RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

137 What factors are associated with diabetic ketoacidosis at diagnosis of type 1 diabetes in young people?
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139 Is vertebroplasty more effective than placebo for recent or painful osteoporotic vertebral fracture?
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141 What is the predictive power of existing, and recently proposed, stroke risk stratification schemes for observed vascular event rates in older patients with atrial fibrillation?

Glucose monitoring in type 1 diabetes

Earlier this year we published two crossover trials of the artificial pancreas, a closed loop system linking a continuous glucose monitor and a subcutaneous insulin infusion pump (*BMJ* 2011; 342:d1855). The widespread use of such a device is probably still a long way off, but what about the continuous glucose monitor alone, a technology that has been around for at least a decade?

In a *BMJ* paper this week John Pickup and colleagues note that "uptake of continuous glucose monitoring in clinical practice has been limited to date because the evidence for its effectiveness has appeared only recently and has varied between studies. As a result, funding from national health services and insurance reimbursement has been restricted." In response to this uncertainty these authors conducted a meta-analysis of individual data from nearly 900 patients in six randomised controlled trials (p 138).


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Their regression model found that, for a patient using continuous monitoring daily, HbA_{1c} would fall by about 0.9% (9 mmol/mol) when the baseline HbA1c is 10% (86 mmol/mol) over a couple of months. Median exposure to hypoglycaemia seemed to be reduced by about a fifth during continuous glucose monitoring compared with self monitoring of blood glucose. The included trials were not, however, set up or powered to study the incidence of hypoglycaemia.

The overall conclusions from this study are probably not definitive enough to change practice, but the data will now allow the cost effectiveness of continuous glucose monitoring to be calculated for different patient groups according to their baseline HbA_{1c} percentage, usage of continuous monitoring, and age. Although this is quite specialist research, we thought its relevance to clinical researchers, health economists, and policy makers made it a suitable paper for the *BMJ*.

Interpreting borderline statistical significance

In the Research Methods and Reporting section, Allan Hackshaw and Amy Kirkwood explain why borderline significance in the primary end point of a trial does not necessarily mean that the intervention was ineffective (p 142). If you're confused about P values and confidence intervals, read this and be reassured by the message that "the true effect of an intervention is more likely to lie around the middle of a confidence interval (that is, the point estimate) than at either end."

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Ketoacidosis at diagnosis of type 1 diabetes

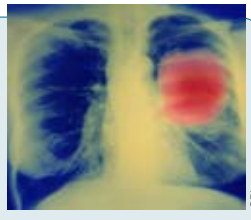
Why do so many children with type 1 diabetes present only when they've developed ketoacidosis? Studies have suggested a wide range of risk factors relating to clinical and personal characteristics and health services, but nobody to date has pulled all this evidence together.

Now Juliet Usher-Smith and colleagues' systematic review has found that younger age (particularly <2 years old), misdiagnosis, delayed diagnosis, minority ethnicity, and lack of health insurance (at least in the United States) were consistently associated with ketoacidosis at the time of diagnosis of diabetes (p 137). But the quality of the primary research wasn't great overall, hence the authors rightly describe their review as exploratory and suggest that further research focuses on developing age specific preventive interventions. The findings should be reasonably generalisable, however, as the review included 46 cohort studies from 31 developed countries covering more than 24 000 children.

Meanwhile, might this paper also inform health education? The risk of ketoacidosis at diagnosis was lower for patients in circumstances where diabetes was more likely to be spotted—when they had better educated parents, had a first degree relative with type 1 diabetes, or were in a population with relatively high background incidence. Editorialist Sasigarn Bowden picks up the theme of raising awareness and cites an Italian campaign where education among doctors and the public was associated with the incidence of ketoacidosis in newly diagnosed type 1 diabetes plummeting from 78% to almost zero at the University Hospital of Parma (http://bit.ly/qaq0b7) (p 103).

LATEST RESEARCH: For this and other new research articles see www.bmj.com/research

Survival and risk of adverse events in elderly patients receiving postoperative adjuvant chemotherapy for resected stage II-IIIA lung cancer In this observational cohort study, which included data from over 3000 older people treated for lung cancer in the United States, Juan Wisnivesky and colleagues found that use of platinum based adjuvant chemotherapy was associated with reduced mortality but an increased risk of serious adverse events. About a fifth of the patients studied received such therapy (doi:10.1136/bmj.d4013).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Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review

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EDITORIAL by Bowden

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STUDY QUESTION What factors are associated with diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults?

SUMMARY ANSWER Children of younger age, exposed to diagnostic error, from ethnic minorities, without health insurance (in the US), with lower body mass index, with a preceding infection, and with delayed treatment were more likely to present with diabetic ketoacidosis at the onset of type 1 diabetes. Children with close relatives with type 1 diabetes, parents with higher education levels, and living in areas with higher incidence of type 1 diabetes were less likely to present with diabetic ketoacidosis.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
A substantial proportion of children and young adults with newly diagnosed type 1 diabetes present in diabetic ketoacidosis. This review of the factors associated with diabetic ketoacidosis at diagnosis shows that there is potential time and opportunity to intervene between symptom onset and development of diabetic ketoacidosis both for parents and clinicians.

Selection criteria for studies

We searched PubMed, EMBASE, Web of Science, Scopus, and Cinahl up to March 2011 for cohort studies including groups of children and young adults presenting with new onset type 1 diabetes which distinguished between those who presented in diabetic ketoacidosis and those who did not. We included studies which had a measurement of either pH or bicarbonate in the definition of diabetic ketoacidosis. We did not restrict the search by language of publication.

Primary outcome(s)

Comparisons of individual, family, physician, disease, and other factors between children and young adults presenting with and without diabetic ketoacidosis at the onset of type 1 diabetes.

Main results and role of chance

We identified 46 studies involving over 24 000 children in 31 countries, with most from North America (Canada, US) or northern Europe (Austria, Finland, Germany, Sweden). Together, they compared 23 different factors (figure). Factors associated with increased risk of diabetic ketoacidosis were younger age (odds ratios for <2 years 3.41 (95% CI 2.54 to 4.59), for <5 years 1.59 (1.38 to 1.84)), diagnostic error (odds ratio 3.35 (2.35 to 4.79)), ethnic minority status, lack of health insurance in the US (odds ratio 3.20 (2.03 to 5.04)), lower body mass index, preceding infection (odds ratio 3.14 (0.94 to 10.47)), and delayed treatment (odds ratio 1.74 (1.10 to 2.77)). Protective factors were having a first degree relative with type 1 diabetes at the time of diagnosis (odds ratio 0.33 (0.08 to 1.26)), higher parental education (odds ratios 0.4 (0.20 to 0.79) and 0.64 (0.43 to 0.94) in two separate studies), and higher background incidence of type 1 diabetes (correlation coefficient −0.715). The mean duration of symptoms was similar between children presenting with or without diabetic ketoacidosis (16.5 (SE 6.2) days and 17.1 (6.0) days respectively) and up to 39% (285/735) had been seen at least once before diagnosis.

Bias, confounding, and other reasons for caution

As this was an exploratory review, the studies varied considerably in terms of design, setting, definition of diabetic ketoacidosis, and quality. Many were retrospective and so subject to recording and recall bias, and a large number did not provide quantitative data for negative findings, implying possible reporting bias. Because of the format of the data, we were not able to assess the independent contribution of each of the factors identified.

Study funding/potential competing interests

JAUS, FMW, and MJT are supported by the National Institute for Health Research and SJS is employed by the Medical Research Council.

INFLUENCE OF INDIVIDUAL FACTORS ON RISK OF DIABETIC KETOACIDOSIS AT DIAGNOSIS OF TYPE 1 DIABETES

	Risk of diabetic ketoacidosis		
	Factors increasing risk	**Factors not affecting risk**	**Factors reducing risk**
More studies, greater consensus ↓ Fewer studies, weaker consensus	Younger age Diagnostic error Ethnic minority status Lack of health insurance (in US) Lower body mass index Preceding infection Delayed treatment Lower socioeconomic status Unemployed mother	Sex Duration of symptoms Rural or urban residence Family structure Time of year Family income No of medical consultations before diagnosis Parental consanguinuity Lack of medical insurance (in France) Father's employment status	Family history of type 1 diabetes Higher parental education Higher background incidence of type 1 diabetes Presence of structured diabetes team
Insufficient evidence	← Pattern and frequency of symptoms Delayed diagnosis →		

Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data

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STUDY QUESTION What is the clinical effectiveness of real time continuous glucose monitoring compared with intermittent self monitoring of capillary blood glucose in people with type 1 diabetes?

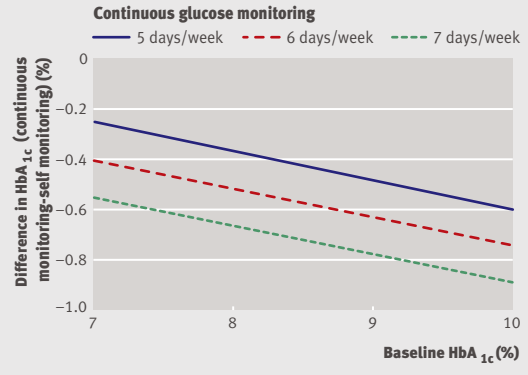
SUMMARY ANSWER Continuous glucose monitoring is associated with a significant reduction in HbA_{1c} compared with self monitoring of blood glucose, which is greatest in those with the highest HbA_{1c} at baseline or who use the sensors frequently. Exposure to hypoglycaemia also is reduced during continuous glucose monitoring.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Randomised controlled trials comparing continuous glucose monitoring and self monitoring of blood glucose in people with type 1 diabetes have reported variable effects. This meta-analysis confirms that overall glycaemic control was improved with continuous glucose monitoring. Since the greatest effect on HbA_{1c} is in those with the worst baseline glycaemic control and in those who use the sensor most often, cost effective and appropriate use of continuous glucose monitoring is likely to be achieved when targeted at this group of people with type 1 diabetes.

Selection criteria for studies

We searched the Cochrane database for randomised controlled trials, Ovid Medline, Embase, Google Scholar, lists of papers supplied by manufacturers, and cited literature. We selected randomised controlled trials of two or more months' duration in men and non-pregnant women with type 1 diabetes that compared real time continuous glucose monitoring with self monitoring of blood glucose and where insulin delivery was the same in both arms. We then carried out a two step meta-analysis of individual patient data, followed by a one step metaregression of the single dataset using Bayesian approaches, so as to explore effects of patient level covariates on outcome.

MODEL ESTIMATED DIFFERENCE IN HBA_{1C} USING CONTINUOUS GLUCOSE MONITORING VERSUS SELF MONITORING OF BLOOD GLUCOSE ACCORDING TO BASELINE HBA_{1C} AND SENSOR USE IN 40 YEAR OLD WITH TYPE 1 DIABETES



Primary outcomes

Final HbA_{1c}, area under the curve of hypoglycaemia (glucose concentration <3.9 mmol/L) and their independent determinants.

Main results and role of chance

Six trials were identified (449 people randomised to continuous glucose monitoring and 443 to self monitoring of blood glucose). The overall mean difference in HbA_{1c} for continuous glucose monitoring versus self monitoring of blood glucose was −0.30% (95% confidence interval −0.43% to −0.17%) (−3.0, −4.3 to −1.7 mmol/mol). A best fit regression model of determinants of final HbA_{1c} showed that for every one day increase of sensor usage per week the effect of continuous glucose monitoring versus self monitoring of blood glucose increased by 0.150% (95% credibility interval −0.194% to −0.106%) (1.5, −1.9 to −1.1 mmol/mol) and every 1% (10 mmol/mol) increase in baseline HbA_{1c} increased the effect by 0.126% (−0.257% to 0.0007%) (1.3, −2.6 to 0.0 mmol/mol). The model estimates that, for example, a patient using the sensor continuously would experience a reduction in HbA_{1c} of about 0.9% (9 mmol/mol) when the baseline HbA_{1c} is 10% (86 mmol/mol). The reduction in area under the curve of hypoglycaemia was −0.28 (−0.46 to −0.09), corresponding to a reduction in median exposure to hypoglycaemia of 23% for continuous glucose monitoring compared with self monitoring of blood glucose. Baseline area under the curve of hypoglycaemia was only weakly related to the effect of continuous glucose monitoring compared with self monitoring of blood glucose on hypoglycaemia outcome, and sensor usage was unrelated to hypoglycaemia at outcome.

Bias, confounding, and other reasons for caution

Caution is needed in interpreting the hypoglycaemia data as none of the trials were designed and powered to study hypoglycaemia, all had low frequency of hypoglycaemia at baseline, and the assessment of hypoglycaemia in the self monitoring of blood glucose arm may have been inadequate.

Study funding/potential competing interests

SCF was supported by the Engineering and Physical Sciences Research Council. JCP has received speaker and advisory board honorariums from Medtronic, a manufacturer of continuous glucose monitoring devices.

Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis

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EDITORIAL by Wilson

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STUDY QUESTION Is vertebroplasty more effective than placebo in patients with osteoporotic vertebral fracture of recent onset (symptoms for ≤6 weeks) or with severe pain (≥8 on a 0-10 numerical rating scale)?

SUMMARY ANSWER Individual patient data meta-analysis from two randomised placebo controlled trials of vertebroplasty, powered for subgroup analyses, failed to show an advantage of vertebroplasty over placebo for participants with pain of recent onset or severe pain.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Double blind randomised placebo controlled trials have failed to confirm the efficacy of vertebroplasty for osteoporotic vertebral compression fractures, although limited power precluded definite conclusions for subgroups. This meta-analysis does not support the hypothesis that selected subgroups would benefit from vertebroplasty.

Selection criteria for studies

Criteria for inclusion in this individual patient data meta-analysis were randomised double blind placebo controlled trials of vertebroplasty for acute osteoporotic vertebral fractures.

Primary outcomes

Primary outcomes were pain (0-10 numerical rating scale) and disability (modified, 23 item Roland-Morris disability questionnaire) at one month.

Main results and role of chance

Data from 209 participants in two trials (Australian trial n=78, US trial n=131) were available for analysis. For participants with pain of recent onset (vertebroplasty n=25, placebo n=32), adjusted between group differences in mean change scores at one month for pain and disability were 0.1 (95% confidence interval −1.4 to 1.6) and 0.2 (−3.0 to 3.4), respectively.For participants with severe pain at baseline (vertebroplasty n=50, placebo n=49) between group differences for pain and disability at one month were 0.3 (−0.8 to 1.5) and 1.4 (−1.2 to 3.9), respectively. The adjusted mean between group differences were all below the minimum clinical important differences for both outcome measures.

Bias, confounding, and other reasons for caution

This individual patient meta-analysis was based on evidence from the two most rigorous trials applied to vertebroplasty to date. Both included a sham control and blinded participants, outcome assessors, and investigators to treatment allocation thereby minimising the potential for bias in estimating the relative treatment effect. The combined data provided greater than 80% power to assess whether vertebroplasty has a 2.5 unit advantage over control for patients with acute fractures of recent onset or with severe pain. The combined data had less power to detect differences between groups for the disability outcome (53% power to detect a 3 unit difference (assuming a standard deviation of 5.5) for the subgroup with recent onset of pain and 77% power for the subgroup with severe pain at baseline). It is unlikely that factors that predict a more favourable outcome from vertebroplasty will be identified.

Study funding/potential competing interests

RHO is supported in part by an Australian National Health and Medical Research Council (NHMRC) population health career development award and RB is supported in part by an NHMRC practitioner fellowship. No other support from any organisation was received for the submitted work. DFK has received research support from Stryker and ArthroCare and is a consultant for CareFusion, JGJ has received an honorarium for lecturing at a course sponsored by Synthes in 2010, is on the GE Healthcare comparative effectiveness advisory board, is a consultant to HealthHelp, and is cofounder and patent holder of PhysioSonics. We have no other relationships or activities that could appear to have influenced the submitted work.

EFFICACY OF VERTEBROPLASTY IN TREATING OSTEOPOROTIC VERTEBRAL FRACTURES

Outcome	Mean (SD) change at 1 month		Adjusted between group difference (95% CI)
	Vertebroplasty	Placebo	
Recent onset pain*:			
Pain	3.1 (3.3)	2.8 (4.0)	0.1 (−1.4 to 1.6)
Disability†	3.8 (5.9)	4.4 (5.4)	0.2 (−3.0 to 3.4)
Severe pain at baseline‡:			
Pain	3.9 (2.9)	3.5 (3.2)	0.3 (−0.8 to 1.5)
Disability†	4.1 (5.9)	3.3 (5.6)	1.4 (−1.2 to 3.9)

*Duration ≤6 weeks.
†Measured using modified, 23 item Roland-Morris disability questionnaire.
‡Measured on 0-10 numerical rating scale, with score ≥8 representing severe pain.

Performance of stroke risk scores in older people with atrial fibrillation not taking warfarin: comparative cohort study from BAFTA trial

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STUDY QUESTION What is the predictive power of existing, and recently proposed, stroke risk stratification schemes for observed vascular event rates in older patients with atrial fibrillation?

SUMMARY ANSWER THE INCREMENTAL RISK SCORES OF CHADS$_2$, Rietbrock, and CHA$_2$DS$_2$-VASc failed to show an increase in risk at the upper range of scores. The tested schemes had similar predictive accuracy, with all except the original CHADS$_2$ predicting better than chance.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Atrial fibrillation is a major cause of avoidable stroke, with evidence based treatments that reduce risk. Several clinical risk stratification schemes, derived mainly from trial cohorts, seek to predict risk levels for stroke and thromboembolism, and thence guide treatment, but their reliability in general populations with atrial fibrillation varies, and their performance in older patients is particularly limited.

Participants and setting

We included 665 patients aged 75 or over with atrial fibrillation randomised in the Birmingham Atrial Fibrillation in the Aged (BAFTA) trial who were not taking warfarin throughout or for part of the study period. Of these patients, 54 (8%) had an ischaemic stroke, four (0.6%) a systemic embolism, and 13 (2%) had a transient ischaemic attack by the end of follow-up.

Design, size, and duration

The BAFTA trial recruited a representative sample of older people based in the community and had few reasons for exclusion. Eligible patients were randomised to warfarin (with a target international normalised ratio of 2.5) or aspirin and followed for an average of 3.5 years. We compared the predictive power of the main existing and recent proposed stroke risk stratification schemes against observed event rates in the aspirin (or warfarin withdrawn) arm of BAFTA.

Main results and the role of chance

The distribution of patients classified into three risk categories was similar across the revised CHADS$_2$, NICE, and ACC/AHA/ESC, with most patients categorised as high risk (65-69%) and the remaining classified as moderate risk. The original CHADS$_2$ identified the least number as high risk (27%). The incremental risk scores of CHADS$_2$, Rietbrock modified CHADS$_2$, and CHA$_2$DS$_2$-VASc failed to show an increase in risk at the upper range of scores. The predictive accuracy was similar across the tested schemes with C statistic ranging from 0.55 (original CHADS$_2$) to 0.62 (Rietbrock), with all except original CHADS$_2$ predicting better than chance. Bootstrapped paired comparisons provided no evidence of significant differences between the discriminatory ability of the schemes.

Bias, confounding and other reasons for caution

There were too few events to inform the comparisons. Patients recruited for the BAFTA trial were those for whom their GP was in equipoise over benefits and risks of treatment and might therefore have been perceived as at lower risk. We could not assess some of the risk factors in the point scoring schemes of CHADS$_2$, Rietbrock, and CHA$_2$DS$_2$-VASc because of the lack of available data. We also cannot account for any unanticipated influence of previous exposure to drug treatment on subsequent embolic events, although sensitivity analysis of those on aspirin throughout generated similar results.

Generalisability to other populations

Findings are probably generalisable to elderly populations living in countries with high background rates of cardiovascular disease.

Study funding/potential competing interests

BAFTA was funded by the Medical Research Council, grant G9900264, with additional support from the National Institute for Health Research (NIHR). The analyses in this paper were supported by Clinical Trial Unit core funding from the NIHR Health Technology Assessment and by the National School for Primary Care Research. GL is an author of CHADS$_2$-VASc.

PERFORMANCE OF RISK STRATIFICATION SCHEMES TO PREDICT ISCHAEMIC STROKE IN PATIENTS AGED ≥75 WITH ATRIAL FIBRILLATION WHO WERE NOT TAKING WARFARIN

Risk scheme	C statistic*	Hazard ratio (95% CI)	P value
Stratum			
CHADS$_2$ original	0.55 (0.49 to 0.61)	1.61 (0.93 to 2.80)	0.09
CHADS$_2$ revised	0.61 (0.57 to 0.66)	3.29 (1.49 to 7.28)	0.003
Framingham:			
Moderate *v* low	0.59 (0.55 to 0.65)	4.99 (1.18 to 21.10)	0.03
High *v* moderate		1.17 (0.68 to 2.03)	0.56
NICE	0.59 (0.54 to 0.63)	2.93 (1.25 to 6.68)	0.01
ACC/AHA/ESC†	0.61 (0.57 to 0.66)	3.29 (1.49 to 7.28)	0.003
ACCP:			
Moderate *v* low	0.60 (0.54 to 0.65)	0.75 (0.09 to 5.89)	0.78
High *v* moderate		2.61 (1.27 to 5.35)	0.009
Scores			
CHADS$_2$ index	0.61 (0.54 to 0.68)	1.35 (1.07 to 1.70)‡	0.01
Rietbrock modified	0.62 (0.59 to 0.68)	1.17 (1.06 to 1.29)‡	0.001
CHA$_2$DS$_2$-VASc	0.60 (0.55 to 0.68)	1.21 (0.99 to1.47)‡	0.06

*Assesses discrimination where 0.5 is non-informative test.
†Equal to CHADS$_2$ revised because of unavailability of risk factors left ventricular fibrillation, mitral stenosis, and prosthetic heart valve in BAFTA data.
‡Per unit increase in score.

Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe

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EDITORIAL by Chen and colleagues

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bmj.com/doc2doc
Discuss this article on doc2doc's pandemic flu forum http://bit.ly/hbOEoZ

STUDY QUESTION Is there an association between pandemic influenza A (H1N1) 2009 vaccine and Guillain-Barré syndrome?

SUMMARY ANSWER In a population of 50 million people in Europe we could not find an increased risk of Guillain-Barré after adjuvanted pandemic influenza A (H1N1) 2009 vaccine.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
The influenza A (H1N1) vaccine used in the United States in 1976 was associated with a sevenfold increase in the risk of Guillain-Barré syndrome. The current study found no evidence for such an increase in risk with the adjuvanted pandemic influenza A (H1N1) 2009 vaccines. Influenza-like illness and respiratory tract infection are important covariates in the association between influenza vaccination and Guillain-Barré syndrome.

Participants and setting
Each case was matched to up to 25 controls on age, sex, index date, and country. The study was done in Sweden, United Kingdom, France, Denmark, and Netherlands within the framework of the VAESCO consortium.

Design, size, and duration
We conducted a distributed case-control study including 104 patients with Guillain-Barré syndrome between 1 November 2009 and 1 April 2010.

Primary outcome, risks, exposures
The primary outcome was new onset of Guillain-Barré syndrome and its variant Miller-Fisher syndrome. The primary exposure was the pandemic influenza A (H1N1) 2009 vaccine with the primary risk window being six weeks after vaccination. We calculated the risk of Guillain-Barré syndrome after vaccination compared with no vaccination. Pooled estimates were calculated with a meta-analytical approach with random effects to account for country differences.

Main results and the role of chance
Case recruitment and vaccine coverage varied between countries; the most common vaccines were adjuvanted (Pandemrix and Focetria). The unadjusted pooled risk estimate was 2.8 (95% confidence interval 1.3 to 6.0). After adjustment for influenza-like illness/upper respiratory tract infection and seasonal influenza vaccination, pandemic influenza vaccine was not associated with an increased risk of Guillain-Barré syndrome (adjusted odds ratio 1.0, 0.3 to 2.7). The confidence interval shows that the absolute effect of vaccination could range from one avoided case of Guillain-Barré syndrome to up to three excess cases within six weeks after vaccination in one million people.

Bias, confounding, and other reasons for caution
Preferential selection of exposed cases was a concern as many physicians were aware of the potential risk. Comparison against objective claims data in the Netherlands, absence of recruitment bias in Denmark and the UK, and the absence of an increased risk suggested little impact of selection bias in these countries. For France and Sweden this could not be excluded.

The most important confounders were accounted for by matching. Respiratory tract infections and seasonal vaccination could be adjusted for only in the UK and Netherlands. Incomplete or biased data on risk factors in Denmark, Sweden, and France led to residual confounding in those countries. The case-control analysis could not fully adjust for confounding by indication.

Generalisability to other populations
As this was a population based study with consistency across multiple European countries the results can probably be generalised to other populations. Other risk factors and confounding factors, however, might have a role. There was limited heterogeneity in risk estimates among the included countries.

Study funding/potential competing interests
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CRUDE AND ADJUSTED ODDS RATIOS (95% CI) FOR ONSET OF GUILLAIN-BARRÉ SYNDROME WITHIN SIX WEEKS OF PANDEMIC INFLUENZA A (H1N1) 2009 VACCINATION

Country	Unadjusted matched analysis*	Adjusted for seasonal influenza vaccination and ILI/URTI
Denmark	9.5 (1.7 to 53)	—
Netherlands	2.5 (0.7 to 9.3)	0.6 (0.1 to 4.4)
Sweden	2.3 (0.5 to 11.7)	1.8 (0.3 to 12)
UK	1.3 (0.3 to 6.4)	0.7 (0.1 to 4.1)
Pooled (all countries)	2.8 (1.3 to 6.0)	—
Pooled (countries with possible adjustment†)	2.0 (0.9 to 4.8)	1.0 (0.3 to 2.7)

ILI/URTI=influenza-like illness/upper respiratory tract infection.
*Matched on age (within 1 year), sex, and index date; additionally matched on general practice in Netherlands and UK.
†Netherlands, Sweden, UK.