Vascular Risk Factors and Depression in Later Life: A Systematic Review and Meta-Analysis

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Reports of the association between cardiovascular risk factors and depression in later life are inconsistent; to establish the nature of their association seems important for prevention and treatment of late-life depression. We searched MEDLINE, EMBASE, and PsycINFO for relevant cohort or case control studies over the last 22 years; 1097 were retrieved; 26 met inclusion criteria. Separate meta-analyses were performed for Risk Factor Composite Scores (RFCS) combining different subsets of risk factors, Framingham Stroke Risk Score, and single factors. We found a positive association (odds ratio [OR]: 1.49; 95% confidence interval [CI]: 1.27–1.75) between RFCS and late-life depression. There was no association between Framingham Stroke Risk Score (OR: 1.25; 95% CI: .99–1.57), hypertension (OR: 1.14; 95% CI: .94–1.40), or dyslipidemia (OR: 1.08; 95% CI: .91–1.28) and late-life depression. The association with smoking was weak (OR: 1.35; 95% CI: 1.00–1.81), whereas positive associations were found with diabetes (OR: 1.51; 95% CI: 1.30–1.76), cardiovascular disease (OR: 1.76; 95% CI: 1.52–2.04), and stroke (OR: 2.11; 95% CI: 1.61–2.77). Moderate to high heterogeneity was found in the results for RFCS, smoking, hypertension, dyslipidemia, and stroke, whereas publication bias was detected for RFCS and diabetes. We therefore found convincing evidence of a strong relationship between key diseases and depression (cardiovascular disease, diabetes, and stroke) and between composite vascular risk and depression but not between some vascular risk factors (hypertension, smoking, dyslipidemia) and depression. More evidence is needed to be accumulated from large longitudinal epidemiological studies, particularly if complemented by neuroimaging.

Key Words: Cardiovascular, major depressive disorder, meta-analysis, old age, risk, stroke

Late-life depression (LLD) and particularly late-onset depression (LOD) have been conceptualized as distinct from depression with early onset (EOD) (1–4). Compared with EOD, LOD is more often associated with no family history of depression and depressive ideation but more psychomotor retardation (5,6), cognitive impairment (especially executive dysfunction [7–9]), lack of insight, poor response to treatment (1), and a greater chance of progression to dementia (10,11). In addition, magnetic resonance imaging studies have demonstrated higher rates and greater severity of white matter hyperintensities in LOD compared with healthy volunteers (12–15) and with EOD patients (15,16).

The differences between early and late-life depression might be due to different underlying pathophysiological mechanisms (17). The term vascular (or subcortical ischemic) depression postulates a link between cerebrovascular disease and later life depression (18–20). It implies that micro-damage to small vessels compromises the integrity of the frontal-subcortical circuits involved in mood regulation (6,16,21–25). The vascular depression hypothesis can explain increased risk of depression after stroke and myocardial infarction (26–28) and the association of LLD with brain scans suggestive of subclinical cerebrovascular disease (12,21,23). However, studies of common cardiovascular risk factors—such as smoking, hypertension, dyslipidemia and diabetes, and depression—have yielded mixed results. Some studies provide support for an association (29–35), whereas others fail to do so (36–46). There is also strong evidence for a reciprocal relationship (47–52). Recent meta-analyses report that depression predicts incident myocardial infarction and earlier death, coronary artery disease, stroke, other cardiovascular diseases (CVDs), and diabetes; apart from common causes of both CVD and depression, potential mechanisms for depression causing CVD span the depressive stress response, lifestyle factors such as exercise and food intake, as well as aspects of the treatments used (47,53).

The importance of vascular risks and diseases preceding depression might not be greater than that of other chronic diseases. Vascular diseases might be associated with depression, not because of associated pathology (i.e., small or large brain vessel disease) but because of their effect on function and the resulting poor quality of life. Consistent with the chronic illness hypothesis, the relationship between vascular risks or diseases and depression was significantly attenuated after controlling for presence of chronic illness (37,54,55), although attribution of variability to one (chronic illness) or the other (vascular risk and disease) will be arbitrary or at least uncertain in most cases. Depression seems associated with poor general health (56), chronic obstructive pulmonary disease (27), chronic renal disease (57), arthritis (27), and loss of hearing or vision (27). Further support for a causal relationship between general chronic illness and depression is provided by a recent prospective cohort study that found an equally strong association between long-term nonvascular conditions and risk of depressive symptoms (46).

Although several systematic reviews have focused on the vascular depression hypothesis (13,20,58–62), the relationship between vascular risk factors (VRFs) or vascular diseases and depression has not been quantified. This systematic review and meta-analysis aims to provide an overview of the literature to date, to quantify the extent to which VRFs or vascular diseases might be associated with or might be risk factors for depression in late life, and to consider the contribution of the associated disability. If vascular risks and pathological changes are etiological factors for depression, we expect to find significant associations even after controlling for the complex effects of chronic illness and disability. Establishing the nature of the relationship

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between VRFs or diseases and LLD is important both in terms of prevention and treatment of depression.

Methods and Materials

Search Strategy

We systematically searched for studies that investigated the association between VRFs and depression in late life. Studies considering vascular diseases such as coronary heart disease together with VRFs were included, because it is a common feature of risk scales to include previous disease. The MEDLINE, EMBASE, and PsycINFO databases were searched for publications in all languages between 1990 and May 2012. The search terms were: ["depress*"] AND ["late life" OR "late onset" OR "older adults" OR "geriatric"]; and second: ["depress*"] AND ["vascular diseases" OR "vascular risk factors" OR "cerebrovascular risk factors" OR "vascular"]. Additional studies were identified from reference lists of relevant reviews and studies. Unpublished literature was identified from the DART Europe E-thesis Portal (dissertations and thesis), ZeTOC (conference proceedings), and Open Grey (Grey Literature) databases. A total of 1097 results were retrieved. After screening of titles and abstracts 140 studies were considered potentially relevant. The inclusion criteria were: cohort or case control studies, age ≥50 years, and frequency or new cases of depression reported with and without VRFs, respectively. After review of the full text, 26 studies met the inclusion criteria. Common reasons for exclusion were review articles, dual publications, or insufficient data to calculate outcome measures. Further reasons for exclusion were "exposure to vascular risk factors not reported" and "depression not reported as an outcome" (Figure 1). Where there was an overlap in samples between studies, the study of higher quality or the one providing stronger evidence was included (e.g., more participants, longitudinal design) (Figure 1).

The quality of the studies was assessed by scoring on a self-devised checklist (Table S1 in Supplement 1) that included the following parameters: sample representativeness, study design, quality of reporting, VRFs measurement, outcome measurement, and confounding factors (Supplement 1). Following the recommendations of the Meta-Analysis of Observational Studies in Epidemiology guidelines, we performed a sensitivity analysis excluding studies with a score below 8 (Table 1).

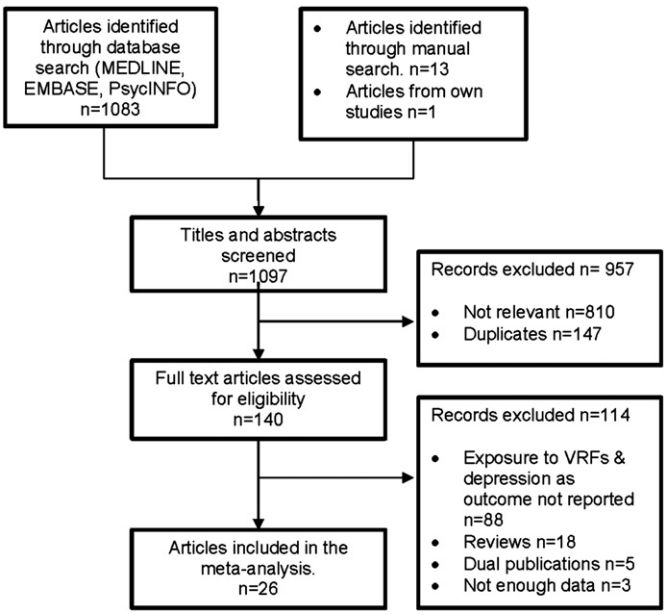

Figure 1. Identification and attrition of studies. VRF, vascular risk factor.

Depression in studies was defined as: 1) diagnosis of major depression, minor depression, or dysthymia according to the DSM-III R, DSM-IV, or other standard psychiatric diagnostic criteria; 2) depressive disorder or depressive symptoms, as defined by scores above a cutoff point on a standard mood rating scale (Centers for Epidemiologic Studies Depression Scale, Hamilton Rating Scale for Depression, or Geriatric Depression Scale). Of the studies included, three did not use these criteria. In two studies depressive symptoms were identified through a single question from a questionnaire (31,33), and one study used data recorded by general practitioners in problem lists of patients (44).

Data Extraction

Data were extracted in a systematic fashion as follows: 1) study characteristics (name, authors, publication year); 2) study design; 3) sample source; 4) sample characteristics (e.g., age, gender); 5) inclusion and exclusion criteria; 6) definition and measures of exposure; 7) definition and measures of outcome; and 8) analysis strategy (statistical models, measures of effect size, confounders that were controlled). Data were extracted independently by both authors, and inconsistencies were resolved by consent.

Data Analysis

A meta-analysis was performed for studies that use a composite measure of vascular risk (Risk Factor Composite Score [RFCS]). The RFCSs included different subsets of risk factors, and different studies used different RFCS groupings (e.g., two, three, or four groups; the low-risk group in some studies comprised participants without risk factors, whereas in other studies it included participants with one risk factor). To make studies comparable, the data were organized into two categories representing low vascular risk (0 or 1 risk factor) and high vascular risk (2 or more risk factors). A separate analysis was performed for studies using the Framingham Stroke Risk Score (FSRS), because it has been specifically developed for assessing the risk of cerebrovascular disease (especially stroke). The FSRS is also well-validated and widely used (63,64), although whether it predicts incident depression in later life is not known. Most importantly, the studies using the FSRS used the same subset and definition of risk factors, thus increasing the reliability of the results. Separate meta-analyses were also conducted for the single factors smoking, hypertension, diabetes, dyslipidemia, CVD, and stroke.

Data were analyzed with Comprehensive Meta-Analysis, version 2.2 (65). First, odds ratios (ORs) with confidence intervals (CIs) were extracted or calculated from the available data (e.g., percentages or fractions, χ^2 with 1 *df*). When it was not possible to compute OR directly, standardized mean differences (Cohen's *d*) were computed from means and SDs or from regression coefficient and transformed to ORs with conventional formulae (66). A random-effects model was used to calculate the pooled mean effect size. The random-effects model was preferred over a fixed effect model, because the included studies are heterogeneous in terms of population characteristics, definition and measurement of vascular risk, and outcomes (implicating that the true effect size varies from one study to another) and also to allow generalization of the results (67). Heterogeneity across studies was assessed with the Cochrane Q statistic ($p < .10$ was considered to indicate statistically significant heterogeneity) and the I^2 statistic (25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively). Publication bias was