RESEARCH

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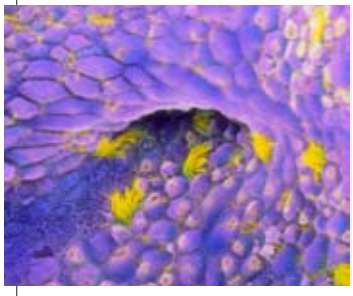
Improving diagnosis of ovarian cancer in primary care

Early diagnosis of ovarian cancer improves prognosis: five year survival among women diagnosed with stage I ovarian cancer is 90%, compared with only 20% for stage III cancer and 6% for stage IV. Currently, however, less than 30% of women are diagnosed with stage I cancer, as the disease has few established risk factors and a range of non-specific symptoms such as loss of appetite, weight loss, and abdominal pain that also occur with less serious and more common conditions.

Using routinely collected data from the QResearch database of general practices in England and Wales, Julia Hippisley-Cox and Carol Coupland have now developed and validated an algorithm to identify women at highest risk of ovarian cancer to facilitate early referral and investigation (p 17). The algorithm was based on simple clinical variables—such as age, family history of ovarian cancer, anaemia, abdominal pain and distension, rectal and postmenopausal bleeding, and loss of appetite and weight—which a patient is likely to be aware of, or which are routinely recorded in general practice. It was successful in predicting 340 (63%) of the 538 new cases of ovarian cancer in the validation cohort over the next two years, which were in the 10% of women with the highest predicted risks. The authors conclude that the algorithm had good discrimination and calibration, and could potentially be integrated into general practice clinical computer systems, to assess risk in women presenting with and without symptoms.

Of course, the development of this algorithm is just the first stage in achieving a routine test for ovarian cancer risk, and in his accompanying editorial (p 9) William Hamilton considers the further steps that will be needed before such computerised support for cancer diagnosis can become a reality.



SPL

GUSTO IMAGES/SPL

How much weight loss is associated with use of GLP-1R agonists?

When first and second line treatments such as metformin and gliclazide have failed, a trial of exanatide is an option for patients with a body mass index over 35, for those with co-morbidities likely to improve with weight loss, or for people (such as lorry drivers) who for occupational reasons would rather avoid insulin, according to NICE guidelines.

The amount of weight loss associated with glucagon-like peptide-1receptor (GLP-1R) agonists may seem a tangential matter, because the key role of these drugs is to improve glycaemic control. But the question is clearly intriguing for readers of bmj.com; Tina Vilsbøll and colleagues' meta-analysis (p 14) is the third most read article online this week. However, beneath promising headlines of a mean 3.2 kg weight loss associated with the drugs, lies complexity and caution—highlighted by Raj Padwal in an accompanying editorial (p 7).

Trials included in the study were not powered to detect differences in weight. And the situation is complicated because many trials compared the GLP-1R agonists with active control drugs, such as insulin, which are known to cause weight gain. Weight loss in trials of GLP-1R agonists compared with placebo was less (1.9 kg) than that seen overall. By comparison, Vilsbøll and colleagues write, non-pharmacological measures achieve 1-5 kg weight loss, and sibutramine and orlistat 3-5 kg weight loss. Given that the safety profile of GLP-1R agonists has yet to be established, Padwal writes that their use cannot be recommended for weight reduction alone until their benefits and risks are clarified.

RESEARCH ONLINE: For these and other new research articles see www.bmj.com/research

Consumption of fried foods and risk of coronary heart disease In Spain, where olive or sunflower oil is used for frying, the consumption of fried foods was not associated with coronary heart disease or with all cause mortality, according to Pilar Guallar-Castillón and colleagues, reporting results from the European Prospective Investigation into Cancer and Nutrition. The Spanish cohort included 40 757 adults aged 29-69, who were free of coronary heart disease at baseline in 1994-96 and were followed up until 2004 (doi:10.1136/bmj.e363).

The decline in coronary heart disease Three studies examine the decline in mortality from coronary heart disease and its determinants in England, Poland, and Denmark (doi:10.1136/bmj.d8059, doi:10.1136/bmj.d8136, doi:10.1136/bmj.e356). Hugh Tunstall-Pedoe draws the findings together in an editorial, saying that the decrease seems to be associated with the effects of evidence based treatments in primary prevention, coronary care, and secondary prevention (doi:10.1136/bmj.d7809).

Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials

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EDITORIAL by Padwal

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Response on bmj.com

Only long-term prospective comparative randomised trials against established drug-treatment of diabetes will provide the basis or not for their effectiveness or safety in diabetes treatment"
Jose Mario Franco de Oliveira, Brazil
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STUDY QUESTION

Does treatment with glucagon-like peptide-1 receptor (GLP-1R) agonists lead to weight loss in patients who are overweight or obese?

SUMMARY ANSWER

GLP-1R agonists, when given to overweight or obese patients with or without type 2 diabetes mellitus, result in a clinically relevant reduction in body weight.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Improved glycaemic control is associated with increased body weight, and GLP-1R agonists enhance glucose homoeostasis and suppress appetite. The current review shows that GLP-1R agonists could improve metabolic regulation and have beneficial effects on body weight, blood pressure, and cholesterol.

Selection criteria for studies

We did electronic searches (Cochrane Library, Medline, Embase, and Web of Science) and manual searches (up to May 2011). Three authors extracted data independently. We identified 25 randomised controlled trials of adult participants who were overweight (body mass index ≥25), with or without type 2 diabetes mellitus, and who were given GLP-1R agonists (exenatide twice daily, exenatide once weekly, or liraglutide once daily) at clinically relevant doses for at least 20 weeks. The trials assessed control groups receiving placebo, oral antidiabetic drugs, or insulin.

Primary outcome

Weight loss. Secondary outcomes were blood pressure, plasma concentrations of cholesterol and liver enzymes, glycaemic control (in patients with type 2 diabetes), and adverse events.

Main results and role of chance

A meta-analysis of 21 trials (n=6411) found that patients allocated to receive GLP-1R agonists achieved a greater weight loss than controls (weighted mean difference −2.9 kg, 95% confidence interval −3.6 to −2.2, using a random effects model. We found evidence of intertrial heterogeneity, but no evidence of bias or small study effects in regression analyses. The results were confirmed in sequential analyses. GLP-1R agonists led to weight loss in patients without diabetes (−3.2 kg, −4.3 to −2.1; three trials) as well as those with diabetes (−2.8 kg, −3.2 to −2.1; 18 trials). GLP-1R agonists had beneficial effects on systolic and diastolic blood pressure, cholesterol, and glycaemic control. We found no significant effect on liver enzymes in the overall analysis. GLP-1R agonists were associated with nausea, diarrhoea, and vomiting, but not with hypoglycaemia. The side effects did not seem to affect the number of losses to follow-up. These findings concur with recent evidence showing that patients' overall satisfaction with GLP-1R agonist treatment is relatively high. Further studies are needed to elucidate the effects of GLP-1R agonists in the treatment of obese patients without diabetes.

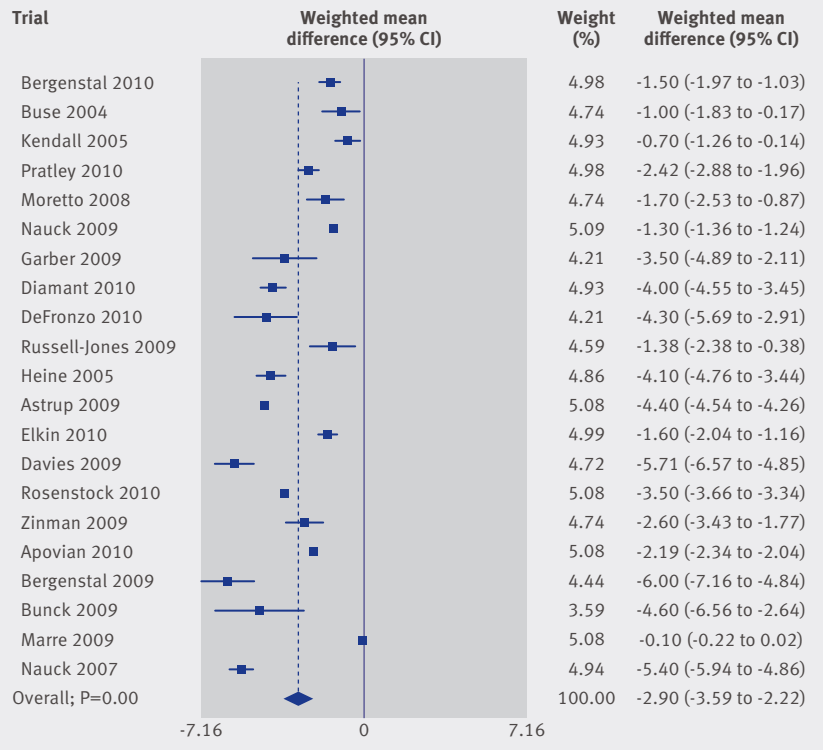
Bias, confounding, and other reasons for caution

All trials had adequate control of selection, assessment, performance, attrition, and reporting bias. All trials were industry funded.

Study funding/potential competing interests

None of the authors have received support from any organisation for the submitted work; have relationships with any organisations that might have an interest in the submitted work; and have relationships or activities that could appear to have influenced the submitted work.

Change in body weight (kg) after at least 20 weeks' treatment of GLP-1R agonists



Vitamin A supplementation in preschool children and risk of hearing loss as adolescents and young adults in rural Nepal: randomised trial cohort follow-up study

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EDITORIAL by Wieringa et al

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STUDY QUESTION

Can periodic vitamin A supplementation in undernourished children lower the risk of hearing loss attributable to purulent (discharging) ear infection?

SUMMARY ANSWER

Supplementing preschool aged Nepalese children with a large dose of vitamin A every four months reduced by over 40% their risk of hearing loss as adolescents or young adults.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Purulent middle ear infections and vitamin A deficiency often coexist as paediatric public health problems in low income countries. Beyond preventing xerophthalmia and reducing child mortality, preschool vitamin A supplementation can reduce the risk of hearing loss, presumably mediated by a reduced purulence of ear infections.

Participants and setting

A cohort of young people aged 14 to 23 years, living in the rural, southern plains district of Sarlahi, Nepal.

Design, size, and duration

We carried out a study of ear health among 2378 participants who, about 17 years earlier as preschoolers, were enrolled into a cluster randomised, placebo controlled trial of vitamin A supplementation. Every four months for the 16 months of the original trial, the participants were visited at home and given a vitamin A or placebo capsule. Parents were queried about their child's morbidity, including ear discharge, for the previous week. To test our a priori hypothesis about the impact of vitamin A on hearing loss from otitis media, trained staff blinded to the original supplement assignment assessed the older trial cohort by audiometry.

Main results and the role of chance

A non-significant 17% reduction in risk of hearing loss (≥30 dB) was found in the worst affected ear among participants allocated to vitamin A versus placebo as preschool aged children (odds ratio 0.83, 95% confidence interval 0.62 to 1.12). Among participants with a history of ear discharge, vitamin A reduced the risk of hearing loss by 42% (0.58, 0.37 to 0.92). There was no difference between participants without reported ear discharge.

Bias, confounding, and other reasons for caution

The possibility that vitamin A supplementation may have caused a reduction in hearing loss from ear infections is strengthened by the randomised design of the trial, repeated use of a validated history of ear discharge, blinding of testing staff to original supplement assignment, and biological plausibility. Still, in both groups about half of the participants alive at the end of the trial, and 71% of those deemed available at follow-up, were examined, introducing a potential for bias and caution in interpretation. Notwithstanding, losses in each supplement group were similar in size and baseline characteristics, and both groups as assessed remained similar at follow-up. Another concern relates to hearing tests being done in rural communities compared with a sound proof room, challenging the control of ambient sound and test accuracy. Anticipating these problems, we used insert earphones to attenuate ambient noise, and paused or restarted hearing tests disturbed by environmental sounds. A sound meter was used to monitor ambient noise throughout the study.

Generalisability to other populations

The increased risk of hearing loss from purulent ear infections may be present in other vitamin A deficient child populations. However, countries distributing vitamin A or otherwise controlling this deficiency may already be reducing this fraction of hearing loss from purulent ear infections.

Study funding/potential competing interests

All researchers are independent of funders of the original trial or follow-up study, the Bill and Melinda Gates Foundation, and the US Agency for International Development.

Odds ratios and absolute risk differences for hearing loss among adolescents and young adults by preschool supplement allocation in Sarlahi, Nepal, 2006-8

Supplement allocation	Total No	No (%)	Odds ratio (95% CI)	% absolute risk difference (95% CI)
Overall:	2370	140 (5.9)	—	—
Placebo	1116	72 (6.5)	1.00	—
Vitamin A	1254	68 (5.4)	0.83 (0.62 to 1.12)	−1.0 (−2.7 to 0.7)
No ear discharge:				
Placebo	902	30 (3.3)	1.00	—
Vitamin A	1012	36 (3.6)	1.07 (0.64 to 1.80)	0.2 (−1.5 to 1.9)
Any ear discharge:				
Placebo	214	42 (19.6)	1.00	—
Vitamin A	242	32 (13.2)	0.58 (0.37 to 0.92)	−7.2 (−13.0 to −1.4)

Effectiveness of vaccine against pandemic influenza A/H1N1 among people with underlying chronic diseases: cohort study, Denmark, 2009-10

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- Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden (*BMJ* 2011;343:d5956)
- Changes in severity of 2009 pandemic A/H1N1 influenza in England: a Bayesian evidence synthesis (*BMJ* 2011;343:d5408)
- Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe (*BMJ* 2011;343:d3908)

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- Discuss on *BMJ*'s Infectious Diseases forum, powered by doc2doc http://bit.ly/nbx5Mm

STUDY QUESTION

How effective is an adjuvanted monovalent vaccine against pandemic influenza A/H1N1 in people with underlying chronic diseases?

SUMMARY ANSWER

The adjuvanted monovalent vaccine protected against laboratory confirmed H1N1 infection in people with underlying chronic diseases.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Epidemiological studies suggest that the monovalent vaccine against H1N1 infection is more than 70% effective in the general population. In the present study it also offered protection against laboratory confirmed H1N1 infection among those with underlying chronic diseases, despite its late availability in the 2009 influenza pandemic.

Participants and setting

The study was based on mandatory national reporting systems and included people under 65 years of age with a diagnosis in the past five years of at least one underlying disease expected to increase the risk of severe illness after influenza.

Design, size, and duration

This historical cohort study included 388 069 people with at least one relevant diagnosis of an underlying chronic disease within the past five years. The cohort was followed from 2 November 2009 to 31 January 2010, and we estimated effectiveness of the pandemic vaccine against laboratory confirmed H1N1 infection. In addition, we investigated the effect of the 2009-10 seasonal influenza vaccine on laboratory confirmed H1N1 infections. We adjusted the estimates of vaccine effectiveness for age and underlying disease.

Main results and the role of chance

Of 799 people who tested positive for H1N1 infection in the cohort, 718 were not vaccinated with the pandemic vaccine, 49 were vaccinated 1-7 days before the date of swabbing for H1N1, 18 were vaccinated 8-14 days before the date of swabbing, and 14 were vaccinated more than 14 days before the date of swabbing. Effectiveness was 49% (95% confidence interval 10% to 71%) more than 14 days after receiving the vaccine. By contrast, an increased risk of laboratory confirmed H1N1 infection was observed during the first 1-7 days after receiving the pandemic vaccine, with vaccine effectiveness estimates of −112% (95% confidence interval −187% to −56%) compared with those who did not receive either the pandemic or the seasonal influenza vaccines. Those who received only the 2009-10 seasonal influenza vaccine had an increased risk of laboratory confirmed H1N1 infection compared with those who were not vaccinated (hazard ratio 2.31, 95% confidence interval 1.65 to 3.23).

Bias, confounding, and other reasons for caution

As the implementation of the vaccination programme coincided with variations in transmission of the influenza virus, we included calendar time in days as the underlying time scale to avoid overestimating vaccine effectiveness. Age and underlying disease were also controlled for in the analyses. However, neither vaccines nor swabs were collected at random, which could have influenced vaccine effectiveness. Knowledge from the intensive care units indicates that clinicians need to seek information about vaccination in the national registers and not from clinical records. Therefore sampling is considered to some extent independent of vaccination status.

Generalisability to other populations

Estimates of vaccine effectiveness from this study are comparable with other studies including those with underlying disease but lower than estimates obtained from studies based on the general population.

Study funding/potential competing interests

This study was supported by European Vaccine Manufacture through a grant managed by EpiConcept. The funder did not influence or participate in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; writing the manuscript; or the decision to submit the article for publication. The researchers were independent of the funder.

Estimated hazard ratios between levels of vaccine status for laboratory confirmed pandemic influenza A/H1N1 2009 infection

Models	Hazard ratio (95% CI) for laboratory confirmed H1N1 infection	
Days after vaccination with pandemic vaccine*:		
>14	0.51	(0.29 to 0.90)
8-14	1.22	(0.75 to 1.99)
1-7	2.12	(1.56 to 2.87)
Seasonal vaccine only	2.31	(1.65 to 3.23)
No vaccine (reference)	1	—

Estimates obtained using proportional hazard regression with stratification on age groups and number of different chronic disease diagnoses.
*Regardless of seasonal influenza vaccination.

Identifying women with suspected ovarian cancer in primary care: derivation and validation of algorithm

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EDITORIAL by Hamilton

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bmj.com
News: UK researchers uncover new high risk gene for ovarian cancer (*BMJ* 2011;343:d5102)
Practice: Recognition and initial management of ovarian cancer: summary of NICE guidance (*BMJ* 2011;342:d2073)

STUDY QUESTION

Can a newly developed and validated algorithm estimate the absolute risk of having ovarian cancer in women with and without symptoms?

SUMMARY ANSWER

The algorithm, which was based on a combination of symptoms and simple variables such as age and family history of ovarian cancer, can help to assess risk at the point of care in women presenting to general practitioners with these symptoms, many of which are non-specific.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Earlier diagnosis of ovarian cancer improves with more targeted investigation of symptomatic patients and increased public awareness of symptoms, which is a major challenge given the non-specific nature of some of the symptoms. An algorithm based on simple clinical variables such as age, family history of ovarian cancer, anaemia, abdominal pain, abdominal distension, rectal bleeding, postmenopausal bleeding, appetite loss, and weight loss, can estimate the absolute risk of ovarian cancer in women with and without these symptoms in primary care.

Participants and setting

We studied 1 158 723 women in the derivation cohort and 608 862 women in the validation cohort. Women were aged 30-84 and did not have a previous diagnosis of ovarian cancer.

Design, size, and duration

In this prospective open cohort study we used routinely collected data from QResearch general practices in England and Wales. We used 375 practices to develop the scores and a separate set of 189 practices to validate the scores. Cox proportional hazards models were used to develop the risk equation. Risk factors examined included age, family history of ovarian cancer, previous cancers other than ovarian, body mass index (BMI), smoking, alcohol, deprivation, loss of appetite, weight loss, abdominal pain, abdominal distension, rectal bleeding, postmenopausal bleeding, urinary frequency, diarrhoea, constipation, tiredness, and anaemia. Measures of calibration and discrimination assessed performance in the validation cohort.

Hazard ratios (95% CI) for final model* for ovarian cancer in derivation cohort. Hazard ratios adjusted for all other terms in table and for age

	HR (95% CI)
Family history of ovarian cancer†	9.8 (5.4 to 17.8)
Haemoglobin <110 g/L in past year†	2.3 (1.7 to 2.9)
Current symptoms:	
Abdominal pain†	7.0 (6.1 to 8.0)
Abdominal distension†	23.1 (18.2 to 29.4)
Appetite loss†	5.2 (3.4 to 7.9)
Rectal bleeding†	2.0 (1.4 to 2.8)
Postmenopausal bleeding†	6.6 (5.1 to 8.5)
Weight loss†	2.0 (1.3 to 3.1)

*Also included fractional polynomial terms for age, which were age$^{-0.5}$, age$^{-0.5}$ ln(age).
†Compared with women without this characteristic.

Main results and the role of chance

In the derivation cohort there were 976 incident cases of ovarian cancer from 2.03 million person years. Independent predictors were age, family history of ovarian cancer (9.8-fold higher risk), anaemia (2.3-fold higher), abdominal pain (sevenfold higher), abdominal distension (23-fold higher), rectal bleeding (twofold higher), postmenopausal bleeding (6.6-fold higher), appetite loss (5.2-fold higher), and weight loss (twofold higher). On validation, the algorithm explained 58% of the variation. The receiver operating characteristics curve (ROC) statistic was 0.84, and the D statistic was 2.38. In total 63% of all ovarian cancers diagnosed over the next two years occurred in the 10% of women with the highest predicted risks.

The algorithm had good discrimination and calibration and, after independent validation in an external cohort, could potentially be used to identify women at highest risk of ovarian cancer to facilitate early referral and investigation. Further research is needed to assess how best to implement the algorithm, its cost effectiveness, and whether, on implementation, it has any impact on health outcomes. A calculator can be found here www.qcancer.org/ovary.

Bias, confounding, and other reasons for caution

Limitations include lack of formally adjudicated outcomes, information bias, missing data, and residual confounding.

Generalisability to other populations

A strength of our study is that we have developed the algorithm in one cohort and validated in a separate cohort representative of the patients who present in primary care.

Study funding/potential competing interests

JH-C is co-director of QResearch, a not-for-profit organisation that is a joint partnership between the University of Nottingham and EMIS (leading commercial supplier of IT for 60% of general practices in the UK); JH-C is also a paid director of ClinRisk, which produces software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care. CC is a paid consultant statistician for ClinRisk.