RESEARCH

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WHAT OUR READERS ARE SAYING

The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes

JEFF PACHOUD/AFP/GETTY IMAGES

This study was published on bmj.com on 31 May but continues to stimulate discussion. Here's what the two most recent rapid respondents say:

"The assertion that . . . 'the benefit of pioglitazone in reducing cardiovascular events is questionable' is wrong and entirely undermines the conclusion that prescribers can legitimately question the risk:benefit ratio of pioglitazone . . . The evidence of a link between pioglitazone and bladder cancer is feeble, whereas the evidence for cardiovascular benefits for pioglitazone is overwhelming and far greater than that for all other medications used in diabetes, most of which have no evidence of cardiovascular benefit."

"The problem with the observational study of Azoulay and colleagues, as with all the observational studies regarding pioglitazone and bladder cancer, is that patients who were prescribed pioglitazone were prescribed this medication for a reason, and this makes these patients different from those who were not. For example, as stated by Azoulay and colleagues, 'Participants prescribed thiazolidinediones were more likely to be obese, to have ever smoked, and to have uncontrolled diabetes than those who never used any thiazolidinedione.' In their study, three factors that on their own might lead to increased bladder cancer were increased among pioglitazone users, removing the validity of proposing a link to pioglitazone itself."

Let us know what you think by submitting your own response

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Cutaneous melanoma attributable to sunbed use
According to this meta-analysis of 27 observational studies, sunbed use is associated with a significant increase in risk of melanoma. This risk increases with number of sunbed sessions and with initial usage at age 35 or younger. The adverse effects of sunbed use are substantial and could be avoided by strict regulations, say the authors.

Physiotherapy intervention in Parkinson's disease
According to this meta-analysis of 29 trials, physiotherapy has short term benefits in Parkinson's disease. A wide range of physiotherapy techniques are currently used to treat Parkinson's disease, with little difference in treatment effects. Large, well designed, randomised controlled trials with improved methods and reporting are needed to assess the efficacy and cost effectiveness of physiotherapy for treating Parkinson's disease in the longer term, say the authors.

Risk of fracture after bariatric surgery in the United Kingdom
According to this cohort study, bariatric surgery does not have a significant effect on the risk of fracture. For the first few years after surgery, these results are reassuring for patients having such operations, but they do not exclude a more protracted adverse influence on skeletal health in the longer term, say the authors.

Integration of balance and strength training into daily life activity to reduce rate of falls in older people (the LiFE study): randomised parallel trial

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EDITORIAL by Morris

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STUDY QUESTION Is a lifestyle integrated approach to balance and strength training effective in reducing the rate of falls in older people?

SUMMARY ANSWER The Lifestyle integrated Functional Exercise (LiFE), a tailored programme taught over five home visits with two booster visits, showed a 31% reduction in the rate of falls in older people.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The LiFE programme provides an alternative to traditional exercise. Functional based exercise should be a focus for interventions to protect older people at risk from falling.

Design

We did a three arm, randomised parallel trial, with assessments measured at baseline, six months, and 12 months after randomisation. Participants were allocated to one of three home taught interventions: the Lifestyle integrated Functional Exercise (LiFE) approach (n=107; balance and strength training and integrated activities into everyday activities), a structured programme (n=105; exercises for balance and lower limb strength, done three times a week), and a sham control programme (n=105; gentle exercise). Randomisation was done by using a computer generated random blocks, stratified by sex and fall history and concealed by an independent secure website.

Participants and setting

People aged 70 years or older who had two or more falls or one injurious fall in the past 12 months, living in the metropolitan area of Sydney, Australia.

Effect of interventions versus control intervention over time, for specific secondary outcomes

Tandem walk time(s) plus error				
F(4,442)=5.10; P=0.001;n=71, 75, 78	F(2,294)=6.6; P=0.002	0.42	F(2,302)=8.9; P<0.001	0.49
Eight level balance hierarchy scale				
n=76, 76, 82	Odds ratio 1.15 (95% CI 0.58 to 1.72); Wald 15.6; P<0.001	0.63	Not significant (P=0.08)	0.29
Right ankle strength (mean kg force)				
F(3.8,399)=2.66; P=0.035; n=68, 71, 75	F(2,282)=5.5; P=0.005	0.40	Not significant (P=0.10)	0.26
Late Life Disability Index (frequency)				
F(2,236)=4.66; P=0.01; n=78, 80, 81	F(1,157)=9.28; P=0.003	0.49	Not significant (P=0.28)	0.17
Activities Specific Balance Confidence scale				
F(4,460)=3.75; P=0.005; n=75, 79, 79	F(2,304)=5.52; P=0.004	0.38	F(2,312)=5.22; P=0.006	0.37

Cohen effect size indicates clinical effectiveness.
*Main effect time×intervention; F(df,error)=measure of variation between groups divided by variation within groups; P.
†No of participants (LiFE, structured exercise, control).

Primary outcome(s)

The main outcome measure was the rate of falls collected by self report in daily calendars. Secondary measures were static and dynamic balance; ankle, knee, and hip strength; balance self efficacy; daily living activities; a measure of participation; habitual physical activity; quality of life status; energy expenditure; body mass index; and fat free mass.

Main results and the role of chance

We recruited 107 LiFE, 105 structured exercise, and 105 control participants. The overall incidence of falls in the LiFE programme was 1.66 per person years, compared with 1.90 in the structured programme and 2.28 in the control group. We saw a significant 31% reduction in the rate of falls for the LiFE group compared with the control group (incidence rate ratio 0.69 (95% confidence interval 0.48 to 0.99)). There was a non-significant reduction in the rate of falls for the structured group compared with the control group (0.81 (0.56 to 1.17)). Static balance on an eight level hierarchy scale, ankle strength, function, and participation were significantly better in the LiFE group than in controls. The LiFE and structure groups had a significant and moderate improvement in dynamic balance compared with controls.

Harms

One participant in the structured programme had a groin strain and surgery for an inguinal hernia and stopped the programme; one LiFE participant was diagnosed with a pelvic stress fracture and attributed this to increased walking and stair climbing, but continued on the programme.

Bias, confounding, and other reasons for caution

The higher confidence interval being close to 1 indicates some caution with interpretation of these results; however, the strong outcomes of the secondary measures point to clear mediators of benefit and confirm the positive fall outcome. We had a slightly lower sample size than preferred, which could lead to a type II error.

Generalisability to other populations

The sample recruited (mean age 83.4 years) was a high risk group, with 60% (n=191) reporting a history of recurrent falls and just over 90% (n=290) having had an injurious fall in the past year.

Study funding/potential competing interests

The trial was funded by a grant from the National Health and Medical Research Council. No other interests.

Trial registration number Australian New Zealand Clinical Trials Registry (ANZCTR) 120600002538.

Efficacy of psychosocial intervention in patients with mild Alzheimer's disease: the multicentre, rater blinded, randomised Danish Alzheimer Intervention Study (DAISY)

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STUDY QUESTION Can multifaceted and semi-tailored psychosocial counselling and support for patients with Alzheimer's disease and their care givers during the first year after diagnosis prevent the emergence of depressive symptoms and improve the quality of life of patients and their care givers and stabilise patients' cognitive function beyond that achieved with well structured support?

SUMMARY ANSWER No, the counselling and support programme did not have any additional significant effect on primary outcomes at 12 months after adjustment for multiple comparisons (though the unadjusted data showed a small effect for depressive symptoms).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Counselling and psychosocial interventions for care givers can have a positive effect on patients with moderate to severe Alzheimer´s disease as well the care givers. However, a semi-tailored programme of counselling, education, and support for patients with mild Alzheimer's disease and their care givers may not improve outcomes.

Design
In this multicentre, rater blinded, randomised controlled trial the intervention consisted of up to seven counselling sessions, five teaching courses, and additional interventions aimed at both the patient and care giver. For both groups, the raters who assessed the participants at six and 12 months provided information and guidance and could refer to local support programmes.

Participants and setting
We recruited 330 outpatients with mild Alzheimer's disease and their 330 primary care givers in five districts.

Primary outcome(s)
Primary outcomes at 12 months for patients were change from baseline in cognitive function (mini-mental state examination), depression (Cornell depression scale), and quality of life (proxy rated European quality of life visual analogue scale (EQ-VAS)). For care givers, outcomes were change from baseline in depression (geriatric depression scale) and quality of life (EQ-VAS).

Main results and the role of chance
Because of multiple testing, statistical significance was set at P<0.0005. At 12 months, there were no significant differences between the two groups in changes from baseline (table). However, a non-significant difference was observed for patients' depression in favour of the intervention before and after adjustment for attrition (P=0.0103 and P=0.0146, respectively).

Harms
We did not identify any significant harm.

Bias, confounding, and other reasons for caution
We included patients and care givers regardless of their expressed needs for intervention. This study was an exploratory trial. We operated with three primary outcomes for patients and two for care givers, which reduced the statistical power of the study.

Generalisability to other populations
Our exploratory trial may be generalised in other populations. However, we propose further research on interventions aimed specifically at patients and care givers with an expressed need for support and with an initial focus on depressive symptoms.

Study funding/potential competing interests
The study was supported by the National Board of Social Services at the Danish Ministry of Social Affairs, the Danish Ministry of Health, and the Danish Health Foundation.

Trial registration number ISRCTN74848736.

Longitudinal effect of intervention and control support for patients and their care givers at 12 months (intention to treat analyses)

	Observed scores			Mean change from baseline		
Primary outcomes	Intervention Mean (95% CI)	Control Mean (95% CI)	P value (*t* test)	Intervention Mean (95% CI)	Control Mean (95% CI)	P value (*t* test)
Patients						
Mini-mental state examination	22.5 (21.8 to 23.2)	22.3 (21.5 to 23.1)	0.7294	−1.55 (−2.19 to −0.91)	−1.80 (−2.56 to −1.04)	0.6502
Cornell depression scale	4.97 (4.20 to 5.74)	5.79 (4.86 to 6.71)	0.1611	−0.20 (−1.04 to 0.64)	1.38 (0.49 to 2.27)	0.0103
EQ-VAS quality of life	58.3 (54.8 to 61.7)	57.9 (54.0 to 61.8)	0.8798	−3.88 (−7.38 to −0.37)	−6.83 (−10.10 to −3.56)	0.2308
Care givers						
EQ-VAS quality of life	79.0 (76.0 to 81.9)	81.6 (78.8 to 84.5)	0.2034	−0.31 (−3.41 to 2.79)	0.20 (−2.31 to 2.71)	0.7799
Geriatric depression scale	5.70 (4.68 to 6.72)	4.97 (3.97 to 5.97)	0.3064	0.96 (0.05 to 1.86)	0.26 (−0.51 to 1.03)	0.2500

EQ-VAS=European quality of life visual analogue scale.

Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics

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EDITORIAL by Rosengren

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Research: Risk of cancer with metal-on-metal hip replacements (*BMJ* 2012;345:e4646)

STUDY QUESTION Are metal-on-metal hip replacements associated with an increased risk of cancer?

SUMMARY ANSWER Compared with both the general population and people with hip replacements with other bearing surfaces, there was no evidence that metal-on-metal hip replacements were associated with a higher risk of cancer in the first seven years after implantation.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Previous studies have shown that metal-on-metal hip replacements can result in metal debris being disseminated throughout the body, causing genotoxicity, but it is unclear if this leads to an increased incidence of cancer. This study shows no increase in the first seven years in either all cancers or specific cancers such as malignant melanoma and haematological, prostate, and renal tract cancers.

Participants and setting

Using a multivariable competing risks flexible parametric survival model we analysed data from all hip replacements recorded between April 2003 and December 2010 on the National Joint Registry of England and Wales that could be linked to hospital episodes statistics data (289 571 hip replacements).

Design, size, and duration

We compared the incidence rate of diagnoses of cancer between people receiving metal-on-metal hip replacements and both the general population and people with hip replacements with other bearing surfaces. Mean follow-up was three years, with 23% of people observed for five to eight years.

Adjusted incidence (% with 95% CI) of new diagnosis of cancer by type of bearing surface used in hip replacement for typical patient aged 60

	Year 1	Year 5
Men		
Resurfacing	0.8 (0.7 to 0.9)	4.8 (4.4 to 5.3)
Stemmed metal-on-metal	1.1 (1.0 to 1.2)	6.2 (5.7 to 6.7)
Other bearing surfaces	1.2 (1.1 to 1.2)	6.7 (6.5 to 7.0)
Women		
Resurfacing	0.5 (0.5 to 0.6)	3.1 (2.8 to 3.4)
Stemmed metal-on-metal	0.7 (0.6 to 0.7)	4.0 (3.7 to 4.3)
Other bearing surfaces	0.7 (0.7 to 0.8)	4.4 (4.2 to 4.5)

Main results and the role of chance

In this group of patients the annual incidence of cancer is around 1%, but metal-on-metal hip replacements were not associated with any increased risk when compared with other bearing surfaces. Nor were they associated with an increased risk of cancer compared with the general population. In all hip replacements the observed incidence of cancers was lower than expected in both men and women. In men the one year observed incidence of cancer was 1.15% (95% confidence interval 0.96% to 1.38%) after stemmed metal-on-metal versus an expected incidence of 1.45% (1.23% to 1.69%), 0.48% (0.37% to 0.62%) after resurfacing versus an expected incidence of 0.77% (0.63% to 0.94%), and 1.66% (1.57% to 1.76%) after replacement with other bearing surfaces versus an expected incidence of 2.13% (2.05% to 2.22%). In women the figures were 0.84% (0.68% to 1.05%) versus 1.22% (1.02% to 1.46%), 0.56% (0.40% to 0.78%) versus 0.73% (0.54% to 0.98%), and 1.15% (1.10% to 1.21%) versus 1.53% (1.47% to 1.59%), respectively.

Bias, confounding, and other reasons for caution

Many cancers have a long latency and thus might not be detected by a follow-up of this duration. Cancers that never require a hospital admission would not be recorded by hospital episode statistics. As patients are selected and not randomised to surgery, a "well patient" effect could account for the lower incidence of some cancers with resurfacing arthroplasty.

Generalisability to other populations

These data might not be generalisable to other populations with different cancer profiles and different indications for surgery.

Study funding/potential competing interests

This study was funded by the National Joint Registry of England and Wales. MP has received funding from DePuy for design of an implant.

Effect of communicating DNA based risk assessments for Crohn's disease on smoking cessation: randomised controlled trial

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STUDY QUESTION Does communicating the risk of developing Crohn's disease based on genotype compared with standard risk assessment motivate smoking cessation among smokers at familial risk?

SUMMARY ANSWER Feedback of DNA based risk assessments for Crohn's disease did not motivate smoking cessation any more or less than communication of standard, non-genetic risk assessment.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Expectations that risk information based on genetics will motivate changes in health behaviour (such as stopping smoking) are high, but current evidence is limited in quantity and quality. We found that communicating genetic risk information to change behaviour had no impact on stopping smoking to reduce the risk of Crohn's disease.

Design

A parallel group, cluster randomised controlled trial, using a computer generated blocked randomisation sequence, with 1:1 allocation of participants in family clusters to risk communication interventions based on either DNA results or non-DNA information (standard risk assessment). The interventions comprised communication of risk assessment for Crohn's disease by postal booklet based on a family history of Crohn's disease and smoking status alone or an additional DNA analysis for risk conferring genotype. Participants were then telephoned by a stop smoking counsellor to review the booklet and deliver a brief standard smoking cessation intervention. The research team collecting outcome data were blind to participants' study arm.

Primary and secondary outcomes by arm. Values are percentages (number with event/total number) of participants unless stated otherwise

Outcomes	DNA arm (n=251)	Non-DNA arm (n=246)	% difference in proportion (95% CI), P value
Primary outcome			
≥1 24 hour quit attempts, measured at six months	35 (73/209)	36 (78/217)	−1 (−10 to 8), 0.83
Secondary outcomes			
7 day abstinence:			
Measured at one week (self report)	11 (27/251)	8 (20/246)	3 (−3 to 8), 0.32
Measured at six months:			
Self report	17 (42/251)	20 (48/246)	−3 (−10 to 4), 0.42
Biochemical validation	4 (9/251)	5 (12/246)	−1 (−5 to 2), 0.47

Participants and setting

The context of the research was UK families with Crohn's disease. Participants were 497 smokers who were first degree relatives of probands with Crohn's disease (mean age 42.6 (SD 14.4) years). More than 95% were white and 59% were women.

Primary outcome

Smoking cessation for 24 hours or longer, assessed at six months.

Main results and the role of chance

The proportion of participants who stopped smoking for 24 hours or longer did not differ between DNA and non-DNA arms: 35% (73/209) versus 36% (78/217): difference −1%, 95% confidence interval −10% to 8% (P=0.83)

Harms

One participant in the DNA arm expressed health concerns attributed to study participation but was reassured and completed follow-up.

Bias, confounding, and other reasons for caution

The magnitude of risk communicated in the DNA arm was greater than that communicated in the non-DNA arm, although this might have been expected to increase the impact of information in the DNA arm. This trial also focused on people at relatively low risk and so was unable to assess the possible impact of genetic risk information of higher magnitudes. The primary endpoint was based on self reported smoking behaviour, although this was supported by a biochemically validated cessation outcome.

Generalisability to other populations

The communicated risks of Crohn's disease were in the range expected and observed for other common, complex conditions. This increases the possibility of the findings being generalisable to a wide range of conditions for which testing is now being offered.

Study funding/potential competing interests

This study was funded as part of a grant from the Medical Research Council, UK (G0500274). See full paper for funding sources. We have no competing interests.

Trial registration number

Current Controlled Trials ISRCTN21633644.

Effectiveness of provider incentives for anaemia reduction in rural China: a cluster randomised trial

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STUDY QUESTION What is the impact of providing information, subsidies, and financial incentives for anaemia reduction to Chinese primary school principals on student anaemia rates?

SUMMARY ANSWER Provider incentives for anaemia reduction were moderately effective in reducing anaemia rates among schoolchildren in rural China.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Rewarding health improvement without specifying how it should be achieved can strengthen creativity and innovation in service delivery. However, performance pay based directly on health outcomes in a developing country has not been tried or evaluated. Direct provider incentives for anaemia reduction were moderately effective in reducing anaemia among rural Chinese schoolchildren, but, interactions with other, pre-existing incentives led to substantially larger effects.

Design

Sample schools were randomly assigned to a control group with no intervention or to one of three intervention arms: (*a*) an "information arm," in which principals received information about anaemia; (*b*) a "subsidy arm," in which principals received information and unconditional subsidies; and (*c*) an "incentive arm," in which principals received information, subsidies, and financial incentives for reducing anaemia among students. We allocated 27 schools to the control group, 15 to the information arm, 15 to the subsidy arm, and 15 to the incentive arm. The randomisation procedure was repeated until balance was achieved in haemoglobin concentration across the four arms. Participants and enumerators were not explicitly informed of study arm allocation, but we cannot rule out that some became aware of it.

Participants and setting

The project was conducted in 72 randomly selected rural primary schools in northwest China. The participants were 3553 fourth and fifth grade students aged 9-11 years.

Effects of information, subsidies, and incentives for reducing anaemia

	Change in haemoglobin concentration (g/L)		Anaemic	
Trial arms compared	Difference (95% CI)	P value	Marginal effects (95% CI)	P value
Information *v* control	1.5 (−1.1 to 4.1)	0.245	−0.02 (−0.06 to 0.02)	0.364
Subsidy *v* control	0.8 (−1.8 to 3.3)	0.548	−0.03 (−0.07 to 0.02)	0.220
Incentive *v* control	2.4 (−0.0 to 4.9)	0.054	−0.05 (−0.09 to −0.01)	0.019
Subsidy *v* information	−0.8 (−3.7 to 2.2)	0.62	−0.01 (−0.05 to 0.04)	0.80
Incentive *v* information	0.9 (−2.0 to 3.8)	0.53	−0.03 (−0.07 to 0.02)	0.25
Incentive *v* subsidy	1.7 (−1.2 to 4.6)	0.26	−0.02(−0.06 to 0.02)	0.37

Effects estimated with multilevel mixed effect linear regression (for haemoglobin concentration) or logistic regression (for anaemia) with multivariable adjustment

Primary outcome(s)

The primary outcome measure was change in student haemoglobin concentrations between the baseline survey in October 2009 and the follow-up survey in May 2010.

Main results and the role of chance

Results were estimated using baseline adjusted and multivariable adjusted mixed linear models. Multivariable adjusted models show that mean student haemoglobin concentration rose by 1.5 g/L (95% CI −1.1 to 4.1, P=0.245) in information schools, 0.8 g/L (−1.8 to 3.3, P=0.548) in subsidy schools, and 2.4 g/L (0 to 4.9, P=0.054) in incentive schools compared with controls. This increase corresponded to a reduction in prevalence of anaemia (haemoglobin concentration <115 g/L) of 24% in incentive schools. Interactions with pre-existing incentives in some schools to achieve good academic performance led to much larger gains in the information and incentive arms: when combined with test score incentives, associated increases in student haemoglobin concentration were 9.8 g/L (4.1 to 15.5, P<0.01) larger in information schools and 8.6 g/L (2.1 to 15.1, P<0.01) larger in incentive schools.

Harms

No participant harm was reported.

Bias, confounding, and other reasons for caution

As in other studies, there is presumably error in our haemoglobin concentration measurement, but this should not be correlated with assignment to experimental arms. Our randomisation procedure was re-randomisation until balance was achieved in haemoglobin concentration across the four study arms. Our study was not powered ex ante to detect meaningful differences between intervention arms. Because the pre-existing incentives for academic performance were not randomly assigned, interactions with trial arms should be interpreted cautiously.

Generalisability to other populations

We selected study schools according to criteria set by China's government in its policy for consolidating rural schools. However, our results may not generalise to other Chinese schools or to other cultural and institutional settings—particularly where performance incentives are less common.

Study funding/potential competing interests

The project was funded by the International Initiative for Impact Evaluation (3IE), the Leibniz Institute of Agricultural Development in Central and Eastern Europe (IAMO), and Stanford University; with supplemental funding from Pfizer (see full article for details).

Trial registration number

ISRCTN76158086