RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

191 Has the true causal association between body mass index and mortality been underestimated because of reverse causality?

192 Do single nucleotide polymorphisms commonly associated with type 2 diabetes help to identify incident cases and enhance phenotype based models of prediction?

193 How does exposure to ionising radiation affect the risk of heart disease and stroke at low to moderate organ doses?

194 Is it cost effective to use circulating biomarkers in the prioritisation of patients with stable angina waiting for coronary artery bypass graft surgery?

195 How do the different treatments for localised prostate cancer affect quality of life in men younger than 70 years?

Radiation exposure and circulatory disease risk

A large cohort study of atomic bomb survivors in this week's *BMJ* supports a link between radiation exposure and circulatory disease (p 193). Previous studies have shown that high doses of radiation to the heart or head and neck from radiotherapy cause an excess of deaths from heart disease or stroke. But whether relatively low doses of radiation (under 1 Gy) increase the risk is uncertain. This is an important public health question because of the increasing use of multiple CT scans and interventional radiographic procedures.

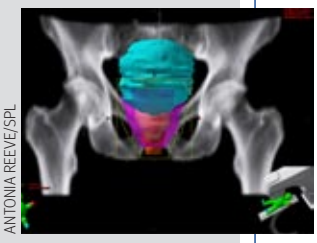
Yukiko Shimizu and colleagues looked at the risk of heart disease and stroke in 86 611 people from Hiroshima and Nagasaki. The participants were followed up prospectively from 1950 to 2003 as part of the Japanese atomic bomb survivor Life Span Study and had received estimated radiation doses of 0 to >2 Gy. A dose-response analysis showed a significantly elevated risk of heart disease and stroke with doses above 0.5 Gy, although the risk at lower doses was unclear. Stroke and heart disease accounted for about 210 excess deaths associated with radiation exposure—about a third as many as the total excess number of deaths from cancer among atomic bomb survivors in the Life Span Study.

Although a causal link is not certain, the study provides the strongest evidence to date of an association between circulatory disease and moderate radiation exposure. Further studies are needed to more precisely estimate the risk at low doses, say the authors. And editorialist Mark Little recommends looking at whether the biological mechanisms operating at high doses of radiation also apply to lower doses (p 162).

Video: How to get published in the *BMJ*

We've produced a short video to help you find out about getting research published in the *BMJ*. It includes interviews with published authors and clips from some of the short films we often commission to accompany important research articles. See it at bmj.com/video/research.dtl, or view on the *BMJ*'s YouTube channel at youtube.com/bmjmedia. We can also supply this video in DVD format if you would like to include it in a presentation but do not have a suitable internet connection—email jhayes@bmj.com for more details.

Quality of life after treatment for prostate cancer


ANTONIA REEVE/SPL

Observational studies have shown that the various treatment options for prostate cancer have broadly equivalent survival rates. This, along with the fact that five year relative survival is now as high as 77% in England, means that treatment choice is increasingly being based on quality of life considerations.

David P Smith and colleagues assessed quality of life in 1642 men treated for prostate cancer compared with 495 controls in New South Wales, Australia (p 195). All the six treatment types studied were associated with persistently altered quality of life at three years.

Cases in all treatment groups reported worse sexual function than controls, with those who had undergone androgen deprivation therapy most severely affected. Men who underwent radical prostatectomy had the worst urinary function, whereas those who had external beam radiation therapy had the worst bowel function.

Although several other studies have looked at quality of life after treatment for prostate cancer, this study quantifies the outcomes associated with particular treatments and has particularly robust methodology—it had a control group, it used well validated questionnaires to measure self reported quality of life, and it had a long follow-up.

LATEST RESEARCH: For these and other new research articles see http://www.bmj.com/channels/research.dtl


STRDEL/AFP/GETTY

The effect of maternal child marriage on morbidity and mortality of children under 5 in India

Adolescent motherhood contributes to high rates of infant and child mortality in India and elsewhere, but it's not known whether this increased risk is due to mothers giving birth at an earlier age or to the social vulnerability of women who marry young. In this cross-sectional analysis of more than 10 000 women, malnutrition was more likely in children born to women who married before age 18—who made up 73% of the nationally representative sample—than in those of women married as adults. However, early maternal marriage didn't seem to be associated with child mortality and low birth weight (doi:10.1136/bmj.b4258).

Non-invasive cardiac stress testing before non-cardiac surgery

In this retrospective population based cohort study, non-invasive cardiac stress testing before elective surgery was associated with improved one year survival and reduced hospital stay in patients who were at high risk for cardiac complications. The operations were non-cardiac and of intermediate to high risk. On the other hand, stress testing was associated with only minor improvements in survival for intermediate risk patients and with slightly decreased survival in low risk individuals. These findings are in line with the American College of Cardiology and American Heart Association guidelines, which recommend preoperative non-invasive stress testing in individuals with clinical risk factors for cardiac complications (doi:10.1136/bmj.b5526).

The association between BMI and mortality using offspring BMI as an indicator of own BMI: large intergenerational mortality study

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STUDY QUESTION Do the associations of body mass index (BMI) and mortality reported from conventional observational studies underestimate the true causal association between BMI and mortality because of reverse causality?

SUMMARY ANSWER Use of offspring BMI as a predictor of own BMI, a technique that avoids problems of reverse causality, suggests that previously reported positive associations of BMI with all cause and cardiovascular disease mortality underestimate the causal effects, whereas previously reported associations of low BMI with elevated lung cancer and respiratory disease mortality are non-causal.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The association of BMI and mortality is U shaped, with the highest mortality risk in people who are in the most underweight and most overweight groups. This research suggests that the elevated mortality observed in people with low BMI probably relates to their having pre-existing disease, whereas the adverse influences of overweight and obesity are of greater magnitude than previously thought.

Participants and setting
A total of 1 018 012 mother-son pairs and 1 004 617 father-son pairs taken from a large intergenerational prospective population based database covering the general population of Sweden were analysed.

Design, size, and duration
We related all cause and cause specific mortality in mothers and fathers to the BMI of their offspring measured during conscription examinations at around the age of 18 years. The analysis included up to 50 years of follow-up.

Main results and the role of chance
For some causes of death, the patterns of associations between offspring BMI and mortality were similar to those seen between own BMI and mortality in previous studies. Parental mortality from diabetes, coronary heart disease, and kidney cancer had the strongest positive associations with offspring BMI. For example, the hazard ratio (HR) for coronary heart disease per standard deviation increase in offspring BMI for mothers was 1.15 (95% CI 1.14 to 1.17) and for fathers was 1.10 (1.09 to 1.11). However, in contrast to the inverse association of own BMI with lung cancer and respiratory disease mortality seen in other studies, there was a positive association between offspring BMI and lung cancer mortality in mothers (1.12, 1.09 to 1.15) and fathers (1.03, 1.02 to 1.05) and between offspring BMI and respiratory mortality in mothers (1.05, 1.02 to 1.08) and fathers (1.02, 1.00 to 1.04). When offspring BMI was used as an instrumental variable for paternal BMI in a subset of father-son pairs (n=72 815), the causal association between BMI and paternal cardiovascular disease mortality (HR per standard deviation of BMI 1.82, 95% CI 1.17 to 2.83) was stronger than that indicated by the directly observed association between own BMI and cardiovascular disease mortality (1.45, 1.31 to 1.61; table).

Bias, confounding, and other reasons for caution
Particularly with respect to mortality of mothers, factors such as smoking and alcohol intake during pregnancy may be related to offspring BMI; thus findings for paternal mortality have greater credence.

Generalisability to other populations
BMI and mortality risks are similar across developed countries and it is likely that the implications of our study are applicable to other populations.

Study funding/potential competing interests
The Medical Research Council (G0600705) and the University of Bristol provide core funding for the Medical Research Council Centre of Causal Analyses in Translational Epidemiology. JACS and DAL were also funded by MRC Collaborative Project Grant G0601625. AF is funded by a Medical Research Council research fellowship. The authors declare no competing interests.

HAZARD RATIOS FOR FATHERS' ALL CAUSE AND CAUSE SPECIFIC MORTALITY PER STANDARD DEVIATION OF OFFSPRING CONSCRIPTION BMI AND FATHERS' OWN BMI

	Offspring BMI (adjusted for age)	Offspring BMI (adjusted for age, social class, and education)	Fathers' BMI (adjusted for age)	Fathers' BMI (adjusted for age, social class, and education)	Instrumental variable estimation for fathers' BMI (adjusted for age, social class and education)
All cause	1.04 (1.00 to 1.08); P=0.064	1.03 (0.99 to 1.07); P=0.144	1.10 (1.05 to 1.16); P<0.001	1.09 (1.04 to 1.15); P=0.001	1.16 (0.96 to 1.39); P=0.120
Cause specific					
Cardiovascular disease related	1.14 (1.05 to 1.25); P=0.003	1.13 (1.04 to 1.24); P=0.006	1.47 (1.33 to 1.64); P<0.001	1.45 (1.31 to 1.61); P<0.001	1.82 (1.17 to 2.83); P=0.008
Not Cardiovascular disease related	1.02 (0.97 to 1.06); P=0.462	1.01 (0.97 to 1.05); P=0.680	1.04 (0.98 to 1.09); P=0.210	1.02 (0.97 to 1.08); P=0.411	1.06 (0.86 to 1.30); P=0.591

Analyses based on father-son pairs with BMI measured in both individuals (n=72 815)
The F test for the strength of offspring BMI as instrument for own BMI is 6356

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Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study

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- Common mental disorder and obesity: insight from four repeat measures over 19 years: prospective Whitehall II cohort study (2009;339:b3765)
- Diagnosis-specific sickness absence as a predictor of mortality: the Whitehall II prospective cohort study (2008;337:a1469)

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:4838

STUDY QUESTION Do common single nucleotide polymorphisms associated with type 2 diabetes effectively distinguish incident cases of type 2 diabetes and add to phenotype based models developed to estimate the absolute risk of type 2 diabetes?

SUMMARY ANSWER In the UK setting, information on 20 type 2 diabetes associated genotypes did not improve prediction of future diabetes, either alone or in combination with two established phenotype based risk models.

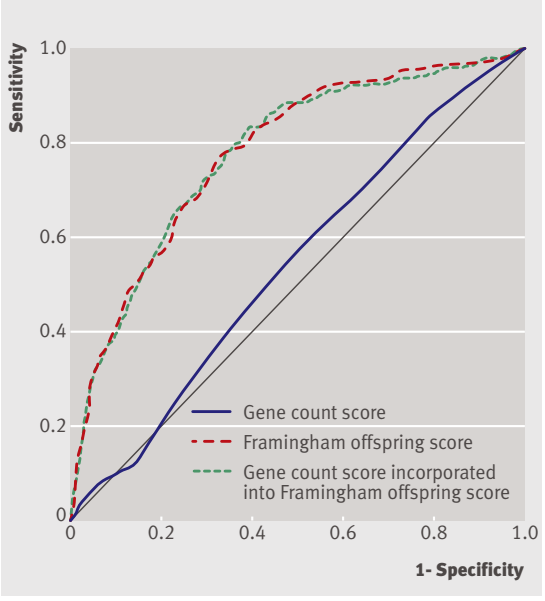
WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Common single nucleotide polymorphisms associated with susceptibility to type 2 diabetes have been identified, but whether a comprehensive panel of diabetes associated genotypes will help in predicting incident diabetes is unknown. The major translational application of currently known common type 2 diabetes associated genotypes is likely to arise from the insight they provide on causes of disease and therapeutic targets.

Participants and setting
The Whitehall II study is a workplace based prospective cohort of 5535 initially healthy white participants (mean age 49 years, 33% women). During a 10 year follow-up, 302 developed type 2 diabetes.

Design, size, and duration
We calculated the Cambridge type 2 diabetes risk score and the Framingham offspring study type 2 diabetes risk score for each participant and genotyped 20 single nucleotide polymorphisms associated with susceptibility to type 2 diabetes in candidate gene studies or genome-wide association scans. Cases of incident type 2 diabetes were defined on the basis of a standard oral glucose tolerance test, self reported doctor's diagnosis, or the use of anti-diabetic drugs.

Main results and the role of chance
A genetic score based on the number of risk alleles carried (range 0-40; area under the receiver operating characteristics curve 0.54, 95% confidence interval 0.50 to 0.58) did not effectively discriminate cases of diabetes. Both the Cambridge risk score (area under curve 0.72, 0.69 to 0.76) and the Framingham offspring risk score (area under curve 0.78, 0.75 to 0.82) had better discrimination. Adding genetic information to phenotype based risk models did not improve discrimination, had only a small effect on model calibration, and led to a net reclassification improvement of less than 5% when added to the Cambridge risk score and no improvement when added to the Framingham score.

RECEIVER OPERATING CHARACTERISTICS CURVES



Bias, confounding, and other reasons for caution
A workplace based cohort is not representative of the general population, but the observed excellent performance of the two phenotype based risk functions for type 2 diabetes (both of which were developed and validated in general populations) suggests that this may not substantially affect the conclusions. DNA was collected some time after baseline, which could have introduced a survivor bias. However, this is likely to be small given the modest effect of the alleles on risk of diabetes and the long natural history of the disease.

Generalisability to other populations
Our findings may not be generalisable to people of non-European ancestry, but similar analyses in populations of European ancestry have yielded broadly similar findings (www.ucl.ac.uk/genetic-epidemiology/WebMaterial).

Study funding/potential competing interests
Funding was provided by the Medical Research Council, British Heart Foundation, National Institute on Aging US, NIH; John D and Catherine T MacArthur Foundation Research Networks; Academy of Finland; BUPA Foundation; and Stroke Association. ADH is on the editorial board of *Drug and Therapeutics Bulletin*, a BMJ Group publication, and has provided non-remunerated advice to GlaxoSmithKline and London Genetics.

Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003

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EDITORIAL by Little

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STUDY QUESTION To what degree does exposure to ionising radiation confer risk of heart disease and stroke at low to moderate organ doses, especially below 1 Gray (Gy)?

SUMMARY ANSWER Atomic bomb survivors in Japan had excess relative risks of 14% per Gy for heart disease and 9% per Gy for stroke, with evidence that misdiagnosis or sociodemographic, lifestyle, and medical risk factors did not confound the risk estimates, although uncertainty exists about the degree of risk below about 0.5 Gy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Radiotherapy studies have clearly documented risks of heart disease and stroke at organ doses of several Gy, but previous lower dose studies have had substantial limitations and mixed results. This study provides the strongest evidence to date of the risks of circulatory disease at radiation doses under 1 Gy.

Participants and setting

We included more than 86 000 survivors of the atomic bombs in Hiroshima and Nagasaki, Japan. Participants were of both sexes and all ages at exposure, with estimated radiation doses of 0 to >2 Gy (38 500 with doses <5 mGy, 42 300 with 5-499 mGy, and 5800 with ≥500 mGy).

Design, size, and duration

Virtually 100% complete follow-up of mortality for 53 years (1950-2003) ascertained 8400 deaths from heart disease and 9600 from stroke.

Main results and the role of chance

A dose-response analysis indicated that the excess relative risk per Gy for heart disease was 14% (95% confidence interval 6% to 23%, P<0.001). A linear model provided the best fit, suggesting excess risk even at lower doses, and the best estimate of a threshold value from a dose-threshold analysis was 0 Gy (no threshold), with an upper 95% confidence limit of 0.5 Gy. Nevertheless, the dose-response effect over the restricted dose range 0-0.5 Gy was not statistically significant. For stroke, the estimated excess relative risk per Gy was 9% (1% to 17%, P=0.02) on the basis of a linear dose-response model, but an indication of possible upward curvature suggested relatively little risk at low doses. Stroke and heart disease together account for about one third as many radiation associated excess deaths as do cancers among atomic bomb survivors.

Bias, confounding, and other reasons for caution

Prospective data on smoking, alcohol intake, education, occupation, obesity, and diabetes had almost no impact on the radiation risk estimates for either stroke or heart disease, and misdiagnosis of cancers as circulatory diseases could not account for the associations seen. However, data were not available on all risk factors for circulatory disease (such as psychosocial factors, diet, and physical exercise), and an autopsy substudy indicated misdiagnosis on death certificates of at least 8% for heart disease and 14% for stroke. Furthermore, the dose-response association was unclear for ischaemic heart disease but was stronger for some other subcategories of heart disease.

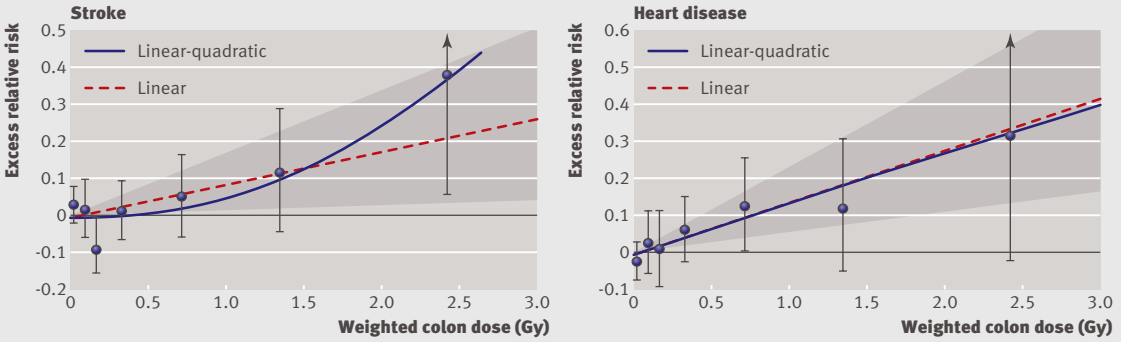
Generalisability to other populations

The larger number of cases of stroke than of heart disease is typical for Japan but not for Western populations. The limited nutrition available in the early post-war years may have altered risk patterns in Japan. The entire body was exposed to similar radiation doses, rather than just the heart or brain.

Study funding/potential competing interests

The Radiation Effects Research Foundation is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare and the US Department of Energy, the latter in part through the US National Academy of Sciences.

RADIATION DOSE-RESPONSE RELATION (EXCESS RELATIVE RISK) FOR DEATH FROM STROKE AND HEART DISEASE



Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles.

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:b5349

Assessing the cost effectiveness of using prognostic biomarkers with decision models: case study in prioritising patients waiting for coronary artery surgery

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STUDY QUESTION What are the effectiveness and cost effectiveness of using information from circulating biomarkers to inform the prioritisation process of patients with stable angina awaiting coronary artery bypass graft surgery (CABG)?

SUMMARY ANSWER The widely available biomarker estimated glomerular filtration rate (eGFR) is cost effective, when combined with other simple risk information, in prioritising patients waiting for CABG; prioritisation strategies including the novel biomarker highly sensitive C reactive protein (CRP) are unlikely to be cost effective. The common practice of ordering the waiting lists for CABG only informally, without the aid of any prognostic risk score, is not cost effective.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Circulating prognostic biomarkers have been widely proposed as adjuncts to the management of many diseases, but their costs and any impact on quality adjusted survival are commonly smaller than those associated with interventions. This study provides empirical evidence of the importance of assessing the cost effectiveness of prognostic biomarkers.

Main results

Using a cost effectiveness threshold of £20 000-£30 000 (€22 000-€33 000; $32 000-$48 000) per additional quality adjusted life year (QALY), a prioritisation strategy using a risk score with eGFR was the most cost effective strategy (cost per additional QALY was <£410 compared with Ontario urgency score). The impact on population health of implementing this strategy was 800 QALYs per 100 000 patients at an additional cost of £245 000 to the National Health Service. The prioritisation strategies using a risk score with CRP were not cost effective at current prices of the CRP test.

Design

Decision analytical model comparing four prioritisation strategies without biomarkers (no formal prioritisation, two urgency scores, and a risk score) and three strategies based on a risk score using biomarkers (routinely assessed (eGFR), novel (CRP), or both). The order in which to perform CABG in a cohort of patients was determined by each prioritisation strategy, and mean lifetime costs and QALYs were estimated and compared.

Source(s) of effectiveness

The risk of cardiovascular events (cardiovascular death, myocardial infarction, or stroke) while on the waiting list for CABG, procedural risk, and risk after CABG were estimated from 9935 patients in the Swedish Coronary Angiography and Angioplasty Registry between 2000 and 2005. The prognostic effect (relative risk) of biomarkers was obtained from meta-analyses of published literature.

Data sources

A lifetime time horizon was used and risk of cardiovascular events was extrapolated from the Swedish data utilising a Markov model. To cost resource use we used NHS reference costs and estimates from the literature. The estimates were also used for quality adjustment weights.

Results of sensitivity analysis

The results were not sensitive to different maximum waiting times or the estimated relative risk of biomarkers. The cost effectiveness of using novel biomarkers is sensitive to the cost of the test itself. At a cost of £3 (£2) per CRP test (£6 in the base case analysis) the cost effectiveness ratio of a risk score with CRP+eGFR compared with a risk score with eGFR alone was £29 000 (£19 000).

Limitations

We developed a new risk equation in our Swedish dataset and carried out external validation in a smaller UK dataset. This risk score requires further validation and refinement. While data imputation may have diluted the effect of the prioritisation strategies including CRP, the relative risks estimates for CRP are likely to be inflated because of publication bias and inadequate adjustment for the routinely recorded factors known to relate to both CRP and outcome (including smoking, diabetes, obesity, and lipids).

Study funding/potential competing interests

This study was funded by a grant from the Health Technology Assessment programme, HTA 05-40 and a National Institute for Health Research programme grant (RP-PG-0407-10314). We have no competing interests.

INCREMENTAL COST EFFECTIVENESS RATIOS (ICERs) FOR NON-DOMINATED PRIORITISATION STRATEGIES USING THREE DIFFERENT MAXIMUM WAITING TIMES

Comparison	Maximum waiting time		
	90 days	40 days	15 days
Ontario urgency score *v* no formal prioritisation	88	55	31
Risk score with eGFR *v* Ontario urgency score	405	380	362
Risk score with CRP+eGFR *v* risk score with eGFR	57 842	133 287	374 371

ICERs reported as cost (£) per quality adjusted life year
New Zealand urgency score, risk score without biomarker, and risk score with CRP were excluded from cost effectiveness calculation owing to dominance or extended dominance

eGFR=estimated glomerular filtration rate; CRP=C reactive protein

Quality of life three years after diagnosis of localised prostate cancer: population based cohort study

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Clinical review. Clinically localised prostate cancer (2006;333:1102-6)

This is a summary of a paper that was published on bmj.com as *BMJ* 2009;339:b4817

STUDY QUESTION How do the different treatments for localised prostate cancer affect quality of life in men aged less than 70 years?

SUMMARY ANSWER Each treatment for localised prostate cancer causes persistent effects on quality of life, in particular sexual function.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Observational studies have shown that the treatments for localised prostate cancer commonly affect short term to medium term quality of life. Our study shows that relative to a normal ageing population, men on each of the main treatments for localised prostate cancer have persistently altered quality of life. Sexual function is compromised in men receiving any of the main treatments, whereas bowel and urinary problems vary in severity and frequency on the basis of treatment type.

Participants and setting

All men aged less than 70 years, resident in New South Wales, diagnosed with prostate cancer between October 2000 and October 2002, and notified to the New South Wales central cancer registry were eligible for this study. A control group, frequency matched to cases by age and area of residence, was selected from the New South Wales electoral roll.

Design, size, and duration

This was a population wide prospective cohort study of 1642 men with localised prostate cancer and 495 controls. Data were obtained from cases as soon after diagnosis as possible and then each year up to three years after diagnosis. Controls were interviewed at baseline and then at one, two, and five years after baseline. We assessed general health specific and disease specific function and "bother" each year by using validated tools, and obtained clinical data on treatment type from medical notes. Multivariable proportional odds ordinal logistic regression models were fitted for each outcome, adjusting for baseline score, time since baseline, and age.

Main results and the role of chance

After adjusting for confounders, cases in all treatment groups had worse sexual function than controls, in particular men who had undergone androgen deprivation therapy (odds ratio (OR) 0.02, 95% CI 0.01 to 0.07). Men treated surgically reported the worst urinary function (adjusted OR 0.17, 95% CI 0.13 to 0.22). Bowel function was poorest in cases who had external beam radiotherapy (adjusted OR 0.44, 95% CI 0.30 to 0.64).

Bias, confounding, and other reasons for caution

Only moderate response rates were achieved: 64% in cases and 63% in controls. Eight doctors refused any approach to their recently diagnosed patients, but these doctors had higher than average patient volumes. In most cases, questions about pre-diagnostic quality of life were asked after treatment had been initiated. Cases may have recalled their pre-diagnostic quality of life differently depending on when the initial interview was done and how their quality of life was at that time.

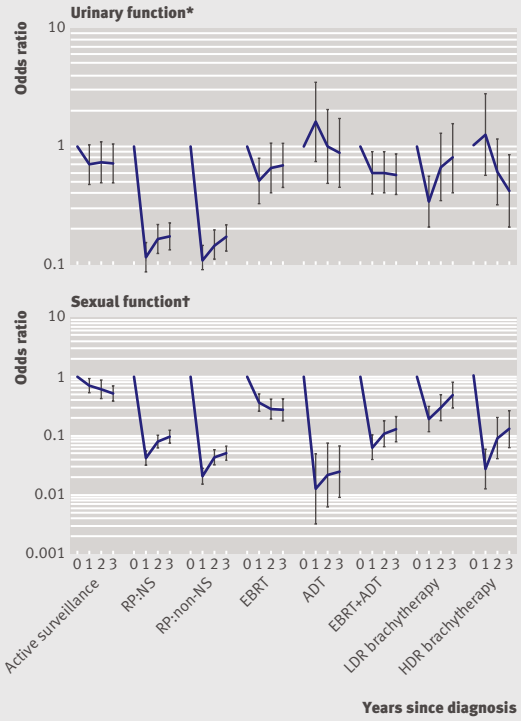
Generalisability to other populations

Comparison with reported results from studies in Europe and America suggest our findings accurately reflect outcomes for men aged less than 70 years who were treated for localised prostate cancer in the early 2000s in developed countries.

Study funding/potential competing interests

This research was funded by grants from the Australian Government Department of Veterans' Affairs and the National Health and Medical Research Council of Australia. The authors were independent from the funders in all aspects of the study design, analysis of data, and writing of the manuscript.

ADJUSTED ODDS RATIOS FOR URINARY AND SEXUAL FUNCTION SCORES HIGHER THAN THOSE IN CONTROL GROUP



*Adjusted for age, baseline urinary function, country of birth, and comorbidity score. †Adjusted for age, baseline sexual function, accessibility of residence, income, and comorbidity score. Abbreviations: ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; HDR, high dose rate; LDR, low dose rate; RP: NS, nerve sparing radical prostatectomy; RP: non-NS, non-nerve sparing radical prostatectomy