Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion

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Study funding/competing interests
This study was supported by the Yale University Open Data Access project.

STUDY QUESTION Do published results of industry funded trials of recombinant human bone morphogenetic protein 2 (rhBMP-2) in spinal fusion match underlying trial data?

SUMMARY ANSWER Reporting of adverse event data in trial publications was so sparse and inconsistent that any systematic review based solely on publicly available data would not provide a proper evaluation of the safety of rhBMP-2.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Concern is increasing about non-reporting of clinical study outcomes and adverse events, particularly from industry funded studies. While access to individual participant data for research purposes remains the ideal, open access to summary data from internal industry reports should be more quickly and readily achievable.

Participants and setting
The manufacturer of rhBMP-2 (Medtronic; Minneapolis, MN) provided complete individual participant data for all their clinical studies of rhMBP-2 in patients undergoing spinal fusion surgery for treatment of degenerative disc disease, spondylolisthesis, or other relevant spinal conditions. They also provided relevant internal reports, protocols, and citation details. Separately, we identified journal publications and conference abstracts for this set of studies through comprehensive literature searches.

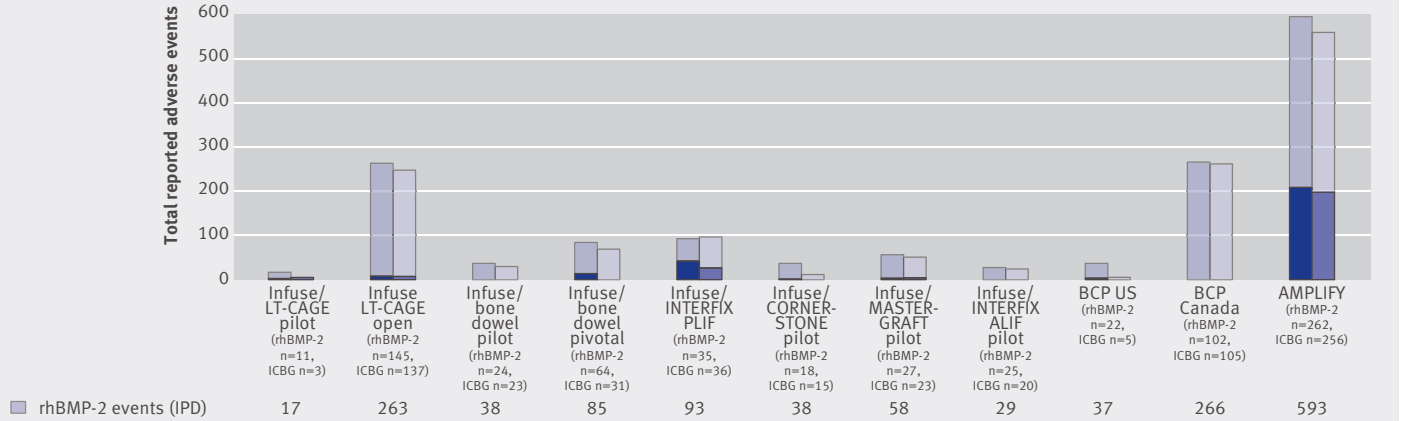
Design
We compared meta-analyses of three different data sources: confidential individual participant data, confidential internal industry reports, and publicly available journal publications and conference abstracts. We also compared the type and number of adverse events reported across sources.

Primary outcomes
Meta-analyses were performed for pain outcomes (Oswestry disability index, SF-36 physical component score, back pain, leg pain) and fusion success for all Medtronic randomised controlled trials comparing rhBMP-2 against iliac crest bone graft. All adverse events were included in the comparison.

Main results and the role of chance
10 of the 13 known randomised controlled trials and one of four known single arm studies have been published in a scientific journal. Extremely limited data for one further randomised controlled trial were available from conference abstracts. No abstract or journal article reported all of the clinical outcomes known to have been collected. Only 56% to 88% of known collected outcomes could be identified by combining all publications and abstracts for each trial. Results of meta-analyses from different sources were almost identical for pain and function outcomes and were not substantially changed by incorporating unpublished data. Far fewer total adverse events were reported across publications than were collected in the individual participant data. Around 18.5% of adverse events recorded in such data from randomised controlled trials have been reported in the entire published literature (19% of rhBMP-2 events, 18% of iliac crest bone graft events); this figure was 10.5% for randomised controlled trials of rhBMP-2 in its licensed preparation (12% rhBMP-2, 9% iliac crest bone graft).

Bias, confounding, and other reasons for caution
We cannot exclude the possibility of errors in the individual participant data; a "forensic" examination of data collection procedures was outside the aims and resources of this investigation.

Total number of adverse events reported in Medtronic randomised controlled trials comparing recombinant human bone morphogenetic protein 2 (rhBMP-2) with iliac crest bone graft (ICBG): individual participant data (IPD) versus publications



	Infuse/ LT-CAGE pilot (rhBMP-2 n=11, ICBG n=3)	Infuse LT-CAGE open (rhBMP-2 n=145, ICBG n=137)	Infuse/ bone dowel pilot (rhBMP-2 n=24, ICBG n=23)	Infuse/ bone dowel pivotal (rhBMP-2 n=64, ICBG n=31)	Infuse/ INTERFIX PLIF (rhBMP-2 n=35, ICBG n=36)	Infuse/ CORNER-STONE pilot (rhBMP-2 n=18, ICBG n=15)	Infuse/ MASTER-GRAFT pilot (rhBMP-2 n=27, ICBG n=23)	Infuse/ INTERFIX ALIF pilot (rhBMP-2 n=25, ICBG n=20)	BCP US (rhBMP-2 n=22, ICBG n=5)	BCP Canada (rhBMP-2 n=102, ICBG n=105)	AMPLIFY (rhBMP-2 n=262, ICBG n=256)
rhBMP-2 events (IPD)	17	263	38	85	93	38	58	29	37	266	593
ICBG events (IPD)	7	247	31	70	97	13	51	25	6	262	558
rhBMP-2 events (published)	3	9	0	14	43	2	4	0	4	0	209
ICBG events (published)	6	8	0	0	27	1	5	0	0	0	198

The effect of rising food prices on food consumption: systematic review with meta-regression

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- Analysis: Food policies for healthy populations and healthy economies (*BMJ* 2012;344:e2801)
- Analysis: Potential causes and health effects of rising global food prices (*BMJ* 2009;339:b2403)

STUDY QUESTION

How does the relation between food prices and the demand for food vary worldwide according to food type, country income level, and household income level?

SUMMARY ANSWER

The relation between food price and demand was strongest for animal source foods (meat, fish, and dairy) and weakest for cereals and fats. For all food groups, the relation was stronger in lower than in higher income countries and among poorer households within countries.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The relation between food price and demand varies according to the type of food and the income level of the country, but as yet there has been no worldwide summary of the relative strength of these relations. Combined worldwide evidence identifies that in all countries the relation between food price and demand is stronger for animal source foods than for cereals and fats, and stronger in low income than high income countries and among the poorest households within countries.

Selection criteria for studies

We systematically searched online databases of peer reviewed and grey literature, hand searched reference lists, and contacted authors. Cross sectional, cohort, experimental, and quasi-experimental studies with English abstracts were included. Eligible studies used nationally representative data from 1990 onwards derived from national aggregate data sources, household surveys, or supermarket/home scanners.

Primary outcome

The quantification of the relation between food price and food demand (own price food elasticities).

Main results and role of chance

We identified 136 studies reporting a total of 3495 own price food elasticities from 162 different countries. Price elasticities are coefficients that describe the percentage by which the demanded quantity of a food changes in response to a 1% increase in the price of the food. To investigate how these elasticities varied according to food groups and income levels we designed meta-regression models. The highest predicted price elasticities were for animal source foods (meat, fish, and dairy) and the lowest were for cereals and fats. For all food groups, the relation was stronger in lower income countries and among poorer households within countries. These results were adjusted for potential confounding factors such as study methods, whether the study was published in a peer reviewed journal, the type of data, and mean year of data. Based on our predicted price elasticities, a 10% increase in the global price of cereals would reduce demand for cereals by 6.1% in low income countries and 4.3% in high income countries, equivalent to 301 kJ (72 kcal) and 167 kJ (40 kcal) reductions on average in cereal availability per person per day in low and high income countries, respectively. Our analysis also suggests that poorer people in poor countries will be affected the most and highlights that higher food prices may substantially increase their risks of undernutrition.

Predicted mean (95% confidence interval) percentage change in food demand for 1% increase in food price by country wealth category*

Food groups	Low income† (n=1412)	High income† (n=1124)
Meat	−0.78 (−0.83 to −0.73)	−0.60 (−0.66 to −0.54)
Fish	−0.80 (−0.85 to −0.74)	−0.61 (−0.67 to −0.55)
Dairy	−0.78 (−0.84 to −0.73)	−0.60 (−0.66 to −0.54)
Cereals	−0.61 (−0.66 to −0.56)	−0.43 (−0.48 to −0.36)
Fats and oils	−0.60 (−0.65 to −0.54)	−0.42 (−0.48 to −0.35)

*Predictions based on random effects meta-regression model. Model covariates set to their mean for food elasticity prediction. Data year set to 2008.
†Gross National Income per capita of ≤$1025 ($1.00 (£0.65; €0.76) for low income and ≥$12 476 for high income countries. Data taken from World Bank database for 2011.

Bias, confounding, and other reasons for caution

Study inclusion criteria limited the years of data used (from 1990 onwards only), the acceptable analysis techniques (no single equation methods), and the food groups included (foods were aggregated into standard groups). Data were sparse for some world regions, particularly Australasia and South America. The relation between food price and demand was assumed to be linear.

Study funding/potential competing interests

This study was partly supported by the Leverhulme Centre for Integrative Research on Agriculture and Health. We have no competing interests.

Effect of home based HIV counselling and testing intervention in rural South Africa: cluster randomised trial

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- Research: Outreach education for integration of HIV/AIDS care, antiretroviral treatment, and tuberculosis care in primary care clinics in South Africa (*BMJ* 2011;342:d2022)
- Research: Impact of Stepping Stones on incidence of HIV and HSV-2 and sexual behaviour in rural South Africa (*BMJ* 2008;337:a506)

STUDY QUESTION

What effect does home based HIV counselling and testing have on the prevalence of HIV testing and reported behavioural changes in a rural subdistrict of South Africa?

SUMMARY ANSWER

Home based HIV counselling and testing increased the prevalence of HIV testing in a rural setting with high levels of stigma. Benefits also included a higher uptake of couple counselling and testing and reduced sexual risk behaviour.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Many countries are struggling to meet HIV prevention and treatment targets owing to low uptake of facility based HIV testing. Home based testing is being promoted in several quarters but without strong evidence of its effectiveness over standard testing. This study found high levels of acceptance of home based HIV testing with benefits beyond the actual testing, including lower sexual risk behaviour and more couple counselling and testing.

Design

In this cluster randomised controlled trial, lay counsellors conducted door to door outreach and offered home based HIV counselling and testing to all consenting adults and to adolescents aged 14-17 years with guardian consent. Control clusters received standard care which consisted of HIV counselling and testing services at local clinics.

Participants and setting

16 communities (clusters) in uMzimkhulu subdistrict, KwaZulu-Natal province, South Africa.

Primary outcome

Prevalence of testing for HIV.

Estimates of effect of home based HIV counselling and testing on prevalence of HIV testing

	No/No in group (%)		
Testing for HIV during study period	Intervention arm	Control arm	Prevalence ratio* (95% CI)
Overall	1392/2025 (69)	997/2129 (47)	1.54 (1.32 to 1.81)
Women	1162/1541 (75)	808/1551 (52)	1.51 (1.29 to 1.78)
Men	229/484 (47)	189/578 (32)	1.52 (1.19 to 1.95)
First ever HIV test	640/1391 (46)	373/997 (37)	1.20 (0.97 to 1.49)

Data were adjusted for clusters and households within clusters.
*Prevalence ratios for difference between intervention and control arms.

Main results and the role of chance

The prevalence of having an HIV test during the study period was 69% in the intervention arm versus 47% in the control arm (prevalence ratio 1.54, 95% confidence interval 1.32 to 1.81). More couples in the intervention arm had counselling and testing together than in the control arm (2.15, 1.61 to 2.87). The intervention had broader effects beyond HIV testing, with a 55% reduction in multiple partners (0.45, 0.33 to 0.62) and a stronger effect among those who had an HIV test (0.37, 0.24 to 0.58) and a 45% reduction in casual sexual partners (0.55, 0.42 to 0.73).

Harms

No cases of harm were identified during the study period.

Bias, confounding, and other reasons for caution

Outcomes were self reported and could have been subject to social acceptability or recall bias. The questions related to sexual risk behaviour were taken from validated tools with indices of self reported sexual activities. Study outcomes were collected by a team not involved in the delivery of the intervention. We assessed potential confounding owing to baseline differences, but inclusion of these factors in the model did not change the estimated prevalence ratio for the main outcome measure.

Generalisability to other populations

This study was undertaken in a rural, predominantly female headed area of South Africa with male migration for work. The mean age of survey participants was 41 years, reported levels of sexual risk behaviour and intimate partner violence were low, and stigma was moderately high. The area could therefore be representative of many rural parts of Africa.

Study funding/potential competing interests

This study was funded by the South African Medical Research Council and by the President's Emergency Plan for AIDS Relief through the Centers for Disease Control and Prevention under the terms of 5U2GPS001137. TD and DJ were also supported by the South African National Research Foundation. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Trial registration number

Current Controlled Trials ISRCTN31271935.

Patients' attitudes about the use of placebo treatments: telephone survey

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- Research: Components of placebo effect (*BMJ* 2008;336:999)
- Research: Prescribing "placebo treatments" (*BMJ* 2008;337:a1938)

STUDY QUESTION

What are the attitudes of US patients about the use of placebo treatments in medical care?

SUMMARY ANSWER

Most patients (50-84%) surveyed judged it acceptable for doctors to recommend placebo treatments under conditions that varied according to the doctors' level of certainty about the benefits and safety of the treatment, the purpose of the treatment, and the transparency with which the treatment was described to patients.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The prescription of placebo treatments is ethically controversial, yet there is growing evidence of the use of such treatments in medical care. However, the perspectives of US patients have been missing from this debate.

Participants and setting

Surveys were completed by 853 members of Kaiser Permanente Northern California, aged 18-75, who had been seen by a primary care provider for a chronic health problem at least once in the prior six months.

Design

Using a computer aided telephone interview system, trained interviewers administered a one time telephone survey, which took respondents an average of 20 minutes to complete.

Primary outcomes

Knowledge of placebos and the placebo effect (see table for definition), beliefs regarding connection between the mind, body, and illness; placebo mechanisms; and the acceptability of doctors recommending placebo treatments under various scenarios.

Main results and the role of chance

The response rate was 53.4% (853/1598) of all members who were eligible to participate and 73.2% (853/1165) of all who could be reached by telephone. Only 21.9% (95% confidence interval (19.1% to 24.7%) of respondents judged that it was never acceptable for doctors to recommend placebo treatments. While 76% (73% to 79%) judged it was acceptable for doctors to recommend a placebo treatment if they thought it would benefit and not harm patients, fewer (50%, 47% to 53%) considered it acceptable if doctors were uncertain of the benefit.

Bias, confounding, and other reasons for caution

The survey captures patients' opinions about a series of plausible hypothetical scenarios rather than actual behaviors and experiences.

Generalisability to other populations

The study sample was representative of the population of northern California but may not be representative of US patients in general. Our sample was more highly educated (≥44% college graduates) than the US population, had health insurance coverage through Kaiser Permanente Northern California, and had seen a physician within the past six months for a chronic medical condition.

Study funding/potential competing interests

This research was supported by the intramural research program of the US National Institutes of Health. The opinions expressed are those of the authors and do not necessarily reflect the policies or views of the National Institutes of Health or the Department of Health and Human Services. The funding sources for this research had no role in the study design, data collection, analysis or interpretation of data, writing of the report, or the decision to submit the paper for publication.

General opinions about placebo treatments*

Statements	Opinions (% of participants, 95% CI)			
	Strongly agree	Somewhat agree	Somewhat disagree	Strongly disagree
Doctors should never recommend placebo treatments to patients	11.4 (9.2 to 13.5)	10.5 (8.5 to 12.6)	38.7 (35.4 to 42.0)	39.4 (36.1 to 42.7)
It is acceptable for doctors to recommend a placebo treatment if they believe the treatment will benefit the patients and not cause harm	31.9 (28.8 to 35.1)	44.3 (41.0 to 47.7)	12.4 (10.2 to 14.6)	11.3 (9.2 to 13.5)
It is acceptable for doctors to recommend a placebo treatment if they are uncertain about whether the treatment will provide a benefit for patients, so long as the doctors believes it is safe	14.2 (11.8 to 16.6)	35.9 (32.6 to 39.1)	25.6 (22.6 to 28.5)	24.4 (21.5 to 27.3)
In general, it is acceptable for doctors to offer a safe placebo treatment if it addresses the patients' need to feel like they are being given something to get better	30.8 (27.7 to 34.0)	39.1 (35.8 to 42.4)	13.2 (10.9 to 15.5)	16.8 (14.3 to 19.4)

*Patients experience a placebo effect when they get better after taking a treatment, not because of the treatment itself, but because patients expect they will benefit from the treatment. Participants were asked to assume that a placebo treatment is a treatment that only works because it can produce a placebo effect. Placebo treatments can be sugar pills or other treatments used to create a placebo effect.