Fertility treatment and risk of childhood and adolescent mental disorders: register based cohort study

Bjørn Bay,[1 2] Erik Lykke Mortensen,[3] Dorte Hvidtjørn,[4] Ulrik Schiøler Kesmodel[1 2]

School of Public Health, Section for Epidemiology, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark

[2]Fertility Clinic, Department of Obstetrics and Gynaecology, Aarhus University Hospital, Brendstrupgaardsvej 100, 8200 Aarhus N, Denmark

[3]Institute of Public Health and Center for Healthy Aging, University of Copenhagen, Oester Farimagsgade 5, 1353 Copenhagen K, Denmark

[4]Epidemiology, Institute of Public Health, University of Southern Denmark, J.B. Winsloews Vej 9B, 5000 Odense C, Denmark

Correspondence to: B Bay
bjornbay@me.com

Cite this as: *BMJ* 2013;347:f3978
doi: 10.1136/bmj.f3978

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f3978

bmj.com

Research: Effect of pregnancy planning and fertility treatment on cognitive outcomes in children at ages 3 and 5 (*BMJ* 2011;343:d4473)

For all the latest BMJ Group articles on psychiatry go to bmj.com/specialties/psychiatry

STUDY QUESTION Do children conceived after fertility treatment have higher, comparable, or lower risk of mental disorders in childhood or adolescence compared with children born after spontaneous conception?

SUMMARY ANSWER There was an increased risk of mental disorders in children born after ovulation induction/intrauterine insemination, while children born after in vitro fertilisation or intracytoplasmic sperm injection (IVF/ICSI) had a similar overall risk to children conceived spontaneously.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Children born after fertility treatment have an increased risk of some perinatal outcomes, though long term development has been sparsely investigated and few have studied children born after induced ovulation. Though the overall long term development of children born after IVF/ICSI is comparable with that of children conceived spontaneously, children born after induced ovulation seem to have a small increased risk of autism, hyperkinetic disorders, conduct, emotional or social disorder, and tic disorders, but the absolute risks are low

Participants and setting

Participants in this study were all children born between 1995 and 2003 in Denmark.

Design, size, and duration

This population based cohort study included 588 967 children with follow-up in 2012 when the children were aged 8-17. Information was obtained from Danish national health registers and linked with the unique Danish personal identification number.

Main results and the role of chance

The absolute risk of any of the included mental disorders was 3.9% among children born after spontaneous conception, 3.5% in IVF/ICSI children, and 4.1% in children born after ovulation induction/intrauterine insemination. The risk of mental disorders in children born after IVF/ICSI compared with spontaneously conceived children was not increased, except for a borderline significant increased risk of tic disorders (hazard ratio 1.4, 95% confidence interval 1.0 to 1.9, absolute risk 0.3%). By contrast, children born after ovulation induction/intrauterine insemination had small but significantly increased risks of any mental disorder (1.2, 1.1 to 1.3; absolute risk 4.1%), autism spectrum disorders (1.2, 1.1 to 1.4; 1.5%), hyperkinetic disorders (1.2, 1.1 to 1.4; 1.7%), conduct, emotional, or social disorder (1.2, 1.0 to 1.5; 0.8%), and tic disorders (1.5, 1.2 to 2.0; 0.4%). There was no systematic risk related to any specific type of hormonal drug treatment.

Bias, confounding, and other reasons for caution

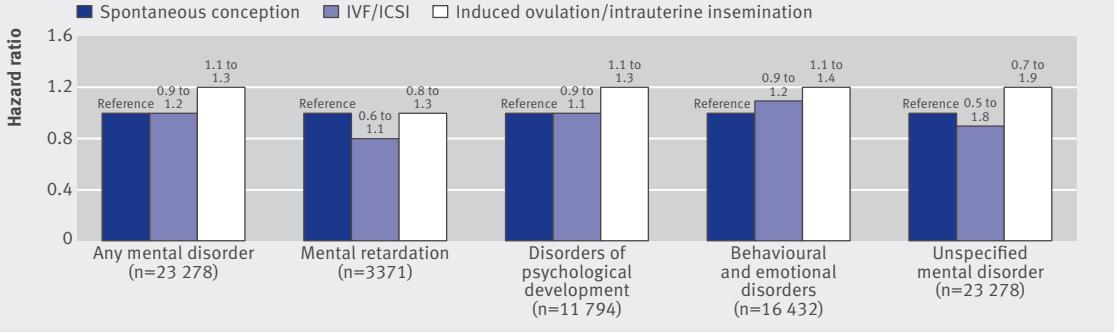
Although Danish national health registers are considered a source of high quality data covering the entire population, no registers are complete. Analyses were adjusted for maternal age, parity, educational level, smoking in pregnancy, psychiatric history, birth year, child's sex, and multiplicity. We cannot, however, rule out residual confounding.

While IVF/ICSI is more complex than ovulation induction/intrauterine insemination and includes both hormonal stimulation and in vitro manipulation of gametes, we found no relation with IVF/ICSI but instead an association with ovulation induction/intrauterine insemination, which includes hormonal treatment alone. The specific hormonal treatments differ mainly by the use of clomiphene citrate in induced ovulation. As we found no association with the use of this drug, the increased risk might not originate from the treatment but rather from underlying causes of parental subfertility in the ovulation induction/intrauterine insemination group.

Generalisability to other populations

The mechanisms of adverse effects related to fertility treatment or subfertility in the parents are not completely understood. The associations found in this study might therefore not be applicable in other populations where availability and procedures of fertility treatment are different.

Method of conception and hazard ratios for mental disorders in children, Denmark 1995-2012



Renal outcomes associated with invasive versus conservative management of acute coronary syndrome: propensity matched cohort study

Matthew T James,[1 2] Marcello Tonelli,[3] William A Ghali,[1 2] Merril L Knudtson,[1] Peter Faris,[2] Braden J Manns,[1 2] Neesh Pannu,[3] P Diane Galbraith,[2] Brenda R Hemmelgarn,[1 2] For the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) and Alberta Kidney Disease Network Investigators

[1]Department of Medicine, University of Calgary, Foothills Medical Centre, 1403 29th St NW, Calgary, Alberta, T2N 2T9, Canada
[2]Department of Community Health Sciences, University of Calgary, Alberta, Canada
[3]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
Correspondence to: M T James
mjames@ucalgary.ca

Cite this as: *BMJ* 2013;347:f4151
doi: 10.1136/bmj.f4151

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f4151

Study funding/potential competing interests
This study was funded by the Kidney Foundation of Canada.

STUDY QUESTION Is early invasive management of acute coronary syndrome associated with adverse renal outcomes and mortality, and do the risks or benefits of early invasive management differ in people with pre-existing chronic kidney disease?

SUMMARY ANSWER People who received early invasive management for non-ST segment elevation acute coronary syndrome were modestly more likely to develop acute kidney injury. They were, however, at similar risk of requiring dialysis and progression to end stage renal disease and had better long term survival than patients treated conservatively.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
People with pre-existing chronic kidney disease are less likely to receive invasive management of acute coronary syndrome. In this study, early invasive management was associated with similar relative risks of acute kidney injury, end stage renal disease, and survival across varying levels of baseline estimated glomerular filtration rate (eGFR), suggesting similar relative risks and benefits of early invasive management in people with and without pre-existing chronic kidney disease.

Participants and setting
Adults admitted to hospital with non-ST elevation acute coronary syndrome in Alberta, Canada between 2004 and 2009.

Interventions and outcome measures
Participants were stratified by baseline eGFR and matched 1:1 on their propensity score for early invasive management. We compared the risks of acute kidney injury, kidney injury requiring dialysis, progression to end stage renal disease, and all cause mortality between those who received early invasive versus conservative treatment (n=3384 matched pairs).

Design, size, and duration
Propensity score matched cohort study examining in-hospital and long term renal outcomes over a median of 2.5 years.

Main results and the role of chance
Early invasive management was associated with an increased risk of acute kidney injury (10.3 *v* 8.7%, risk ratio 1.18, 95% confidence interval 1.03 to 1.36; P=0.019) but no difference in the risk of acute kidney injury requiring dialysis or progression to end stage renal disease. Early invasive management was associated with reduced long term mortality.

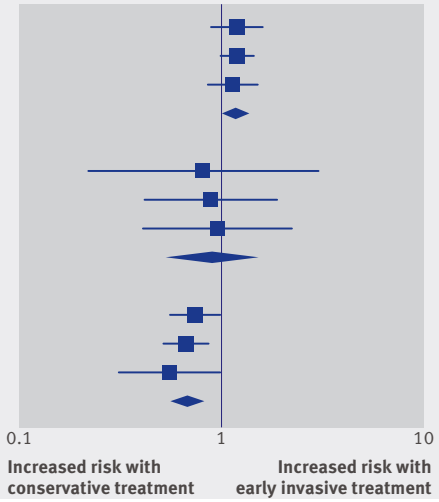
Bias, confounding, and other reasons for caution
Residual confounding remains possible owing to unmeasured variables such as frailty, which may influence both treatment selection and outcomes.

Generalisability to other populations
The study was conducted in a single geographical region in Canada. The availability and utilisation of cardiac catheterisation and rates of revascularisation after non-ST acute coronary syndrome may differ in other settings.

Outcomes with early invasive versus conservative management among propensity score matched patients admitted to hospital for non-ST elevation acute coronary syndrome, stratified by baseline estimated glomerular filtration rate (eGFR)

	No of matched pairs	No (events/100 person years) Early invasive treatment	Conservative treatment	Risk ratio (95% CI)	P interaction	Risk ratio (95% CI)
Acute kidney injury*						
eGFR ≥60	1948	95 (4.9)	80 (4.1)			1.19 (0.89 to 1.59)
eGFR 30-59	1363	213 (15.6)	179 (13.1)		0.996	1.19 (0.99 to 1.43)
eGFR <30	73	41 (56.2)	36 (49.3)			1.14 (0.86 to 1.51)
Overall	3384	349 (10.3)	295 (8.7)			1.18 (1.03 to 1.36)
End stage renal disease						
eGFR ≥60	1948	4 (0.1)	5 (0.1)			0.80 (0.22 to 3.00)
eGFR 30-59	1363	13 (0.4)	15 (0.4)		0.975	0.88 (0.42 to 1.86)
eGFR <30	73	11 (9.6)	11 (10.4)			0.96 (0.41 to 2.22)
Overall	3384	28 (0.3)	31 (0.4)			0.91 (0.55 to 1.49)
Mortality						
eGFR ≥60	1948	78 (1.6)	105 (2.2)			0.74 (0.56 to 0.99)
eGFR 30-59	1363	97 (3.0)	148 (4.4)		0.624	0.66 (0.52 to 0.85)
eGFR <30	73	21 (15.1)	33 (28.4)			0.55 (0.31 to 0.98)
Overall	3384	196 (2.4)	286 (3.4)			0.69 (0.58 to 0.82)

*Values are numbers (percentages) of participants



Effectiveness of pertussis vaccines for adolescents and adults: case-control study

Roger Baxter, Joan Bartlett, Ali Rowhani-Rahbar, Bruce Fireman, Nicola P Klein

Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza, Oakland, CA 94612, USA
Correspondence to: R Baxter
roger.baxter@kp.org

Cite this as: *BMJ* 2013;347:f4249
doi: 10.1136/bmj.f4249

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f4249

STUDY QUESTION

How effective are reduced acellular pertussis (Tdap) vaccines in preventing pertussis in adolescents and adults?

SUMMARY ANSWER

Tdap vaccines were moderately effective, reducing the risk of pertussis by about 60%, and the level of effectiveness was generally similar in people regardless of whether they had received all whole cell or all acellular pertussis vaccines in early childhood.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Studies have shown that the protection from acellular pertussis vaccines given in early childhood wanes substantially over time. This paper shows that the Tdap booster adds a moderate amount of protection against pertussis but also highlights the need for improved vaccines to prevent future outbreaks.

Participants and setting

All cases and controls were members of Kaiser Permanente Northern California, an integrated healthcare delivery system with electronic clinical data on 3.2 million members. The study period was from January 2006 to December 2011, a period that included the largest pertussis outbreak in California in over 50 years.

Design, size, and duration

In this case-control study, cases were people aged 11 years and older who tested positive for pertussis by polymerase chain reaction (PCR) during the study period. We used two different control groups for comparison: people who tested negative for pertussis during the study period and matched controls from the general Kaiser Permanente Northern California population. We used conditional logistic regression to estimate the association of Tdap vaccination with the odds of pertussis infection, with adjustment for calendar time, pertussis vaccine type received in early childhood, age, sex, race or ethnic group, and medical clinic. We calculated vaccine effectiveness as 1 minus the adjusted odds ratio. The study population included 668 cases, 10 098 PCR negative controls, and 21 599 Kaiser Permanente Northern California matched controls.

Effectiveness of acellular pertussis vaccine in preventing polymerase chain reaction (PCR) confirmed pertussis in overall study population, Kaiser Permanente Northern California (KPNC), 2006-11

Comparison group for PCR positive cases	Vaccine effectiveness (%) (95% CI)	P value
PCR negative controls	53.0 (41.9 to 62.0)	<0.001
KPNC (entire health plan population) controls	64.0 (55.5 to 70.9)	<0.001

Primary outcome

PCR confirmed pertussis.

Main results and the role of chance

Tdap vaccination rates were 24.0% in PCR positive cases and 31.9% in PCR negative controls (P<0.001). Tdap vaccination was estimated to reduce the risk of PCR confirmed pertussis by 53% (95% confidence interval 42% to 62%) in the comparison with PCR controls and by 64% (56% to 71%) in the comparison with Kaiser Permanente Northern California controls. The effectiveness of Tdap vaccines was broadly similar across subgroups who had received either whole cell or acellular pertussis vaccines in infancy.

Bias, confounding, and other reasons for caution

As an observational study, it is subject to confounding from unmeasured factors related to both Tdap vaccination and pertussis infection, such as the presence of pertussis infection in the household. If vaccinated cases were milder and care was delayed, this could result in more cases of pertussis that are PCR negative, leading to an underestimate of vaccine failures and a corresponding overestimate of vaccine effectiveness, especially in the comparison of cases with PCR negative controls. Problems with sensitivity or specificity of the PCR test that are not related to vaccination status would lead to an underestimate of vaccine effectiveness.

Generalisability

This study estimated vaccine effectiveness in the context of a large outbreak of pertussis in California in a diverse population that was generally vaccinated according to US guidelines.

Study funding/potential competing interests

No specific funding.

Practices and impact of primary outcome adjustment in randomized controlled trials: meta-epidemiologic study

Nazmus Saquib, Juliann Saquib, John P A Ioannidis

Stanford Prevention Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA
Correspondence to: J P A Ioannidis
jioannid@stanford.edu

Cite this as: *BMJ* 2013;347:f4313
doi: 10.1136/bmj.f4313

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f4313

STUDY QUESTION

Do adjustment practices for primary outcomes of randomized controlled trials impact study results and conclusions?

SUMMARY ANSWER

There is large diversity on whether and how analyses of primary outcomes are adjusted in randomized controlled trials, and these choices can sometimes change the nominal significance of the results, particularly when the presence of an effect is tenuous.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Covariates are handled in diverse ways in the analysis of primary outcomes of randomized controlled trials. It is common for analysis plans on adjustments to differ between protocols and published papers, but this can be discerned only when protocols are obtained from authors, since detailed information on the analysis plan is rarely available. Moreover, unadjusted versus adjusted results sometimes differ in the level of nominal significance, and investigators usually select to report the more favorable results.

Selection criteria for studies

We searched for randomized controlled trials published in print in 2009 in 25 high impact biomedical journals. We randomly selected 200 from the 684 eligible main trial papers. We tried to retrieve protocols of these trials from trial registries, design papers, and directly from the authors.

Primary outcome

We examined differences in level of nominal statistical significance between unadjusted and adjusted models of the primary outcome.

Main results and role of chance

19% (38/199) of trials provided both unadjusted and adjusted analyses. In 18% of the comparisons (7/40, two trials had two comparisons each), nominal statistical significance was discordant between the two types of analyses. In six of these seven cases, authors focused primarily on the result that was more favorable or less unfavorable for the experimental treatment. Protocol information was rarely published. Of the 60 protocols that we were able to retrieve (most of them directly contributed by the authors), the adjustment plan did not match the main paper in 47% (28/60) of the trials: 21 reported analyses that had not been specified in the protocol and seven did not report analyses that had been specified in the protocol.

Bias, confounding, and other reasons for caution

10 of the 38 trials that reported both types of analyses were missing on one or both effect estimates. Hence we were unable to examine the magnitude of the differences and had to rely on the reported nominal significance. For more than two thirds of the trials, it was not possible to retrieve the trial protocols from the authors.

Study funding/potential competing interests

This study received no funding. We have no competing interests.

Flow diagram for 199 evaluated trials: availability of information on model adjustment for primary outcomes from trial registry, design paper, or full protocol provided by trial authors