RESEARCH

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Opium use and mortality in Golestan Cohort Study This prospective cohort study of 50,000 adults in Iran found that opium users have an increased risk of death from multiple causes compared with non-users. Increased risks were also seen in people who used low amounts of opium for a long period and those who had no major illness before use.


PRESS ASSOCIATION

Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses

Bianca Hemmingsen,[1] Louise Lundby Christensen,[2] Jørn Wetterslev,[1] Allan Vaag,[3] Christian Gluud,[1] Søren S Lund,[4] Thomas Almdal[4]

[1]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark
[2]Department of Paediatrics, Hvidovre University Hospital, Hvidovre, Denmark
[3]Department of Endocrinology, Rigshospitalet, Copenhagen University Hospital
[4]Steno Diabetes Centre, Gentofte, Denmark
Correspondence to: B Hemmingsen **bh@ctu.rh.dk**

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Diabetes articles from across *BMJ* Group

STUDY QUESTION To compare the benefits and harms of metformin and insulin versus insulin alone in randomised clinical trials of patients with type 2 diabetes.

SUMMARY ANSWER There was no evidence or even a trend towards improved all cause mortality or cardiovascular mortality with metformin and insulin, compared with insulin alone in type 2 diabetes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Current guidelines recommend combining metformin with insulin instead of using insulin alone to treat type 2 diabetes. Compared with insulin alone, the combination treatment did not have a significant effect on all cause mortality or cardiovascular mortality.

Selection criteria for studies

We searched the Cochrane Library, Medline, Embase, Science Citation Index Expanded, Latin American Caribbean Health Sciences Literature, and Cumulative Index to Nursing and Allied Health Literature up to March 2011. We also hand searched reference lists and conference proceedings, searched the US Food and Drug Administration website, and contacted relevant authors and relevant pharmaceutical companies. We included randomised clinical trials of patients with type 2 diabetes older than 18 years, comparing metformin and insulin versus insulin alone.

Primary outcome(s)

All cause and cardiovascular mortality in patients with type 2 diabetes.

Main results and role of chance

We included 26 randomised trials with 2286 participants, of which 23 trials with 2117 participants could provide data. Data were sparse for outcomes relevant to patients. We found no significant effects for metformin and insulin treatment versus insulin alone on all cause mortality (relative risk 1.30, 95% confidence interval 0.57 to 2.99) and cardiovascular mortality (1.70, 0.35 to 8.30). Trial sequential analyses showed that more trials were needed before reliable conclusions could be drawn regarding these outcomes. In the fixed effect model, but not in the random effects model, severe hypoglycaemia was significantly more frequent with metformin and insulin than with insulin alone (2.83, 1.17 to 6.86). In a random effects model, metformin and insulin resulted in a reduction in HbA_{1c} (mean difference −0.60%, −0.89 to −0.31), weight gain (−1.68 kg, −2.22 to −1.13), and insulin dose (−18.65 U/day, −22.70 to −14.60) compared with insulin alone. Trial sequential analyses showed evidence was sufficient for a reduction in HbA_{1c} of 0.5%, reduction in weight of 1 kg, and reduction in insulin dose of 5 U/day.

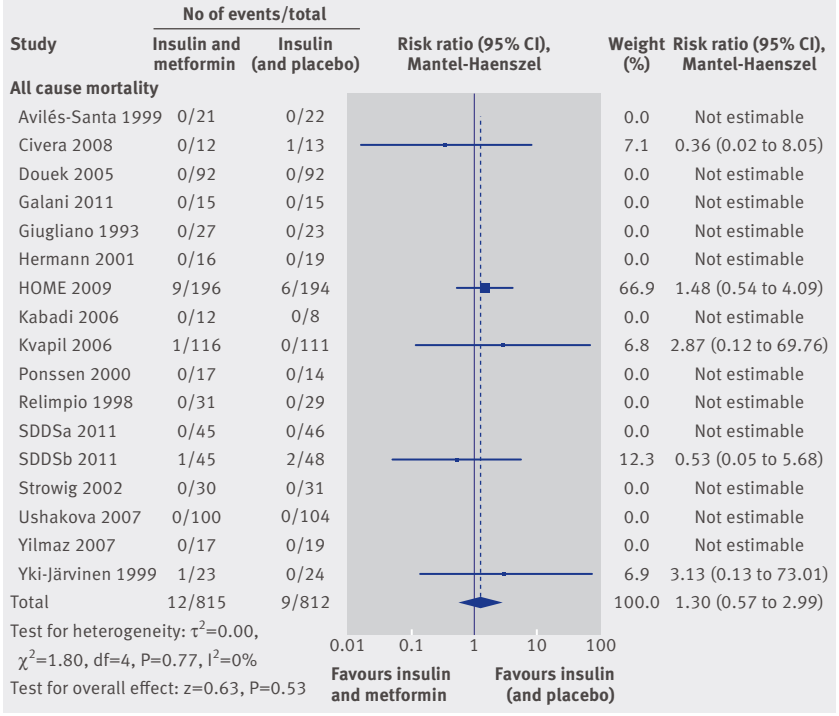
Bias, confounding, and other reasons for caution

All trials had high risk of bias and only two were classified as having a lower risk of bias. Data were sparse for patient relevant outcomes. Most trials had a short duration (only two trials had intervention duration longer than 2 years), and had differences in metformin doses and types of insulin regimen used. The participant characteristics were heterogeneous among trials.

Study funding/potential competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: the study received funding from the Copenhagen Insulin and Metformin Therapy Trial Group; LLC, SSL, AV, and TA have reported equity in Novo Nordisk A/S; SSL and AV have received fees from Novo Nordisk A/S for speech making; LLC was employed at Steno Diabetes Centre, Gentofte, Denmark, when the systematic review began; TA is employed at Steno Diabetes Center, which is an academic institution owned by Novo Nordisk A/S; BH, JW, and CG have no conflicts of interest to declare; after the initial draft of the present manuscript, SSL took up a position at Boehringer Ingelheim, Ingelheim, Germany.

Trial outcomes in all cause mortality



Effect of implementation of Integrated Management of Neonatal and Childhood Illness (IMNCI) programme on neonatal and infant mortality: cluster randomised controlled trial

Nita Bhandari,[1] Sarmila Mazumder,[1] Sunita Taneja,[1] Halvor Sommerfelt,[2] Tor A Strand,[2] on behalf of the IMNCI Evaluation Study Group

EDITORIAL by Dickson and Chopra

[1]Centre for Health Research and Development, Society for Applied Studies, 45, Kalu Sarai, New Delhi-110016, India
[2]Centre for International Health, University of Bergen and Norwegian Institute of Public Health, Norway
Correspondence to: N Bhandari
CHRD@sas.org.in

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STUDY QUESTION What is the effect of the Indian Integrated Management of Neonatal and Childhood Illness (IMNCI) programme on mortality in the first year of life?

SUMMARY ANSWER IMNCI, which includes home visits for newborn care and improved treatment of child illnesses, significantly reduced infant mortality overall and neonatal mortality in babies born at home.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous smaller evaluations of community based newborn care interventions showed a 15-61% relative reduction in neonatal mortality rate and a variable effect on infant mortality rate. IMNCI significantly reduced the infant mortality rate in all enrolled children and the neonatal mortality rate in the subgroup of babies born at home.

Design

This was a cluster randomised controlled trial.

Participants and setting

We included 29 667 births in nine intervention clusters and 30 813 births in nine control clusters (total population 1.1 million) in Haryana, India.

Primary outcome(s)

The primary outcomes were infant mortality rate (death between birth and day 365 of life), neonatal mortality rate (death between birth and day 28), and neonatal mortality rate after the first 24 hours of life (death between day 2 and day 28) among live births in the study area between 1 January 2008 and 31 March 2010.

Main results and the role of chance

Infant mortality rate (adjusted hazard ratio 0.85, 95% confidence interval 0.77 to 0.94) and neonatal mortality rate beyond 24 hours (0.86, 0.79 to 0.95) were significantly lower in the intervention clusters than in the control clusters. The adjusted hazard ratio for neonatal death was 0.91 (0.80 to 1.03). We found a significant interaction between place of birth and effect of the intervention for all mortality outcomes except post-neonatal mortality rate, for which the effect was similar in babies born at home (hazard ratio 0.73, 0.63 to 0.84) and those born in health facilities (0.81, 0.69 to 0.96). We found a substantial effect on neonatal mortality rate among home born babies (adjusted hazard ratio 0.80, 0.68 to 0.93) but not among the facility born babies (1.06, 0.91 to1.23) (P value for interaction=0.001). Neonatal mortality rate beyond the first 24 hours (adjusted hazard ratio 0.76, 0.65 to 0.90) was also significantly lower in the intervention clusters than in the control clusters among home births but not among facility births. The intervention substantially improved newborn care practices.

Harms

No harms were identified.

Bias, confounding, and other reasons for caution

Even after randomisation, some differences existed in characteristics of the population between intervention and control clusters, but we adjusted the effects for these confounders. Independent teams measured outcomes, but the teams may not have been totally blind to the intervention.

Generalisability to other populations

The results are generalisable to similar rural and semi-urban populations where infant mortality is high and a substantial proportion of births occur at home.

Study funding/potential competing interests

Funded by the World Health Organization, Geneva (USAID umbrella grant); United Nations Children's Fund, New Delhi; and the GLOBVAC Program of the Research Council of Norway grant No 183722.

Trial registration number

Clinical trials NCT00474981; ICMR Clinical Trial Registry CTRI/2009/091/000715.

Effect of intervention on mortality outcomes in intervention and control clusters

	All births		Home births	
All live births	Intervention/control (n=29 667/30 813)	Hazard ratio (95% CI)*	Intervention/control (n=18 536/15 827)	Hazard ratio (95% CI)*
Infant deaths (1-365 days)	1925/2136	0.85 (0.77 to 0.94)	1146/1143	0.77 (0.69 to 0.87)
Neonatal deaths (1-28 days)	1244/1326	0.91 (0.80 to 1.03)	668/643	0.80 (0.68 to 0.93)
Neonatal deaths beyond first 24 hours (2-28 days)	635/709	0.86 (0.79 to 0.95)†	356/366	0.76 (0.65 to 0.90)†
Perinatal deaths (stillbirths and 1-7 day deaths)‡	1630/1850	0.89 (0.78 to 1.00)	799/787	0.80 (0.69 to 0.92)
Post-neonatal deaths (29-365 days)	681/809	0.76 (0.67 to 0.85)	478/500	0.73 (0.63 to 0.84)†

* Cox proportional hazard model adjusted for cluster design (shared frailty option, random effects model) and potential confounders (toilet inside house, illiterate mother, schedule caste or tribe, possession of mobile phone, family with below poverty line card, distance from primary health centre to nearest point on highway, percentage of home births in cluster).
†Adjusted for cluster design with robust standard errors rather than shared frailty option (as model failed to yield estimates) and potential confounders (as above).
‡Total number in intervention and control clusters included live births and stillbirths.

Impact of managed clinical networks on NHS specialist neonatal services in England: population based study

C Gale, S Santhakumaran, S Nagarajan, Y Statnikov, N Modi, on behalf of the Neonatal Data Analysis Unit and the Medicines for Neonates Investigator Group

EDITORIAL by Phibbs

Section of Neonatal Medicine, Department of Medicine, Chelsea and Westminster Hospital campus, Imperial College London, London SW10 9NH, UK
Correspondence to: N Modi
n.modi@imperial.ac.uk

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STUDY QUESTION

After the reorganisation of neonatal services in England in 2003 are preterm babies more likely to be delivered at, and less likely to have an acute transfer to, a hospital providing specialist care, and are babies from multiple birth sets less likely to be separated?

SUMMARY ANSWER

Since reorganisation there has been an increase in the proportion of babies born at 27-28 weeks' gestation in hospitals providing the highest volume of intensive care but also an increase in the proportion transferred to another hospital within 24 hours of birth, and of these a third are to a neonatal unit providing equivalent or lower level care. Babies from a third of multiple birth sets continue to be separated to receive care in different hospitals.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Reorganisations within the National Health Service are rarely subjected to rigorous evaluation. Delivery and initial management of preterm babies in hospitals providing specialist high volume neonatal intensive care are associated with improved outcomes; acute postnatal transfer is associated with adverse outcomes. The top down national reorganisation of neonatal services in England has been associated with limited success in achieving predefined aims; the change in transfer patterns indicates continuing inadequacies in neonatal intensive care cot capacity and poor coordination between maternity and neonatal services.

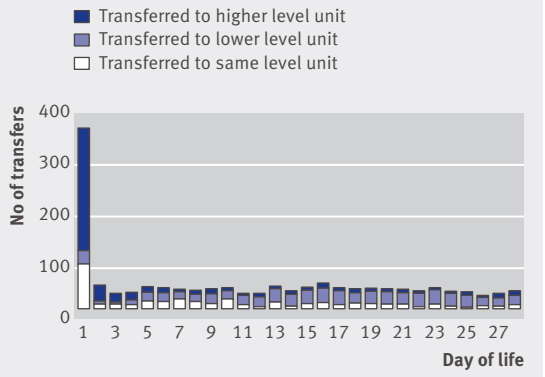
Participants and setting

We compared data from epochs before and after the reorganisation. Aggregate data for epoch one (1 September 1998 to 31 August 2000) were available for 3522 live births at 27-28 weeks' gestation from 294 maternity and neonatal units in England, Wales, and Northern Ireland. These were obtained from the Confidential Enquiry into Stillbirths and Deaths in Infancy Project 27/28 report. Anonymised patient data for epoch two (1 January 2009 to 31 December 2010) were available for 2919 babies in the same gestational age range from 146 neonatal units in England contributing data to the National Neonatal Research Database at the Neonatal Data Analysis Unit.

Design, size, and duration

A population-wide observational comparison of the proportions of babies born at hospitals providing the highest volume of neonatal specialist care, having acute (within 24 hours of birth) or late (24 hours to 28 days) transfer and babies from multiple births separated by transfer.

Postnatal transfers in epoch 2 by postnatal age and neonatal unit level at receiving hospital



The intervention examined was the national reorganisation of neonatal services.

Main results and the role of chance

After reorganisation, there have been increases in the proportions of babies born at hospitals providing the highest volume of neonatal specialist care (from 18% to 49%; odds ratio 4.30, 95% confidence interval 3.83 to 4.82; P<0.001) and in acute and late postnatal transfers (from 7% to 12% and 18% to 22%, respectively; P<0.001). Around a third of multiple birth sets continue to be separated by transfer. In epoch two, 32% of acute transfers were to a neonatal unit providing an equivalent or lower level of care . Results are robust to sensitivity analyses to examine differences between epochs and clustering effects.

Bias, confounding, and other reasons for caution

Historical data representing epoch one were available only in aggregate, precluding examination of temporal trends and confounders. This limits the extent to which differences between epochs can be attributed to reorganisation.

Generalisability to other populations

Conclusions are generalisable to national reorganisations of neonatal services and to similar populations of very preterm babies.

Study funding/potential competing interests

The Neonatal Data Analysis Unit is supported by a Programme Grant for Applied Research from the National Institute of Health Research and unrestricted grants from the Department of Health, Danone, and Abbott International.

Widening access to UK medical education for under-represented socioeconomic groups: modelling the impact of the UKCAT in the 2009 cohort

Paul A Tiffin,[1] Jonathan S Dowell,[2] John C McLachlan[3]

[1]School for Medicine and Health, Wolfson Research Institute, Durham University Queen's Campus, Stockton-on-Tees TS17 6BH, UK
[2]Dundee University School of Medicine, Dundee, UK
[3]The Holliday Building, Durham University Queen's Campus, UK
Correspondence to: P A Tiffin
p.a.tiffin@durham.ac.uk

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STUDY QUESTION

Does the way medical schools use the UK clinical aptitude test (UKCAT) affect the sociodemographic profile of those made offers or entering medicine?

SUMMARY ANSWER

Candidates from under-represented groups did not seem to be disadvantaged when applying to medical schools that used UKCAT as a threshold score (strong use) compared with use in borderline cases or as a weighted factor (weak or moderate use). Comparison of UKCAT usage favoured males, applicants from non-selective state schools, and those from social class 4 or 5, with the impact greater on offers made than on entrance.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

UKCAT scores may be less sensitive to school type attended and favour males compared with A level attainment. Strong use of the UKCAT translated into more equitable provision of place offers for under-represented groups.

Participants and setting

Applicants to 22 British medical schools using the UKCAT as a component of the admissions procedure.

Design, size, and duration

Prospective cohort study totalling 8459 applicants, relating to 24 844 applications during the 2009-10 round of selection for medical school.

Main results and the role of chance

The multilevel multiple logistic regression models developed varied between medical schools according to UKCAT usage. For example, a candidate from a non-professional background was independently less likely to receive a conditional offer of a place than an applicant from a higher social class when applying to an institution with weak use of the UKCAT (odds ratio 0.51, 95% confidence interval 0.45 to 0.60). No such effect was observed where UKCAT scores served as a threshold to influence the selection process (1.27, 0.84 to 1.91). Regarding admissions, stronger use of the test was associated with increased odds of entrants being male, from a low socioeconomic background and state (non-grammar) schools, the last observation being of borderline statistical significance. Weaker use of the test was associated with an increased odds of entrants having relatively low academic attainment (5.19, 2.02 to 13.33) and English as a second language (2.15, 1.03 to 4.48).

Bias, confounding, and other reasons for caution

About one quarter of applicants had missing data for advanced school qualifications or socioeconomic status. The modelling of data on offers made could not control for individuals applying to more than one UKCAT school and therefore observations were not totally independent statistically. Other influences on offer and acceptance may not be included in the dataset.

Generalisability to other populations

The use of the UKCAT is likely to have a positive impact on widening access to medicine for school leavers. We excluded graduate entry and widening participation courses from the analysis and therefore these findings may not generalise to postgraduate and older applicants. The results may also not generalise to non-UK settings and dental applicants.

Study funding/potential competing interests

This study was funded by the UKCAT consortium of universities through a grant to Durham University. JSD and JCMcL are members of the UKCAT Consortium Board and Research Panel.

Multilevel multiple logistic regression analysis for predicting entry to medical schools (2679 applicants with complete data), with medical school group using UKCAT in borderline cases (weak use) as baseline category. Values are adjusted odds ratios (95% confidence intervals)*

	UKCAT usage by medical school group	
Characteristic of entrant	As a factor (moderate use)	As a threshold (strong use)
Male	1.54 (1.13 to 2.10)	1.74 (1.25 to 2.41)
English as second language	0.47 (0.22 to 0.97)	0.61 (0.39 to 1.24)
State (non-grammar) school	1.22 (0.77 to 1.95)	1.60 (0.97 to 2.62)
Social class 4 or 5	3.57 (1.03 to 12.39)	3.38 (0.94 to 12.12)
Low academic attainment†	0.19 (0.07 to 0.50)	0.72 (0.28 to 1.91)

*Adjusted for individual institutional random effects and available sociodemographic predictors (age, sex, English speaking status, socioeconomic background, UKCAT score, A level or equivalent attainment, ethnicity, and school type attended), excluding dependent variable.
†Obtaining less than AAB grades or equivalent at first A level sitting.