## Diagnostic suspicion and referral bias in studies of venous thromboembolism and oral contraceptive use

Heinemann and colleagues have described their recent study[1] on 'diagnostic suspicion and referral bias' as a rebuttal of previous studies Throughout their paper, they make several comparisons with a previous paper from the USA and with our previous study on the same subject[2,3] These two previous papers had demonstrated that diagnostic biases are largely absent from case–control studies on oral contraceptives and venous thrombosis Several differences in design between their study and the two previous studies are so fundamental that a comparison is impossible

Heinemann and colleagues state that, in our study, only patients from anticoagulation clinics were included and that it was completely hospital-based, which is not a true reflection of our methods We used existing data from diagnostic referral centers in Amsterdam[3] These referral centers serve both general and specialist physicians, and see patients from a rather well-defined geographic area, for whom anti-coagulation might be indicated if the diagnosis is confirmed (thrombosis services in The Netherlands work on a regional basis) These referral centers have an excellent international track record in research on the diagnosis of venous thrombosis[4–6] Over the years, 'state-of-the-art' diagnostic tools were used, and the physicians working in those centers adhered to the policy that objective diagnosis of venous thrombosis was necessary For verification, follow-up was used to make certain that venous thrombosis had been rightfully excluded In our study, all patients without objective evaluation (a minority) were not taken into account Likewise, in the study from the USA, all future cases and controls underwent the same diagnostic procedures in the same center[2] The study by Heinemann and colleagues, in contrast, relied on 'usual medical practice' of 21 different centers[1] One consequence was that the 'non-case' control group in their study was not verified by objective means (it is described as 'signs that did not lead to the final diagnosis of venous thromboembolism by the treating physician...'), without any reference to objective verification[1] This latter category does simply not exist in our study, nor in the US study, since all referred persons would have been subjected to at least one method of objective diagnosis The percentage of 'non-cases' (about 40%) among the women who were referred with the suspicion of venous thrombosis also contrasts with other diagnostic studies (in which the number of non-cases is much higher) and points either to a selected patient population or to uncertain diagnoses

Moreover, from the definition of the other categories, variously termed 'potential, possible and probable', it is clear that clinical suspicion plays a major role, and objective diagnosis only a minor role As such, the study by Heinemann and colleagues cannot distinguish between clinical suspicion and objective diagnosis

In our study, patients were enrolled in prospectively operating diagnostic facilities, intimately linked to regional treatment services In contrast, in the study by Heinemann and colleagues, it is not clear whether the patients are incident cases of venous thrombosis, or whether they had a venous thrombosis earlier in their medical history Thus, pill use might have been assessed retrospectively In addition, Heinemann and his group include women with a previous history of venous thrombosis, while we limited them to those with first-ever venous thrombosis A second venous thrombosis is often more difficult to diagnose, even by objective means, because of residual vascular abnormalities For etiological research, preference is almost always with first diagnoses (oral contraceptive use may very well depend on a previous episode of thromboembolism)

Finally, the authors propose a new mechanism for diagnostic and referral bias by insisting that it plays a role in those who were very extensively investigated, as well as in those who were minimally investigated Moreover, the stratification into diagnostic intensity (according to the amount of technical diagnosis[1]) is different from the stratification of 'definite, possible, potential, etc ', which obscures the analysis Perhaps, these new definitions also explain why the findings


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of Heinemann's group are different from all older epidemiological studies that discussed the clinical certainty of diagnosis of venous thrombosis and found no evidence of diagnostic bias in the association with oral contraceptive use[7–12]

In summary, it is not surprising that the limitations in objectivity of diagnosis in the Heinemann study, as well as the pooling of several uncertain categories in the analysis, will lead to a dilution of the contrast in oral contraceptive use between 'cases' and 'non-case' controls A methodological comparison with previous studies is impossible because of the different origins of patients, the very different diagnostic procedures, and the differences in definition of the diagnostic categories When considering the above, it is unclear whether subgroup analyses of the very mixed group of patients and diagnostic procedures in the study by Heinemann and colleagues can shed any light upon the existence of 'diagnostic and referral bias'

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