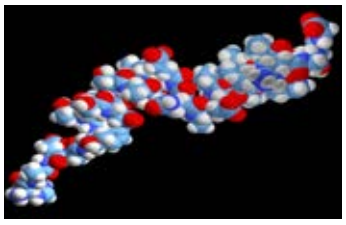
research

Major congenital malformation risk increased in overweight and obese mothers p 471

New risk prediction model for colorectal cancer survival p 472



Incretin based treatment in type 2 diabetes not linked to increase in all cause mortality p 474

ORIGINAL RESEARCH Cohort study of 1.2 million singletons

Risk of major congenital malformations in relation to maternal overweight and obesity severity

Persson M, Cnattingius S, Villamor E, et al

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Study question Does the risk of congenital malformations increase with maternal overweight and obesity severity?

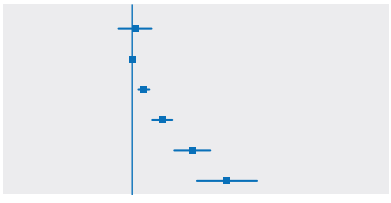
Methods This population based cohort study included 1 243 957 liveborn singleton infants from 2001 to 2014 in Sweden. The authors obtained data on maternal body mass index from the first prenatal visit, maternal and pregnancy characteristics, and diagnoses of malformations in the offspring during the first year of life by individual record linkages of nationwide Swedish registries. They estimated the risks of major congenital malformations in the offspring in relation to maternal body mass index.

Study answer and limitations A total of 43 550 (3.5%) offspring had some major congenital malformation, and the most common subgroup was congenital heart defects (n=20 074; 1.6%). Compared with the offspring of normal weight mothers (malformation risk 3.4%), the proportions and adjusted risk ratios of any major congenital malformation in the offspring of mothers with a higher body mass index were, respectively, 3.5% and 1.05 (95% confidence interval 1.02 to 1.07) for overweight mothers, 3.8% and 1.12 (1.08 to 1.15) for women in obesity class I, 4.2% and 1.23 (1.17 to 1.30) for women in obesity class II, and 4.7% and 1.37 (1.26 to 1.49) for women in obesity class III. The authors did not have data on abortions. If some malformations were less likely to be prenatally diagnosed in obese compared with normal weight mothers leading to a lower rate of induced abortion, the authors might have overestimated the risks of malformations in the offspring of obese mothers. However, risks may be underestimated if obesity is associated with malformations leading to spontaneous abortion.

What this study adds The risks of any major congenital malformation progressively increase with maternal overweight and obesity severity.

Funding, competing interests, data sharing
Funded by the National Institutes of Health (R01DK105-948-01), Swedish Research Council for Health, Working Life and Welfare (grant 2014-0073) and the Swedish Research Council (grant 2013-2429), the Karolinska Institutet (distinguished professor award to SC, grant 2368/10-221), and Stockholm County Council. The funders were not involved in the design or conduct of the study. No additional data are available.

BMI (kg/m²)	Events (%)	Adjusted risk ratio (95% CI)
Overall	43 550 (3.5)	
<18.5	1020 (3.4)	1.01 (0.95 to 1.08)
18.5 to <25	25 713 (3.4)	1.00 (ref)
25 to <30	11 050 (3.5)	1.05 (1.02 to 1.07)
30 to <35	3903 (3.8)	1.12 (1.08 to 1.15)
35 to <40	1335 (4.2)	1.23 (1.17 to 1.30)
≥40	529 (4.7)	1.37 (1.26 to 1.49)



Major congenital malformations in liveborn singletons by maternal body mass index (BMI). Variables adjusted for are in the full paper on bmj.com

Predicting survival in patients with colorectal cancer

ORIGINAL RESEARCH Cohort study

Development and validation of risk prediction equations to estimate survival in patients with colorectal cancer

Hippisley-Cox J, Coupland C

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Study question Can we develop and externally validate risk prediction equations to estimate absolute and conditional survival in patients with colorectal cancer to provide better individualised information for patients and clinicians to inform treatment decisions?

Methods This cohort study used routinely collected data from English general practices contributing to the QResearch database linked to the national cancer registry. The derivation cohort included 44 145 patients with colorectal cancer from 947 practices, and separate equations were derived for men and women aged 15-99 years. The authors used cause specific hazards models to predict risks of deaths from colorectal cancer and from other causes, accounting for competing risks and combined risk estimates to obtain risks of all cause mortality. They tested age, ethnicity, deprivation, cancer stage, cancer grade, surgery, chemotherapy, radiotherapy, smoking status, alcohol consumption, body mass index, family history of bowel cancer, anaemia, liver function test result, comorbidities, use of statins and aspirin, clinical values for anaemia, and platelet count. The equations were validated in 15 214 patients with colorectal cancer from 305 different QResearch practices and 437 821 patients with colorectal cancer from the Public Health England cancer registry. Measures of calibration and discrimination were determined in both validation cohorts.

Study answer and limitations The final models included several variables in men and women: age, deprivation score, cancer stage, cancer grade, smoking status, colorectal surgery, chemotherapy, family history of bowel cancer, raised platelet count, abnormal liver function test result, cardiovascular disease, diabetes, chronic renal disease, chronic obstructive pulmonary disease, and prescribed aspirin and statins at diagnosis. Improved survival in women was associated with younger age, earlier stage of cancer, well or moderately differentiated grade, colorectal cancer surgery (adjusted hazard ratio 0.50), family history of bowel cancer (adjusted hazard ratio 0.62), and prescriptions for statins (adjusted hazard ratio 0.77) and aspirin (adjusted hazard ratio 0.83) at diagnosis with comparable results for men. The risk equations were well calibrated. Discrimination was good in both validation cohorts. The five year survival equations explained 42.6% of the variation in survival time for women in the QResearch validation cohort; and the D statistic was 1.77, and Harrell's C statistic was 0.79 (both measures of discrimination, with higher values indicating better discrimination). Values were similar in men.

What this study adds The authors have developed and validated new risk prediction equations to predict overall and conditional survival of patients with colorectal cancer, accounting for clinical and demographic characteristics. These equations can help provide more individualised information for patients to inform decision making and follow-up.

COMMENTARY New models will help, but shouldn't be used in isolation

By estimating the probability of given outcomes for individuals based on a combination of clinical and sociodemographic characteristics, the growing number of risk prediction models has the potential to support decision making by patients and clinicians.

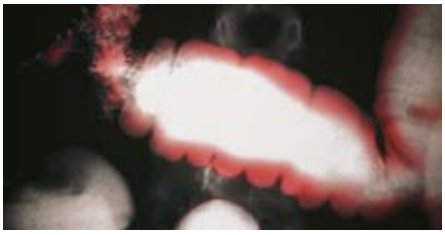
In a linked paper, Hippisley-Cox and Coupland use data from a large UK primary care database to develop models to estimate survival in men and women after a diagnosis of colorectal cancer.[1] They then validate them in a separate set of patients within the same database and in the Public Health England cancer registry. Using established statistical measures of performance, they show that the models are reasonably good at ranking people according to their survival, and the predicted survival estimates closely match those observed in the study populations and other studies.

Compared with existing models, these new ones have several advantages.[2 3] Firstly, they are applicable to all patients with colorectal cancer, whereas existing models apply to patient subgroups. Secondly, the survival estimates can be updated conditional on the number of years survived since diagnosis, allowing patients and clinicians to obtain dynamic survival estimates annually up to nine years after diagnosis. Thirdly, the models provide estimates for both all cause mortality and colorectal cancer specific mortality.

The authors provide a web based calculator (http://qcancer.org/colorectal-survival/index.php) and suggest this could be used by patients and clinicians to inform discussions about cancer treatment and follow-up.

Currently, discussions about treatment are based mainly on stage at diagnosis and trial evidence of the effectiveness of standard treatments.[4] Although other comorbidities and overall performance status are taken into consideration, this is largely through subjective assessments.

By providing more objective estimates of mortality risk from other causes alongside colorectal cancer specific mortality, these new models help put the risks from colorectal cancer into context for individual patients and so facilitate more individualised and informed discussions and decisions.



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Research is now needed to assess the clinical value of these models to patients and their doctors

Competing risks

For example, patients with a low risk of dying from colorectal cancer and a high risk of dying from other causes may be more inclined to decline aggressive treatments compared with those whose risk of death is predominantly due to colorectal cancer.

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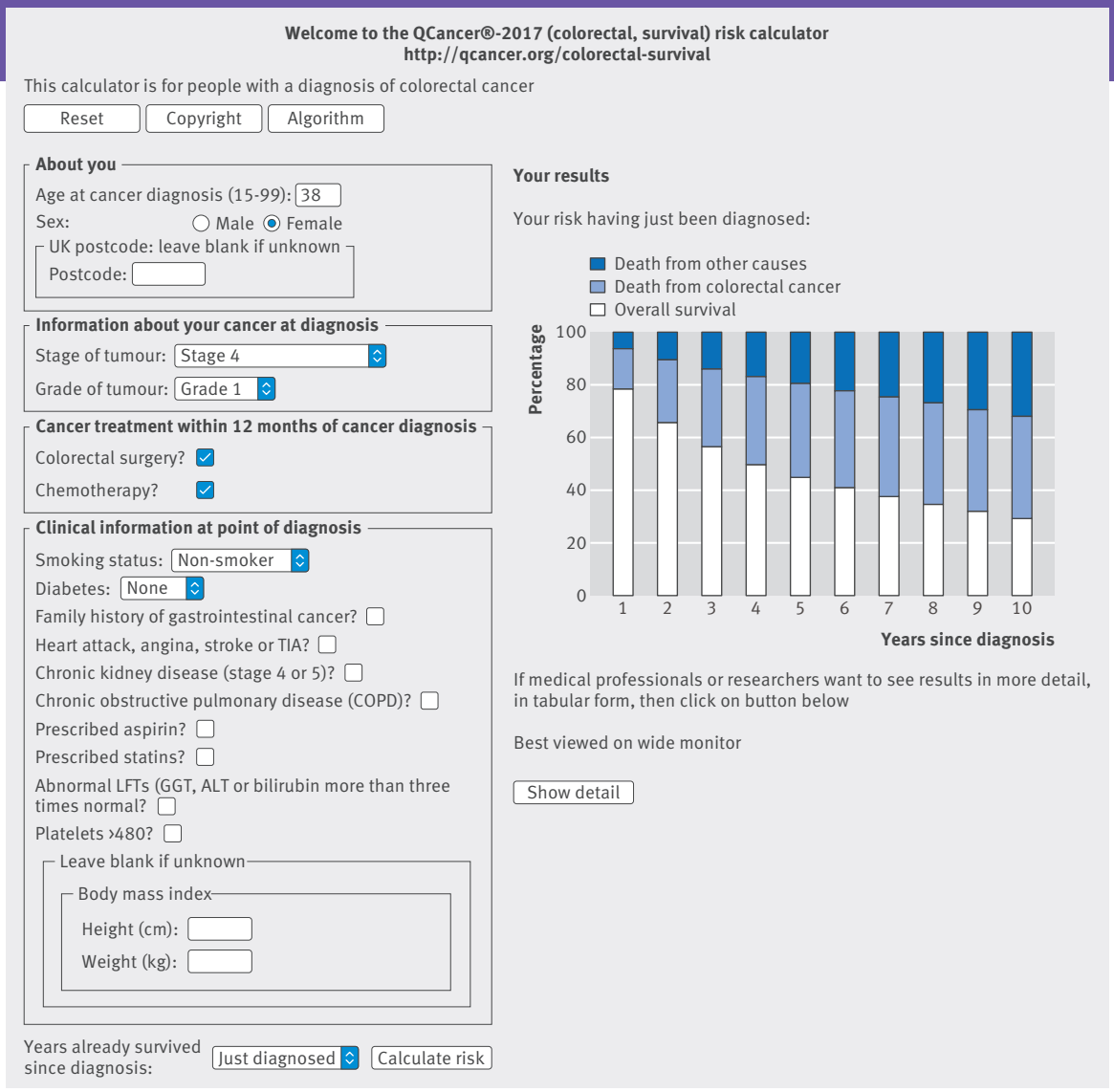

Web calculator showing clinical example of a 38 year old woman with grade 1, stage 4 colorectal cancer who has had a hemicolectomy and chemotherapy

Funding, competing interests, data sharing

This study was not externally funded. See bmj.com for competing interests and data sharing.

These more accurate, longer term, and dynamic estimates of overall survival may also help with future planning and to inform decisions around follow-up. A recent review[5] highlighted the ongoing controversy around optimal surveillance protocols and suggested a need for risk models to enable personalised follow-up. Ideally such models would include additional risk factors known to influence recurrence rates, such as anastomotic leakage, but these data may not have been available to the authors.

Inevitably there are limitations to Hippisley-Cox and Coupland's new risk prediction models. They were developed using observational data collected retrospectively from electronic patient records across England from 1998. The observed effects of treatment therefore reflect both the effect of the treatment given and the characteristics of the individuals who were offered then accepted that treatment. The result is that, for example, surgery for colorectal cancer appears to reduce the risk of death from causes other than colorectal cancer, presumably because patients with few comorbidities were more likely to be treated with surgery. Similarly, chemotherapy appears to increase mortality (relative to no chemotherapy) in those with stage 1 or 2 disease, which may reflect, among other things, the greater use of chemotherapy among patients with stage 2 disease and other poor prognostic indicators.[6]

No radiotherapy

Radiotherapy is also missing from the risk models as its association with mortality did not reach statistical significance during model development. All chemotherapy regimens are combined in a binary yes or no variable, which does not reflect the full variation of treatments and associated outcomes.

Additionally, molecular features are increasingly used to classify tumours and guide response to adjuvant chemotherapy,[7] and these are absent from the models. Finally, the models do not consider the impact of treatments on morbidity and quality of life, which influences treatment decisions.

Because of these limitations, the new models should not be relied on to predict the effects on mortality of contemporary chemotherapy and surgery in individual patients. Instead, clinicians should continue to interpret mortality estimates derived from these models using additional context from trials quantifying the effects of treatments, or appropriate decision aids.[8] Patients would then see estimates of the absolute benefits of treatment in the context of their other comorbidities.

Used in this way, these models might enable more individualised discussions about prognosis before treatment and in those who have completed treatment, and enhance the process of informed consent.[9] Used in isolation, the new models may complicate an already difficult decision about the best treatment option. As with all risk models, development and validation is only the first step in implementation,[10] and research is now needed to assess the clinical value of these models to patients and their doctors.

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Incretin based treatments and mortality in patients with type 2 diabetes

Liu J, Li L, Deng K, et al

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Find this at: http://dx.doi.org/10.1136/bmj.j2499

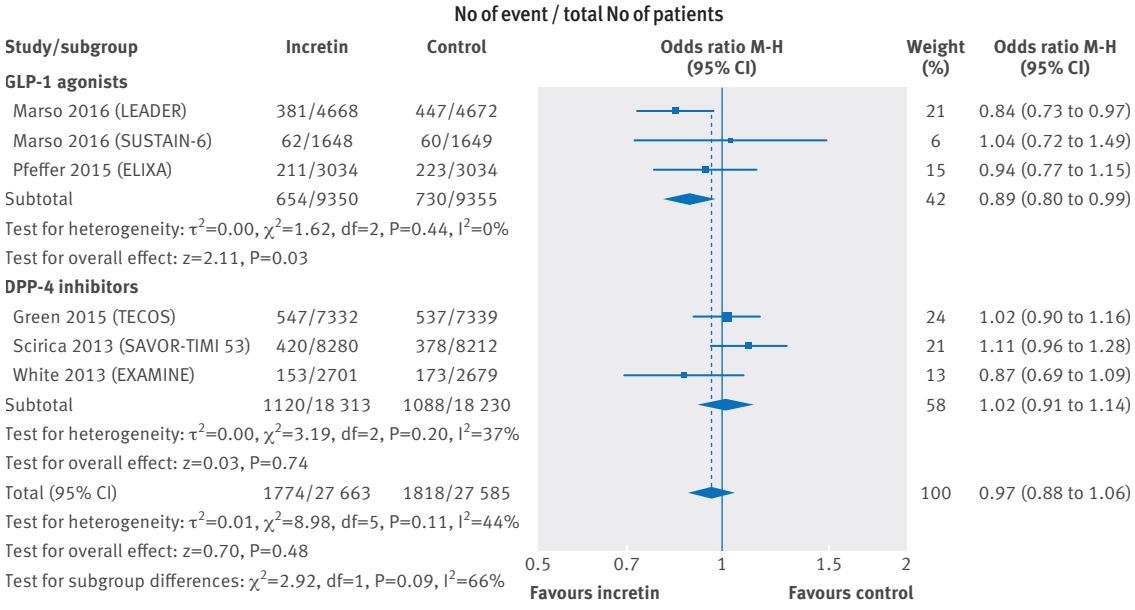
Study question Does treatment with incretin based drugs increase all cause mortality in patients with type 2 diabetes?

Methods Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched for randomised controlled trials that compared glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors with placebo or active antidiabetic drugs in patients with type 2 diabetes and explicitly reported data on mortality. Peto's method was used as the primary approach to pool effect estimates from trials, and random-effect meta-regression analyses for six prespecified hypotheses were applied to explore heterogeneity. Sensitivity analyses using alternative statistical approaches were conducted, and quality of evidence was assessed by the GRADE approach.

Study answer and limitations In total, 189 trials were eligible, 77 of which reported no events (deaths). Meta-analysis of all trials showed no difference in all cause mortality between incretin based treatment versus control (1925/84 136 *v* 1963/67 478; odds ratio 0.96, 95% confidence interval 0.90 to 1.02, I^2=0%; risk difference in events 3 fewer (95% confidence interval 7 fewer to 1 more) per 1000 patients with type 2 diabetes over five years; moderate quality evidence). Results suggested the possibility of a mortality benefit with GLP-1 agonists but not DPP-4 inhibitors, but the subgroup hypothesis had low credibility. Sensitivity analyses showed no important differences in the estimates of effects. The findings might be limited with selectively reporting of data regarding death, relatively short follow-up in included studies, and the lack of direct comparisons between GLP-1 agonists and DPP-4 inhibitors.

What this study adds The current evidence does not support the hypothesis that incretin based treatment increases all cause mortality in patients with type 2 diabetes. Further studies are warranted to examine if the effect differs between GLP-1 agonists versus DPP-4 inhibitors.

Funding, competing interests, data sharing The National Natural Science Foundation of China, "Thousand Youth Talents Plan" of China and Sichuan Province, and Young Investigator Award of Sichuan University funded the study. There are no competing interests, and no additional data are available.



All cause mortality in patients with type 2 diabetes receiving incretin based treatment versus placebo in large cardiovascular outcomes trials

GRADE evidence profile of incretin based treatment and all cause mortality in randomised controlled trials in patients with type 2 diabetes

	Study event rates			Anticipated absolute effects (5 year time frame)		
No of participants (studies), follow-up	With control	With incretin	Odds ratio (95% CI)	Risk with control	Risk difference with incretin (95% CI)	Quality of evidence
151 614 (189), 12-234 weeks	1963/67 478 (2.9%)	1925/84 136 (2.3%)	0.96 (0.90 to 1.02)	71/1000	3 fewer (7 fewer to 1 more)	Moderate