Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis

Dorothea Nitsch, Morgan Grams, Yingying Sang, Corri Black, Massimo Cirillo, Ognjenka Djurdjev, Kunitoshi Iseki, Simerjot K Jassal, Heejin Kimm, Florian Kronenberg, Cecilia M Øien, Andrew S Levey, Adeera Levin, Mark Woodward, Brenda R Hemmelgarn for the Chronic Kidney Disease Prognosis Consortium

Correspondence to: A S Levey, Chronic Kidney Disease Prognosis Consortium. 615 N Wolfe Street, Baltimore, MD 21205, USA
ckdpc@jhmi.edu

Cite this as: *BMJ* 2013;346:f324
doi: 10.1136/bmj.f324

Details of the authors' affiliations are given in the full article on bmj.com

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f324

STUDY QUESTION

Do the associations of estimated glomerular filtration rate (eGFR) and albuminuria with outcomes of all-cause mortality, cardiovascular mortality, and end stage renal disease differ by sex?

SUMMARY ANSWER

Low eGFR and albuminuria are at least as potent risk factors for all-cause mortality, cardiovascular mortality, and end stage renal disease in women as they are in men.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

US and UK women have lower incidence rates of end stage renal disease than men, raising questions about the importance of low eGFR and albuminuria as risk factors for outcomes of chronic kidney disease. We found that reduced eGFR and albuminuria are both independently associated with an increased risk of mortality and end stage renal disease in both women and men from the general population.

Selection criteria for studies

This random effects meta-analysis used pooled individual data for 2 051 158 participants (54% women) from 46 cohorts from Europe, North and South America, Asia, and Australasia: 26 general population cohorts (n=1 861 052 participants), seven cohorts at high risk of cardiovascular disease (n=151 494), and 13 cohorts with chronic kidney disease (n=38 612). Eligible cohorts (except the chronic kidney disease cohorts) had at least 1000 participants, outcomes of either mortality or end stage renal disease of ≥50 events, and baseline measurements of estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min/1.73 m^2) and urinary albumin-creatinine ratio (mg/g).

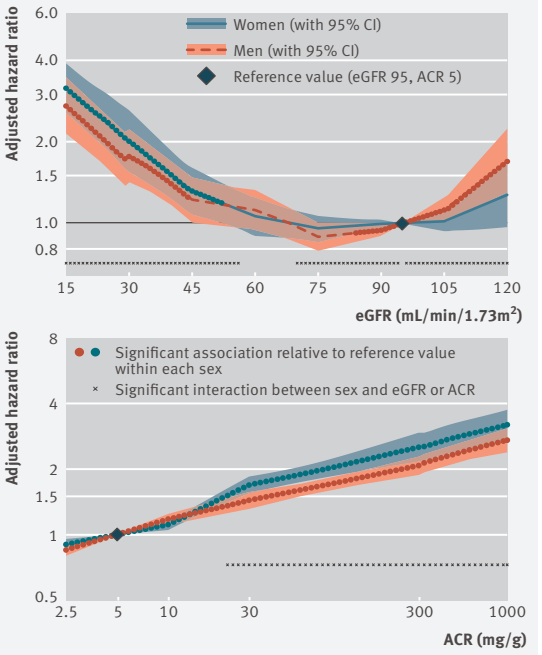
Primary outcome(s)

The primary study outcomes were all-cause mortality, cardiovascular mortality (death due to myocardial infarction, heart failure, stroke, or sudden cardiac death), and end stage renal disease (initiation of renal replacement therapy or death due to kidney disease other than acute kidney injury).

Main results and role of chance

All-cause and cardiovascular mortality risk was higher in men at all levels of eGFR and urinary albumin-creatinine ratio. While higher risk was associated with lower eGFR and higher albumin-creatinine ratio in both sexes, the risk relationship for all-cause and cardiovascular mortality was steeper in women than in men. Compared with an eGFR of 95 mL/min/1.73 m^2, the adjusted hazard ratio for eGFR of 45 was 1.32 (95% CI 1.08 to 1.61) in women and 1.22 (1.00 to 1.48) in men (P for interaction <0.01). Compared with an albumin-creatinine ratio of 5, the hazard ratio for all-cause mortality at a ratio of 30 was 1.69 (1.54 to 1.84) in women and 1.43 (1.31 to 1.57) in men (P for interaction <0.01). Conversely, there was no evidence of a sex difference in associations of eGFR and albumin-creatinine ratio with risk of end stage renal disease.

Risks of all-cause mortality by estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (ACR)



Hazard ratios adjusted for age, sex, race, smoking status, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and eGFR splines or albuminuria

Bias, confounding, and other reasons for caution

There were no studies from the African continent and few black participants. The analysis was based on serum creatinine measurements and urine albumin-creatinine ratio at a single time point. As in all observational studies, residual confounding is possible, and we were unable to adjust for potential confounders including socioeconomic status and physical activity.

Study funding/potential competing interests

The Chronic Kidney Disease Prognosis Consortium Data Coordinating Center is funded in part by a programme grant from the US National Kidney Foundation (whose funding sources include Abbott) and an investigator initiated research grant from Amgen. Several sources have supported enrolment and data collection, laboratory measurements, and follow-up in the collaborating cohorts (see bmj.com for details).

Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial

Richard B Frobell,[1] Harald P Roos,[1] Ewa M Roos,[2] Frank W Roemer,[3 4] Jonas Ranstam,[1] L Stefan Lohmander[1 2 5]

EDITORIAL by Levy and colleagues

[1]Department of Orthopaedics, Clinical Sciences Lund, Lund University, Sweden
[2]Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
[3]Department of Radiology, University of Erlangen, Erlangen, Germany
[4]Quantitative Imaging Center (QIC), Department of Radiology, Boston University School of Medicine, Boston, MA, USA
[5]Department of Orthopaedics and Traumatology, University of Southern Denmark, Odense, Denmark
Correspondence to: R B Frobell, Department of Orthopaedics, Lund University Hospital, SE-22185 Lund, Sweden
Richard.frobell@med.lu.se

Cite this as: *BMJ* 2013;346:f232
doi: 10.1136/bmj.f232

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f232

bmj.com/podcasts

Listen to a podcast about management of cruciate ligament tear five years on with Richard Frobell, an associate professor in the Department of Orthopaedics at Lund University, Sweden

STUDY QUESTION

In young active adults with an acute anterior cruciate ligament (ACL) rupture, do patient reported or radiographic outcomes after five years differ between those treated with rehabilitation plus early ACL reconstruction and those treated with rehabilitation and optional delayed ACL reconstruction?

SUMMARY ANSWER

At five years, patients assigned to rehabilitation plus early ACL reconstruction did not differ significantly in patient reported or radiographic outcomes from those assigned to initial rehabilitation with the option of having a later reconstruction if needed.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The relative efficacy of surgical reconstruction and rehabilitation for short and long term outcomes of ACL rupture is debated. Clinicians and young active adult patients should consider rehabilitation as a primary treatment option following an acute ACL tear.

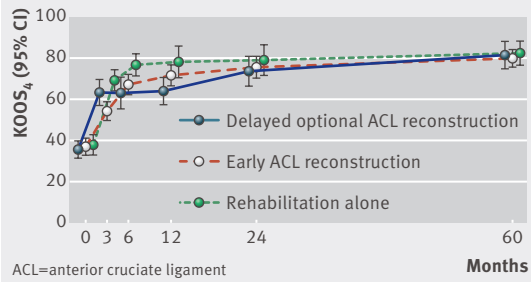
Design

This was an extended follow-up of a prospective randomised trial comparing two treatment strategies: early ACL reconstruction and delayed optional reconstruction. All patients received similar structured rehabilitation.

Participants and setting

We enrolled 121 young active adults (mean age 26 years) with an acute ACL injury to a previously uninjured knee at the departments of orthopaedics at Skåne University Hospital and Helsingborg Hospital, Sweden. One patient was lost to five year follow-up.

Knee injury and osteoarthritis outcome score (KOOS) over five years in KANON study



ACL=anterior cruciate ligament
$KOOS_4$=mean value of four of five KOOS subscales

Primary outcome(s)

The primary outcome was mean change from baseline to five years in the average score for four of the five subscales of the knee injury and osteoarthritis outcome score ($KOOS_4$; 0-100, worst to best).

Main results and the role of chance

Thirty (51%) patients assigned to optional delayed ACL reconstruction had a delayed reconstruction (seven between two and five years). The mean improvement in $KOOS_4$ score from baseline to five years was 42.9 points for those assigned to rehabilitation plus early ACL reconstruction and 44.9 for those assigned to rehabilitation plus optional delayed reconstruction (between group difference 2.0 points, 95% confidence interval −8.5 to 4.5; P=0.54 after adjustment for the baseline score). We found no statistically significant between group differences in $KOOS_4$, any of the KOOS subscales, SF-36, Tegner activity scale, or incident radiographic osteoarthritis of the index knee in the full analysis set or in the as treated analysis.

Harms

We found no evidence of one treatment being more harmful than the other over two or five years.

Bias, confounding, and other reasons for caution

Patients and surgeons were blinded to allocation but not to treatment. Primary and secondary outcomes were patient reported. Radiographs were read blinded to allocation.

Generalisability to other populations

Our results apply to young active adults but not to professional athletes or to less than moderately active adults.

Study funding/potential competing interests

The KANON study received funding from the Swedish Research Council, Medical Faculty of Lund University, Region Skåne, Thelma Zoegas Fund, Stig & Ragna Gorthon Research Foundation, Swedish National Centre for Research in Sports, Crafoord Foundation, Tore Nilsson Research Fund, and Pfizer Global Research. LSL has received honorariums for lectures from Pfizer.

Trial registration number

Current Controlled Trials ISRCTN84752559.

bmj.com Cardiology updates from BMJ Group are at bmj.com/specialties/cardiovascular-medicine

Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study

Karl Michaëlsson,[1] Håkan Melhus,[2] Eva Warensjö Lemming,[1] Alicja Wolk,[3] Liisa Byberg[1]

[1]Department of Surgical Sciences, Section of Orthopedics, Uppsala University, SE-751 85 Uppsala, Sweden
[2]Department of Medical Sciences, Section of Clinical Pharmacology, Uppsala University, Uppsala, Sweden
[3]Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
Correspondence to: K Michaëlsson
karl.michaelsson@surgsci.uu.se
Cite this as: *BMJ* 2013;346:f228
doi: 10.1136/bmj.f228

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f228

STUDY QUESTION

What is the association of long term intake of dietary and supplemental calcium with mortality from all causes and cardiovascular disease?

SUMMARY ANSWER

High intakes of calcium (>1400 mg/day) are associated with higher mortality from all causes and cardiovascular disease.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A low calcium intake is associated with a higher risk of fracture, stroke, and fatal ischaemic heart disease. Meta-analyses of randomised studies have, however, shown a higher risk of ischaemic heart disease and stroke with use of calcium supplements. In our Swedish cohort study of women, high intakes of calcium were associated with higher mortality from all causes, cardiovascular disease, and ischaemic heart disease but not from stroke.

Participants and setting

61 433 women (born between 1914 and 1948) from the Swedish mammography cohort, a population based cohort established in 1987.

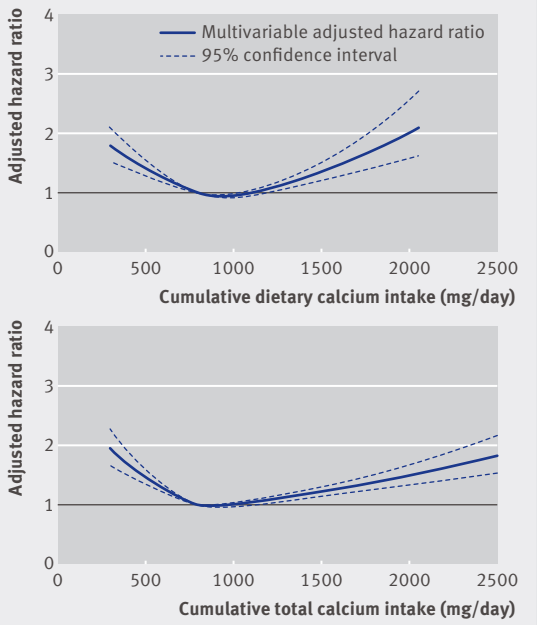
Design, size, and duration

During a median of 19 years of follow-up, primary outcome measures were identified from registry data: time to death from all causes (n=11 944) and from cardiovascular disease (n=3862), ischaemic heart disease (n=1932), and stroke (n=1100). We assessed dietary intake and supplemental use of calcium by food frequency questionnaires at baseline and in 1997 for 38 984 women.

Main results and the role of chance

The risk patterns with dietary calcium intake were non-linear, with higher rates concentrated around the lowest (<600 mg/day) and highest calcium intakes (≥1400 mg/day). Compared with intakes between 600 and 1000 mg/day, intakes above 1400 mg/day were associated with higher deaths from all causes (hazard ratio 1.40, 95% confidence interval 1.17 to 1.67), cardiovascular disease (1.49, 1.09 to 2.02), and ischaemic heart disease (2.14, 1.48 to 3.09) but not from stroke (0.73, 0.33 to 1.65). After sensitivity analysis, the higher rate of death with a low calcium intake was no longer apparent. Calcium tablet use (6% users; 500 mg calcium per tablet) was not associated with death from all causes or with cause specific mortality, but among users the hazard ratio for all cause mortality in those with a dietary calcium intake above 1400 mg/day was 2.57 (1.19 to 5.55).

Multivariable adjusted spline curves for relation between cumulative average of dietary and total calcium intake with time to death from all causes



Bias, confounding, and other reasons for caution

Dietary assessment methods are prone to several limitations, affecting both the precision and accuracy of the measurement. We performed several different types of sensitivity analyses. Accordingly, without being causally linked to death, a low calcium intake could therefore be viewed as a marker of frailty or a less healthy behaviour associated with a higher mortality. Irrespective of analytical approach, the observational study design precludes conclusions about causality, and cautious interpretations of the results are therefore recommended.

Generalisability to other populations

Our results might not apply to people of other ethnic origins or to men.

Study funding/potential competing interests

This study was funded by the Swedish Research Council.

Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses

Keith Hawton,[1] Helen Bergen,[1] Sue Simkin,[1] Sue Dodd,[2] Phil Pocock,[3] William Bernal,[4] David Gunnell,[5] Navneet Kapur[6]

[1]University of Oxford Centre for Suicide Research, Department of Psychiatry, Warneford Hospital, Headington, Oxford OX3 7JX, UK
[2]Post Authorisation Signal Unit, Vigilance and Risk Management of Medicines, Medicines and Healthcare products Regulatory Agency, London, UK
[3]Statistics and Clinical Audit, NHS Blood and Transplant, Stoke Gifford, Bristol, UK
[4]Liver Intensive Therapy Unit, Institute of Liver Studies, King's College Hospital, London, UK
[5]University of Bristol, School of Social and Community Medicine, Canynge Hall, Bristol UK
[6]University of Manchester, Centre for Suicide Prevention, University Place, Manchester, UK
Correspondence to: K Hawton
keith.hawton@psych.ox.ac.uk

Cite this as: *BMJ* 2013;346:f403
doi: 10.1136/bmj.f403

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f403

STUDY QUESTION

Since its implementation in the United Kingdom in September 1998, has legislation to restrict pack sizes of paracetamol had a long term effect on death from paracetamol poisoning and on liver unit activity?

SUMMARY ANSWER

In the 11 years after the 1998 legislation, there were significant reductions in deaths due to paracetamol overdose in England and Wales, with some indication of a reduced number of registrations for transplantation at liver units.

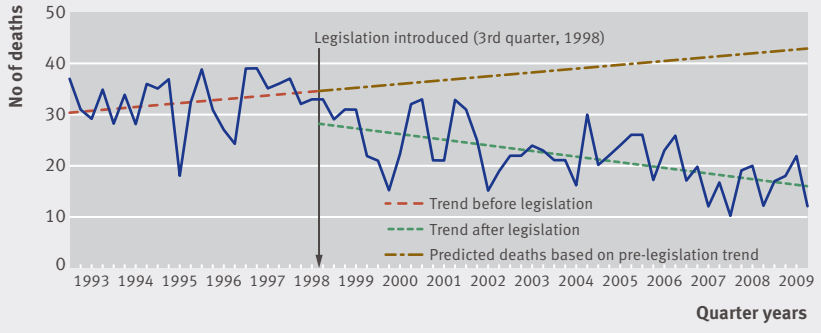
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The 1998 legislation has been shown to have short term positive effects on deaths and liver unit activity. This study shows that it has had long term benefits in terms of fewer deaths due to paracetamol poisoning; less robust evidence indicates fewer registrations to liver units and transplantations following paracetamol induced hepatotoxicity.

Participants and setting

For people aged 10 years and over, data from the Office for National Statistics were obtained for all deaths from single drug poisoning (suicides, deaths of undetermined intent ("open" verdict), and accidental poisonings) in England and Wales during 1993-2009 that involved paracetamol and common paracetamol compounds (with or without alcohol). We also examined registrations at UK liver units for liver transplantation and actual transplantations due to paracetamol poisoning in residents of England and Wales between 1995 and 2009. Data for liver unit activity were obtained from NHS Blood and Transplant.

Suicide and open verdict deaths involving paracetamol and best fit regression lines related to 1998 legislation



Design, size, and duration

Interrupted time series analyses to assess mean quarterly changes in deaths and liver unit activity from October 1998 to the end of 2009, relative to projected rates of deaths and liver unit activity without the legislation based on pre-legislation trends.

Main results and the role of chance

Following the legislation, there was an estimated average reduction of 17 (95% confidence interval −25 to −9) deaths per quarter involving paracetamol only that received suicide or open verdicts, compared with the expected number based on pre-legislation trends. This decrease represented a 43% reduction or an estimated 765 fewer deaths over the 11 years after the legislation. A similar effect was found when accidental poisoning deaths were included, and when a conservative method of analysis was used. This decrease was largely unaltered after controlling for a non-significant reduction in deaths involving other methods of poisoning and also suicides by all methods. There was a 61% reduction in the number of registrations for liver transplantation for paracetamol induced hepatotoxicity (−11 (−20 to −1) registrations per quarter). But no reduction was seen in actual transplantations (−3 (−12 to 6)), nor in registrations after a conservative method of analysis was used.

Bias, confounding, and other reasons for caution

Only data for deaths from poisoning with pure paracetamol and paracetamol compounds (with or without alcohol) were used, not deaths involving paracetamol consumed with other drugs. We were not able to estimate possible substitution of paracetamol overdoses with other methods of poisoning or self harm, but there was a non-significant reduction in total suicides (by all methods) during the post-legislation period, as well as in suicides by ingestion. These changes and improved hospital management of paracetamol poisoning could have contributed to the findings.

Generalisability to other populations

The UK approach to reducing pack sizes of drugs is likely to apply to the prevention of poisoning in other settings.

Study funding/potential competing interests

This paper was funded by the National Institute for Health Research under its Programme Grants for Applied Research scheme (RP-PG-0606-1247). The funder had no role in the study design, analysis, interpretation of data, or the writing of the report. We have no conflicting interests.