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Author's reply: Dr Karunakaran rightly points out some problems with the interpretation of the Essock *et al* (1996) naturalistic study of clozapine. However, despite its imperfections, that study deserves some attention, both because it was a large study and because its naturalistic design attempted to replicate the conditions in which clozapine would be given in real clinical practice. The randomisation was not imperfect but unbalanced. The study was indeed not blinded, but this usually favours the experimental treatment, in this case clozapine. Application of the Structured Clinical Interview for DSM–IV confirmed that 95% of cases had a diagnosis of schizophrenia or schizoaffective disorder. It is indeed difficult to decide what outcome data to use, as I mention in my paper. However, despite the number of crossovers, an intention-to-treat analysis in such a large sample would be expected to show some difference if the effect of clozapine is substantial. In the Kane *et al* (2001) study I did use intention-to-treat data, but also repeated the analysis with non-intention-to-treat data, because of the curiously high drop-out rate in the comparison group.

My analysis was meant to draw attention to the fact that results of different studies are quite discrepant. The largest study to date, and one that appears to be methodologically robust, found only slight differences between clozapine and haloperidol, which are of doubtful clinical relevance (Rosenheck *et al*, 1997). In this situation simply quoting the results of a meta-analysis may be misleading.

Dr Kho is right to point out that long-term studies find smaller effects. This cannot be attributed to drop-out rates in the Rosenheck *et al* (1997) study, at least, where the higher drop-out rate in the haloperidol group would tend to produce an inflated difference between clozapine and the comparator drug. We also cannot assume that short-term studies simply measure pharmacological effects and long-term studies are confounded by non-compliance. Drugs may have different short- and long-term pharmacological effects. Short-term studies might be more likely to be confounded by non-specific factors such as differential expectations of treatments.

Essock, S. M., Hargreaves, W. A., Covell, N. H., *et al* (1996) Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacology Bulletin*, **32**, 683–697.

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Parental age difference and schizophrenia

To offer hypotheses based simply on clinical experience is pathetically out of date. Perhaps it may be allowed, for a moment, in deference to my advancing years.

Fifty years ago, with some other purpose in mind, I surveyed some 370 cases of schizophrenia in young men. It struck me that, with mild but undue frequency, there was a tendency for their parents' ages to be unusual in one of two ways – either by there being a >10-year age difference in the couple, or by the mother being older than the father. In decades of practice since, my impression has remained that this association with schizophrenia occurs a little too often to be accidental. Of course, to prove that would have required time, money, thousands of cases, and the inclination to undertake a major statistical enterprise, and none of those was in my reach.

It is therefore gratifying now to find that, at long last, my hypothesis has been solidly supported, albeit inadvertently, by Zammit *et al* (2003). They demonstrate, in a 26-year follow-up of some 50 000 teenagers, that advancing paternal age is a risk factor for schizophrenia, while maternal age is not – the latter being a significant negative finding to which, however, they pay no further attention. Since this means that, compared with the normal population, people with schizophrenia tend to have fathers who are older but mothers who are not, it follows necessarily that the age difference between the parents also tends to be greater than in the general population.

This does away with Zammit *et al*'s hypothesis that advancing paternal age is pathogenic for schizophrenia by virtue of increasing germ cell mutations. There is no need to invoke genetic mutation with age, given the linkage they have uncovered, in passing, between parental age difference and schizophrenia. A more economical hypothesis is that to be born to a statistically off-centre parental couple is a risk factor for schizophrenia – or, in more ordinary language, there is some psychological risk in being the child of an odd couple.

Are there other social oddities waiting to be identified statistically in schizophrenogenic couples?

Zammit, S., Allebeck, P., Dalman, C., *et al* (2003) Paternal age and risk for schizophrenia. *British Journal of Psychiatry*, **183**, 405–408.

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Authors' reply: Dr Bourne suggests that as advancing paternal, but not maternal age is associated with schizophrenia, then people with schizophrenia tend to have fathers who are older than the normal population, but mothers who are not. This is incorrect. In our study, as others have previously shown, advancing maternal age *is* associated with schizophrenia, but this association can be explained by paternal age, a consequence of the fact that there is strong correlation between parental ages.

Dr Bourne makes an interesting point, however, based on his observations in clinical practice that large differences in parental ages may result in some sort of psychological risk factor for schizophrenia in the offspring. In fact, the absolute difference between parental ages in our study is associated with schizophrenia in the crude analysis, but this association is eliminated after adjusting for the effects of paternal age (Table 1). As paternal age increases,

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Table 1 Crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for developing schizophrenia according to maternal–paternal age difference

Parental age difference (years)	Number in cohort (%)	Number with schizophrenia (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[1]
0–1[2]	10757 (23)	64 (0.59)	1.0	1.0
2–3	12711 (27)	85 (0.67)	1.1 (0.8–1.6)	1.1 (0.8–1.5)
4–5	9345 (20)	69 (0.74)	1.2 (0.9–1.7)	1.2 (0.8–1.7)
6–9	9260 (20)	77 (0.83)	1.4 (1.0–2.0)	1.2 (0.9–1.8)
10–47	4332 (10)	40 (0.92)	1.6 (1.0–2.3)	1.2 (0.8–1.9)
Linear trend across categories			1.12 (1.03–1.21)	1.06 (0.96–1.16)[3]

1. Adjusted for paternal age.
2. Baseline comparison group.
3. $P=0.249$.

the difference between maternal and paternal ages must also increase given the biological age threshold for motherhood. However, in younger fathers with older mothers, even large differences in parental ages is not associated with increasing risk of schizophrenia. In contrast, the association between advancing paternal age and risk of developing schizophrenia is not altered by adjusting for parental differences. The hypothesis of increasing germ cell mutations remains the most likely explanation for this association between advancing paternal age and risk of schizophrenia.

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Physical illness and schizophrenia

I read with interest the report by McCreadie (2003), which concludes that the lifestyle of people with schizophrenia must give cause for concern in relation to coronary heart disease. Despite being at an increased risk of developing various physical health problems, the detection rate and treatment of physical illness among people with mental illness is very poor (Koran *et al*, 1989). The reasons why this vulnerable group of patients do not receive the physical health care they deserve are manifold and need to be addressed. They range from physical symptoms being misinterpreted as part of psychiatric illness by professionals, to poor social skills, lack of motivation, cognitive impairment and social isolation occurring as part of mental illness making individuals with schizophrenia less likely to report symptoms and adhere to treatment. When they do present themselves, their lack of social skills and the stigma of mental illness may also make it less likely that they receive good care (Phelan *et al*, 2001).

Services focusing on lifestyle changes geared to the particular needs of people with severe mental illness should be planned. Periodic medical reviews by general practitioners using essential checklists should be mandatory. Inability to clearly appreciate or describe a medical problem, compounded by a reluctance to discuss such problems, contributes to the lack of attention to medical problems in patients with schizophrenia. Thorough, routine physical examination whenever a patient is seen is the best way forward but it is doubtful whether psychiatric services have the resources and time to implement this. It is necessary for a medical orientation on the part of psychiatrists while evaluating all patients. Refresher training should be regularly provided for psychiatrists and key members of multidisciplinary community psychiatric teams. This could encompass elements of detection, management and preventive counselling (Lambert *et al*, 2003). To ensure appropriate care for comorbid medical problems there should be active efforts on the part of general practitioners as well as mental health teams.

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Antidepressant effects of repetitive transcranial magnetic stimulation

The report by Martin *et al* (2003) seems in conflict with previous meta-analyses of repetitive transcranial magnetic stimulation (rTMS) (Holtzheimer *et al*, 2001; McNamara *et al*, 2001; Burt *et al*, 2002). We wish to provide a broader context for interpreting these results.

The analysis by Martin *et al* was designed to minimise type 1 error – to identify the level of confidence that can be placed in purported antidepressant effects of rTMS. It combined only studies with similar methodologies, included only studies that met high standards of randomisation and blinding, and analysed only end-point depression ratings (rather than analysing change scores or controlling for baseline depression severity). With this approach, the review found a statistically significant effect size for high-frequency (>1 Hz) rTMS applied to the left prefrontal cortex (-0.35, 95% CI -0.66 to -0.04, $P=0.03$), but did not find evidence that antidepressant effects were *clinically* significant or that they persisted over time.

The other meta-analyses attempted to minimise type 2 error – to identify whether there is reason to believe that rTMS might have significant antidepressant properties warranting further investigation. They combined studies with different methodologies and calculated effect sizes based on changes in depression severity over time. Such a technique can be important when analysing studies where different treatment arms may start at different baselines. Using these analytic techniques, prior meta-analyses found effect sizes for high-frequency, left prefrontal rTMS ranging from 0.5 to 0.8, suggesting that rTMS does

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