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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indeed have *statistically* significant antidepressant effects. However, these analyses all agree that the *clinical* significance of these effects is not yet established.

The results of the Martin *et al* review do not suggest at all that rTMS has no antidepressant effects. On the contrary, this methodologically rigorous review identifies statistically (but not clinically) significant, short-term antidepressant effects for 2 weeks of high-frequency, left prefrontal rTMS and recommends further studies to establish efficacy and identify optimal parameters. Even more importantly, numerous studies have shown that rTMS alters brain functioning, with effects ranging from altered gene expression in animals to modified cerebral perfusion in humans; in many cases, these effects are very similar to those seen with established antidepressant treatments.

With these points in mind, we offer the following recommendations to help guide use of rTMS in clinical and research settings.

(a) Given the small clinical effects seen with rTMS in studies to date, it does not seem that rTMS is appropriate for widespread clinical use at this time.

(b) Large, multi-site trials are warranted to clarify the antidepressant effects of rTMS.

(c) Future studies of rTMS should incorporate several improvements in study design, including appropriate (and well-documented) randomisation, adequate blinding of subjects and therapists (probably requiring an improved sham condition), and better assessment of the duration of any antidepressant effects.

(d) More research should be directed at clarifying which patient and treatment characteristics might lead to greater antidepressant effects with rTMS.

(e) More research should be directed at identifying and testing potential mechanisms by which rTMS produces antidepressant effects.

Declaration of interest

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Evidence in cannabis research

The article by Coffey *et al* (2003) regarding adolescent precursors of cannabis dependence has a number of substantial problems in the measures used, the analysis of data and the reporting and discussion of their findings. One of the study's major findings is that the 'relationship between cannabis dependence and persistent frequent drinking in adolescence changed direction, from a risk association in the univariate model to a *protective* association in the adjusted model' (Coffey *et al*, 2003: p. 333, emphasis added). The use of the term protective implies causality, rather than the negative correlation which more accurately portrays the statistical relationship. It also tacitly implies a value judgement that heavy drinking is preferable to cannabis dependence.

This study utilises logistic regression for the majority of its statistical analysis without adequately considering some important caveats. First and foremost, as already mentioned, correlation does not equal causality. This is particularly the case when there are a substantial number of independent variables associated with the dependent variable. In the case of cannabis use, as the authors point out, there are many independent variables related to cannabis use, such as socio-economic status (not discussed), parental drug use patterns (not discussed), antisocial behaviour, cigarette smoking and level of education, to name a few that are known. Statistical texts (e.g. Gravetter & Wallnau, 1996) point out that to gain the best measure from the use of logistic regression, there should be few independent variables that are unrelated to each other and that 'a regression solution is extremely sensitive to the combination of variables that is included in it' (Tabachnick & Fidell, 1996: p. 126).

These issues are particularly concerning when such papers can be reported in the mass media (as this study was) on a topic such as cannabis use, which generates strong public responses and is the forum for a great deal of misinformation and manipulation of research results to suit political and ideological agendas. The simple acknowledgement of study limitations would substantially improve the quality of the debate surrounding such a complex social, psychological and medical problem.

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The media response to Coffey *et al* (2003) was predictable. 'Anti-drug campaigners say new research, showing one in three teenagers who smokes cannabis weekly becomes hooked by their early 20s, proves that it should not be treated as a "soft" drug. The shocking study found teens who used cannabis every week were at high risk of addiction' (Lawrence, 2003). Coffey is quoted as saying, 'The message here is that

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