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]

1 Heath I. There must be limits to the medicalisation of human distress. *BMJ* 1999; **318**: 439–40.

2 Manoranjitham SD, Rajkumar AP, Thangadurai P, Prasad J, Jayakaran R, Jacob KS. Risk factors for suicide in rural south India. *Br J Psychiatry* 2010; **196**: 26–30.

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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.

1 Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. *Br J Psychiatry* 2009; **195**: 7–14.

2 Baron-Cohen S, Knickmeyer RC, Belmonte MK. Sex differences in the brain: implications for explaning autism. *Science* 2005; **310**: 819–23.

3 Voracek M, Loibl LM. Scientometric analysis and bibliography of digit ratio (2D:4D) research, 1998–2008. *Psychol Rep* 2009; **104**: 922–56.

4 McIntyre MH. The use of digit ratios as markers for perinatal androgen action. *Reprod Biol Endocrinol* 2006; **4**: 10.

5 Manning JT, Baron-Cohen S, Wheelwright S, Sanders G. The 2nd to 4th digit ratio and autism. *Dev Med Child Neurol* 2001; **43**: 160–4.

6 Voracek M. Digit ratio (2D:4D) as a marker for mental disorders: low (masculinized) 2D:4D in autism-spectrum disorders, high (feminized) 2D:4D in schizophrenic-spectrum disorders. *Behav Brain Sci* 2008; **31**: 283–4.

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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