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RESEARCH

THIS WEEK'S RESEARCH QUESTIONS

Long term treatment with metformin and vitamin B-12 deficiency

Metformin can cause malabsorption of vitamin B-12 and may also lower serum concentrations of folate and increase those of homocysteine. But the physiological effects of these changes might be missed in patients on long term metformin treatment because they could be masked by or confused with the complications of diabetes.

Coen Stehouwer and colleagues' HOME (Hyperinsulinaemia: the Outcome of ts Metabolic Effects) trial evaluated the effects of metformin in nearly 400 Dutch outpatients with type 2 diabetes (p 1177). Participants were randomised to metformin or placebo in addition to insulin. The researchers followed them for up to 52 months to assess metabolic, microvascular, and macrovascular outcomes and quality of life and found that treatment with metformin raised the risk of vitamin B-12 deficiency, with the effect increasing over time. Hence they recommend monitoring of vitamin B-12 levels during long term treatment with metformin. But editorialists Josep Vidal-Alaball and Christopher Butler are disappointed that the paper reported only the trial's metabolic outcomes, and they don't think monitoring should be introduced until it has been tested in a trial (p 1147).

Incidence of hypertensive disorders in pregnancy after bariatric surgery

The list of benefits grows ever longer for bariatric surgery in severe or complicated obesity, and now Wendy L Bennett and colleagues have found that the surgery is associated with substantially lower rates of hypertensive disorders during subsequent pregnancy (p 1180). Their retrospective cohort study used claims data for 2002-6 from seven insurance plans in the United States, and they acknowledge the limitations of this design. One of the reviewers who helped us appraise this paper summed it up well: "the question that it addresses is a relevant one; the methodology is probably as sound as one can get with the available data; and dealing with obesity in women of reproductive age is certainly a major issue nowadays. The main issue is to revise the manuscript into something that, along with its strengths and limitations, can be understood properly by the average reader." Did that work? Let us know in a rapid response on bmj.com.

Invitations to screening for diabetes

RTIMAGES

Current policy about invitations to screening in many countries, including the United Kingdom, dictates that patients should be able to exert "informed choice." This goes further than "informed consent" because it acknowledges that patients' values will alter how they handle information about benefits and harms. But what do patients make of this, and does their socioeconomic status affect their decisions?

Theresa Marteau and colleagues' randomised controlled trial compared the effect of two invitation letters—one standard, one validated as facilitating informed choice—on the uptake of screening for type 2 diabetes for adults in English primary care (p 1176). Just over half the invited patients turned up for screening, a disappointingly low yield, and there was no difference between the study groups. Nor was there any interaction between the type of invitation and social deprivation, but attendance fell significantly with increasing social deprivation in both groups. The authors conclude that "Further attention to invitation content alone is unlikely to achieve equity in uptake of preventive services." Nonetheless, if you'd like to see the invitations, they're available as web extras to the full paper online.

LATEST RESEARCH: For these and other new research articles see http://www.bmj.com/channels/research.dtl

Oral hygiene and cardiovascular health

Interest has been growing in the possible link between dental and cardiovascular disease; it's thought that the chronic infection and inflammation associated with periodontal disease may be to blame. Cesar de Oliveira, Richard Watt, and Mark Hamer investigated whether self reported frequency of toothbrushing (as a proxy of periodontal disease) was associated with risk of cardiovascular disease events in a sample of adults from the Scottish Health Survey. They concluded that poor oral hygiene was associated with a higher risk of cardiovascular disease and low grade inflammation, although a causal association could not be confirmed (doi:10.1136/bmj.c2451). Editorialist Peter Galgut further examines the implications of periodontal disease for other areas of health (doi:10.1136/bmj.c2735).

Impact of an informed choice invitation on uptake of screening for diabetes in primary care (DICISION): randomised trial

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STUDY QUESTION Does an invitation promoting informed choice decrease attendance for diabetes screening compared with a standard invitation, especially among socially deprived groups?

SUMMARY ANSWER Providing information to support choice did not affect attendance for diabetes screening.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Current health policy holds that participation in screening programmes should reflect "informed choices"; consistent with participants' values and informed by knowledge of the individual benefits and harms of screening. Providing information to support choice had no effect on attendance for screening. Overall attendance was, however, suboptimal and more socially deprived groups were less likely to attend.

Design
This was a randomised controlled trial with central randomisation by individual to treatment arm, with consent by opt-out and allocation concealment of the outcome assessors. We compared a previously validated invitation that describes diabetes as a serious potential problem and the possible costs and benefits of screening and treatment, presented in text and pie charts, with a briefer, standard invitation simply describing diabetes as a serious potential problem.

Participants and setting
Our study population comprised 1272 adults aged 40-69 at risk for diabetes and identified from the practice registers of four general practices from two English counties. Deprivation was ascertained from postcode.

Primary outcome(s)
Attendance at screening for diabetes.

Main results and the role of chance
In total, 721 of 1272 (56.7%) participants attended screening; 353 of 633 (55.8%) in the informed choice invitation arm compared with 368 of 639 (57.6%) in the standard invitation arm (difference −1.8%, 95% confidence interval −7.3% to 3.6%, P=0.51). However, attendance fell with increasing deprivation (64.3% in the lowest third *v* 47.5% in the highest third, P<0.001). Per protocol analyses did not affect these findings. Overall, 680 of 721 (94.3%) agreed to answer questionnaires at first attendance and 525 of 721 (72.8%) returned the four week follow-up questionnaires. Intention to make changes to lifestyle at first attendance was unaffected by screening invitation: mean intention to change behaviour if diabetes were to be diagnosed was 5.84 (SD 1.09) in the informed choice arm and 5.84 (SD 1.04) in the standard invitation arm. Satisfaction with the decision to attend (measured by questionnaire at four weeks) was high and unaffected by screening invitation. We thus observed no conflict between efforts to achieve informed choices and attendance at a population health screening programme for diabetes. However, attendance was low, and socially deprived groups, who are most vulnerable to disease, were least likely to attend. Further attention to invitation content alone is unlikely to achieve equity in uptake of preventive services.

Harms
No adverse events were recorded.

Bias, confounding, and other reasons for caution
Internal validity was high for the principal outcome. This was an open trial with central randomisation, and allocation was concealed from those ascertaining outcomes. Potential confounders were equally distributed across trial groups. The measure of social deprivation was, however, based on postcode, which has limited precision for individual measurement. Previous trials suggesting that invitations providing informed choice have no impact on attendance either failed to assess attendance objectively or recruited only those who had opted into the study as opposed to the opt-out method used here, which is preferred for minimising bias.

Generalisability to other populations
External generalisability to similar populations is high; we defined a real world at risk population through primary care and 87.3% of those eligible participated. Generalisability to other populations and screening programmes is unknown. Studies are needed that compare the impact of presenting uncertainty about individual benefit and harm across screening programmes with different types and levels of harm and benefit.

Study funding/potential competing interests
This trial was funded by the Wellcome Trust (grant No 076838). We have no competing interests.

Trial registration number
Current Controlled Trials ISRCTN 73125647.

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ATTENDANCE AT DIABETES SCREENING BY INVITATION TYPE AND SOCIAL DEPRIVATION

	% (No)			
Deprivation third*	Overall (n=1272)	Informed choice invitation (n=633)	Standard invitation (n=639)	% difference in uptake between arms
Overall	56.7 (721)	55.8 (353)	57.6 (368)	−1.8 (−7.3 to 3.6); P=0.51
Lowest	64.3 (272)	64.3 (133)	64.4 (139)	−0.1 (−9.2 to 9.0)
Middle	58.5 (244)	55.8 (116)	61.2 (128)	−5.5 (−14.9 to 4.0)
Highest	47.5 (205)	47.7 (104)	47.2 (101)	0.5 (−8.9 to 9.9)

P=0.50 for interaction between arm and index of multiple deprivation 2007 on uptake.
*Index of multiple deprivation 2007.

CME

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Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial

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EDITORIAL by Vidal-Alaball and Butler

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STUDY QUESTION Does long term treatment with metformin cause vitamin B-12 deficiency in patients with type 2 diabetes receiving treatment with insulin?

SUMMARY ANSWER Long term treatment with metformin increases the risk of vitamin B-12 deficiency, and this effect increases with time.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Metformin is known to induce malabsorption of vitamin B-12 and may be associated with decreased folate concentrations, which might, in turn, result in an increase in homocysteine concentrations. We have shown that long term treatment with metformin causes vitamin B-12 deficiency and might cause higher homocysteine levels, but has no significant effect on folate concentrations. Our data provide a strong case for routine assessment of vitamin B-12 levels during long term treatment with metformin.

Design

This study was part of the Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME) randomised, double blind, placebo controlled trial investigating the effects of metformin on metabolism and on microvascular and macrovascular disease in type 2 diabetes. In addition to insulin, patients were randomly assigned by a computer program to receive either 850 mg of metformin three times a day or 850 mg of placebo thrice daily.

Participants and setting

A total of 390 patients with type 2 diabetes, aged 30-80 years, were included from the outpatient clinics of three non-academic hospitals in the Netherlands.

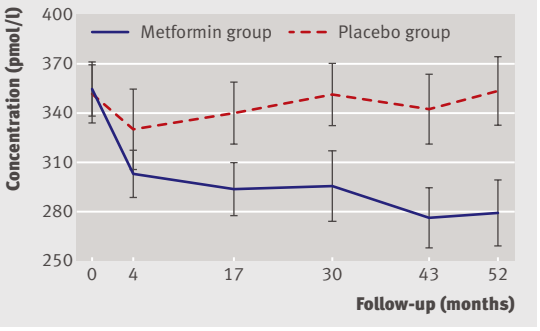
Primary outcomes

The primary outcomes were percentage change in vitamin B-12, folate, and homocysteine concentrations from baseline at 4, 17, 30, 43, and 52 months.

Main results and the role of chance

Compared with placebo, metformin treatment was associated with a mean decrease in vitamin B-12 concentration of −19% (95% confidence interval −24% to −14%; P<0.001) and in folate concentration of −5% (95% CI −10% −0.4%; P=0.033), and an increase in homocysteine concentration of 5% (95% CI −1% to 11%; P=0.091). After adjustment, no significant effect of metformin on folate concentration was found. The absolute risk of vitamin B-12 deficiency (<150 pmol/l) at study end was 7.2 percentage points higher in the metformin group than in the placebo group (95% CI 2.3 to 12.1; P=0.004). The absolute risk of low vitamin B-12 concentration (150-220 pmol/l) at study end was 11.2 percentage points higher in the metformin group (95% CI 4.6 to 17.9; P=0.001). Patients with vitamin B-12 deficiency at study end had a mean homocysteine level of 23.7 µmol/l (95% CI 18.8 to 30.0 µmol/l), compared with a mean homocysteine level of 18.1 µmol/l (95% CI 16.7 to 19.6 µmol/l; P=0.003) for patients with a low vitamin B-12 concentration and 14.9 µmol/l (95% CI 14.3 to 15.5 µmol/l; P<0.001 compared with vitamin B-12 deficiency; P=0.005 compared with low vitamin B-12) for patients with a normal vitamin B-12 concentration (>220 pmol/l).

CONCENTRATIONS OF VITAMIN B-12



Harms

At the end of the study period, 19 patients (9.9%) in the metformin group and five (2.7%) in the placebo group had vitamin B-12 deficiency, whereas 35 patients (18.2%) and 13 patients (7.0%), respectively, had a low vitamin B-12 concentration.

Bias, confounding, and other reasons for caution

We measured only total vitamin B-12 levels and not levels of holotranscobalamin II or methylmalonic acid, which may have been more precise indicators of vitamin B-12 status.

Generalisability to other populations

Given its non-academic setting, the study findings are generalisable to patients in a community setting. The studied patients were predominantly white, however, and the results might not necessarily be valid for other ethnicities.

Study funding/potential competing interests

The HOME trial was supported by grants from Altana, Lifescan, Merck Santé, Merck Sharp & Dohme, and Novo Nordisk. All authors declare financial support for the submitted work from Merck Sharp & Dohme.

Trial registration number

Clinicaltrials.gov NCT00375388.

Glycated haemoglobin A1c for diagnosing diabetes in Chinese population: cross sectional epidemiological survey

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STUDY QUESTION Could glycated haemoglobin A1c (HbA_{1c}) be a diagnostic criterion for diabetes in the Chinese population?

SUMMARY ANSWER In the Chinese population, an HbA_{1c} threshold of 6.3% might be accepted as a diagnostic criterion for diabetes owing to the distribution of hyperglycaemic categories and its convenience.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS An international expert committee published a report in 2009 recommending the use of an HbA_{1c} value of 6.5% or more as a diagnostic criterion for diabetes; however, the optimal threshold for detecting diabetes varies by ethnic group. This study found that a threshold of HbA_{1c} 6.3% may identify diabetes in the Chinese population and was more efficient than a fasting plasma glucose threshold of 7.0 mmol/l in people at high risk of diabetes.

Participants and setting

During 2007-8 we recruited 4886 Chinese people aged over 20 years and without a history of diabetes in Shanghai, China.

Design

We used the oral glucose tolerance test, which is considered to be the gold standard for diagnosing diabetes, in all participants and based the diagnosis of diabetes on the World Health Organization's 1999 criteria. We evaluated the performance of glycated haemoglobin A1c (HbA_{1c}) in diagnosing diabetes by means of the receiver operating characteristics curve. Thresholds were 1, 2, 3, and 4 standard deviations above the normal mean. An experienced technician who was blinded to the study measured HbA_{1c} by high performance liquid chromatography.

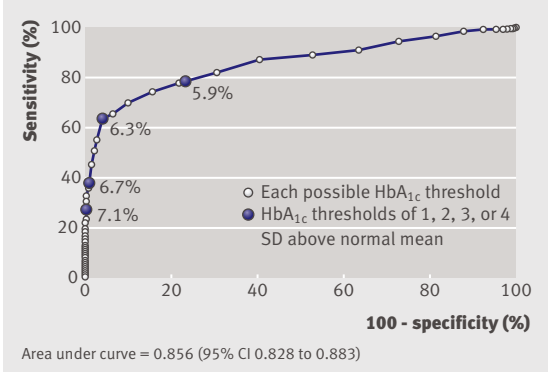
Primary outcome(s)

The primary outcome was the performance of HbA_{1c} at increasing thresholds for diagnosing diabetes.

Main results and the role of chance

The dataset included data from 3748 participants with normal glucose tolerance, 837 with impaired glucose regulation, and 301 with diabetes. Of the 301 participants with diabetes, 128 (43%) had isolated high two hour post-load plasma glucose concentrations. The area under the receiver operating characteristics curve for detecting undiagnosed diabetes was 0.856 (95% confidence interval 0.828 to 0.883) for HbA_{1c} alone and 0.920 (0.900 to 0.941) for fasting plasma glucose alone. Very high specificity (96.1%, 95% confidence interval 95.5% to 96.7%) was achieved at an HbA_{1c} threshold of 6.3% (2 SD above the normal mean). The corresponding sensitivity was 62.8% (57.1% to 68.3%), which was equivalent to that of a fasting plasma glucose threshold of 7.0 mmol/l (57.5%, 51.7% to 63.1%) in detecting undiagnosed diabetes. In participants at high risk of diabetes, the HbA_{1c} threshold of 6.3% showed significantly higher sensitivity (66.9%, 61.0% to 72.5%) than either fasting plasma glucose ≥7.0 mmol/l (54.4%, 48.3% to 60.4%) or HbA_{1c} ≥6.5% (53.7%, 47.6% to 59.7%) (P<0.01).

RECEIVER OPERATING CHARACTERISTICS CURVE OF HbA_{1C} FOR DETECTING DIABETES AT EACH POSSIBLE HbA_{1C} THRESHOLD



Area under curve = 0.856 (95% CI 0.828 to 0.883)

Bias, confounding, and other reasons for caution

Patients with a history of diabetes of less than three months might not be identified by HbA_{1c} measurement. The use of HbA_{1c} could be considered invalid in conditions that shorten or prolong the survival of erythrocytes.

Generalisability to other populations

The optimal thresholds of HbA_{1c} for identifying diabetes vary by ethnic groups, as racial disparities in HbA_{1c} levels exist. In the Chinese population, a threshold of HbA_{1c} 6.3% might be accepted as a diagnostic criterion for diabetes owing to the distribution of hyperglycaemic categories and its convenience.

Study funding/potential competing interests

YB and XM contributed equally to this work. This work was funded by the Shanghai United Developing Technology Project of Municipal Hospitals, Chinese National 973 Project, Shanghai Key Laboratory of Diabetes Mellitus, Major Program of Shanghai Municipality for Basic Research, and National Key Technology R&D Program of China. The authors are independent from the funders in all aspects of the study design, analysis of data, and writing the manuscript.

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- Editorial: Diagnosis of diabetes using the oral glucose tolerance test (*BMJ* 2009;339:b4354)
- Research: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (*BMJ* 2000;321:405-12)
- Research: Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? (*BMJ* 1998;317:371-75)

Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study

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EDITORIAL by Boily et al

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Listen to a podcast about HIV transmission in serodiscordant couples with Anne Buvé at http://podcasts.bmj.com/bmj/

STUDY QUESTION What is the risk of HIV transmission in stable heterosexual serodiscordant couples in which the infected partner is taking combined antiretroviral treatment?

SUMMARY ANSWER After 417 couple years of follow-up, more than 7000 unprotected acts of intercourse, and 47 natural pregnancies, there were no cases of HIV transmission when the infected partner of a steady heterosexual couple was taking combined antiretroviral therapy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Use of combined antiretroviral therapy has been associated with reduced sexual transmission of HIV. Though we cannot rule out the possibility of heterosexual transmission from people with HIV taking combined antiretroviral treatment, the risk is probably low.

Participants and setting

Stable heterosexual couples in which one partner had HIV (index partner) and the other reported the sexual relationship as the only risk exposure were recruited in an HIV clinic in Madrid, Spain.

Design, size, and duration

In a cross sectional analysis of HIV seroprevalence, we included the 648 couples in which the non-index partner came to the clinic for his or her first HIV test. All 424 heterosexual couples serodiscordant for HIV who returned for at least one follow-up visit were included in a prospective cohort analysis. Couples were recruited and followed from 1989 to 2008.

Main results and the role of chance

The prevalence of HIV infection at enrolment was 9.2% (44/476) among partners of index partners not taking antiretroviral treatment, 8.7% (2/23) in partners of index partners taking monotherapy or dual therapy, and zero in partners of index partners taking combined therapy (0/149; P<0.001). The stratified analyses ruled out the main potential confounding factors. During follow-up, the 341 serodiscordant couples in which the index partner was not taking antiretroviral treatment had about 11 000 acts of intercourse without condoms, 50 natural pregnancies, and five HIV seroconversions (0.0004 per unprotected intercourse, 95% confidence interval 0.0001 to 0.0010); 294 of these couples always used condoms, accounting for about 42 000 acts of intercourse, 136 risk exposures from condom failure, and one HIV seroconversion. The reduction in relative risk associated with condom use was 93% (42% to 99%). In 144 couples in which the index partner was taking combined antiretroviral treatment, there were over 7000 unprotected acts of intercourse and 47 natural pregnancies but no HIV seroconversion (0 to 0.0005 per unprotected intercourse).

Bias, confounding, and other reasons for caution

HIV seroprevalence and seroincidence was zero in partners when their index partner was taking combined antiretroviral treatment, though this seroincidence did not differ significantly from that in partners of untreated index partners. Self reported data on sexual behaviour was based on six month recall, and, in the context of a preventive intervention, the use of condoms might have been over-reported. The information was collected before the non-index partner's serological status was known, which reduces differential biases. About 59% of couples were lost to the follow-up with no explanation, but this is unlikely to be related to HIV seroconversion in the partner.

Generalisability to other populations

These results might not apply to casual partners or to homosexual relationships between men, given the more frequent circumstances favouring transmission, such as anal sex or sexually transmitted infections. In developing countries the risk and the probability of HIV transmission per risk exposure might be higher than the estimates in our study.

HIV TRANSMISSION ACCORDING TO ANTIRETROVIRAL TREATMENT OF INDEX PARTNER

	No treatment	Combined treatment
Cross sectional analysis		
No of couples	476	149
HIV infection in non-index partners (seroprevalence)	44 (9.2%)	0 (0%)*
Cohort analysis		
No of couples	341	144
Couple years of follow-up	863	417
No of seroconversions in follow-up	5	0
Rate per 100 couple years (95% CI)	0.6 (0.2 to 1.4)	0 (0 to 1.1)
Transmission per 1000 risk exposures (95% CI)	0.4 (0.1 to 1.0)	0 (0 to 0.5)
No of natural pregnancies	50	47

*P<0.001, two sided Fisher's exact test for comparison of percentages.

Study funding/potential competing interests

This work was supported by FIPSE (foundation formed by the Spanish Ministry of Health, Abbott Laboratories, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmith-Kline, Merck Sharp and Dohme, and Roche) and by the Spanish Network for Research on AIDS (RIS), which is funded by the Instituto de Salud Carlos III.

Impact of bariatric surgery on hypertensive disorders in pregnancy: retrospective analysis of insurance claims data

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STUDY QUESTION Do women who are pregnant and deliver after bariatric surgery for extreme obesity have lower rates of hypertensive disorders in pregnancy compared with women who had a delivery before bariatric surgery?

SUMMARY ANSWER In this insured population of women who had a pregnancy and delivery and underwent bariatric surgery during 2002-6, delivery after surgery was associated with substantially lower rates of all severities of hypertensive disorders in pregnancy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Obesity is a risk factor for hypertensive disorders in pregnancy, defined as chronic hypertension complicating a pregnancy, gestational hypertension, pre-eclampsia, and eclampsia. Women who undergo bariatric surgery for obesity have improved perinatal outcomes in subsequent pregnancies. In this large retrospective analysis of US women, bariatric surgery was associated with lower rates of all severities of hypertensive disorders in subsequent pregnancies

Design, participants, and setting

This retrospective cohort study used claims data for 2002-6 from seven insurance plans in the United States. We included 585 women aged 16-45 who had undergone bariatric surgery, had at least one delivery, and had continuous insurance coverage during pregnancy plus two weeks after delivery.

Main results and the role of chance

Among the 585 women who had undergone bariatric surgery and had a delivery, 269 delivered before surgery and 316 delivered after surgery. In 82% of all women the surgery was gastric bypass. Women who delivered before surgery were younger at the time of delivery (mean age 31.3 *v* 32.5) but had higher rates of pre-existing diabetes and gestational diabetes mellitus. Compared with women who delivered before surgery, women who delivered after surgery had substantially lower rates of pre-eclampsia and eclampsia (odds ratio 0.20, 95% confidence interval 0.09 to 0.44), chronic hypertension complicating pregnancy (0.39, 0.20 to 0.74), and gestational hypertension (0.16, 0.07 to 0.37), even after adjustment for age at delivery, multiple pregnancy, surgical procedure, pre-existing diabetes, and insurance plan.

Bias, confounding, and other reasons for caution

Administrative claims data lack clinical information and are susceptible to errors in coding. We anticipate, however, that such errors would be no different in women who had deliveries before or after surgery, thus limiting any introduced study bias.

Confounding by indication could have occurred. For example, an obese woman with gestational hypertension might have been more likely to subsequently undergo bariatric surgery if she developed chronic hypertension after her pregnancy or had other comorbidities associated with obesity that made her eligible for bariatric surgery. If this occurred, the number of diagnoses of hypertensive disorder in pregnancy in the women who delivered before surgery could be increased and bias our results.

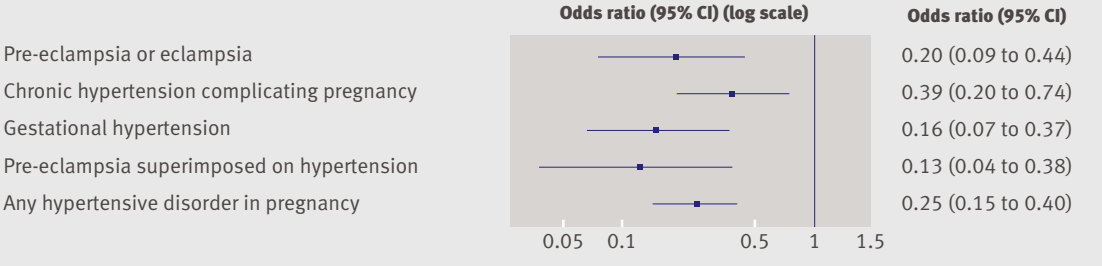
Generalisability to other populations

Results are generalisable to a commercially insured population of obese women considered to be eligible for bariatric surgery.

Study funding/potential competing interests:

The dataset used in this study was created for a research project on the patterns of obesity care within selected BlueCross BlueShield plans. The original development of the dataset was funded by unrestricted research grants from Ethicon Endo-Surgery, Pfizer, and GlaxoSmithKline. Data and database development support were provided by the BlueCross BlueShield Association (Tennessee, Hawaii, Michigan, North Carolina), Highmark (Pennsylvania), Independence BlueCross (Pennsylvania), and Wellmark BlueCross BlueShield (Iowa and South Dakota). The BlueCross BlueShield plans were invited to review the manuscript but they did not have any direct role in the design and conduct of the study, data management or analysis, interpretation of the data, or preparation of the manuscript.

ODDS RATIOS FOR HYPERTENSIVE DISORDERS IN PREGNANCY IN DELIVERY AFTER *v* BEFORE BARIATRIC SURGERY



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Practice: Obesity and pregnancy (*BMJ* 2008;337:a2450)
Research: Pre-eclampsia and risk of cardiovascular disease and cancer in later life (*BMJ* 2007;335:974)