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Vascular disease risk factors as determinants of incident depressive symptoms: a prospective community-based study

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ABSTRACT

Background. The potential association between vascular disease and depression have been the focus for much clinical psychiatric research, although few epidemiological prospective studies have looked into this association.

Aims. This study explores the *a priori* hypothesis of a prospective association between cardiovascular disease or its risk factors and incident depressive symptoms.

Method. A prospective primary care based study derived from a multi-centre randomized controlled trial of moderate hypertension. 2584 moderately-hypertensive volunteers were followed-up for 54 months when five assessments of depressive symptoms, vascular disease and its risk factors were made.

Results. We found an association between the dependent variable (incident depressive symptoms measured with the Self-CARE-D) and baseline smoker status, low serum cholesterol levels, poorer cognitive function (particularly executive dysfunction), female gender and increasing age. These associations were independent of all other cardiovascular risk factors (ECG evidence of ischaemia or arrythmia, systolic or diastolic blood pressure, blood pressure decline along the trial and body mass index).

Conclusions. Our results do not support the hypothesis of a specific association between vascular disease or its risk factors and incident depressive symptoms.

INTRODUCTION

Cardiovascular disease and depression have been thought to be related since the nineteenth century. Post suggested that 'subtle cerebral changes may make ageing persons increasingly liable to affective disturbance …' (Post, 1962). This triggered several lines of research on vascular factors and depression. Hence, hypertension was suggested to increase the risk of depression (Rabkin *et al*. 1983), although this has not always been replicated and may be explained by the psychological impact of the diagnosis or the treatment (Mann *et al*. 1984). Furthermore, hypotension has also been reported to increase risk for depression (Paterniti *et al*. 2000). Mortality related to cardiovascular disease has also been consistently linked to depression, although the basis for this effect has been open to different interpretations (Rabins *et al*. 1985; Murphy *et al*. 1987; Vogt *et al*. 1994; Abas *et al*. 2002). More robust evidence exists for an association between depression and cerebrovascular disease, such as stroke (Eastwood *et al*. 1989), vascular dementia (Sultzer *et al*. 1993) or deep white matter lesions (de Groot *et al*. 2000). Recent claims for a specific form of depression related to vascular disease, so-called

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vascular depression (Alexopoulos *et al.* 1997), still lack longitudinal epidemiological support (Lyness *et al.* 2000; Stewart *et al.* 2001).

This study sets out to investigate the *a priori* hypothesis of a prospective association between cardiovascular disease or its risk factors and incident depressive symptoms, analysing longitudinal data from the psychiatric substudy inserted in the MRC treatment trial of hypertension in older adults (Bird *et al.* 1990; MRC Working Party, 1992).

METHODS

Study design and sample

The designs of both the Medical Research Council treatment trial (MRC Working Party, 1992) and its psychiatric substudy are described in detail elsewhere (Bird *et al.* 1990; Prince *et al.* 1996). The MRC trial compared mortality and morbidity among 4396 subjects randomized to receive beta-blocker, a thiazide diuretic or placebo. Inclusion criteria were age 65–74 years and systolic blood pressure 160–209 mmHg. Exclusion criteria were current anti-hypertensive medication and serious cardiovascular, cerebrovascular or other intercurrent illnesses, including dementia. Participants were recruited in 226 UK MRC General Practice Research Framework practices after invitations had been sent to all registered patients within the eligible age range. The first 2680 participants in the MRC elderly hypertension trial were offered the chance to participate in the psychiatric substudy when depressive symptoms and cognitive function were assessed during the 54-month follow-up period on five occasions at months 0, 1, 9, 27 and 54 (Bird *et al.* 1990).

Measures

Depressive symptoms Self-CARE-D

Depressive symptoms were measured on five occasions using the Self-CARE-D (Bird *et al.* 1987) during the 54-month study period. The Self-CARE-D is a 12-item self-rating questionnaire derived from the depression scale of the CARE package (Gurland *et al.* 1977). The Self-CARE-D was validated for use among primary care attenders in North London (Bird *et al.* 1987). It discriminated between elderly subjects with and without clinical depression with a sensitivity of 77%, a specificity of 98%, a positive predictive value (PPV) of 96% and negative predictive value (NPV) of 85%, using a cut-point of 5/6. Agreement against diagnoses made by independent psychiatric assessment was adequate with a kappa coefficient of 0·77. In a more recent report (Banerjee *et al.* 1998) the Self-CARE-D was validated against the semi-structured Geriatric Mental State interview with diagnoses generated by the computerized AGECAT algorithm (Copeland *et al.* 1986) for use among recipients of homecare populations showing an adequate level of diagnostic agreement (0·77).

Independent variables

Risk factors for vascular disease. Information was recorded at baseline for the following risk factors for vascular disease: systolic and diastolic blood pressure, serum cholesterol, body mass index and smoking behaviour at entry to the trial (ex-smokers were not distinguished from never smokers). Repeated measures of blood pressure over the 54-month trial period allowed the decline in systolic blood pressure from baseline to be calculated. Thus, we calculated the mean of successive measures and subtracted it from the baseline value. Information on participants' gender and age was also available from baseline.

Evidence of vascular disease. Signs of arrhythmia or ischaemia on electrocardiogram (ECG).

Baseline cognitive function. Upon entry to the MRC trial (1983–1985), henceforward referred to as baseline, cognitive tests had been administered to all subjects. Fluid intelligence was measured using: (1) the Paired Associate Learning Test (PALT; Inglis, 1959); (2) the Trail Making Test (TMT; Reltan, 1959); and (3) Raven's Progressive Matrices (RPM; Raven, 1940). The TMT and PALT were repeated 1 month later. For these two tests the mean of the entry and 1 month measure was used to minimize random error. Principal component analysis with varimax rotation was used to extract a single factor from the three baseline measures of cognitive function, accounting for 51% of the variance with adequate loading values for the three baseline (RPM 0·79, TMT 0·60 and PALT 0·64). Pre-morbid IQ (crystallized intelligence)

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was also measured at baseline using the New Adult Reading Test (NART; Nelson & O'Connell, 1978).

Statistical analysis

We decided *a priori* to use continuous rather than dichotomous depression scores in order to maximize precision in the assessment of outcome over the baseline and four subsequent repeated follow-up assessments. However, we re-analysed data using a dichotomous outcome to check for consistency, using an outcome that corresponded approximately to a concept of clinically significant depression (6 or more points on the Self-CARE-D, i.e. the recommended cut-off for primary-care based populations). Thus, log-transformed continuous Self-CARE-D scores were analysed using linear regression (StataCorp, 1999). All available data were used and the correlations of predictor variables with the SELF-CARE-D scores on the same participant over time were modelled by introducing a random intercept into the linear regression model. This method yields unbiased estimates if data are missed at random. By using random effects models, estimates of the effects of repeated measure predictor variables that vary both within and between subjects, such as blood pressure, combine information from both within and between subject variability.

The following strategy was adopted for multivariable analysis. All analyses included the potential confounders, age and sex, as explanatory variables. Each of the variables (serum cholesterol levels, smoking status at entry, evidence of ischaemia or arrythmia on ECG, systolic and diastolic blood pressure, baseline cognitive function) were individually used as additional explanatory variables. The variables were then entered into a best-fit final explanatory model, which was also adjusted for baseline depression scores.

RESULTS

The sample

The first 2680 participants in the MRC elderly hypertension trial were offered the chance to participate in the psychiatric substudy; 29 participants refused to participate. Of the remaining 2651 participants, 2584 (97·5%) contributed adequate data on the main explanatory variables constituting the current sample ($n=2584$). Of these 2584, 58% were female and 42% male. The mean age at entry to the trial was 70·3 years. 197 (8%) subjects were depressed at baseline using the 5/6 cut-off on the Self-CARE-D. 748 participants (28·9%) died during the study period but these did not differ systematically from those who survived in age, gender, serum cholesterol levels, body mass index, diastolic or systolic blood pressure at entry, entry evidence of arrythmia or ischaemia on ECG, baseline cognitive function or antidepressant use at entry. Additional baseline characteristics of participants have been reported in more detail elsewhere (Abas *et al.* 2002).

Table 1. *Bivariate associations between depressive symptoms and vascular or cognitive variables* (*after adjusting for age and gender*)

Variables	Coefficient	95% CI	z	$p<\|z\|$
Gender	0·21	0·16/0·26	8·97	0·000
Age at entry	0·01	0·005/0·02	3·26	0·001
Baseline depression	0·14	1·07/1·22	30·38	0·000
Serum cholesterol	−0·02	−0·04/−0·006	−2·60	0·009
Smoking status	0·12	0·06/0·18	4·13	0·000
Body mass index	−0·001	−0·007/0·004	−0·50	0·616
Systolic BP	−0·00	−0·001/0·0001	−1·58	0·114
Diastolic BP	0·000	−0·0005/0·002	1·09	0·275
Mean BP	0·002	−0·001/0·002	0·75	0·455
Systolic BP decline	−0·000	−0·002/0·0007	−0·99	0·322
ECG ischaemia	−0·009	0·05/0·03	−0·43	0·668
ECG arrythmia	−0·007	−0·07/0·05	−0·23	0·815
PALT scores	0·003	−0·003/0·001	0·79	0·430
NART scores	−0·001	−0·003/0·001	−0·94	0·345
TMT scores	0·002	0·001/0·002	6·51	0·000
Cognitive factor	−0·06	−0·08/−0·36	−5·01	0·000

Univariate associations with depressive symptoms

Female sex ($p=0·0001$), older age ($p=0·001$) at entry and the more impaired scores on the cognitive function factor ($p=0·0001$) were all statistically significantly associated with depressive symptoms over the follow-up period. Table 1 shows bivariate associations between vascular and cognitive variables and depressive symptoms after adjusting for the potential confounding effects of gender and age. We found that lower serum cholesterol levels ($p=0·009$) and being a smoker at entry ($p=0·0001$) were statistically significantly associated with depressive symptoms. We found no evidence

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Table 2. *Multivariate associations between depression scores and independent variables**

	Coefficient (95% CI)	*z*	*p*
Gender	0·24 (0·19/0·29)	9·18	0·000
Age at entry	0·01 (0·003/0·02)	2·60	0·009
Baseline cognitive function†	−0·05 (−0·08/−0·03)	−4·51	0·000
Serum cholesterol	−0·02 (−0·04/0·0007)	−2·02	0·000
Baseline smoking status‡	0·11 (0·05/0·17)	3·61	0·043
Baseline depression	1·14 (1·06/1·21)	29·76	0·000

* Model adjusted for all blood pressure measures, arrhythmia, or ischaemia on ECG, body mass index and Clinical treatment group.

† Common cognitive factor extracted from cognitive tests used at baseline (see text).

‡ Currrent smoker *v.* non-smoker or ex-smoker at baseline.

for significant associations between any of the remaining vascular risk factors (body mass index (BMI), systolic or diastolic blood pressure, mean blood pressure, systolic blood pressure decline through the study period) nor vascular disease (ECG evidence of ischaemia or arrythmia) and depressive symptoms. While both the common cognitive tests factor and the TMT scores were associated with depressive symptoms, the PALT and NART scores were not.

Independent associations with incident depressive symptoms

The final best-fit explanatory model is summarized in Table 2 showing multivariable independent associations with incident depressive symptoms. Low serum cholesterol levels, cigarette smoking, poorer cognitive function, older age and female gender were associated with incident depressive symptoms independently of vascular disease and vascular risk factors. Adjusting for baseline depression in order to ensure the incident nature of the outcome did not materially change either the direction or the strength of these independent associations.

DISCUSSION

Methodological issues

In interpreting our results we have to bear in mind some limitations of the study design that have already been detailed elsewhere (Bird *et al.* 1990). In brief, generalizability of our findings might be limited as the sample consists of mildly hypertensive older people who volunteered to participate in a treatment trial. However, the sample is primary-care based and the size is large. Another potential limitation is that our measure of depression consisted of a self-report questionnaire (Self-CARE-D), which is arguably less precise an assessment tool than structured clinical interviews using established clinical criteria. Nevertheless, this instrument has repeatedly shown acceptable degrees of both reliability and validity against clinical criteria (Bird *et al.* 1987; Upadhyaya & Stanley, 1997; Banerjee *et al.* 1998). When we reanalysed the model using a validated dichotomous 5/6 cut off for the Self-CARE-D we found virtually parallel results. The main strength of the study is the thorough prospective gathering of exposure to both vascular risk factors and ECG established vascular disease. Adjusting for all these vascular factors is likely to reduce remaining potential risk for residual confounding which has indeed been recently reported as minimal in this particular sample (Abas *et al.* 2002).

Gender, age and cognitive function

Many previous studies have found female gender to be associated with depression (Prince *et al.* 1998; Copeland *et al.* 1999) or depressive symptoms (Fuhrer *et al.* 1992). Disability was not explicitly controlled for in this study, other than indirectly through the contribution made by vascular disease and cognitive impairment, and might confound the reported association between incident depressive symptoms and increasing age (Prince *et al.* 1998). A large paneuropean study found no constant association between age and depression (Copeland *et al.* 1999). Poorer cognitive function has been repeatedly found to be associated with depressive symptoms (Prince *et al.* 1996), although this association might also be explained by the confounding or mediating effect of disability (Cervilla *et al.* 2000). Interestingly, the only individual cognitive test associated with depression was the TMT, a measure of executive dysfunction, which has been suggested as a specific cognitive deficit in older people with depression (Alexopoulos *et al.* 2000).

Smoking

Smoking has been repeatedly found to associate significantly with depression in previous studies (Kendler *et al.* 1993; Breslau *et al.* 1998; Dierker *et al.* 2002). Some studies have postulated a

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familial or genetic common aetiology for smoking and depression (Kendler *et al*. 1993; Dierker *et al*. 2002). Our findings exclude the influence of vascular disease in the association between smoking and depression adding support to theories explaining the association on psychosocial or behavioural mechanisms (Ockene *et al*. 1982). However, physiological mechanisms independent of the vascular effects studied here cannot be ruled out (Pomerleau & Pomerleau, 1991).

Low serum cholesterol

Our findings on cholesterol replicate previous reports in favour of an association between depressive states and low serum cholesterol (Maes *et al*. 1996; Steegmans *et al*. 2000). One possible mechanism is that lower serum esterified cholesterol may be accompanied by an increase in the membrane cholesterol/phospolipid ratio affecting membrane viscosity (Jonas *et al*. 1987). Altered membrane viscosity, in turn, may determine changes in both density or functioning of serotonergic or catecholaminergic receptors (Maguire & Druse, 1989). This links with evidence for a role of cholesterol in 5-HT reuptake and release (Block & Edwards, 1987), resulting in potential reduction of 5-HT neuronal activity (Hawton *et al*. 1993). Additionally, depression is associated with low $\omega 3$ essential fatty acids levels which may be used in the synthesis of cholesterol (Maes *et al*. 1996). Another potential explanation has been found in a hypothetical role of increased interleukin-2, which would induce melatonin suppression, leading to both depression and a decrease in serum cholesterol levels (Penttinen, 1995). However, interleukin-2 enhances atherosclerosis and vascular disease. Therefore, our results do not support the latter hypothesis as our finding is independent of vascular disease and vascular risk factors. Similarly, the association between depression and low serum cholesterol has also been explained as the result of a confounding effect by low appetite in depression leading to low cholesterol levels (Bolton *et al*. 1996). This notion, again, is not supported by our findings, given that we adjusted for BMI.

Other vascular factors

Most previous results showing a positive association between vascular disease or its risk factors and depression (Rabkin *et al*. 1983; Carney *et al*. 1987; Fava *et al*. 1996; González *et al*. 1996) are based on potentially biased clinical samples. The same is true for those studies suggesting an association between cerebrovascular disease, and in particular deep white matter hyperintensities (DWMHs), and a subtype of elderly depression (Alexopoulos *et al*. 1997; Krishnan *et al*. 1997), with the exception of a large community-based study by de Groot *et al*. (2000). However, DWMHs do not seem to be specific to late-life depression, as they have also been reported to be associated with both vascular disease (hypertension, carotid artery disease) and normal aging (Fazekas *et al*. 1988; Guttmann *et al*. 1998). In addition, Abas *et al*. (2002) found that depression in this sample determined higher risk for mortality 11 years later, although this was not due to cardiovascular disease. As with other previous longitudinal community-based studies (Lyness *et al*. 2000; Stewart *et al*. 2001), our study found no association between incident depressive symptoms and vascular disease, suggesting that any effect of vascular disease might just be due to its additive contribution to general disease induced disability (Prince *et al*. 1998; Lyness *et al*. 2000; Stewart *et al*. 2001).

CONCLUSION

In summary, this large primary care based longitudinal study finds an association between incident depressive symptoms and baseline smoking, low serum cholesterol levels and poorer cognitive function (particularly executive dysfunction). Incident depressive symptoms were, however, not associated with established vascular disease evidenced by ECG or its risk factors, suggesting an absence of specificity in the role of vascular disease as determinant of incident depressive symptoms. Admittedly, our study did not look directly into the association between depressive symptoms (or indeed any specific depressive syndrome) and either DWMHs or cerebrovascular disease in general (Alexopoulos *et al*. 1997; Alexopoulos, 2001). Future community-based prospective studies including neuroimaging, depressive-symptom profile and longitudinal outcome of cases are needed.

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