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EDITORIAL by Salmon

Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey

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STUDY QUESTION

Based on a further survey of archived appendix specimens, what is the prevalence of abnormal prion protein (PrP) associated with variant-Creutzfeldt-Jakob Disease (vCJD) in the UK population, and is a wider birth cohort than previously thought affected?

SUMMARY ANSWER

This study corroborates previous studies and suggests that abnormal prion infection, indicative of subclinical vCJD in the population, is much more prevalent than the 177 clinical cases of vCJD to date would suggest.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Widespread exposure of the UK population to bovine spongiform encephalopathy prions led to the emergence of vCJD, characterised by accumulation of vCJD prions in the lymphoreticular system, preceding invasion of the central nervous system. The point estimate (1 in 2000) of this study was double that found previously. Genetic testing of positive appendixes for the *PRNP* codon 129 genotype revealed a high proportion to be valine homozygous (25%) compared with the frequency in the normal population, and in contrast to vCJD cases, which all have been methionine homozygous.

Participants and setting

The unlinked anonymous technique was used before laboratory screening started. We collected tissue blocks, archived between 2000 and 2012, from pathology departments across the United Kingdom. AntiPrP antibodies were used to test for the presence of abnormal PrP.

Main results and the role of chance

In 32 441 formalin fixed paraffin embedded appendix samples we found 16 specimens positive for abnormal PrP, indicating a prevalence overall of 493 per million population (95% confidence interval 282 to 801 per million). The prevalence in those born in 1941-60 (733 per million) was not significantly different from those born between 1961 and 1985 (412 per million). Prevalence was similar in both sexes and across the three broad geographical areas sampled. This study corroborates previous studies and suggests a high prevalence of abnormal prion infection, indicative of subclinical vCJD in the population compared with the 177 vCJD cases to date. These findings have important implications for the management of blood and blood products and for the handling of surgical instruments.

Generalisability to other populations

This study was conducted in the United Kingdom where exposure to BSE has been substantial. The prevalence estimate of abnormal prion cannot be generalised to other countries with lower or absent exposure to BSE.

Study funding/potential competing interests

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Prevalence of abnormal prion protein in appendix samples from operations conducted in England between 2000 and 2012 by area, sex, and birth cohort

	North east and north west		South east coast, south west, and London		East and West Midlands		
Birth cohort	Female	Male	Female	Male	Female	Male	Total*
1941-60	0/930	1/951	1/1761	2/1508	1/1097	1/1131	6/8181
1961-85	3/2895	0/3002	1/4863	4/4657	0/2805	1/3195	10/24 260
Total	3/3825	1/3953	2/6624	7/6165	1/3902	2/4326	16/32 441

*Includes cases where sex was unknown.

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Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials

Blood Pressure Lowering Treatment Trialists' Collaboration

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STUDY QUESTION

Do the effects of lowering blood pressure on the risk of cardiovascular events differ between people with and without chronic kidney disease?

SUMMARY ANSWER

The proportional reductions in risk of cardiovascular complications with lowered blood pressure are similar in people with and without chronic kidney disease, but people with kidney disease gain larger absolute benefits because their baseline risk is higher.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Blood pressure lowering is an effective strategy for preventing cardiovascular events, and this study shows that this is also true among people with chronic kidney disease. There is, however, little evidence to support the preferential choice of particular drug classes for the prevention of cardiovascular events in people with chronic kidney disease.

Selection criteria for studies

Meta-analysis of participating randomised trials of drugs used to lower blood pressure compared with placebo or each other or comparing different blood pressure targets, with at least 1000 patient years of follow-up per arm. We included 26 trials. Of the 152 290 participants, 30 295 had reduced estimated glomerular filtration rate (eGFR), which was defined as eGFR <60 mL/min/1.73m^2.

Primary outcome

Major cardiovascular events (stroke, myocardial infarction, heart failure, or cardiovascular death).

Main results and role of chance

Blood pressure lowering regimens reduced the risk of major cardiovascular events by 17% per 5 mm Hg reduction in systolic blood pressure in both people with (hazard ratio 0.83, 95% confidence interval 0.76 to 0.90) and without chronic kidney disease (0.83, 0.79 to 0.88) (P=1.00 for homogeneity). The absolute benefit for major cardiovascular events, however, was higher in people with chronic kidney disease (number needed to treat (NNT) for preventing one event over an average of four years was 35) than in people without chronic kidney disease (NNT=53). The results were similar irrespective of whether blood pressure was reduced by regimens based on angiotensin converting enzyme inhibitors, calcium antagonists, or diuretics/β blockers. There was no evidence that the effects of different drug classes on major cardiovascular events varied between patients with different eGFR (all P>0.60 for homogeneity). Similar findings were observed for secondary outcomes—namely, stroke, coronary heart disease, heart failure, cardiovascular disease, and total mortality.

Effects of blood pressure lowering per 5 mm Hg reduction in systolic blood pressure on risk of major cardiovascular events according to estimated glomerular filtration rate (eGFR)

eGFR (ml/min/1.73m^2)	Relative effects		Absolute effect*
	Hazard ratio (95% CI)	P for homogeneity	
eGFR ≥60	0.83 (0.79 to 0.88)	1.00	53
eGFR <60	0.83 (0.76 to 0.90)		35
Overall	0.83 (0.79 to 0.87)	—	47

*NNT for average of four years.

Bias, confounding, and other reasons for caution

The studies in the meta-analysis included few people with advanced chronic kidney disease. There were also limited numbers of people with proteinuria available in this study. We could not evaluate the angiotensin receptor blockers or separate evaluations of β blockers or diuretics alone. There was also uncertainty in estimation of the blood pressure reduction in each trial.

Study funding/potential competing interests

This project was funded by the National Health and Medical Research Council of Australia, and several of the contributors have received funding from the pharmaceutical industry (see bmj.com).

Burden of adhesions in abdominal and pelvic surgery: systematic review and meta-analysis

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STUDY QUESTION

What are the incidence and effects of adhesion related complications (small bowel obstruction, difficulties at reoperation, infertility, and chronic pain) after abdominal surgery?

SUMMARY ANSWER

At least 2% of patients develop adhesive small bowel obstruction and 6% develop an iatrogenic bowel injury following adhesiolysis; adhesions prolong operative time by 15 minutes; pregnancy rate drops by about 50% after abdominal surgery; and adhesions are related to chronic abdominal or pelvic pain in half of patients.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Adhesion formation is a common cause of long term complications after abdominal or pelvic surgery, but clinicians often underestimate the incidence of such complications. Detailed and systematically analysed knowledge of the
large disease burden of adhesions is now available and may be used for better preoperative patient counselling and operative management and to power future trials of anti-adhesive barriers

Selection criteria for studies

We searched the Central, PubMed, and Embase databases from January 1990 to December 2012 for all studies that reported on adhesion related complications in a cohort of patients who had peritoneal surgery. We applied no restrictions to type of study, publication status, or language.

Primary outcome

The primary outcome was the incidence of adhesive small bowel obstruction. Other important outcomes were the incidence of enterotomy during reoperation, the difference in operative time between patients with and without previous surgery, and the pregnancy rate after surgery.

Main results and role of chance

We included 196 eligible cohorts, representing 150 797 patients. Almost 1 in 10 patients had an episode of small bowel obstruction after abdominal operation. In patients with a known cause, adhesions were the single most common cause of bowel obstruction. The incidence of adhesive small bowel obstruction was 2% (95% confidence interval 2% to 3%; I^2=93%); presence of adhesions was generally confirmed by emergent reoperation. Operative time was significantly prolonged in patients with previous surgery, and performing adhesiolysis caused a significant risk of iatrogenic bowel injury. Sensitivity and subgroup analyses did not change our findings.

Bias, confounding, and other reasons for caution

The quantitative results should be interpreted with some caution, as we found large heterogeneity. Local variations in operative techniques, environmental factors, and the case mix seem to influence the incidence of adhesion related complication. Publication bias cannot be completely excluded, as we found asymmetry in some funnel plots. Part of this asymmetry is explained by clinical heterogeneity between the patient group included in different studies rather than by publication bias. Some smaller low quality studies reporting lower incidences were possibly not identified. Our scenario analyses, however, showed that our results were quite robust, so we do not expect that these smaller low quality studies would change our results.

Study funding/potential competing interests

No external funding was obtained for this research.

Incidence of adhesion related complications in follow-up after peritoneal surgery

Outcome	No of studies; patients	Result (95% CI)	Heterogeneity (I^2)
Postoperative small bowel obstruction, any cause	61; 107 949	9% (7% to 10%)	99%
Adhesive small bowel obstruction (ASBO)	87; 110 076	2.4% (2.1% to 2.8%)	93%
Mortality from adhesive small bowel obstruction	19; 20 466	2.5% (1.9% to 3.0%)	58%
Length of hospital stay due to ASBO	5; 464	7.8 (3.6 to 11.9) days	0%
Enterotomy during reoperation	39; 7607	3.3% (2.5% to 4.1%)	86%
Enterotomy during adhesiolysis	16; 2565	5.8% (3.7% to 7.9%)	89%
Operative time	13; 7467	15.2 (9.3 to 21.1) mins	85%
Pregnancy rate after surgery	10; 1004	50% (37% to 63%)	94%
Fertility treatment after surgery	3; 269	23% (18% to 29%)	19%
Chronic pain after surgery	1; 198	40% (34% to 47%)	Not applicable

Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study

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STUDY QUESTION

What is the comparative effectiveness of drug and exercise interventions in reducing the risk of mortality?

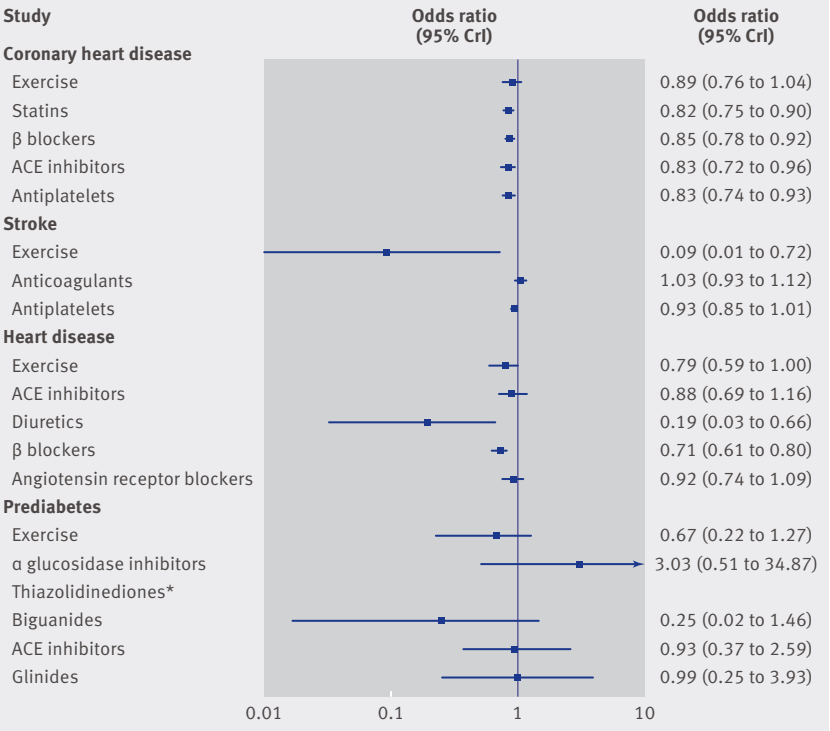
SUMMARY ANSWER

Exercise and many drug interventions are often potentially similar in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The comparative mortality benefits of exercise and drug interventions are unknown. Based on available data on the secondary prevention of coronary heart disease, stroke, heart failure, and prediabetes (impaired glucose tolerance and impaired fasting glucose) physical activity is potentially as effective as many drug interventions.

Effects of exercise and drug interventions on mortality outcomes



Odds ratios <1.00 favour intervention compared with control. ACE=angiotensin converting enzyme
*Number of data points for thiazolidinediones was insufficient to obtain an estimate of odds ratio compared with control.

Selection criteria for studies

We searched Medline and the Cochrane Database of Systematic Reviews up to May 2013 for meta-analyses of randomised controlled trials with mortality outcomes comparing the effectiveness of exercise and drug interventions with each other or with control (placebo or usual care). Relevant drug options for each of the four conditions that had evidence on exercise interventions were statins, β blockers, angiotensin converting enzyme inhibitors, and antiplatelets for the secondary prevention of coronary heart disease; anticoagulants and antiplatelets for stroke; angiotensin converting enzyme inhibitors, diuretics, β blockers, and angiotensin receptor blockers for heart failure; α glucosidase inhibitors, thiazolidinediones, biguanides, angiotensin converting enzyme inhibitors, and glinides for prediabetes.

Primary outcome

Mortality outcomes.

Main results and role of chance

Our metaepidemiological review collectively included 305 randomised controlled trials with 339 274 participants. Of those, 57 trials concerned exercise interventions and included 14 716 participants. Across all four conditions with evidence on the effectiveness of exercise on mortality outcomes (secondary prevention of coronary heart disease, rehabilitation of stroke, treatment of heart failure, prevention of diabetes), no statistically detectable differences were evident between exercise and drug interventions in the secondary prevention of coronary heart disease and prediabetes. Physical activity interventions were more effective than drug treatment among patients with stroke (odds ratios, exercise *v* anticoagulants 0.09, 95% credible interval 0.01 to 0.70 and exercise *v* antiplatelets 0.10, 0.01 to 0.62). Diuretics were more effective than exercise in heart failure (exercise *v* diuretics 4.11, 1.17 to 24.76).

Bias, confounding, and other reasons for caution

The characteristics of exercise interventions varied across the treatment areas. Differences included the mode of physical activity and its frequency, intensity, and duration. Given the indirect nature of the available evidence, it remains a possibility that potential imbalances in the distribution of unobserved or unmeasured effect modifiers across the treatment comparisons impacted the findings, potentially confounding the comparative estimates between drugs and exercise.

Study funding/potential competing interests

We have no competing interests.