Purpose in Life and Cerebral Infarcts in Community-Dwelling Older People

Lei Yu, PhD; Patricia A. Boyle, PhD; Robert S. Wilson, PhD; Steven R. Levine, MD; Julie A. Schneider, MD; David A. Bennett, MD

Background and Purpose—Purpose in life, the sense that life has meaning and direction, is associated with reduced risks of adverse health outcomes. However, it remains unknown whether purpose in life protects against the risk of cerebral infarcts among community-dwelling older people. We tested the hypothesis that greater purpose in life is associated with lower risk of cerebral infarcts.

Methods—Participants came from the Rush Memory and Aging Project. Each participant completed a standard measure of purpose in life. Uniform neuropathologic examination identified macroscopic infarcts and microinfarcts, blinded to clinical information. Association of purpose in life with cerebral infarcts was examined in ordinal logistic regression models using a semiquantitative outcome.

Results—Four hundred fifty-three participants were included in the analyses. The mean score on the measure of purpose was 3.5 (SD, 0.5; range, 2.1–5.0). Macroscopic infarcts were found in 154 (34.0%) people, and microinfarcts were found in 128 (28.3%) people. Greater purpose in life was associated with a lower odds of having more macroscopic infarcts (odds ratio, 0.535; 95% confidence interval, 0.346–0.826; P=0.005), but we did not find association with microinfarcts (odds ratio, 0.780; 95% confidence interval, 0.495–1.229; P=0.283). These results persisted after adjusting for vascular risk factors of body mass index, history of smoking, diabetes mellitus, and blood pressure, as well as measures of negative affect, physical activity, and clinical stroke. The association with macroscopic infaracts was driven by lacunar infarcts, and was independent of cerebral atherosclerosis and arteriolosclerosis.

Conclusions—Purpose in life may affect risk for cerebral infarcts, specifically macroscopic lacunar infarcts. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.008010.)

Key Words: aging ♦ cerebral infarcts ♦ lacunar ♦ purpose in life

Purpose in life, a psychosocial construct, which involves having meaning and goal-directedness in life, is a key component of psychological well-being. Older people with a greater sense of purpose are less likely to develop adverse health outcomes, including mortality, decline in physical function, frailty, disability, Alzheimer’s disease (AD), and clinical stroke. The neurobiological basis underlying the beneficial effect of purpose in life is not well understood but may be related to other psychosocial factors that have been shown to influence cardiovascular disease risk. However, the relationship of purpose in life with cerebral infarct pathology is unknown. Clinical strokes are largely underreported in old age. Neuroimaging captures more infarcts but may miss those that are under 3 mm or microscopic.

In this study, using data from community-dwelling older people enrolled in the Rush Memory and Aging Project, we tested the hypothesis that greater purpose is associated with lower risk of cerebral infarcts. All participants completed a standard assessment of purpose in life, were followed over multiple years and underwent autopsy after death. Our primary analysis examined associations of purpose with infarcts (macroscopic versus microscopic), and we evaluated significant associations by further controlling for a series of potential confounding factors. We also examined the associations with specific subtypes of infarcts.

Methods

Participants

The Rush Memory and Aging Project is an ongoing clinical-pathological cohort study of aging and dementia. The study was approved by the Institutional Review Board of Rush University Medical Center. Each participant signed an informed consent and an Anatomic Gift...
Purpose in Life

Assessment of purpose in life was performed annually using a modified 10-item measure derived from Ryff’s and Keyes’s scales of Psychological Well-being. During the assessment, participants rated their level of agreement with each item on a 5-point Likert scale. Ratings for negatively worded items were flipped, and scores at the item level were then averaged to obtain a composite score with a higher score indicating a greater sense of purpose in life, as reported previously. A valid score requires ≥8 items answered by the participants, and 99.3% of the participants in the analysis answered all 10 items.

In the primary analysis, the first valid score of purpose was used to examine the association with cerebral infarcts. Longitudinal data were also used to assess the potential change in purpose in life over time.

Table 1. Basic Characteristics of the Study Participants (n=453)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at analytic baseline, y</td>
<td>83.9 (6.0)</td>
</tr>
<tr>
<td>Age at death, y</td>
<td>89.6 (6.3)</td>
</tr>
<tr>
<td>Female sex</td>
<td>310 (68.4%)</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.5 (2.8)</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>3.5 (0.5)</td>
</tr>
<tr>
<td>Length of follow-up, y</td>
<td>5.7 (3.0)</td>
</tr>
<tr>
<td>Macroscopic infarcts</td>
<td></td>
</tr>
<tr>
<td>No infarct</td>
<td>239 (66.0%)</td>
</tr>
<tr>
<td>1 infarct</td>
<td>76 (16.8%)</td>
</tr>
<tr>
<td>Multiple infarcts</td>
<td>78 (17.2%)</td>
</tr>
<tr>
<td>Microinfarcts</td>
<td></td>
</tr>
<tr>
<td>No infarct</td>
<td>325 (71.7%)</td>
</tr>
<tr>
<td>1 infarct</td>
<td>81 (17.9%)</td>
</tr>
<tr>
<td>Multiple infarcts</td>
<td>47 (10.4%)</td>
</tr>
<tr>
<td>Cortical macroscopic infarcts</td>
<td></td>
</tr>
<tr>
<td>No infarct</td>
<td>394 (87.0%)</td>
</tr>
<tr>
<td>1 infarct</td>
<td>44 (9.7%)</td>
</tr>
<tr>
<td>Multiple infarcts</td>
<td>15 (3.3%)</td>
</tr>
<tr>
<td>Subcortical macroscopic infarcts</td>
<td></td>
</tr>
<tr>
<td>No infarct</td>
<td>336 (74.2%)</td>
</tr>
<tr>
<td>1 infarct</td>
<td>64 (14.1%)</td>
</tr>
<tr>
<td>Multiple infarcts</td>
<td>53 (11.7%)</td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td></td>
</tr>
<tr>
<td>No infarct</td>
<td>358 (79.0%)</td>
</tr>
<tr>
<td>1 infarct</td>
<td>60 (13.3%)</td>
</tr>
<tr>
<td>Multiple infarcts</td>
<td>35 (7.7%)</td>
</tr>
<tr>
<td>Nonlacunar infarcts</td>
<td></td>
</tr>
<tr>
<td>No infarct</td>
<td>404 (89.2%)</td>
</tr>
<tr>
<td>1 infarct</td>
<td>41 (9.1%)</td>
</tr>
<tr>
<td>Multiple infarcts</td>
<td>8 (1.8%)</td>
</tr>
</tbody>
</table>

Cerebral Infarct and Other Pathologies

Brains were removed, weighed, and 1 hemisphere was cut coronally into 1-cm slabs and fixed in 4% paraformaldehyde. Macroscopic cerebral infarcts (ie, infarcts visible to naked eyes) were identified using slabs or pictures from both the hemispheres, and confirmed by histological review. Blocks from ≥2 brain regions were cut into 6-μm sections, which were stained with hematoxylin/eosin and examined for microinfarcts using microscopy. We restricted our analysis to chronic infarcts. Lacunar infarcts were subcortical macroscopic infarcts that had all dimensions ≤10 mm, and nonlacunar infarcts had dimensions ≥10 mm. Each infarct measure was rated on a 3-level scale, including no infarct, 1 infarct, and multiple infarcts. Assessment of AD pathology and other cerebral vessel diseases are described in the online-only Data Supplement.

Clinical Stroke and Other Covariates

Details on clinical stroke diagnosis and assessment of other covariates are available in the online-only Data Supplement.

Statistical Analysis

To test the association of purpose in life with risk of cerebral infarcts, we first fit an ordinal logistic regression model with 3-level measure of total macroscopic infarcts as the categorical outcome, and the scores of purpose in life as the predictor, adjusted for age at death, sex, and education. We repeated the model for microinfarcts. Both models estimate the odds ratios of the presence of infarct, as well as of multiple infarcts, for every 1 U increase in the score of purpose in life. Next, we performed a series of analyses to assess the robustness of significant associations (online-only Data Supplement). Finally, we explored whether the association differed by cortical versus subcortical infarcts using separate regression models. The score test assessed proportional odds assumptions, which were adequately met in all models. Analyses were performed using SAS/STAT software, version 9.3 (SAS Institute Inc, Cary, NC) and we used a nominal threshold of P<0.05 for statistical significance.

Results

In 453 older people, 114 (25.3%) had clinical stroke. Nearly twice as many participants had macroscopic or micro infarcts at autopsy (n=216; 47.7%). Specifically, 76 (16.8%) had 1 macroscopic infarct, and 78 (17.2%) had ≥2 macroscopic infarcts; 81 (17.9%) had 1 microinfarct and 47 (10.4%) had ≥2 microinfarcts. Participants with macroscopic infarcts were more likely to have microinfarcts (P=0.001). Older age at death was associated with greater odds of both macroscopic (P=0.035) and microscopic (P=0.032) infarcts. We found no association of sex or years of education with either type of infarct. The mean score on the measure of purpose in life was 3.5 (SD, 0.5; range, 2.1–5.0). Comparing an individual with greater purpose (90th percentile) with one with less purpose (10th percentile), the score of our measure differed by ≈1 U. Figure shows that the level of purpose in life differs by macroscopic infarcts but not by microinfarcts.

Purpose in Life and Macroscopic Infarcts

In an ordinal logistic regression model adjusted for demographics, greater purpose in life was associated with lower odds of macroscopic infarcts (Table 2). Specifically, a 1-U increase of the score for purpose in life reduced the odds of having ≥1 macroscopic infarcts by ≈50% (odds ratio, 0.535; 95% confidence interval, 0.346–0.826; P=0.005). By contrast, we did not find an association of purpose with microinfarcts. We examined the potential sex difference in association...
of purpose with infarcts by adding a term for sex–purpose interaction; these were not significant suggesting no sex differences (Table I in the online-only Data Supplement). To account for the correlation between the 2 infarct outcomes, we reexamined simultaneously the associations of purpose in life with macroscopic and microinfarcts by fitting a bivariate Dale model. Results were unchanged (Table II in the online-only Data Supplement).

Next, by leveraging longitudinal data for purpose in life, we assessed change in purpose over time (online-only Data Supplement) and examined whether the association with infarcts was influenced by such change. On average, there was a small decline in purpose in life relative to baseline differences (annual rate of decline, −0.044; \( P < 0.001 \)). The association with infarcts persisted after adjustment for the individual-specific change in purpose in life (Table III in the online-only Data Supplement). These results support the relatively trait-like property of purpose in life.

Separately, we explicitly examined the extent to which purpose in life measured many years versus just a few years before death differ by adding a model term for time from purpose assessment to death and its interaction with purpose. The interaction term was not significant, suggesting that the associations were not dependent on time between assessment and death (Table IV in the online-only Data Supplement).

We examined whether the relationship between purpose in life and macroscopic infarcts was affected by potential confounders (Table V in the online-only Data Supplement). First, because purpose in life reduces the adverse effect of AD pathology on change in cognition,\(^{13}\) we investigated whether the association of purpose with macroscopic infarcts is influenced by AD pathology. Burden of AD pathology did not differ by infarcts status, and greater purpose in life was still associated with lower odds for more macroscopic infarcts after controlling for the burden of AD pathology.

Second, because purpose in life has been associated with vascular risk factors,\(^{19}\) we repeated our model by including terms for body mass index, history of smoking, diabetes mellitus, and blood pressure. Higher systolic blood pressure was associated with greater odds for more macroscopic infarcts (\( P=0.015 \)). However, the association of purpose in life and macroscopic infarcts persisted after controlling for these vascular risk factors.

Figure. A–D, Boxplot of purpose in life by burdens of a specific type of cerebral infarcts (0=no infarct; 1=1 infarct; and 2=multiple infarcts). Here each box is defined by the interquartile range, the bar inside the box is the median, and the whiskers are bounded by 1.5\times interquartile range.
Fourth, purpose in life is associated with physical activity. Including the covariate for total daily activity, the association of purpose with macroscopic infarcts persisted. Finally, only a proportion of participants with macroscopic infarcts had a diagnosis of clinical stroke. We controlled for clinical stroke to examine whether the association of purpose in life with macroscopic infarcts is driven by those with clinical diagnosis. Notably, although clinical stroke was strongly associated with greater odds for macroscopic infarcts, the result on purpose in life was essentially unchanged.

**Purpose in Life and Lacunar Infarcts**

To further explore whether the association with macroscopic infarcts differs by the anatomic location, we fit separate logistic regression models for cortical and subcortical macroscopic infarcts. A greater purpose in life was associated with fewer subcortical macroscopic infarcts but not with cortical macroscopic infarcts (Table 3). Because subcortical macroscopic infarcts can be further categorized into lacunar and nonlacunar infarcts, we also tested the associations with these subtypes of subcortical infarcts. The association was significant only with respect to the lacunar infarcts (Table 4), particularly gray matter lacunar infarcts (Table VI in the online-only Data Supplement).

Finally, to assess whether the effect of purpose in life works through vessel diseases, we investigated the relationship with cerebral arteriosclerosis and atherosclerosis. Purpose in life was not associated with the measure of arteriosclerosis to either arteriolosclerosis or atherosclerosis. Furthermore, the association persisted after controlling for clinical stroke. Second, the earlier study focused only on the outcome of clinical stroke in general, we were able to examine the associations with more specific subtypes of infarcts. Interestingly, we found that the most robust association is with lacunar infarcts.

Reasons for the differential association of purpose with infarct subtypes are not clear. One potential mechanism would be through small vessel disease (or arteriolosclerosis), which is more commonly related to lacunar infarcts. Indeed, purpose in life is not related to either arteriolosclerosis or atherosclerosis. Furthermore, the association persists after adjusting for burdens of arteriolosclerosis and atherosclerosis. This finding suggests that the association of purpose in life with cerebral infarct is probably independent of vessel disease.

More broadly, the neurobiological basis of the protective effect of purpose in life and other psychosocial constructs is complex and poorly understood. Our previous finding on purpose and AD pathology is consistent with the neural reserve theory, such that purpose is not directly related to AD pathology, instead older people with greater purpose tend to function better cognitively, whereas AD pathology accumulates in the brain. A recent study on neural correlates of purpose shows a positive association between purpose and insular cortex gray

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### Table 2. Purpose in Life With Macroscopic Infarcts and Microinfarcts

<table>
<thead>
<tr>
<th></th>
<th>Macroscopic Infarcts</th>
<th>Microinfarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORs (95% CIs), P Values</td>
<td>ORs (95% CIs), P Values</td>
</tr>
<tr>
<td>Age at death</td>
<td>1.028 (0.995–1.061), 0.098</td>
<td>1.034 (0.999–1.070), 0.060</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.253 (0.809–1.942), 0.313</td>
<td>0.937 (0.588–1.495), 0.785</td>
</tr>
<tr>
<td>Education</td>
<td>0.950 (0.882–1.024), 0.179</td>
<td>1.004 (0.929–1.084), 0.927</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>0.533 (0.346–0.826), 0.005</td>
<td>0.780 (0.495–1.229), 0.283</td>
</tr>
</tbody>
</table>

The logits model the odds of more infarct pathology against less infarct pathology (ie, 1, 2, or more vs 0; and ≥2 vs 0 or 1). CI indicates confidence interval; and OR, odds ratio.

### Table 4. Purpose in Life With Lacunar and Nonlacunar Infarcts

<table>
<thead>
<tr>
<th></th>
<th>Lacunar Infarcts</th>
<th>Nonlacunar Infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORs (95% CIs), P Values</td>
<td>ORs (95% CIs), P Values</td>
</tr>
<tr>
<td>Age at death</td>
<td>1.017 (0.979–1.056), 0.389</td>
<td>1.009 (0.960–1.060), 0.728</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.228 (0.733–2.059), 0.436</td>
<td>1.073 (0.545–2.110), 0.839</td>
</tr>
<tr>
<td>Education</td>
<td>0.942 (0.863–1.030), 0.189</td>
<td>0.987 (0.880–1.106), 0.821</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>0.502 (0.300–0.838), 0.009</td>
<td>0.669 (0.345–1.300), 0.236</td>
</tr>
</tbody>
</table>

The logits model the odds of more infarct pathology against less infarct pathology (ie, 1, 2, or more vs 0; and ≥2 vs 0 or 1). CI indicates confidence interval; and OR, odds ratio.

(P = 0.619) or atherosclerosis (P = 0.828). In a model adjusted for demographics and both the measures of arteriolosclerosis and atherosclerosis, the association of purpose in life and lacunar infarcts robustly retained (Table VII in the online-only Data Supplement).

### Discussion

We found that a greater sense of purpose in life is associated with <50% reduced likelihood of cerebral infarcts. The result was robust against the adjustment for several confounders. The association seems to be driven by lacunar infarcts, independent of cerebral large or small vessel disease.

A previous study shows that purpose in life is associated with a reduced risk of clinical strokes in a group of participants aged 53 to 105 years. We extend this finding in several ways. Although the earlier study reports that <4% of the participants had clinical stroke >4 years of follow-up, our data show that at autopsy >30% of our participants had macroscopic infarcts and >25% had microinfarcts. This difference suggests that purpose in life is protective for silent infarcts, as well as clinical stroke. Thus, the association persists after controlling for clinical stroke. Second, the earlier study focused only on the outcome of clinical stroke in general, we were able to examine the associations with more specific subtypes of infarcts. Interestingly, we found that the most robust association is with lacunar infarcts.

Reasons for the differential association of purpose with infarct subtypes are not clear. One potential mechanism would be through small vessel disease (or arteriolosclerosis), which is more commonly related to lacunar infarcts. Indeed, we confirm that more severe arteriolosclerosis is associated with more lacunar infarcts. However, purpose in life is not related to either arteriolosclerosis or atherosclerosis. Furthermore, the association persists after adjustment for burdens of arteriolosclerosis and atherosclerosis. This finding suggests that the association of purpose in life with cerebral infarct is probably independent of vessel disease.

More broadly, the neurobiological basis of the protective effect of purpose in life and other psychosocial constructs is complex and poorly understood. Our previous finding on purpose and AD pathology is consistent with the neural reserve theory, such that purpose is not directly related to AD pathology, instead older people with greater purpose tend to function better cognitively, whereas AD pathology accumulates in the brain. A recent study on neural correlates of purpose shows a positive association between purpose and insular cortex gray.
matter volume.\textsuperscript{25} Different from the finding on AD, in this study, we show a direct relationship between greater purpose and lower risk for infarct pathology. Thus, purpose in life may work through other pathways to influence health outcomes in old age.

There are 2 other possible explanations for the association of purpose in life with infarcts. First, purpose may reduce the risk of infarcts by promoting healthy lifestyles. Previous work suggests that purpose is associated with lower cardiovascular disease risk.\textsuperscript{19,26} However, the findings in our study persist after we adjusted for vascular risks of body mass index, history of smoking, diabetes mellitus, and blood pressure. Although purpose in life is correlated with physical activity, controlling for daily activity in our data did not attenuate our finding. Stress or stress-related factors may also play a role in the association of purpose with infarcts. One study found that the combination of social inhibition and negative affect increased risk for cardiovascular events and mortality in patients with coronary artery disease.\textsuperscript{27} However, our findings persist after the adjustment for measures of negative affect.

Second, purpose may directly be implicated in neuroendocrine function. Earlier studies show that psychological well-being is correlated with many biological markers, such as salivary cortisol level, epinephrine, and norepinephrine.\textsuperscript{28} Other potential mechanisms include inflammatory and potentially procoagulant and endothelial dysfunction markers, such as high sensitivity C-reactive protein, interleukin-6, soluble intercellular adhesion molecule, monocyte chemotractant protein-1, interleukin-8, homocysteine, von Willebrand factor, E-selectin, P-selectin, and tumor necrosis factor-\alpha.\textsuperscript{11,29} Further work is needed to address these potential mechanistic pathways.

Purpose in life is correlated with many other psychological constructs, including sense of coherence, resilience, and optimism.\textsuperscript{30} Importantly, purpose in life constitutes a distinct dimension of psychological well-being and is a potentially modifiable factor that promotes healthy aging. One study reported that dispositional optimism protects against stroke,\textsuperscript{31} and that purpose is associated with a lower risk even after controlling for optimism.\textsuperscript{32} These measures have not been collected in our cohort and we cannot directly examine their relationships with purpose.

This study has the following strengths. Purpose in life was documented in community-dwelling people without dementia. Participants were followed for >5 years and underwent neuropathologic examination after death with high rates of autopsy. Our finding on association of purpose with reduced risk of infarct pathology is robust against confounding variables. Limitations are also noted. Although people >80 years represent the fastest growing segment of the population; participants were older and had higher levels of education compared with the general population. Therefore, results may not generalize to other groups. Our finding that the association of purpose in life is primarily driven by lacunar infarcts requires replication from other studies.

Acknowledgments

We are grateful to all the participants of the Rush Memory and Aging Project. We also thank the staff at the Rush Alzheimer’s Disease Center for this work.

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Disclosures

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References

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http://stroke.ahajournals.org/content/early/2015/03/19/STROKEAHA.114.008010

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/03/20/STROKEAHA.114.008010.DC1

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SUPPLEMENTAL MATERIAL

Purpose in Life and Cerebral Infarcts in Community Dwelling Older Persons
Supplemental Methods

Diagnosis of Clinical Stroke
Clinical diagnosis of stroke was made by a neurologist with expertise in dementia. Blinded to all postmortem data, the neurologist reviewed all available clinical data and rendered the most likely clinical diagnosis at the time of death. Case conferences including one or more neurologists and a neuropsychologist were used for consensus on selected cases. Details were described previously.1

AD pathology and Cerebral Vessel Diseases
We used a global continuous measure to assess the burden of AD pathology. The measure was based on neuritic and diffused plaques as well as neurofibrillary tangles. Briefly, counts of each AD index were recorded from 5 predetermined brain regions, which were standardized and averaged across the regions. These scores were then averaged to obtain the composite measure of AD pathology.2 Both arteriolosclerosis and atherosclerosis were assessed using a semiquantitative measure from 0 (none) to 3 (severe). The measure of arteriolosclerosis captures the histologic changes commonly found in the small vessels of the brain in aging, and the measure of atherosclerosis captures the accumulation of fatty deposits on the walls of large vessels.

Assessment of Other Covariates
Sex, years of education, and history of smoking were self reported. Body mass index (BMI) was calculated as the ratio of weight in kilograms and height in meters squared.5 Sitting blood pressure readings were taken twice and measures of systolic and diastolic blood pressure were obtained by averaging the two readings. Diabetes was determined based on both participant’s self report and the use of diabetes medication. Depressive symptom was assessed using a ten-item version of the Center for Epidemiologic Studies Depression scale (CES-D).6 Harm avoidance was assessed using a 35-item Harm Avoidance scale from Cloninger’s Temperament and Character Inventory.7 Childhood adversity was assessed based on a 16-item questionnaire focusing on childhood emotional and physical trauma.8 Loneliness assessment was based on a modified version of the de Jong-Gierveld Loneliness Scale.9 Total daily physical activity was calculated as the mean sum of all 24-hour activity counts recorded by actigraphs for up to a period of 10 days.

For the variables with repeated measure, including BMI, blood pressures, diabetes, depressive symptom, and loneliness, data were taken at the same visit as purpose in life assessment. The variables of history of smoking, harm avoidance, and childhood adversity were measured once. Data for total daily physical activity became available later in the study; therefore the first valid assessment was used for the analysis.

Assessment of Change in Purpose in Life
We used a linear mixed model to examine potential change in purpose in life. In this model repeated measures of purpose assessment were the longitudinal outcome. The model included terms for age, sex, education, time in years since the first purpose assessment, and the interaction of time with the other variables. The term for time estimated the mean annual rate of change.
(slope) in purpose. We estimated person-specific slopes of change in purpose for each participant from the same model. These person-specific slopes were used to examine whether the association with infarcts was influenced by change in purpose. To do so, we augmented the logistic regression in the primary analysis by adding a model term for the slopes of change in purpose.

**Sensitivity Analysis of Significant Associations**

We performed a series of sensitivity analyses to assess significant associations. First, since macroscopic and microinfarcts are strongly comorbid, we fit a bivariate Dale model to estimate simultaneously the association of purpose in life with both macroscopic and microinfarcts while accounting for the correlation between these two outcomes. Second, other psychosocial, clinical and pathological factors may confound the association of purpose with infarcts; we therefore augmented our primary models by controlling for additional covariates including AD pathology, vascular risk factors, (that is, body mass index (BMI), smoking history, diabetes and blood pressure), measures of negative affect (that is, depressive symptoms, childhood adverse experience, harm avoidance and loneliness), physical activity and diagnosis of clinical stroke. Finally, we explored whether the association differed by anatomical location (that is cortical versus subcortical). To do so, we repeated the ordinal logistic regression separately for cortical and subcortical infarcts.
References

Supplemental Table I Purpose in life with macroscopic infarcts and microinfarcts, sex by purpose interaction

<table>
<thead>
<tr>
<th></th>
<th>Macroscopic infarcts log(OR) (SE), p-values</th>
<th>Microinfarcts log(OR) (SE), p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>0.027 (0.017), .110</td>
<td>0.031 (0.018), .075</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.294 (0.311), .345</td>
<td>0.141 (0.317), .656</td>
</tr>
<tr>
<td>Education</td>
<td>-0.052 (0.038), .174</td>
<td>0.002 (0.040), .964</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>-0.677 (0.276), .014</td>
<td>-0.405 (0.285), .154</td>
</tr>
<tr>
<td>Sex × purpose interaction</td>
<td>0.145 (0.461), .754</td>
<td>0.470 (0.489), .336</td>
</tr>
</tbody>
</table>

The analysis was conducted using ordinal logistic regression with a 3-level infarcts measure, macroscopic infarcts and microinfarcts separately, as the outcome, and age at death, sex, education, the score of purpose in life measure, as well as the sex and purpose interaction as the predictors. The logits model the odds of more infarct pathology against less infarct pathology (that is, 1, 2 or more versus 0; and 2 or more versus 0 or 1).
OR: Odd ratio; SE: Standard error.
Supplemental Table II Purpose in life with macroscopic infarcts and microinfarcts, using bivariate Dale model

<table>
<thead>
<tr>
<th></th>
<th>Macroscopic infarcts ORs (95% CIs), p-values</th>
<th>Microinfarcts ORs (95% CIs), p-values</th>
<th>Correlation of macro and micro infarcts ORs (95% CIs), p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>1.026 (0.994, 1.060), .118</td>
<td>1.036 (1.001, 1.072), .044</td>
<td>0.978 (0.920, 1.040), 0.483</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.234 (0.796, 1.915), .348</td>
<td>0.962 (0.608, 1.522), .869</td>
<td>0.854 (0.322, 2.266), 0.751</td>
</tr>
<tr>
<td>Education</td>
<td>0.956 (0.888, 1.029), .234</td>
<td>1.008 (0.932, 1.089), .848</td>
<td>1.100 (0.939, 1.290), 0.238</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>0.525 (0.342, 0.804), .003</td>
<td>0.764 (0.487, 1.199), .243</td>
<td>0.308 (0.224, 1.654), 0.330</td>
</tr>
</tbody>
</table>

The analysis was conducted using a bivariate Dale model with two 3-level infarcts measures, macro and microscopic simultaneously, as the outcome, and age at death, sex, education, and the score of purpose in life measure as the predictors. The logits model the odds of more infarct pathology against less infarct pathology (that is, 1, 2 or more versus 0; and 2 or more versus 0 or 1). In addition, the model assesses the correlation between the two infarct outcomes as well as the association of each predictor with such correlation.
### Supplemental Table III Purpose in life with macroscopic infarcts and microinfarcts, adjusted for change in purpose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Macroscopic infarcts OR (95% CIs), p-values</th>
<th>Microinfarcts OR (95% CIs), p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>1.021 (0.987, 1.056), .228</td>
<td>1.034 (0.998, 1.072), .062</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.311 (0.842, 2.040), .230</td>
<td>0.932 (0.583, 1.492), .771</td>
</tr>
<tr>
<td>Education</td>
<td>0.951 (0.883, 1.025), .189</td>
<td>1.004 (0.929, 1.084), .927</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>0.530 (0.342, 0.820), .004</td>
<td>0.780 (0.495, 1.230), .286</td>
</tr>
<tr>
<td>Change in purpose</td>
<td>1.097 (0.971, 1.240), .135</td>
<td>0.989 (0.873, 1.122), .867</td>
</tr>
</tbody>
</table>

The analysis was conducted using ordinal logistic regression with a 3-level infarcts measure, macroscopic infarcts and microinfarcts separately, as the outcome, and age at death, sex, education, baseline score of purpose in life, as well as the annual rate of change in purpose as the predictors. The logits model the odds of more infarct pathology against less infarct pathology (that is, 1, 2 or more versus 0; and 2 or more versus 0 or 1).
### Supplemental Table IV Purpose in life with macroscopic infarcts and microinfarcts, time to death by purpose interaction

<table>
<thead>
<tr>
<th></th>
<th>Macroscopic infarcts</th>
<th>Micorinfarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>log(OR) (SE), p-values</td>
<td>log(OR) (SE), p-values</td>
</tr>
<tr>
<td>Age at death</td>
<td>0.014 (0.017), .417</td>
<td>0.012 (0.018), .501</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.294 (0.226), .193</td>
<td>0.011 (0.241), .964</td>
</tr>
<tr>
<td>Education</td>
<td>-0.053 (0.038), .164</td>
<td>0.003 (0.040), .940</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>-0.659 (0.238), .006</td>
<td>-0.338 (0.256), .186</td>
</tr>
<tr>
<td>Time to death</td>
<td>0.046 (0.054), .395</td>
<td>0.097 (0.055), .080</td>
</tr>
<tr>
<td>Time to death × purpose interaction</td>
<td>-0.066 (0.072), .363</td>
<td>-0.052 (0.076), .490</td>
</tr>
</tbody>
</table>

The analysis was conducted using ordinal logistic regression with a 3-level infarcts measure, macroscopic infarcts and microinfarcts separately, as the outcome, and age at death, sex, education, the score of purpose in life measure, time from purpose assessment to death, as well as the time to death and purpose interaction as the predictors. The logits model the odds of more infarct pathology against less infarct pathology (that is, 1, 2 or more versus 0; and 2 or more versus 0 or 1).

OR: Odd ratio; SE: Standard error.
Supplemental Table V Purpose in life with macroscopic infarcts, adjusted for potential confounders

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (N=452) ORs (95% CIs), p</th>
<th>Model 2 (N=433) ORs (95% CIs), p</th>
<th>Model 3 (N=353) ORs (95% CIs), p</th>
<th>Model 4 (N=292) ORs (95% CIs), p</th>
<th>Model 5 (N=450) ORs (95% CIs), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>1.026 (0.993, 1.060), .117</td>
<td>1.030 (0.994, 1.068), .100</td>
<td>1.015 (0.978, 1.053), .430</td>
<td>1.011 (0.972, 1.052), .587</td>
<td>1.027 (0.993, 1.061), .118</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.261 (0.812, 1.957), .301</td>
<td>1.313 (0.830, 2.079), .244</td>
<td>1.409 (0.845, 2.348), .189</td>
<td>1.349 (0.785, 2.319), .278</td>
<td>1.438 (0.918, 2.254), .113</td>
</tr>
<tr>
<td>Education</td>
<td>0.949 (0.881, 1.023), .172</td>
<td>0.964 (0.892, 1.043), .360</td>
<td>0.965 (0.886, 1.051), .412</td>
<td>0.955 (0.872, 1.045), .315</td>
<td>0.948 (0.878, 1.023), .167</td>
</tr>
<tr>
<td>AD pathology</td>
<td>1.001 (0.703-1.426), .995</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMI</td>
<td>-</td>
<td>1.004 (0.958-1.052), .876</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>1.128 (0.778-1.635), .525</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hx of smoking</td>
<td>-</td>
<td>1.725 (0.929, 3.201), .084</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-</td>
<td>1.018 (1.003, 1.032), .015</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-</td>
<td>0.996 (0.974, 1.019), .757</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Depressive symptom</td>
<td>-</td>
<td>-</td>
<td>0.978 (0.844, 1.134), .771</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Harm avoidance</td>
<td>-</td>
<td>-</td>
<td>1.024 (0.990, 1.059), .164</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adverse experience</td>
<td>-</td>
<td>-</td>
<td>1.035 (1.001, 1.070), .044</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Loneliness</td>
<td>-</td>
<td>-</td>
<td>1.142 (0.759, 1.717), .524</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Physical activity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.843 (0.700, 1.016), .073</td>
<td>-</td>
</tr>
<tr>
<td>Clinical strokes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.957 (1.927, 4.538), &lt;.001</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>0.532 (0.343, 0.825), .005</td>
<td>0.575 (0.363, 0.911), .018</td>
<td>0.554 (0.319, 0.961), .036</td>
<td>0.366 (0.209, 0.642), .001</td>
<td>0.555 (0.357, 0.864), .009</td>
</tr>
</tbody>
</table>

The analyses were conducted using ordinal logistic regression with a 3-level macroscopic infarcts measure as the outcome, and age at death, sex, education, and the score of purpose in life measure as the predictors. Model 1 further included AD pathology, model 2 included vascular risk factors of BMI, diabetes, history of smoking, blood pressures, model 3 was based on a subset of the sample and included measures for negative affect, model 4 was based on a subset of the sample and included a measure for physical activity, and model 5 included a term for clinical diagnosis of strokes. The logits model the odds of more infarct pathology against less infarct pathology (that is, 1, 2 or more versus 0; and 2 or more versus 0 or 1).

AD = Alzheimer’s disease, BMI = body mass index, BP = blood pressure
Supplemental Table VI Purpose in life with lacunar infarcts (gray matter vs white matter)

<table>
<thead>
<tr>
<th></th>
<th>Gray matter lacunar infarcts ORs (95% CIs), p-values</th>
<th>White matter lacunar infarcts ORs (95% CIs), p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>0.987 (0.943, 1.032), .562</td>
<td>1.053 (1.004, 1.105), .034</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.128 (0.601, 2.115), .708</td>
<td>1.531 (0.826, 2.836), .176</td>
</tr>
<tr>
<td>Education</td>
<td>0.966 (0.867, 1.076), .528</td>
<td>0.944 (0.849, 1.050), .290</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>0.488 (0.262, 0.909), .024</td>
<td>0.633 (0.340, 1.178), .149</td>
</tr>
</tbody>
</table>

The analysis was conducted using ordinal logistic regression with a 3-level infarcts measure, gray matter lacunar infarcts and white matter lacunar infarcts separately, as the outcome, and age at death, sex, education, and the score of purpose in life measure as the predictors. The logits model the odds of more infarct pathology against less infarct pathology (that is, 1, 2 or more versus 0; and 2 or more versus 0 or 1).
Supplemental Table VII Purpose in life with subcortical infarcts, adjusted for vessel diseases

<table>
<thead>
<tr>
<th></th>
<th>Lacunar infarcts ORs (95% CIs), p-values</th>
<th>Nonlacunar infarcts ORs (95% CIs), p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>1.005 (0.967, 1.045), .789</td>
<td>0.993 (0.944, 1.045), .796</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.237 (0.733, 2.088), .427</td>
<td>1.063 (0.533, 2.120), .862</td>
</tr>
<tr>
<td>Education</td>
<td>0.946 (0.865, 1.035), .227</td>
<td>0.998 (0.888, 1.120), .967</td>
</tr>
<tr>
<td>Purpose in life</td>
<td>0.495 (0.293, 0.834), .008</td>
<td>0.668 (0.338, 1.323), .247</td>
</tr>
<tr>
<td>Arteriolosclerosis</td>
<td>1.439 (1.096, 1.889), .009</td>
<td>1.466 (1.026, 2.096), .036</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>1.298 (0.977, 1.725), .072</td>
<td>1.523 (1.053, 2.203), .026</td>
</tr>
</tbody>
</table>

The analysis was conducted using ordinal logistic regression with a 3-level infarcts measure, lacunar and nonlacunar separately, as the outcome, and age at death, sex, education, the score of purpose in life measure, arteriolosclerosis and atherosclerosis as the predictors. The logits model the odds of more infarct pathology against less infarct pathology (that is, 1, 2 or more versus 0; and 2 or more versus 0 or 1).