RESEARCH

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ISM/SPL

WHAT OUR READERS ARE SAYING

Association of systolic and diastolic blood pressure and all cause mortality in people with newly diagnosed type 2 diabetes

ALAMY

In this retrospective cohort study (p 18), blood pressure below 130/80 mm Hg was not associated with reduced risk of all cause mortality in patients with newly diagnosed diabetes, with or without known cardiovascular disease. Low blood pressure, particularly below 110/75 mm Hg, was associated with an increased risk for poor outcomes. The approach "the lower the better" might not apply to blood pressure control beyond a critical level in high risk patients, say the authors.

A rapid respondent is enthusiastic: "It is refreshing to read an article highlighting the risks of tighter blood pressure control in diabetic patients. But we have to remember that it is a retrospective study, so we don't know when a patient's glycaemic index breached the diabetes threshold and when patients were diagnosed. Furthermore, who measured patients' blood pressures and by what method? The question remains whether retrospective analysis of data is the best method to investigate such associations. Maybe this has made a good case for using a prospective study to look further into this topic."

Suicides associated with the 2008-10 economic recession in England

According to this time trend analysis (*BMJ* 2012;345:e5142) published on 14 August, the financial crisis that started in 2008 has been associated with about 1000 excess suicides in England. A rapid respondent said:

"The debt behind household disposable income troughed in 1998 and then increased at a historically unprecedented rate until the crisis of 2008. Data from the Office for National Statistics show that suicides peaked in 1998. They troughed in 2008. In other words there is a reciprocal relationship between the two. Any thoughts on the part of psychiatrists that the corner had been turned in suicide rates in the noughties now seems misplaced. It may well be that the boom artificially reduced the suicide figures, which are now returning to a longer trend. During the bubble more people commit more and more financially; it's only when the bubble bursts that the economic reckoning is had. Unemployment clearly is an important factor in this, but there are other considerations in the current economic climate that leave larger parts of the population vulnerable. The only policy decision I would suggest is we have no more credit booms. No doubt we will learn this until the next time."

RESEARCH ONLINE:

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Risks of harms when using antifibrinolytics in cardiac surgery

Results from network meta-analyses of randomised and observational studies imply that concerns about the safety of aprotinin use in patients undergoing cardiac surgery still remain. Tranexamic and epsilon-aminocaproic acid are effective alternatives that may be safer for patients, say the authors.

Effect of tranexamic acid on mortality in patients with traumatic bleeding

According to this prespecified analysis of data from the international multicentre randomised controlled trial (the CRASH-2 trial), tranexamic acid can be administered safely to a wide spectrum of patients with traumatic bleeding and should not be restricted to the most severely injured patients. The authors qualify this finding, however, by reminding us that absence of evidence of heterogeneity by baseline risk of death should not be taken as evidence of absence. In the lowest risk group the precision of the estimated effect is low, and there remains some uncertainty, they say.

SPL

The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison in a systematic review

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- News: Primary care trusts reverse advice to ophthalmologists to use cheaper drug for wet age related macular degeneration (*BMJ* 2012;345:e5161)
- Feature: Why using Avastin for eye disease is so difficult (*BMJ* 2012;344:e3012)
- Analysis: Implications of "not me" drugs for health systems: lessons from age related macular degeneration (*BMJ* 2012;344:e2941)

STUDY QUESTION What is the relative effectiveness of ranibizumab compared with bevacizumab for the treatment of diabetic macular oedema?

SUMMARY ANSWER Results indicate no difference in relative effectiveness between bevacizumab and ranibizumab, but wide credible intervals (Bayesian probability intervals) cannot exclude the possibility that either drug might be superior.

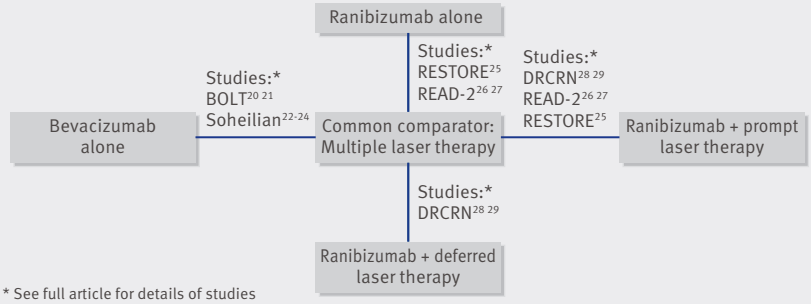
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Ranibizumab and bevacizumab have been shown to be effective in treating diabetic macular oedema, but no direct, head to head trials have been published. Through indirect comparison, no evidence to suggest a difference in effectiveness between bevacizumab and ranibizumab was found, but wide credible intervals cannot exclude a greater improvement, or worse outcome, for either drug.

Selection criteria for studies

Studies eligible for inclusion in this indirect comparison were randomised trials evaluating ranibizumab or bevacizumab for treatment of diabetic macular oedema if they had a common comparator and sufficient methodological similarity. Databases searched included Medline (1996–September 2011), Embase (1996–September 2011), the Cochrane Central Register of Controlled Trials (Issue 4, 2011), and selected meeting abstracts.

Network diagram of different studies of ranibizumab or bevacizumab with common comparator



* See full article for details of studies

Primary outcome(s)

The primary outcome measures were proportions of patients with an improvement in best corrected visual acuity of more than two lines on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, mean change in best corrected visual acuity, and mean change in central macular thickness.

Main results and role of chance

Five randomised controlled trials with follow-up of 6–12 months and a common comparator (multiple laser treatment) were sufficiently similar to be included in the indirect comparison. The proportion of patients with an improvement of more than two lines on the ETDRS scale was 21/77 participants (27%) for bevacizumab and 60/152 participants (39%) for ranibizumab (odds ratio 0.95 (95% credible interval 0.23 to 4.32)). However, the wide credible intervals cannot exclude a greater improvement, or worse outcome, for either drug. The mean change in best corrected visual acuity non-significantly favoured bevacizumab (treatment effect −0.08 logMAR units (−0.19 to 0.04)). The difference in mean change in central macular thickness was not statistically significant between ranibizumab and bevacizumab, but wide credible intervals cannot exclude the possibility that one drug is superior (treatment effect −6.9 μm (−88.5 to 65.4)).

Bias, confounding, and other reasons for caution

A lack of evidence resulted in wide credible intervals and low precision. Therefore, although results indicate no significant difference, the possibility that one drug is superior cannot be excluded. There were differences between study populations, but these were judged to be sufficiently homogeneous for indirect comparison. Indirect comparison methodology can be subject to several levels of uncertainty. We need a head to head trial of ranibizumab and bevacizumab in diabetic macular oedema.

Study funding/potential competing interests:

No funding. JAF, DS, PR, and NW have undertaken an Evidence Review Group report for the National Institute for Health and Clinical Excellence (NICE) on ranibizumab for diabetic macular oedema.

Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study

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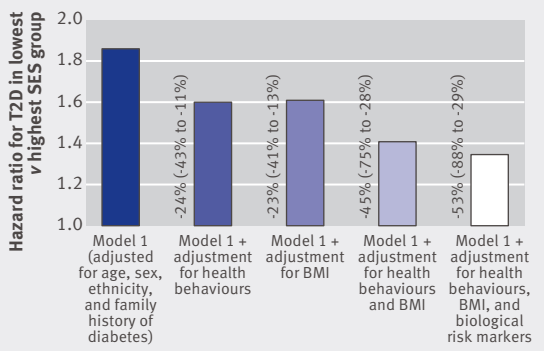
STUDY QUESTION In English civil servants, how much do modifiable risk factors contribute to social inequalities in type 2 diabetes?

SUMMARY ANSWER Health behaviours and obesity contribute to a large proportion of social inequalities in incidence of type 2 diabetes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Differences in lifestyle related risk factors may be partly responsible for the higher incidence of type 2 diabetes in the most disadvantaged socioeconomic groups, but previous studies have offered only a one-off measurement of these factors. Health behaviours and body mass index, when assessed repeatedly over time, explained almost half of the association between socioeconomic status and incidence of type 2 diabetes.

Contribution of long term exposure to modifiable risk factors to social inequalities in incidence of type 2 diabetes



BMI=body mass index; SES=socioeconomic status

Participants and setting

Participants were 7237 adults without diabetes (mean age 49.4 years, 2196 women) from the Whitehall II study.

Design, size, and duration

This was a prospective cohort study with risk factors measured four times and diabetes status assessed seven times over the follow-up. Baseline screening was in 1991-93 and the last follow-up in 2007-09. We repeatedly assessed health behaviours (smoking, alcohol consumption, diet, and physical activity), body mass index, and biological risk markers (systolic blood pressure, triglycerides, and high density lipoprotein cholesterol).

Main results and the role of chance

Over a mean follow-up of 14.2 years, 818 incident diabetes cases were identified. Participants in the lowest occupational category had a 1.86-fold (hazard ratio 1.86, 95% confidence interval 1.48 to 2.32) greater risk of developing diabetes relative to those in the highest category. Health behaviours and body mass index explained 33% (−1% to 78%) of this socioeconomic differential when risk factors were assessed at study baseline (attenuation of hazard ratio from 1.86 to 1.51), 36% (22% to 66%) when they were assessed repeatedly over the follow-up (attenuated hazard ratio 1.48), and 45% (28% to 75%) when we accounted for long term exposure over the follow-up (attenuated hazard ratio 1.41). With additional adjustment for biological risk markers, a total of 53% (29% to 88%) of the socioeconomic differential was explained (hazard ratio 1.35, 1.05 to 1.72).

Bias, confounding, and other reasons for caution

Despite a high response to the survey at the successive data collection phases, loss to follow-up accumulated over the extended time period. We used an imputation procedure to replace missing values for the risk factors considered. Our sensitivity analyses showed that results from analyses using complete case data differed little from those using imputed data.

Generalisability to other populations

As the findings were from an occupational cohort, they may not fully apply to the general population, which also includes people not in paid employment.

Study funding/potential competing interests

The study was funded by the British Medical Research Council; the British Heart Foundation; the British Health and Safety Executive; the British Department of Health; the US National Heart, Lung, and Blood Institute; and the US National Institute on Aging.

Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22 844 patient years of follow-up from randomised trials

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Listen to a podcast interview with Sripal Bangalore, the author of this research paper on drug eluting stents in patients with diabetes, at bmj.com/multimedia

Clinical review: Anticipating and managing bleeding complications in patients with coronary stents who are receiving dual antiplatelet treatment (*BMJ* 2011;343:d4264)

STUDY QUESTION What is the efficacy and safety of currently used drug eluting stents compared with each other and compared with bare metal stents in patients with diabetes?

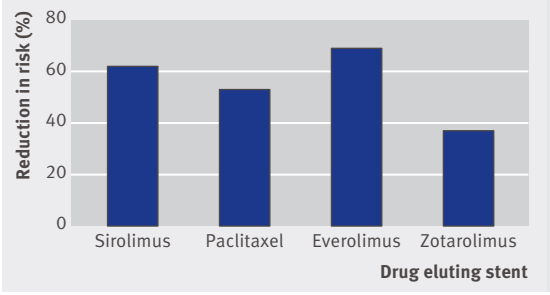
SUMMARY ANSWER Among patients with diabetes treated with coronary stents all currently available drug eluting stents were efficacious without compromising safety compared with bare metal stents. There were relative differences among the drug eluting stents, such that the everolimus eluting stent was the most efficacious and safe.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The long term efficacy and safety of various drug eluting and bare metal stents in patients with diabetes is controversial, with various reports of superiority of paclitaxel eluting stents, sirolimus eluting stents, or everolimus eluting stents. This mixed treatment comparison meta-analysis showed that, compared with bare metal stents, currently available drug eluting stents were efficacious without compromising safety. Everolimus eluting stents were the most efficacious and safe stents in patients with diabetes

Selection criteria for studies

We searched PubMed, Embase, and CENTRAL up to April 2012 for randomised clinical trials of four durable polymer drug eluting stents (sirolimus eluting stents, paclitaxel eluting stents, everolimus eluting stents, and zotarolimus eluting stents) compared with each other or with bare metal stents for the treatment of de novo coronary lesions and enrolling at least 50 patients with diabetes.

Reduction in risk of target vessel revascularisation with drug eluting stents compared with bare metal stents in patients with diabetes



Primary outcomes

Efficacy (target vessel revascularisation) and safety (death, myocardial infarction, stent thrombosis).

Main results and role of chance

From 42 trials with 22 844 patient years of follow-up, when compared with bare metal stents (reference rate ratio 1), all of the currently used drug eluting stents were associated with a significant reduction in target vessel revascularisation (37% to 69%), though the efficacy varied with the type of stent (everolimus eluting stents were similar to sirolimus eluting stents, which were more efficacious than paclitaxel eluting stents, which were similar to zotarolimus eluting stents, which were more efficacious than bare metal stents). There was about an 87% probability that everolimus eluting stents were the most efficacious compared with all others, though there were limited usable data for the zotarolimus eluting Resolute stent in patients with diabetes. The median target vessel revascularisation rate with bare metal stents was 109.40 per 1000 patient years of follow-up, and the rate with the most efficacious drug eluting stent (everolimus eluting stent) was 34.55 per 1000 patient years. Moreover, there was no increased risk of any safety outcome (including very late stent thrombosis) with any drug eluting stents compared with bare metal stents. There was about a 62% probability that the everolimus eluting stent was the safest stent for the outcome of "any" stent thrombosis. For all of the above analyses, sensitivity analyses in trials in which patients had used clopidogrel for more than six months; in trials at low risk of bias; in trials after exclusion of acute coronary syndrome trials; and in the direct comparison meta-analysis yielded largely consistent results.

Bias, confounding, and other reasons for caution

As in other meta-analyses, though we undertook detailed sensitivity analyses on many variables, we could have missed clinically relevant differences because of the heterogeneity of the study protocols. Such differences would best be assessed in a meta-analysis of individual patient data.

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. SB is on the advisory boards of Boehringer Ingelheim and Daiichi Sankyo and DEC was prinicpal investigator on the Medtronic EDUCATE trial.

Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial

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STUDY QUESTION Does a low glycaemic index diet in pregnancy reduce the recurrence of fetal macrosomia in pregnant women without diabetes?

SUMMARY ANSWER A low glycaemic index diet in pregnancy had no effect on infants' birth weight, but it did have a significant positive effect on gestational weight gain and on maternal glucose intolerance.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Fetal macrosomia is associated with significant maternal and neonatal morbidity and confers an elevated risk of childhood obesity. A low glycaemic index diet in pregnancy had no effect on infants' birth weight in a group at risk of fetal macrosomia, but it reduced gestational weight gain and maternal glucose intolerance.

Design

This was a randomised controlled trial in which the control arm received routine antenatal care and women randomised to the intervention group started a eucaloric low glycaemic index diet from early pregnancy after a single dietary education session.

Participants and setting

All secundigravid women who had previously delivered a macrosomic infant weighing greater than 4 kg were identified on first contact with the hospital and recruited at first antenatal consultation. Of 909 assessed for eligibility, 800 were randomised. Exclusion criteria included any underlying medical disorders, including a previous history of gestational diabetes, and use of any drugs.

Primary outcome(s)

The primary outcome measure was difference in birth weight. The secondary outcome measure was difference in gestational weight gain.

Main results and the role of chance

We found no significant difference between the two groups in absolute birth weight, birthweight centile, or ponderal index. Significantly less gestational weight gain occurred in women in the intervention arm (12.2 *v* 13.7 kg; mean difference −1.3, 95% confidence interval −2.4 to −0.2; P=0.01). We also found a lower rate of glucose intolerance in the intervention arm: 21% compared with 28% of controls had a fasting glucose of 5.1 mmol/L or greater or a one hour glucose challenge test of greater than 7.8 mmol/L (P=0.02).

Harms

We identified no adverse outcomes associated with the use of a low glycaemic index diet in pregnancy.

Bias, confounding, and other reasons for caution

A blinded randomised trial of a dietary intervention is not possible. Our results, therefore, may have been subject to the limitations of the Hawthorne effect. Nonetheless, the finding of a significant difference between the two groups in terms of gestational weight gain and glucose intolerance would suggest that any potential Hawthorne effect was small.

Generalisability to other populations

The use of a low glycaemic index diet in pregnancy is a simple, safe, and effective measure to improve maternal glucose homoeostasis and to reduce gestational weight gain.

Study funding/potential competing interests

This trial was funded by the Health Research Board of Ireland, with additional financial support from the National Maternity Hospital Medical Fund.

Trial registration number

Controlled Clinical Trials ISRCTN54392969.

Comparison of infant, fetal, and maternal outcomes between intervention and control groups. Values are mean (SD) unless stated otherwise

Outcome	Intervention group (n=372)	Control group (n=387)	Mean difference (95% CI)	P value
Birth weight (g)	4034 (510)	4006 (497)	28.6 (−45.6 to 102.8)	0.449
Birthweight centile	70.5 (25.6)	72.8 (25.6)	−1.6 (−5.39 to 2.2)	0.409
Birthweight difference* from first pregnancy (g)	−214.2 (541)	−250.8 (512)	−36.6 (−120.15 to 46.95)	0.507
Estimated fetal weight at 34 weeks (g)	2631 (326)	2616 (368)	14.74 (−40.89 to 70.38)	0.603
Fetal anterior abdominal wall width at 34 weeks (mm)	5.0 (1.3)	5.1 (1.2)	−0.108 (−0.323 to 0.107)	0.323
Glucose challenge test at 28 weeks (mmol/L)	6.47 (1.4)	6.67 (1.7)	−0.205 (−0.44 to 0.031)	0.088
Cord blood glucose (mmol/L)	4.17 (1.1)	4.16 (1.2)	0.014 (−0.19 to 0.217)	0.896
Weight gain at 24 weeks (kg)	5.3 (2.7)	5.5 (2.7)	−0.244 (−0.786 to 0.299)	0.378
Weight gain at 28 weeks (kg)	7.1 (2.8)	7.7 (3.0)	−0.593 (−1.072 to −0.114)	0.015
Weight gain at 34 weeks (kg)	10.1 (3.7)	10.9 (3.9)	−0.83 (−1.48 to −0.182)	0.012
Weight gain at 40 weeks (kg)	12.2 (4.4)	13.7 (4.9)	−1.346 (−2.451 to −0.241)	0.017
Glucose challenge test >7.8 mmol/L	54/350 (15)	79/371 (21)	—	0.04
28 week fasting glucose ≥5.1 mmol/L or glucose challenge test >7.8 mmol/L	67/320 (21)	100/352 (28)	—	0.02

*Birth weight in second pregnancy minus birth weight in first pregnancy.

Association of systolic and diastolic blood pressure and all cause mortality in people with newly diagnosed type 2 diabetes: retrospective cohort study

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STUDY QUESTION

Does aggressive control of blood pressure harm rather than protect patients at high risk of cardiovascular disease?

SUMMARY ANSWER

In patients with newly diagnosed diabetes, with or without known cardiovascular disease, blood pressure below 130/80 mm Hg was not associated with a reduced risk of all cause mortality; low blood pressure (particularly <110/75 mm Hg) was associated with poor outcomes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

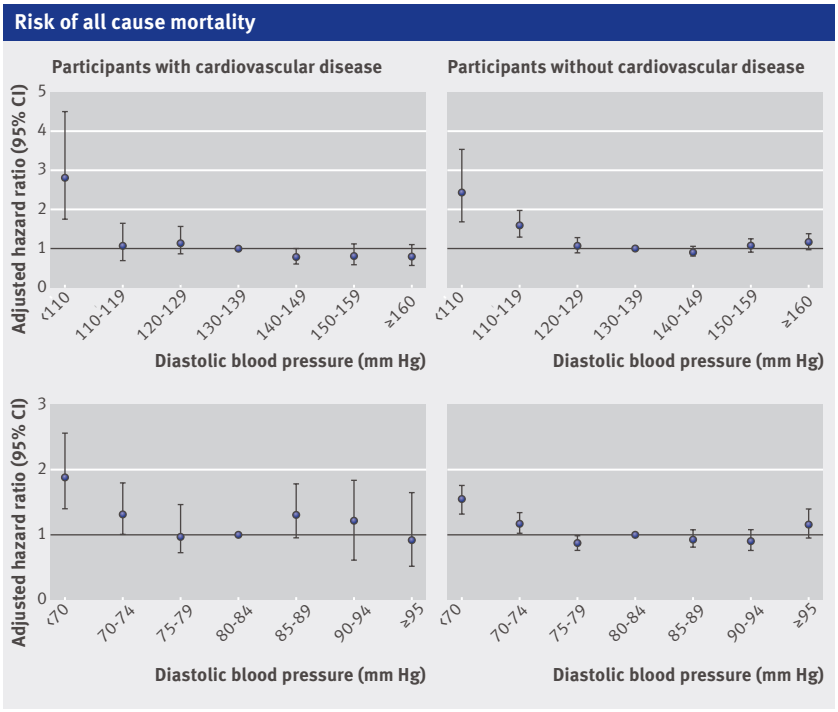
Guidelines recommend that patients at high risk of cardiovascular disease should maintain blood pressure below 130/85 mm Hg. The "lower the better" approach might not apply to blood pressure control beyond a critical level in high risk patients.

Participants and setting

We obtained data from the United Kingdom General Practice Research Database between 1990 and 2005, for 126 092 adult patients (≥18 years old) with a new diagnosis of type 2 diabetes and who had been registered with participating practices for at least 12 months.

Design

Retrospective cohort study.



Primary outcome(s)

Risk of all cause mortality.

Main results and the role of chance

Before diagnosis, 12 379 (9.8%) patients had established cardiovascular disease (myocardial infarction or stroke). During a median follow-up of 3.5 years, 25 495 (20.2%) deaths were recorded. In people with cardiovascular disease, tight controls for systolic (<130 mm Hg) and diastolic (<80 mm Hg) blood pressure were not associated with improved survival after adjustment for baseline characteristics (age at diagnosis, sex, practice level clustering, deprivation score, body mass index, smoking, HbA_{1c} and cholesterol levels, and blood pressure). Furthermore, low blood pressure was associated with an increased risk of all cause mortality. Compared with patients who received usual control of systolic blood pressure (130-139 mm Hg), the hazard ratio of all cause mortality was 2.79 (95% confidence interval 1.74 to 4.48, P<0.001) for systolic blood pressure at 110 mm Hg. Compared with patients who received usual control of diastolic blood pressure (80-84 mm Hg), the hazard ratios were 1.32 (1.02 to 1.78, P=0.04) for diastolic blood pressure at 70-74 mm Hg, and 1.89 (1.40 to 2.56, P<0.001) for diastolic blood pressure lower than 70 mm Hg. We found similar associations in patients without cardiovascular disease.

Bias, confounding, and other reasons for caution

Because of the observational nature of this study, our findings of increased risk of death related to tight control of systolic and diastolic blood pressure do not imply causality. Comorbid conditions were inconsistently coded in the database, particularly in the early part of the study period; therefore, we were unable to adjust for underlying comorbid conditions including microvascular complications. However, we adjusted for other indicators of health, including socioeconomic status.

Generalisability to other populations

The General Practice Research Database has been used extensively for health service and epidemiological research, and is one of the main data sources for research into UK primary care.

Study funding/potential competing interests

This study received funding from the European Community Seventh Framework Programme (grant agreement 277047). CM is funded by the Higher Education Funding Council for England and the National Institute for Health Research. EV and MH are partly funded by the National Institute for Health Research.

Prediction models for risk of developing type 2 diabetes: systematic literature search and independent external validation study

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STUDY QUESTION

Are existing models for predicting the risk of type 2 diabetes valid tools to identify people at high risk and do they sufficiently quantify the risk?

SUMMARY ANSWER

Most existing prediction models perform well to identify those at high risk of type 2 diabetes but cannot sufficiently quantify risk of future diabetes. Use of such models needs to be further investigated in clinical and public health practice.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Although the importance of external validation of prediction models is now widely acknowledged, only a quarter of existing prediction models for future type 2 diabetes have been externally validated. An evaluation and comparison of the performance of 25 prediction models, identified through a systematic literature search, in an independent Dutch cohort with over 10 years of follow-up showed that they can identify people at high risk of developing diabetes and those that include biomarkers perform slightly better. Most models overestimated the actual risk of diabetes.

Selection criteria for studies

We performed systematic search of published English, German, and Dutch literature in PubMed until February 2011 to identify prediction models for diabetes. We applied identified models to the Dutch cohort of the European Prospective Investigation into Cancer and Nutrition cohort study (EPIC-NL). We included 38 379 participants (aged 20-70), with a case cohort study in a random subcohort of 2506 individuals.

External validation and comparison of prediction models for medium term (5-10 year) risk of future type 2 diabetes

Performance of model	Measure/ assessment	Findings	Interpretation
Discrimination	C statistic	Basic models: 74-84% correctly classified; extended models: 81-93% correctly classified	Good discrimination between individuals with and without diabetes
Calibration	Hosmer-Lemeshow x^2; observed to expected ratio; calibration slope; calibration plot	Predictions deviate significantly from observed outcomes	Adjustment necessary to quantify actual risk of future diabetes

Primary outcome

The outcome was incident type 2 diabetes, with 924 cases in the full EPIC-NL cohort (79 in the random subcohort) during a median follow-up of 10.2 years.

Main results and role of chance

Of 7756 possible citations, we identified 16 studies containing a total of 25 prediction models. We considered 12 models as basic because they used variables that can be assessed non-invasively and 13 models as extended because they additionally included conventional biomarkers such as glucose concentration. In our population, the C statistics (95% confidence interval) for the basic models ranged from 0.74 (0.73 to 0.75) to 0.84 (0.82 to 0.85) for risk at 7.5 years. For prediction models including biomarkers C statistics ranged from 0.81 (0.80 to 0.83) to 0.93 (0.92 to 0.94). Most prediction models overestimated the observed risk of diabetes, particularly at higher observed risks. After adjustment for differences in incidence of diabetes, calibration improved considerably.

Bias, confounding, and other reasons for caution

Our review was limited by the published reports. In addition, validation of a large number of prediction models for type 2 diabetes requires an extensive dataset with many different variables, including different definitions for one variable. Although the EPIC-NL cohort is a comprehensive cohort with most information readily available, we had to make assumptions for certain variables. This could have influenced our results, particularly for calibration.

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