RESEARCH

Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis

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Abstract

Objective To provide an accurate assessment of complications of pregnancy in women with chronic hypertension, including comparison with population pregnancy data (US) to inform pre-pregnancy and antenatal management strategies.

Design Systematic review and meta-analysis.

Data sources Embase, Medline, and Web of Science were searched without language restrictions, from first publication until June 2013; the bibliographies of relevant articles and reviews were hand searched for additional reports.

Study selection Studies involving pregnant women with chronic hypertension, including retrospective and prospective cohorts, population studies, and appropriate arms of randomised controlled trials, were included.

Data extraction Pooled incidence for each pregnancy outcome was reported and, for US studies, compared with US general population incidence from the National Vital Statistics Report (2006).

Results 55 eligible studies were identified, encompassing 795 221 pregnancies. Women with chronic hypertension had high pooled incidences of superimposed pre-eclampsia (25.9%, 95% confidence interval 21.0% to 31.5 %), caesarean section (41.4%, 35.5% to 47.7%), preterm delivery <37 weeks' gestation (28.1% (22.6 to 34.4%), birth weight <2500 g (16.9%, 13.1% to 21.5%), neonatal unit admission (20.5%, 15.7% to 26.4%), and perinatal death (4.0%, 2.9% to 5.4%). However, considerable heterogeneity existed in the reported incidence of all outcomes (τ^2=0.286-0.766), with a substantial range of incidences in individual studies around these averages; additional meta-regression did not identify any influential demographic factors. The incidences (the meta-analysis average from US studies) of adverse outcomes in women with chronic hypertension were compared with women from the US national population dataset and showed higher risks in those with chronic hypertension: relative risks were 7.7 (95% confidence interval 5.7 to 10.1) for superimposed pre-eclampsia compared with pre-eclampsia, 1.3 (1.1 to 1.5) for caesarean section, 2.7 (1.9 to 3.6) for preterm delivery <37 weeks' gestation, 2.7 (1.9 to 3.8) for birth weight <2500 g, 3.2 (2.2 to 4.4) for neonatal unit admission, and 4.2 (2.7 to 6.5) for perinatal death.

Conclusions This systematic review, reporting meta-analysed data from studies of pregnant women with chronic hypertension, shows that adverse outcomes of pregnancy are common and emphasises a need for heightened antenatal surveillance. A consistent strategy to study women with chronic hypertension is needed, as previous study designs have been diverse. These findings should inform counselling and contribute to optimisation of maternal health, drug treatment, and pre-pregnancy management in women affected by chronic hypertension.

Introduction

Chronic hypertension complicates between 1% and 5% of pregnancies,[1-4] but this estimate is drawn from a small number of population based studies, including publications from more than 20 years ago. Recent demographic changes in the antenatal population suggest that chronic hypertension in pregnancy may be an increasing clinical problem. In populations in which maternal age at childbirth is increasing, the association of hypertension with advancing age will inevitably contribute to a greater prevalence of chronic hypertension.[5] In the United States, for example, chronic hypertension is likely to have paralleled the increase in first deliveries in women aged over 35 years from 1% to 8% that occurred between 1970 and 2006.[6] Maternal age may not be the only factor; a recent population based study in the United States suggests that the prevalence of chronic hypertension in pregnancy increased between 1995-96 and 2007-08, despite adjustment for maternal age.[4] An increase in other risk factors for chronic hypertension, including obesity and the metabolic syndrome, is likely to contribute.[7 8] Globally, therefore, the number of women entering pregnancy with established chronic hypertension is set to rise.[9]

Chronic hypertension is associated with poor outcomes of pregnancy.[10] Numerous case-control studies frequently identify chronic hypertension as a risk factor for most known adverse events for mother and fetus.[11-13] Retrospective and prospective cohort studies, intervention trials, and observational studies for high risk pregnancies similarly document higher rates of complications of pregnancy in women with chronic hypertension.[8 14-16] Individually, these reports, usually from single centre studies, provide valuable data for a given population, but they are of limited use for wider extrapolation. Nevertheless, collectively, they may enable accurate assessment of pregnancy outcomes in affected women.

Primary and secondary healthcare professionals involved in the management of women of childbearing age with chronic hypertension include family doctors, clinical pharmacologists, cardiologists, nephrologists, endocrinologists, and general physicians. All may be called on to provide information for women planning a pregnancy. Pregnancy is frequently the first time when chronic hypertension is identified by midwives and obstetricians.[17] In the absence of a strong evidence base for accurate risk assessment in chronic hypertension, providing useful estimates of adverse pregnancy outcomes presents a challenge. The objective of this study was to conduct a meta-analysis of population based, multicentre, and single centre studies, to provide a reliable assessment of risks of pregnancy in women with chronic hypertension, drawing comparison with outcomes available from US studies and the US general population (2006) of pregnant women.

Methods

Literature review

We did a comprehensive literature review using the databases PubMed/Medline (via OVID), Embase (via OVID), and Web of Science. We tailored search strategies to each database. We used MeSH and free text terms in conjunction to increase sensitivity to potentially appropriate studies. Where MeSH terms were not used (Web of Science), we identified search terms and all possible synonyms and spellings obtained and used them in the search strategy. In Web of Science, we selected the "lemmatisation" option. We searched pregnancy complications and outcomes terms and chronic hypertension terms separately, and then combined them in each database. The study protocol is provided in supplementary information 1. We applied no limits other than the search strategy to databases. We searched databases from the time of first publication (Medline 1946, Embase 1947, Web of Science 1899) until June 2013.

Study selection criteria

We included prospective and retrospective cohort studies. We reviewed randomised controlled trials, excluding the treatment arm if a difference existed in outcomes and including both arms if no benefit of the intervention was seen. We excluded case-control studies, case reports, reviews, letters to editors, and animal/in vitro studies.

To minimise selection bias, we did not include studies that excluded women with superimposed pre-eclampsia or categorised women with chronic hypertension and superimposed pre-eclampsia together with low risk women with pre-eclampsia, as this was one of the outcomes of interest. We considered studies with fewer than 20 women with chronic hypertension to be non-representative, and we excluded studies that did not report relevant outcome data.

Data extraction

KB and BP independently reviewed abstracts and full texts, and LC reviewed any discrepancies. The same authors independently extracted and tabulated data from selected full texts. When two studies included the same cohort, we included only the report with the largest number of women or most relevant outcomes.

We followed PRISMA guidelines for all procedures and reporting.[18] We used the Newcastle-Ottawa scale to grade cohort studies. We considered multi-fetal gestations as one pregnancy for maternal outcomes and two pregnancies for fetal outcomes. We recorded details of other potential confounders and adjustments, including age, secondary hypertension, body mass index, weight, parity, smoking, and ethnicity. Manuscripts not published in English were translated by native speaking physicians. We included abstracts if a definition of chronic hypertension and relevant outcomes were described.

We examined and reported definitions of chronic hypertension and superimposed pre-eclampsia (when available) for each included study. For purposes of analysis, we used the following definitions: preterm delivery—delivery before 37 weeks' gestation (up to 36^{+6}); low birth weight—below 2500 g; perinatal death—fetal death after 20 weeks' gestation including stillbirth and neonatal death up to 1 month; neonatal unit admission—admission to neonatal intensive care or special care baby unit.

Statistical analysis

We used mixed effects logistic regression for meta-analysis, using the Stata command "xtmelogit." We used extracted data to calculate estimated pooled incidences, 95% confidence intervals, and predicted 95% incidence ranges (prediction intervals) of adverse outcomes. Prediction intervals have been proposed as being akin to a reference range for that parameter across the population, allowing more appropriate interpretation and extrapolation into clinical practice.[19] Ninety five per cent prediction intervals show the uncertainty of the range of possible percentage incidences for a new study population, whereas 95% confidence intervals show the uncertainty about the estimate of the average percentage incidence across study populations.

We used mixed effects logistic regression, which allows for random variation at more than one level, on the assumption that significant heterogeneity would exist both between individuals and between studies and that each study would be likely to include covariates that could influence outcomes. We used the τ^2 statistic to describe heterogeneity and did subgroup analyses according to seven groupings selected before analysis: country's economic wealth according to World Bank classification (gross national income per capita),[20] study period, inclusion or exclusion of multiple pregnancies, inclusion or exclusion of congenital abnormalities, inclusion or exclusion of women with secondary hypertension, study design, and study definition of chronic hypertension. We also stratified studies reporting incidences of superimposed pre-eclampsia according to the study definition of superimposed pre-eclampsia. We used forest plots to assess overall effect. We calculated risk ratios for US studies relative to separate comparator data obtained from the Centers for Disease Control and Prevention's vital statistics 2006 (US national statistics) for pooled incidences and for individual study outcomes.[21]

We also did meta-regression using "xtmelogit" regression to identify the influence of potential modifiers of outcome including parity, maternal age, and ethnicity on the relation between chronic hypertension and subsequent outcome. As individual level data were unavailable, we used aggregate data

for each study (mean and standard deviation for age, and proportions of nulliparous/multiparous and white/non-white women). We made estimates of mean age if categories of ranges were presented. We used Stata version 11 for all statistical analyses, and all tests and confidence intervals were two sided with a significance level of 0.05.

Results

Figure 1⇓ shows the study selection process. Following title/abstract screening, 208 papers remained for full text review. Four abstracts were unavailable for analysis despite repeated attempts to contact the authors. Fifty five studies, comprising 795 221 pregnancies and 812 772 infants, met inclusion criteria and are reported in tables 1⇓, 2⇓, 3⇓, and 4⇓.[15 16 22-74] All studies achieved a total Newcastle-Ottawa grading score of 5 to 7, and no studies were excluded following grading. Newcastle-Ottawa gradings are shown in supplementary information 2.

Five studies were randomised controlled trials, including a primary analysis,[16] three secondary analyses of studies that did not have differences between treatment and placebo arms,[15 22 24] and one study that reported a difference in outcomes between the treatment (L-arginine supplementation) and placebo arm,[23] so only the placebo arm was included. One study included both prospective and retrospective data and was categorised as retrospective as this was the larger group.[32]

Maternal demographics of women with chronic hypertension, if reported, are shown in online supplementary information 2. Individual study definitions of chronic hypertension and categories according to definition are shown in tables 1⇓, 2⇓, 3⇓, and 4⇓ and in more detail in online supplementary information 3. Study definitions for superimposed pre-eclampsia are shown in online supplementary information 4. Table 5⇓ shows pooled incidences and prediction intervals of adverse pregnancy outcomes. Table 6⇓ shows risk ratios of adverse pregnancy outcomes from US studies compared with US population data.

The relative risk of superimposed pre-eclampsia in women with chronic hypertension was on average across study populations nearly eightfold higher than was pre-eclampsia in the general pregnancy population, and all adverse neonatal outcomes were at least twice as likely to occur compared with the general population.

The meta-analysis summary results and 95% confidence intervals relate to the average percentage incidence across studies. However, heterogeneity existed in most analyses, as seen by τ^2 values above zero. Thus genuine variation in incidences exists across study populations; in other words, in some populations the true incidence is well above the average, and in others it is well below the average. This is shown by wide 95% prediction intervals for the potential percentage incidence in a new study population. Only the limits of the prediction interval for superimposed pre-eclampsia excluded the US national data incidence of pre-eclampsia, which shows that the increased rate was evident across the different settings of the studies.

Figures 2⇓, 3⇓, 4⇓, 5⇓, 6⇓, and 7⇓ show forest plots for the pooled incidence of superimposed pre-eclampsia, caesarean section, preterm delivery before 37 weeks' gestation, birth weight <2500 g, perinatal death, and neonatal unit admission. Heterogeneity of incidence of superimposed pre-eclampsia seemed to be lower in randomised controlled trials (τ^2=0.026) than in population studies (τ^2=0.438) and was greater in prospective cohort (τ^2=0.83) and retrospective cohort studies (τ^2=1.080). Stratification of studies according to study definitions

of superimposed pre-eclampsia did not further reduce heterogeneity measured by τ^2. The incidence of neonatal unit admission was lower in one population study (7.1%, 95% confidence interval 6.0% to 9.2%) compared with randomised controlled trials (20.1%, 19.5% to 24.3%), but only one population study was included in this subgroup analysis.

Further comparison of τ^2 did not identify any significant influence of multiple pregnancies, congenital abnormalities, period of delivery, country's economic wealth, inclusion of secondary hypertension, maternal age, parity, ethnicity, or study definition of chronic hypertension on the degree of heterogeneity (τ^2>0.2 for all subgroups) or proportion of women with adverse events.

Discussion

This meta-analysis of 55 studies from 25 countries, including 795 221 pregnancies and spanning four decades, confirms that chronic hypertension is associated with adverse pregnancy outcomes. The pooled average incidence, across study populations, of superimposed pre-eclampsia, caesarean section, preterm delivery before 37 weeks' gestation, birth weight <2500 g, perinatal death, and neonatal unit admission were all significantly higher in US studies than the general US pregnancy population. Moreover, for superimposed pre-eclampsia, the limits of the 95% prediction intervals (reference range) for the US based studies were higher than the rate of pre-eclampsia reported in the US population. Heterogeneity between studies existed, and 95% prediction intervals were broad. Incidences of superimposed pre-eclampsia reported by randomised controlled trials were less heterogeneous than for other study designs but similar to the overall pooled incidence of superimposed pre-eclampsia in women with chronic hypertension. However, meta-regression did not identify any other underlying causes of heterogeneity, suggesting that either populations with chronic hypertension are varied or determination of chronic hypertension and outcomes may not be consistent.

Strengths and weaknesses of study

Studies were carefully selected according to a rigorous search strategy to enable unbiased inclusion of retrospectively or prospectively studied cohorts, population studies, or randomised controlled trials. For example, superimposed pre-eclampsia has been shown to be associated with worse pregnancy outcomes,[15 75-79] but some reports, initially assessed for the purpose of this study, excluded women with chronic hypertension and superimposed pre-eclampsia. This would lead to an underestimation of other adverse events, so we did not include these publications in the analysis. In other studies, women with superimposed pre-eclampsia were frequently grouped with other women with pre-eclampsia alone, precluding useful risk assessment for women with chronic hypertension. These studies were also excluded from meta-analysis.

Despite the selection of relevant and appropriately performed studies, we observed substantial diversity of reported incidences of adverse outcome. This is likely to reflect variations in the selection of women studied and difficulties of measurement but also true differences within the population of women with chronic hypertension. We conducted exploration to identify important confounders, including maternal age, ethnicity, economic wealth of country, decade of deliveries reported, parity, inclusion of secondary hypertension, multiple pregnancies and congenital birth defects, study design, and study definition of chronic hypertension. Although randomised controlled trials

were more consistent than other study designs, we found no systematic differences in mean event rates to explain the disparity in outcomes. Most papers did not report relevant baseline demographics defining the population studied, which limited the assessment of confounders. Coexisting factors including maternal age and ethnicity, recognised to be associated with both chronic hypertension and adverse pregnancy outcome, may contribute to confounding, but their relative effects are unknown.

Few studies in the meta-analysis reported control data, so a direct comparison of outcomes between women with chronic hypertension and normotensive women was not possible. To provide clinical context and relevance, we selected US population data (2006)[21] as a separate population for comparison against the US chronic hypertension studies, because these data provide the most comprehensive national annual statistics. Although US population data also report outcomes in high risk women, including those with chronic hypertension, the proportion of women with chronic hypertension in this dataset is small and therefore unlikely to influence the overall incidence of adverse outcomes. We chose the dataset from 2006 as being sufficiently recent to be clinically relevant but not too chronologically distant from the years in which most of the studies were conducted.

We could not elucidate the effect of differing antihypertensive treatments on the maternal and perinatal outcomes, as insufficient information was provided to allow subanalysis by drug group. This problem is made more complex by scenarios that include changing treatment over the gestation—for example, when a pregnant woman starts pregnancy while taking one drug, stops all treatment during the mid-trimester blood pressure nadir, and then restarts with a different drug when her blood pressure exceeds a certain threshold. In addition, many population based registry studies may record prescriptions from a database, rather than provide data that confirm that treatment has been taken. Thus assigning an individual woman to any drug treatment is difficult even within trimesters.

Strengths and weaknesses in relation to other studies

To our knowledge, few other detailed meta-analyses of outcomes of pregnancy in women with chronic hypertension have been reported. Population studies have reported data from large numbers of women with chronic hypertension and can be a useful guide to risks of pregnancy, but their generalisability is unclear. Population studies are limited by inaccuracies of coding collected for billing purposes and are susceptible to under-recognition of hypertension in pregnancy and misclassification. For example, Roberts and colleagues compared hospital discharge and birth databases with medical records and identified significant under-reporting of chronic hypertension.[3] Inadequacies of coding are also particularly relevant to accurate diagnosis of pre-eclampsia.[80] Women are more likely to be reported to have chronic hypertension if it had been recorded in an admission before pregnancy,[3] suggesting that women with more severe or longstanding chronic hypertension may be more likely to be included in population studies.

No threshold of blood pressure that predicts poor pregnancy outcomes has been identified, and an association between both systolic and diastolic blood pressure and adverse events has been reported.[81] Similarly, the length of time between diagnosis of hypertension and pregnancy is associated with more adverse events.[24] Chronic hypertension may be undetectable in early

pregnancy owing to systemic vasodilatation and reduced vascular resistance,[82] resulting in a fall in blood pressure, so women with a blood pressure below 140/90 mm Hg before 20 weeks' gestation would be excluded from many of the studies assessed, unless they were already taking antihypertensive drugs during or before pregnancy. The identification of women with chronic hypertension is therefore challenging, and the fact that multiple different definitions of chronic hypertension were given is unsurprising. This may explain some diversity in incidence of adverse events between studies; however, categorisation of studies according to definition of chronic hypertension did not reduce heterogeneity between outcomes.

In keeping with the challenges of diagnosing chronic hypertension, identification of superimposed pre-eclampsia remains difficult, and uncertainties exist. Research definitions have gone some way towards standardising diagnoses.[83] In this meta-analysis, 16 (30%) studies did not report diagnostic criteria, and the remainder used 18 varying, though valid, definitions of superimposed pre-eclampsia. Lack of consistency is likely to affect the heterogeneity of outcomes across studies.

Although women with more severe chronic hypertension, managed in specialist clinics, may be over-represented in some cohort studies, pregnancy outcomes did not differ by definition of inclusion criteria. Lack of blood pressures at first antenatal visit or use of antihypertensive drugs in early pregnancy precluded assessment of outcomes by severity of hypertension, although degree of hypertension clearly affects the decision for treatment and outcomes may therefore be influenced by severity. The findings of this study remain applicable to the women with chronic hypertension most frequently encountered and most in need of specialist advice.

Meanings of study and implications for physicians and health providers

The most recent UK Confidential Enquiry into Maternal and Child Health identified chronic disease as an underlying factor in preventable maternal deaths.[84] Consequently, the first recommendation stated that "Pre-pregnancy counselling services, . . . for women with pre-existing medical illnesses . . . are a key part of maternity services," supported by the National Institute for Health and Care Excellence's guidelines for the management of hypertension in pregnancy.[85] Furthermore, the American Congress of Obstetricians and Gynecologists' recent practice bulletin recommends that women with chronic hypertension "should be evaluated before conception to ascertain possible end-organ involvement."[86] Systematic reviews and meta-analyses can provide data more readily inferable to the individual, but no large aggregate analysis of pregnancy outcome in women with chronic hypertension has previously been reported. This meta-analysis of outcomes can be used before pregnancy and antenatally by healthcare professionals (including those not providing direct maternity care) advising women with chronic hypertension regarding possible adverse pregnancy events.

Accessibility to healthcare professionals and facilitation of early referral will allow drug treatment to be optimised on an individual basis (for example, starting aspirin and planning a change from cardio-renoprotective angiotensin converting enzyme inhibitors and angiotensin-II receptor blockers to alternative non-teratogenic antihypertensive drugs at the first positive pregnancy test or pre-pregnancy) or enable reassurance regarding continuation of drugs that are safe in pregnancy, to reduce the risk of complications including cerebrovascular events.

Debate is ongoing as to how antihypertensive treatment influences outcomes. Although reasonable evidence from a Cochrane systematic review shows that use of antihypertensive drugs halves the incidence of severe hypertension, it has not been shown to affect any other outcomes, including risk of pre-eclampsia, perinatal death, preterm birth, or small for gestational age babies.[87] Recent work has found that the risk of certain malformations such as congenital heart disease is similar in women taking angiotensin converting enzyme inhibitors and those with underlying hypertension taking no treatment, both having increased risk compared with normotensive controls, suggesting that the hypertension itself may contribute to congenital malformations.[88] Systematic reviews have also identified that a greater mean difference in mean arterial pressure with antihypertensive treatment is associated with the birth of a higher proportion of small for gestational age infants,[89] providing the basis for the Chronic Hypertension In Pregnancy Study (CHIPS). This study, which has recently completed recruitment of more than 1000 women with hypertension in pregnancy, but is yet to report, was designed to determine whether tight or less tight blood pressure control influences the likelihood of pregnancy loss or neonatal intensive care unit admission.[90] A recent study showing that women with chronic hypertension taking antihypertensive drugs have worse perinatal outcomes than do those not on treatment was unable to adjust for severity of underlying hypertension and indicates the need for future prospective studies to explore the influence of pre-existing disease severity.[91]

While the debate on the use and type of antihypertensive drugs continues, other beneficial management strategies needing implementation before or in early pregnancy include lifestyle adjustments (such as weight loss).[92] Our group has previously shown that women with chronic hypertension who continue to smoke in pregnancy are at greater risk of superimposed pre-eclampsia (compared with non-smokers), so smoking cessation is also an essential component of counselling.

Future research

Increasing numbers of pregnancies will be complicated by chronic hypertension as the trend continues for women to delay conception, together with the global epidemic of obesity. The consequences of complicated pregnancy outcome are not only costly in the short term, but the long term health consequence for the offspring of women with chronic hypertension and the subsequent financial burden should be acknowledged.[93] The findings of this meta-analysis support the need for improved understanding of the pathophysiology of chronic hypertension, to inform the development of predictive and diagnostic tools and enhance therapeutic interventions to reduce adverse pregnancy outcomes. The continuing uncertainty about maternal and perinatal effects of antihypertensive treatment shows the need for large observational studies (for example, through population registers) and randomised controlled trials of drug treatment in women with chronic hypertension, to determine optimal management for mother and fetus. As severity of hypertension will always confound need for treatment and perinatal outcomes, this must be considered for appropriate conclusions to be drawn.

Conclusions

Chronic hypertension is associated with a high incidence of adverse pregnancy outcomes compared with a general population, as exemplified in this report by US data. This finding should be interpreted within the limitations of the study. Our results support the importance of increased antenatal surveillance for women with chronic hypertension to enable early identification of evolving complications. Women should receive pre-pregnancy counselling to optimise their health before pregnancy and to inform them of the increased maternal and fetal risks associated with their hypertension. Strategies to predict those at greatest risk, determine optimal drug treatments, and reduce adverse pregnancy outcomes are needed.

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What is already known on this topic

Women with chronic hypertension have worse outcomes of pregnancy

The magnitude of pregnancy risk for women with chronic hypertension is uncertain from pre-existing data

What this study adds

This systematic review and meta-analysis shows that women with chronic hypertension have a high pooled incidence of superimposed pre-eclampsia and all other pregnancy complications

Compared with the US general pregnancy population, the incidence of superimposed pre-eclampsia on average across study populations was nearly eightfold higher compared with pre-eclampsia

Women with chronic hypertension in US studies have an approximately threefold increased risk of delivery before 37 weeks' gestation, birth weight <2500 g, and neonatal intensive care admission and fourfold increased risk of perinatal death compared with the US general pregnancy population

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Tables

Table 1| Overview of randomised controlled trials of pregnancy outcomes in women with chronic hypertension included in meta-analysis

Author, year published	Study years	Country	No of women	No of births	Multiple gestations included	Secondary causes of chronic hypertension excluded	Congenital abnormalities excluded	Definition of chronic hypertension*	Newcastle-Ottowa grade
August et al, 2004[22]	2003	USA	110	110	No	Creatinine >1.2 mg/dL excluded	No	3	7
Chappell et al, 2008[15]	2003-05	UK and Netherlands	822	822	No	No	No	2	7
Neri et al, 2010[23]	2006-08	Italy	40	40	No	Known cardiac or renal disease excluded	Yes	1	6
Sibai et al, 1998[24]	?-1998	USA	763	763	No	Type 1 diabetes excluded	No	4	7
Weitz et al, 1987[16]	?-1986	USA	25	25	No	No evidence of proteinuria (24 hour urine protein <100 mg)	No	2	6

*1=systolic blood pressure >140 or diastolic blood pressure >90 mm Hg and/or history of hypertension; 2=diastolic blood pressure >90 mm Hg and/or history of hypertension; 3=history of hypertension before pregnancy or presence of hypertension before 20 weeks with no blood pressure definition; 4=blood pressure >140/90 mm Hg; 5=history of hypertension only; 6=antihypertensive drug treatment before 20 weeks; 7=other.

Table 2| **Overview of population studies of pregnancy outcomes in women with chronic hypertension included in meta-analysis**

Author, year published	Study years	Country	No of women	No of births	Multiple gestations included	Secondary causes of chronic hypertension excluded	Congenital abnormalities excluded	Definition of chronic hypertension*	Newcastle-Ottowa grade
Allen et al, 2004[25]	1988-2000	Canada	1242	1258	Yes	No	Yes	3	7
Bateman et al, 2012[26]	1995-2008	USA	731 694 (649 899 primary, 81 795 secondary)	750 078	Yes	Primary and secondary defined	No	5	7
Broekhuijsen et al, 2012[27]	2002-07	Netherlands	1609	1609	No	"Relevant comorbidity excluded"	Yes	2	6
Rasmussen et al, 2006[28]	1999-2002	Norway	1116	1116	No	Women with renal disease, cardiac disease, diabetes mellitus excluded	No	4	7
Roberts et al, 2005[29]	2000-02	Australia	2162	2162	No	No	No	2	7
Su et al, 2013[30]	2005	Taiwan	2727	2727	No	No	No	2	7
Zetterstrom et al, 2008[31]	1992-2004	Sweden	4749	4749	No	No	No	1	7

*1=systolic blood pressure >140 or diastolic blood pressure >90 mm Hg and/or history of hypertension; 2=diastolic blood pressure >90 mm Hg and/or history of hypertension; 3=history of hypertension before pregnancy or presence of hypertension before 20 weeks with no blood pressure definition; 4=blood pressure >140/90 mm Hg; 5=history of hypertension only; 6=antihypertensive drug treatment before 20 weeks; 7=other.

Table 3| Overview of prospective studies of pregnancy outcomes in women with chronic hypertension included in meta-analysis

Author, year published	Study years	Country	No of women	No of births	Multiple gestations included	Secondary causes of chronic hypertension excluded	Congenital abnormalities excluded	Definition of chronic hypertension*	Newcastle-Ottowa grade
Attolou et al, 1998[32]	1995-96	Benin	64	64	No	Cardiac or renal disease excluded	No	2	7
Curet et al, 1979[33]	1973-79	USA	66	72	Yes	"No diabetes, cardiac or renal disease"	No	1	6
Fleischer et al, 1986[34]	1982-84	USA	55	55	No	No	No	1	6
Gant et al, 1977[35]	?-1977	USA	63	63	No	"Essential hypertension only"	No	3	6
Hartikainen et al, 1998[36]	1985-86	Finland	396	396	No	No	No	1	7
Inigo Riesgo et al, 2008[37]	2001-07	Mexico	110	110	No	"Mild chronic hypertension without other disease"	No	1	6
Jacquemyn et al, 2006[38]	2001-02	Belgium	2393	2393	No	No	No	1	7
Mabie et al, 1986[39]	1980-84	USA	156	169	Yes	No	No	2	6
Onyiriuka and Okolo, 2005[40]	1992-94	Nigeria	20	20	No	"Free of major diseases such as diabetes mellitus, sickle cell anaemia, renal failure and heart disease"	No	2	6
Ray, 2001[41]	1986-95	Canada	459	459	No	No	No	1	7
Rey and Couturier, 1994[42]	1987-91	Canada	298	Unknown	Unknown	No	No	1	7
Rey, 1997[43]	1987-91	USA	208	208	Yes	Renal disease and pre-pregnancy diabetes excluded	No	1	7
Roncaglia et al, 2008[44]	2000-06	Italy	182	182	No	Excluded proteinuria at first visit	Yes	1	7
Ruiz et al, 2001[45]	1996-97	Mexico	66	66	No	No	No	5	7
Segel et al, 2001[46]	1995-2001	USA	131	131	No	No	No	1	6
Sibai et al, 1983[47]	1980-82	USA	211	215	No	No	No	6	6
Sibai et al, 1986[48]	1978-84	USA	44	44	No	No	No	6	6
Sun et al, 2007[49]	2001-05	China	121	121	No	No	No	2	7
Valsecchi et al, 1999[50]	1993-96	Italy	26	26	No	No	No	3	6
Zeeman et al, 2004[51]	1999-2002	USA	87	87	No	No	No	2	6

*1=systolic blood pressure >140 or diastolic blood pressure >90 mm Hg and/or history of hypertension; 2=diastolic blood pressure >90 mm Hg and/or history of hypertension; 3=history of hypertension before pregnancy or presence of hypertension before 20 weeks with no blood pressure definition; 4=blood pressure >140/90 mm Hg; 5=history of hypertension only; 6=antihypertensive drug treatment before 20 weeks; 7=other.

Table 4| Overview of retrospective studies of pregnancy outcomes in women with chronic hypertension included in meta-analysis

Author, year published	Study years	Country	No of women	No of births	Multiple gestations included	Secondary causes of chronic hypertension excluded	Congenital abnormalities excluded	Definition of chronic hypertension*	Newcastle-Ottowa grade
Ales et al, 1989[52]	1981	USA	30	31	Yes	No	No	2	6
Bagga et al, 2007[53]	1995-2004	India	72	72	No	No	No	7	6
Banhidy et al, 2010[54]	1980-96	Hungary	1579	1627	Yes	"Secondary hypertension excluded"	Yes	2	6
Comino-Delado et al, 1986[55]	1984	Spain	447	447	No	No	No	1	5
Delmis et al, 1993[56]	1987-90	Croatia	210	210	Yes	No	No	1	7
Ferrazzani et al, 2011[57]	1986-95	Italy	210	210	No	No	No	3	6
Fields et al, 1996[58]	1990-92	Israel	52	52	No	No	No	1	6
Frusca et al, 1998[59]	1993-95	Italy	78	78	No	No proteinuria at entry or secondary hypertension	Yes	7	7
Gilbert et al, 2007[60]	1991-2001	USA	29 842	29 917	Yes	No	No	2	7
Jain, 1997[61]	1982-87	USA	2048	2048	No	No	No	3	6
Lecarpentier, 2013[62]	2004-07	France	211	211	No	Secondary hypertension excluded	Yes	6	6
Lydakis et al, 1998[63]	1980-97	UK	152	213	No	Diabetes, renal disease, secondary forms of hypertension excluded	No	1	5
Machado et al, 1996[64]	1988-92	Portugal	97	98	Yes	No	No	1	6
Ono et al, 2013[65]	2006-09	Japan	120	120	No	Secondary hypertension excluded	No	1	7
Parry et al, 1998[66]	1992-95	USA	70	70	No	Secondary hypertension excluded	Yes	1	7
Pietrantoni et al, 1994[67]	1987	USA	109	109	No	No	No	1	6
Sass et al, 1990[68]	1985-86	Brazil	189	189	No	No	No	1	6
Tuuli et al, 2011[69]	1990-2008	USA	1032	1032	No	No	Yes	2	7
Vanek et al, 2004[70]	1988-99	Israel	1807	1807	No	No	No	2	7
Velentgas et al, 1994[71]	?-1994	USA	4014	4014	No	Not complicated by cardiac disease, renal disease, diabetes mellitus	No	3	7
Vigi-De-Gracia et al, 2004[72]	1996-2001	Panama	154	157	Yes	No	No	7	6
Wilson et al, 2012[73]	2008-10	USA	165	165	No	No	No	5	6
Zeeman et al, 2003[74]	?-2003	USA	117	117	No	No	No	2	6

*1=systolic blood pressure >140 or diastolic blood pressure >90 mm Hg and/or history of hypertension; 2=diastolic blood pressure >90 mm Hg and/or history of hypertension; 3=history of hypertension before pregnancy or presence of hypertension before 20 weeks with no blood pressure definition; 4=blood pressure >140/90 mm Hg; 5=history of hypertension only; 6=antihypertensive drug treatment before 20 weeks; 7=other.

Table 5| Estimated incidence and prediction intervals of adverse pregnancy outcomes for women with chronic hypertension

Outcome	No of studies	Estimated incidence (%) (95% CI)	Prediction intervals (95%)	Heterogeneity τ^2
Superimposed pre-eclampsia	38	25.9 (21.0 to 31.5)	5.5 to 67.2	0.766
Caesarean section	27	41.4 (35.5 to 47.7)	15.5 to 73.2	0.413
Pre-term delivery (<37 weeks)	30	28.1 (22.6 to 34.4)	6.8 to 67.6	0.286
Birth weight <2500 g	14	16.9 (13.1 to 21.5)	5.7 to 40.6	0.286
Neonatal intensive care	16	20.5 (15.7 to 26.4)	5.9 to 51.3	0.403
Perinatal death	27	4.0 (2.9 to 5.4)	0.9 to 16.4	0.544

95% prediction intervals show uncertainty of range of possible incidence percentages for new study population, whereas 95% confidence intervals show uncertainty about estimate of average percentage incidence across study populations.

Table 6| **Estimated incidence and prediction intervals of adverse pregnancy outcomes for women with chronic hypertension: studies conducted in United States compared with US general population data**[21]

Outcome	No of studies	Estimated incidence (%) (95% CI)	Prediction interval (95%)	US general population incidence (%)	Risk ratio (95% CI)	Heterogeneity τ^2
Superimposed pre-eclampsia	38	29.2 (21.6 to 38.2)	6.6 to 70.3	3.8	7.7 (5.7 to 10.1)	0.623
Caesarean section	27	42.4 (35.0 to 50.1)	18.4 to 70.7	32.9	1.3 (1.1 to 1.5)	0.258
Pre-term delivery (<37 weeks)	30	33.0 (23.7 to 44.0)	7.8 to 74.1	12.2	2.7 (1.9 to 3.6)	0.526
Birth weight <2500 g	14	22.2 (15.4 to 30.9)	5.1 to 60.5	8.2	2.7 (1.9 to 3.8)	0.225
Neonatal intensive care	16	19.3 (13.4 to 27.0)	5.0 to 51.9	6.1	3.2 (2.2 to 4.4)	0.246
Perinatal death	27	4.6 (3.0 to 7.1)	1.0 to 18.9	1.1	4.2 (2.7 to 6.5)	0.429

95% prediction intervals show uncertainty of range of possible incidence percentages for new study population, whereas 95% confidence intervals show uncertainty about estimate of average percentage incidence across study populations.

Figures

Fig 1 Flow chart of study selection process

Study	Incidence (95% CI)	Weight (%)	Incidence (95% CI)
Randomised controlled trials			
August et al 2004		25.21	33.64 (24.91 to 43.27)
Chappell et al 2008		26.25	21.90 (19.11 to 24.88)
Sibai et al 1998		26.26	25.29 (22.25 to 28.54)
Weitz et al 1987		22.28	36.00 (17.97 to 57.48)
Overall: τ^2=0.026		100.00	25.88 (21.07 to 31.35)
Population studies			
Allen et al 2004		12.61	38.24 (35.53 to 41.01)
Bateman et al 2012		12.67	26.40 (26.30 to 26.50)
Broekhuijsen et al 2012		12.57	10.88 (9.40 to 12.50)
Comino-Delado 1986		12.52	44.52 (39.85 to 49.26)
Curet et al 1979		11.78	42.42 (30.34 to 55.21)
Rasmussen et al 2006		12.58	19.39 (17.11 to 21.83)
Roberts et al 2005		12.64	33.81 (31.82 to 35.85)
Zetterstrom et al 2008		12.64	13.39 (12.44 to 14.39)
Overall: τ^2=0.438		100.00	26.42 (18.41 to 36.36)
Prospective cohort studies			
Gant et al 1977		7.10	53.97 (40.94 to 66.61)
Hartikainen et al 1998		7.30	6.57 (4.33 to 9.47)
Inigo Riesgo et al 2008		6.65	5.45 (2.03 to 11.49)
Mabie et al 1986		7.39	37.18 (29.59 to 45.27)
Onyiriuka and Okolo 2005		6.22	35.00 (15.39 to 59.22)
Ray 2001		7.54	21.27 (18.01 to 24.82)
Rey 1997		7.41	26.44 (20.58 to 32.99)
Rey and Couturier 1994		7.49	21.22 (17.20 to 25.70)
Roncaglia et al 2008		7.23	13.19 (8.64 to 18.98)
Ruiz et al 2001		7.07	34.85 (23.53 to 47.58)
Sibai et al 1983		7.20	9.95 (6.27 to 14.81)
Sibai et al 1986		6.91	52.27 (36.69 to 67.54)
Sun et al 2007		7.34	52.89 (43.61 to 62.03)
Zeeman et al 2004		7.14	27.59 (18.54 to 38.21)
Overall: τ^2=0.833		100.00	24.52 (16.52 to 34.78)
Retrospective cohort studies			
Ales et al 1989		5.47	16.67 (5.64 to 34.72)
Attolou et al 1998		6.15	31.25 (20.24 to 44.06)
Bagga et al 2007		6.02	16.67 (8.92 to 27.30)
Delmis et al 1993		6.53	58.57 (51.59 to 65.31)
Ferrazzani et al 2011		6.48	24.88 (19.12 to 31.38)
Fields et al 1996		6.06	32.69 (20.33 to 47.11)
Frusca et al 1998		5.51	3.85 (0.80 to 10.83)
Gilbert et al 2007		6.68	6.29 (6.02 to 6.57)
Lecarpentier 2013		6.47	23.22 (17.70 to 29.51)
Lydakis et al 1998		6.39	22.37 (16.02 to 29.83)
Machado et al 1996		6.16	16.49 (9.73 to 25.40)
Ono et al 2013		6.33	23.33 (16.10 to 31.93)
Pietrantoni et al 1994		6.22	17.43 (10.83 to 25.87)
Tuuli et al 2011		6.65	47.38 (44.30 to 50.48)
Vigi-De-Gracia et al 2004		6.40	77.92 (70.54 to 84.20)
Wilson et al 2012		6.49	52.12 (44.22 to 59.95)
Overall: τ^2=1.080		100.00	26.05 (17.24 to 37.31)
MELR overall: τ^2=0.766			25.91 (21.01 to 31.49)

0   50   100

Fig 2 Forest plot of studies of superimposed pre-eclampsia in women with chronic hypertension stratified according to study design. MELR=mixed effects logistic regression

Study	Incidence (95% CI)	Weight (%)	Incidence (95% CI)
Randomised controlled trials			
August et al 2004		48.34	50.00 (40.32 to 59.68)
Chappell et al 2008		51.66	49.88 (46.41 to 53.35)
Overall: τ^2=0.000		100.00	49.89 (46.69 to 53.10)
Population studies			
Bateman et al 2012		25.24	56.10 (55.99 to 56.21)
Broekhuijsen et al 2012		25.04	24.92 (22.82 to 27.11)
Comino-Delado 1986		24.59	27.29 (23.21 to 31.68)
Roberts et al 2005		25.12	38.99 (36.93 to 41.08)
Overall: τ^2=0.283		100.00	36.20 (25.13 to 48.95)
Prospective cohort studies			
Fleischer 1986		9.31	30.91 (19.41 to 44.81)
Hartikainen et al 1998		10.51	22.73 (18.69 to 27.18)
Inigo Riesgo et al 2008		10.03	59.09 (49.31 to 68.37)
Mabie et al 1986		10.24	39.10 (31.40 to 47.23)
Rey 1997		10.40	50.48 (43.48 to 57.47)
Rey and Couturier 1994		10.58	38.46 (33.53 to 43.58)
Roncaglia et al 2008		10.18	23.63 (17.66 to 30.48)
Ruiz et al 2001		9.33	80.30 (68.68 to 89.07)
Sibai et al 1983		10.23	21.33 (16.00 to 27.48)
Sibai et al 1986		9.20	47.73 (32.46 to 63.31)
Overall: τ^2=0.574		100.00	40.33 (29.35 to 52.37)
Retrospective cohort studies			
Ales et al 1989		7.89	36.67 (19.93 to 56.14)
Bagga et al 2007		8.75	31.94 (21.44 to 43.99)
Lydakis et al 1998		9.30	35.53 (27.94 to 43.69)
Machado et al 1996		9.07	46.39 (36.20 to 56.81)
Ono et al 2013		9.21	53.33 (44.01 to 62.49)
Parry et al 1998		8.55	21.43 (12.52 to 32.87)
Pietrantoni et al 1994		9.14	43.12 (33.67 to 52.95)
Tuuli et al 2011		9.81	54.55 (51.46 to 57.62)
Vanek et al 2005		9.83	24.96 (22.98 to 27.02)
Vigi-De-Gracia et al 2004		9.26	71.43 (63.60 to 78.41)
Zeeman et al 2013		9.19	58.12 (48.64 to 67.18)
Overall: τ^2=0.364		100.00	43.17 (34.26 to 52.54)
MELR overall: τ^2=0.413			41.43 (35.47 to 47.65)

0   50   100

Fig 3 Forest plot of studies of caesarean section in women with chronic hypertension stratified according to study design. MELR=mixed effects logistic regression

Fig 4 Forest plot of studies of preterm delivery before 37 weeks' gestation in women with chronic hypertension stratified according to study design. MELR=mixed effects logistic regression

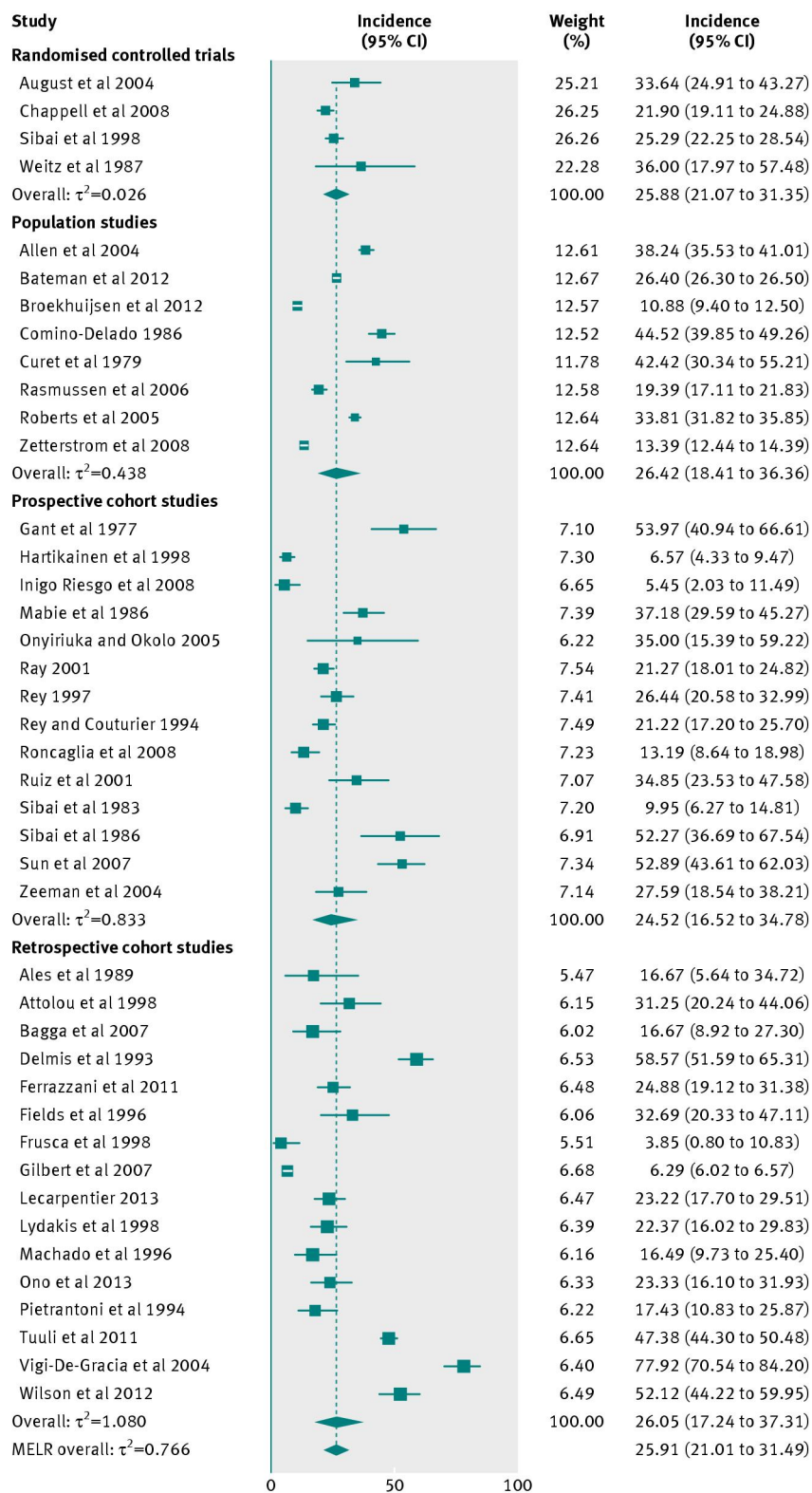**Fig 5** Forest plot of studies of birth weight <2500 g in women with chronic hypertension stratified according to study design. MELR=mixed effects logistic regression

Study	Incidence (95% CI)	Weight (%)	Incidence (95% CI)
Randomised controlled trials			
Chappell et al 2008		49.55	2.92 (1.88 to 4.31)
Sibai et al 1998		50.45	4.59 (3.22 to 6.32)
Overall: τ^2=0.019		100.00	3.70 (2.70 to 5.05)
Population studies			
Comino-Delado 1986		34.51	2.91 (1.56 to 4.92)
Curet et al 1979		27.80	4.17 (0.87 to 11.70)
Zetterstrom et al 2008		37.70	1.33 (1.02 to 1.69)
Overall: τ^2=0.129		100.00	2.00 (1.10 to 3.61)
Prospective cohort studies			
Hartikainen et al 1998		12.87	2.78 (1.39 to 4.92)
Mabie et al 1986		11.40	2.37 (0.65 to 5.95)
Ray 2001		13.72	4.46 (2.93 to 6.47)
Rey 1997		12.90	6.25 (3.37 to 10.45)
Rey and Couturier 1994		13.19	3.98 (2.24 to 6.48)
Sibai et al 1983		11.97	2.84 (1.05 to 6.09)
Sibai et al 1986		12.03	25.00 (13.19 to 40.34)
Sun et al 2007		11.92	5.79 (2.36 to 11.56)
Overall: τ^2=0.447		100.00	4.79 (2.90 to 7.80)
Retrospective cohort studies			
Ales et al 1989		5.45	3.23 (0.08 to 16.70)
Attolou et al 1998		6.30	4.69 (0.98 to 13.09)
Bagga et al 2007		6.89	8.33 (3.12 to 17.26)
Delmis et al 1993		8.37	17.73 (12.92 to 23.43)
Ferrazzani et al 2011		6.94	1.95 (0.53 to 4.92)
Gilbert et al 2007		8.83	2.21 (2.05 to 2.39)
Lecarpentier 2013		7.43	3.79 (1.65 to 7.33)
Machado et al 1996		6.68	4.08 (1.12 to 10.12)
Ono et al 2013		6.36	1.67 (0.20 to 5.89)
Parry et al 1998		6.88	8.57 (3.21 to 17.73)
Pieratoni et al 1994		6.72	3.67 (1.01 to 9.13)
Vanek et al 2005		8.17	1.00 (0.59 to 1.57)
Vigil de Gracia et al 2004		7.95	11.69 (7.08 to 17.84)
Zeeman et al 2003		7.05	5.13 (1.90 to 10.83)
Overall: τ^2=0.657		100.00	4.11 (2.57 to 6.52)
MELR overall: τ^2=0.544			3.99 (2.95 to 5.38)

0   50   100

Fig 6 Forest plot of studies of neonatal unit admission in women with chronic hypertension stratified according to study design. MELR=mixed effects logistic regression

Fig 7 Forest plot of studies of perinatal death in women with chronic hypertension stratified according to study design. MELR=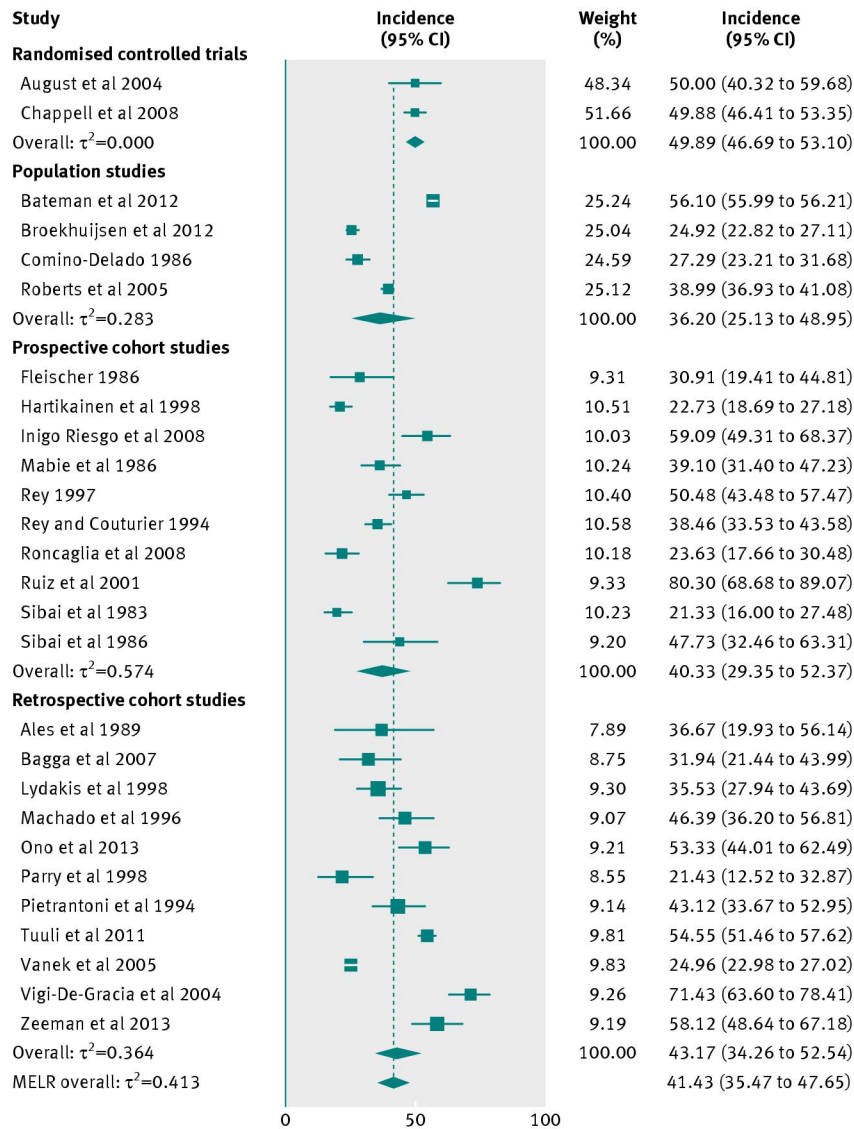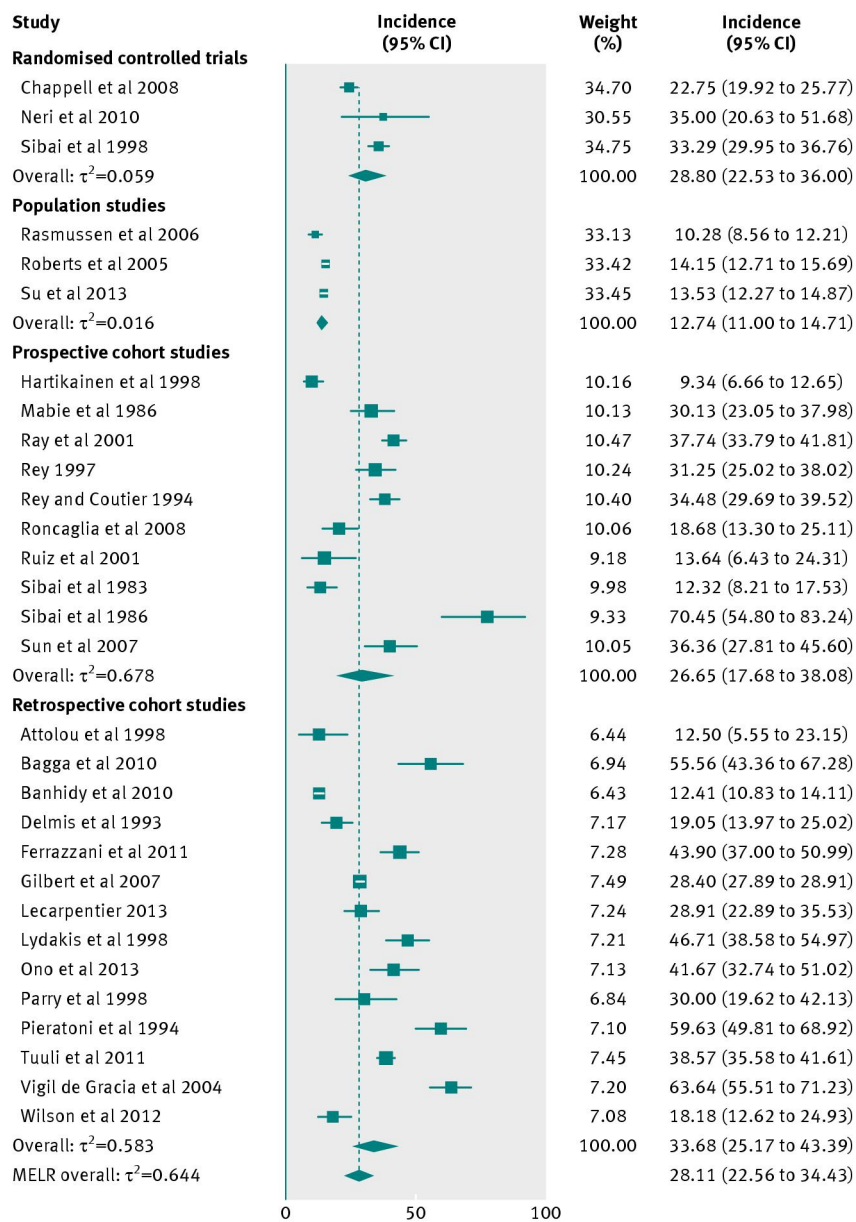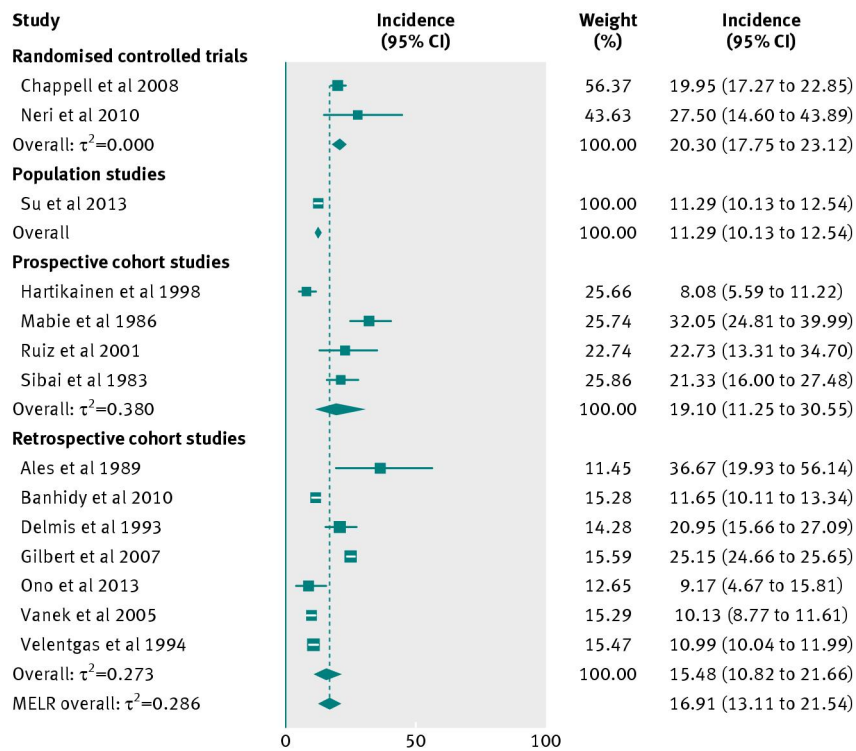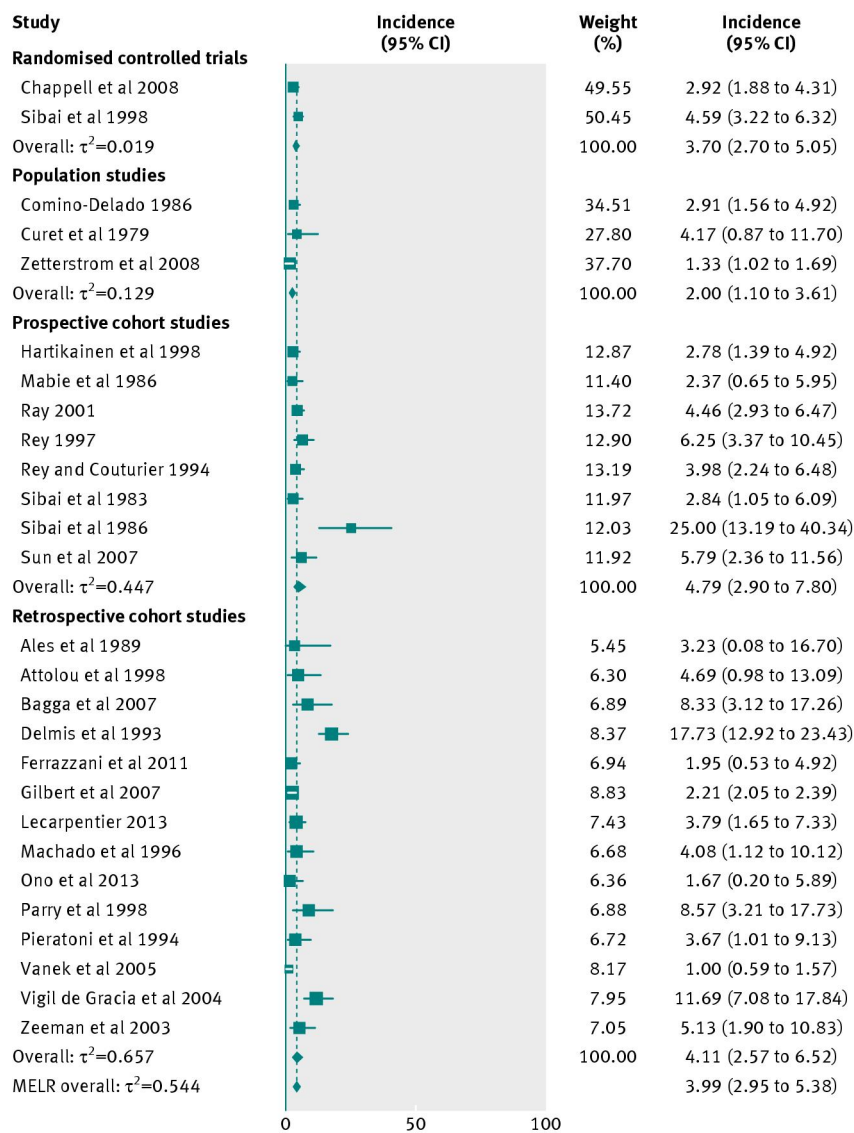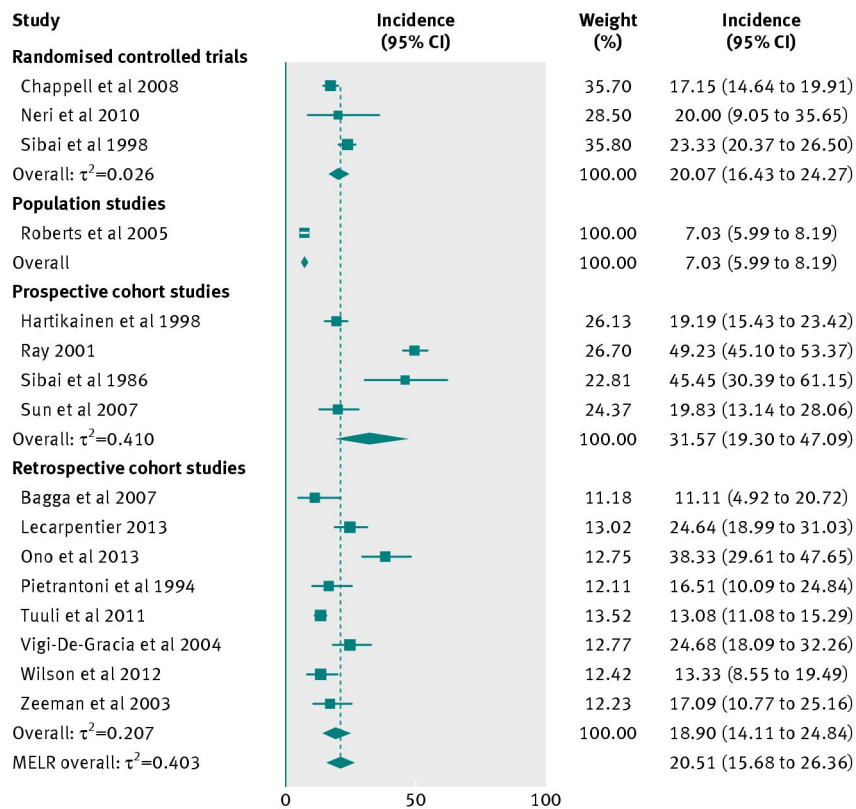mixed effects logistic regression