Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study

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Cite this as: *BMJ* 2013;346:f457
doi: 10.1136/bmj.f457

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f457

bmj.com
- Research: Inconsistent reporting of surrogate outcomes in randomised clinical trials (*BMJ* 2010;341:c3653)
- Analysis: The idolatry of the surrogate (*BMJ* 2011;343:d7995)

STUDY QUESTION

Do treatment effects in randomised controlled trials reporting surrogate primary outcomes differ from those in randomised trials reporting final patient relevant primary outcomes?

SUMMARY ANSWER

Trials reporting surrogate primary outcomes were more likely to report larger treatment effects than trials reporting final patient relevant outcomes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Surrogate outcomes are often used in clinical trials as a substitute for final patient relevant outcomes. The advantages of surrogate outcomes over final outcomes are that they may occur faster or may be easier to assess, thereby shortening the duration, size, and cost of trials. In the absence of patient relevant outcomes, policymakers should rely on validated surrogate outcomes and take into account the potential uncertainty in their prediction of treatment benefits and harms.

Selection criteria for studies

We searched Medline through PubMed for all randomised trials published in 2005 and 2006 in six high impact medical journals: *Annals of Internal Medicine*, *BMJ*, *Journal of the American Medical Association*, *Lancet*, *New England Journal of Medicine*, and *PLoS Medicine*. To be included studies had to be interventional trials that were not multi-arm or secondary analyses, had been terminated early, used an equivalence or non-inferiority design, or reported a mixed primary outcome—that is, contained both surrogate and final patient relevant outcomes.

Primary outcomes

Binary outcomes were recorded as number of patients and events in each arm of the trial. Trials using surrogate and final patient relevant outcomes were compared using the ratio of odds ratios; a value >1.0 implies that trials with surrogate outcomes report larger intervention effects than trials with final patient relevant outcomes.

Main results and role of chance

A total of 84 trials using surrogate outcomes and 101 using final patient relevant outcomes were considered for analyses. Study characteristics of the trials using surrogate outcomes and final patient relevant outcomes were well balanced, except for median sample size (371 *v* 741) and single centre status (23% *v* 9%). Risk of bias did not differ between the trial types. Primary analysis showed trials reporting surrogate endpoints to have larger treatment effects than the trials reporting final patient relevant outcomes, with a ratio of odds ratios of 1.47 (95% confidence interval 1.07 to 2.01). This result was consistent across adjusted and sensitivity analyses.

Bias, confounding, and other reasons for caution

Although treatment effects may be truly larger in trials using surrogate outcomes than in trials using final patient relevant outcomes, alternative explanations for our findings include small study effect bias, publication bias, and single centre effect bias.

Study funding/potential competing interests

OC is funded by a University of Exeter Medical School PhD studentship.

Comparison of treatment effects of trials using surrogate outcomes with trials using final patient relevant outcomes: primary and sensitivity analyses

Method of analysis	Risk ratio* (95% CI)		Ratio of odds ratios or relative risk ratio (95% CI)	
	Surrogate outcomes	Patient relevant outcomes	Unadjusted	Adjusted†
Primary analysis:				
Binary outcomes (51 surrogate *v* 83 patient relevant)	0.51 (0.42 to 0.60)	0.76 (0.70 to 0.82)	1.47 (1.07 to 2.01)	1.46 (1.05 to 2.04)
Sensitivity analyses:				
Inclusion of risk ratios as reported by authors (57 *v* 86)	0.56 (0.48 to 0.65)	0.80 (0.75 to 0.86)	1.38 (1.12 to 1.71)	1.36 (1.08 to 1.70)
Inclusion of continuous outcomes (84 *v* 101)	0.46 (0.39 to 0.54)	0.68 (0.62 to 0.74)	1.44 (0.83 to 2.49)	1.48 (0.83 to 2.62)
Binary outcomes, matched pairs (43 *v* 43)	0.48 (0.39 to 0.59)	0.68 (0.61 to 0.77)	1.38 (1.01 to 1.88)	—

*Pooled using DerSimonian and Laird random effects meta-analyses.
†Adjusted for trial level characteristics of clinical area of intervention, patient population, type of intervention, sponsor, journal, mean sample size, and mean follow-up time.

Promotion of physical activity and fitness in sedentary patients with Parkinson's disease: randomised controlled trial

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Cite this as: *BMJ* 2013;346:f576
doi: 10.1136/bmj.f576

This is a summary of a paper that was published on bmj.com as *BMJ* 2103;346:f576

bmj.com

- Research: Physiotherapy intervention in Parkinson's disease (*BMJ* 2012;345:e5004)
- Practice: Diagnosis and pharmacological management of Parkinson's disease: summary of SIGN guidelines (*BMJ* 2010;340:b5614)

STUDY QUESTION

To evaluate whether a multifaceted behavioural change programme increases physical activities in patients with Parkinson's disease.

SUMMARY ANSWER

The ParkFit behavioural change programme did not increase overall physical activity, as measured with the LASA physical activity questionnaire (LAPAQ).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Patients with Parkinson's disease might benefit from physical activity and exercise, but how they can be motivated to change their sedentary lifestyle and persistently increase their level of physical activities remains unclear. Although the ParkFit programme did not increase the overall volume of physical activities, greater participation in specific elements of physical activity and an improved fitness were seen among ParkFit patients, without more falls and without a change in quality of life.

Design

This was a multicentre, randomised controlled trial to increase physical activity levels in sedentary patients with Parkinson's disease. Patients were randomly assigned to the ParkFit programme or a matched general physiotherapy intervention.

Participants and setting

Thirty-two community hospitals in the Netherlands, which participate in a nationwide professional network (ParkinsonNet), recruited 586 sedentary patients with idiopathic Parkinson's disease aged between 40 and 75 years with mild to moderate disease severity (Hoehn and Yahr stage ≤3).

Primary outcome(s)

The primary endpoint was the level of physical activity, measured every six months using a standardised seven day recall (LAPAQ), for a period of two years.

Main results and the role of chance

During follow-up, the overall time spent on physical activities was comparable between the two groups (adjusted group difference 7%, 95% confidence interval −3% to 17%; P=0.19). Analyses of three secondary outcomes indicated increased physical activity in ParkFit patients, as suggested by the activity diary (difference 30%; P<0.001), the activity monitor (difference 12%; P<0.001), and the six minute walk test (difference 4.8 m; P=0.05). Quality of life, as measured by the Parkinson's disease questionnaire (PDQ-39), did not differ between ParkFit patients and controls (difference −0.9 points; P=0.14).

Harms

The number of fallers was comparable between ParkFit patients (184/299; 62%) and controls (191/287; 67%).

Bias, confounding, and other reasons for caution

This study highlights several challenges for future studies in this new field, in particular with regard to the choice for the outcome measures to document changes in physical activity.

Generalisability to other populations

The results can be extended to patients with other chronic conditions or healthy older people who lead a sedentary lifestyle.

Effect of intervention on primary and secondary outcome measures

	ParkFit		Controls		Estimated difference (95% CI)*	P value
	No	Effect of intervention	No	Effect of intervention		
Primary outcome: physical activity measured with LAPAQ—median (IQR) hours/week						
Baseline	299	12.8 (8.3-20.3)	287	13.8 (8.3-23.9)	7% (−3% to 17%)	0.19
6 months	285	13.2 (9.2-20.5)	277	14.2 (8.5-22.0)		
12 months	281	12.5 (7.2-21.1)	277	12.4 (7.3-17.9)		
18 months	277	12.3 (7.0-19.0)	271	12.3 (6.8-19.1)		
24 months	273	12.5 (6.3-18.4)	267	12.0 (7.0-18.3)		
Secondary outcome measures (mean change from baseline to 6-24 months)						
Activity diary—hours/week	275	1.3	273	0.5	30% (17% to 45%)	<0.001
Activity monitor—kcal/day	254	38.7	258	−14.2	12% (7% to 16%)	<0.001
Quality of life—Parkinson's disease questionnaire (PDQ-39)	278	0.1	276	1.7	−0.9 (−2.1 to 0.3)	0.14
Physical fitness—six minute walk test (6MWT)	255	8.4	253	−1.6	4.8 (0.1 to 9.6)	0.05

IQR=interquartile range; LAPAQ=LASA physical activity questionnaire.
*Estimated relative difference, based on mixed model analysis.

Mental disorders and vulnerability to homicidal death: Swedish nationwide cohort study

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EDITORIAL by Webb et al

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Cite this as: *BMJ* 2013;346:f557
doi: 10.1136/bmj.f557

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f557

STUDY QUESTION

Do people with mental disorders have increased vulnerability to homicidal death?

SUMMARY ANSWER

After adjustment for sociodemographic confounders, people with mental disorders, including those with substance use disorders, personality disorders, depression, anxiety disorders, or schizophrenia, had greatly increased risks of homicidal death.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The perpetration of homicide by people with mental disorders has received much attention, but their risk of being victims of homicide has rarely been examined. This comprehensive study used nationwide sociodemographic, outpatient, and inpatient data from Sweden and found an increased risk of homicidal death among people with mental health disorders.

Participants and setting

Study participants were all people aged 17 years or older in Sweden.

Design, size, and duration

We did a nationwide cohort study (n=7 253 516) to examine the associations between mental disorders and homicidal death during eight years of follow-up (2001-08). We ascertained mental disorders during the same period from all outpatient and inpatient diagnoses nationwide. We used Cox regression to calculate hazard ratios for the associations between mental disorders and homicidal death, while adjusting for sociodemographic confounders and examining the potential modifying effect of comorbid substance use.

Main results and the role of chance

Six hundred and fifteen homicidal deaths occurred in 54.4 million person years of follow-up. The mortality rate due to homicide (per 100 000 person years) was 2.8 among people with mental disorders compared with 1.1 in the general population. After adjustment for sociodemographic confounders, any mental disorder was associated with a 4.9-fold (95% confidence interval 4.0 to 6.0) risk of homicidal death, relative to people without mental disorders. We found strong associations irrespective of age, sex, or other sociodemographic characteristics. Although the risk of homicidal death was highest among people with substance use disorders (approximately ninefold risk), the risk was also increased among those with personality disorders (3.2-fold), depression (2.6-fold), anxiety disorders (2.2-fold), or schizophrenia (1.8-fold), and did not seem to be explained by comorbid substance use. Sociodemographic risk factors included male sex, being unmarried, and low socioeconomic status.

Bias, confounding, and other reasons for caution

Limitations of the study included the inability to examine mental disorders that were undiagnosed, so that the reported prevalence of mental disorders probably underestimated the true prevalence. However, because Sweden has universal access to healthcare and we used all outpatient and inpatient diagnoses nationwide, ascertainment was more complete than in most previous studies. The results were adjusted for broadly measured sociodemographic confounders, although residual confounding is possible.

Generalisability to other populations

The extent to which these findings are generalisable to countries with different social contexts and healthcare systems is unclear, although they are compatible with findings from smaller studies in other Western countries.

Study funding/potential competing interests

This study was supported by grants from the National Institute of Drug Abuse, the Swedish Research Council, and ALF project grant, Lund, Sweden.

Adjusted hazard ratios for associations between mental disorders and homicidal death in Sweden (2001-08)

	Adjusted hazard ratio (95% CI)*	
Mental disorders	Total population	No substance use†
Any mental disorder	4.91 (3.99 to 6.03)	2.13 (1.52 to 2.99)
Substance use disorders	9.37 (7.39 to 11.88)	Not estimable
Schizophrenia	1.82 (0.85 to 3.86)	1.75 (0.65 to 4.73)
Depression	2.55 (1.70 to 3.83)	2.61 (1.58 to 4.33)
Anxiety disorders	2.16 (1.32 to 3.52)	2.51 (1.37 to 4.59)
Personality disorders	3.21 (1.70 to 6.06)	4.58 (1.46 to 14.38)

*Adjusted for sex, age, marital status, country of birth, education, and employment status.
†Excluding people with any outpatient or inpatient diagnosis of substance use disorders (n=160 762; 2.2%).

Income inequality and 30 day outcomes after acute myocardial infarction, heart failure, and pneumonia: retrospective cohort study

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Cite this as: *BMJ* 2013;346:f521
doi: 10.1136/bmj.f521

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f521

STUDY QUESTION I

s income inequality associated with the risk of mortality and readmission within 30 days of first hospitalization?

SUMMARY ANSWER

Among patients hospitalized with acute myocardial in farction, heart failure, and pneumonia, exposure to higher levels of income inequality was associated with increased risk of readmission, but not mortality.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Income inequality has been associated with a variety of adverse effects on health; however, it is unknown whether this association extends to short term outcomes after admission to an acute care hospital. Higher levels of income inequality were not associated with an increased risk of death within 30 days of admission; but for all three conditions, patients exposed to higher levels of inequality had increased risk of readmission within 30 days of discharge.

Participants and setting

Medicare recipients aged 65 years and older and who had been discharged with a principal diagnosis of acute myocardial infarction (MI), heart failure, or pneumonia from an acute care hospital in the United States, between 2006 and 2008.

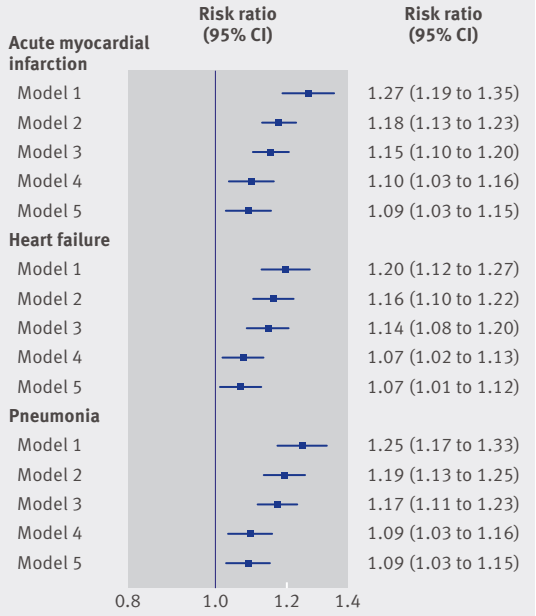
Design, size, and duration

Using a retrospective cohort design, we developed a series of hierarchical logistic regression models to estimate the association between income inequality (as measured by a 0.05 unit increase in the Gini coefficient at the US state level) and a patient's risk of mortality and readmission. We sequentially controlled for patient, hospital, other state, and patient socioeconomic characteristics.

Main results and the role of chance

For mortality analyses, we identified 555 962 admissions to 4348 hospitals for acute MI, 1 092 285 admissions to 4484 hospitals for heart failure, and 1 146 414 admissions to 4520 hospitals for pneumonia. For readmission analyses, we found 553 037 hospitalizations in 4262 hospitals for acute MI, 1 345 909 hospitalizations in 4494 hospitals for heart failure, and 1 345 909 hospitalizations in 4524 hospitals for pneumonia. Income inequality, as measured by the three year average Gini coefficient, varied from 0.41 in Utah to 0.50 in New York. In multilevel models adjusted for covariates, there was no significant association between income inequality and mortality within 30 days of admission for any of the conditions we studied. By contrast, a 0.05 increase in the Gini coefficient was associated with increased risk of rehospitalization for acute myocardial infarction (risk ratio 1.09, 95% confidence interval 1.03 to 1.15), heart failure (1.07, 1.01 to 1.12), and pneumonia (1.09, 1.03 to 1.15). Further adjustment for individual income and educational achievement did not significantly attenuate these findings.

Risk of 30 day readmission associated with income inequality for patients with acute MI, heart failure, and pneumonia



Model 1=unadjusted
Model 2=adjusted for patient age, sex, and comorbidities
Model 3=model 2 plus adjustment for hospital characteristics
Model 4=model 2 plus adjustment for state characteristics
Model 5=model 2 plus adjustment for socioeconomic variables at patient level

Bias, confounding, and other reasons for caution

Although our models included many potential confounders, the observational nature of the study means that we cannot eliminate the possibility of residual confounding. Moreover, some of the factors we treated as confounders could be considered to lie on the causal pathway between inequality and the outcomes we investigated. We estimated patient income and education on the basis of zip codes, which could have led to misclassification. Finally, we measured and analyzed the effects of inequality at the state level, and alternative choices of geographic aggregation could have yielded different results.

Generalizability to other populations

Our analysis included only Medicare beneficiaries with three health conditions. Age, diagnosis, and insurance status may modify the association between inequality and outcome, and our findings should be generalized with caution.

Study funding/potential competing interests

See bmj.com for details.

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- Research: Income inequality, mortality, and self rated health (*BMJ* 2009;339:b4471)
- Research: The global impact of income inequality on health by age (*BMJ* 2007;335:873)
- Research: Child wellbeing and income inequality in rich societies (*BMJ* 2007;335:1080)
- Research: Relations of income inequality and family income to chronic medical conditions and mental health disorders (*BMJ* 2002;324:20)