RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

639 Are objective measures of physical capability associated with all cause mortality?

640 What has happened to deaths from methadone overdose since its supervised administration for opioid dependence was introduced in England and Scotland and prescribing rates have risen?

641 Is use of antipsychotic drugs associated with an increased risk of venous thromboembolism?

642 Do Norwegian citizens think the rarity of a disease justifies ignoring considerations about the cost of orphan drugs?

Supervision of methadone therapy

CORDELIA MOLLOY/SPL

Methadone maintenance treatment can substantially reduce mortality among people dependent on opioids such as heroin. But misuse, unsanctioned coadministration, and poor compliance can all lead to death from overdose. In fact, during the 1990s, methadone was implicated in as many drug related deaths in the United Kingdom as was heroin. In the mid to late 1990s, prescribing practice in the UK was changed with the aim of reducing deaths from overdose; daily dispensing and supervision of methadone dosing were introduced or expanded.

John Strang and colleagues looked at publicly available mortality data from England and Scotland between 1993 and 2008 to assess the effect of these changes (p 640). They saw a striking reduction in deaths caused by methadone overdose in both Scotland and England over that period, with the timing of the improvements related to the introduction of widespread supervision of methadone dosing.

The authors believe that this improvement in safety might previously have gone undetected because methadone prescribing also increased substantially over the same period. Here they have controlled for that confounding by using an index of the number of deaths related to methadone per million defined daily doses. Given the continuing political controversy over opiate substitution, tools like this index that help to accurately assess the value of policy changes are welcome.

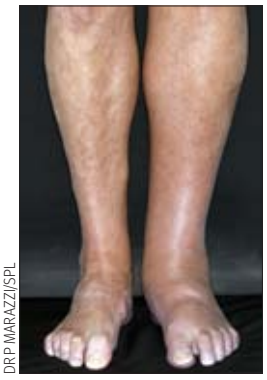
Poor physical capability and mortality in older people

Whether someone can manage the physical tasks of everyday living can reflect on their general health. Rachel Cooper and colleagues undertook a systematic review and meta-analysis to investigate whether this ability, known as physical capability, has any effect on mortality among people in the community (p 639).

MARTYN F CHILLMAID/SPL

Overall the authors found that people who performed less well in four objective tests of physical capability—grip strength, walking speed, chair rising, and standing balance times—were at higher risk of all cause mortality. The association of walking speed, chair rising, and standing balance with mortality only applied to adults aged more than 70; however, the association of grip strength with mortality was also found in populations under 60.

This research received substantial media coverage, although many outlets took the main message to be that a strong handshake increases longevity. BBC News, for example, ran the headline "Firm handshake link to long life" (http://bbc.in/agerPc). Grip strength, however, is more than just the strength of a person's handshake and is rather a technical, physiological characteristic that is measured with a machine.



DR P MARAZZI/SPL

Venous thromboembolism and antipsychotic drugs

The *BMJ* has published several studies arising from the QRESEARCH database (www.qresearch.org), which holds the anonymised primary care clinical records of more than 11 million people registered over the past 16 years with more than 500 UK general practices. The latest, from Chris Parker and colleagues, is a nested case-control study showing that prescribing of antipsychotic drugs (for indications including nausea and vertigo as well as mental health disorders) is associated with significantly increased relative risks of venous thromboembolism, particularly among new users and those prescribed atypical antipsychotic drugs (p 641). The relative risks look alarming. But the authors rightly report the absolute risks too, which show four extra cases annually per 10 000 among patients of all ages and 10 extra cases per 10 000 among the over 65s.

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

Techniques to combine data in mixed methods studies

Mixed methods studies that collect both qualitative and quantitative data—for example, patient views on a new intervention as well as information on its efficacy—are becoming more common in health research, but integrating these two types of data is tricky. Alicia O'Cathain and colleagues cover in a Research Methods & Reporting paper three ways to combine qualitative and quantitative data in mixed methods studies (doi:10.1136/bmj.c4587). The techniques they recommend are triangulation—comparing the findings from both approaches to find common themes and important differences—"following a thread"—following a question or theme from one approach across to the other approach—and creating a mixed methods matrix—using a table where rows contain cases that have both qualitative and quantitative data and columns display different data collected on each case. By combining qualitative and quantitative data effectively, mixed methods research should yield a "whole greater than the sum of the parts."

CME

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Objectively measured physical capability levels and mortality: systematic review and meta-analysis

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STUDY QUESTION

Are objective measures of physical capability associated with all cause mortality in community dwelling populations?

SUMMARY ANSWER

Older people who perform less well in tests of grip strength, walking speed, chair rising, and standing balance have higher rates of all cause mortality, and the association between grip strength and mortality is also seen in younger populations.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Growing evidence suggests that grip strength, walking speed, chair rising, and standing balance are useful markers of current and future health. Consistent evidence of associations between these four measures and all cause mortality in older populations indicates that they may provide useful tools for identifying older people at higher risk of death.

Selection criteria for studies

We identified studies by searching Medline and Embase (up to May 2009) and the reference lists of eligible papers. We also contacted study investigators for unpublished results. Eligible observational studies were those done in people of any age living in the community that had examined the association of at least one of the four specified measures of physical capability (grip strength, walking speed, chair rising, and standing balance) with mortality.

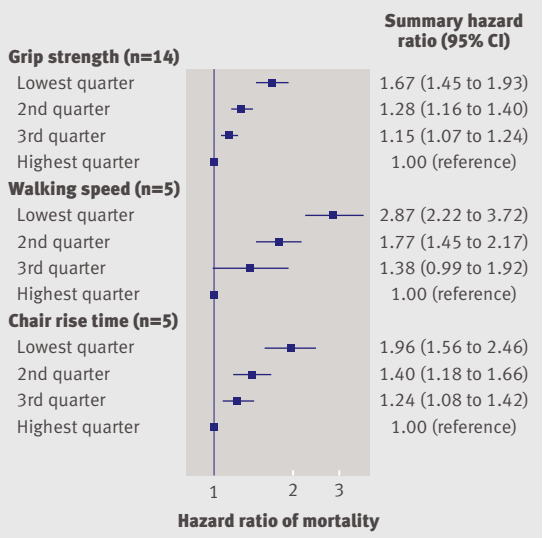
Primary outcome

The primary outcome was all cause mortality.

Main results and role of chance

We found consistent evidence of associations between all four measures of physical capability and mortality; people who performed less well in these tests were at higher risk of all cause mortality. For example, the summary hazard ratio for mortality comparing the weakest with the strongest quarter of grip strength (14 studies, 53 476 participants) was 1.67 (95% confidence interval 1.45 to 1.93) after adjustment for age, sex, and body size (I^2 =84.0%, 74% to 90%; P from Q statistic <0.001), and that comparing the slowest with the fastest quarter of walking speed (five studies, 14 692 participants) was 2.87 (2.22 to 3.72) (I^2 =25.2%, 0% to 70%; P=0.25). As standing balance had not been measured in comparable ways across studies (n=5), we could not do meta-analyses of these results. However, all studies found some evidence that poorer performance in standing balance tests was associated with higher mortality.

SUMMARY HAZARD RATIOS OF MORTALITY COMPARING EACH QUARTER OF GRIP STRENGTH, WALKING SPEED AND CHAIR RISE TIME WITH HIGHEST QUARTER



Adjusted for age, sex (where appropriate), and body size (n=No of data points)

Bias, confounding, and other reasons for caution

Although most estimates of effects from individual studies were in the same direction, the results from meta-analyses should be interpreted with some caution as we detected heterogeneity between studies that did not seem to be explained by age, sex, length of follow-up, or country. We found no evidence of publication bias, and including unpublished results should have minimised this. Results were adjusted for age, sex, and body size, but confounding by other factors could partially explain our findings. With the exception of studies examining grip strength, most have been done exclusively in older populations and have relatively short follow-up, so whether similar associations would be found if these measures had been recorded at younger ages or if follow-up had been longer is unclear.

Study funding/potential competing interests

This project was originally funded by a grant from the UK Medical Research Council Population Health Sciences Research Network. RC originally received support from this grant but is now receiving support from the New Dynamics of Ageing (RES-353-25-0001). Work was also supported in part by the National Institutes of Health and Intramural Research Program, National Institute on Aging, NIH. Peggy M Cawthon has had relationships with Merck and Amgen, and Yves Rolland has had relationships with Amgen, Pierre Fabre, Cheisy, Novartis, and Servier.

Response on bmj.com

"All systematic reviews need not have meta-analysis. Heterogeneity may be the result of clinical heterogeneity (owing to variation in participants, interventions, and outcomes), methodological heterogeneity (owing to variation in study design and bias), or statistical heterogeneity (owing to variation in intervention effects)"

Pankaj B Shah, associate professor, Department of Community Medicine, Chennai, India

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Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland

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STUDY QUESTION Did the introduction of supervision of methadone administration, during a period of major expansion of methadone treatment for heroin addiction, successfully reduce the frequency of deaths due to overdose of methadone?

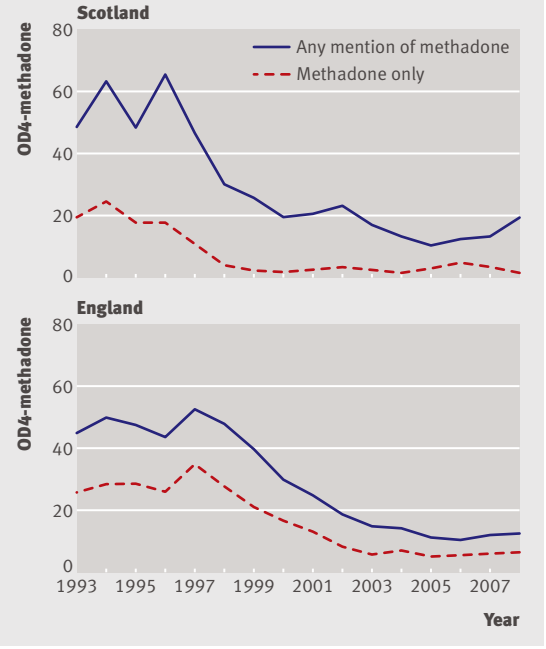
SUMMARY ANSWER The OD4 index (overdose deaths per million daily dispensed doses) for methadone reduced markedly (approximately fourfold), first in Scotland and then in England, coinciding with the different timings of introduction of supervised consumption

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Methadone maintenance treatment has repeatedly been shown to reduce mortality substantially among heroin addicts entering treatment, but misuse of methadone is associated with risk of death from overdose. Progressive introduction and use of facilities for supervision of methadone consumption during the 1990s was associated with a major reduction in death due to methadone overdose.

Design

We calculated annual national defined daily doses from total quantities of methadone prescribed annually (mg) divided by a representative daily dose (60 mg). Deaths from overdose were coded for methadone as the only drug involved (sole drug) or one of the drugs implicated (any mention). We developed the OD4 index (overdose deaths per million daily dispensed doses) to measure deaths due to overdose of methadone while correcting for changes in the extent of prescribing. We examined annual OD4-methadone and changes over epochs of four years against introduction of supervised dosing in Scotland and England.

OD4-METHADONE INDEX (OVERDOSE DEATHS PER MILLION DAILY DISPENSED DOSES) IN SCOTLAND AND ENGLAND, 1993-2008



Cases and settings

We included all deaths from overdose in Scotland and England (separately), annually between 1993 and 2008, identified by coroners as involving methadone (the numerator for calculating OD4). We obtained data on quantities of methadone (mg) prescribed within the NHS (England and Scotland) for treatment of drug dependence, annually between 1993 and 2008 (the denominator for calculating OD4).

Primary outcomes

The primary outcome was OD4-methadone index and its change as supervised dosing was introduced in Scotland (1995-2000) and England (1999-2005).

Main results and role of chance

OD4-methadone decreased substantially over the 16 year study period, with three distinct phases: an initial steady state, a rapid decline, and then a new steady state. Over the four epochs of four years each between 1993 and 2008, OD4-methadone reduced significantly ($P<0.05$) in 10 of 12 epoch changes. In Scotland, it decreased from 19.3 (95% confidence interval 15 to 24) to 3.0 (2.4 to 3.5) for methadone deaths (sole drug) and from 58 to 14 for deaths with any mention of methadone. In England, it decreased from 27.1 (25 to 29) to 5.8 (5.3 to 6.3) for methadone deaths (sole drug) and from 46 to 12 for deaths with any mention of methadone. Reductions in OD4-methadone track the timing of introduction of supervised methadone consumption (first in Scotland, then in England). This occurred over periods of major increases in methadone prescribing (18-fold in Scotland, sevenfold in England).

Reasons for caution

Other changes in methadone prescribing and dispensing do not explain the decline in deaths. Identification of deaths related to overdose of methadone depends on toxicological examinations and the reporting practices of coroners.

Generalisability to other populations

We have shown the feasibility of tracking OD4-methadone in two countries. OD4 investigation of other drugs (such as buprenorphine) and in other countries (especially when policy and practice change) should be straightforward adaptations of this method.

Study funding/potential competing interests

The study received no specific funding.

CME

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Antipsychotic drugs and risk of venous thromboembolism: nested case-control study

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EDITORIAL by Liperoti and Gambassi

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STUDY QUESTION Is use of antipsychotic drugs associated with an increased risk of venous thromboembolism?

SUMMARY ANSWER Use of antipsychotic drugs is associated with an increased risk of venous thromboembolism, which is more marked among new users and those prescribed atypical antipsychotic drugs.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Antipsychotic drugs have been associated with an increased risk of venous thromboembolism in case reports and small studies. In a large primary care population there was an association between use of antipsychotic drugs and risk of venous thromboembolism, which was greater among new users and those prescribed atypical antipsychotic drugs.

Participants and setting

We used an open cohort of patients derived from routinely collected data from 453 general practices contributing to the QResearch database.

Design, size, and duration

In this population based case-control study each patient (case) with a first ever record of venous thromboembolism between 1 January 1996 and 1 July 2007 was matched with up to four controls by age, calendar time, sex, and practice. Odds ratios for venous thromboembolism were adjusted for socioeconomic status, comorbidity, and concomitant drug exposure and estimated according to timing, type, potency, duration, and dose of antipsychotics and for individual antipsychotics with a sufficiently high level of use. We compared the risk between new users and continuing users. We also calculated the numbers needed to harm per year for all patients aged 16 and over and for those aged 65 and over and estimated the number of additional cases of venous thromboembolism expected per 10 000 treated patients per year.

Main results and the role of chance

There were 25 532 eligible cases (15 975 with deep vein thrombosis and 9557 with pulmonary embolism) and 89 491 matched controls from a study population of 7 267 673. Individuals prescribed antipsychotic drugs in the previous 24 months had a 35% greater risk of venous thromboembolism than non-users, despite adjustment for potential risk factors (odds ratio 1.32, 95% confidence interval 1.23 to 1.42). Patients who had started a new drug in the previous three months had about twice the risk (1.97, 1.66 to 2.33). The risk was greater for individuals prescribed atypical drugs (adjusted odds ratio 1.73 (1.37 to 2.17) versus 1.28 (1.18 to 1.38) for conventional drugs). It also tended to be greater for patients prescribed low potency drugs (1.99 (1.52 to 2.62) versus 1.28 (1.18 to 1.38) for high potency drugs). The estimated number of extra cases of venous thromboembolism per 10 000 patients treated over one year was 4 (3 to 5) in patients of all ages and 10 (7 to 13) for patients aged 65 and over.

Bias, confounding, and other reasons for caution

Observational studies, with their large representative populations and their potential for longer term follow-up, have limitations, notably bias and unmeasured confounding.

Generalisability to other populations

Our study has good face validity and is likely to be generalisable as it was carried out in a large primary care population, which is representative of where most patients in the United Kingdom are assessed, treated, and followed up.

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any institution for the submitted work. JH-C is codirector of QResearch, a not-for-profit organisation that is a joint partnership between the University of Nottingham and EMIS. EMIS is the leading supplier of IT for 60% of UK general practices. This work and any views expressed within it are solely those of the co-authors and not of any affiliated bodies or organisations.

EXCESS CASES (95% CI) OF EACH OUTCOME PER 10 000 PATIENTS PRESCRIBED ANTIPSYCHOTICS OVER ONE YEAR

	All ages	Age ≥65
Any antipsychotic use in past 24 months	4 (3 to 5)	10 (7 to 13)
Timing of antipsychotic use:		
Current (within last 3 months)	7 (5 to 9)	17 (12 to 22)
New user of antipsychotics within past 3 months	11 (8 to 16)	29 (20 to 40)
Continuing user of antipsychotics within past 3 months	3 (1 to 6)	9 (3 to 15)
Recent (4-12 months before)	4 (2 to 6)	11 (6 to 16)
Past (13-24 months before)	Non-significant	Non-significant
Types of antipsychotic received in past 24 months:		
Conventional only	3 (2 to 4)	8 (5 to 11)
Atypical only	9 (4 to 14)	22 (11 to 35)
Conventional and atypical	9 (2 to 20)	23 (5 to 51)

Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67

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EDITORIAL by McCabe and colleagues

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STUDY QUESTION

Is there a societal preference for prioritising the treatment of rare diseases that could justify ignoring cost effectiveness thresholds for orphan drugs?

SUMMARY ANSWER

There is little evidence that a societal preference for rarity in itself exists.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Orphan drugs—those targeting diseases with very low prevalence—often fail to meet standard cost effectiveness thresholds for public reimbursement. Debate about exempting orphan drugs from such criteria centres on whether a societal preference for rarity exists. Our results suggest that no preference for rarity exists.

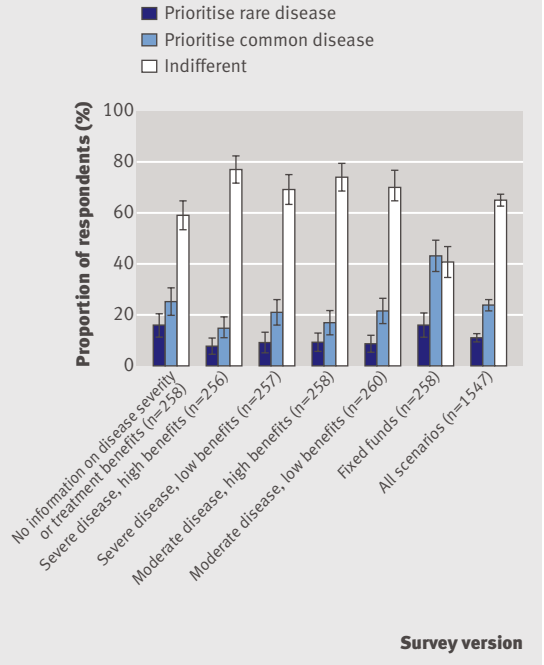
Participants and setting

In total, 1547 Norwegians aged 40-67 responded to an internet based survey in August 2009.

Design

Respondents chose between funding treatment for a rare disease and funding treatment for a common disease and then were asked to allocate funds if it were possible to treat some patients from each group, for each of two scenarios: identical treatment costs per patient and higher costs for the rare disease. Descriptions of the rare and common disease differed only in terms of disease prevalence. We randomised respondents to disease descriptions that provided either no information or different combinations of information on the severity of the disease (severe *v* moderate) and expected benefits of treatment (high *v* low). All respondents rated five statements on attitudes to equity.

RESPONDENTS' PRIORITISATION OF USE OF EXTRA HEALTHCARE FUNDS FOR TREATING 100 PATIENTS WITH RARE DISEASE VERSUS 100 WITH COMMON DISEASE



Survey version

Primary outcome(s)

Our primary outcome was the proportion of respondents who favoured prioritising treatment of patients with rare disease versus those with common disease.

Main results and the role of chance

For the equal cost scenario, 11.2% (95% confidence interval 9.6% to 12.8%) of respondents favoured treating the rare disease, 24.9% (21.7% to 26.0%) the common disease, and 64.9% (62.6% to 67.3%) were indifferent. When the rare disease was four times more costly to treat, the respective results were 7.4% (6.1% to 8.7%), 45.3% (42.8% to 47.8%), and 47.3% (44.8% to 49.8%). Rankings on attitude to equity using a five point Likert scale (5=completely agree) indicated strong support for the statements that patients with rare disease "should have the right to treatment even if more expensive" (mean score 4.5, SD 0.86) and "resources should be used to provide the greatest possible health benefits" (3.9, 1.23).

Bias, confounding, and other reasons for caution

Results from the costly rare disease scenario are difficult to interpret because there is no way to distinguish between a specific preference for rarity and a general preference for fairness. Sampling methods might result in over-representation of respondents with strong views, with uncertain effect on outcomes.

Generalisability to other populations

Results are representative to the extent that Norwegian values are similar to those in other societies.

Study funding/potential competing interests

This research was supported by grants from the Norwegian Research Council and the health economics research programme at the University of Oslo. ISK has received gifts, travel funds, honorariums, consultancy fees, or salary from a wide range of public institutions, not for profit organisations or for profit organisations that may have an interest in orphan drugs.