changes in thickness and area both contributed to the volume differences across groups in these gyri, even if the thickness and area results did not themselves reach statistical significance after rigorously controlling for overall brain changes.

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Michael P. Harms, Department of Psychiatry (Box 8134), Washington University School of Medicine, 660 S. Euclid Ave, St Louis, MO 63110, USA. Email: mharms@conte.wustl.edu; **Lei Wang**, Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago; **Carolina Campanella**, Department of Psychiatry, Washington University School of Medicine, St Louis; **Kristina Aldridge**, **Amanda J. Moffitt**, Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, Columbia; **John Kuelper**, Department of Psychiatry, Washington University School of Medicine, St Louis; **J. Tilak Ratnanather**, **Michael I. Miller**, Center for Imaging Science, The Johns Hopkins University, Baltimore; **Deanna M. Barch**, Department of Psychiatry, Washington University School of Medicine and Department of Psychology, Washington University, St Louis; **John G. Csernansky**, Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, USA

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Risk factors for suicide

The article by Manoranjitham *et al*[1] provides a great deal of insight into the risk factors for suicide in rural India. The study was conducted with the best possible methodology, using the surveillance system method carried out by a community health worker who is part of the same community. The authors employed verbal autopsy, pair matched the suicide case and control groups, used more than one informant to obtain the information, used the Structured Clinical Interview for DSM–III–R (SCID) to establish the psychiatric diagnosis and their study was adequately powered to investigate the desired outcome. The authors were very humble in acknowledging the limitations of the study which cannot be avoided in any set up. However, some of the issues need to be addressed before accepting the fact that it is not the psychiatric diagnosis but ongoing stress and chronic pain that are the most important predictors of suicide.

The results showed that 37% of the suicide group had a psychiatric diagnosis. However, the authors did not mention whether it was the current diagnosis or lifetime diagnosis. It is possible that the surveillance system which has been operational for so many years is also helpful in picking up psychiatric diagnosis early and arranging treatment, leading to lower rates of current psychiatric diagnosis in the suicide cases. The authors also did not provide any information about the relatives, as the information obtained about the person who completed suicide was collected by the health team and their accuracy can vary depending on the relationship, closeness and duration of stay of the informant with the person who died.

Further, although there was significant difference in some of the variables (living alone, break in steady relationship) between the two groups in the bivariate analysis, data presented in Table 3 suggest that these variables have not been included in the multivariate analysis. The arbitrary definition of 'ongoing stress' and 'chronic pain' is also not very clear. Studies in the past have reported that many physical illnesses are also risk factors for suicide,[2] but the authors did not provide any information with respect to this, nor did they use the same data in the analysis. Another important issue which needs to be considered is that the authors subsumed pain symptoms of 1 year duration under the risk factor of 'chronic pain'. It is well known that individuals with depression in primary care manifest their depression with somatic symptoms, especially painful symptoms.[3,4] This underlying depression was not picked up by SCID, resulting in such low prevalence of affective disorders in both groups. Previous studies[5] have used life events as a single variable while trying to find the association of risk factors with suicide. Here, the authors have possibly analysed them as individual risk factors and therefore acute stress has not emerged as an important predictor. Similarly, the issue of comorbidity (presence of more than one psychiatric diagnosis or presence of psychiatric and physical illness together) has not been addressed.

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Prabhakar Holikatti, Department of Psychiatry, Postgraduate Institute of Medical Education and Research (PGIMER,) Chandigarh, India; **Sandeep Grover**, Department of Psychiatry, PGIMER, Chandigarh, India. Email: drsandeepg2002@yahoo.com

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Authors' reply: We would like to clarify the points raised by Holikatti & Grover. We presented the current psychiatric diagnoses within the past month as assessed by the interview. The therapeutic effects of the surveillance system and the variance due to interviewing first-degree relatives are in common to both cases and controls, and hence we believe that these factors did not affect the results of our study. We could not include the variables 'living alone' and 'break in steady relationship', which were significant in the bivariate analyses, in the multivariate procedure as these variables were absent among the controls and hence it is not possible to calculate odds ratios and to include them in logistic regression.

Our study had *a priori* definitions for 'chronic pain' and 'ongoing stress' described in the paper, which also provides the details of psychiatric diagnoses. Holikatti & Grover suggest that chronic pain symptoms can be attributed to underlying depressive disorders. However, the contemporary classificatory systems in psychiatry have not approved the concept of 'masked depression' and they have not included pain symptoms in their diagnostic criteria for depression. Pain is a subjective experience, which has a psychological component. Psychiatrists tend to attribute human

distress to disease and medicalise all depression.[1] Our data argue that psychosocial stress and social isolation, rather than psychiatric morbidity, are risk factors for suicide in rural south India.[2]

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S. D. Manoranjitham, Department of Psychiatric Nursing; **A. P. Rajkumar**, Department of Psychiatry; **K. S. Jacob**, Department of Psychiatry, Christian Medical College, Vellore 632002, India. Email: ksjacob@cmcvellore.ac.in

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Fetal androgens and autism

In their comprehensive meta-analysis of the literature on prenatal risk factors for autism, Gardener *et al*[1] examined and summarised more than 50 such antecedents. Under prenatal factors associated with an increased risk of later autism in the child, Gardener *et al* listed advanced parental age, maternal use of medication, maternal birth place abroad, bleeding, gestational diabetes, and sibling rank. The authors were rightly cautious to draw strong conclusions from these meta-analytic findings, as the evidence for a role of any of these prenatal risk factors in the aetiology of autism is not sufficient, although on the whole this set of findings suggests that complications during pregnancy in general might contribute to an increased risk for autism.

Fetal sex-hormone profiles might be added to the above list of identified prenatal antecedents of autism. The sex difference in the lifetime prevalence of autism-spectrum disorders, wherein boys and men exceed girls and women by a large margin, is well-known and has partly been attributed to possible influences of early (i.e. organisational) sex-hormone action which contributes to gender differences in neurocircuitry and neuroanatomy.[2]

A role of fetal androgens for autism is suggested by recent research on the second-to-fourth digit ratio (2D:4D), a currently widely studied biomarker.[3] Many researchers believe that 2D:4D might provide a useful retrospective window into the prenatal sex-hormonal milieu during critical neurodevelopmental phases of fetal life (i.e. the second trimester) and might be a biomarker for prenatal testosterone exposure and sensitivity specifically.[4] Human 2D:4D is sexually differentiated (lower in the male than in the female gender), and gender and individual differences in 2D:4D emerge prenatally and are preserved during the growth phases of postnatal life.[4] Among other supportive evidence for the validity of this anatomical marker, lower (i.e. more male-typical) 2D:4D has been found to be associated with higher sensitivity to testosterone (as effectuated through functional polymorphisms in the androgen receptor gene) and with a higher testosterone-to-oestradiol ratio, as assayed from the amniotic fluid.[4]

Consistent with the above reasoning and background, Manning *et al*[5] found that children with autism or high-functioning autism (Asperger syndrome), as well as their unaffected first-degree relatives (i.e. siblings, mothers, and fathers), have conspicuously lower (i.e. hypermasculinised) 2D:4D than healthy general population controls. Since then, the gist of this interesting evidence has been independently replicated by some ten further studies (reviewed elsewhere).[6] Inter alia, the evidence base now includes successful replications across ethnicity (East Asians and Caucasians) and similar findings of a low (masculinised) 2D:4D among children with various subtypes of attention-deficit/hyperactivity disorder,[6] all in all indicating that the effect is robust.

Of note, the initial study in this line of research (Manning *et al*),[5] as well as subsequent related research reports, are found in PubMed when using the search terms Gardener *et al*[1] used. So it may well be that Gardener *et al* did not include this literature in their meta-analysis on the grounds that they categorised it under 'medical hypotheses', one of their listed non-eligibility criteria. However, it is interesting that Gardener *et al*, in their discussion, also noted the following general limitations: (a) only few prenatal risk factors for autism have been examined in multiple studies; (b) generally, fewer than six studies for any of these factors could be included; and (c) when risk factors were examined across multiple studies, the evidence was, for the most part, inconsistent. A formal meta-analysis of the emerging literature on 2D:4D and autism is beyond the present scope, but it is evident from one review[6] that the limitations noted by Gardener *et al* do not apply for this literature. All in all, the evidence points to a possible role of masculinised sex-hormone profiles, already arising *in utero*, as a further prenatal risk factor in the pathways leading to the neurodevelopmental disorder autism.

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Martin Voracek, Department of Basic Psychological Research, School of Psychology, University of Vienna, Liebiggasse 5, Rm 03-46, A-1010 Vienna, Austria. Email: martin.voracek@univie.ac.at

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Authors' reply: We note with interest the comments raised by Voracek. He suggests that sex-hormone exposures *in utero* may play a role in the aetiology of autism, and that the second-to-fourth digit (2D:4D) ratio may be a marker for fetal androgen exposure. This seems to be a plausible hypothesis, and we believe that the potential association between the 2D:4D ratio and autism risk deserves further exploration. More importantly, studies on the direct effect of fetal sex-hormone profiles on autism risk are warranted.

However, the 2D:4D ratio was not included in our meta-analysis of potential prenatal risk factors for autism because it was not considered to be a prenatal exposure variable itself, although it likely represents the effects of prenatal exposures, in particular sex steroid hormones. There are many characteristics that become evident after birth that are likely due to prenatal exposures, but in our meta-analysis of risk factors for autism we focused only on those variables that could be assessed during the prenatal period (e.g. maternal medication use, parental age). Voracek speculates 'that Gardener *et al* did not include this