LETTER TO THE EDITOR

Is hyperhomocysteinaemia a minor risk factor for venous thrombosis or subject to publication bias?

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To the Editor,

In the editorial by Lugthart[1], we were surprised to find hyperhomocysteinaemia being classified as a known risk factor for venous thrombosis. The consensus now is that hyperhomocysteinaemia is not a risk factor for venous thrombosis. The lack of dissemination of this in the general field of medicine might have to do with several findings. First, patients with cystathionine β-synthase deficiency (CBSD), leading to homocystinuria, have a high risk of thrombosis.[2] Reduction of homocysteine levels with B vitamins in these patients led to a spectacular decrease of 80% in the absolute cumulative risk of any thrombosis in one landmark study.[2] However, homocysteine levels in patients with CBSD are much higher than 100 µmol/l, while homocysteine levels in the normal population are much lower. Therefore, translating treatment of homocystinuria in patients with CBSD to a normal population needs to be done with caution. Indeed (second reason), trials with vitamin B in individuals without CBSD have not shown a decrease in risk of venous thrombosis.[3,4]

A third reason why it has been believed that hyperhomocysteinaemia is a cause of venous thrombosis is due to Mendelian randomisation studies. Individuals with the MTHFR C677T mutation, who have genetically higher levels of homocysteine, are at increased risk of venous thrombosis according to the latest meta-analysis on this issue, conducted in 2005.[5] However, the authors did not exclude the possibility of publication bias. To do so, we drew a funnel plot on the data of this meta-analysis[5] including 52 of 54 studies (data not retrievable for 2). As shown in *figure 1*, potential publication bias cannot be excluded, i.e. smaller studies or studies of lower quality reporting against an association might be underrepresented. Moreover, in 2007 Bezemer et al.[6] found no association between MTHFR C677T genotype and venous thrombosis (see diamond in *figure 1*), providing further evidence that the association between hyperhomocysteinaemia and venous thrombosis is probably biased.

Altogether, hyperhomocysteinaemia appears to be a very minor risk factor for venous thrombosis in general, based on evidence that might have been subject to publication bias, without the possibility to intervene on the attributable risk. In accordance, it is no longer mentioned in the list of risk factors for venous thrombosis in acknowledged guidelines (American College of Chest Physicians,[7] National Clinical Guideline Center from the UK[8]). We appeal for a consistent and similar policy in the general field of medicine in order to prevent further misperception on this topic.

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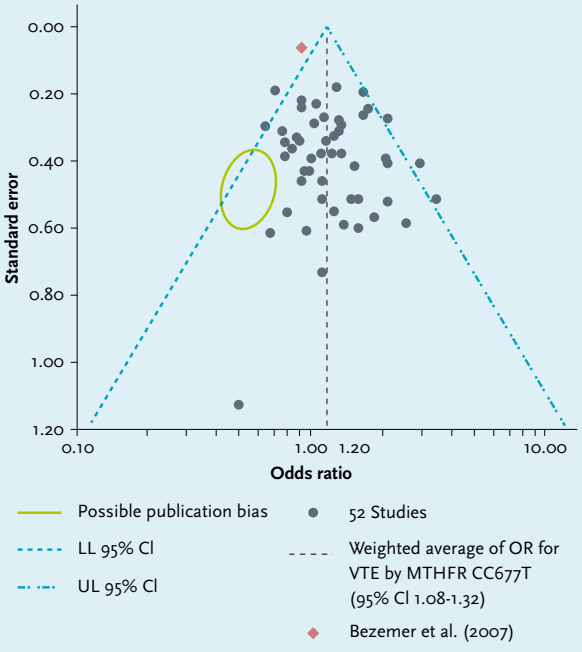
Figure 1. *Funnel plot with pseudo 95% confidence intervals (dotted-dashed lines). We see the precision of a study (estimated by the standard error of the effect) plotted against its reported odds ratio (estimate of the relative risk of VTE by the MTHFR CC677T mutation). In general, the precision of a study increases with its size and when it approaches the 'true' effect size (dashed line). Possible publication bias can be identified when a 'gap' between the dashed line and a 95% confidence interval line is observed (i.e. the funnel plot is not symmetric). Often, this concerns small studies (low precision) supporting the 0-hypothesis, which might be the case here (indicated by the green circle)*



LL = lower limit of pseudo 95% confidence interval; UL = upper limit of pseudo 95% confidence interval; VTE = venous thromboembolism.

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