

## Vascular risk factors and incident late-life depression in a Korean population

JAE-MIN KIM, ROBERT STEWART, SUNG-WAN KIM, SU-JIN YANG, IL-SEON SHIN and JIN-SANG YOON

**Background** Causal relationships between vascular factors and late-life depression are controversial.

**Aims** To investigate prospective associations between risk factors for vascular disease and incidence of late-life depression.

**Method** Of 661 community participants aged 65 years or over, without depression at baseline, 521 (79%) were re-evaluated 2 years later. At baseline and follow-up, a diagnostic interview for depression was carried out and information on vascular status, disability and cognitive function was gathered.

**Results** Pre-existing heart disease, incident stroke and lower baseline high-density lipoprotein cholesterol level were significantly associated with incidence of late-life depression, independently of disability and cognitive function.

**Conclusions** These results provide some support for a vascular aetiology of late-life depression. However, important risk factors for cerebrovascular disease such as hypertension and diabetes were not implicated, and the associations with lipid levels might still be explained by affective states earlier in life.

**Declaration of interest** None. Funding detailed in Acknowledgements.

There has been increasing interest in the relationship between vascular disease and depression in later life. However, the importance of conventional vascular risk factors in this association is uncertain (Stewart *et al*, 2001; Cervilla *et al*, 2004). Furthermore, most studies have been cross-sectional in design, which is potentially problematic since depression is known to be a risk factor for cerebrovascular disease (Larson *et al*, 2001) and the direction of cause and effect is not clear. In a previous community study we found that previous stroke and lower high-density lipoprotein (HDL) cholesterol level were significantly associated with depression independently of disability and cognitive function (Kim *et al*, 2004). Associations with hypertension and diabetes, on the other hand, were less evident. We subsequently followed the study cohort over a 2-year period and investigated prospectively the associations between risk factors for vascular disease and incidence of late-life depression.

### METHOD

This study was part of a community-based prospective survey of late-life psychiatric morbidity carried out in Kwangju, South Korea, from 2001 to 2003, in collaboration with the 10/66 Dementia Research Group's research programme in developing countries (Prince *et al*, 2003).

### Baseline sample and measurements

A cross-sectional survey of a geographically defined population was carried out in 2001. The sampling procedure and measurements have been described previously (Kim *et al*, 2003a, 2004). In brief, 732 community residents aged 65 years or over, on national residents registration lists within two areas of Kwangju, South Korea, were interviewed. Interviews included a fully

structured diagnostic interview for depression, examinations for vascular disease risk and formal assessment of disability and cognitive function.

### Depression

Depression was assessed using the community version of the Geriatric Mental State (GMS) diagnostic schedule (GMS B3; Copeland *et al*, 1986). This is a fully structured diagnostic instrument, in wide international use, with an accompanying computerised algorithm. The GMS B3 was translated into Korean according to a formal standardisation process (Kim *et al*, 2003b). As in other studies, a stage-one (non-hierarchical) confidence level of 3 or above in the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) algorithm (Copeland *et al*, 1986) was used to define depression of clinical significance.

### Vascular disease risk

Self-reported diagnoses of and treatment histories for stroke, heart disease, hypertension and diabetes were recorded. Stroke was classified only if there was a clear history of sudden onset of unilateral paralysis and/or loss of speech and/or blindness lasting for at least 2 days. Heart disease was classified on the basis of a previous medical diagnosis with a clear time of onset. Resting blood pressure was taken with an automatic sphygmomanometer on the left arm in the sitting position. The lower of two consecutive readings was used. Blood samples were taken in a fasting state and were carried out in the mornings where possible. The following assays were performed: glucose, total cholesterol, HDL, low-density lipoprotein (LDL) and triglycerides.

### Other potential risk factors for depression

Demographic data on age, gender and education were recorded. Disability was assessed by the Korean version of the World Health Organization Disability Assessment Schedule II (WHODAS II; Kim *et al*, 2005). Cognitive function was evaluated by the Korean version of the Mini-Mental State Examination (MMSE; Park & Kwon, 1990).

### Follow-up evaluation

Follow-up evaluation was carried out in 2003. The mean (s.d.) follow-up period

was 2.4 (0.3) years. Diagnosis of depression (GMS-AGECAT) and information on new-onset vascular disease and risk (stroke, heart disease, hypertension and diabetes) during the 2-year interval were ascertained. The vascular examination, WHODAS II schedule and blood assays described above were also repeated. Responses to certain individual GMS questions at follow-up were also extracted for exploratory secondary analyses. These consisted of four psychological depressive symptoms (depressed mood, tearfulness, guilt and pessimism) and three vegetative symptoms (poor appetite, weight loss and sleep disturbance).

**Statistical analysis**

For the analysis reported here, participants with depression at baseline were excluded, and depression at follow-up was treated as the dependent variable for primary analyses. Baseline characteristics of participants and non-participants at follow-up were compared. Initial unadjusted analyses were carried out to investigate vascular factors associated with incident depression. For categorical independent variables, presence at baseline and onset during the follow-up period were considered separately. For continuous independent variables, baseline levels and changes in levels over the follow-up period were considered separately. Incident depression was compared across quintiles of baseline/change scores. Where curvilinear relationships were suggested, associations were tested entering both linear and quadratic terms for independent variable quintiles. Associations between independent and dependent variables were further analysed using stepwise logistic regression models to investigate confounding by demographic characteristics, and mediation by change in level of disability (WHODAS II) from baseline to follow-up.

**RESULTS**

**Follow-up status**

Of 732 participants at baseline, 631 (86.2%) did not have depression and formed the potential baseline population. Of these, 521 (83%) completed all evaluations at follow-up and comprised the study sample. Of the remaining 110, contact could not be established with 40 (36%), 23 (21%) had died, 21 (19%) refused to participate, 18 (16%) had changed address

and 8 (7%) were too unwell to participate. Baseline characteristics of participants and non-participants at follow-up are compared in Table 1. There were no substantial differences in the demographic characteristics, disability and cognitive function between the two groups.

**Descriptive data**

Of the 521 participants, 63 (12%) incident cases of depression were identified. Pre-existing stroke, heart disease, hypertension and diabetes had been identified in 21 (4%), 99 (19%), 141 (27%) and 47 (9%) participants, respectively. New-onset cases of stroke, heart disease, hypertension and diabetes were found in 20 (4%), 31 (6%), 57 (11%) and 26 (5%) participants, respectively. Mean (s.d.) baseline vascular examination measurements were as follows: systolic blood pressure 146 (25) mmHg; diastolic blood pressure 88 (23) mmHg; blood glucose 106 (54) mg/dl; total cholesterol 175 (35) mg/dl; HDL cholesterol 49 (15) mg/dl; LDL cholesterol 95 (32) mg/dl; triglycerides 156 (89) mg/dl. Mean (s.d.) changes in levels from baseline to follow-up were as follows: systolic blood pressure +2 (28) mmHg; diastolic blood pressure -3 (24) mmHg; blood glucose +2 (54) mg/dl; total cholesterol +6

(32) mg/dl; HDL cholesterol -1 (13) mg/dl; LDL cholesterol +14 (36) mg/dl; triglycerides +15 (91) mg/dl; and WHODAS II score +1 (12) units.

**Associations between vascular disorders and incident depression**

Unadjusted associations between vascular disorders and incident depression are summarised in Table 2. Incident depression was significantly associated with heart disease at baseline and with stroke occurring during the follow-up period. Associations with baseline or incident hypertension or diabetes were all positive, but were weak and not statistically significant.

Associations between incident depression and lipid levels are summarised in Table 3. For baseline total cholesterol, a significant U-shaped association with incident depression was observed, with highest risk in those with lower or higher baseline levels. This pattern was similar but not significant for LDL cholesterol. For HDL cholesterol, a strong and significant linear association was found between decreasing levels and increased incidence of depression. For changes in lipid levels over the follow-up period, U-shaped associations were suggested for total and LDL

**Table 1** Comparison of baseline characteristics between eligible participants who completed both examinations and those lost to follow-up

Baseline status	Completed follow-up (n=521)	Lost to follow-up (n=110)	Statistical coefficient <sup>1</sup>	P
Age, years: mean (s.d.)	72.7 (5.5)	73.2 (5.7)	t=1.53	0.093
Gender, women: n (%)	287 (55.1)	65 (59.1)	χ <sup>2</sup> =1.1, d.f.=1	0.30
Education, years: median (IQR)	1 (0-6)	2 (3-9)	U=40 253	0.12
WHODAS II scores, median (IQR)	2 (0-7)	3 (0-8)	U=41 857	0.34
MMSE scores, median (IQR)	24 (21-27)	25 (20-28)	U=42 254	0.51

IQR, interquartile range; WHODAS II, World Health Organization Disability Assessment Schedule II; MMSE, Mini-Mental State Examination.  
1. t-test, χ<sup>2</sup>-test or Mann-Whitney U-test, as appropriate.

**Table 2** Associations between self-reported vascular risk factors and incidence of depression (n=521)

Self-report	Pre-existing risk factor		Incident risk factor	
	OR (95% CI)	P	OR (95% CI)	P
Stroke	1.6 (0.6-4.4)	0.37	2.3 (1.0-5.1)	0.040
Heart disease	2.1 (1.3-3.3)	0.003	1.1 (0.5-1.1)	0.83
Hypertension	1.1 (0.7-1.8)	0.59	1.5 (0.8-2.8)	0.16
Diabetes	1.4 (0.7-2.7)	0.38	1.0 (0.4-2.5)	0.99

**Table 3** Unadjusted associations between lipid levels and incidence of depression

Quintiles of exposure	Incident depression (%) by quintiles of independent variables			
	Total cholesterol	HDL cholesterol	LDL cholesterol	Triglycerides
<b>Baseline score</b>				
1 (lowest)	21.3	22.3	19.0	15.7
2	15.4	19.0	17.3	13.9
3	10.0	12.2	15.0	15.0
4	10.7	10.0	9.9	13.8
5 (highest)	18.3	9.7	13.8	17.3
<i>P</i> (linear)	0.41	0.005	0.16	0.81
<i>P</i> (quadratic)	0.034	0.71	0.63	0.58
<b>Change in score</b>				
1 (decrease)	24.0	14.0	20.0	19.6
2	14.8	15.4	15.4	13.7
3	11.3	14.0	12.0	12.5
4	14.9	18.0	13.7	16.3
5 (increase)	20.0	23.1	24.0	22.2
<i>P</i> (linear)	0.65	0.21	0.71	0.62
<i>P</i> (quadratic)	0.072	0.56	0.082	0.96

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

cholesterol, with highest risk in participants with declining or increasing levels. However, associations fell just short of statistical significance. No associations were found between incident depression and baseline blood pressure or blood glucose, nor with changes in these factors over the follow-up period (data not shown).

### Multivariate analysis

Results of logistic regression analyses are summarised in Table 4. In general, odds ratios were not changed substantially following each adjustment. In the fully adjusted model, independent associations were found with baseline heart disease and lower level of HDL cholesterol, and the association with incident stroke bordered on statistical significance. The quadratic term for the relationship between quintiles of baseline total cholesterol and incident depression also remained significant after adjustment for all factors listed in Table 4 (unadjusted odds ratio=1.32,  $P=0.009$ ; adjusted odds ratio=1.29,  $P=0.015$ ).

### Secondary analyses

Of the 521 followed-up participants who were not depressed at the baseline, 7 (1%) were taking antidepressants. No marked

or consistent differences were found in the results when the above analyses were repeated excluding this group. Results were also not changed if baseline WHODAS II score was entered, rather than change from baseline to follow-up.

The prevalence at follow-up of four psychological depressive symptoms were: depressed mood 42%, tearfulness 31%, guilt 14%, and pessimism 23%; and of three vegetative symptoms were: poor appetite 33%, weight loss 27% and sleep disturbance 42%. In a secondary analysis, pre-existing heart disease was significantly associated with depressed mood, tearfulness and guilt ( $P<0.05$ ) and was associated with pessimism at borderline levels of

statistical significance ( $P=0.060$ ). Incident stroke was significantly associated with all four of these symptoms ( $P<0.05$ ). No significant associations were found between either of these factors and the three vegetative symptoms ( $P>0.20$ ). Lower baseline HDL cholesterol levels, on the other hand, were significantly associated with all seven symptoms ( $P<0.05$ ). The quadratic term for total cholesterol was significantly associated with all but five outcomes ( $P<0.05$ ) and was associated with the remaining two at borderline levels of significance (for guilt  $P=0.064$ ; for pessimism  $P=0.071$ ).

## DISCUSSION

The principal findings of this community-based longitudinal study were that heart disease and lower HDL cholesterol at baseline predicted an increased risk of incident depression at follow-up. Incident depression was also associated with stroke occurring in the follow-up period, and with both high and low baseline total cholesterol levels. Level of disability and cognitive function only partly explained these associations.

### Methodological issues

Most previous community studies investigating the association between vascular risk factors and depression in older people have been cross-sectional in design (Stewart *et al*, 2001; Kim *et al*, 2004). This limits the extent to which causal relationships can be clarified, particularly for factors such as blood pressure and lipid levels, which may well be altered in depressed states. Previous prospective studies have been limited in number and also in the use of brief screening instruments to define

**Table 4** Adjusted associations between vascular factors and incidence of depression. Odds ratios derived from logistic regression models are displayed with 95% confidence intervals

Association	Pre-existing heart disease	Incident stroke	Lower HDL cholesterol <sup>1</sup>
Unadjusted	2.1** (1.3–3.3)	2.3* (1.0–5.1)	1.3** (1.1–1.6)
Adjusted for age, gender, education	2.4** (1.5–4.0)	2.4* (1.0–5.4)	1.3** (1.1–1.6)
plus change in disability (WHODAS II)	2.3** (1.4–3.8)	2.3 (1.0–5.2)	1.3** (1.1–1.6)
plus baseline cognitive function (MMSE)	2.2** (1.3–3.7)	2.2 (1.0–5.0)	1.3* (1.1–1.6)

HDL, high-density lipoprotein; WHODAS II, World Health Organization Disability Assessment Schedule II; MMSE, Mini-Mental State Examination.

1. Entered in decreasing quintiles.

\* $P<0.05$ , \*\* $P<0.01$ .

depression (Lyness *et al*, 2000), or by the specific nature of the cohorts analysed (Cervilla *et al*, 2004). Strengths of our study were that prospective data on both depression and potential risk factors were obtained from a community population, and that depression was ascertained using a widely validated diagnostic instrument. The follow-up rate was reasonable and not apparently differential with respect to risk factors of interest. A limitation of the study was that information on some vascular factors such as stroke and heart disease relied on self-reported diagnoses and corroboration by medical records was not possible. Neuroimaging was also not feasible in this population. Furthermore, it should be borne in mind that most participants will have had moderate levels of depression, and the results may not be generalisable to secondary care clinical samples with more severe syndromes.

### Heart disease, stroke and depression

Reported heart disease was significantly associated with incidence of late-life depression in the present study, consistent with other research (Hippisley-Cox *et al*, 1998). Depression following myocardial infarction has been associated with higher mortality, and it is likely that the true association between cardiovascular disease and depression is underestimated because of differential mortality. Associations between previous stroke and depression are also well recognised in community samples (Fuh *et al*, 1997; Stewart *et al*, 2001; Kim *et al*, 2004). In our study the association was stronger for stroke occurring during the follow-up period than for that reported at baseline. This is likely to reflect a reduction in risk with increased duration since exposure, but might also be accounted for by differential attrition. As with previous cross-sectional studies, we found that this association was not entirely explained by level of disability (Stewart *et al*, 2001; Kim *et al*, 2004) which, as for heart disease, may reflect either specific biological causal pathways or unmeasured psychological factors (such as the impact of the diagnosis). In this respect, it is noteworthy that the association (in contrast to that of lipid levels) appeared to be principally explained by cognitive rather than vegetative symptoms, which supports the latter causal pathway over the former.

### Total cholesterol levels and depression

Previous studies investigating the association between total cholesterol levels and depression in later life have reported conflicting findings. Some have found significant associations with low cholesterol levels (Morgan *et al*, 1993), while others have found no associations (Blazer *et al*, 2002; Kim *et al*, 2004). In this prospective study we found that risk of depression at follow-up was associated with both high and low total cholesterol levels at baseline. Incident depression also appeared to be associated with both rising and falling total cholesterol levels over the follow-up period, although these associations fell below conventional levels of statistical significance. These findings are likely to represent mixed processes. High cholesterol, as a risk factor for arterial disease, may also be a risk factor for depression. Low cholesterol, on the other hand, is associated with frailty and poor health (Corti *et al*, 1997), which in turn are important risk factors for depression. Hypocholesterolaemia might also have direct risk effects, for example through reduced serotonin levels (Engelberg, 1992). Unfortunately data were not collected on cholesterol-lowering agents. However, we believe that the use of these agents is rare in this population and is unlikely to explain our observed associations.

### Vascular risk factors and depression

In a previous cross-sectional analysis of the baseline population for this study, we had found that low HDL cholesterol levels were associated with depression (Kim *et al*, 2004). In this prospective analysis, low HDL cholesterol also predicted incident depression. Furthermore, there were no apparent changes in HDL cholesterol levels in participants who became depressed, reducing the likelihood of reverse causality as an explanation. White matter abnormalities on neuroimaging are found more frequently than expected in people with late-life depression (de Groot *et al*, 2000), supporting vascular aetiology in at least some cases. However, population-based studies have frequently failed to find associations between depression and conventional vascular risk factors such as hypertension and diabetes (Jones-Webb *et al*, 1996; Rajala *et al*, 1997; Stewart *et al*, 2001). Where associations have been

found, it is unclear whether these are specific to the disorders themselves or explained by well-recognised associations between depression and worse physical health. The association with an atherogenic lipid profile is consistent with a vascular basis for late-life depression, but the weak or absent associations with reported hypertension or diabetes (or with recorded blood pressure or blood glucose) are not supportive. A neuropathological study also found that late-life depression was associated with arterial atheroma rather than microvascular disease (Thomas *et al*, 2001), and it is possible that vascular mechanisms underlying late-life depression have a different pattern to those implicated in stroke and vascular dementia. However, it is also possible that associations are explained by earlier unrecalled affective states which increase risk for both cardiovascular pathology and late-life depression. Vascular disease, vascular risk factors and depression are common conditions in older populations, and are associated with high levels of morbidity. Our findings provide some epidemiological support for vascular factors in the aetiology of late-life depression (Alexopoulos *et al*, 1997). However, prospective data over a longer follow-up period (possibly from early adulthood) are likely to be required before firm conclusions can be drawn concerning the direction of association between these two processes.

### ACKNOWLEDGEMENTS

We thank participants for their cooperation with this study. The study was funded by a grant from the Korea Health 21 R & D, Ministry of Health and Welfare, Republic of Korea (A050113).

### REFERENCES

- Alexopoulos, G. S., Meyers, B. S., Young, R. C., *et al* (1997) 'Vascular depression' hypothesis. *Archives of General Psychiatry*, **54**, 915–922.
- Blazer, D. G., Burchett, B. B. & Fillenbaum, G. G. (2002) APOE e4 and low cholesterol as risks for depression in a biracial elderly community sample. *American Journal of Geriatric Psychiatry*, **10**, 515–520.
- Cervilla, J., Prince, M. & Rabe-Hesketh, S. (2004) Vascular disease risk factors as determinants of incident depressive symptoms: a prospective community-based study. *Psychological Medicine*, **34**, 635–641.
- Copeland, J. R. M., Dewey, M. E. & Griffiths-Jones, H. M. (1986) A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGE-CAT. *Psychological Medicine*, **16**, 89–99.
- Corti, M.-C., Guralnik, J. M., Salive, M. E., *et al* (1997) Clarifying the direct relation between total cholesterol levels and death from coronary heart

disease in older persons. *Annals of Internal Medicine*, **126**, 753–760.

**de Groot, J. C., de Leeuw, F. E., Oudkerk, M., et al (2000)** Cerebral white matter lesions and depressive symptoms in elderly adults. *Archives of General Psychiatry*, **57**, 1071–1076.

**Engelberg, H. (1992)** Low serum cholesterol and suicide. *Lancet*, **339**, 727–729.

**Fuh, J. L., Liu, H. C., Wang, S. J., et al (1997)** Poststroke depression among the Chinese elderly in a rural community. *Stroke*, **28**, 1126–1129.

**Hippisley-Cox, J., Fielding, K., Pringle, M. (1998)** Depression as a risk factor for ischaemic heart disease in men: population based case–control study. *BMJ*, **316**, 1714–1719.

**Jones-Webb, R., Jacobs Jr., D. R., Flack, J. M., et al (1996)** Relationships between depressive symptoms, anxiety, alcohol consumption, and blood pressure: results from the CARDIA Study. *Alcoholism: Clinical and Experimental Research*, **20**, 420–427.

**Kim, J.-M., Stewart, R., Shin, I.-S., et al (2003a)** Limb length and dementia in an older Korean population. *Journal of Neurology, Neurosurgery and Psychiatry*, **74**, 427–432.

**Kim, J.-M., Stewart, R., Prince, M., et al (2003b)** Diagnosing dementia in a developing nation: an evaluation of the GMS–AGECAT algorithm in an older Korean population. *International Journal of Geriatric Psychiatry*, **18**, 331–336.

**Kim, J.-M., Stewart, R., Shin, I.-S., et al (2004)** Vascular disease/risk and late-life depression in a Korean community population. *British Journal of Psychiatry*, **185**, 102–107.

JAE-MIN KIM, MD, PhD, Department of Psychiatry and Depression Clinical Research Centre, Chonnam National University Medical School, Kwangju; ROBERT STEWART, MD, MRCPsych, King's College London (Institute of Psychiatry), London, UK; SUNG-WAN KIM, MD, PhD, SU-JIN YANG, MD, PhD, IL-SEON SHIN, MD, PhD, JIN-SANG YOON, MD, PhD, Department of Psychiatry and Depression Clinical Research Centre, Chonnam National University Medical School, Kwangju, Korea

Correspondence: Professor Jin-Sang Yoon, Department of Psychiatry, Chonnam National University Medical School, 5 Hak-Dong, Dong-gu, Kwangju 501-757, Republic of Korea. Tel. +82 62 220 6142; fax: +82 62 225 2351; email: jsyoon@chonnam.ac.kr

(First received 7 July 2005, final revision 21 November 2005, accepted 19 December 2005)

**Kim, J.-M., Stewart, R., Glozier, N., et al (2005)** Physical health, depression and cognitive function as correlates of disability in an older Korean population. *International Journal of Geriatric Psychiatry*, **20**, 160–167.

**Larson, S. L., Owens, P. L., Ford, D., et al (2001)** Depressive disorder, dysthymia, and risk of stroke. Thirteen-year follow-up from the Baltimore Epidemiologic Catchment Area Study. *Stroke*, **32**, 1979–1983.

**Lyness, J. M., King, D. A., Conwell, Y., et al (2000)** Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. *American Journal of Psychiatry*, **157**, 1499–1501.

**Morgan, R. E., Palinkas, L. A., Barrett-Connor, E. L., et al (1993)** Plasma cholesterol and depressive symptoms in older men. *Lancet*, **341**, 75–79.

**Park, J. H. & Kwon, Y. C. (1990)** Modification of the mini-mental state examination for use in the elderly in a non-western society: Part I. Development of Korean

version of Mini-Mental State Examination. *International Journal of Geriatric Psychiatry*, **5**, 381–387.

**Prince, M., Acosta, D., Chiu, H., et al (2003)** Dementia diagnosis in developing countries: a cross-cultural validation study. *Lancet*, **361**, 909–917.

**Rajala, U., Keinanen-Kiukkaanniemi, S. & Kevela, S. L. (1997)** Non-insulin-dependent diabetes mellitus and depression in a middle-aged Finnish population. *Social Psychiatry and Psychiatric Epidemiology*, **32**, 363–367.

**Stewart, R., Prince, M., Mann, A., et al (2001)** Stroke, vascular risk factors and depression. Cross-sectional study in a UK Caribbean-born population. *British Journal of Psychiatry*, **178**, 23–28.

**Thomas, A. J., Ferrier, I. N., Kalaria, R. N., et al (2001)** A neuropathological study of vascular factors in late-life depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **70**, 83–87.