Response to Letter by van der Jagt et al
(published in the January 2008 issue)

Response:
We thank Dr van der Jagt et al for their interest in our meta-analysis on the risk of rupture of unruptured aneurysms, and for their considerations on methodological quality of the parent articles included in the review and on the influence of publication bias on the results of the review.

In our meta-analysis we rated the quality of a study as high when it fulfilled all three following criteria: prospective study design, loss to follow-up <3% and a clear diagnosis of subarachnoid hemorrhage.1 van der Jagt et al suggest that size and location of the aneurysms should have been taken into account as quality criteria because these factors might have confounded our rupture risks.2 We agree that size and location of the aneurysm are very important risk factors for the risk of rupture of intracranial aneurysms. Moreover, one of the main aims of our study was to investigate the relation between aneurysm characteristics and the risk of rupture and, therefore, we calculated relative risks of rupture for aneurysms of different sizes and locations. However, we do not consider these factors confounders because they do not influence the internal validity of our meta-analysis, but only affect the generalizability of our results, the overall rupture risks.

The second issue addressed was publication bias. A funnel plot showed an asymmetrical distribution to the right of the plot, at higher rupture risks. Unfortunately, this plot was not constructed correctly. First, the asymmetry is not as profound as shown in the plot because only one of our included studies had a yearly rupture risk of >8% and not two as suggested. Second, an overall rupture risk of 1.2% per year for all included studies was used. This contrasts with what we reported. Because growth and rupture of aneurysms are not constant over time,3 we reported the overall rupture risk for three different periods of follow-up (<5, 5 to 10 and >10 years). The 1.2% mentioned by van der Jagt as overall rupture risk for all studies was the risk found in studies with a mean follow-up of <5 years and, therefore, only these studies should have been included in the plot. For this subset of 12 studies, 5 reported a rupture risk of <1.2% per year and 7 a risk higher than 1.2% per year, which is less asymmetrical a distribution than suggested by the funnel plot from van de Jagt et al. Moreover, if funnel plots are constructed also for the two other follow-up periods separately, there is no asymmetry toward higher rupture risks in these other follow-up periods. There may be several explanations for asymmetry found in the funnel plot of studies with a relatively short follow-up. We consider publication bias not a very likely explanation, because in case of risks of rupture there is no obvious reason for investigators and journal editors to underreport low rupture risks. A much more likely explanation for the asymmetry, in our opinion, is heterogeneity of the study population. All dots representing small studies with rupture risks higher than 2.5% are derived from Japanese or Finnish studies. In Japan and Finland the incidence of subarachnoid hemorrhage is much higher than that in other Western countries.4 If these studies are left out the asymmetry is eliminated.

We agree with van der Jagt that there is room for improvement of methodological quality in studies on risks of rupture of intracranial aneurysm. New follow-up studies should have a prospective study design, provide detailed information on follow-up of patients and data-analysis, and report the number of subarachnoid hemorrhage and the number of follow-up years for all subgroups of patients to allow multivariable analysis of risk factors and time dependent risks of rupture. There is, however, no indication that publication bias or confounding related to aneurysm size or location played an important role in our updated meta-analysis.

Disclosures
None.

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