and Up Study* is managed by the Sax Institute in collaboration with major partner Cancer Council New South Wales; and partners the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; *beyondblue: the national depression initiative*; Ageing, Disability and Home Care, NSW Family and Community Services; Australian Red Cross Blood Service and UnitingCare Ageing. JML is supported by a National Health and Medical Research Council - Australian Biomedical Fellowship. JT is supported by a PEARLS (Preeclampsia Research Laboratories) PhD scholarship. SJL is the recipient of a University of Western Sydney Postgraduate Research Award and an Ingham Health Research Institute scholarship. The sponsors were not involved in the analysis, or interpretation of the data; and preparation, review, or approval of the manuscript for the study reported here.

DATA SHARING

There is no additional data available.

ETHICS

The *45 and Up Study* received ethics approval from the University of NSW Human Research Ethics Committee (HREC 10186) and the current study was approved by the University of Western Sydney Human Research Ethics Committee (H8561).

CONTRIBUTORSHIP

All authors included on a paper fulfil the criteria of authorship and there are no other individuals that meet the criteria for authorship. JML had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and is guarantor. JT, CLC, KY, SJL, CT, AM, AO, AH and JML conceived and designed the study. JT, CLC, KY and JML drafted the manuscript. JML supervised the study and was responsible for the statistical analysis. All authors participated in interpreting the data and critically revising the manuscript.

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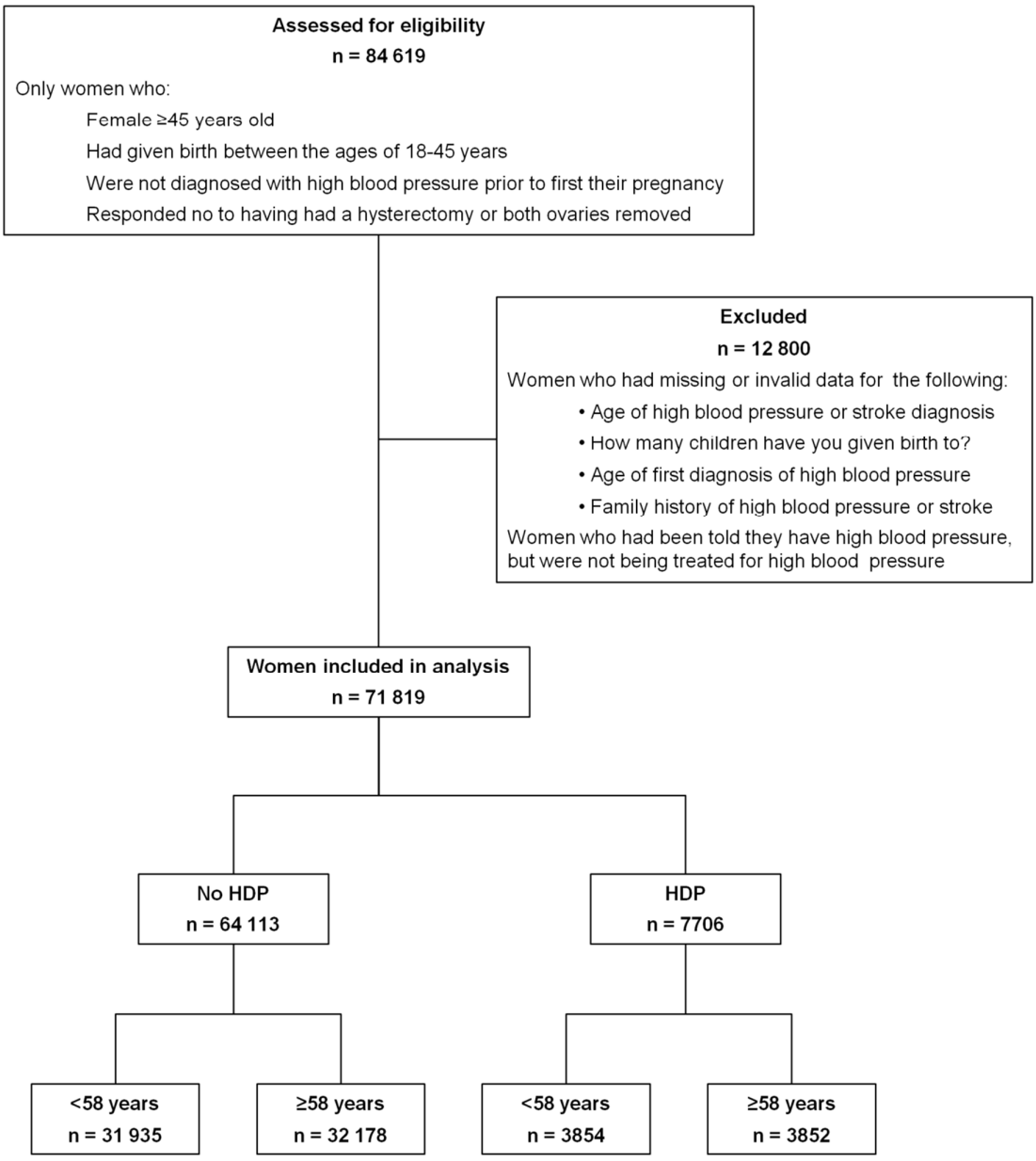

Figure 1. Participants included in the study.

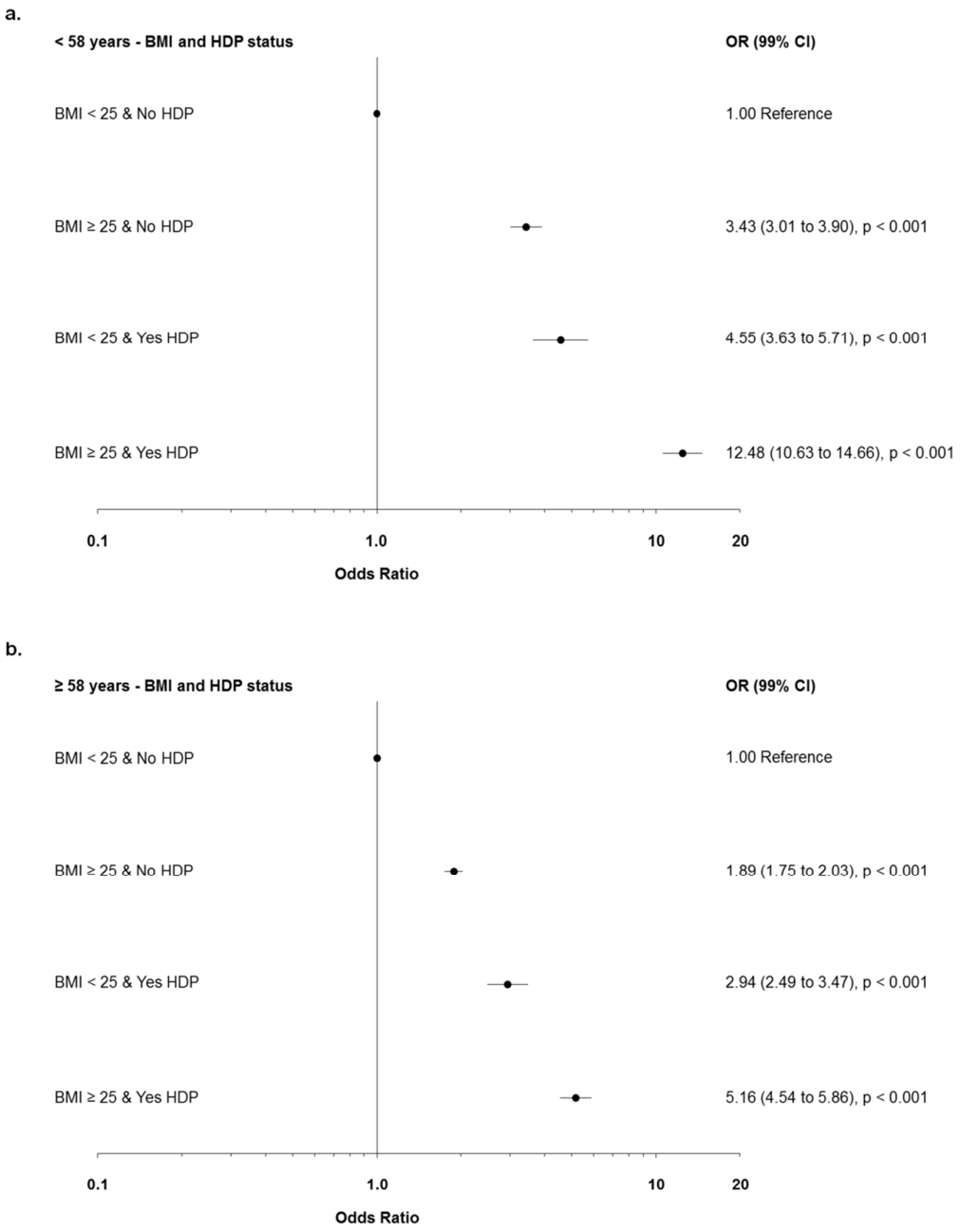

Figure 2. The odds of having high blood pressure depending on a woman's BMI and whether she had a hypertensive disorder of pregnancy (HDP), compared to women with present day BMI < 25 who were normotensive during pregnancy, stratified by current age.

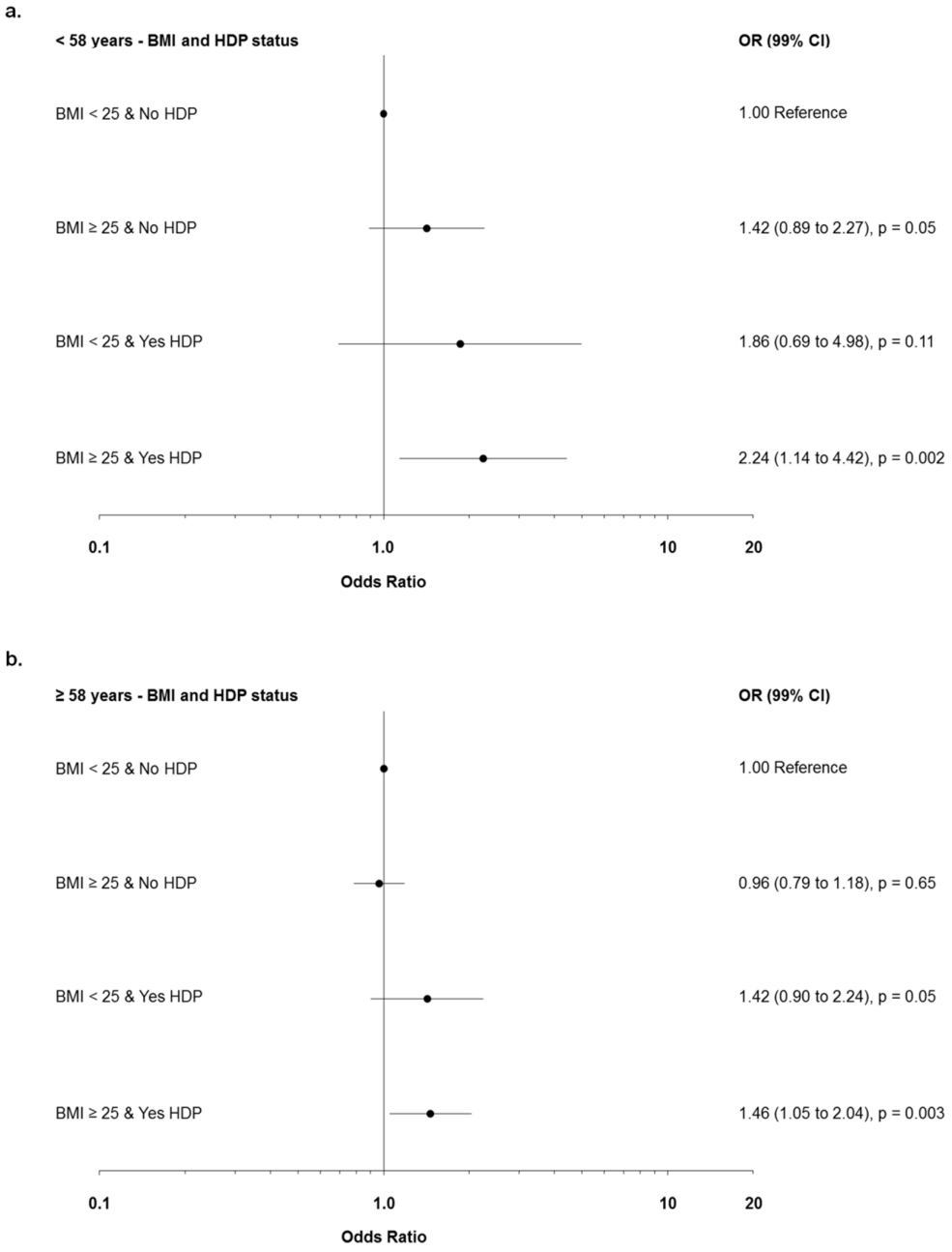

Figure 3. The odds of having stroke depending on a woman's BMI and whether she had a hypertensive disorder of pregnancy (HDP), compared to women with present day BMI < 25 who were normotensive during pregnancy, stratified by current age.

Table 1. Socio-demographic factors and health risk factors associated with hypertensive disorders of pregnancy

Characteristics	Status	N (% column)	% HDP	Odds ratio (99% CI)†
Family history of High BP	No	33 349 (46)	7	1.00
	Yes	38 470 (54)	14	2.14 (2.00 to 2.30)‡
Family history of Stroke	No	53 416 (74)	10	1.00
	Yes	18 403 (26)	13	1.13 (1.05 to 1.21)‡
Smoking status	Never	46 832 (65)	11	1.00
	Past	19 996 (28)	11	0.95 (0.89 to 1.02)
	Current	4 669 (7)	9	0.79 (0.69 to 0.91)‡
Past oral contraceptive use	No	12 339 (17)	9	1.00
	Yes	58 440 (81)	11	1.28 (1.17 to 1.40)‡
Number of Children	1	7 581 (11)	9	1.00
	2	29 298 (41)	10	1.10 (0.98 to 1.23)
	3	21 441 (30)	11	1.23 (1.09 to 1.38)‡
	4 or more	13 499 (19)	12	1.46 (1.29 to 1.65)‡

% HDP - the percentage of women who responded yes to having had high blood pressure when pregnany. Percentages do not consistently total to 100% due to missing values.

†Adjusted for family history of high blood pressure, family history of stroke, smoking status, history of oral contraceptive use, and number of children.

‡ $p < 0.01$

Table 2. Association between high blood pressure when pregnant and maternal cardiovascular disease in later life

CVD	Current Age	HDP	Cases (n)	Crude Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)†
High blood pressure	<58	No	31 935	1·00 reference	
		Yes	3 854	4.89 (4.40 to 5.43)	3.79 (3.38 to 4.24)‡
	≥58	No	32 178	1.00 reference	
		Yes	3 852	3.51 (3.21 to 3.84)	2.83 (2.58 to 3.12)‡
Stroke	<58	No	35 613	1·00 reference	
		Yes	176	1.92 (1.17 to 3.16)	1.69 (1.02 to 2.82)‡
	≥58	No	35 128	1·00 reference	
		Yes	902	1.45 (1.13 to 1.85)	1.46 (1.13 to 1.88)‡

†analysis adjusted for country of origin, income level, BMI, smoking status, alcohol consumption, physical activity, family history of high blood pressure (for high blood pressure analysis), family history of stroke (for stroke analysis), history of oral contraceptive use, history of menopausal hormone therapy, and number of children.

‡ $p < 0.01$