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Contents

Putative high risk for psychosis should not be considered a disorder

The paper by Fusar-Poli and colleagues on functioning and quality of life (QoL) in people meeting supposed 'high-risk' status for psychosis[1] concludes, *inter alia*, that high-risk individuals do not differ statistically from individuals with established psychotic disorders in terms of QoL. This conclusion is used to help justify the views of the authors that 'impairments in functioning and QoL are key features of the high-risk state' (p. 201) and that high risk is 'not just a state of risk' but a 'disorder' (in their title). However, reference to the original paper by Francey and colleagues[2] shows that QoL was actually *higher* in high-risk individuals than a first-episode psychosis comparison group. Thus the meta-analytic results shown in Fig. 2(b) of the paper by Fusar-Poli *et al*[1] are incorrect and, should the correct data be applied, would show that supposed high-risk individuals have overall better QoL than those with a 'true' psychotic illness.

Also of relevance in the study of Francey *et al*[2] was that QoL did not distinguish those high-risk individuals who supposedly transitioned to psychosis from those who did not, again throwing doubt on the views of Fusar-Poli *et al* that these supposed deficits reinforce the case for 'prevention of transition' (p. 204) and 'treatment of the current condition'. These latter 'clinical implications' are not, to my mind, supported by the data presented and disavow the fact that the majority of people supposedly at high risk for psychosis do not develop a psychotic illness and also that no treatment has consistently and replicably been shown to alter the likelihood of such transition.[3] Hence, the assumption that the data presented should persuade us that the high-risk state is a 'disorder' or even a 'condition' is beyond me.

Finally, the authors attribute to me a view that high-risk individuals are 'not at all dysfunctional' (p. 200), but this is disingenuous: the point is that the supposed high-risk state is composed of a heterogeneous group of individuals and that many of them cannot be considered to have a 'disorder' in a heuristic, predictive or treatment sense.

1 Fusar-Poli P, Rocchetti M, Sardella A, Avila A, Brandizzi M, Caverzasi E, et al. Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *Br J Psychiatry* 2015; **207**: 198–206.

2 Francey SM, Jackson HJ, Phillips LJ, Wood SJ, Yung AR, McGorry PD. Sustained attention in young people at high risk of psychosis does not predict transition to psychosis. *Schizophr Res* 2005; **79**: 127–36.

3 Castle DJ. Is it appropriate to treat people at high-risk of psychosis before first onset? *Med J Australia* 2012; **196**: 557.

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Authors' reply: Following the letter by Castle, we confirm an error in the secondary outcomes reported in Fig. 2(b) of our manuscript. We have now corrected it, and repeated the literature search by adopting an additional search criterion. We have directly contacted the leading authors of the largest clinical high-risk studies conducted in the past decade to seek additional quality of life (QoL) comparisons between high-risk patients and those with first-episode psychosis. We have then repeated the meta-analysis (see Fig. 1 below), which now included 238 patients at high risk compared with 205 patients with psychosis. The final results were unchanged as compared to those reported in our original analysis.[1] There is no meta-analytical difference between the subjective QoL of patients at high risk of psychosis and those with frank psychosis (Hedges' $g = 0.211$, 95% CI −0.148 to 0.571, $P = 0.249$; $Q = 9.518$, d.f. = 3, $I^2 = 68.48$, $P = 0.023$). This secondary meta-analytical comparison is based on a few studies only. However, should new studies become available in the near future, and eventually show a better subjective QoL in clinical high-risk patients as compared with controls, the core finding of our analysis would still remain unchanged. Indeed, our primary aim was to show that patients clinically at high risk for psychosis have significant impairments in functioning and QoL when compared with healthy controls: patients with psychosis were used as a benchmark group for comparative purposes only.

1 Fusar-Poli P, Rocchetti M, Sardella A, Avila A, Brandizzi M, Caverzasi E, et al. Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *Br J Psychiatry* 2015; **207**: 198–206.

2 Addington J, Penn D, Woods SW, Addington D, Perkins DO. Social functioning in individuals at clinical high risk for psychosis. *Schizophr Res* 2008; **99**: 119–24.

Study name	Outcome	Hedges' *g*	Lower limit	Upper limit	*P*
Addington *et al* (2008)[2]	QLS-role	0.507	0.217	0.796	0.001
Bechdolf *et al* (2005)[3]	MSQoL	0.119	−0.303	0.542	0.580
Francey *et al* (2005)[4]	QLS	0.441	0.021	0.860	0.039
Koike *et al* (2013)[5]	WHOQOL-BREF	0.376	−0.899	0.146	0.158
Overall random		0.211	−0.148	0.571	0.249

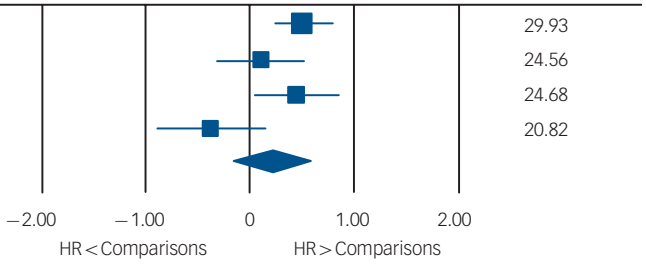

Fig. 1 Meta-analytical comparison of quality of life between patients at high clinical risk for psychosis and patients diagnosed with frank psychosis (Comparisons).

HR, high risk; MSQoL, Modular System for Quality of Life; QLS, Quality of Life Scale; QLS-role, role functioning subscale of the Quality of Life Scale; WHOQOL-BREF, abbreviated version of the World Health Organization Quality of Life assessment.

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3 Bechdolf A, Pukrop R, Kohn D, Tschinkel S, Veith V, Schultze-Lutter F, et al. Subjective quality of life in subjects at risk for a first episode of psychosis: a comparison with first episode schizophrenia patients and healthy controls. *Schizophr Res* 2005; **79**: 137–43.

4 Francey SM, Jackson HJ, Phillips LJ, Wood SJ, Yung AR, McGorry PD. Sustained attention in young people at high risk of psychosis does not predict transition to psychosis. *Schizophr Res* 2005; **79**: 127–36.

5 Koike S, Takano Y, Iwashiro N, Satomura Y, Suga M, Nagai T, et al. A multimodal approach to investigate biomarkers for psychosis in a clinical setting: the integrative neuroimaging studies in schizophrenia targeting for early intervention and prevention (IN-STEP) project. *Schizophr Res* 2013; **143**: 116–24.

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Childhood environment and intergenerational transmission of depression

Plant and colleagues, in a very interesting and elegant study,[1] found that maternal depression during pregnancy was associated with: offspring depression in adulthood (odds ratio (OR) 3.4), maternal depression during offspring's childhood (OR = 4.8), and offspring exposure to child maltreatment (OR = 2.4). However, as the authors said, 'when childhood factors (i.e. child maltreatment, maternal depression 1–16 years) were entered at the second steps, prenatal maternal depression no longer predicted significantly offspring depression'. In our view, these findings are suggestive that the key causal factor is not maternal depression during pregnancy, but maternal depression during offspring childhood and child maltreatment (probably the former promoting the later). Since maternal depression during pregnancy probably does not directly cause child maltreatment or later maternal depression, these two should not be viewed as mediators or mechanisms of the association found between maternal depression during pregnancy with offspring depression in adulthood. Since after adding the childhood factors there is no statistical correlation of maternal depression during pregnancy with offspring depression in adulthood anymore, this seems suggestive that maternal depression during pregnancy is more probably a marker of mothers with higher risk of developing depression during offspring childhood and of offering/allowing maladaptive parental behaviour. This is in line with previous studies showing that environmental factors, especially maladaptive parental behaviour, were total or partial mediators of the association between parental and offspring depressive symptoms.[2–4] Despite maternal depression during pregnancy being a marker of an at-risk mother–child dyad, the actual causal factors seem to be the factors happening during childhood: maternal depression and parental behaviour. So, preventive measures should focus on screening mothers with depression (during pregnancy, but especially during offspring childhood), providing treatment and support for adequate parental behaviour.

However, the authors' conclusions go in the opposite direction. In the paper's discussion, it is stated 'we did not find that exposure to maternal depression after birth contributes to this association (maternal depression during pregnancy with offspring depression in adulthood). This suggests that exposure to maternal depression specifically during pregnancy represents a unique setting for the intergenerational transmission of risk for depression'. However, the results section states 'offspring exposure to maternal depression during childhood (1–16 years) was associated significantly with offspring adulthood depression (OR = 4.2)'. They see their study 'in line with the theoretical premise of fetal programming', related to elevated levels of maternal glucocorticoids at the intrauterine environment. Finally, for preventive measures, they emphasise screening and treating expectant mothers with depression, supporting the use of antidepressants during pregnancy. These are valuable measures, but not supported by this study results.

In summary, in our perspective, this extremely well-done study supports the view that childhood factors (parental behaviour and maternal depression) have key causal implications on intergenerational transmission of depression. Preventive measures should focus mainly on childhood, providing treatment and support for adequate parental behaviour.

1 Plant DT, Pariante CM, Sharp D, Pawlby S. Maternal depression during pregnancy and offspring depression in adulthood: role of child maltreatment. *Br J Psychiatry* 2015; **207**: 213–20.

2 Johnson JG, Cohen P, Kasen S, Smailes E, Brook JS. Association of maladaptive parental behavior with psychiatric disorder among parents and their offspring. *Arch Gen Psychiatry* 2001; **58**: 453–60.

3 Tully EC, Iacono WG, McGue M. An adoption study of parental depression as an environmental liability for adolescent depression and childhood disruptive disorders. *Am J Psychiatry* 2008; **165**: 1148–54.

4 Elgar FJ, Mills RS, McGrath PJ, Waschbusch DA, Brownridge DA. Maternal and paternal depressive symptoms and child maladjustment: the mediating role of parental behavior. *J Abnorm Child Psychol* 2007; **35**: 943–55.

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Authors' reply: We thank Moreira-Almeida & Junqueira de Souza for their interesting correspondence on our paper. Indeed, we regard childhood environmental factors as highly important to the intergenerational pathways for the transmission of depression. Nevertheless, maternal depression during pregnancy in itself has been identified as a significant risk factor for offspring depression, not only in our sample, but also in other samples of varying demographics and size.[1,2]

There are plausible and documented mechanisms linking a mother's depression in pregnancy with her child's increased vulnerability to experiencing maltreatment; namely, changes to the mother–child attachment relationship, maladaptive caregiving behaviours, interparental conflict and increased offspring reactive temperament.[3] Such mechanisms likely operate by compromising levels of care and protection afforded by a mother, as well as directly affecting stress resiliency in her developing child, thereby increasing her child's vulnerability to being exposed to, and experiencing, episodes of maltreatment. Depression is a disorder with a recurrent course,[4] thereby meaning the likelihood of depression after birth is elevated following an episode during pregnancy. Additionally, the temporal precedence of antenatal depression to childhood maltreatment and further maternal depression after birth adds to the logic as to why antenatal depression should be considered as a primary risk factor in the intergenerational transmission of depression, and the aforementioned childhood adversities as mediators to this trajectory.

As Moreira-Almeida & Junqueira de Souza correctly highlight, in our multiple hierarchical regression models, maternal depression during pregnancy was not found to predict offspring adulthood

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