Acute lymphoblastic leukaemia in children – is there a role for *MTHFR*?

Over the last 10 years genetic variation in folate metabolism has received considerable scientific attention, but findings have been inconsistent, with many studies based on small numbers. Koppen *et al* (2010) recently reported on a meta-analysis of 14 studies that had investigated genetic polymorphisms in enzymes involved in folate metabolism in relation to both childhood and adult acute lymphoblastic leukaemia (ALL), concluding that both *MTHFR* 677 C>T and *MTHFR* 1298A>C were likely to be associated with decreased susceptibility to ALL in childhood.

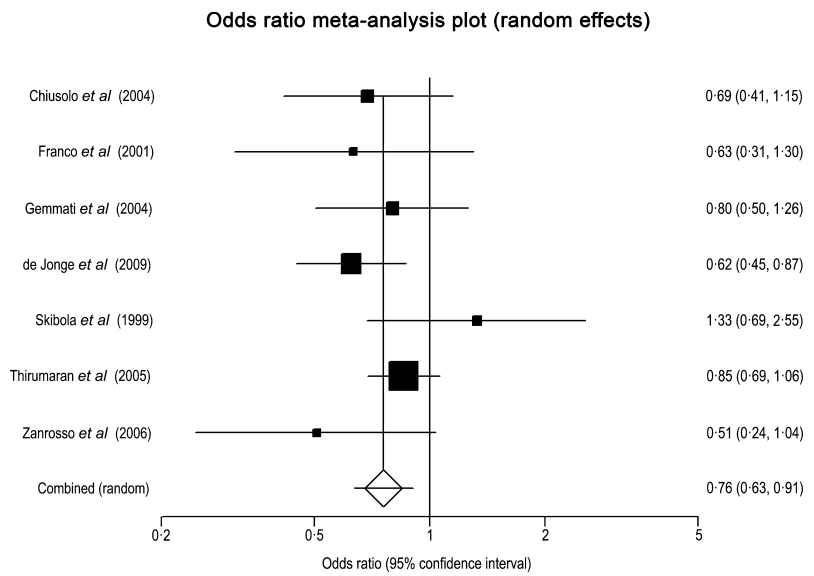

Fig. 1. MTHFR 677CT and susceptibility to childhood ALL reproduced from Koppen *et al*, 2010.

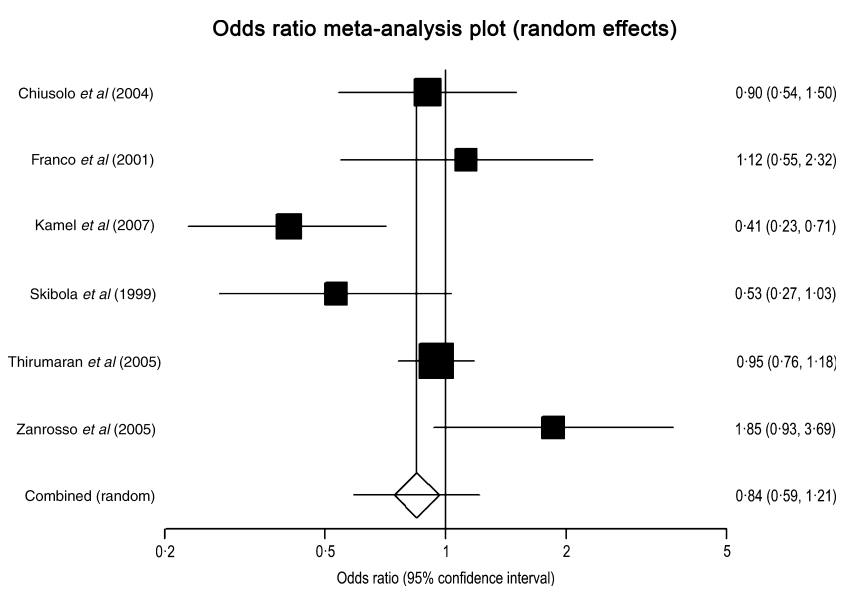

Fig. 2. MTHFR 1298AC and susceptibility to childhood ALL, reproduced from Koppen *et al*, 2010.

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We were however, somewhat surprised to see the authors combined data from children and adults in the same plot, despite the fact that two previous meta-analyses, neither of which were referenced by Koppen *et al* (2010), stratified their data by diagnostic age (Pereira *et al*, 2006; Zintzaras *et al*, 2006). Indeed, the meta-analysis plots of childhood ALL (Figures 1 and 2 reproduced from Koppen *et al*, 2010) included two studies that contained no data on children at all (Skibola *et al*, 1999; Gemmati *et al*, 2004) as well as one study that comprised both children and adults (Chiusolo *et al*, 2004). Whilst this was acknowledged in the text in the case of the study by Gemmati *et al* (2004), no such recognition was afforded our own UK study (Skibola *et al*, 1999). Moreover several published studies where no association with *MTHFR* 677 was observed are missing from the review, including data from Canada (Krajinovic *et al*, 2004)($n = 270$), Turkey (Balta *et al*, 2003) ($n = 144$) and Slovenia (Petra *et al*, 2007) ($n = 68$).

From their comprehensive meta analysis of 4894 individuals Pereira *et al* (2006) concluded that whilst the *MTHFR* 677 polymorphism is important for risk of ALL, it is confined to adults. This is supported by recent data from the largest study to date, which included 939 children with ALL recruited into the United Kingdom Childhood Cancer Study (http://www.UKCCS.org) (Lightfoot *et al*, 2010).

Given the missing childhood data and the inclusion of adult data, we believe that the conclusion for a protective role for *MTHFR* among children drawn by the authors of the recent meta-analysis (Koppen *et al*, 2010), is misleading.

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