

What is already known on this topic

Increased paternal age is associated with several diseases, possibly due to the age associated increase in sporadic de novo mutations in male germ cells

Several studies have reported an association between paternal age at conception and their offspring's risk of schizophrenia

If this association was due to de novo mutations one would expect to find a stronger association between paternal age and schizophrenia in cases with no family history of the disorder

What this study adds

There is a strong positive association between paternal age and schizophrenia that is not due to sociodemographic, birth related, or socioeconomic factors or family history or early parental death

Paternal age is only weakly associated with other non-schizophrenic non-affective psychosis

This association is stronger in those with no family history of schizophrenia, supporting the hypothesis that accumulating de novo mutations in the germ lines of older fathers could play an important part in the aetiology of schizophrenia

- El Saadi O, Pedersen CB, McNeil TF, Saha S, Welham J, O'Callaghan E, et al. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. *Schizophr Res* 2004;67:227-36.
- Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, et al. Advancing paternal age and the risk of schizophrenia. *Arch Gen Psychiatry* 2001;58:361-7.
- Zammit S, Allebeck P, Dalman C, Lundberg I, Hemmingson T, Owen MJ, et al. Paternal age and risk for schizophrenia. *Br J Psychiatry* 2003; 183:405-8.
- Crow JF. The high spontaneous mutation rate: is it a health risk? *Proc Natl Acad Sci USA* 1997;94:8380-6.
- Zhang Y, Kreger BE, Dorgan JF, Cupples LA, Myers RH, Splansky GL, et al. Parental age at child's birth and son's risk of prostate cancer. The Framingham study. *Am J Epidemiol* 1999;150:1208-12.
- Hemminki K, Kyronen P. Parental age and risk of sporadic and familial cancer in offspring: implications for germ cell mutagenesis. *Epidemiology* 1999;10:747-51.
- Wilkin DJ, Szabo JK, Cameron R, Henderson S, Bellus GA, Mack ML, et al. Mutations in fibroblast growth-factor receptor 3 in sporadic cases of achondroplasia occur exclusively on the paternally derived chromosome. *Am J Hum Genet* 1998;63:711-6.
- Crow JF. Development. There's something curious about paternal-age effects. *Science* 2003;301:606-7.
- Malaspina D, Corcoran C, Fahim C, Berman A, Harkavy-Friedman J, Yale S, et al. Paternal age and sporadic schizophrenia: evidence for de novo mutations. *Am J Med Genet* 2002;114:299-303.
- Dalman C, Thomas HV, David AS, Gentz J, Lewis G, Allebeck P. Signs of asphyxia at birth and risk of schizophrenia. Population-based case-control study. *Br J Psychiatry* 2001;179:403-8.
- Gunnell D, Rasmussen F, Fouskakis D, Tynelius P, Harrison G. Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. *Am J Epidemiol* 2003;158:291-300.
- Pearlson GD. Neurobiology of schizophrenia. *Ann Neurol* 2000;48:556-66.
- Velakoulis D, Wood SJ, McGorry PD, Pantelis C. Evidence for progression of brain structural abnormalities in schizophrenia: beyond the neurodevelopmental model. *Aust N Z J Psychiatry* 2000;34 suppl:S113-26.
- Sipos A, Harrison G, Gunnell D, Amin S, Singh SP. Patterns and predictors of hospitalisation in first-episode psychosis. Prospective cohort study. *Br J Psychiatry* 2001;178:518-23.
- Dalman C, Broms J, Cullberg J, Allebeck P. Young cases of schizophrenia identified in a national inpatient register—are the diagnoses valid? *Soc Psychiatry Psychiatr Epidemiol* 2002;37:527-31.
- David AS, Malmberg A, Brandt L, Allebeck P, Lewis G. IQ and risk for schizophrenia: a population-based cohort study. *Psychol Med* 1997;27:1311-23.
- Office of National Statistics. *Birth statistics: review of the registrar general on births and family building patterns in England and Wales—F.M1*. London: Stationery Office, 2002.
- Brewin J, Cantwell R, Dalkin T, Fox R, Medley I, Glazebrook C, et al. Incidence of schizophrenia in Nottingham. A comparison of two cohorts, 1978-80 and 1992-94. *Br J Psychiatry* 1997;171:140-4. (Accepted 4 August 2004)

doi 10.1136/bmj.38243.672396.55

Conclusions

Our findings confirm advancing paternal age as a strong independent risk factor for schizophrenia and indicate that 15.5% of cases of schizophrenia in our cohort could be due to the patient having a father who was aged >30 years at birth. We found a stronger association in subjects without a family history of schizophrenia, providing further evidence to support the theory that accumulating de novo mutations in the germ cells of older fathers might contribute to an increased risk of schizophrenia in their offspring.

In England and Wales the average paternal age has increased from 29.2 years in 1980 to 32.1 in 2002.²⁰ Assuming a background annual incidence rate for schizophrenia of 10/100 000²¹ and that the association is causal, our results suggest that the increase in paternal age since 1980 could account for 710 out of the 6633 new cases of schizophrenia diagnosed in the United Kingdom in 2002.

We thank Christina Dalman, Peter Allebeck, and Susanne Wicks for their helpful comments, Stan Zammit for his help with accessing all the relevant literature, and Geoff Adams for statistical/database support.

Contributors: See bmj.com

Funding: Stanley Medical Research Institute.

Competing interests: None declared.

Ethical approval: The ethics committee at the Karolinska Institute, Stockholm, Sweden, approved this study.

- Brown AS, Schaefer CA, Wyatt RJ, Begg MD, Goetz R, Bresnahan MA, et al. Paternal age and risk of schizophrenia in adult offspring. *Am J Psychiatry* 2002;159:1528-33.
- Byrne M, Agerbo E, Ewald H, Eaton WW, Mortensen PB. Parental age and risk of schizophrenia: a case-control study. *Arch Gen Psychiatry* 2003; 60:673-8.
- Dalman C, Allebeck P. Paternal age and schizophrenia: further support for an association. *Am J Psychiatry* 2002;159:1591-2.

Corrections and clarifications

ABC of preterm birth: Immediate care of the preterm infant

A drug dosage cited in this article by Peter W Fowle and William McGuire substantially understated the correct dose (9 October, pp 845-8). In the box entitled "Drugs used in acute resuscitation of the preterm infant" (p 847), we correctly stated that the dosage of dextrose (in needed) is 2.5 ml/kg, but the amount of 10% dextrose to be given is in fact 250 mg/kg (not 250 µg/kg, as was stated).

The PROGRESS trial three years later: time for more action, less distraction (commentary)

A misspelling of someone's name was not picked up until after this commentary by Stephen MacMahon and colleagues had gone to press (23 October, p 970-1). In the contributors section, Jeffrey Cutler's name was misspelt.

Second drug firm found guilty of "switching" patients to new drugs

GlaxoSmithKline (GSK) wishes to point out that, contrary to what was reported in the opening section of this news article by Zosia Kmietowicz (16 October, p 875), the Airways Integrated Management Service (AIMS) was not found in breach of the Code of Practice of the Prescription Medicines Code of Practice Authority (set up by the Association of British Pharmaceutical Industry). GSK has not been told to withdraw the service. However, as was stated later in the article in a statement from GSK, "GSK accepts that the materials used to introduce [AIMS] to practices were, although unintentionally, in breach of the Code of Practice and has agreed to withdraw these materials." The company affirms that it has now withdrawn the materials and that it remains fully committed to the spirit and the letter of the Code of Practice.