Supplementary methods

Search algorithm

Our literature search was performed for titles, abstracts and keywords on three databases (Medline, Scopus, Cochrane) using the following combination of search terms (algorithm):

(((cerebral OR brain) AND (microangiopathy OR micro-angiopathy OR microvessel OR "small vessel" OR small-vessel OR microvascular OR microbleed* OR microhemorrhage* OR dot-like hemosiderin OR leukoaraiosis OR "Virchow-Robin" OR (perivascular AND space*) OR ((lacunar OR lacunae OR lacunes) AND (infarct* OR stroke*)))) OR ("white matter" AND (disease OR diseases OR hyperintensit* OR lesion OR lesions)))

AND

(((cardiac OR cardio OR heart OR ventricular OR ventricle OR myocardium OR myocardial) AND (mass OR hypertrophy OR hypertrophic OR thickened OR thickening OR enlargement OR enlarged)) OR LVMI OR LVM)

The search was originally performed in the Medline (through PubMed) database on 23 May 2018 and was then updated on 28 December 2019 with the additional inclusion of the Scopus and Cochrane databases. The search yielded a total of 1,959 articles (PubMed, 798; Scopus, 1,113; Cochrane, 57), which were reduced to 1,456 after removing the duplicates. Thus, 1,456 unique titles derived through our search were cumulatively screened for eligibility. Articles derived through the search were sorted by publication date.

Statistical analysis

We performed random-effect meta-analysis to pool our data. Our main approach utilized the DerSirmonian and Laird (DL) method for calculation of the between-study variance, the estimate of the combined effect for heterogeneity via the Mantel–Haenszel method and the calculation of confidence intervals (CI) with the Wald-type normal distribution.[37] This standard approach is currently the most widely used.[38] However, for our main analyses, we also sought to perform four additional approaches, in order to confirm the robustness of our findings:

(1) We used the Paule-Mandel (PM) estimator (equivalent to the Empirical Bayes [EB] estimator[39]) to calculate the between-study variance. It has been shown that the PM estimator performs better than the DL, mainly when heterogeneity increases; in those cases it approximates τ^2 better than the DL.[40] Additionally, despite it being an iterative method, it has been mathematically proven that convergence of the iteration process always occurs.[34]

(2) We used the (original) Hartung-Knapp (HK) method (also known as Hartung-Knapp-Sidik-Jonkman [HKSJ] method[41]) to calculate the overall effect CI. This method utilizes a modification factor (q) that is used to multiply the overall effect variance and then provides the CI via a *t*-distribution. It has been shown to perform better than the standard approach in many instances.[38,42] However, there are several concerns regarding the use of this method. For instance, when few (≤5) studies are pooled the method may be too conservative.[37,38] Additionally, in those cases the implications of using the modification factor for any given meta-analysis are hard to predict.[43] On the contrary, in instances where heterogeneity is very low, the method may produce a CI that is counterintuitively narrower than the standard approach.[41,43,44]

(3) In order to specifically address this last issue, a modification to the HK method has been proposed by Knapp and Hartung,[36] termed here mHK. We used the mHK approach to calculate the overall effect CI as our 3rd approach. In this method the multiplicative term of HK is constrained at $q \geq 1$. This forces the CI to be at least as wide as in the standard approach. Use of the mHK method has been supported, mainly when few studies are pooled and the involved standard errors vary.[41] However, when very few studies are pooled, the method is overly conservative and leads to significant loss in power.[43] As such, many have suggested various other modification methods in order to better refine the HK method, which will not be discussed here.[43,45]

(4) Finally, we simultaneously used the PM estimator along with the HK method. The PM iteration process attempts to find a positive τ^2 such that $q=1$.[36] It is therefore apparent that if the PM estimator of τ^2 is in fact positive, then $q=1$ and the HK modification will produce no effect on the overall effect variance.[36,37] Therefore this approach is comparable to *approach (1)* with the exception that it utilizes a *t*-distribution, instead of the normal. This is often beneficial, as it has been shown that for a small (<16) number of pooled studies the *t*-distribution performs better in terms of coverage than the normal.[46] However, this method becomes overly conservative as the number of studies decreases. If, on the other hand, τ^2 is negative in the first cycle of the PM iteration, then the process stops, τ^2 is set at 0 and q is calculated at a value <1.[36,41] In that special case, applying the HK modification will result in a quantitatively smaller overall effect variance (than that of *approach 1*), potentially producing a narrower CI (than that of *approach 1*).