The trajectory of functional status before and after vascular events

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ABSTRACT

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Background: Previous studies that have examined functional status in relation to vascular events have focused on the short term after events and have measured functional status a limited number of times. The trajectories of functional status before and after vascular events are not well characterized, and the factors influencing these trajectories are not well known.

Methods: A comprehensive, structured, narrative review was performed on the topic of trajectories of disability and cognition surrounding vascular events. Then using 2 large population-based epidemiologic cohorts, the Northern Manhattan Study (NOMAS) and the Cardiovascular Health Study (CHS), trajectories of functional status were examined. In Analysis A, in NOMAS, the effect of inflammatory biomarkers (interleukin-6 [IL6], tumor necrosis factor receptor-1 [TNFR1], C-reactive protein [CRP], and lipoprotein-associated phospholipase-A2 [LpPLA2]) on the intercept and slope of functional status was determined over a median of 13 years, measured with yearly assessments by the Barthel index. In Analysis B, in NOMAS, a similar modeling strategy was used to examine whether subclinical ischemic disease on brain MRIs, measured by subclinical brain infarct (SBI) and white matter hyperintensity volume (WMHV), was associated with functional trajectories. In Analysis C, in CHS, participants had yearly assessments of disability with a combined activities of daily living (ADL) and instrumental ADL scale. The slope of change in disability was compared before and after vascular events (stroke and myocardial infarction [MI]).

Results: In Analysis A, CRP (-0.41 BI points per 1 SD increase, 95% CI -0.82 to 0.002) and LpPLA2 (-0.40, 95% CI -0.75 to -0.04) were associated with baseline BI but not change over time. TNFR1 was associated with baseline BI (-0.93, 95% CI -1.59 to -0.26) and change over time (-0.36 BI points per year, 95% CI -0.69 to -0.03). In Analysis B, functional change was -0.85 BI points per year (95%CI -1.01 to -0.69); among those with SBI there were -0.88 additional points annually (-1.44 to -0.32). In WMHV models, annual functional change was -1.04 points (-1.2 to -0.88), with -0.74 additional points annually per SD WMHV increase (-0.99 to -0.49). In Analysis C, stroke (0.88, 95% CI 0.57-1.20, $p<0.0001$) was associated with a greater acute increase in disability than MI (0.20, 0.06-0.35, $p=0.006$). The annual

increase in disability before stroke (0.06 points per year, 0.002-0.12, p=0.04) more than tripled after stroke (0.15 additional points per year, 0.004-0.30, p=0.04). The annual increase in disability before MI (0.04 points per year, 0.004-0.08, p=0.03) did not change significantly after MI (0.02 additional points per year, -0.07-0.11, p=0.7).

Conclusions: In these large population-based studies with repeated measures of functional status and disability over long-term follow-up, several trajectories were found. In Analysis A, TNFR1 predicted worse overall functional status as well as accelerated decline over time. In Analysis B, both SBI and WMHV were associated with accelerated decline. In Analysis C, there was a steeper decline in function after stroke but not MI. These findings help to elucidate the course and potential etiologies of long-term functional decline related to vascular events, and they suggest directions for future research in this area.

TABLE OF CONTENTS

LIST OF CHARTS, GRAPHS, and ILLUSTRATIONS

The Figures appear at the end of the body text in each section. In the Comprehensive Literature Review and Specific Aims, the figures are numbered by lower case Roman numerals (i, ii, iii, etc.). In the subsequent sections, figures have a prefix indicating the section (A, B, C, or D) followed by the sequential number of the figure.

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DEDICATION

This dissertation is dedicated to my parents, who have always supported me with love and consideration. This work is also dedicated to my wife Surleen, who has supported me not only in completing this degree, but in every other area of my life, and to whom I am eternally grateful.

Comprehensive literature review and specific aims

Abstract

In this review, I will summarize prior studies that have examined trajectories of patient-centered outcomes surrounding vascular events. I will first introduce the concept of disability, review factors that influence disability, and then outline the traditional conception of stroke. I will then introduce a new paradigm, in which cerebrovascular disease is conceived as a progressive condition with cumulative effects on functional status instead of just a condition that causes discrete events.

I will discuss several lines of research that support this paradigm. The first area of research has shown that vascular risk factors cause not only discrete stroke events but also progressive cerebrovascular dysfunction. The second line of research has shown that subclinical brain infarcts (SBIs) and white matter hyperintensities (WMHs) are common, influenced by vascular risk factors, and are associated with functional status. Newer imaging technology is also beginning to reveal other markers of structural cerebrovascular dysfunction that might illuminate the progressive nature of cerebrovascular disease and its long-term effects on functional status. Next, I will briefly discuss traumatic brain injury (TBI) as a condition analogous to stroke in that it involves a sudden brain injury but manifests beyond the acute recovery period with accelerated decline in functional status and cognitive ability. This similarity may be exploited in research to lead to the identification of pathophysiologies that overlap with those of stroke, and it may inform study designs that attempt to model long-term patient-centered outcomes.

Neurodegenerative diseases are a class of progressive neurological conditions causing cognitive and functional decline, and aside from vascular dementia, these have traditionally been thought of as distinct from cerebrovascular disease. However, recent research has shown similar risk factors and pathological processes for both neurodegenerative disease and cerebrovascular disease, and these processes may contribute to some of the long-term decline seen with stroke. Inflammatory processes, both systemic and specific to the nervous system, have been implicated not only in neurodegenerative diseases but also cerebrovascular disease, and these processes may play a role in progressive vascular and cerebral dysfunction related to vascular events.

With this as background, I will review recent research on patient-centered outcome trajectories surrounding vascular events. In turn, I will discuss studies examining disability, those examining cognition, and those examining other outcomes. Then, I will review the few studies comparing

trajectories before and after vascular events, and then summarize studies that have examined functional trajectories immediately before death. I will close with the specific aims and hypotheses for the analyses in this dissertation.

Disability and factors influencing it

An individual's functional status is closely tied to disease. The World Health Organization classifies functioning on a continuum and identifies three levels: impairment in a body part, disability (or "activity") on the level of an individual, and handicap (or "participation") defined by the person's position in an environment or social context.[1] Disability is an important patient-centered outcome whose relationship with vascular disease requires further elucidation. Disability is commonly measured by an individual's performance in activities of daily living (ADLs), including tasks such as personal hygiene, dressing and undressing, feeding, transfers and ambulation, and bowel and bladder management.[2, 3] Instrumental ADLs (IADLs) assess more complex activities required for community participation, such as handling personal finances, meal preparation, shopping, travelling, doing housework, using the telephone, and taking medications.[4] There is a hierarchical relationship between some IADL items and ADL items, with IADL impairment becoming evident with less severe dysfunction.[5]

As diverse organizations have highlighted,[6] disability is essential to study, for several reasons. This outcome may more accurately reflect the burden of disease in a population compared to discrete events such as MI, which have a differential functional impact in different people. By focusing on events or mortality, one may underestimate the burden of diseases.[7] Understanding the population impact of diseases on disability is important considering the aging of the population, which will increase the number of disabled individuals over the next few decades.[8, 9] The pattern and time course of disability in older age has also been changing. Recent studies suggest that there has been a "compression of morbidity" over time, with disability and health conditions occurring closer to the end of life currently compared to earlier time periods.[10, 11]

Several factors affect long-term disability, including age, cognitive function, self-rated health, and social supports.[12-14] Several diseases also cause disability, including but not limited to cerebrovascular disease, arthritis, cardiac disease, depression, and cognitive disorders. Among the disease states that

affect disability, stroke causes perhaps the greatest burden.[15-17] Three months after a stroke, 30-50% of stroke survivors are functionally dependent, 15-30% are permanently disabled, and 20% require institutional care.[18] Considering the staggering prevalence of stroke – 5.8 million among those age 20 and above in 2005[19] – post-stroke disability is of primary public health importance. In a longitudinal analysis in the Health and Retirement Survey (HRS) among 24,186 individuals with a mean of 10.2 years of follow-up,[20] physical functioning was assessed biennially and was compared among those with different diseases. Memory-related disease and stroke were associated with the most disability, and the combination of both was associated with 5.75 physical functioning difficulties. Disability is costly, to an individual and to society, and places a burden not only on the disabled but also on family and caregivers. In the Survey of Health, Ageing and Retirement in Europe (SHARE), 62,127 individuals were surveyed in 2 waves in several European countries, 1256 of whom had stroke.[21] About one third had moderate ADL limitations and 6.6% had severe limitations. Those with severe ADL limitations had 1.45 more hospital days, used 14.86 more hours of paid home nursing, and used 100 more hours in a month of informal help. The burden of stroke is large, and more research is needed to lessen the impact of post-stroke disability.

Stroke: traditional conception and new paradigm

With a stroke, there is sudden vessel blockage (with ischemic stroke) or rupture (with hemorrhagic stroke) in the brain causing damage or dysfunction of the brain region fed by the vascular territory affected. There are several major, well-established, individual-level attributes and disease states that have been associated with increased risk of ischemic and hemorrhagic stroke, including age, sex, hypertension, smoking, diabetes, dyslipidemia, and others.[22] Perhaps due to a focus on the acute vessel blockage or rupture event, stroke is traditionally seen as a discrete event. The damage caused by a stroke in a particular brain region results in an impairment, such as unilateral weakness, dysarthria, or ataxia. There is often an improvement in impairment in the weeks and months after stroke, due to unclear mechanisms that may include reduction in edema, regrowth of damaged neurons, increased neural activity in contralateral or supplementary brain regions, or change in brain network performance.[23, 24] Even if there is no reduction in impairment through these processes, there may be improvement in disability as an

individual learns compensatory strategies and starts to use assistive devices such as a cane or walker. Hence, there is a predictable degree of recovery[25] within 3-6 months of the stroke, and prior research on the natural history of disability after stroke has shown varying degrees of functional recovery within 6-12 months.[26-33]

Using the traditional paradigm of stroke as a discrete event, it is assumed that, following the 3-6 month recovery period after stroke, functional status would more or less stabilize unless recurrent events occur[34-37] (Figure i), and that the same slope of functional decline prior to stroke – which was due to the cumulative effects of aging -- would resume after recovery from stroke. However, there is growing evidence that a paradigm may be more appropriate in which the effect of cerebrovascular disease on disability is viewed in a continuous, ongoing manner. In other words, stroke may be more effectively considered as an ongoing, chronic condition with effects on function, instead of a discrete event. Stroke may accelerate functional decline over time, over and above the slight progressive decline in function over time resulting from cognitive aging,[38] which is a non-pathological process that is as yet not well understood. There is a link between cognitive function and functional status, and it appears that cognitive deficits pre-date physical functional limitations and likely play a causal role in their development.[39, 40] According to this new paradigm of the effect of cerebrovascular disease on functional status, there may be an accelerated decline over time after recovery from stroke, even in the absence of recurrent clinical events (Figure i).

There have been recent advances in epidemiological studies that have examined decline surrounding vascular events such as stroke. First, there has been an expansion of the time-line in studies on this topic, with longer term follow-up in larger cohorts. Second, there has been a focus more on patient-centered outcomes rather than just vascular events and mortality. Third, there has been a shift of focus from the surveillance of discrete events such as stroke, myocardial infarction (MI), and death, to the repeated measurement of outcomes such as disability, quality of life, cognitive function, and mood. This has allowed researchers to analyze the trajectories of these important patient-centered outcomes over time, and in relation to vascular events. This new ability has enabled researchers to clarify the pathophysiology of vascular dysfunction and its population impact. In this review, I will outline the conceptual basis for this new paradigm of cerebrovascular disease as a progressive condition and then

discuss recent epidemiological studies that have focused on trajectories of patient-centered outcomes in relation to vascular events.

Vascular risk factors and progressive cerebrovascular dysfunction

There are several lines of evidence that support a paradigm of progressive cerebrovascular dysfunction. First, stroke is caused by conditions that may have an ongoing and cumulative effect on vessel dysfunction, including vascular risk factors and inflammatory states.[41] Diabetes diagnosed in those in "mid-life" (those with an age range of 48-67 years) has been shown to be associated with a 19% greater cognitive decline over 20 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) study.[42] The degree of decline was sensitive to the degree of control and duration of diabetes as well. In the Framingham Heart Study,[43] the third generation cohort had their first examination between 2002-2005, when baseline diabetes and covariate status was ascertained, and their second examination between 2008-11, when cognitive screening and MRI were performed. Diabetes was associated with poorer cognitive performance on multiple measures after adjustment for confounders. The relationship between diabetes and attention was mediated through reduced volume in the total cerebrum, frontal lobe, and occipital gray matter. The relationship between diabetes and visual memory was also mediated by these measures as well as by hippocampal size. Recent studies have suggested that insulin resistance in cells of the central nervous system, specifically the hippocampus, may play a causal role in cognitive dysfunction and Alzheimer's dementia.[44] Diabetes is usually conceived as a condition involving systemic insulin resistance, but the cognitive effects of insulin resistance and related changes in cell signaling may be specific to cells of the nervous system.

Furthermore, pulse pressure has been associated with quicker progression to dementia in those free of dementia at baseline.[45] Elevated blood pressure has been shown to be associated with accelerated decline in gait speed, even in those who had controlled hypertension, and even after adjustment for confounders.[46] Elevated blood pressure and blood pressure variability have also been associated with impaired white matter integrity measured by fractional anisotropy among 311 individuals with 10 years of follow-up.[47] Finally, higher blood pressure and pulse pressure were cross-sectionally

associated with subclinical cerebrovascular disease among the "youngest old" in a study of 113 individuals without stroke and dementia.[48]

Subclinical infarcts and white matter hyperintensities

Subclinical infarcts are discrete brain infarcts that by definition are not associated with discrete events but are rather detectable only by brain imaging. Similarly, white matter disease (also called leukoaraiosis) has been measured according to different definitions but generally refers to areas of white matter structural damage in the brain due to vessel dysfunction, which are only detectable by brain imaging. Specifically, small vessel disease causes chronic ischemia which leads to demyelination and axonal loss. In a study that examined the molecular structure of axons in regions surrounding lacunar infarcts and microinfarcts,[49] node of Ranvier segments and adjacent paranodal segments were examined. There was evidence of impaired cell to cell adhesion and signaling between axons and oligodendrocytes, suggesting that the area of dysfunction surrounding microinfarcts extends beyond visibly injured tissue. Future studies will hopefully clarify the pathophysiology of WMHs.

In terms of the epidemiology of subclinical cerebrovascular disease, subclinical infarcts have been found to be at least 5 times as prevalent as clinical strokes, suggesting that a focus on discrete clinical stroke events reveals only the tip of the iceberg of the burden of cerebrovascular disease.[50, 51] In the Northern Manhattan Study, SBI was present in 18% of 892 stroke-free individuals.[52] WMHs were present in 96% of individuals older than 60 years of age in CHS and in 95% in the Rotterdam Scan Study.[53] Silent acute infarcts have also been detected in up to 4.2% of individuals with dementia in previous studies.[54]

Traditional vascular risk factors and inflammatory states cause subclinical infarcts and WMH in addition to recurrent clinically evident strokes.[55] For example, elevated blood pressure and blood pressure variability have been shown to have a dose-dependent effect on WMHV and SBI.[56] The vascular causes of worsening white matter grade have been shown to have a differential impact depending upon initial grade.[57] In the Rush Memory and Aging Project, 167 dementia-free elderly individuals had actigraphy to measure physical activity, and had measurements of WMHV on MRI.[58] In a cross-sectional analysis, there was a significant interaction between physical activity and WMHV. Specifically, although

there was an association between greater WMHV and lower motor function among those with average and low physical activity, there was no association among those with high activity, suggesting a protective effect of high levels of physical activity. The progression of white matter lesions over time has not been found to have a significant genetic component, and it is likely that behavioral and environmental factors, as well as the above medical conditions, have a more causative role.[59]

Subclinical infarcts and WMHs have been associated with the occurrence of "hard" vascular outcomes and mortality in multiple studies. White matter disease may predict future stroke independently of traditional risk factors.[60] The extent of WMHV has been associated with recurrent stroke within 90 days of stroke.[61] In CHS, white matter grade and ventricular volume were associated with longevity.[62] In the ARIC study, among those who had 2 MRIs spaced about 10 years apart, there was WMH progression in 23% of 972 participants, and smoking showed a dose-dependent association with progression.[63] In another analysis in ARIC,[64] metabolic syndrome and an insulin resistance score (created using principal components analysis of 11 factors) were associated with new lacunar infarcts but not progression of WMHV. In the Athens Stroke Registry, among 1892 stroke patients, leukoaraiosis independently predicted stroke recurrence, with a hazard ratio of 1.86.[65] In a longitudinal analysis in the ARIC study, 1884 individuals aged 50-73 years had MRI in 1993-1995 and were followed for a mean of 14.5 years.[66] Subclinical brain lesions <3 mm (HR 3.47) and >=3 mm (HR 1.94) were associated with increased risk of stroke, as was WMHV. The presence of both sizes of subclinical lesions was associated with a marked 8-fold increase in risk, and these lesions also increased risk of fatal stroke. In addition to causing direct injury to white matter regions, WMH may work through other mechanisms. For example, among 575 patients with arterial disease (including cerebrovascular, cardiac, peripheral, and aortic), 2 MRIs were performed around 4 years apart.[67] Deep and periventricular WMHs were associated with reduced parenchymal cerebral blood flow between the 2 time-points.

Subclinical infarcts and WMHs have been associated not only with vascular events but also with cognitive impairment[68, 69] and reduced functional status over the long term.[50, 70] White matter disease may mediate the relationship between hypertension and disability.[71] Even in younger individuals free of cardiovascular disease but at risk due to a family history of early cardiac disease, white matter lesion burden was inversely associated with manual dexterity (as measured by the Grooved Pegboard test).[72]

When regional WMHV was tested separately in adjusted models, this association was also seen for WMHV in each brain lobe except for the temporal and occipital lobes. Asymptomatic brain MRI abnormalities, including WMHs and infarcts, have been associated with functional impairment cross-sectionally,[73] at 3 months,[74] and over 4 years of follow-up.[70] In a case-control study performed in Singapore, the burden of small vessel disease and large vessel disease was summarized in a weighted score of "cerebrovascular disease" among 305 cases with cognitive impairment and 94 controls.[75] A higher cerebrovascular disease score was associated with worse cognitive function. WMHV was associated with global deficits, and cerebral microbleeds were associated with domain-specific deficits. In the Leukoaraiosis and Disability study,[76] among 633 older individuals over 2.4 years of follow-up, 29.5% of those with severe WMHV transitioned to death or disability, compared to 10% with mild WMHV. Also, cognitive decline was seen among those who had increase in WMHV over time. In a prior analysis using the MRI cohort of the Northern Manhattan Study (NOMAS),[77] in an adjusted model, WMHV was associated with poorer episodic memory, processing speed, and semantic memory. Among those above the median age, WMHV was associated with poorer episodic and semantic memory. Hence, several studies have demonstrated a consistent association between subclinical cerebrovascular disease and functional and cognitive impairment.

The risk of recurrence of clinical events such as stroke and MI is high soon after an event, and the period of risk may remain elevated for an extended period.[78] It is similarly conceivable that the risk of subclinical cerebrovascular disease may be elevated for a period of time after a clinical event. However, future research on the trajectories of these changes is required to better characterize whether such a risk window exists. In summary, prior studies show a strong relationship between imaging markers of silent brain infarcts and white matter disease and stroke risk factors, and emerging evidence suggests a link between such markers and disability and cognitive dysfunction.

Newer structural markers of cerebrovascular dysfunction

Newer imaging and analytic approaches have been able to identify brain structural changes and other evidence of cerebrovascular dysfunction that cause progressive cognitive and functional decline. For example, among 241 initially stroke- and dementia-free participants in the Swedish National Study on

Aging and Care in Kungsholmen, diffusion tensor imaging was performed and WMHV was estimated.[79] Vascular risk factors and APOE-epsilon-4 status were associated with impaired white matter integrity and cognitive decline. Among 232 individuals with cognitive impairment, graph theory was applied to diffusion tensor imaging data. WMHV was associated with reduced nodal efficiency, decreased cortical thickness, and impaired executive and memory function.[80]

In another example, thirty-two participants in the Determinants of Dementia After Stroke study had MRI at the time of stroke and 6 months later.[81] Probabilistic tractography was used to identify the cortical regions associated with acute infarct, and "change in focal cortical thickness" was calculated as change exceeding change in the reference regions. The authors summarized the results as follows: "(1) acute infarcts induced focal degenerative changes in cortical regions connected to the infarct; (2) this was paralleled by a degeneration of connecting fiber tracts; (3) the degree of cortical thinning correlated with the loss of microstructural integrity in connecting white matter tracts; and (4) remote effects were seen regardless of the fate of the acute infarct, i.e., whether the infarct turned into a cavitating or noncavitating lesion. These findings highlight secondary neurodegeneration as an important feature of brain infarcts and may have implications for the understanding of structural and functional reorganization after stroke." These findings highlight the likely role of secondary neurodegeneration in tracts affected by stroke, which likely has a long-term effect on disability.

In a cross-sectional analysis among 1906 non-demented participants in the ARIC study,[82] WMHV and infarcts were associated with lower cognitive performance, and these associations were partially mediated by regional cerebral cortical volume, thought to be a marker of structural integrity. Specifically, the posterior region of interest included: "hippocampus, parahippocampal gyrus, entorhinal cortex, inferior parietal lobule, precuneus and cuneus"; and the frontal region of interest included: "rostral/caudal anterior cingulate, rostral/caudal midfrontal, lateral orbital frontal, medial orbital frontal, paracentral, pars opercularis, pars triangularis, precentral, superior frontal, and frontal pole."[82] The authors suggest that the occurrence of microinfarcts may be the process that links WMHV, infarcts, regional cerebral cortical volume, and cognition.

In a cross-sectional analysis among 426 individuals with cerebral small vessel disease but no dementia in the Nijmegen Diffusion tensor and MRI Cohort,[83] relationships among WMHV, cortical

thickness, network measures, and cognition were examined. WMHV was associated with thinner cortex in frontotemporal regions but thicker cortex in paracentral regions. Network disruption, measured using graph theory, was associated with WMHV and cognition. When tested together, cortical thickness but not WMHV was associated with cognitive function, and cortical thickness mediated the relationship between WMHV and cognitive function.

In summary, newer imaging and analytic techniques may be able to detect previously undetectable structural and functional brain dysfunction that could underlie the progressive disability and cognitive changes seen in epidemiological studies.

Traumatic brain injury

Traumatic brain injury (TBI) may provide a useful neurological condition, analogous to stroke, that could illuminate the progressive nature of cerebrovascular disease. The course of TBI has traditionally been conceptualized similarly as stroke: an acute event causes a decrement in function, followed by a period of recovery with progressive functional improvement, after which functional ability plateaus.[84] Several studies, however, have shown a progressive decline in cognitive function in the long term after TBI, in the intermediate follow-up period of 1-2 years as well as up to 30 years of follow-up.[84] Even after mild TBI, recovery of mood, cognition, and concussion symptoms extends beyond 1 year, and a significant proportion of individuals (16% of 260) had impairments in complex attention at 1 year from injury.[85]
Among 478 individuals in the TBI Model Systems National Database followed up 10 years after TBI, age was a major predictor of functional decline over time.[86] In another analysis in this cohort using a sample size of 3870 individuals,[87] trajectories of Glasgow Outcome Scale-Extended scores increased after TBI, reached a maximum at 10 years of follow-up, then decreased thereafter.

These declines have been paralleled by structural changes in the brain, manifested by expansion of the original lesion size, regional and diffuse atrophy, and loss of integrity of white matter tracts. Protein deposition and inflammation have been implicated as pathophysiological processes for this decline and associated structural change. The concept of “negative plasticity” has been introduced to explain this process.[84] Specifically, this view describes a “self-reinforcing, downward spiral of negative brain plasticity whereby declining brain function is attributable to a combination of disuse (called ‘reduced schedules of

activity'), reduced quality of sensory-perceptual processing, and weakened neuromodulatory control. In combination, these factors increase reliance on simplified cognitive processing at the expense of more complex processing capacity (called 'negative learning'). These processing changes result in brain changes, which in turn result in further disuse, perceptual compromise and reduced neuromodulatory control."[84] With TBI, an initial injury would lead to impairments that reduce functional ability and social interaction, which may "foster brain adaptations to simpler and more habitual cognitive processes at the expense of complex processing."[84]

Cognitive decline is common after TBI. Cognitive change after recovery from TBI was tested among 33 patients with moderate to severe TBI.[88] Comprehensive neuropsychological testing was compared between 1 year post-TBI and 2-5 years after injury. There was heterogeneity in the patterns of change in cognition, and there was decline on at least 2 neuropsychological measures in 27.3% of the cohort.

One underlying mechanism of long-term decline after TBI is progressive atrophy. Fifty-six moderate-severe traumatic brain injury patients were compared to 12 healthy controls on 2 MRIs, one done 5 months after injury and one 20 months after injury.[89] Those with TBI had progressive atrophy during this period, 96% in at least one brain region, and 75% in at least 3 of 4 regions (whole brain, corpus callosum, and right and left hippocampi). The authors suggest that the chronic atrophy may be due to "tissue shrinkage—the result of lost neuropil, protein and/or fluids—or to cell death, with disconnection and disuse, inflammation and delayed apoptosis contributing independently or interactively."[89]

Microstructural disruption may also play a role in progressive dysfunction after TBI. Among 12 patients with TBI, repeated diffusion tensor imaging was performed at 1 week, 7 months, and 21 months from injury (on average), and neuropsychological testing was performed concomitantly with imaging.[90] There was continual change in structural volumes, fractional anisotropy, and mean diffusivity in the chronic phase, with some patients experiencing long-term decline in neuropsychological function corresponding to these imaging changes.

Inflammatory processes may also be involved in the long-term decline seen after TBI. A recent review article summarized the various inflammatory processes involved after TBI.[91] An early inflammatory

response after injury involves several cell types, including astrocytes, microglia, macrophages, neutrophils, and T cells. However, this response may become maladaptive if sustained and cause ongoing tissue damage. Specifically, neutrophils may promote neuronal cell death and destruction of surrounding cell types. Also, reactive oxygen species have been implicated in ongoing brain tissue damage after TBI, and early trials have suggested a protective effect of anti-oxidant therapies (e.g. N-actyl cysteine) during the early recovery period. Amantadine has also been proven to be effective when administered for 4 weeks in the subacute phase of recovery after TBI (4-16 weeks after injury), but the mechanism of effect is not certain.

There may also be chronic effects of injury that does not involve head trauma, and emerging research is examining the long-term effects of non-head trauma and falls. For example, in the Health and Retirement Survey (HRS), disability trajectories after accident injury, not only involving head trauma, were examined over 10 years of follow-up in 591 individuals.[92] Functional data were examined 2 years before injury and 8 years post-injury. Five distinct trajectories were identified (Figure ii). Sex, number of health conditions, and insurance status were associated with individual trajectories. Among 754 individuals followed with monthly disability assessments over 12 years, there were 4 trajectories of change in disability after a fall that were highly influenced by pre-fall functional status.[93]

In summary, the pathophysiological processes involved in TBI may overlap with those involved in cerebrovascular dysfunction, and the epidemiological study of TBI may inform studies of the long-term cognitive and functional effect of stroke and vascular disease.

Neurodegenerative disease

Neurodegenerative diseases such as Alzheimer's dementia have traditionally been conceived of as progressive conditions with cumulative negative effects on cognitive performance, functional status, and social participation. Recent research has begun to show that neurodegenerative diseases share pathophysiological processes with cerebrovascular disease. Among experts in stroke and neurodegenerative disease, there has been a recent recognition of the vascular components of dementia, and a call for further research to elucidate the relationships and mechanisms by which stroke and vascular dysfunction cause progressive cognitive and functional decline.[94] For many years, the entity of

vascular dementia was conceived as a condition in which focal infarcts caused cognitive impairment and a step-wise dementia. However, currently there has been a growing recognition that both neurodegenerative dementia and vascular dysfunction often co-exist, and that they share pathophysiological mechanisms and risk factors.

Often, neurodegenerative dementia and cerebrovascular disease coexist. Among 393 cognitively unimpaired elderly individuals in the Mayo Clinic Study of Aging, those with imaging evidence of increased cortical amyloid as well as those with evidence of subclinical brain ischemic vascular disease had increased cognitive decline, and the presence of both showed additive and not synergistic effects.[95] Genetic overlap among Alzheimer's disease, CRP, and plasma lipids was found in a study that examined data from multiple genome-wide association studies with a total of >200,000 individuals, suggesting overlapping pathophysiologies among neurodegenerative, inflammatory, and vascular conditions.[96]

Subclinical cerebrovascular injury has been associated with subsequent cognitive deficits and decline. WMHV are associated with cognitive decline and, along with infarcts and cerebral microbleeds, cause vascular dementia. Sensitive MRI techniques can identify white matter tracts through diffusion tensor imaging, which may be able to detect disruption of white matter tracts even before WMHs manifest. Progression of periventricular WMHV was seen in the Rotterdam Scan Study between 2 MRIs spaced 3 years apart and was associated with declines in information processing speed and cognition.[97] Even in the absence of clinical cognitive impairment, a stroke can cause delayed cognitive deficits. Fifteen months after stroke, among 115 stroke survivors without baseline dementia, 31% had a drop in cognitive function as measured by the MMSE, and 9% developed incident dementia.[98] Over approximately 20 years of follow-up among 6514 participants in the Rotterdam Study who were free of dementia at baseline, atrial fibrillation was associated with higher risk of incident dementia, independently of clinical stroke and vascular risk factors.[99] Subclinical cerebrovascular disease was thought to be a possible cause. Among 3117 individuals with mild cognitive impairment and 6603 individuals with normal cognitive function, the Framingham Stroke Risk Profile score was associated with baseline cognition as well as decline in cognitive scores over time.[100]

The direction of causation can also occur in the opposite direction, in which cognitive deficits predate and may cause clinical stroke events. Subjective memory complaints have been associated with

risk of subsequent stroke among 9152 participants in the Rotterdam Study, with a hazard ratio of 1.20, and authors suggested that "subjective memory complaints may be a marker of cerebral microvascular injuries."[101] The cerebral cortex has reduced perfusion in Alzheimer's disease, and this is thought to involve several processes: small vessel disease, amyloid angiopathy, abnormal vascular contractility, and secondary upregulation of vascular endothelial growth factor.[102] Although there has traditionally been a focus on the pathological effects of Alzheimer's disease on the arterial system, there is growing evidence in animal models that this dementia also affects the structure and function of the venous system, resulting in abnormal venules that potentiate the arterial abnormalities seen in this disease.[103] Among 72 patients with stroke or transient ischemic attack (TIA) with cognitive impairment, a carbon-11-labeled Pittsburgh compound B positron emission tomography (PET) scan was performed, and cognitive assessments were performed at 3-6 months and annually thereafter for 3 years.[104] There was a significant decline in mini-mental state examination (MMSE) scores over follow-up among those with Alzheimer's disease–like Aβ deposition but not those without, and there was a steeper decline in MMSE and Montreal Cognitive Assessment scores among those with this pattern of Aβ deposition.

In addition to pathological evidence of neurodegenerative disease and cerebrovascular disease, processes that do not manifest during routine pathological analysis seem to effect long-term cognitive changes. In an in-depth longitudinal study of 856 individuals with pathological analysis of brain tissue, the majority of variance in cognitive decline was not explained by traditional pathological evidence of Alzheimer's disease, Lewy body dementia, and cerebrovascular disease.[105]

In summary, there are several points of connection between neurodegenerative dementia and cerebrovascular disease, with overlapping risk factors, shared pathophysiological processes, and bidirectional patterns of influence between the 2 conditions. However, more research is needed to clarify these shared relationships.

Inflammatory processes

Another line of evidence suggests that serum biomarkers of inflammation may be able to detect subclinical risk of vascular disease, and hence may be able to link stroke pathophysiology with ongoing, continuous changes in function. Prior research has identified a significant role of inflammation in

atherosclerosis and stroke[106, 107] as well as significant associations between stroke and inflammatory biomarkers, such as leukocyte count[108] and high-sensitivity C-reactive protein (hsCRP).[109-113] Some studies have suggested that hsCRP also predicts prognosis after stroke.[110, 114] Prior research in NOMAS has identified a link between inflammatory markers and MI, mortality, and carotid plaque thickness.[115, 116] In CHS, interleukin-6 (IL6) and CRP have been associated with white matter lesions,[117] and other studies have found associations between CRP and stroke severity and mortality.[118] Other markers of immune activity have also been implicated. For example, it appears that B-lymphocyte activation is linked to delayed cognitive decline after stroke in a mouse model as well as in pathological analysis of post-mortem specimens.[119] In the Framingham Offspring study, a cross-sectional analysis was performed among stroke-free individuals testing associations among biomarkers (systemic and vascular inflammatory biomarkers and markers of oxidative stress) and MRI findings (WMHV, SBI, and cerebral microbleeds).[120] Cerebral microbleeds were associated with higher levels of tumor necrosis factor receptor-2 (TNFR2) and myeloperoxidase, and WMHV and SBI were associated with higher levels of osteoprotegerin, intercellular adhesion molecule 1, lipoprotein-associated phospholipase A2 mass, and lower myeloperoxidase levels. Neutrophil counts and neutrophil-to-lymphocyte ratios were independently associated with 3-month outcomes among 846 intravenous thrombolysis-treated patients, suggesting the importance of inflammatory states in outcome after acute stroke treatment.[121]

Interactions have also been found between vascular risk factors and inflammatory states. Forty individuals, 19 with diabetes, had comprehensive neuropsychological measurements, physical examinations, MRI, and inflammatory marker analysis twice over 2 years.[122] Cerebral autoregulation was associated with functional status. Also, those with diabetes had worse cerebral vasoregulation and cognitive function over time, and higher cortisol and CRP levels were associated with decline in vasoregulation.

A single ischemic stroke may cause changes in inflammatory profiles[123] that may have an ongoing deleterious effect on brain structure and function[124] that may persist years after stroke.[125] Beyond the association with vascular outcomes, inflammation has been associated with quality of life (QOL) in a limited number of studies,[126-129] but the association of inflammatory markers with disability has not been well-studied, particularly among minority populations.

Inflammatory processes have been implicated not only in cerebrovascular disease but in other neurological diseases as well. In a large pathological study of individuals who had had TBI, there was increased microglial activity peaking 3 months after TBI but remaining elevated for several years.[130] It is well-known that Alzheimer's dementia pathogenesis involves inflammatory processes.[131] The accumulation of amyloid-β activates microglia, which cause an acute inflammatory response to attempt to clear the abnormal protein. However, a persistent inflammatory response ensues, causing retraction of microglial processes and resulting in functional and structural changes. Implicated in this process are the cytokines tumor necrosis factor-alpha, IL6, interleukin-1α, and GM-CS. More recent research suggests that inflammatory processes may be the primary drivers of the structural and functional brain changes seen in the disease, and not just responses to abnormal buildup of proteins.[132] These immunological and inflammatory processes may promote neurodegenerative disease independently of the buildup of amyloid proteins. These inflammatory processes may originate from within the central nervous system or be tied to systemic inflammatory states or conditions. A distinction that may be useful in understanding these processes may be between adaptive and innate neuro-inflammatory processes.[132] Studies in animal models have also suggested that neutrophil invasion of the central nervous system plays a key role in the development of Alzheimer's dementia, begins before the onset of cognitive decline and peaks at the time of first detection of memory loss. Studies in mice even suggest that depleting circulating neutrophils restores cognitive functioning.[133] Finally, in a mouse model, exogenously applied beta-2-microglobulin caused cognitive impairment and reduced neurogenesis.[134] In summary, inflammatory processes have been found to play a significant role in vascular disease and progressive neurodegenerative disease, but more research is needed to clarify the effects of inflammatory states on long-term functional trajectories.

Limitations of previous research

The proposed research seeks to fill 2 major areas of deficiency in the existing literature. The first area is a lack of quality data delineating the long-term course of disability in relation to vascular disease, particularly stroke.[135] Several studies on predictors of functional outcomes pre-date important shifts in paradigms of treatment (of cholesterol and blood pressure, for example), obesity prevalence, and population patterns of aging. Also, in many prior studies, vascular disease and vascular events are not

reliably ascertained, precluding accurate causal inference about the relationship between vascular disease and functional outcomes. Several studies have examined disability in various cohorts, including the Asset and Health Dynamics Among the Oldest Old cohort,[136] the Health and Retirement Survey,[137] the Baltimore Longitudinal Study of Aging,[138] the National Health and Nutrition Examination Survey,[139] the National Health Interview Survey,[140] National Long-Term Care Survey,[141] and the Panel Study of Income Dynamics.[142] However, there are significant limitations of these studies: some of these are not longitudinal cohorts with repeated measures of functional status; none of these cohorts has examined inflammatory and imaging markers as exposures; and reliable and thorough validation and subtyping of vascular events are lacking.

The second understudied area that would be addressed by the proposed research involves trajectory analysis of functional outcomes in relation to stroke. Specifically, trajectory analysis requires multiple repeated measures over time within an individual to allow the estimation of the initial level, slope, and shape of the curve representing change of the outcome over time (Figure iii). In other fields, including multiple sclerosis and critical care, there has been an explicit interest in modeling the course and trajectory of functional status before and after discrete clinical events. For example, in multiple sclerosis there are clinically distinct syndromes defined by different trajectories of change in functional status, and diagnostic and treatment approaches are tailored to the particular syndrome (Figure iv). In critical care medicine, there has been an interest in modeling different trajectories of function before and after admission to an intensive care unit (Figure v), with implications for trial design and understanding the biological effects of critical illness.[143, 144] However, to our knowledge, such a conceptual approach has not yet been applied to stroke trials, perhaps because of a conceptualization of stroke in prior research as a discrete event with time-limited effects on function, as well as a focus of clinical trials on acute stroke treatments and interventions, which prioritize short-term outcomes and adverse events.

Historically, most studies of disability and stroke have examined the course of functional change only after stroke and have not examined the course of functional status before the event.[26-33] Most of these studies had short-term follow-up and measured disability once, reducing precision and precluding detailed modeling of the trajectories of outcomes over time. Also, most studies of disability after stroke

have included only hospitalized patients with limited follow-up, and relatively few population-based studies have examined predictors of functional status with long-term follow-up.[145]

My previous research

In order to address this deficiency in the literature, we examined, in the stroke-free, population-based cohort of NOMAS (please see below for further details of the NOMAS study design),[146] vascular predictors of functional status as measured by the Barthel Index (BI). Using models adjusted for demographic, medical, and social risk factors, we found an annual decline of 1.02 BI points ($p<0.0001$). Predictors of change in BI over time included: age (-0.08 BI points per year; $p<0.0001$), male sex (0.32 per year, compared to female; $p<0.0001$), diabetes (-0.37 per year, compared to non-diabetics; $p=0.0003$), and hypercholesterolemia (0.20 per year, compared to no hypercholesterolemia; $p=0.006$). Using validated and specialist-adjudicated data on the vascular events of stroke and myocardial infarction (MI), we found that results did not change when stroke and MI were censored. The magnitude and significance of predictors of BI were similar for motor and non-motor domains. Hence, diabetes but not hypertension was a strong predictor of long-term function, even when vascular events occurring during follow-up were censored. The research proposed here was designed to clarify the role of inflammatory and imaging markers in predicting long-term disability.

We also examined predictors of long-term functional status and the slope of decline over 5 years of annual follow-up in a cohort of stroke patients (n=525), who are distinct from the subjects in the prospective NOMAS cohort of initially stroke-free participants described above (please see below for further details of the NOMAS study design).[147] In this stroke patient cohort, mean age was 68.6$\pm$12.4 years, 45.5% were male, 54.7% Hispanic, 54.7% had Medicaid/no insurance, and 35.1% had moderate stroke. The proportion with BI$\geq$95 declined over time (OR 0.91, 95% CI 0.84-0.99). Predictors of functional status included increasing age, stroke severity, urinary incontinence, diabetes, marital status, and left-sided stroke. Changes in BI by insurance status were confirmed by a significant interaction term (β for interaction = -0.167, $p=0.034$); those with Medicaid / no insurance declined (OR 0.84, $p=0.003$), whereas those with Medicare/private insurance did not (OR 0.99, $p=0.92$). An important unresolved

question was whether the observed decline in this study was due to the stroke (or related factors) or simply a result of the aging process.

Another analysis in the NOMAS prospective cohort of initially stroke-free participants addressed this question.[148] We examined 210 participants who experienced an ischemic stroke during follow-up and lived more than 6 months after stroke. There was no difference in the rate of functional decline over time before and after stroke (p=0.51), with a decline of 0.96 BI points per year before stroke (p<.0001) and 1.24 after stroke (p=0.001). However, when stratified by insurance status, among those with Medicaid or no insurance, in a fully adjusted model, there was a difference in slope before and after stroke (p=0.04), with a decline of 0.58 BI points per year before stroke (p=0.02) and 1.94 after stroke (p=0.001) (Figure vi).

Research on patient-centered outcome trajectories surrounding vascular events

I performed a systematic review on studies of trajectories of patient-centered outcomes surrounding vascular events. Using MEDLINE, PubMed, and Google Scholar, I included all possible combinations of the following search terms: "stroke," "trajectory," "trajectories," "cerebrovascular," "myocardial infarction," "disability," "curve," "growth," "cognition," "cognitive," "functional," and "function." Publication time included all studies published from 1950 to December 1, 2015. All studies were reviewed in full for relevance, and reference lists were reviewed for potentially relevant studies. Due to the heterogeneity in the study designs and outcomes of studies, no strict exclusion criteria were used, and studies are summarized in narrative form.

Studies examining disability

Several studies examined the long-term course of disability surrounding vascular events. Among over 64,000 individuals who had stroke from 2008-2010 in the Swedish Stroke Register, functional dependence was seen in 16.2% of survivors at 3 months, but this proportion increased to 28.3% at 12 months.[149]

In another analysis in HRS among 9237 individuals ≥65 years of age,[150] the joint trajectories of physical, emotional, and cognitive function were analyzed with biennial assessments over 12 years of follow-up. Individuals were almost equally divided into one of 4 distinct trajectories of change over time:

1) minimal impairment, 2) moderate impairment with increasing cognitive deficit, 3) moderate impairment with increasing physical and emotional deficit, and 4) significant and increasing impairment. Also, worse trajectories were predicted by lower education, income, and net worth.

In a prospective study in the Collaborative Evaluation of Rehabilitation in Stroke Across Europe project, 4 rehabilitation centers in Europe assessed 532 stroke patients at 5 years from stroke who had at least a minimal initial impairment.[151] As shown in Figure vii, there was a decline between 6 months and 5 years in BI and motor performance (measured by the Rivermead Motor Assessment), but no differences when the 2-month and 5-year time points were compared.

Among 3186 older individuals in Taiwan followed over 4 waves over 11 years,[152] latent class growth curve modeling identified 3 trajectories of function: 1) maintained function (85% of the cohort), 2) progressive disability (11%), and 3) consistent disability (4%). Male sex, higher education, less comorbidity burden, and fewer depressive symptoms were associated with the maintained function trajectory.

In another study among 810 Taiwanese individuals followed biennially over 10 years,[153] hypertension and depression predicted increased disability among the cohort as a whole whereas diabetes was predictive only among those who died during follow-up.

Finally, in the Whitehall II study, among 5376 participants, comprehensive motor function was assessed and vascular risk was summarized at several time-points over 16 years with the Framingham general cardiovascular disease risk score.[154] The development of mobility limitations was associated with worse cardiovascular risk profiles, independently of cognitive status and SES.

Studies examining cognition

Several studies examined cognitive function related to vascular events. The authors of a study examining repeated measures of MMSE after 167 cases of intracerebral hemorrhage claimed that "prognostic factors for cognitive decline after ICH are already present when ICH occurs, suggesting a process of ongoing cognitive impairment instead of new-onset decline induced by the ICH itself."[155] However, the basis for this claim is tenuous, since pre-ICH cognitive status was estimated by a different measure than

the outcome and was assessed retrospectively, raising questions about bias in the estimation of pre-ICH cognition. Prospective follow-up began only after ICH.

Among 538 individuals free of overt stroke, neurological disease, and cardiac disease,[156] there were on average 2.3 assessments of cognitive function spaced 2.1 years apart. Baseline carotid intima thickness was associated with accelerated cognitive decline on multiple tests of verbal, nonverbal, and executive function.

Among 6476 elderly individuals, cognitive function was assessed 5 times over 9 years.[157] Baseline depressive symptoms, functional status, and stroke were associated with lower cognitive function but not accelerated decline over time, perhaps due to the advanced age of the cohort.

Other outcomes

Predominantly male (98%) veterans with ischemic stroke in 2007 (n=3811) were followed for 1-year trajectories of 3 outcomes: nursing home care, home care, and mortality.[158] Latent class growth analysis was used to identify 5 different trajectories, as summarized by the authors as follows: "Members of the cohort had one of the following 5 trajectories: 49% had a Rapid Recovery trajectory with little or no use of care during the 12 months, 15% had a Steady Recovery trajectory with initially high nursing or home care that tapered off during a 1- to 3-month period; 9% had a Long-Term Home Care trajectory with consistently high home care use during the 12 months, 13% had a Long-Term Nursing Home trajectory with consistently high nursing home use during the 12 months, and 14% had an Unstable trajectory with multiple transitions between nursing home, home care, and acute care."[158]

Studies comparing trajectories before and after vascular events

Several recent studies have compared trajectories of outcomes before and after vascular events. In an analysis in the Health and Retirement Survey (HRS), cognitive function as measured by the modified telephone interview for cognitive status (TICS-m) scale was assessed every 2 years over a mean of 4.1 years of follow-up.[159] Compared to Whites, Blacks had greater cognitive decline in adjusted models. Incident stroke caused reduced cognitive function that did not differ by race, and there were no significant differences in slope of change over time post-stroke. In another analysis in HRS, the course of functional

and cognitive impairment was compared before and after stroke (with 432 hospitalizations) and MI (with 450 hospitalizations).[160] Using a combined measure of ADLs and IADLs, there was a greater increase in disability at the time of stroke compared to MI. Difference in pre- and post-stroke slopes of change depended on initial impairment levels. Stroke but not MI was associated with higher odds of cognitive impairment.

In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, the course of cognitive function was compared before and after stroke among 515 individuals who had stroke, and 23057 who remained stroke-free, during a mean follow-up of 6.1 years.[161] There was a significantly steeper decline in cognitive function after stroke in the areas of global cognition and executive function. The risk of cognitive impairment was higher after stroke compared to before stroke, with an odds ratio of 1.23 per year (95% CI 1.10-1.38).

In HRS, trajectories of biennially measured memory performance were analyzed before and after nonfatal stroke (n=1189), before fatal stroke (n=385), and among 15,766 individuals who did not experience stroke over 10 years of follow-up.[162] Among stroke survivors, the pre-stroke decline in memory performance was greater than among those who remained stroke-free, and those who died of stroke had even greater declines. There was no significant difference in slope of change in memory performance before and after stroke. Limitations of this analysis were the long intervals between memory assessments, the self-report of stroke, and the large amount of missing data regarding stroke timing.

Among 17341 participants in HRS,[163] there were biennial assessments of a composite memory score over 10 years of follow-up. There were 3 types of individuals: stroke survivors (n=1169), stroke decedents (n=405), and those who did not experience stroke during follow-up (n=15767). Stroke was defined by self-report or report of a proxy but not confirmed by specialist review, and there was a significant amount of missing data on month (8.3%) and year (10.5%) of stroke. Also, there was a significant amount of loss to follow-up (37%). Overall, pre-stroke decline in memory performance was greater in older individuals compared to younger individuals. Females had slightly steeper declines in memory performance pre-stroke compared to males, but there were no significant differences among the stroke-free cohort. For those in the older age stratum, there was a steeper decline in memory performance after stroke compared to before (-0.15 vs. -0.07 points/year, p = 0.003).

In the ARIC study,[164] a change score in 3 cognitive measures was calculated over approximately 14 years, and 2 MRIs were performed over a similar time interval (10 years) and scored for presence of infarcts, WMHV, and ventricular size. There was ongoing surveillance for hospitalizations, and type of hospitalization was categorized using ICD-9 codes. For those who were hospitalized during follow-up, there was a decline in performance on the Digit Symbol Substitution Test. When trajectories of change in cognitive performance were compared pre- and post-hospitalization, there was accelerated decline in the Digit Symbol Substitution test after hospitalization, with an additional 0.20 digit-symbol pairs/year (95% CI 0.12–0.27), and accelerated decline in the Word Fluency Test after hospitalization, with an additional 0.09 words/year (95% CI 0.02–0.17). Hospitalized patients had greater development of atrophy. Overall, critical illness and major surgical hospitalizations were associated with greater cognitive decline and MRI changes.

In ARIC, trajectories of self-rated health were examined over a median of 17.6 years in 11,188 individuals who remained disease-free, 1071 individuals who developed MI, and 809 who developed stroke.[165] Higher neighborhood income was strongly associated with better self-rated health and less prevalent comorbidities. There was no difference in the slope of change in self-rated health over time before and after stroke in this analysis.

Among 687 community-dwelling elderly individuals assessed for life space mobility, those with surgical hospitalizations had greater drop in mobility at the time of hospitalization compared to those with non-surgical admissions, who had no significant recovery over time.[166]

Functional trajectories immediately before death

Among 213 individuals >70 years of age who entered hospice care over a 13-year period, 5 functional trajectories in the last year of life were identified with monthly telephone assessments, and the 21% with neurodegenerative disease had the worst trajectory.[167] In the last year of life, 6 distinct trajectories of disability were identified among 552 decedents, and hospital admissions were common, with 71% with at least one admission and 45% with more than one.[168] Hospital admissions were associated with worse disability.

Summary

The recent epidemiological studies reviewed here suggest areas of further research to clarify the relationships between vascular disease, particularly stroke and MI, and the long-term course of functional status. Most studies that have compared the course of outcomes before and after vascular events have focused on cognition and not functional status. Furthermore, the precision and identification of events during follow-up have not always been reliable. Also, the mechanisms and pathophysiological processes underlying the patterns of decline seen in previous literature are not known and need to be examined. Due to these gaps in the literature, several important questions remain unanswered. First, what is the impact of vascular disease on disability in the absence of recurrent clinical events? It is unclear whether intensive preventive efforts, similar to those used to prevent clinical vascular events, would have an impact on subclinical events, progression of white matter disease, and disability.[169]

There is an underlying assumption behind the current choice of outcome and timing in clinical trials: that the functional outcomes (for example, modified Rankin scale [MRS]) are stable and well-represented at 3, 6, or 12 months after stroke. But these are untested assumptions that, according to the research presented here, may not be plausible. Rather, post-stroke patients with different recovery trajectories may represent different disease or recovery states, and may respond differently to interventions, just as the different subtypes of ischemic stroke may be considered different disease entities, since the mechanisms of vessel blockage are distinct in each.

An explicit focus on the trajectories of disability as an outcome in observational studies and treatment trials would be required to address these unresolved questions. Also, the optimal means to detect the severity or risk of subclinical events is not certain. The associations among strokes discovered on imaging, white matter microvascular disease, and long-term functional status are not well delineated. Social support and socioeconomic status affect access to care, control of risk factors, and vascular outcomes after stroke,[170, 171] but the effect of these factors on functional status after stroke is not known. Finally, the mechanisms influencing long-term disability trajectories, including subclinical vascular disease and inflammatory states, need to be clarified.

Specific Aims

Stroke is the leading cause of disability[17] and a significant cause of cognitive impairment and depression in the immediate post-stroke period.[172-174] Stroke is traditionally seen as a discrete event, and it is assumed that, following the 3-6 month recovery period after stroke, functional status would more or less stabilize unless recurrent events occur. Indeed, the short-term effects of stroke on disability are well-described, but the long-term course of functional status before and after stroke is less clear.[175, 176] In contrast to this traditional view of stroke, there is growing evidence that a paradigm may be more appropriate in which the effect of cerebrovascular disease on disability is viewed in a continuous, ongoing manner. In other words, stroke may be more effectively considered as an ongoing, chronic condition with effects on function, instead of just a discrete event. For example, stroke is caused by conditions that may have an ongoing and cumulative effect on vessel dysfunction, including vascular risk factors and inflammatory states. In addition to causing recurrent strokes, such processes cause subclinical infarcts and white matter disease that may reduce functional status over the long term.[50, 70] It is also possible that individual strokes cause injury to the brain that lead to a chronic and degenerative process with progressive damage, dysfunction, and functional decline.

The proposed etiologic model for the current analyses is presented in Figure viii (note that this is not intended to be a directed acyclic graph). Vascular risk factors have a direct impact on vessel dysfunction (including subclinical infarcts and clinical strokes) as well as an indirect effect, mediated through systemic inflammation. Systemic inflammatory states cause elevations in serum biomarkers, which are measured in order to quantify the degree of inflammation present. Other factors, indicated by 'U1' and not measured in this analysis, also influence systemic inflammation. A different set of unmeasured factors, U2, influence vascular dysfunction and stroke. Vessel dysfunction is detected, in part, by structural brain changes measured on brain MRI as subclinical brain infarcts and white matter disease. Vascular dysfunction causes impairment in blood flow and structural damage to the brain, which causes cognitive and physical impairments. These impairments cause impaired functional status by affecting an individual's performance in ADLs and IADLs.

In analysis 'A,' several groups of variables are considered confounders of the relationship between inflammatory markers and functional status, and were adjusted for sequentially in groups: demographic

variables. vascular risk factors. social variables, and mood and cognitive variables. Also, in final models there was adjustment for stroke and MI occurring during follow-up in order to determine whether the associations between inflammatory biomarkers and functional status were independent of these events. The adjustment plan was similar for analysis 'B.' In addition, as described below, a basic mediation analysis was performed in analysis B, using all functional data before and after the time of MRI. The unique timing of the MRI during follow-up allows a test of whether MRI findings mediate the relationship between certain factors (described below) and functional status.

The objective of this research is to identify individuals at risk of steep decline in functional status, and to describe the long-term trajectory of these outcomes before and after major vascular events. Our central hypotheses are that stroke can cause a decline in function over the long term even in the absence of recurrent clinical vascular events, and that vascular risk factors and inflammatory and imaging markers predict an accelerated decline. We further hypothesize that this effect will be specific to stroke and brain injury, rather than to vascular events, such as myocardial infarction (MI), more generally, and we will test this by comparing effects of stroke to those of MI. We will study two large observational cohorts, the Northern Manhattan Study (NOMAS) and the Cardiovascular Health Study (CHS) to enhance the validity of these hypotheses. The **hypotheses and aims** for this proposal are:

Hypothesis #1: Serum inflammatory biomarkers and cerebral white matter disease independently predict worse functional status in NOMAS in those free of stroke at baseline.

Specific Aim #1: a) **[Analysis A]** To determine whether levels of serum inflammatory biomarkers measured at the time of enrollment (interleukin-6, tumor necrosis factor alpha receptor-1, C-reactive protein, lipoprotein-associated phospholipase-A2) are associated with lower Barthel index (BI) scores and a steeper slope of decline in a multiethnic cohort, using multivariable regression and adjusting for baseline demographic characteristics (age, sex), vascular risk factors (diabetes, hypertension, hypercholesterolemia), behavioral factors (smoking and alcohol use), social variables (marital status, insurance status, number of friends), and cognitive factors (depressed mood, performance on mini-mental state examination).

b) **[Analysis B]** In a subset of the cohort in which study brain MRI was performed, to determine whether volumes of cerebral white matter disease and subclinical brain infarcts are associated with BI, using the same approach as (a).

Analyses A and B will use repeated measures of functional status with the BI to estimate the trajectories of BI over time, and will describe how the primary predictors affect the intercept and slope of the estimated trajectories (Figure iii). Figure ix graphically displays the effect on the estimated trajectory of a change in intercept, and Figure x displays the effect of a change in slope.

Hypothesis #2: In order to delineate the unique effect of stroke on functional change that results particularly from vascular disease, we will use myocardial infarction (MI) as a comparison or control group. We hypothesize that the slope of decline in functional status over the long term is steeper after stroke than before stroke. The slopes of decline before and after MI are similar.

Specific Aim #2: **[Analysis C]** To determine, in CHS, using multivariable regression, censoring for recurrent stroke and adjusting for demographic, vascular, behavioral, social, and cognitive factors, whether the slope of functional status (measured by the National Center for Health Statistic Supplement on Aging IADL score) is different before and after stroke. A similar model will be applied to functional status before and after MI.

Figure xi graphically depicts the parameters that will be estimated in the models used in Analysis C.

Figure i. Conceptual depiction of the trajectory of functional status in relation to stroke

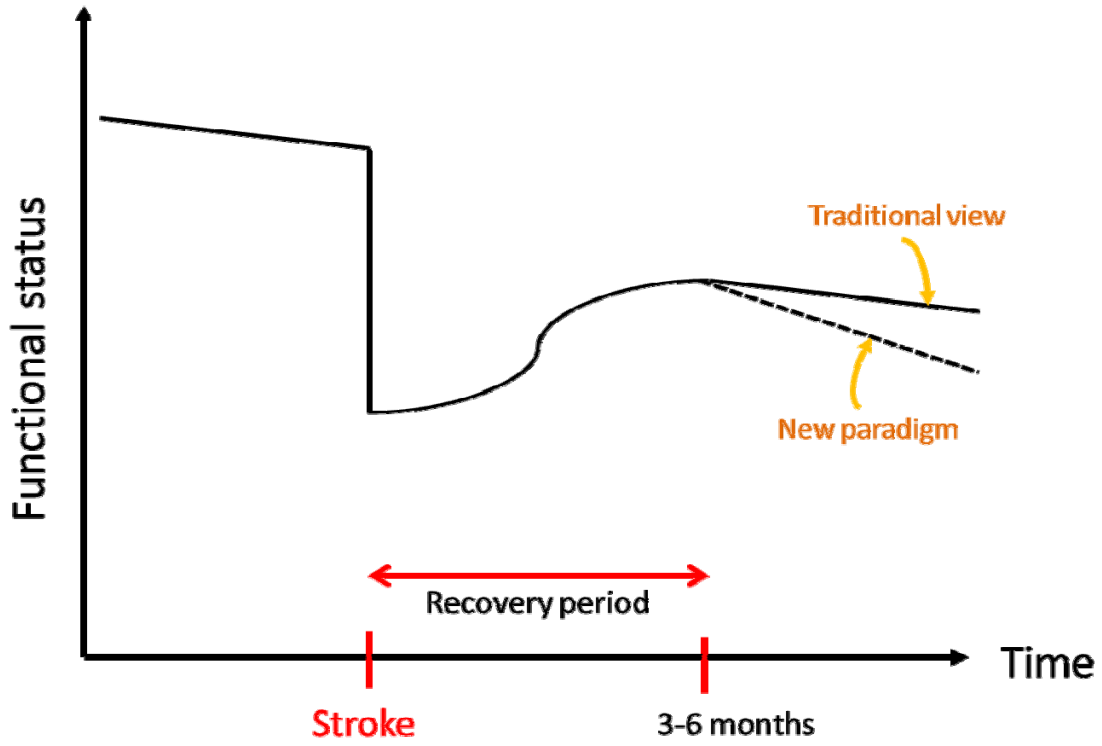


Figure ii. Trajectories of functional limitations after injury in the Health and Retirement Survey. Reproduced from Bell et al.[92]

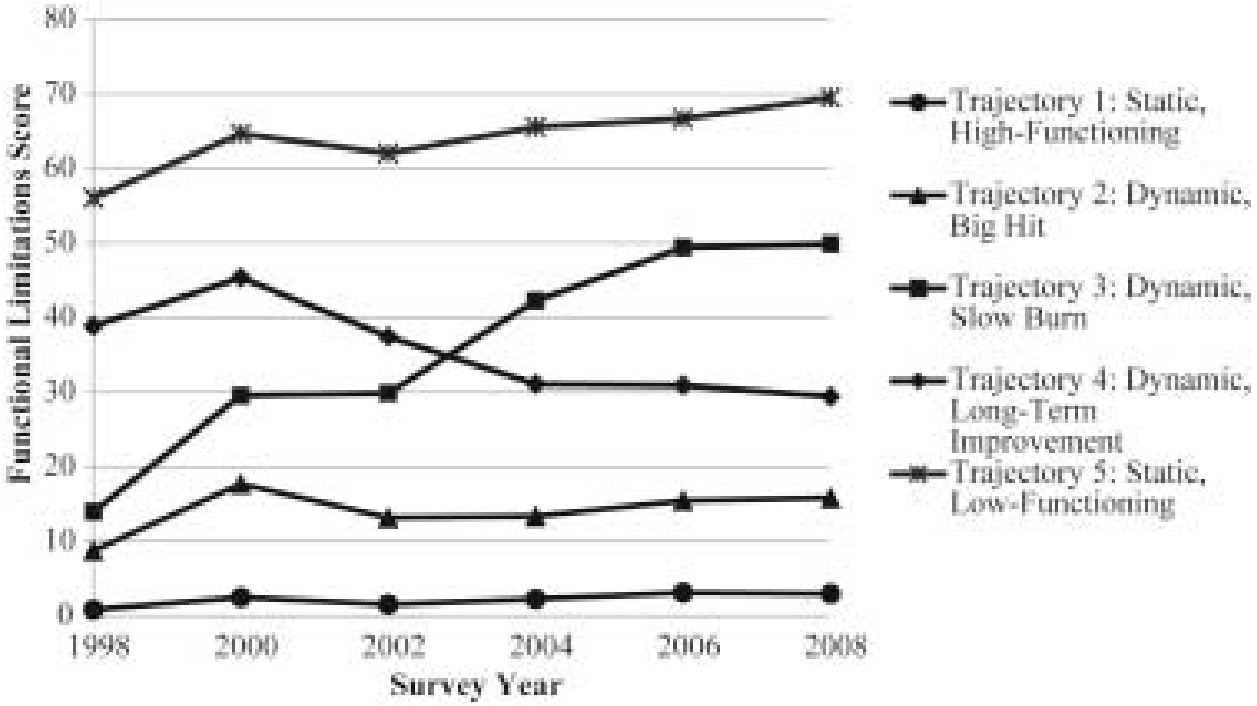


Figure iii. Estimation of functional trajectory over time from repeated measures

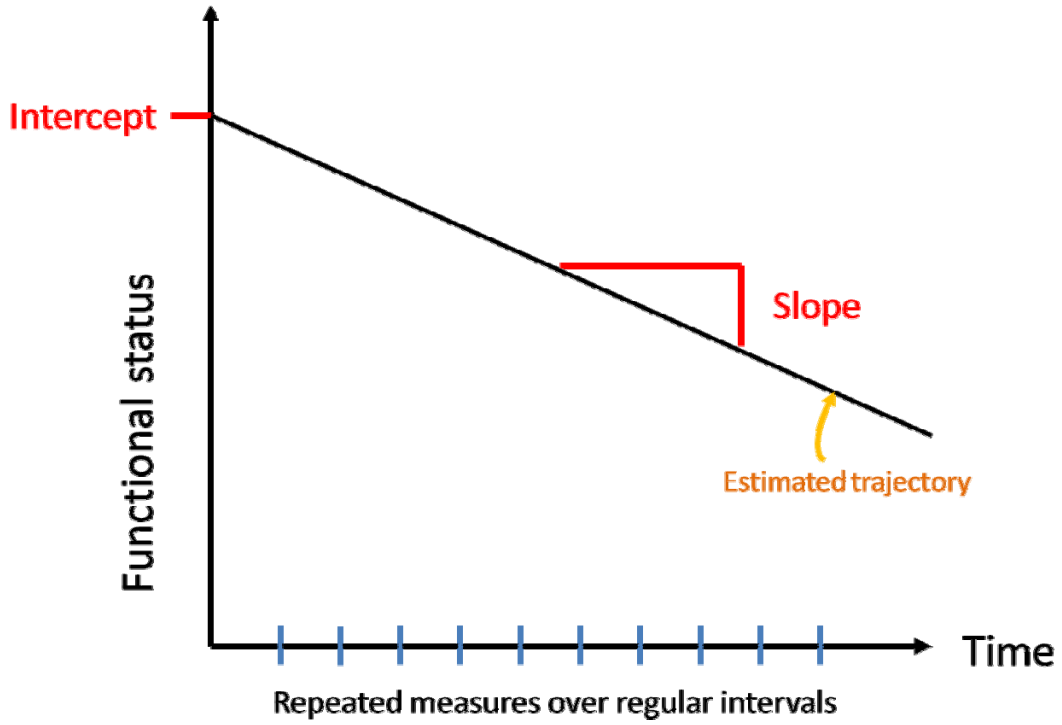


Figure iv. Patterns of functional trajectories in multiple sclerosis

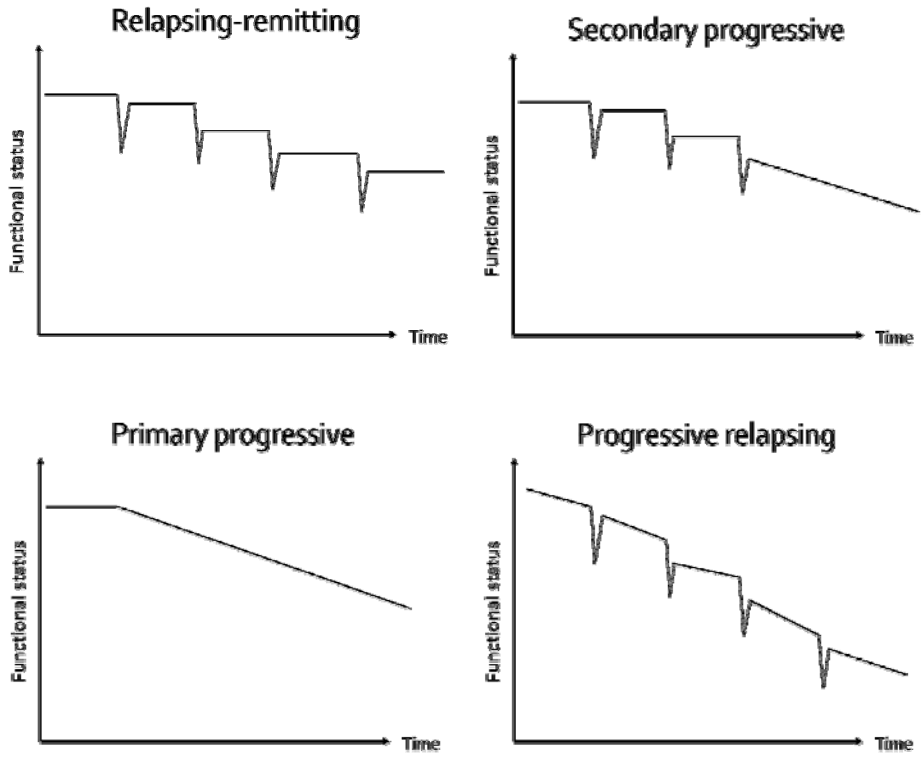


Figure v. Trajectories of function in relation to admission to intensive care units. Figure reproduced from Iwashyna. *Am J Resp Crit Care Med* 2012[143]

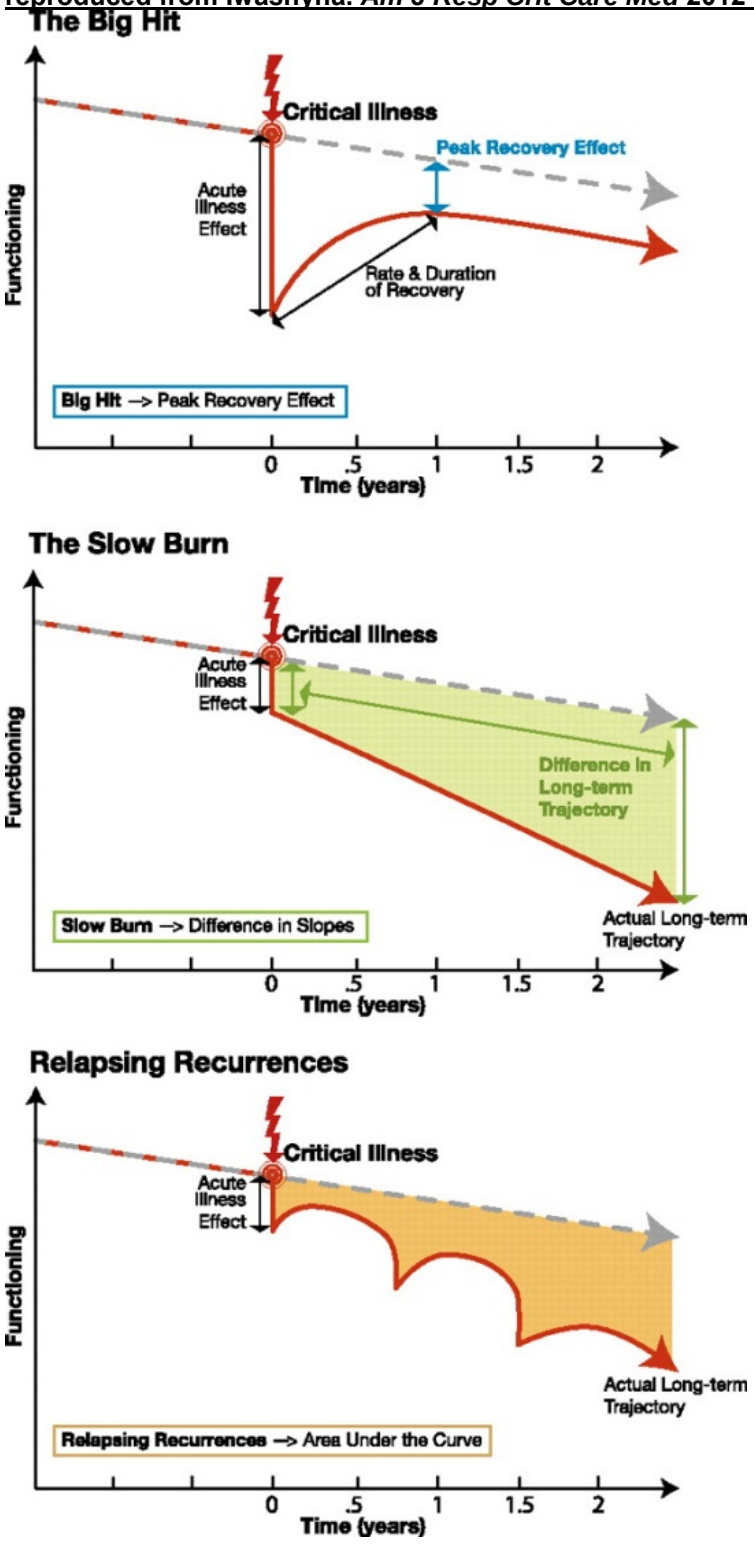


Figure vi. Conceptual depiction of the course of functional status before and after stroke among those with Medicaid or no insurance. Reproduced from Dhamoon *Stroke* 2012;43:2180-2184.[148]

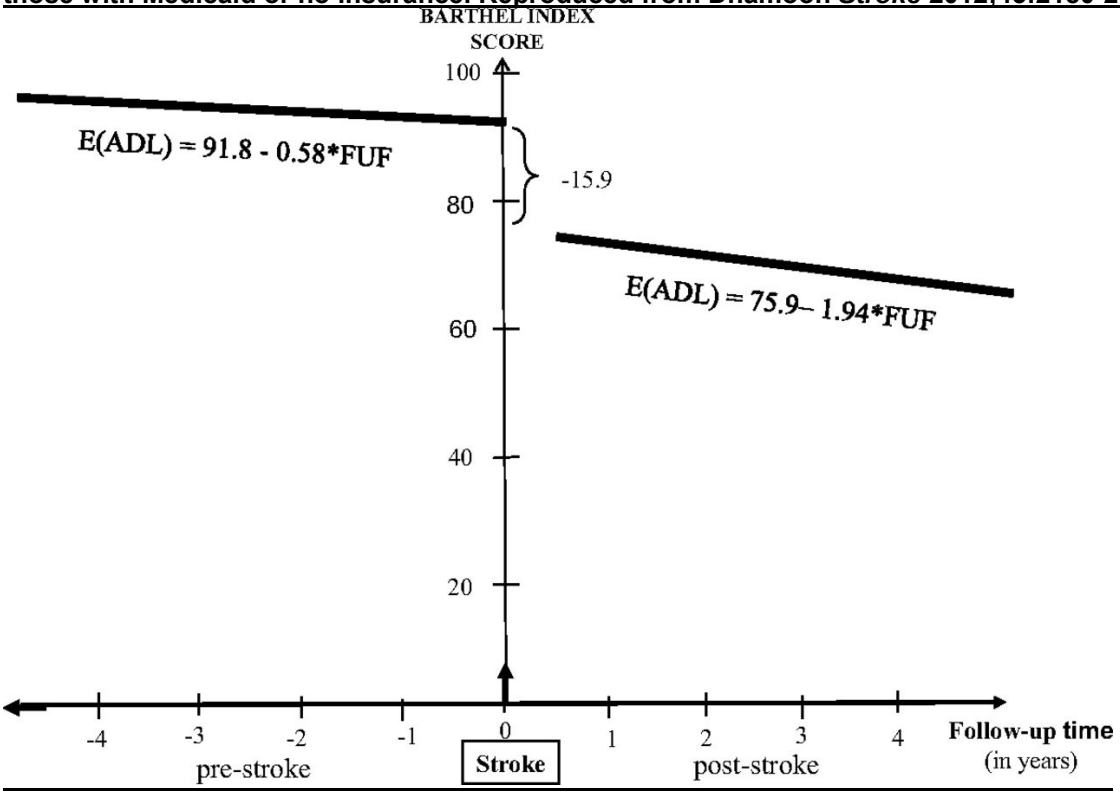
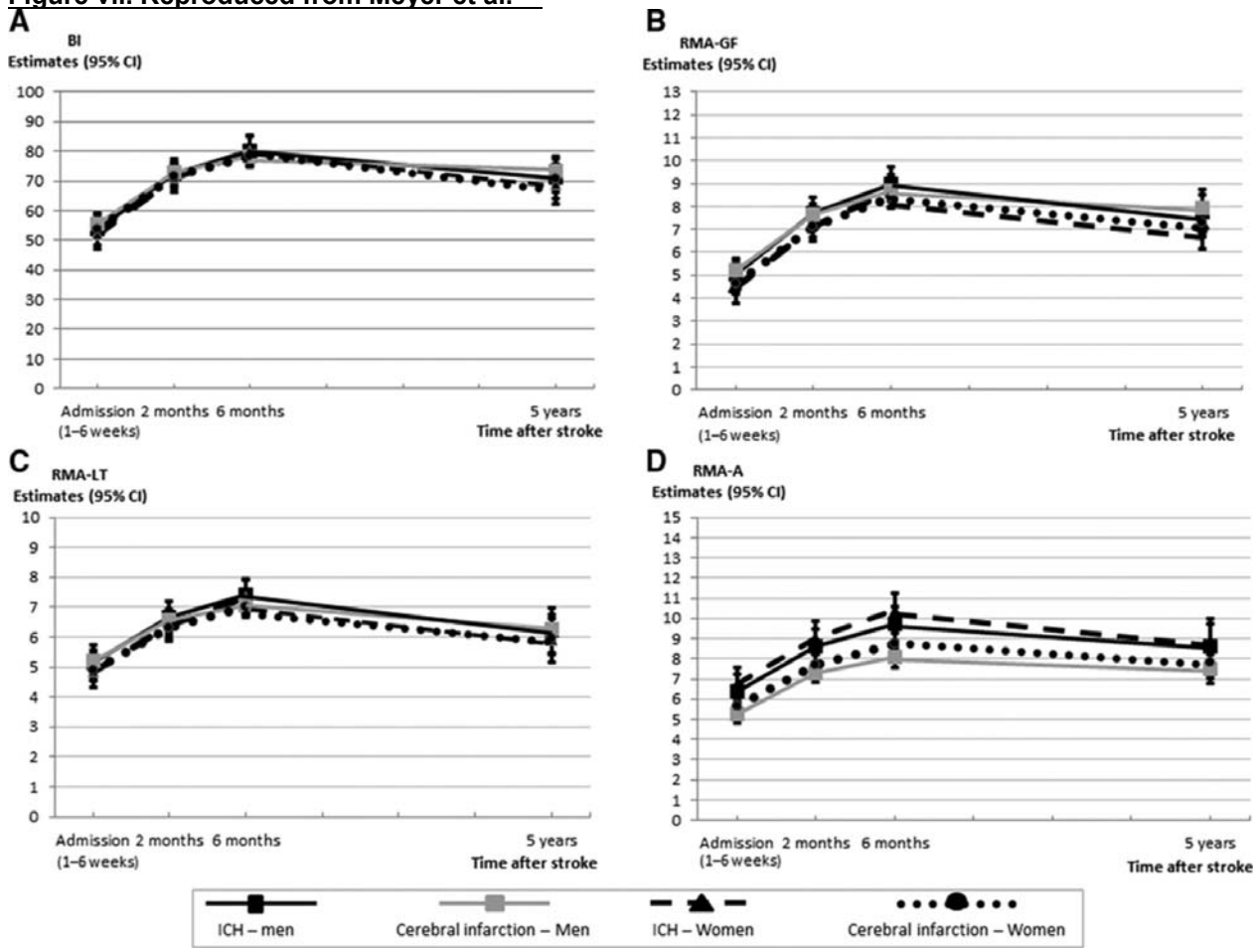


Figure vii. Reproduced from Meyer et al.[151]



"Recovery patterns of (A) the Barthel Index (BI), (B) Rivermead Motor Assessment of Gross Function (RMA-GF), (C) RMA of Leg and Trunk function (RMA-LT), and (D) RMA of Arm function (RMA-A) from admission to the rehabilitation center up to 5 years after stroke. ICH indicates intracerebral hemorrhage."[151]

Figure viii. Etiologic model for the proposed analyses

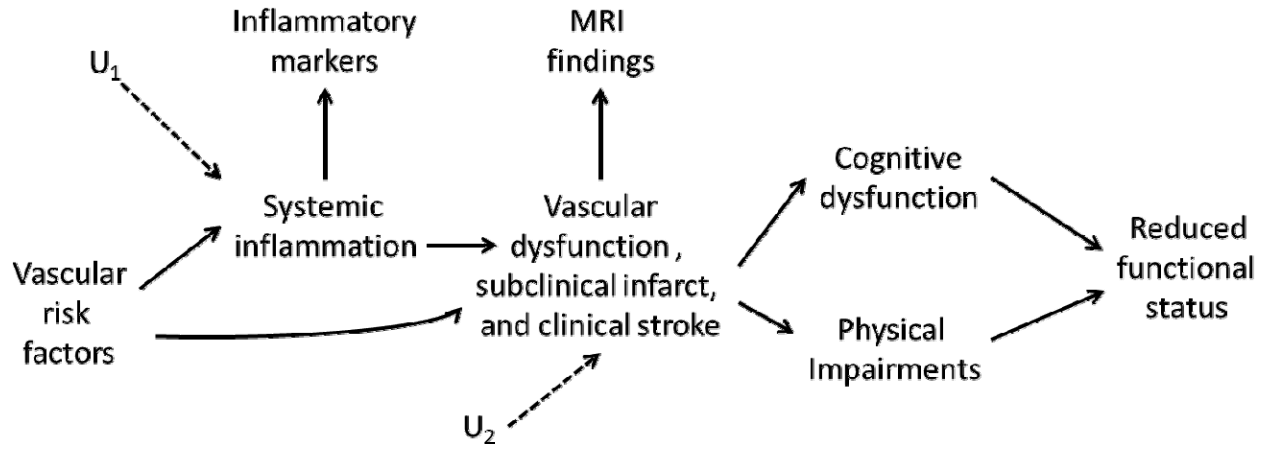


Figure ix. Conceptual depiction of change in intercept of functional trajectory

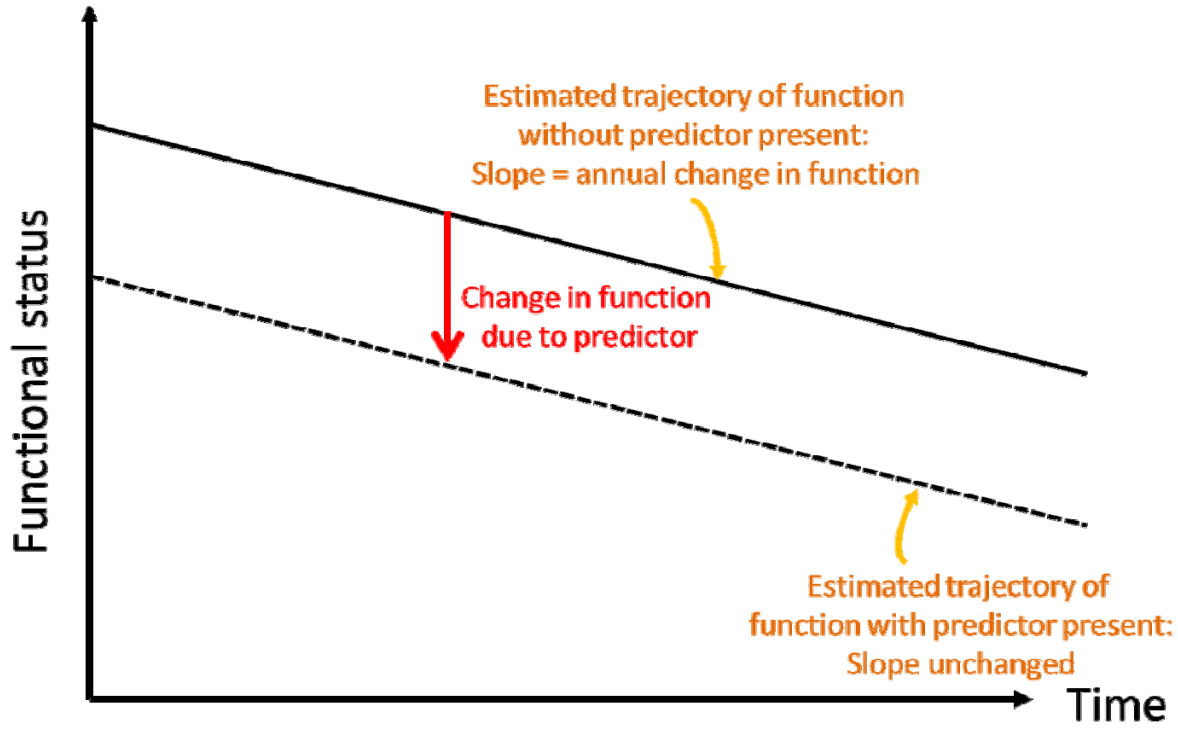


Figure x. Conceptual depiction of change in slope of functional trajectory

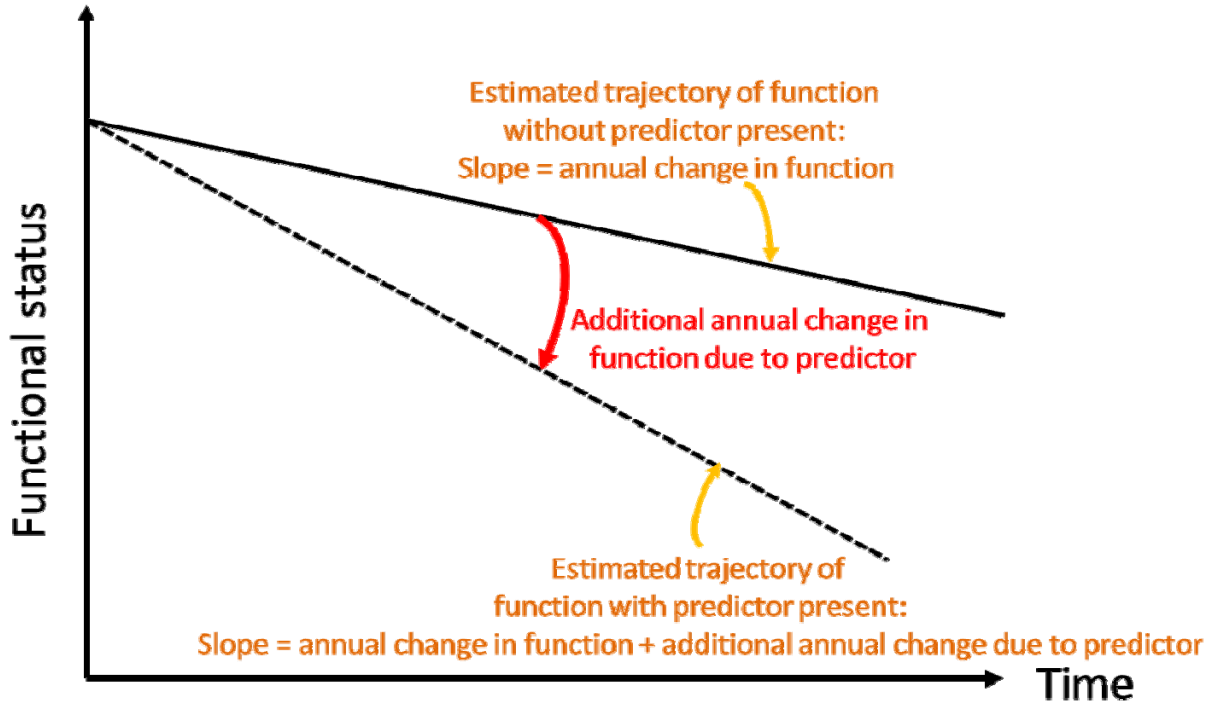
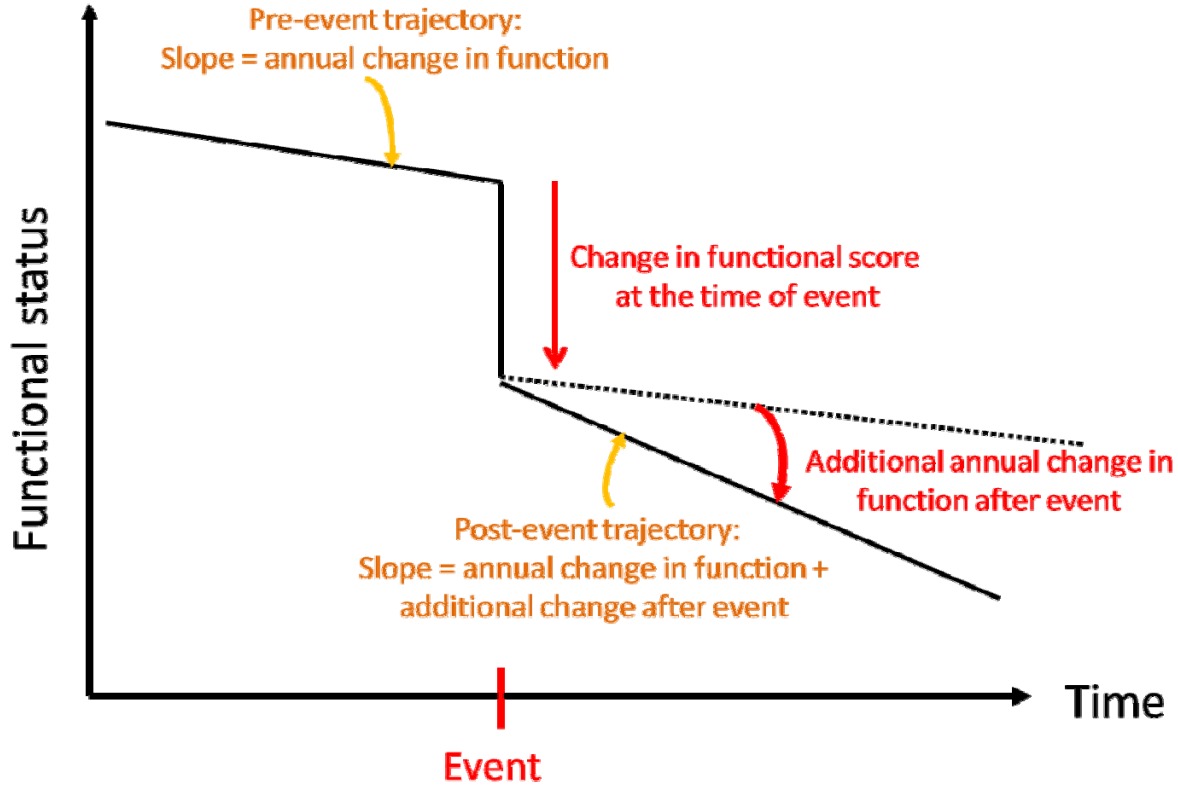


Figure xi. Conceptual depiction of estimated parameters in Analysis C.



Analysis A:

Inflammatory biomarkers predict disability independently of vascular events: the Northern Manhattan Study

Abstract

Background: Inflammatory biomarkers have been previously associated with stroke and mortality, but inflammation may also have detrimental effects beyond acute events. The association of these biomarkers with functional status is not well defined. We hypothesized that serum levels of high-sensitivity C-reactive protein (CRP), interleukin-6 (IL6), lipoprotein-associated phospholipase A2 (LpPLA2), and tumor necrosis factor receptor-1 (TNFR1) predict long-term functional status independently of vascular risk factors and stroke and myocardial infarction (MI) occurring during follow-up.

Methods: In the prospective, multiethnic Northern Manhattan Study, stroke-free individuals in northern Manhattan aged ≥40 years had annual assessments of disability with the Barthel index (BI), for a median of 13 years. BI was analyzed as a continuous variable (range 0-100). Baseline demographics, risk factors, and laboratory studies were collected, including CRP (n=2240), IL6 (n=1679), LpPLA2 mass and activity (n=1912), and TNFR1 (n=1863). Separate generalized estimating equation models estimated standardized associations between each biomarker and 1) baseline functional status and 2) change in function over time, adjusting for demographics, vascular risk factors, social variables, cognition, and depression measured at baseline, and stroke and MI occurring during follow-up.

Results: Mean age was 69 (SD 10) years, 36% were male, 54% Hispanic, 74% had hypertension, 22% diabetes; 337 MIs and 369 first strokes occurred during follow-up. CRP (-0.41, 95% CI -0.82 to 0.002) and LpPLA2 (-0.40, 95% CI -0.75 to -0.04) were associated with baseline BI but not change over time. TNFR1 was associated with baseline BI (-0.93, 95% CI -1.59 to -0.26) and change over time (-0.36 BI points per year, 95% CI -0.69 to -0.03).

Conclusions: In this large population-based study, higher serum inflammatory biomarker levels were associated with disability, even when adjusting for baseline covariates and stroke and MI occurring during follow-up. Elevated TNFR1 predicted greater disability over time, suggesting that systemic inflammation may contribute to long-term functional decline and disability.

Introduction

Serum biomarkers of inflammation may be able to detect subclinical risk of vascular disease, and hence may be able to link stroke pathophysiology with ongoing, continuous changes in function. Prior research has identified a significant role of inflammation in atherosclerosis and stroke[106, 107] as well as significant associations between stroke and inflammatory biomarkers, such as leukocyte count[108] and high-sensitivity C-reactive protein (hsCRP).[109-113] Some studies have suggested that hsCRP also predicts prognosis after stroke.[110, 114]

Prior research in the Northern Manhattan Study (NOMAS) has identified associations between inflammatory markers and MI, mortality, and carotid plaque thickness.[115, 116] In the Cardiovascular Health Study (CHS), interleukin-6 (IL6) and CRP have been associated with white matter lesions,[117] and other studies have found associations between CRP and stroke severity and mortality.[118] It appears that B-lymphocyte activation is linked to delayed cognitive decline after stroke in a mouse model as well as in pathological analysis of post-mortem specimens.[119]

Interactions have also been found between vascular risk factors and inflammatory states. Forty individuals, 19 with diabetes, had comprehensive neuropsychological measurements, physical examinations, MRI, and inflammatory marker analysis twice over 2 years.[122] Cerebral autoregulation was associated with functional status. Also, those with diabetes had worse cerebral vasoregulation and cognitive function over time, and higher cortisol and CRP levels were associated with decline in vasoregulation.

A single ischemic stroke may cause changes in inflammatory profiles[123] that may have an ongoing deleterious effect on brain structure and function[124] that may persist years after stroke.[125] Beyond the association with vascular outcomes, inflammation has been associated with quality of life (QOL) in a limited number of studies,[126-129] but the association of inflammatory markers with disability has not been well-studied, particularly among minority populations.

We hypothesized that elevated levels of serum inflammatory biomarkers independently predict worse functional status in those free of stroke at baseline. We studied this hypothesis in NOMAS in those who have data on serum biomarkers. Four biomarkers were studied: CRP, IL6, tumor necrosis factor receptor-1 (TNFR1), and lipoprotein-associated phospholipase-A2 (LpPLA2). CRP is an acute phase

reactant that reflects acute inflammatory states and tissue injury.[177] In addition, it may be directly implicated in pro-atherogenic processes, and several large epidemiologic studies have shown associations between higher CRP levels and vascular events and mortality. IL6 is an inflammatory cytokine that is also elevated with brain injury, predominantly expressed in brain white matter, and may be involved with recovery in traumatic brain injury and neuropathy.[178] Elevated IL6 has been associated with various types of dementia and stroke. TNFR1 is one of the 2 major receptors to which TNF binds, and binding to TNFR1 causes enhancement of inflammation and engages pathways meant to clear pathogens, including cytotoxic effects.[179] Elevated serum TNFR1 levels have been associated with autoimmune diseases and vascular conditions including stroke. LpPLA2 is an inflammatory biomarker secreted by immune cells in the walls of arteries and is involved in the inflammatory processes occurring in atherosclerotic plaque.[180] Elevated LpPLA2 has been associated with coronary heart disease and vascular events in previous studies. No known studies have tested the associations of the above biomarkers with trajectories of functional status.

Methods

Historically, NOMAS developed over time as a series of distinct studies with disparate designs. Initially, patients who experienced a first ischemic stroke were enrolled in a stroke incidence study and were followed over time as part of a stroke case follow-up study. A case-control study was then developed with individuals free of stroke who were identified by random-digit dialing serving as the controls. Finally, a prospective cohort study enrolled individuals free of stroke at baseline and is currently following up living subjects.

The cohort that was the focus of this analysis is the NOMAS population-based prospective cohort of those free of stroke at baseline, which was originally designed to evaluate the effects of medical, socio-economic, serum, and imaging risk factors for incident vascular disease and other outcomes in a multi-ethnic community. A total of 3298 participants were recruited by random digit dialing of both published and unpublished telephone numbers between 1993 and 2001. Subjects were enrolled if they: 1) were at least 40 years of age; 2) lived in a pre-defined geographic area of northern Manhattan for at least 3 months in a household with a telephone; and 3) did not have a history of stroke. The study was approved

by the institutional review boards of Columbia University and the University of Miami, and informed consent was obtained from all participants. Further characteristics of the cohort have been outlined in prior publications.[181-183]

Baseline Evaluation

Trained bilingual research assistants interviewed participants and collected data using standardized questions regarding the following conditions: hypertension, diabetes, hypercholesterolemia, cigarette smoking, alcohol use, and cardiac conditions.[184] All participants underwent a thorough baseline examination including comprehensive medical history, physical examination, review of medical records, functional status assessed by the BI, quality of life (QOL) assessed by the Spitzer QOL index (QLI), and fasting blood samples.

Follow-up

All participants are followed annually via phone screening to detect change in vital status, new neurological or cardiac symptoms and events, interval hospitalizations, cognitive function, and functional status via the Barthel index (BI). Only two subjects have been completely lost to follow-up after their baseline examination, and the average annual contact rate is 99%.

A positive screen for any potential cardiac or neurological event is followed by an in-person assessment to determine whether a vascular outcome has occurred. In addition, all admissions and discharges are screened for hospitalizations and outcomes that may not have been captured by telephone interview. Nearly 70% of vascular events lead to hospitalizations at Columbia-Presbyterian Hospital. Hospital records are reviewed to classify outcomes as previously reported.[183] Stroke includes ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, but not transient ischemic attack or venous sinus thrombosis. At least 2 stroke neurologists verify and classify all stroke cases. MI is defined by criteria adapted from the Cardiac Arrhythmia Suppression trial[185] and the Lipid Research Clinics Coronary Primary Prevention trial[186] requiring at least 2 of the 3 following criteria: (a) ischemic cardiac pain determined to be typical angina; (b) cardiac marker abnormalities defined as abnormal CK-

MB fraction or troponin I values; and (c) ischemic EKG abnormalities. Diagnosis of MI is adjudicated by cardiologists independently after review of all clinical data.

There were 435 MIs occurring during follow-up, 225 (51.72%) definite, 112 (25.75%) probable, and 98 (22.53%) possible. For this analysis, only definite and probable MI were included (n=337). Out of first MIs occurring during follow-up (n=333), 184 (55.3%) were definite, 81 (24.3%) were probable, and 68 (20.4%) were possible. There were 369 first strokes occurring during follow-up, 322 (87.26%) infarcts, 35 (9.49%) intracerebral hemorrhages (ICH), 8 (2.17%) subarachnoid hemorrhages (SAH), and 4 (1.08%) unknown. All were included in this analysis.

Study outcome

The BI, developed in 1965[187] and later modified,[188] measures an individual's performance in 10 ADLs and has been extensively used in stroke observational studies and clinical trials as a measure of post-stroke disability.[189] The scale ranges from 0 to 100 in 5-point increments, with 100 indicating normal physical functioning. Previous research has demonstrated the reliability of phone assessments of function using the BI.[190] Although it is an ordinal scale, recent research has advocated analyzing the scale as a continuous variable due to increased power to detect associations, ability to describe the course of change over time in linear form, and avoidance of potential misclassification due to crude categorization.[191-193]

One limit of the BI is that it is subject to ceiling effects, because the difficulty of ADL performance is relatively low compared to more complex tasks such as IADLs, or more complicated cognitive tasks. Hence, in a population that is not expected to have significant disability, such as the stroke-free, population-based NOMAS cohort, the BI may not capture subtle or early deficits in functional status. Estimation of a ceiling effect of a measure should ideally be performed in the cohort under analysis, and the estimate in one population does not necessarily translate to the cohort under analysis.[194] There are several ways to estimate ceiling effects, the most effective of which involve comparisons of the properties of the scale to other scales measuring related constructs.[195] The following metrics can be calculated for each scale and compared among the scales: effect size[196], standardized response mean,[197] paired t-statistic,[198] or relative efficiency.[199] Also, the distribution of maximum scores on each scale can be

compared to estimate the ceiling effect. There is a plan to perform these analyses using functional and quality of life measures that began to be assessed on follow-up visits in NOMAS approximately 2 years ago. These analyses would estimate not only ceiling effects but also responsiveness and statistical estimates of meaningful clinical change. However, at the time of this analysis there was not sufficient data to complete these analyses.

Explanatory variables: Inflammatory biomarkers

In 2240 participants, blood samples were collected at baseline and the following were measured using immunoassays: hsCRP (using enzyme-linked immunosorbence), IL6, TNFR1, and LpPLA2 mass and activity (PLAC assay; diaDexus Inc, South San Francisco, CA). Laboratory personnel were blinded to patient clinical data and markers were run in the same participants. Serum samples for IL6 and CRP were drawn into EDTA tubes at baseline, spun immediately at 3,000 g at 4°C for 20 min, and frozen at –70°C for later analysis. Inflammatory marker levels were then measured in batched samples by enzyme-linked immunosorbent assay using monoclonal antibodies to IL6 with a lower limit of detection of 0.1 pg/ml (Biosource International, Camarillo, Calif., USA) and hsCRP with a lower limit of detection of 0.1 mg/l (BioCheck Inc., Foster City, Calif., USA). Each participant had a maximum of only one measurement of each inflammatory biomarker.

The distributions of all 4 biomarkers (IL6, TNFR1, CRP, and LpPLA2—mass assay and activity assay) were determined (Table A2). The pattern of missing inflammatory labs was examined, and the most common missing pattern was missing values for LpPLA2 mass and activity, reflecting the fact that these labs were added to the inflammatory laboratory panel later in time. For non-normally distributed biomarkers, log transformations were performed (Table A2 and Figure A2). Although not required to satisfy model assumptions, log transformations were performed in order to approximate a normal distribution of the variable to be consistent with prior analyses. There were 67 “0” values for IL6. The next highest value, above 0, was 0.005. These “0” values were assigned a value of 0.0025 for the log transformed analyses. There were 2 “0” values for TNFR1. The next highest value, above 0, was 0.09. These “0” values were assigned a value of 0.045 for the log transformed analyses. In secondary analysis, a value of 0.000001 was assigned to the “0” values for each of IL6 and TNFR1. For IL6, there

were 36 values that were >2000, including 35 values of 5000, which were determined to be due to coding error of high values; these were excluded for the non-quartile analyses of IL6. Inflammatory biomarker values were centered to the mean of all values. Quartiles of each biomarker were also used as categorical variables using the lowest quartile as the referent group. Additionally, CRP was categorized according to the three CDC/AHA risk stratification levels: <1 mg/L; 1-3 mg/L; and >3 mg/L (Appendix A2).[200] In secondary analysis, we explored CRP-dominant versus IL-6-dominant profiles, as outlined in Appendix A2, as primary predictors, as previously described.[201]

Covariates

All analytic models were adjusted for the following variables: age, sex, race-ethnicity, body mass index (weight in kilograms divided by the square of height in meters), self-reported hypercholesterolemia, diabetes mellitus (defined by self-report, fasting blood glucose level ≥126 mg/dL, or insulin/oral hypoglycemic use), hypertension (defined as a systolic blood pressure recording ≥140 mmHg or a diastolic blood pressure recording ≥90 mm Hg based on the average of two blood pressure measurements or the patient's self-report of a history of hypertension or antihypertensive use), smoking (defined as either nonsmoker or smoker within the last year), alcohol use (with moderate alcohol use classified as 1 drink/month to 2 drinks/day), social variables (marital status, insurance status [classified as uninsured, Medicaid, Medicare, or private insurance], number of friends [individuals whom the participant knows well enough to visit in their homes], years living in the community), and cognitive factors (depressed mood, and performance on mini-mental state examination [analyzed as a continuous variable]). Of note, there was no evidence of over-reporting of hypertension by self-report. Specifically, 1729 individuals (52.4%) self-reported hypertension, and 2067 (62.7%) had a systolic blood pressure recording ≥140 mmHg or a diastolic blood pressure recording ≥90 mm Hg based on the average of two blood pressure measurements. There were 700 (21.2%) who did not self-report hypertension and had elevated blood pressure readings as defined above, There were 1357 (41.2%) who did self-report hypertension and had elevated blood pressure readings at the time of evaluation. The definitive way to identify over- or under-diagnosis of hypertension by self-report would be to perform ambulatory blood

pressure monitoring in all participants. However, the composite definition of hypertension seems to be an accurate method of identifying cases of hypertension in this population.

Statistical analysis

The goal of this analysis was to determine whether levels of serum inflammatory biomarkers (IL6, TNFR1, CRP, and LpPLA2) were associated with baseline BI and a steeper slope of decline over time (Figure iii). We first calculated the distribution of main explanatory variables, baseline covariates, and BI, and we compared the distributions of variables based on availability of inflammatory lab data to detect differences in the inflammatory lab cohort compared to the prospective cohort. Then, each biomarker exposure was analyzed separately. Due to correlations among repeated measures of outcomes in the same individual, regression models based upon generalized estimating equations (GEE) with an identity link function were used to assess the association between main explanatory variables and repeated measurements of BI, adjusting for baseline demographic variables (age, sex, race-ethnicity), medical risk factors (BMI, diabetes, hypertension, hypercholesterolemia), smoking and alcohol use, social variables (marital status, insurance status, number of friends, number of years in the community), and cognitive factors (depressed mood, performance on mini-mental state examination). In model building, we sequentially added groups of variables in a pre-specified manner based upon the standards of the field. Specifically, the first model included no covariates, and successive models included demographic variables, vascular risk factors, social variables, and cognitive and mood factors.

In order to assess whether the main explanatory variables were associated with the slope of change in outcomes over time, we included interaction terms between time of follow-up assessment and the variable. All significant interactions with time were included in the final model. We used QIC for GEE models and AIC for mixed models as the model selection criteria after considering candidate final models. Various model diagnostics including tests of linearity, residual plots, and goodness of fit measures were used to evaluate the final model. There was no evidence to suggest lack of linearity in the final models. As a working correlation structure for the GEE models we chose the exchangeable (intraclass) structure and compared the QIC obtained with this model with one using the unstructured working correlation structure. We chose the exchangeable model, with the lower QIC, as the final model. In order to assess

whether interval vascular events such as clinical stroke and MI were implicated in the trajectory of functional status, we ran a second set of models in which stroke and MI were included as time-varying covariates. MI was defined as definite and probable MI (not including possible MI). A sensitivity analysis was performed in which possible MI was added to the definition of MI, and models did not significantly differ and are not presented here. We also performed a sensitivity analysis in which those with baseline coronary artery disease were excluded, and models did not significantly differ and are not presented here. In a separate analysis, we assessed whether interval non-stroke and non-MI hospitalizations were related to changes in functional status, using a similar strategy as above.

We also pursued an alternative modeling strategy using mixed models. For the mixed models approach, we first calculated intraclass correlation coefficients using an 'empty' or 'random intercept only' model to determine the proportion of variance that is due to between-person variation. This model was used as a baseline for comparison for subsequent models. We then determined whether there was an effect of time on average on the outcome of functional status by determining whether there was a fixed effect of time. We also determined whether the average effect of time varies across individuals by determining the random effect of time. We added covariates in a similar manner as for the analyses described above.

There are several differences in the way that mixed models and GEE models analyze correlated data, and in the results that are generated from each. GEE is a population-average model that estimates an overall population effect, whereas mixed models estimate an overall population effect (fixed effect) but also allow for individual variation around this average (random effects).[202, 203] GEE models use a working correlation structure, which can be specified among several possibilities, and the fit of each structure can be compared using the QIC, as outlined above. Although the standard errors that are estimated from this method are robust, the population correlation structure is assumed and not directly specified, as it must be with mixed models. Hence, mixed models may be more prone to erroneous results as a result of misspecification. However, the advantage of using mixed models to analyze time trends in outcomes is that repeated measures over time have an inherent order or sequence, and mixed models can explicitly specify this structure, as opposed to GEE models. Also, different findings when using mixed models compared to GEE models may be related to different handling of missing data and the greater

preservation of data in the mixed models (because there is no need to delete case-wise if selected outcome data for an individual are missing). Hence, although results from both analyses will be presented here, the mixed model results should be considered the "primary" model results.

A basic analysis of the mediation effect of each biomarker was performed, in which adjusted models incorporating each biomarker were compared to an adjusted model without any biomarker, and the magnitude and direction of the time trend was compared between models. Also, the QIC was compared between models.

We examined the effect of hospitalization on functional status in several ways, and determined whether loss to follow-up was related to hospitalization, which may have introduced bias in the estimation of functional trajectories. We also examined the impact of loss to follow-up in several ways. We first calculated the time between last functional assessment and death. For those with the longest amount of time between last assessment and death, records were examined individually to assess for the reason for loss to follow-up. Secondly, the distribution was determined of the last ADL score measured among those who died. We also calculated the distribution of maximum follow-up times among survivors and examined records for individuals who had maximum follow-up time <10 years to identify possible reasons for loss to follow-up.

Results

Table A1 shows distributions of variables in the cohort, stratified by availability of inflammatory labs. The inflammatory lab cohort consisted of 2551 participants. There were significant differences in the distributions of several variables based on availability of inflammatory lab data, including: age, sex, race-ethnicity, health insurance, physical activity, hypercholesterolemia, and social support. Those who had inflammatory lab data were slightly younger, less often Hispanic, more often married, and more often covered by Medicaid or had no insurance. However, there were no differences in major vascular risk factors.

Appendix A1 and Figure A1 show the distributions of the Barthel index score in the entire prospective cohort. There were a total of 38110 assessments among the 3298 participants in the prospective cohort. Table A2 and Figure A2 show the distributions of biomarkers in the inflammatory lab

cohort, including raw variables and log-transformed variables. Appendix A2 (A) shows the distributions of CRP according to AHA/CDC categories; the majority of individuals had levels >3 mg/L. Appendix A2 (B) shows the conceptual framework of IL6- and CRP-dominant profiles, and (C) shows frequencies of the reference level as well as IL6- and CRP-dominant profiles.

Table A3 shows associations between standardized CRP levels and trajectories of functional status, in unadjusted and adjusted models. In all models, there was a significant annual decline in functional status of around one BI point per year in most models, and of 0.39 points per year in a model adjusted for stroke and MI occurring during follow-up. In addition, in most models, including the fully adjusted model, higher CRP levels were associated with a lower overall mean functional score. Finally, CRP levels were not significantly associated with change in functional status over time. Patterns of association were similar when log of CRP levels was tested as the main predictor – namely, a significant overall annual decline in function, a lower mean overall functional level with higher log of CRP levels, and no significant association between log of CRP levels and change in functional status over time (Table A4). When the AHA/CDC categorization of CRP levels was used (Table A5), similar trends were seen but with reduced significance, possibly due to reduced power from the use of categorical instead of continuous variables.

As shown in Table A6, higher standardized TNFR1 levels were associated with lower overall functional status as well as accelerated decline over time. In the fully adjusted model including adjustment for stroke and MI occurring during follow-up, each SD increase in TNFR1 level was associated with a mean of -0.93 (95% CI -1.59, -0.26) lower BI points overall as well as an additional -0.36 points per year of decline over time (95% CI -0.69, -0.03), over and above the -0.52 points per year of BI decline (95% CI -0.73, -0.31) in the entire cohort. There was a similar pattern when log of TNFR1 levels were examined as primary predictor, though in most models except for the final model, the estimate for the association between log of TNFR1 levels and functional status was not significant (Table A7) (results for unstandardized log of TNFR1 levels are shown in Appendix A3). In a sensitivity analysis in which TNFR1 levels of 0 were set to missing (Appendix A4), in the fully adjusted model, increasing levels of log of TNFR1 were associated with -1.12 BI points overall (95% CI -1.97, -0.27) and -0.34 additional BI points per year (95% CI -0.67, -0.01).

When quartiles of TNFR1 were examined (Appendix A5), higher quartiles of TNFR1 were associated with lower overall BI values as well as additional decline in function over time. In the fully adjusted model, the highest quartile of TNFR1 was associated with an additional -0.72 BI points of decline per year (95% CI -1.34, -0.10) compared to the lowest TNFR1 quartile. Using a dichotomous variable of the highest quartile of TNFR1 versus all other quartiles (Appendix A6), the highest quartile was associated with reduced overall function as well accelerated decline over time in an unadjusted model, but in a fully adjusted model, the highest quartile was only associated with an additional -0.64 BI points of decline per year (95% CI, -1.25, -0.04).

In adjusted models, log of IL6 levels was not associated with either overall mean BI or change in BI over time (Table A8). Results were not meaningfully different in a sensitivity analysis with 0 values set to missing (Appendix A7). When IL6 was dichotomized at the median (Appendix A8), IL6 scores above the median were associated with reduced function overall (-1.10, 95% CI -2.18, -0.02) and decline in function over time (-0.20 BI points per year, 95% CI -0.38, -0.01) in an unadjusted model but not after adjustment.

In adjusted models (Table A9), higher LpPLA2 mass levels were associated with lower mean BI score (-0.40, 95% CI -0.75, -0.04) but not associated with change of BI over time. LpPLA2 activity levels were not associated with either overall mean BI or change in BI over time (Table A10). Neither CRP- nor IL6-dominant profiles were associated with overall mean BI or change in BI over time (Table A11), in unadjusted or adjusted models.

Table A12 shows results using mixed models without covariate adjustment. Model 1 (Table A12 [A]) shows that the between-person variance was 134.91 and within-person variance was 172.18. Hence, the intraclass correlation coefficient was 134.91 / (134.91 + 172.18) = 0.43932. According to this calculation, 43.9% of the variance in BI scores was due to between-person differences and 56.1% was due to within-person variation. The mean BI score was 91.2782. According to the p-value (<0.0001) of the standard error of this intercept (under “solution for fixed effects”), the sample varies significantly in the intercept. Examining model 2 (Table A12 [B]), the AIC was lower (better) when time was added to the model, signifying a better fit with time in the model (Tables A12 [C] and [D]).

Two adjusted linear mixed models were fit in order to evaluate the change of functional status over time in the cohort: one with a linear time trend (Table A13), and one that evaluated change in BI per year of age (Table A14). Both showed a significant decline in functional status over time. Other significant predictors of functional status included: race-ethnicity, diabetes, physical activity, marital status, insurance coverage, depression, cognition measured by the MMSE, and QOL. Unexpectedly, depression was associated with better overall functional status.

Table A15 shows adjusted mixed models individually testing the association between a single biomarker and trajectories of functional status. Similarly to the GEE models, increasing log of CRP and LpPLA2 mass levels were associated with lower overall functional status but not change in function over time; also, LpPLA2 activity levels were not associated with function. Also similar to the GEE models, increasing log of TNFR1 levels were associated with lower overall BI score (-1.05, 95% CI -1.40, -0.70) as well as accelerated decline in function over time (-0.43 additional points per year per unit increase in log of TNFR1 levels, 95% CI -0.62, -0.23). In contrast to the GEE models, increasing log of IL6 levels were significantly associated with accelerated decline in function over time (-0.13 point per year, 95% CI -0.24, -0.02), and there was a trend for lower overall functional status (-0.20, 95% CI -0.41, 0.004).

Table A16 shows an analysis of the mediating effect of each biomarker, comparing adjusted models incorporating each biomarker to an adjusted model without any biomarker. In each case, addition of a biomarker reduced the QIC, indicating better explanatory power with the biomarker included. However, there was no consistent pattern of effect on the annual change in BI score overall.

The effect of hospitalization on functional status was assessed in Appendix A9. In 20.2% of study visits, there was a hospitalization since the last contact (A). Only 24.5% of individuals had no hospitalization during follow-up, and the majority of those who were hospitalized (21.6%) had 1 hospitalization, with a range up to 17 hospitalizations (B). Comparing the number of hospitalizations to the number of study visits (C), the mean of the ratio of number of hospitalizations to number of follow-up visits was 0.20 (D), suggesting on average that there was one hospitalization for every 5 follow-up visits. For a non-stroke/MI hospitalization, the amount of time between pre-hospitalization assessment and post-hospitalization assessment was on average 1.09 years, with an upper quartile of only 1.11 years (E). For all hospitalizations, the corresponding interval was on average 1.05 years, with an upper quartile of 1.11

years (F). These results suggest that hospitalization did not cause selective loss to follow-up or introduce bias into the timing of BI assessments.

The impact of loss to follow-up and death was assessed in Appendix A10. The average time between last functional assessment and death was 0.74 years, with an upper quartile of 0.93 years (A). The distribution of the last BI score assessed before death is summarized in (B) and (C); although there are low scores, the majority of scores (37.2%) are 95 or 100, signifying normal functional status. Those with last BI score before death of <60 more often had a shorter interval between last functional assessment and death (61.2% with interval <0.5 years) compared to those with BI of 60-90 (37.0%) or 95-100 (33.8%). Among survivors, there was a greater proportion with higher BI scores (E) compared to those who died. The average follow-up time among survivors was 15.2 years, with a median of 15.1 years (F).

Conclusions for Analysis A

NOMAS is a large, population-based study with frequent, regular measurements of functional status, numbering over 38,000 overall. Hence, it is well-suited to estimate trajectories of functional status over time and identify factors that influence these trajectories. In the sub-study of NOMAS analyzed here, accurate measurement of inflammatory biomarkers allowed us to elucidate the influence of these biomarkers, and by extension systemic inflammatory states, on trajectories of function over time. Also, adjustment for potentially confounding factors allowed us to estimate the independent effect of these variables on function. Among those with inflammatory biomarker data at baseline, the prevalence of increased biomarker levels was high. When trajectories of functional status were examined, there was an overall decline in functional status over time in the entire cohort. Increasing CRP levels, examined using different cutoffs and variable definitions, were associated with lower overall mean functional score but not with change in slope of function over time. Results were similar for LpPLA2 mass levels. However, for TNFR1, increasing levels were associated not only with overall reduced functional status, but also additional annual decline in function over time. This association was consistent using different cutoffs and transformations of TNFR1.

In addition to GEE models, we also used mixed models to estimate associations, which in most cases confirmed the significance and magnitude of effects seen with GEE models. Although IL6 was not a significant predictor in GEE models, increasing IL6 levels were associated with accelerated decline in function over time using the mixed model approach. Due to improved handling of missing data, with greater preservation of data in the mixed models, as well as a more accurate specification of the time trend with mixed models compared to GEE models, the mixed model results should be considered the primary model results. We also tested whether the annual change in functional status was altered by adding each biomarker in models, but there was no consistent pattern of effect.

For models testing CRP, TNFR1, IL6, LpPLA2, we observed that the estimate for annual change in BI score was significantly reduced after adjusting for depression, cognitive status, and QOL. This is not surprising considering the well-known association between inflammatory processes and depression.[204] However, the effect of inflammatory markers discussed above remained even after adjusting for these factors, suggesting that inflammatory processes have an effect on functional status that is independent of depression.

The data quality in this study was high, and there was no evidence of bias on the timing of follow-up assessments or loss to follow-up. Specifically, we tested the potential effect of hospitalization on data ascertainment and found no evidence of any effect of hospitalization on timing or regularity of follow-up assessments. Also, there was no evidence that there was loss to follow-up in the last functional assessments before death, and overall the average length of follow-up among survivors was an impressive 15.2 years.

Strengths of this analysis include a large, population-based cohort with repeated, regular measurements of functional status with a validated scale. There was also regular surveillance for vascular events and hospitalization and expert adjudication of events. Biomarkers were measured according to standard procedures, and confounders were adjusted for in models. One limitation of the proposed study involves deficiencies in the primary measure. The BI is subject to ceiling effects and is insensitive to small changes in disability.[205] However, the ceiling effects seen with the BI would likely lead to an underestimation of the effect and would be unlikely to result in false positive associations. Hence, if the BI did not have a ceiling effect, the estimated associations would likely be even larger than those

seen in this analysis. Analyzing the BI as a continuous variable is advantageous since this approach can capture and quantify the variance and course of change over time, which would likely not be captured by using a categorical or dichotomous variable.[192, 193] One advantage of the BI is that it is widely used in stroke research, which allows comparison with prior studies, and it is also not a stroke-specific scale, which allows its use in a stroke-free population.

Further discussion of the findings of this analysis will be found in the concluding chapter.

Table A1. Baseline characteristics of the cohort, by availability of labs:

Variable	Cohort with inflammatory labs	Cohort without inflammatory labs	p-value
Number of participants, No. (%)	2551 (77.4)	747 (22.7)	--
Biological characteristics:			
Age, mean (SD), y	69.3 (10.2)	71.3 (10.7)	<0.0001
Body mass index, mean (SD), kg/m^2	27.9 (5.5)	27.5 (5.7)	0.09
Demographics:			
Male, No. (%)	923 (36.2)	304 (40.7)	0.02
Race-ethnicity:			0.0003
Non-Hispanic white, No. (%)	509 (20.0)	181 (24.2)	
Non-Hispanic black, No. (%)	594 (23.3)	209 (28.0)	
Hispanic, No. (%)	1385 (54.3)	343 (45.9)	
Other, No. (%)	63 (2.5)	14 (1.9)	
Received at least high school education, No. (%)	1154 (45.3)	357 (47.8)	0.2
Highest education achieved, No. (%)			0.1
Eighth grade or less	1044 (40.9)	269 (36.0)	
Some high school	352 (13.8)	121 (16.2)	
Completed high school	469 (18.4)	138 (18.5)	
Some college	296 (11.6)	101 (13.5)	
College graduate or more	389 (15.3)	118 (15.8)	
Marital status, No. (%) married	826 (32.4)	216 (28.9)	0.07
Health insurance, No. (%)			0.0004
Medicaid or no insurance	1151 (45.5)	284 (38.2)	
Medicare or private insurance	1381 (54.5)	460 (61.8)	
Medicaid health insurance, No. (%)	886 (34.7)	230 (30.8)	0.045
Medicare health insurance, No. (%)	1573 (61.7)	525 (70.3)	<0.0001
Private insurance, No. (%)	1052 (41.3)	334 (44.7)	0.09
Vascular risk factors, No. (%)			
Hypertension	1886 (73.9)	543 (72.7)	0.5
History of hypertension	1345 (52.7)	384 (51.4)	0.5
Systolic BP, mean (SD)	143.6 (21.0)	144.0 (21.1)	0.6
Diastolic BP, mean (SD)	83.4 (11.1)	82.0 (11.8)	0.003
Alcohol consumption:			0.6
Never Drank	618 (24.2)	203 (27.2)	
Past Drinker	616 (24.2)	183 (24.5)	
Light Drinker	331 (13.0)	90 (12.1)	
Moderate Drinker	854 (33.5)	232 (31.1)	
Intermediate Drinker	93 (3.7)	27 (3.6)	
Heavy Drinker	39 (1.5)	12 (1.6)	
Physical activity:			0.0008
None	1130 (44.3)	259 (34.7)	
Light	1211 (47.5)	415 (55.6)	
Moderate or heavy	283 (11.1)	73 (9.8)	
Diabetes mellitus	557 (21.9)	159 (21.3)	0.7
Smoking:			0.2
Never	1214 (47.6)	331 (44.3)	
Former	947 (37.2)	302 (40.4)	
Current	388 (15.2)	114 (15.3)	
Hypercholesterolemia	1628 (63.8)	422 (56.5)	0.0003
Total cholesterol, mean (SD), mg/dL	202.9 (39.7)	202.4 (42.1)	0.7

High-density lipoprotein, mean (SD), mg/dL	46.6 (14.3)	47.5 (15.8)	0.2
Low-density lipoprotein, mean (SD), mg/dL	129.9 (35.9)	126.3 (34.9)	0.02
History of atrial fibrillation	111 (4.4)	32 (4.3)	0.9
History of coronary heart disease	540 (21.2)	164 (22.0)	0.6
Other medical conditions, No. (%)			
Hamilton depression scale score, mean (SD)	3.26 (3.89)	2.85 (3.68)	0.01
Hamilton depression score ≥12	108 (4.3)	31 (4.3)	0.9
Chronic bronchitis, asthma, or emphysema	310 (12.2)	96 (12.9)	0.6
Mini mental state score, mean (SD)	26.0 (3.74)	26.0 (3.82)	0.9
History of migraine headaches	447 (17.6)	100 (13.4)	0.008
Spitzer quality of life index score	9.15 (1.26)	9.08 (1.42)	0.2
Quality of well-being scale score:			
Overall	0.72	0.71	0.4
Physical activities	0.0079	0.016	<0.0001
Social activities	0.0063	0.013	<0.0001
Mobility	0.0061	0.01	0.005
Symptom/problem complexes	0.26	0.26	0.4
Social variables, No. (%)			
Number of people known well enough to visit with in their homes:			0.2
None	94 (3.7)	36 (4.8)	
1 or 2	276 (10.8)	91 (12.2)	
3 or 4	498 (19.5)	155 (20.8)	
5 or more	1681 (66.0)	464 (62.2)	
Number of times talked to someone on telephone in past week:			0.01
Not at all	54 (2.1)	28 (3.8)	
Once	151 (5.9)	38 (5.1)	
Two to six times	700 (27.5)	232 (31.1)	
Once a day or more	1643 (64.5)	448 (60.1)	
Number of times in past week spent with someone who does not live with you:			0.0009
Not at all	527 (20.7)	171 (22.9)	
Once	487 (19.1)	151 (20.2)	
Two to six times	1071 (42.0)	255 (34.2)	
Once a day or more	465 (18.2)	169 (22.7)	
Have someone you can trust and confide in	2358 (92.6)	681 (91.3)	0.2
Feeling lonely:			0.1
Quite often	364 (14.3)	114 (15.3)	
Sometimes	824 (32.4)	210 (28.2)	
Almost never	1359 (53.4)	421 (56.5)	
See relatives and friends:	1557 (61.1)	430 (57.7)	0.09
As often as want			
Is there someone who would give you help if sick:	2093 (82.2)	606 (81.8)	0.8
Years lived in community	28.8 (16.4)	31.7 (17.5)	<0.0001

Table A2. Distributions of biomarkers

Variable	Mean	Median	Lower quartile	Upper quartile	Std Dev	Min	Max	N missing	N
C-reactive protein, mg/L	5.24	2.55	1.10	5.92	8.86	0.04	120.00	311	2240
Interleukin-6, pg/mL	109.72	1.56	0.80	2.88	723.80	0	5000.00	872	1679
Tumor necrosis factor receptor-1, mg/L	2.57	2.28	1.75	2.97	1.72	0	33.22	688	1863
Lipoprotein-associated phospholipase A2 mass	117.00	115.50	96.52	135.89	29.57	12.12	220.94	639	1912
Lipoprotein-associated phospholipase A2 activity	308.65	306.71	245.34	365.54	88.29	28.12	972.59	614	1937
Log transformed variables:									
Log of C-reactive protein levels	0.92	0.93	0.10	1.78	1.23	-3.08	4.79	311	2240
Log of interleukin-6 levels	0.32	0.44	-0.22	1.06	2.00	-5.99	8.52	872	1679
Log of tumor necrosis factor receptor-1 levels	0.81	0.82	0.56	1.09	0.53	-3.10	3.50	688	1863
Without substitutions for 0 values:									
Log of interleukin-6 levels	0.58	0.50	-0.11	1.09	1.57	-5.30	8.52	939	1612
Log of tumor necrosis factor receptor-1 levels	0.81	0.82	0.56	1.09	0.51	-2.41	3.50	690	1861

Table A3. Associations between standardized C-reactive protein levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-1.02	-1.10, -0.93	<.0001
Change in BI score per SD increase in CRP levels	-0.83	-1.54, -0.12	0.02
Additional annual change in BI score per SD increase in CRP levels	-0.08	-0.21, 0.06	0.3
Adjusted for demographics:*			
Annual change in BI score	-1.03	-1.11, -0.94	<.0001
Change in BI score per SD increase in CRP levels	-0.76	-1.53, 0.01	0.054
Additional annual change in BI score per SD increase in CRP levels	-0.10	-0.24, 0.04	0.17
Adjusted for vascular risk factors:**			
Annual change in BI score	-1.03	-1.11, -0.95	<.0001
Change in BI score per SD increase in CRP levels	-0.44	-1.16, 0.27	0.2
Additional annual change in BI score per SD increase in CRP levels	-0.11	-0.25, 0.04	0.15
Adjusted for social variables:†			
Annual change in BI score	-1.02	-1.10, -0.94	<.0001
Change in BI score per SD increase in CRP levels	-0.38	-1.07, 0.32	0.3
Additional annual change in BI score per SD increase in CRP levels	-0.11	-0.25, 0.03	0.14
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.57	-0.71, -0.43	<.0001
Change in BI score per SD increase in CRP levels	-0.36	-0.76, 0.04	0.07
Additional annual change in BI score per SD increase in CRP levels	0.07	-0.04, 0.17	0.2
Adjusted for stroke and MI:π			
Annual change in BI score	-0.39	-0.52, -0.25	<.0001
Change in BI score per SD increase in CRP levels	-0.41	-0.83, -0.002	0.049
Additional annual change in BI score per SD increase in CRP levels	0.04	-0.06, 0.15	0.4

CRP=C-reactive protein; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A4. Associations between log of C-reactive protein levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-1.01	-1.09, -0.93	<.0001
Change in BI score per unit increase in log of CRP levels	-0.72	-1.13, -0.31	0.0006
Additional annual change in BI score per unit increase in log of CRP levels	-0.03	-0.10, 0.05	0.5
Adjusted for demographics:*			
Annual change in BI score	-1.02	-1.10, -0.94	<.0001
Change in BI score per unit increase in log of CRP levels	-0.79	-1.22, -0.36	0.0003
Additional annual change in BI score per unit increase in log of CRP levels	-0.03	-0.10, 0.04	0.4
Adjusted for vascular risk factors:**			
Annual change in BI score	-1.03	-1.11, -0.94	<.0001
Change in BI score per unit increase in log of CRP levels	-0.40	-0.85, 0.05	0.08
Additional annual change in BI score per unit increase in log of CRP levels	-0.03	-0.11, 0.04	0.4
Adjusted for social variables:†			
Annual change in BI score	-1.01	-1.09, -0.93	<.0001
Change in BI score per unit increase in log of CRP levels	-0.33	-0.78, 0.11	0.14
Additional annual change in BI score per unit increase in log of CRP levels	-0.03	-0.11, 0.04	0.4
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.57	-0.72, -0.43	<.0001
Change in BI score per unit increase in log of CRP levels	-0.30	-0.58, -0.02	0.04
Additional annual change in BI score per unit increase in log of CRP levels	0.00	-0.12, 0.13	0.96
Adjusted for stroke and MI:π			
Annual change in BI score	-0.39	-0.53, -0.26	<.0001
Change in BI score per unit increase in log of CRP levels	-0.34	-0.62, -0.06	0.02
Additional annual change in BI score per unit increase in log of CRP levels	0.02	-0.11, 0.14	0.8

CRP=C-reactive protein; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A5. Associations between C-reactive protein levels, according to AHA/CDC categorization, and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-1.01	-1.17, -0.84	<.0001
Change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.28	-0.79, 1.35	0.6
Change in BI score with >3 mg/L CRP, compared to <1 mg/L	-1.89	-3.00, -0.77	0.0009
Additional annual change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.04	-0.17, 0.26	0.7
Additional annual change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.05	-0.26, 0.16	0.6
Adjusted for demographics:*			
Annual change in BI score	-1.01	-1.17, -0.85	<.0001
Change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.61	-0.62, 1.83	0.3
Change in BI score with >3 mg/L CRP, compared to <1 mg/L	-1.83	-3.06, -0.61	0.0034
Additional annual change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.03	-0.18, 0.25	0.8
Additional annual change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.05	-0.26, 0.15	0.6
Adjusted for vascular risk factors:**			
Annual change in BI score	-1.01	-1.18, -0.85	<.0001
Change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.95	-0.31, 2.22	0.1
Change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.76	-2.08, 0.56	0.3
Additional annual change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.04	-0.17, 0.25	0.7
Additional annual change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.05	-0.26, 0.15	0.6
Adjusted for social variables:†			
Annual change in BI score	-1.00	-1.16, -0.84	<.0001
Change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.86	-0.41, 2.12	0.2
Change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.62	-1.94, 0.70	0.4
Additional annual change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.04	-0.16, 0.25	0.7
Additional annual change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.06	-0.26, 0.15	0.6
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.34	-0.64, -0.05	0.02
Change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.77	0.04, 1.50	0.04
Change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.36	-1.11, 0.39	0.3
Additional annual change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	-0.41	-0.88, 0.06	0.086
Additional annual change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.21	-0.59, 0.16	0.3
Adjusted for stroke and MI:π			
Annual change in BI score	-0.23	-0.52, 0.06	0.1
Change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	0.61	-0.08, 1.31	0.08
Change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.49	-1.22, 0.24	0.2
Additional annual change in BI score with 1-3 mg/L CRP, compared to <1 mg/L	-0.28	-0.73, 0.16	0.2
Additional annual change in BI score with >3 mg/L CRP, compared to <1 mg/L	-0.14	-0.50, 0.23	0.5

CRP=C-reactive protein; BI=Barthel index; MI=myocardial infarction
*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index
†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood
‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index
πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A6. Associations between standardized tumor necrosis factor receptor-1 protein levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-1.07	-1.17, -0.97	<.0001
Change in BI score per SD increase in TNFR1 levels	-2.78	-3.65, -1.91	<.0001
Additional annual change in BI score per SD increase in TNFR1 levels	-0.26	-0.46, -0.06	0.01
Adjusted for demographics:*			
Annual change in BI score	-1.06	-1.16, -0.96	<.0001
Change in BI score per SD increase in TNFR1 levels	-1.78	-2.58, -0.98	<.0001
Additional annual change in BI score per SD increase in TNFR1 levels	-0.21	-0.41, -0.02	0.03
Adjusted for vascular risk factors:**			
Annual change in BI score	-1.08	-1.18, -0.98	<.0001
Change in BI score per SD increase in TNFR1 levels	-1.46	-2.45, -0.47	0.004
Additional annual change in BI score per SD increase in TNFR1 levels	-0.29	-0.47, -0.11	0.002
Adjusted for social variables:†			
Annual change in BI score	-1.08	-1.17, -0.98	<.0001
Change in BI score per SD increase in TNFR1 levels	-1.47	-2.49, -0.45	0.005
Additional annual change in BI score per SD increase in TNFR1 levels	-0.30	-0.48, -0.12	0.001
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.66	-0.86, -0.45	<.0001
Change in BI score per SD increase in TNFR1 levels	-0.78	-1.44, -0.12	0.02
Additional annual change in BI score per SD increase in TNFR1 levels	-0.32	-0.67, 0.02	0.07
Adjusted for stroke and MI:π			
Annual change in BI score	-0.52	-0.73, -0.31	<.0001
Change in BI score per SD increase in TNFR1 levels	-0.93	-1.59, -0.26	0.006
Additional annual change in BI score per SD increase in TNFR1 levels	-0.36	-0.69, -0.03	0.03

TNFR1=tumor necrosis factor receptor-1; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A7. Associations between standardized log of tumor necrosis factor receptor-1 protein levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-1.03	-1.12, -0.94	<.0001
Change in BI score per SD increase in log of TNFR1 levels	-2.36	-3.25, -1.48	<.0001
Additional annual change in BI score per SD increase in log of TNFR1 levels	-0.08	-0.21, 0.04	0.2
Adjusted for demographics:*			
Annual change in BI score	-1.02	-1.11, -0.93	<.0001
Change in BI score per SD increase in log of TNFR1 levels	-1.36	-2.20, -0.53	0.001
Additional annual change in BI score per SD increase in log of TNFR1 levels	-0.06	-0.18, 0.07	0.4
Adjusted for vascular risk factors:**			
Annual change in BI score	-1.03	-1.12, -0.94	<.0001
Change in BI score per SD increase in log of TNFR1 levels	-0.93	-1.76, -0.09	0.03
Additional annual change in BI score per SD increase in log of TNFR1 levels	-0.06	-0.19, 0.07	0.3
Adjusted for social variables:†			
Annual change in BI score	-1.02	-1.11, -0.93	<.0001
Change in BI score per SD increase in log of TNFR1 levels	-0.79	-1.64, 0.05	0.066
Additional annual change in BI score per SD increase in log of TNFR1 levels	-0.07	-0.19, 0.06	0.3
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.51	-0.73, -0.28	<.0001
Change in BI score per SD increase in log of TNFR1 levels	-0.56	-0.98, -0.13	0.01
Additional annual change in BI score per SD increase in log of TNFR1 levels	0.03	-0.26, 0.32	0.8
Adjusted for stroke and MI:π			
Annual change in BI score	-0.47	-0.67, -0.27	<.0001
Change in BI score per SD increase in log of TNFR1 levels	-0.63	-1.07, -0.18	0.006
Additional annual change in BI score per SD increase in log of TNFR1 levels	-0.18	-0.35, -0.002	0.047

TNFR1=tumor necrosis factor receptor-1; BI=Barthel index; MI=myocardial infarction; SD=standard deviation

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A8. Associations between log of interleukin-6 levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-0.98	-1.08, -0.89	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.30	-0.61, 0.01	0.057
Additional annual change in BI score per unit increase in log of IL6 levels	-0.04	-0.11, 0.02	0.2
Adjusted for demographics:*			
Annual change in BI score	-0.99	-1.08, -0.90	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.20	-0.51, 0.11	0.2
Additional annual change in BI score per unit increase in log of IL6 levels	-0.04	-0.11, 0.02	0.2
Adjusted for vascular risk factors:**			
Annual change in BI score	-0.99	-1.09, -0.90	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.13	-0.44, 0.19	0.4
Additional annual change in BI score per unit increase in log of IL6 levels	-0.05	-0.11, 0.02	0.2
Adjusted for social variables:†			
Annual change in BI score	-0.98	-1.07, -0.89	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.12	-0.44, 0.20	0.5
Additional annual change in BI score per unit increase in log of IL6 levels	-0.04	-0.11, 0.03	0.2
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.46	-0.61, -0.31	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.09	-0.28, 0.10	0.3
Additional annual change in BI score per unit increase in log of IL6 levels	0.00	-0.09, 0.08	0.9
Adjusted for stroke and MI:π			
Annual change in BI score	-0.26	-0.42, -0.11	0.0009
Change in BI score per unit increase in log of IL6 levels	-0.16	-0.42, 0.11	0.2
Additional annual change in BI score per unit increase in log of IL6 levels	-0.09	-0.21, 0.02	0.11

IL6=interleukin-6; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A9. Associations between standardized lipoprotein phospholipase-A2 mass levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-0.98	-1.07, -0.89	<.0001
Change in BI score per SD increase in LpPLA2 levels	0.18	-0.33, 0.69	0.5
Additional annual change in BI score per SD increase in LpPLA2 levels	-0.01	-0.10, 0.09	0.9
Adjusted for demographics:*			
Annual change in BI score	-0.98	-1.07, -0.89	<.0001
Change in BI score per SD increase in LpPLA2 levels	0.10	-0.46, 0.66	0.7
Additional annual change in BI score per SD increase in LpPLA2 levels	-0.02	-0.11, 0.07	0.7
Adjusted for vascular risk factors:**			
Annual change in BI score	-0.98	-1.07, -0.90	<.0001
Change in BI score per SD increase in LpPLA2 levels	0.01	-0.56, 0.59	0.96
Additional annual change in BI score per SD increase in LpPLA2 levels	-0.01	-0.11, 0.08	0.8
Adjusted for social variables:†			
Annual change in BI score	-0.97	-1.05, -0.88	<.0001
Change in BI score per SD increase in LpPLA2 levels	-0.07	-0.65, 0.50	0.8
Additional annual change in BI score per SD increase in LpPLA2 levels	0.00	-0.10, 0.09	0.9
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.54	-0.71, -0.38	<.0001
Change in BI score per SD increase in LpPLA2 levels	-0.35	-0.71, 0.00	0.052
Additional annual change in BI score per SD increase in LpPLA2 levels	0.07	-0.12, 0.27	0.4
Adjusted for stroke and MI:π			
Annual change in BI score	-0.43	-0.59, -0.27	<.0001
Change in BI score per SD increase in LpPLA2 levels	-0.40	-0.75, -0.04	0.03
Additional annual change in BI score per SD increase in LpPLA2 levels	0.08	-0.12, 0.28	0.4

LpPLA2=lipoprotein phospholipase-A2; BI=Barthel index; MI=myocardial infarction; SD=standard deviation

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A10. Associations between lipoprotein phospholipase-A2 activity levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-0.99	-1.07, -0.90	<.0001
Change in BI score per unit increase in LpPLA2 levels	0.003	-0.003, 0.008	0.4
Additional annual change in BI score per unit increase in LpPLA2 levels	0.0002	-0.001, 0.0008	0.7
Adjusted for demographics:*			
Annual change in BI score	-0.99	-1.07, -0.90	<.0001
Change in BI score per unit increase in LpPLA2 levels	0.004	-0.002, 0.01	0.2
Additional annual change in BI score per unit increase in LpPLA2 levels	-0.0003	-0.001, 0.0008	0.6
Adjusted for vascular risk factors:**			
Annual change in BI score	-0.99	-1.08, -0.90	<.0001
Change in BI score per unit increase in LpPLA2 levels	0.002	-0.004, 0.01	0.5
Additional annual change in BI score per unit increase in LpPLA2 levels	-0.0002	-0.001, 0.0008	0.7
Adjusted for social variables:†			
Annual change in BI score	-0.98	-1.07, -0.90	<.0001
Change in BI score per unit increase in LpPLA2 levels	0.002	-0.004, 0.01	0.5
Additional annual change in BI score per unit increase in LpPLA2 levels	-0.0003	-0.001, 0.0007	0.6
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.52	-0.68, -0.37	<.0001
Change in BI score per unit increase in LpPLA2 levels	0.001	-0.003, 0.005	0.6
Additional annual change in BI score per unit increase in LpPLA2 levels	-0.0004	-0.002, 0.001	0.7
Adjusted for stroke and MI:π			
Annual change in BI score	-0.41	-0.56, -0.26	<.0001
Change in BI score per unit increase in LpPLA2 levels	0.0006	-0.003, 0.004	0.7
Additional annual change in BI score per unit increase in LpPLA2 levels	-0.0003	-0.002, 0.001	0.7

LpPLA2=lipoprotein phospholipase-A2; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A11. Associations between C-reactive protein and interleukin-6 dominant profiles and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-1.03	-1.19, -0.86	<.0001
Change in BI score with IL6-dominant profile€	-0.31	-1.63, 1.02	0.6
Change in BI score with CRP-dominant profile€	-0.71	-2.02, 0.60	0.3
Additional annual change in BI score with IL6-dominant profile€	0.00	-0.23, 0.23	0.98
Additional annual change in BI score with CRP-dominant profile€	0.16	-0.06, 0.38	0.16
Adjusted for demographics:*			
Annual change in BI score	-1.04	-1.20, -0.87	<.0001
Change in BI score with IL6-dominant profile€	0.64	-0.75, 2.03	0.4
Change in BI score with CRP-dominant profile€	-0.93	-2.32, 0.45	0.2
Additional annual change in BI score with IL6-dominant profile€	0.02	-0.21, 0.24	0.9
Additional annual change in BI score with CRP-dominant profile€	0.16	-0.07, 0.38	0.2
Adjusted for vascular risk factors:**			
Annual change in BI score	-1.04	-1.21, -0.88	<.0001
Change in BI score with IL6-dominant profile€	0.07	-1.33, 1.47	0.9
Change in BI score with CRP-dominant profile€	-0.79	-2.16, 0.57	0.3
Additional annual change in BI score with IL6-dominant profile€	0.03	-0.20, 0.25	0.8
Additional annual change in BI score with CRP-dominant profile€	0.15	-0.07, 0.38	0.2
Adjusted for social variables:†			
Annual change in BI score	-1.04	-1.21, -0.88	<.0001
Change in BI score with IL6-dominant profile€	0.02	-1.35, 1.40	0.97
Change in BI score with CRP-dominant profile€	-0.77	-2.13, 0.59	0.3
Additional annual change in BI score with IL6-dominant profile€	0.06	-0.16, 0.28	0.6
Additional annual change in BI score with CRP-dominant profile€	0.15	-0.08, 0.38	0.2
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.48	-0.72, -0.23	0.0001
Change in BI score with IL6-dominant profile€	-0.35	-1.23, 0.52	0.4
Change in BI score with CRP-dominant profile€	-0.01	-0.82, 0.80	0.98
Additional annual change in BI score with IL6-dominant profile€	0.13	-0.27, 0.53	0.5
Additional annual change in BI score with CRP-dominant profile€	-0.21	-0.69, 0.26	0.4
Adjusted for stroke and MI:π			
Annual change in BI score	-0.35	-0.60, -0.10	0.006
Change in BI score with IL6-dominant profile€	-0.32	-1.20, 0.56	0.5
Change in BI score with CRP-dominant profile€	0.00	-0.80, 0.81	0.99
Additional annual change in BI score with IL6-dominant profile€	0.04	-0.36, 0.44	0.8
Additional annual change in BI score with CRP-dominant profile€	0.02	-0.40, 0.43	0.9

CRP=C-reactive protein; IL6=interleukin-6; BI=Barthel index; MI=myocardial infarction
€compared to reference profiles

*adjusted for: baseline age, sex, and race-ethnicity
**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index
†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood
‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index
πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Table A12. Mixed models results

A) Model 1: 'empty' or 'random intercept only' model

Covariance Parameter Estimates								
Cov Parm	**Subject**	**Estimate**	**Standard Error**	**Z Value**	**Pr > Z**	**Alpha**	**Lower**	**Upper**
Intercept	**ID**	134.91	3.9066	34.53	<.0001	0.05	127.57	142.90
Residual		172.18	1.3071	131.73	<.0001	0.05	169.65	174.77

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	91.2782	0.2175	3297	419.65	<.0001

Fit Statistics	
-2 Res Log Likelihood	311566.7
AIC (Smaller is Better)	311570.7
AICC (Smaller is Better)	311570.7
BIC (Smaller is Better)	311582.9

B) Model 2: assessing fixed effect of time

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	99.3657	0.1650	3297	602.36	<.0001
FUF	-1.6889	0.04769	3187	-35.41	<.0001

Fit Statistics	
-2 Res Log Likelihood	290708.1
AIC (Smaller is Better)	290716.1
AICC (Smaller is Better)	290716.1
BIC (Smaller is Better)	290740.5

C) Model 3: with time

Fit Statistics	
-2 Res Log Likelihood	84898.5
AIC (Smaller is Better)	84906.5
AICC (Smaller is Better)	84906.5
BIC (Smaller is Better)	84930.7

D) Model 3a: without time

Fit Statistics	
-2 Res Log Likelihood	85013.2
AIC (Smaller is Better)	85021.2
AICC (Smaller is Better)	85021.2
BIC (Smaller is Better)	85045.4

Table A13. Linear adjusted mixed model with fixed linear time, random intercept, and covariates

Variable	Change in BI score	95% CI	p-value
Intercept	64.38	60.95, 67.81	<.0001
Annual change in BI score	-0.62	-0.74, -0.51	<.0001
Age at baseline, years	-0.14	-0.17, -0.12	<.0001
Male sex	0.32	-0.17, 0.80	0.2
Black, compared to non-Hispanic White	-0.80	-1.44, -0.17	0.014
Hispanic, compared to non-Hispanic White	0.55	-0.09, 1.19	0.09
Diabetes	-0.68	-1.20, -0.16	0.01
Hypertension	0.29	-0.21, 0.78	0.3
Coronary artery disease	0.35	-0.18, 0.87	0.2
Hypercholesterolemia	0.28	-0.16, 0.73	0.2
Any physical activity	0.80	0.36, 1.24	0.0003
Moderate alcohol use	-0.08	-0.55, 0.39	0.7
Former smoker, compared to never	-0.13	-0.60, 0.34	0.6
Current smoker, compared to never	0.11	-0.53, 0.75	0.7
Body mass index	-0.03	-0.07, 0.01	0.17
Married	-0.50	-0.98, -0.02	0.04
Medicaid or no insurance, compared to Medicare or private insurance	-0.65	-1.15, -0.15	0.01
Number of friends	0.15	-0.45, 0.74	0.6
Depression	2.15	1.11, 3.19	<.0001
Mini-mental state score	0.17	0.11, 0.24	<.0001
Spitzer quality of life index score	4.20	4.09, 4.30	<.0001

BI=Barthel index, CI=confidence interval

Table A14. Linear adjusted mixed model with fixed linear time, random intercept, and covariates, with aging variable as time trend

Variable	Change in BI score	95% CI	p-value
Intercept	66.04	62.63, 69.44	<.0001
Annual change in BI score, per year of age	-0.16	-0.19, -0.14	<.0001
Male sex	0.29	-0.20, 0.78	0.2
Black, compared to non-Hispanic White	-0.87	-1.51, -0.23	0.007
Hispanic, compared to non-Hispanic White	0.40	-0.23, 1.04	0.2
Diabetes	-0.68	-1.20, -0.16	0.01
Hypertension	0.36	-0.14, 0.85	0.16
Coronary artery disease	0.41	-0.11, 0.93	0.12
Hypercholesterolemia	0.27	-0.17, 0.71	0.2
Any physical activity	0.74	0.31, 1.18	0.0008
Moderate alcohol use	-0.11	-0.57, 0.36	0.7
Former smoker, compared to never	-0.13	-0.61, 0.34	0.6
Current smoker, compared to never	0.02	-0.62, 0.66	0.9
Body mass index	-0.04	-0.08, 0.005	0.08
Married	-0.54	-1.03, -0.06	0.03
Medicaid or no insurance, compared to Medicare or private insurance	-0.69	-1.19, -0.19	0.007
Number of friends	0.08	-0.51, 0.68	0.8
Depression	2.11	1.07, 3.15	<.0001
Mini-mental state score	0.15	0.09, 0.22	<.0001
Spitzer quality of life index score	4.23	4.13, 4.34	<.0001

BI=Barthel index, CI=confidence interval

Table A15. Adjusted linear mixed models testing associations between levels of inflammatory biomarkers and trajectories of functional status*

Variable	Change in BI score	95% CI	p-value
CRP model:			
Annual change in BI score	-0.47	-0.62, -0.31	<.0001
Change in BI score per unit increase in log of CRP levels	-0.42	-0.71, -0.14	0.004
Additional annual change in BI score per unit increase in log of CRP levels	-0.01	-0.15, 0.14	0.9
TNFR1 model:			
Annual change in BI score	-0.54	-0.70, -0.37	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-1.05	-1.40, -0.70	<.0001
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.43	-0.62, -0.23	<.0001
IL6 model:			
Annual change in BI score	-0.35	-0.54, -0.16	0.0004
Change in BI score per unit increase in log of IL6 levels	-0.20	-0.41, 0.004	0.055
Additional annual change in BI score per unit increase in log of IL6 levels	-0.13	-0.24, -0.02	0.02
LpPLA2 mass model:			
Annual change in BI score	-0.48	-0.64, -0.32	<.0001
Change in BI score per unit increase in LpPLA2 mass levels	-0.36	-0.68, -0.04	0.03
Additional annual change in BI score per unit increase in LpPLA2 mass levels	0.10	-0.05, 0.26	0.2
LpPLA2 activity model:			
Annual change in BI score	-0.43	-0.99, 0.13	0.13
Change in BI score per unit increase in LpPLA2 activity levels	0.0007	-0.003, 0.004	0.7
Additional annual change in BI score per unit increase in LpPLA2 activity levels	-0.0001	-0.002, 0.002	0.9

CRP=C-reactive protein; TNFR1=tumor necrosis factor receptor-1; IL6=interleukin-6; LpPLA2=lipoprotein phospholipase-A2; BI=Barthel index; MI=myocardial infarction

*All models are adjusted for: baseline age, sex, race-ethnicity, diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, body mass index, marital status, insurance, number of friends, depression, mini-mental state score, Spitzer quality of life index, and stroke or myocardial infarction occurring during follow-up

Table A16. Analysis of inflammatory biomarkers as mediating factors*

Variable	Change in BI score	95% CI	p-value
Model without any biomarker:			
Annual change in BI score	-0.42	-0.51, -0.32	<.0001
QIC value	12433		
CRP model:			
Annual change in BI score	-0.39	-0.53, -0.26	<.0001
Change in BI score per unit increase in log of CRP levels	-0.41	-0.82, 0.002	0.051
Additional annual change in BI score per unit increase in log of CRP levels	0.05	-0.06, 0.16	0.4
QIC value	7625.7		
TNFR1 model:			
Annual change in BI score	-0.52	-0.73, -0.31	<.0001
Change in BI score per unit increase in TNFR1 levels	-0.93	-1.60, -0.26	0.007
Additional annual change in BI score per unit increase in TNFR1 levels	-0.36	-0.69, -0.03	0.03
QIC value	6351.9		
IL6 model:			
Annual change in BI score	-0.26	-0.42, -0.11	0.0009
Change in BI score per unit increase in log of IL6 levels	-0.16	-0.42, 0.11	0.2
Additional annual change in BI score per unit increase in log of IL6 levels	-0.09	-0.21, 0.02	0.11
QIC value	5498.2		
LpPLA2 mass model:			
Annual change in BI score	-0.43	-0.59, -0.27	<.0001
Change in BI score per unit increase in LpPLA2 mass levels	-0.40	-0.76, -0.04	0.03
Additional annual change in BI score per unit increase in LpPLA2 mass levels	0.08	-0.12, 0.28	0.4
QIC value	6410		
LpPLA2 activity model:			
Annual change in BI score	-0.32	-0.93, 0.29	0.3
Change in BI score per unit increase in LpPLA2 activity levels	0.006	-0.003, 0.004	0.7
Additional annual change in BI score per unit increase in LpPLA2 activity levels	-0.0003	-0.002, 0.001	0.7
QIC value	6507.6		

CRP=C-reactive protein; TNFR1=tumor necrosis factor receptor-1; IL6=interleukin-6; LpPLA2=lipoprotein phospholipase-A2; BI=Barthel index; MI=myocardial infarction

*All models are adjusted for: baseline age, sex, race-ethnicity, diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, body mass index, marital status, insurance, number of friends, depression, mini-mental state score, Spitzer quality of life index, and stroke or myocardial infarction occurring during follow-up

Figure A1. Distribution of Barthel index scores in the entire prospective cohort

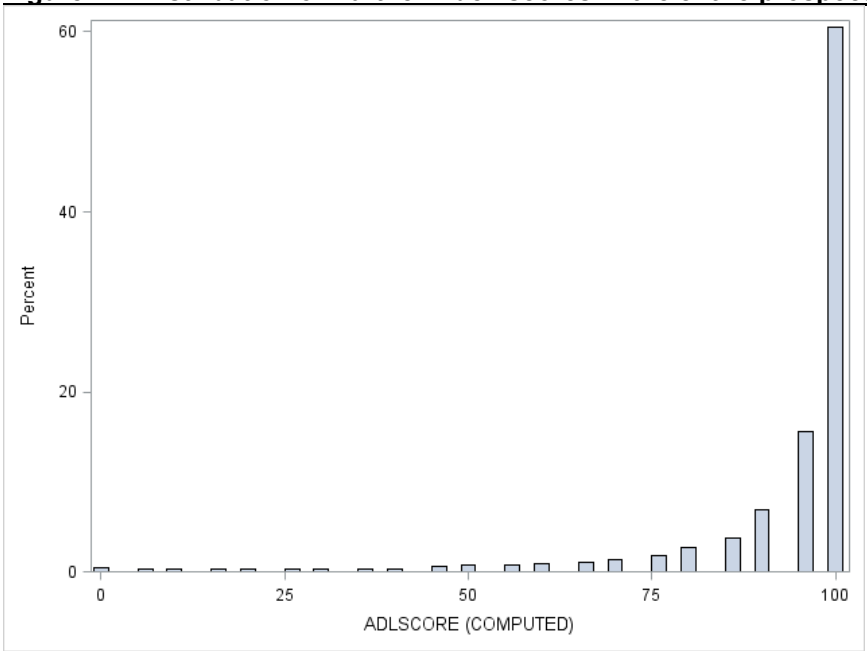
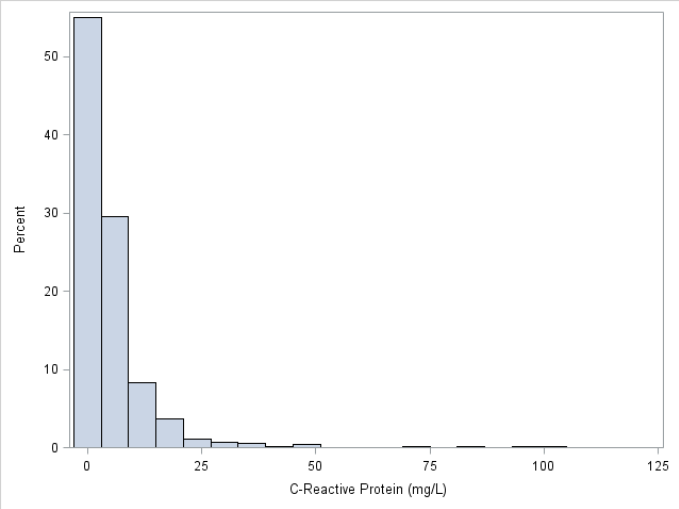
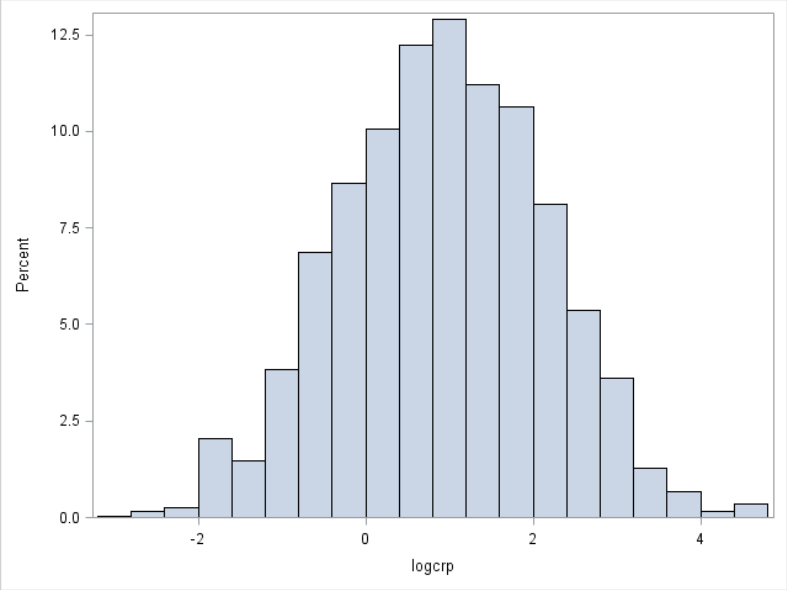


Figure A2. Distributions of raw and transformed inflammatory biomarkers

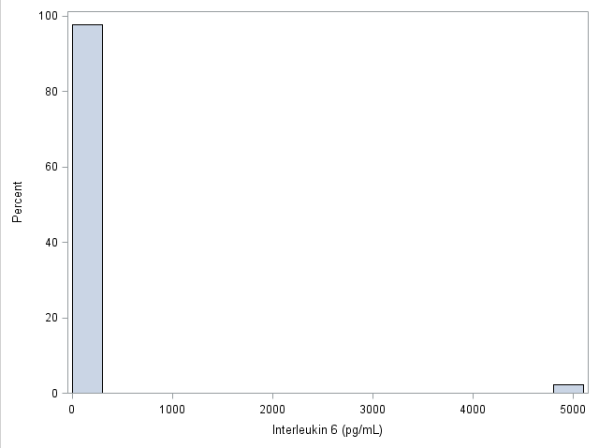
A) C-reactive protein



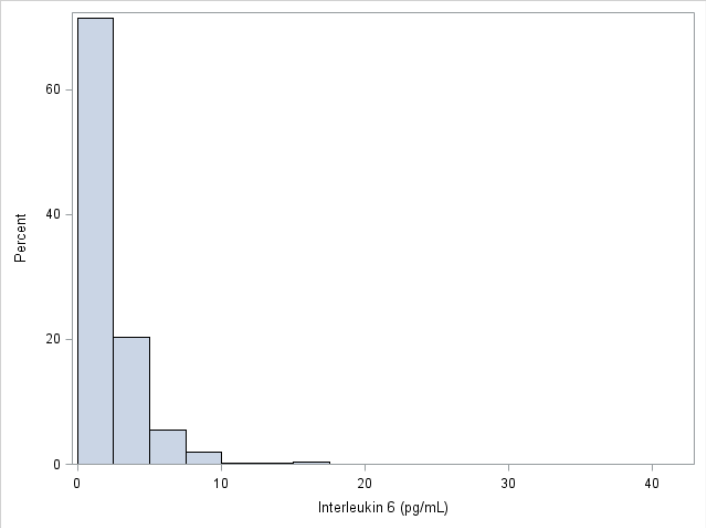
B) log of C-reactive protein



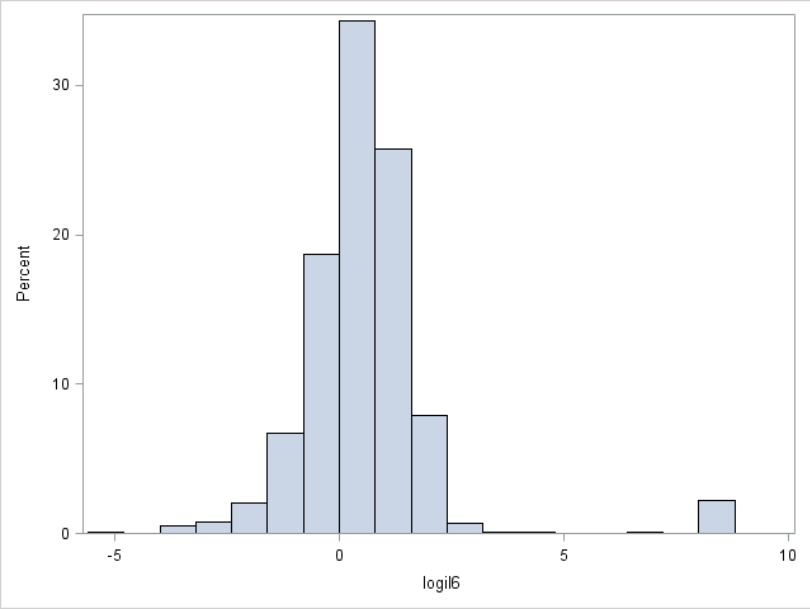
C) Interleukin-6



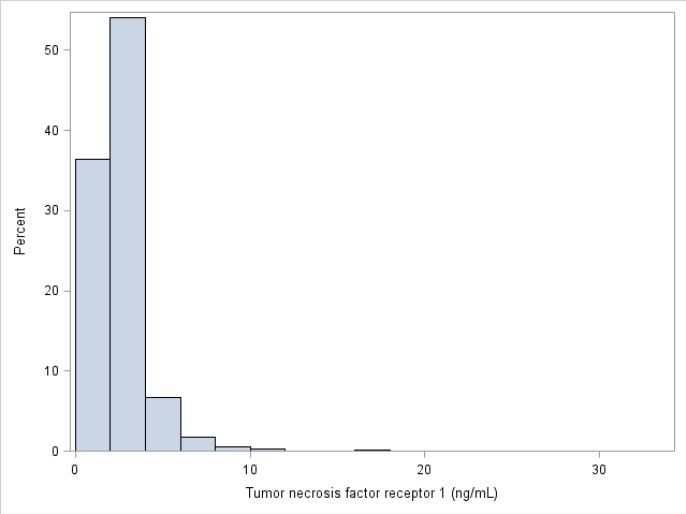
D) Interleukin-6: the graph is truncated, with only IL-6 levels <50 shown



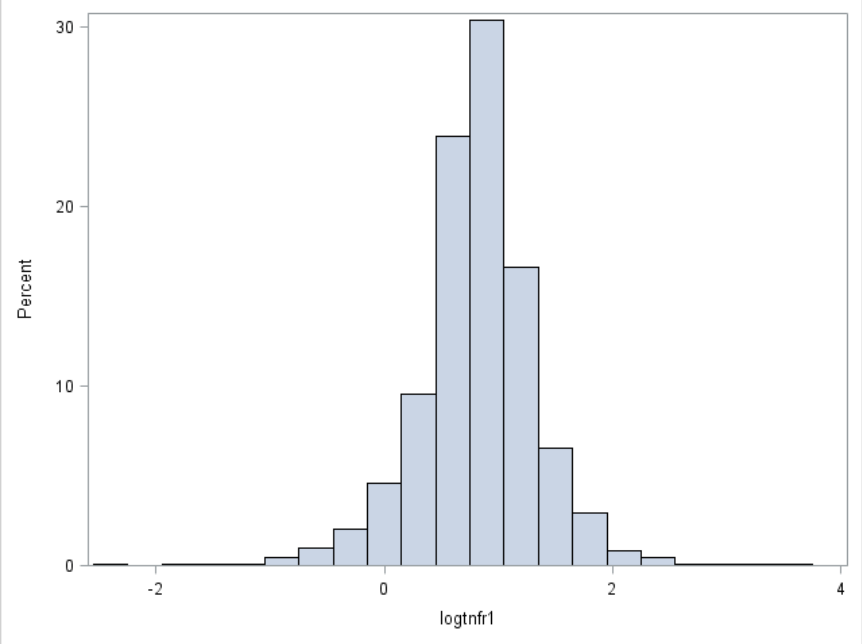
E) log of interleukin-6



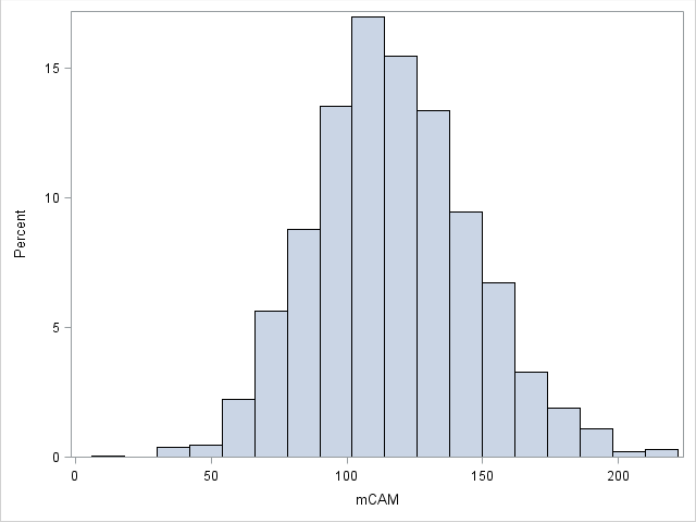
F) Tumor necrosis factor receptor-1



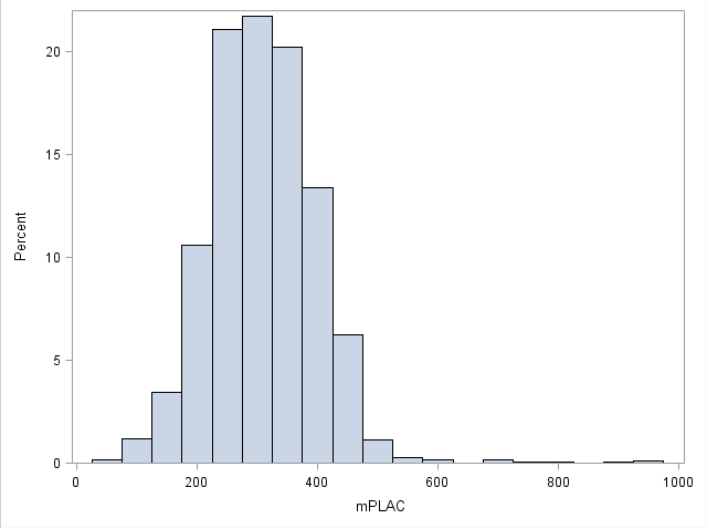
G) log of tumor necrosis factor receptor



H) Lipoprotein phospholipase A2 mass



I) Lipoprotein phospholipase-A2 activity



Analysis B:

Subclinical ischemic brain injury is independently associated with long-term functional decline

Abstract

Background: Stroke is associated with chronic functional decline, but it is unclear whether subclinical brain infarcts (SBI) and white matter hyperintensities (WMH) predict functional decline independently of vascular events.

Methods: In the Northern Manhattan Study, 1290 stroke-free individuals underwent brain MRI and a median of 11 years annual functional assessments with Barthel index (BI; range 0-100) and vascular event surveillance. WMH volume (% total cranial volume) was treated continuously. Generalized estimating equation models tested associations between WMH and SBI, and BI, adjusting for demographic, vascular, cognitive, and social risk factors, and stroke and myocardial infarction during follow-up.

Results: Mean age was 70.6 (SD 9.0) years, 40% of participants were male, 66% Hispanic; 193 (16%) had SBI; and mean WMH was 0.68 (SD 0.84). Functional change was -0.85 BI points per year (95%CI -1.01 to -0.69); among those with SBI there were -0.88 additional points annually (-1.44 to -0.32). In WMH models, annual functional change was -1.04 points (-1.2 to -0.88), with -0.74 additional points annually per SD WMH increase (-0.99 to -0.49).

Conclusions: Subclinical ischemic brain injury predicts doubling of decline in function over time, independently of risk factors and vascular events.

Introduction

Subclinical infarcts are discrete brain infarcts that by definition are not associated with discrete events but are rather detectable only by brain imaging. Similarly, white matter disease generally refers to areas of white matter structural damage in the brain due to vessel dysfunction, which are only detectable by brain imaging. Strikingly, subclinical infarcts have been found to be at least 5 times as prevalent as clinical strokes, suggesting that a focus on discrete clinical stroke events reveals only the tip of the iceberg of the burden of cerebrovascular disease.[50] White matter hyperintensities (WMHs) were present in 96% of individuals older than 60 years of age in CHS and in 95% in the Rotterdam Scan Study.[53] Silent acute infarcts have also been detected in up to 4.2% of individuals with dementia in previous studies.[54]

Traditional vascular risk factors and inflammatory states cause subclinical infarcts and WMH in addition to recurrent clinically evident strokes. The vascular causes of worsening white matter grade have been shown to have a differential impact depending upon initial grade.[57] In the Rush Memory and Aging Project, there was an association between greater WMH volume (WMHV) and lower motor function among those with average and low physical activity.[58] The progression of white matter lesions over time has not been found to have a significant genetic component, and it is likely that behavioral and environmental factors, as well as medical conditions, have a more causative role.[59]

Subclinical infarcts and WMHs have been associated with the occurrence of "hard" vascular outcomes and mortality in multiple studies, including stroke.[60, 61, 65, 66] and longevity.[62] Subclinical infarcts and WMHs have also been associated with cognitive impairment[68, 69] and reduced functional status over the long term.[50, 70] White matter disease may mediate the relationship between hypertension and disability.[71] Even in younger individuals free of cardiovascular disease but at risk due to a family history of early cardiac disease, white matter lesion burden was inversely associated with manual dexterity (as measured by the Grooved Pegboard test).[72] When regional WMHV was tested separately in adjusted models, this association was also seen for WMHV in each brain lobe except for the temporal and occipital lobes. Asymptomatic brain MRI abnormalities, including WMHs and infarcts, have been associated with functional impairment cross-sectionally,[73] at 3 months,[74] and over 4 years of follow-up.[70] In a case-control study performed in Singapore, the burden of small vessel disease and large vessel disease was summarized in a weighted score of "cerebrovascular disease" among 305 cases with cognitive

impairment and 94 controls.[75] A higher cerebrovascular disease score was associated with worse cognitive function. WMHV was associated with global deficits and cerebral microbleeds were associated with domain-specific deficits. In the Leukoaraiosis and Disability study,[76] among 633 older individuals over 2.4 years of follow-up, 29.5% of those with severe WMHV transitioned to death or disability, compared to 10% with mild WMHV. Also, cognitive decline was seen among those who had increase in WMHV over time. In a prior analysis using the MRI cohort of NOMAS,[77] in an adjusted model, WMHV was associated with poorer episodic memory, processing speed, and semantic memory. Among those above the median age, WMHV was associated with poorer episodic and semantic memory.

Despite these prior studies, the influence of SBI and WMHV on longitudinal trajectories of functional status is not well delineated. We hypothesized that SBI and increasing volumes of cerebral white matter disease independently predicted worse baseline functional status and slope of change over time in those free of stroke at baseline. We studied these hypotheses in the Northern Manhattan Study (NOMAS) in an MRI substudy.

Methods

The NOMAS MRI study is a substudy of the prospective cohort that began in 2003 and included individuals: 1) older than age 50 years, 2) without contraindications to MRI, 3) without clinical stroke and 4) able to provide signed informed consent. Baseline characteristics of the MRI cohort (n=1290) are similar to the overall NOMAS prospective study. Each participant received a comprehensive battery of standardized neuropsychological tests at entry. Imaging was performed on a 1.5T MRI system (Philips Medical Systems, Best, Netherlands), including the following sequences: axial T1, axial T2, axial proton density, dual-spin echo, diffusion weighted imaging, and FLAIR. After image acquisition, data were transferred to the University of California at Davis for morphometric analysis of TCV and WMHV using T1 and fluid-attenuated inversion recovery sequences.[77] The images are now stored at Columbia and at the University of Miami and have been further processed by Dr. Clinton Wright for more advanced categorization of WMH and silent brain infarcts (SBI). An operator traced dura mater, and non-brain structures were manually removed from images. Total cranial volume (TCV) constituted the sum of whole brain volume voxels from the T1 segmentation process. WMHV was calculated as “the sum of voxels

≥3.5 standard deviations above the mean image intensity multiplied by pixel dimensions and section thickness."[77]

The FreeSurfer image analysis software (version 5.1) was used to perform volumetric segmentation of lobar gray matter (GM) volumes and hippocampal volumes. As previously described, "all T1-weighted MRIs underwent motion correction, skull stripping, and transformations into Talaraich space before segmentation, identification of gray/white matter boundaries, automated topology correction, and surface deformation. Through 3-dimensional segmentation methods, neuroanatomic labels for regional white matter and cortical GM parcellations were assigned to each voxel using a probabilistic atlas and Bayesian classification rule. FreeSurfer provides an estimate of hippocampal volume, and 68 cortical GM parcellations were summed to estimate frontal, temporal, occipital, and parietal lobe GM volumes using recommended methods."[77]

Explanatory variables

Two datasets were used in this analysis, the "original" dataset and "new" dataset. In the original dataset, total WMH volumes were calculated after correcting for TCV and were treated as a continuous (log transformed) and categorical variable (quartiles) consistent with previous analyses in NOMAS.[206-208] SBIs were defined as lesions greater than 3 mm in size, distinct from the circle of Willis in the basal ganglia, and of similar intensity as cerebrospinal fluid. The location and size of SBIs were recorded.[209] In the new dataset, according to personal communication from Jose Gutierrez, MD, who read the images: "All T1 axial sequences were analyzed systematically. First, we rated small voids (i.e. parenchymal hypodensities) of < 5 mm in axial diameter without associated FLAIR hyperintensities as small perivascular spaces (SPVS). Due to the high number of SPVS observed and the inability to accurately count each of them, a semi-quantitative score was created. The extent of SPVS by anatomical brain region was rated as 0=No SPVS voids, 1=1-3 voids, 2=4 or more voids in each of 12 anatomical brain regions. The total SPVS score was created by adding the subscores for each of the 12 anatomical regions. This method has good to excellent reliability. Parenchymal voids observed in 3D T1 and FLAIR sequences with a diameter of > 5 mm were individually characterized for the purpose of classifying them as large perivascular spaces (LPVS) or lacunar infarcts (LI) in the following brain regions: inferior third of

putamen and anterior perforating substance, upper two thirds of putamen, anterior limb of internal capsule, thalamus, head of the caudate, globus pallidus, subinsular cortex, the frontal, parietal, temporal (including the hippocampus) and occipital white matter. Brainstem areas included the midbrain, pons, medulla, middle cerebellar peduncle and the cerebellum. Each hypodensity was measured in its longest axial diameter and perpendicularly to it. The number of axial images in which the same void was observed was used to calculate the vertical diameter (# slices x slice thickness). The void volume was calculated with the abc/2 formula used to obtain the volume of ellipsoid bodies. Using a cutoff of 5 mm in axial images yielded a minimum effective diameter of 3 mm typically used to differentiate small from large perivascular spaces or infarcts. We also noted the appearance of large hypointensities on the FLAIR sequence, such as cavitation (defined by a corresponding FLAIR hypointensity as compared to the brain parenchyma intensity), lack of cavitation (defined by isointensity), and white matter hyperintensity (WMH, defined by a hyperintense lesion) as well as the presence and extent of a hyperintense rim around each cavitated void (thick, equivocal or absent). Finally, we rated the intensity of each void on proton density images as hypointense, isointense or hyperintense in respect to the lateral ventricle CSF. The collection of these data was performed blindly to demographic or clinical information, and the rater did not define whether the hypointensities were compatible with a LPVS or a LI at the time of the readings."

Location of SBI was recorded according to specific brain region, and then recoded according to cortical or subcortical location. Lacunar infarct location was categorized into cortical, subcortical, and brainstem.

Covariates

All analytic models were adjusted for the following variables: age, sex, body mass index (body weight in kilograms divided by the square of height in meters), self-reported hypercholesterolemia, diabetes mellitus (defined by self-report, fasting blood glucose level $\geq$126 mg/dL, or insulin/oral hypoglycemic use), hypertension (defined as a systolic blood pressure recording $\geq$140 mmHg or a diastolic blood pressure recording $\geq$90 mm Hg based on the average of two blood pressure measurements or the patient's self-report of a history of hypertension or antihypertensive use), smoking (defined as either nonsmoker or smoker within the last year), alcohol use (with moderate alcohol use classified as 1 drink/month to 2

drinks/day), social variables (marital status, insurance status [classified as uninsured, Medicaid, Medicare, or private insurance], number of friends [individuals whom the participant knows well enough to visit in their homes], years living in the community), and cognitive factors (depressed mood, and performance on mini-mental state examination [analyzed as a continuous variable]).

Statistical analysis

The goal of this analysis was to determine whether increasing volumes of cerebral white matter disease and SBI are associated with BI and a steeper slope of decline. Each outcome was analyzed in separate models, using an approach similar to that outlined under Statistical Analysis in Analysis A above.

A sensitivity analysis was performed among those with BI 95 or 100 at 'baseline': for 1087 individuals, this is the ADL measurement closest to and prior to the MRI date. For 193 others (largely Household Members, those enrolled at a later date and identified as members of the household of subjects already enrolled), this was the ADL measurement at the time of MRI. The number of those with BI 95 or 100 at 'baseline' was 267 + 869 = 1136 (see Appendix B7 for distribution of baseline BI scores).

A basic mediation analysis was performed, testing whether imaging findings mediated the effect of diabetes and insurance status. For this analysis, all functional measures, before and after MRI, were included. There were 9210 (53.2%) BI assessments performed before MRI and 8089 (46.8%) performed after MRI. Changes in the magnitude of the effect estimates for diabetes and insurance were calculated when each MRI variable was included in fully adjusted models. A change in magnitude of 10% was deemed to represent meaningful mediation.

The association between location of SBI (cortical, subcortical, and both) and trajectories of functional status was examined in separate models as well as with a multi-level categorical location variable in a single model.

Among those with inflammatory biomarker data in the MRI cohort, a basic mediation analysis was performed testing whether MRI evidence of ischemic injury mediated the association between inflammatory biomarkers and functional status. First, the distributions of inflammatory biomarkers in the MRI cohort were examined. Then, the magnitude of the effect estimates for each biomarker was compared between models with each MRI variable and those without the MRI variable.

The influence of cognition, measured by the MMSE, on functional status was examined in several ways. The association between MMSE and overall functional status was examined, as well as the association with change in functional status over time. Next, interaction with education was examined by including interaction terms between MMSE and education in the model. Two-way interactions between MRI variables and MMSE were examined as well as 3-way interactions among these variables and time.

Due to potential mismeasurement in the hypercholesterolemia variable related to inclusion of statin treatment in the variable definition, the levels of cholesterol subtypes were used in place of the hypercholesterolemia variable in secondary analyses. Apolipoprotein E (APOE) status was adjusted for, and APOE status was not associated with change in BI or slope of change in BI over time (results not shown).

Results

Table B1 compares the distributions of baseline variables among those in the MRI cohort to those in the prospective cohort who were not in the MRI cohort. Those in the MRI cohort were younger, more often male, Hispanic, married, and covered by Medicare, and had more social support. Those in the MRI cohort also had a more favorable vascular risk profile, with lower prevalence of hypertension, diabetes, and coronary artery disease, and had overall lower levels of inflammatory biomarkers. There was a mean of 6.1 (SD 3.4) years between baseline enrollment into NOMAS and time of MRI (Appendix B4). Appendix B7 shows the distribution of baseline BI score (soonest BI measurement at or after MRI) in the MRI cohort; there were 1136 (88.8%) with a score of 95 or 100 at baseline. In the original dataset, among 1238 individuals with data on SBI, there were 193 (15.6%) with SBI and 1045 (84.4%) without. Table B2 shows the distribution of number of SBI per individual, showing a skewed distribution with most individuals having no SBI. According to the new dataset (Appendix B2), 244 (20.2%) had SBI (A), 508 (42.1%) had at least one large perivascular space (B and C), 215 (17.8%) had at least one lacunar infarct (D and E), and most individuals had a total perivascular space score of 4 (193, 16.0%), with a range of 0-22 (F).

Appendix B1 shows the distributions of brain locations for SBIs in the original dataset, first by brain location (A), then summarized by cortical versus subcortical locations (B-D). Out of 1238

individuals, 83 (6.7%) had cortical/superficial SBI location, 88 (7.1%) had subcortical SBI, and 22 (1.8%) had both. Appendix B3 summarizes the location of lacunar infarcts in the new dataset. There were 109 subcortical, 255 cortical, and 13 brainstem lacunar infarcts (C). Out of the entire MRI cohort, there were 117 (9.1%) with cortical SBI, 53 (4.1%) with subcortical SBI, and 44 (3.4%) with both (D).

Table B3 and Figure B1 show the distributions of white matter hyperintensity volume, shown as raw volumes as well as adjusted for total cranial volume. The adjusted volume (WMHV as % of total cranial volume) was used in all analyses presented here. The mean of the maximum follow-up time per person, from time of MRI to last follow-up assessment, was 7.30 years (SD 2.06, median 7.42 years).

As shown in Table B4, the presence of SBI was strongly and consistently associated with accelerated decline in function over time, with the magnitude of the association varying little between the unadjusted model (-1.10 BI points per year, 95% CI -1.64, -0.56) and the full adjusted model (-0.88, 95% CI -1.43, -0.32). SBI was not associated with change in overall functional status. SBI had a similar effect on mobility and non-mobility domains of the BI (Appendix B9), proportional to the portion of the BI comprising each domain.

Similarly, adjusted WMHV was associated with accelerated functional decline, with -0.82 additional BI points per year (95% CI -1.06, -0.57) per unit increase in WMHV in an unadjusted model and -0.74 additional points per year (95% CI -0.99, -0.49) in a fully adjusted model (Table B5). Adjusted WMHV had a similar effect on mobility and non-mobility domains of the BI (Appendix B10), proportional to the portion of the BI comprising each domain.

Using the recent re-definition of SBI ('new' dataset), results were similar (Table B6), with -1.00 additional BI points per year (95% CI -1.49, -0.51) with SBI in an unadjusted model, and -0.89 additional points per year (95% CI -1.42, -0.36) in a fully adjusted model. SBI had a similar effect on mobility and non-mobility domains of the BI (Appendix B11), proportional to the portion of the BI comprising each domain.

In contrast, there were no significant associations between overall BI, change in BI over time, and large perivascular spaces (LPVS) in unadjusted or adjusted models, either with a dichotomous definition of LPVS (Table B7) or one that incorporated the number of LPVS per individual (Table B8). Similarly, when the perivascular space score was tested (Table B9), there were no significant associations with

overall BI score or change in BI over time, in unadjusted or adjusted models, and when mobility and non-mobility domains of the BI were tested separately (Appendix B14).

There was a significant and consistent association between presence of lacunar infarcts and accelerated decline in functional status over time (Table B10), with a change of -1.20 BI additional points per year (95% CI -1.74, -0.66) with lacunar infarcts in an unadjusted model, and -1.11 points per year (95% CI -1.69, -0.53) in a fully adjusted model. Results were similar when the number of lacunar infarcts was tested (Table B11 and Appendix B8), with an additional decline of -0.40 points per year (95% CI -0.72, -0.08) with each additional lacunar infarct. Presence of lacunar infarct had a similar effect on mobility and non-mobility domains of the BI (Appendix B12), and the number of lacunar infarcts had a similar effect (Appendix B13), proportional to the portion of the BI comprising each domain.

Sensitivity analysis was performed among those with BI score of 95 or 100 at baseline (n=1136, Appendix B15). Although the magnitude of overall decline and the magnitude of additional decline with MRI variables were both slightly reduced in most models, there were still highly significant associations paralleling the findings in models among the entire cohort. For example, SBI as defined in the original dataset was associated with additional decline of -0.88 points per year (95% CI -1.44, -0.32) in the entire cohort and -0.79 points per year (95% CI -1.34, -0.24) among those with BI of 95 or 100 at baseline.

Table B12 shows results from an analysis testing whether MRI findings mediate the effect of 2 variables on functional status: diabetes and insurance status. For SBI (original and new definitions), WMHV, and lacunar infarct, addition of the MRI variable reduced the effect estimate for diabetes by about 4%. SPVS did not reduce the effect for diabetes. For all variables except WMHV, adding the MRI variable reduced the effect estimate for Medicaid or insurance (versus Medicare or private insurance) by around 15%, and adding WMHV reduced the effect estimate by 25%.

Table B13 shows models testing the association between location of SBI and functional status. The original dataset was examined first. When tested in separate models, superficial (or cortical) SBI location (-0.79 points per year, 95% CI -1.63, 0.06) and subcortical location (-1.11, 95% CI -1.81, -0.41) were both associated with accelerated decline in functional status over time, but not with overall BI score. When tested in the same model, subcortical location was associated with accelerated decline over time (-0.90 additional BI points per year, 95% CI -1.60, -0.20) but not cortical location (-0.49, 95% CI -1.36,

0.38), and neither was associated with overall BI score. Individuals with both cortical and subcortical SBI had more than double the additional decline in functional status than those with subcortical SBI alone (-2.68 points per year, 95% CI -5.03, -0.32). When the new dataset was examined, cortical (-0.95 points per year, 95% CI -1.72, -0.17) and subcortical (-1.35, 95% CI -2.37, -0.33) SBI were individually associated with accelerated decline in functional status over time, and there was a trend for an association of similar magnitude with both cortical and subcortical SBI (-1.23, 95% CI -2.63, 0.17).

A series of models tested whether MRI evidence of ischemic injury mediated the association between inflammatory biomarkers and functional status. Appendix B5 summarizes the distributions of inflammatory biomarkers (CRP, TNFR1, IL6, and LpPLA2 mass and activity) among those with biomarker data in the MRI cohort (ranging from 610 individuals with IL6 values to 792 with CRP values). Appendix B6 compares the distributions of baseline characteristics between those in the MRI cohort with at least one inflammatory biomarker result (911 [70.6%]) to those without any biomarker result (368 [29.4%]). The only substantive difference in vascular risk factor profile was a higher prevalence of hypercholesterolemia among those with biomarker data compared to those without (64.5% vs. 55.2%). As shown in Table B14, CRP was not associated with overall function or change in functional status over time, but log of CRP levels was associated with accelerated decline in functional status over time. However, adding either SBI or WMHV to the model did not appreciably change this estimate, suggesting no significant mediation effect. There was a similar pattern when the new definition of SBI was examined (Table B18). IL6 and log of IL6 levels were not significantly associated with overall function or change in functional status over time in unadjusted or adjusted models, limiting the evaluation of mediation by MRI variables (Tables B15 and B19). TNFR1 levels were associated with additional decline in BI over time in unadjusted and adjusted models (Table B16), but the addition of SBI or WMHV did not appreciably change the effect estimate for this association. There was a similar pattern when the new definition of SBI was used (Table B20). LpPLA2 mass and activity levels were not associated with overall function or change in function over time in unadjusted or adjusted models, limiting the evaluation of mediation by MRI variables (Table B17). When the association between inflammatory biomarkers and MRI variables was examined (Table B21), no significant associations were found for any of the examined biomarkers as untransformed variables.

Next, the influence of cognition -- as measured by the mini-mental state examination score (MMSE) -- on functional status was examined (Table B22). Higher MMSE was associated with better functional status (0.22 BI points per point of MMSE in the MRI cohort, 95% CI 0.08, 0.35), and when effect of MMSE on slope of functional change was examined, MMSE was associated with a more favorable slope of decline over time (0.04 BI points per year, 95% CI 0.02, 0.06) but not overall function. In the entire cohort but not the MRI cohort, MMSE was associated with more favorable slope of functional decline in those with high school education, compared to those without (0.06 BI points per year, 95% CI 0.01, 0.11).

Sensitivity analysis was also done without BMI in models, due to possible correlation between BMI and hypercholesterolemia, which found no substantive differences in results (results not shown). Also, in secondary analysis, the levels of cholesterol subtypes were examined in place of the hypercholesterolemia variable, and there were no substantive changes in the estimates for the main predictors (results not shown).

The interactions among SBI, cognition, and functional status were further examined in the original dataset in fully adjusted models (Table B23). In a model without interaction terms with time, SBI was associated with lower function (-2.63 BI points, 95% CI -4.87, -0.39) and higher MMSE scores were associated with higher functional status (0.28, 95% CI 0.06, 0.51). When interaction with time was examined, SBI was associated with an additional -0.88 points of decline (95% CI -1.44, -0.32) over time, and MMSE was associated with 0.05 BI points per year (95% CI -0.01, 0.10) per point of MMSE. There was no significant interaction between SBI and MMSE. However, when 3-way interactions with time were examined, there was an annual decline in function overall (-0.89 BI points per year, 95% CI -1.06, -0.71), an additional -0.77 points of decline (95% CI -1.31, -0.24) per year in those with SBI, a reduced slope of decline with highest MMSE scores (0.07 BI points per year, 95% CI 0.02, 0.13), and a steeper decline in functional status per point of MMSE in those with SBI (-0.18 BI points per year, 95% CI -0.32, -0.04). When interactions among WMHV, cognition, and functional status were examined (Table B24), 2-way and 3-way interactions among time, MMSE, and WMHV were not significant in final models.

Interactions among cognition, SBI, and functional status were also examined in the new dataset (Table B25). SBI was associated with -2.60 BI points (95% CI -4.51, -0.69) and MMSE was associated

with 0.24 BI points (95% CI 0.04, 0.45) on average. When interactions with time were examined, SBI was associated with an additional -0.90 BI points per year (95% CI -1.43, -0.36) and MMSE was associated with 0.05 additional BI points per year (95% CI -0.004, 0.11). In the final model testing 3-way interactions, SBI was associated with accelerated functional decline (-0.80 BI points per year, 95% CI -1.32, -0.29), MMSE was associated with reduced decline (0.07 BI points per year, 95% CI 0.01, 0.13), and there was a steeper decline in functional status per point of MMSE in those with SBI (-0.15 BI points per year, 95% CI -0.28, -0.02).

A similar pattern of associations was seen when lacunar infarcts (LI) were tested (Table B26). In the final model testing 3-way interactions, presence of lacunar infarct was associated with accelerated functional decline of -1.03 BI points per year (95% CI -1.60, -0.46), MMSE was associated with reduced decline (0.07 BI points per year, 95% CI 0.01, 0.13), and there was a steeper decline in functional status per point of MMSE in those with LI (-0.15 BI points per year, 95% CI -0.29, -0.01).

Conclusions for Analysis B

The MRI sub-study of NOMAS is a large sub-cohort with unique MRI imaging data on participants. Since individuals from the prospective cohort of NOMAS were enrolled into the MRI sub-study on average 6.1 years from enrollment into NOMAS, the MRI sub-study participants were comparatively younger and healthier, and 88.8% were functionally normal (BI score of 95 or 100) at the time of MRI. Despite healthy risk factor profiles and good functional status, 15.6-20.2% had SBI on imaging, depending on the classification system used. According to the original classification system, SBI location was evenly divided between subcortical (7.1%) and cortical (6.7%) location, whereas with the new classification system there were more cortical (9.1%) than subcortical (4.1%) SBI, and more with both (3.4%) compared to the original system (1.8%). Due to these discrepancies, we present data using both classification systems. For WMHV, the mean value was 0.7% of TCV, with a range up to 6.2%. Although less than the entire prospective cohort, the mean follow-up time in the MRI sub-study was 7.3 years, which allowed robust estimation of long-term trajectories of functional status after MRI.

Using different measures of SBI, we found a strong, consistent, independent, and significant effect on accelerated decline in function over time of around -0.90 BI points per year, over and above the

annual decline in function due to aging. This was seen with both the original and new classification system, with WMHV (per unit increase), and when mobility and non-mobility domains of the BI were examined as separate outcomes. This pattern of association was seen with MRI imaging markers believed to be caused by vascular impairment (SBI, lacunar infarcts, and WMHV) but not with other MRI structural findings, such as LPVS, which are not believed to be caused directly by a primary vascular pathology. There was a greater decline in functional status with increasing number of SBIs and lacunar infarcts, reflecting a dose-response relationship that supports biological plausibility of the association. Also, these associations were seen even among those with no disability at baseline (BI of 95 or 100), which emphasizes the "silent" or "subclinical" nature of these predictors, and yet their strong predictive power on trajectories of functional status.

The causal relationship between MRI findings of subclinical ischemic brain injury and functional decline must be further elucidated. We began to test this relationship by assessing the mediating effect of MRI findings (measured on average 6.1 years after baseline assessment) with baseline diabetes and insurance status, two factors that have been demonstrated to be strong predictors of functional decline in this cohort. Indeed, the addition of MRI markers of subclinical ischemic damage (SBI, lacunar infarct, and WMHV) reduced the effect size for diabetes by about 4%, and reduced the effect size for insurance status by 15-25%. Hence, part of the effects of diabetes and insurance status on functional status may be to cause subclinical ischemic brain injury, which would only be apparent if an MRI were done to image this injury.

We found evidence for a relationship between location of SBI and accelerated functional decline over time, but patterns were not consistent with different measurements of SBI. Using the original classification of SBI, subcortical but not cortical location was associated with accelerated decline over time, and presence of SBI in both locations was associated with the most decline. With the new classification system, the magnitude of additional decline over time with cortical and subcortical SBI was similar, and presence of SBI in both locations was not associated with any incremental decline over time.

We examined the interrelationships among inflammatory biomarkers, MRI imaging findings, and trajectories of functional status. Inflammatory biomarkers were measured at study enrollment, and MRI was done on average 6.1 years later, so the potential mediating effect was tested of MRI evidence of

subclinical brain ischemic injury on the association between inflammatory states and functional status. However, no significant mediating effect was seen for any of the inflammatory biomarkers or MRI measures.

There are well-known associations among cognitive status, education level, and functional status, and we examined these relationships in this analysis as well. We found a significant association between higher cognitive level and improved function, even when adjusting for SBI. Higher cognitive performance was also associated with reduced slope of decline over time in functional status, but when 3-way interactions with time were tested, among those with SBI, there was an inverse relationship between cognition and decline in functional status. This was true in the original dataset as well as the new dataset, and with lacunar infarcts as well as SBI.

Strengths of this study include the large population-based cohort, the accurate assessment of events during follow-up, minimal loss to follow-up, the use of state-of-the-art imaging and measurement of subclinical brain vascular disease, and the repeated measures of functional outcomes that allow trajectory analysis. A limitation of this analysis is that, in the MRI substudy, participants were recruited from the prospective cohort and most often obtained MRI imaging during follow-up instead of at baseline. The MRI cohort selects individuals who will be able to return for follow up and imaging and may reflect a healthy survivor bias, which may reduce power to detect declines in functional status.

Further discussion of the findings of this analysis will be found in the concluding chapter.

Table B1. Baseline characteristics of the cohort, comparing MRI to non-MRI subjects:

Variable	MRI cohort	Non-MRI cohort	p-value
Number of participants, No. (%)	1290 (36.9)	2208 (63.1)	-
Biological characteristics:			
Age, mean (SD), y	64.5 (8.4)	72.2 (10.3)	<0.0001
Body mass index, mean (SD), kg/m^2	28.0 (4.8)	27.8 (5.9)	0.4
Demographics:			
Male, No. (%)	510 (39.5)	790 (35.8)	0.03
Race-ethnicity:			<0.0001
Non-Hispanic white, No. (%)	191 (14.8)	526 (23.8)	
Non-Hispanic black, No. (%)	223 (17.3)	601 (27.2)	
Hispanic, No. (%)	847 (65.7)	1029 (46.6)	
Other, No. (%)	29 (2.3)	51 (2.3)	
Received at least high school education, No. (%)	592 (45.9)	1012 (45.9)	0.9
Highest education achieved, No. (%)			0.005
Eighth grade or less	523 (40.5)	864 (39.2)	
Some high school	175 (13.6)	330 (15.0)	
Completed high school	200 (15.5)	431 (19.5)	
Some college	182 (14.1)	250 (11.3)	
College graduate or more	210 (16.3)	331 (15.0)	
Marital status, No. (%) married	543 (42.1)	634 (28.8)	<0.0001
Health insurance, No. (%)			0.002
Medicaid or no insurance	613 (47.5)	918 (42.0)	
Medicare or private insurance	677 (52.5)	1267 (58.0)	
Medicaid health insurance, No. (%)	418 (32.4)	769 (34.8)	0.1
Medicare health insurance, No. (%)	597 (46.3)	1595 (72.3)	<0.0001
Private insurance, No. (%)	541 (41.9)	929 (42.1)	0.9
Vascular risk factors, No. (%)			
Hypertension	861 (66.7)	1685 (76.4)	<0.0001
History of hypertension	618 (47.9)	1228 (55.6)	<0.0001
Systolic BP, mean (SD)	140.6 (19.8)	145.2 (21.5)	<0.0001
Diastolic BP, mean (SD)	83.6 (10.6)	82.8 (11.6)	0.04
Alcohol consumption:			<0.0001
Never Drank	264 (20.5)	570 (25.8)	
Past Drinker	256 (19.8)	585 (26.5)	
Light Drinker	163 (12.6)	286 (13.0)	
Moderate Drinker	530 (41.1)	659 (29.9)	
Intermediate Drinker	49 (3.8)	78 (3.5)	
Heavy Drinker	28 (2.2)	29 (1.3)	
Physical activity:			0.1
None	564 (44.3)	921 (41.7)	
Any	710 (55.7)	1286 (58.3)	
Diabetes mellitus	245 (19.0)	513 (23.3)	0.003
Smoking:			0.4
Never	612 (47.4)	1032 (46.8)	
Former	496 (38.5)	826 (37.5)	
Current	182 (14.1)	347 (15.7)	
Hypercholesterolemia	797 (61.8)	1356 (61.4)	0.8
Total cholesterol, mean (SD), mg/dL	202.4 (38.3)	2097 (41.1)	0.7
High-density lipoprotein, mean (SD), mg/dL			
Low-density lipoprotein, mean (SD), mg/dL	130.0 (34.8)	128.8 (36.3)	0.4

History of atrial fibrillation	31 (2.4)	116 (5.3)	<0.0001
History of coronary heart disease	177 (13.7)	547 (24.8)	<0.0001
Other medical conditions, No. (%)			
Hamilton depression scale score, mean (SD)	3.1 (3.8)	3.2 (3.9)	0.7
Chronic bronchitis, asthma, or emphysema	120 (9.3)	302 (13.7)	0.0001
Mini mental state score, mean (SD)	26.7 (3.3)	25.6 (3.9)	<0.0001
History of migraine headaches	231 (17.9)	346 (15.7)	0.09
Spitzer quality of life index score	9.3 (1.0)	9.0 (1.4)	<0.0001
Social variables, No. (%)			
Number of years living in community	25.3 (14.9)	31.6 (17.0)	<0.0001
Number of people known well enough to visit with in their homes:			0.002
None	36 (2.8)	104 (4.7)	
1 or 2	124 (9.6)	272 (12.3)	
3 or 4	263 (20.4)	441 (20.0)	
5 or more	867 (67.2)	1387 (62.9)	
Number of times talked to someone on telephone in past week:			0.3
Not at all	24 (1.9)	63 (2.9)	
Once	76 (5.9)	129 (5.9)	
Two to six times	373 (28.9)	639 (29.0)	
Once a day or more	817 (63.3)	1372 (62.3)	
Number of times in past week spent with someone who does not live with you:			0.0004
Not at all	239 (18.5)	502 (22.8)	
Once	294 (22.8)	404 (18.3)	
Two to six times	529 (41.0)	858 (38.9)	
Once a day or more	228 (17.7)	441 (20.0)	
Have someone you can trust and confide in	1211 (93.9)	2013 (91.4)	0.008
Feeling lonely:			0.5
Quite often	172 (13.3)	321 (14.6)	
Sometimes	397 (30.8)	691 (31.4)	
Almost never	721 (55.9)	1189 (54.0)	
See relatives and friends:			0.9
Not as often as want	512 (39.7)	877 (39.9)	
As often as want	778 (60.3)	1324 (60.2)	
Is there someone who would give you help if sick	1108 (86.0)	1779 (80.9)	0.0001
Inflammatory markers, mean (SD):			
CRP (n=792 / 1448)	4.46 (7.26)	5.67 (9.60)	0.0008
logCRP (n=792 / 1448)	0.82 (1.19)	0.98 (1.24)	0.002
IL-6 (n=605 / 1037)	1.97 (3.00)	2.40 (0.12)	0.01
logIL-6 (n=581 / 994)	0.29 (0.98)	0.46 (1.02)	0.001
TNFR1 (n=651 / 1212)	2.23 (0.03)	2.76 (2.02)	<0.0001
mCAM (n=685 / 1227)	116.6 (29.0)	117.2 (29.9)	0.6
mPLAC (n=695 / 1242)	301.8 (90.1)	312.5 (87.1)	0.01

Table B2. Number of silent brain infarcts per subject, original dataset

Number	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1045	84.41	1045	84.41
1	146	11.79	1191	96.20
2	32	2.58	1223	98.79
3	9	0.73	1232	99.52
4	5	0.40	1237	99.92
5	1	0.08	1238	100.00

Table B3. Distribution of white matter hyperintensity volume variables, original dataset

Variable	Mean	Median	Lower Quartile	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
White matter hyperintensity volume	7.84	4.16	2.39	8.64	9.92	0.00	87.89	2	1288
Total cranial volume	1152.27	1142.61	1064.83	1233.11	122.65	819.61	1547.78	2	1288
Adjusted white matter hyperintensity volume	0.007	0.004	0.002	0.008	0.008	0	0.062	2	1288

Table B4. Unadjusted and adjusted models of the association between silent brain infarcts and functional status, using the original dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-0.89	-1.04, -0.74	<.0001
Change in BI with SBI	-0.82	-3.00, 1.36	0.5
Additional annual change with SBI	-1.10	-1.64, -0.56	<.0001
Adjusted for demographics:†			
Annual change in BI	-0.91	-1.06, -0.75	<.0001
Change in BI with SBI	0.97	-1.36, 3.31	0.4
Additional annual change with SBI	-1.11	-1.67, -0.55	<.0001
Adjusted for vascular risk factors:*			
Annual change in BI	-0.91	-1.06, -0.75	<.0001
Change in BI with SBI	1.08	-1.26, 3.41	0.4
Additional annual change with SBI	-1.11	-1.67, -0.55	<.0001
Adjusted for social variables:**			
Annual change in BI	-0.91	-1.06, -0.75	<.0001
Change in BI with SBI	1.21	-1.13, 3.54	0.3
Additional annual change with SBI	-1.10	-1.66, -0.55	0.0001
Adjusted for cognition:π			
Annual change in BI	-0.91	-1.06, -0.75	<.0001
Change in BI with SBI	1.25	-1.09, 3.58	0.3
Additional annual change with SBI	-1.09	-1.64, -0.53	0.0001
Adjusted for quality of life and depression: ††			
Annual change in BI	-0.96	-1.13, -0.80	<.0001
Change in BI with SBI	0.91	-1.62, 3.44	0.5
Additional annual change with SBI	-1.03	-1.61, -0.45	0.0005
Adjusted for stroke and MI: ‡			
Annual change in BI	-0.85	-1.01, -0.69	<.0001
Change in BI with SBI	1.11	-1.27, 3.49	0.4
Additional annual change with SBI	-0.88	-1.43, -0.32	0.002

BI=Barthel index; CI=confidence interval; SBI=silent brain infarct; MI=myocardial infarction
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Table B5. Unadjusted and adjusted models of the association between standardized white matter hyperintensity volume (WMH/TCV) and functional status, using the original dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-1.12	-1.28, -0.97	<.0001
Change in BI with 1 unit increase in WMH	-1.08	-2.08, -0.09	0.03
Additional annual change with 1 unit increase in WMH	-0.82	-1.06, -0.57	<.0001
Adjusted for demographics:†			
Annual change in BI	-1.14	-1.30, -0.98	<.0001
Change in BI with 1 unit increase in WMH	0.13	-0.92, 1.18	0.8
Additional annual change with 1 unit increase in WMH	-0.82	-1.07, -0.57	<.0001
Adjusted for vascular risk factors:*			
Annual change in BI	-1.17	-1.34, -1.00	<.0001
Change in BI with 1 unit increase in WMH	0.30	-0.89, 1.48	0.6
Additional annual change with 1 unit increase in WMH	-0.78	-1.04, -0.52	<.0001
Adjusted for social variables:**			
Annual change in BI	-1.17	-1.34, -1.00	<.0001
Change in BI with 1 unit increase in WMH	0.34	-0.86, 1.53	0.6
Additional annual change with 1 unit increase in WMH	-0.78	-1.04, -0.52	<.0001
Adjusted for cognition:π			
Annual change in BI	-1.17	-1.34, -1.00	<.0001
Change in BI with 1 unit increase in WMH	0.31	-0.89, 1.51	0.6
Additional annual change with 1 unit increase in WMH	-0.78	-1.04, -0.52	<.0001
Adjusted for quality of life and depression: ††			
Annual change in BI	-1.18	-1.34, -1.01	<.0001
Change in BI with 1 unit increase in WMH	0.35	-0.83, 1.52	0.6
Additional annual change with 1 unit increase in WMH	-0.78	-1.04, -0.52	<.0001
Adjusted for stroke and MI: ‡			
Annual change in BI	-1.04	-1.20, -0.88	<.0001
Change in BI with 1 unit increase in WMH	0.59	-0.50, 1.68	0.3
Additional annual change with 1 unit increase in WMH	-0.74	-0.99, -0.49	<.0001

BI=Barthel index; CI=confidence interval; WMH=white matter hyperintensity; TCV=total cranial volume; MI=myocardial infarction

†adjusted for age at time of MRI, sex, race

*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI

**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community

πadditionally adjusted for mini-mental state score

†† additionally adjusted for Spitzer quality of life index and depression

‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Table B6. Unadjusted and adjusted models of the association between silent brain infarcts and functional status, using the new dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-0.86	-1.02, -0.71	<.0001
Change in BI with SBI	-1.20	-2.97, 0.57	0.2
Additional annual change with SBI	-1.00	-1.49, -0.51	<.0001
Adjusted for demographics:†			
Annual change in BI	-0.88	-1.03, -0.72	<.0001
Change in BI with SBI	0.37	-1.55, 2.28	0.7
Additional annual change with SBI	-1.00	-1.50, -0.50	<.0001
Adjusted for vascular risk factors:*			
Annual change in BI	-0.92	-1.09, -0.75	<.0001
Change in BI with SBI	0.47	-1.72, 2.66	0.7
Additional annual change with SBI	-1.00	-1.54, -0.46	0.0003
Adjusted for social variables:**			
Annual change in BI	-0.92	-1.09, -0.75	<.0001
Change in BI with SBI	0.67	-1.55, 2.88	0.6
Additional annual change with SBI	-1.00	-1.53, -0.46	0.0003
Adjusted for cognition:π			
Annual change in BI	-0.92	-1.09, -0.75	<.0001
Change in BI with SBI	0.67	-1.55, 2.89	0.6
Additional annual change with SBI	-0.99	-1.53, -0.46	0.0003
Adjusted for quality of life and depression: ††			
Annual change in BI	-0.93	-1.10, -0.76	<.0001
Change in BI with SBI	0.58	-1.65, 2.81	0.6
Additional annual change with SBI	-0.99	-1.52, -0.45	0.0003
Adjusted for stroke and MI: ‡			
Annual change in BI	-0.82	-0.98, -0.66	<.0001
Change in BI with SBI	1.07	-1.06, 3.20	0.3
Additional annual change with SBI	-0.89	-1.42, -0.36	0.001

BI=Barthel index; CI=confidence interval; SBI=silent brain infarct; MI=myocardial infarction
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Table B7. Unadjusted and adjusted models of the association between large perivascular spaces and functional status, using the new dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-1.01	-1.21, -0.81	<.0001
Change in BI with LPVS	0.14	-0.96, 1.24	0.8
Additional annual change with LPVS	-0.07	-0.37, 0.24	0.7
Adjusted for demographics:†			
Annual change in BI	-1.03	-1.23, -0.83	<.0001
Change in BI with LPVS	-0.17	-1.37, 1.03	0.8
Additional annual change with LPVS	-0.03	-0.34, 0.28	0.8
Adjusted for vascular risk factors:*			
Annual change in BI	-1.04	-1.25, -0.83	<.0001
Change in BI with LPVS	0.13	-1.28, 1.54	0.9
Additional annual change with LPVS	-0.13	-0.46, 0.21	0.4
Adjusted for social variables:**			
Annual change in BI	-1.04	-1.25, -0.83	<.0001
Change in BI with LPVS	0.11	-1.31, 1.53	0.9
Additional annual change with LPVS	-0.13	-0.46, 0.21	0.5
Adjusted for cognition:π			
Annual change in BI	-1.04	-1.25, -0.83	<.0001
Change in BI with LPVS	0.14	-1.27, 1.55	0.8
Additional annual change with LPVS	-0.13	-0.46, 0.21	0.4
Adjusted for quality of life and depression: ††			
Annual change in BI	-1.04	-1.25, -0.84	<.0001
Change in BI with LPVS	0.38	-1.02, 1.78	0.6
Additional annual change with LPVS	-0.15	-0.48, 0.19	0.4
Adjusted for stroke and MI: ‡			
Annual change in BI	-0.92	-1.12, -0.72	<.0001
Change in BI with LPVS	0.74	-0.64, 2.13	0.3
Additional annual change with LPVS	-0.13	-0.46, 0.20	0.4

BI=Barthel index; CI=confidence interval; LPVS=large perivascular space; MI=myocardial infarction
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Table B8. Unadjusted and adjusted models of the association between number of large perivascular spaces and functional status, using the new dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-1.05	-1.23, -0.87	<.0001
Change in BI with 1 additional LPVS	-0.03	-0.52, 0.47	0.9
Additional annual change with 1 additional LPVS	0.03	-0.09, 0.15	0.7
Adjusted for demographics:†			
Annual change in BI	-1.08	-1.26, -0.89	<.0001
Change in BI with 1 additional LPVS	-0.10	-0.63, 0.43	0.7
Additional annual change with 1 additional LPVS	0.05	-0.07, 0.17	0.4
Adjusted for vascular risk factors:*			
Annual change in BI	-1.11	-1.30, -0.91	<.0001
Change in BI with 1 additional LPVS	0.0003	-0.61, 0.61	0.99
Additional annual change with 1 additional LPVS	0.04	-0.08, 0.16	0.5
Adjusted for social variables:**			
Annual change in BI	-1.10	-1.30, -0.91	<.0001
Change in BI with 1 additional LPVS	-0.01	-0.62, 0.59	0.96
Additional annual change with 1 additional LPVS	0.04	-0.08, 0.16	0.5
Adjusted for cognition:π			
Annual change in BI	-1.11	-1.30, -0.91	<.0001
Change in BI with 1 additional LPVS	-0.02	-0.62, 0.58	0.9
Additional annual change with 1 additional LPVS	0.04	-0.08, 0.16	0.5
Adjusted for quality of life and depression: ††			
Annual change in BI	-1.11	-1.30, -0.92	<.0001
Change in BI with 1 additional LPVS	0.08	-0.51, 0.68	0.8
Additional annual change with 1 additional LPVS	0.03	-0.09, 0.15	0.6
Adjusted for stroke and MI: ‡			
Annual change in BI	-0.99	-1.17, -0.80	<.0001
Change in BI with 1 additional LPVS	0.20	-0.39, 0.79	0.5
Additional annual change with 1 additional LPVS	0.04	-0.08, 0.17	0.5

BI=Barthel index; CI=confidence interval; LPVS=large perivascular space; MI=myocardial infarction
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Table B9. Unadjusted and adjusted models of the association between perivascular space score and functional status, using the new dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-0.83	-1.10, -0.56	<.0001
Change in BI with 1 point increase in SPVS	-0.09	-0.25, 0.08	0.3
Additional annual change with 1 point increase in SPVS	-0.04	-0.08, 0.005	0.08
Adjusted for demographics:†			
Annual change in BI	-0.84	-1.11, -0.56	<.0001
Change in BI with 1 point increase in SPVS	0.06	-0.11, 0.24	0.5
Additional annual change with 1 point increase in SPVS	-0.04	-0.08, 0.01	0.08
Adjusted for vascular risk factors:*			
Annual change in BI	-0.90	-1.19, -0.62	<.0001
Change in BI with 1 point increase in SPVS	0.08	-0.12, 0.27	0.4
Additional annual change with 1 point increase in SPVS	-0.03	-0.08, 0.01	0.14
Adjusted for social variables:**			
Annual change in BI	-0.90	-1.19, -0.62	<.0001
Change in BI with 1 point increase in SPVS	0.08	-0.12, 0.27	0.4
Additional annual change with 1 point increase in SPVS	-0.03	-0.08, 0.01	0.14
Adjusted for cognition:π			
Annual change in BI	-0.90	-1.19, -0.62	<.0001
Change in BI with 1 point increase in SPVS	0.08	-0.12, 0.27	0.4
Additional annual change with 1 point increase in SPVS	-0.03	-0.08, 0.01	0.13
Adjusted for quality of life and depression: ††			
Annual change in BI	-0.90	-1.18, -0.61	<.0001
Change in BI with 1 point increase in SPVS	0.14	-0.06, 0.33	0.17
Additional annual change with 1 point increase in SPVS	-0.04	-0.08, 0.01	0.11
Adjusted for stroke and MI: ‡			
Annual change in BI	-0.82	-1.09, -0.54	<.0001
Change in BI with 1 point increase in SPVS	0.15	-0.04, 0.34	0.12
Additional annual change with 1 point increase in SPVS	-0.03	-0.07, 0.02	0.2

BI=Barthel index; CI=confidence interval; SPVS=score of perivascular spaces; MI=myocardial infarction
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Table B10. Unadjusted and adjusted models of the association between lacunar infarcts and functional status, using the new dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-0.85	-1.01, -0.70	<.0001
Change in BI with lacunar infarct	-0.74	-2.62, 1.14	0.4
Additional annual change with lacunar infarct	-1.20	-1.74, -0.66	<.0001
Adjusted for demographics:†			
Annual change in BI	-0.87	-1.02, -0.72	<.0001
Change in BI with lacunar infarct	1.05	-0.99, 3.08	0.3
Additional annual change with lacunar infarct	-1.22	-1.77, -0.66	<.0001
Adjusted for vascular risk factors:*			
Annual change in BI	-0.91	-1.08, -0.75	<.0001
Change in BI with lacunar infarct	1.15	-1.18, 3.48	0.3
Additional annual change with lacunar infarct	-1.20	-1.80, -0.61	<.0001
Adjusted for social variables:**			
Annual change in BI	-0.91	-1.08, -0.75	<.0001
Change in BI with lacunar infarct	1.31	-1.05, 3.67	0.3
Additional annual change with lacunar infarct	-1.20	-1.80, -0.61	<.0001
Adjusted for cognition:π			
Annual change in BI	-0.91	-1.08, -0.75	<.0001
Change in BI with lacunar infarct	1.34	-1.01, 3.70	0.3
Additional annual change with lacunar infarct	-1.21	-1.80, -0.61	<.0001
Adjusted for quality of life and depression: ††			
Annual change in BI	-0.92	-1.09, -0.76	<.0001
Change in BI with lacunar infarct	1.26	-1.12, 3.64	0.3
Additional annual change with lacunar infarct	-1.19	-1.79, -0.60	<.0001
Adjusted for stroke and MI: ‡			
Annual change in BI	-0.81	-0.97, -0.65	<.0001
Change in BI with lacunar infarct	1.61	-0.65, 3.86	0.16
Additional annual change with lacunar infarct	-1.11	-1.69, -0.53	0.0002

BI=Barthel index; CI=confidence interval; MI=myocardial infarction

†adjusted for age at time of MRI, sex, race

*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI

**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community

πadditionally adjusted for mini-mental state score

†† additionally adjusted for Spitzer quality of life index and depression

‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Table B11. Unadjusted and adjusted models of the association between number of lacunar infarcts and functional status, using the new dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-0.90	-1.06, -0.75	<.0001
Change in BI with 1 additional lacunar infarct	-1.05	-2.42, 0.32	0.13
Additional annual change with 1 additional lacunar infarct	-0.51	-0.84, -0.19	0.002
Adjusted for demographics:†			
Annual change in BI	-0.92	-1.07, -0.76	<.0001
Change in BI with 1 additional lacunar infarct	-0.24	-1.71, 1.22	0.7
Additional annual change with 1 additional lacunar infarct	-0.52	-0.85, -0.18	0.003
Adjusted for vascular risk factors:*			
Annual change in BI	-0.97	-1.14, -0.81	<.0001
Change in BI with 1 additional lacunar infarct	-0.32	-1.91, 1.26	0.7
Additional annual change with 1 additional lacunar infarct	-0.45	-0.79, -0.11	0.009
Adjusted for social variables:**			
Annual change in BI	-0.97	-1.14, -0.81	<.0001
Change in BI with 1 additional lacunar infarct	-0.29	-1.90, 1.32	0.7
Additional annual change with 1 additional lacunar infarct	-0.45	-0.79, -0.11	0.009
Adjusted for cognition:π			
Annual change in BI	-0.97	-1.14, -0.81	<.0001
Change in BI with 1 additional lacunar infarct	-0.26	-1.87, 1.35	0.7
Additional annual change with 1 additional lacunar infarct	-0.45	-0.79, -0.11	0.009
Adjusted for quality of life and depression: ††			
Annual change in BI	-0.98	-1.15, -0.82	<.0001
Change in BI with 1 additional lacunar infarct	-0.29	-1.91, 1.32	0.7
Additional annual change with 1 additional lacunar infarct	-0.44	-0.78, -0.11	0.01
Adjusted for stroke and MI: ‡			
Annual change in BI	-0.87	-1.03, -0.71	<.0001
Change in BI with 1 additional lacunar infarct	-0.12	-1.56, 1.31	0.9
Additional annual change with 1 additional lacunar infarct	-0.40	-0.72, -0.08	0.014

BI=Barthel index; CI=confidence interval; MI=myocardial infarction

†adjusted for age at time of MRI, sex, race

*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI

**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community

πadditionally adjusted for mini-mental state score

†† additionally adjusted for Spitzer quality of life index and depression

‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Table B12. Models testing mediation by MRI variables

	Model without mediator			Model with mediator		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Testing SBI, original dataset:*						
Diabetes	-1.57	-2.59, -0.55	0.003	-1.51	-2.55, -0.47	0.004
Medicaid or no insurance	-1.11	-1.81, -0.42	0.002	-0.95	-1.64, -0.27	0.007
SBI, versus no SBI	--	--	--	-1.48	-2.68, -0.27	0.016
Testing adjusted WMHV, original dataset:*						
Diabetes	-1.57	-2.59, -0.55	0.003	-1.53	-2.57, -0.49	0.004
Medicaid or no insurance	-1.11	-1.81, -0.42	0.002	-0.83	-1.51, -0.14	0.018
WMHV, per SD	--	--	--	-1.00	-1.53, -0.48	0.0002
Testing SBI, new dataset:*						
Diabetes	-1.57	-2.59, -0.55	0.003	-1.51	-2.55, -0.47	0.004
Medicaid or no insurance	-1.11	-1.81, -0.42	0.002	-0.91	-1.59, -0.23	0.008
SBI, versus no SBI	--	--	--	-1.13	-2.14, -0.11	0.03
Testing LI, new dataset:*						
Diabetes	-1.57	-2.59, -0.55	0.003	-1.51	-2.55, -0.46	0.005
Medicaid or no insurance	-1.11	-1.81, -0.42	0.002	-0.91	-1.59, -0.23	0.009
LI, versus no LI	--	--	--	-1.24	-2.32, -0.16	0.025
Testing number of LI, new dataset:*						
Diabetes	-1.57	-2.59, -0.55	0.003	-1.46	-2.51, -0.42	0.006
Medicaid or no insurance	-1.11	-1.81, -0.42	0.002	-0.93	-1.60, -0.26	0.007
LI, per additional LI	--	--	--	-0.71	-1.25, -0.16	0.011
Testing SPVS, new dataset:*						
Diabetes	-1.57	-2.59, -0.55	0.003	-1.55	-2.59, -0.51	0.0034
Medicaid or no insurance	-1.11	-1.81, -0.42	0.002	-0.95	-1.63, -0.28	0.006
SPVS, per additional point	--	--	--	0.01	-0.10, 0.11	0.9

BI=Barthel index; CI=confidence interval; SBI=silent brain infarct; WMHV=white matter hyperintensity volume; SD=standard deviation; LI=lacunar infarct; SPVS=score of perivascular spaces; MI=myocardial infarction

*model additionally adjusted for: time of follow-up, age at time of MRI, sex, race-ethnicity, physical activity, alcohol use, body mass index, depression, mini-mental state score, follow-up after MRI, and stroke and myocardial infarction occurring during follow-up.

Table B13. Adjusted models of the association between location of silent brain infarct and functional status*

Variable	Change in BI score	95% CI	p-value
Original dataset, superficial/cortical location:			
Annual change in BI	-0.92	-1.08, -0.76	<.0001
Change in BI with superficial SBI location	0.27	-3.29, 3.83	0.9
Additional annual change with superficial SBI location	-0.79	-1.63, 0.06	0.068
Original dataset, subcortical location:			
Annual change in BI	-0.88	-1.04, -0.72	<.0001
Change in BI with subcortical SBI location	1.21	-1.87, 4.29	0.4
Additional annual change with subcortical SBI location	-1.11	-1.81, -0.41	0.002
Original dataset, testing location:			
Annual change in BI	-0.85	-1.01, -0.69	<.0001
Change in BI with cortical SBI location†	0.70	-2.93, 4.34	0.7
Change in BI with subcortical SBI location†	1.81	-1.14, 4.76	0.2
Change in BI with both cortical and subcortical SBI location†	0.73	-9.15, 10.62	0.9
Additional annual change with cortical SBI location†	-0.49	-1.36, 0.38	0.3
Additional annual change with subcortical SBI location†	-0.90	-1.60, -0.20	0.01
Additional annual change with both cortical and subcortical SBI location†	-2.68	-5.03, -0.32	0.03
New dataset, testing location:			
Annual change in BI	-0.82	-0.98, -0.66	<.0001
Change in BI with cortical SBI location†	2.33	-0.31, 4.98	0.084
Change in BI with subcortical SBI location†	3.54	-0.45, 7.53	0.082
Change in BI with both cortical and subcortical SBI location†	-0.74	-6.84, 5.36	0.8
Additional annual change with cortical SBI location†	-0.95	-1.72, -0.17	0.017
Additional annual change with subcortical SBI location†	-1.35	-2.37, -0.33	0.009
Additional annual change with both cortical and subcortical SBI location†	-1.23	-2.63, 0.17	0.086

BI=Barthel index; CI=confidence interval; MI=myocardial infarction

*models are additionally adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, body mass index, marital status, insurance status, number of friends, mini-mental state score, and stroke and myocardial infarction occurring during follow-up

†versus no SBI

Table B14. Models testing mediation of the MRI markers-functional status association by C-reactive protein, original dataset*

	Model without mediator			Model testing WMH mediation†			Model testing SBI mediation		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted CRP models:									
Annual change in BI	-0.56	-0.66, -0.47	<.0001	-0.56	-0.65, -0.47	<.0001	-0.49	-0.58, -0.39	<.0001
Change in BI with 1 unit increase in CRP	0.00	-0.05, 0.04	0.9	0.00	-0.04, 0.04	0.99	-0.005	-0.05, 0.04	0.8
Additional annual BI change with 1 unit increase in CRP	-0.01	-0.02, 0.005	0.2	-0.01	-0.02, 0.003	0.12	-0.01	-0.02, 0.005	0.2
Change in BI score per unit of mediator	--	--	--	0.75	0.29, 1.21	0.0013	1.15	0.01, 2.30	0.049
Additional annual BI change per unit of mediator	--	--	--	-0.34	-0.46, -0.22	<.0001	-0.45	-0.72, -0.17	0.0014
Adjusted CRP models:‡									
Annual change in BI	-0.47	-0.57, -0.37	<.0001	-0.48	-0.57, -0.38	<.0001	-0.42	-0.52, -0.32	<.0001
Change in BI with 1 unit increase in CRP	0.01	-0.05, 0.08	0.6	0.02	-0.04, 0.08	0.5	0.01	-0.05, 0.07	0.7
Additional annual BI change with 1 unit increase in CRP	-0.01	-0.03, 0.004	0.12	-0.01	-0.03, 0.002	0.082	-0.01	-0.03, 0.004	0.13
Change in BI score per unit of mediator	--	--	--	1.22	0.71, 1.74	<.0001	1.37	0.09, 2.64	0.035
Additional annual BI change per unit of mediator	--	--	--	-0.30	-0.42, -0.18	<.0001	-0.34	-0.60, -0.08	0.011
Unadjusted log of CRP models:									
Annual change in BI	-0.53	-0.63, -0.44	<.0001	-0.54	-0.63, -0.45	<.0001	-0.46	-0.56, -0.36	<.0001
Change in BI with 1 unit increase in log of CRP	-0.04	-0.33, 0.25	0.8	-0.05	-0.33, 0.24	0.7	-0.05	-0.34, 0.24	0.7
Additional annual BI change with 1 unit increase in log of CRP	-0.09	-0.17, -0.01	0.03	-0.09	-0.16, -0.02	0.02	-0.09	-0.16, -0.01	0.03
Change in BI score per unit of mediator	--	--	--	0.74	0.29, 1.20	0.001	1.14	0.0009, 2.28	0.0498
Additional annual BI change per unit of mediator	--	--	--	-0.34	-0.46, -0.22	<.0001	-0.44	-0.72, -0.17	0.0014
Adjusted log of CRP models:‡									

Annual change in BI	-0.46	-0.55, -0.36	<.0001	-0.46	-0.55, -0.37	<.0001	-0.40	-0.50, -0.30	<.0001
Change in BI with 1 unit increase in log of CRP	0.29	-0.11, 0.69	0.15	0.31	-0.07, 0.69	0.11	0.29	-0.11, 0.68	0.15
Additional annual BI change with 1 unit increase in log of CRP	-0.09	-0.17, -0.01	0.02	-0.10	-0.17, -0.02	0.011	-0.09	-0.17, -0.01	0.02
Change in BI score per unit of mediator	--	--	--	1.21	0.70, 1.73	<.0001	1.37	0.11, 2.63	0.03
Additional annual BI change per unit of mediator	--	--	--	-0.30	-0.42, -0.18	<.0001	-0.34	-0.60, -0.08	0.01

* BI=Barthel index score; WMH=white matter hyperintensity volume; SBI=silent brain infarct; CRP=C-reactive protein;
†per standard deviation change
‡models are additionally adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, physical activity, alcohol use, body mass index, insurance status, mini-mental state score, depression, and stroke and myocardial infarction occurring during follow-up

Table B15. Models testing mediation of the MRI markers-functional status association by interleukin-6, original dataset*

	Model without mediator			Model testing WMH mediation†			Model testing SBI mediation		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted IL6 models:									
Annual change in BI	-0.53	-0.66, -0.41	<.0001	-0.54	-0.66, -0.42	<.0001	-0.45	-0.58, -0.33	<.0001
Change in BI with 1 unit increase in IL6	-0.02	-0.10, 0.06	0.7	-0.02	-0.10, 0.06	0.6	-0.01	-0.09, 0.07	0.8
Additional annual BI change with 1 unit increase in IL6	-0.02	-0.07, 0.02	0.3	-0.02	-0.06, 0.02	0.3	-0.03	-0.07, 0.02	0.2
Change in BI score per unit of mediator	--	--	--	0.72	0.20, 1.24	0.007	1.16	-0.11, 2.43	0.074
Additional annual BI change per unit of mediator	--	--	--	-0.34	-0.48, -0.20	<.0001	-0.45	-0.78, -0.12	0.008
Adjusted IL6 models:‡									
Annual change in BI	-0.45	-0.57, -0.33	<.0001	-0.46	-0.58, -0.34	<.0001	-0.40	-0.52, -0.28	<.0001
Change in BI with 1 unit increase in IL6	0.07	-0.06, 0.20	0.3	0.07	-0.05, 0.19	0.3	0.07	-0.06, 0.21	0.3
Additional annual BI change with 1 unit increase in IL6	-0.02	-0.06, 0.02	0.3	-0.02	-0.06, 0.02	0.3	-0.02	-0.07, 0.02	0.3
Change in BI score per unit of mediator	--	--	--	1.13	0.54, 1.71	0.0002	0.98	-0.38, 2.35	0.16
Additional annual BI change per unit of mediator	--	--	--	-0.30	-0.44, -0.16	<.0001	-0.31	-0.61, -0.01	0.046
Unadjusted log of IL6 models:									
Annual change in BI	-0.54	-0.64, -0.44	<.0001	-0.57	-0.67, -0.46	<.0001	-0.45	-0.55, -0.35	<.0001
Change in BI with 1 unit increase in log of IL6	0.11	-0.30, 0.52	0.6	0.08	-0.34, 0.49	0.7	0.13	-0.29, 0.55	0.5
Additional annual BI change with 1 unit increase in log of IL6	-0.10	-0.20, 0.01	0.07	-0.08	-0.18, 0.03	0.16	-0.10	-0.21, 0.004	0.058
Change in BI score per unit of mediator	--	--	--	0.68	0.13, 1.24	0.016	1.32	-0.02, 2.67	0.053
Additional annual BI change per unit of mediator	--	--	--	-0.35	-0.50, -0.20	<.0001	-0.52	-0.87, -0.17	0.004
Adjusted log of IL6 models:‡									

Annual change in BI	-0.45	-0.55, -0.35	<.0001	-0.48	-0.59, -0.38	<.0001	-0.39	-0.50, -0.29	<.0001
Change in BI with 1 unit increase in log of IL6	0.37	-0.14, 0.89	0.15	0.29	-0.21, 0.80	0.3	0.38	-0.13, 0.90	0.1455
Additional annual BI change with 1 unit increase in log of IL6	-0.10	-0.21, 0.02	0.09	-0.08	-0.19, 0.03	0.2	-0.10	-0.22, 0.01	0.0786
Change in BI score per unit of mediator	--	--	--	1.09	0.49, 1.69	0.0004	1.20	-0.24, 2.63	0.10
Additional annual BI change per unit of mediator	--	--	--	-0.30	-0.43, -0.16	<.0001	-0.38	-0.70, -0.05	0.02

* BI=Barthel index score; WMH=white matter hyperintensity volume; SBI=silent brain infarct; IL6=interleukin-6;
†per standard deviation change
‡models are additionally adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, physical activity, alcohol use, body mass index, insurance status, mini-mental state score, depression, and stroke and myocardial infarction occurring during follow-up

Table B16. Models testing mediation of the MRI markers-functional status association by tumor necrosis factor receptor-1, original dataset*

	Model without mediator			Model testing WMH mediation†			Model testing SBI mediation		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted TNFR1 models:									
Annual change in BI	-0.20	-0.56, 0.15	0.3	-0.22	-0.58, 0.13	0.2	-0.14	-0.48, 0.21	0.4
Change in BI with 1 unit increase in TNFR1	-0.50	-1.11, 0.11	0.11	-0.47	-1.07, 0.13	0.12	-0.50	-1.10, 0.11	0.11
Additional annual BI change with 1 unit increase in TNFR1	-0.20	-0.37, -0.03	0.02	-0.19	-0.37, -0.02	0.03	-0.20	-0.37, -0.03	0.02
Change in BI score per unit of mediator	--	--	--	0.80	0.28, 1.33	0.003	1.01	-0.40, 2.42	0.16
Additional annual BI change per unit of mediator	--	--	--	-0.35	-0.49, -0.21	<.0001	-0.46	-0.81, -0.12	0.008
Adjusted TNFR1 models:‡									
Annual change in BI	-0.16	-0.52, 0.21	0.4	-0.18	-0.55, 0.19	0.4	-0.11	-0.47, 0.25	0.6
Change in BI with 1 unit increase in TNFR1	0.21	-0.57, 1.00	0.6	0.17	-0.59, 0.93	0.7	0.19	-0.59, 0.97	0.6
Additional annual BI change with 1 unit increase in TNFR1	-0.18	-0.36, -0.01	0.04	-0.18	-0.36, -0.005	0.04	-0.18	-0.36, -0.01	0.04
Change in BI score per unit of mediator	--	--	--	1.28	0.71, 1.84	<.0001	1.03	-0.51, 2.58	0.2
Additional annual BI change per unit of mediator	--	--	--	-0.31	-0.44, -0.17	<.0001	-0.35	-0.67, -0.03	0.03

* BI=Barthel index score; WMH=white matter hyperintensity volume; SBI=silent brain infarct; TNFR1=tumor necrosis factor receptor-1;
†per standard deviation change
‡models are additionally adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, physical activity, alcohol use, body mass index, insurance status, mini-mental state score, depression, and stroke and myocardial infarction occurring during follow-up

Table B17. Models testing mediation of the MRI markers-functional status association by lipoprotein phospholipase A2, original dataset*

	Model without mediator			Model testing WMH mediation†			Model testing SBI mediation		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted LpPLA2 mass models:									
Annual change in BI	-0.74	-1.12, -0.35	0.0002	-0.79	-1.13, -0.44	<.0001	-0.70	-1.08, -0.32	0.0003
Change in BI with 1 unit increase in LpPLA2 mass	-0.0007	-0.02, 0.02	0.9	-0.003	-0.02, 0.01	0.8	-0.001	-0.02, 0.01	0.9
Additional annual BI change with 1 unit increase in LpPLA2 mass	0.001	-0.002, 0.004	0.4	0.002	-0.001, 0.005	0.2	0.002	-0.002, 0.005	0.3
Change in BI score per unit of mediator	--	--	--	1.00	0.48, 1.51	0.0002	1.32	-0.23, 2.87	0.096
Additional annual BI change per unit of mediator	--	--	--	-0.39	-0.52, -0.26	<.0001	-0.51	-0.87, -0.14	0.007
Adjusted LpPLA2 mass models:‡									
Annual change in BI	-0.58	-0.96, -0.21	0.0022	-0.64	-0.99, -0.29	0.0003	-0.57	-0.94, -0.19	0.003
Change in BI with 1 unit increase in LpPLA2 mass	-0.01	-0.03, 0.01	0.2	-0.01	-0.03, 0.01	0.15	-0.01	-0.03, 0.01	0.2
Additional annual BI change with 1 unit increase in LpPLA2 mass	0.0007	-0.002, 0.004	0.7	0.001	-0.002, 0.004	0.4	0.001	-0.002, 0.004	0.5
Change in BI score per unit of mediator	--	--	--	1.44	0.87, 2.01	<.0001	1.53	-0.16, 3.22	0.076
Additional annual BI change per unit of mediator	--	--	--	-0.34	-0.48, -0.21	<.0001	-0.36	-0.71, -0.02	0.039
Unadjusted LpPLA2 activity models:									
Annual change in BI	-0.56	-0.87, -0.26	0.0003	-0.55	-0.84, -0.26	0.0002	-0.50	-0.80, -0.20	0.0011
Change in BI with 1 unit increase in LpPLA2 activity	0.001	-0.003, 0.006	0.5	0.001	-0.003, 0.006	0.5	0.001	-0.003, 0.005	0.6
Additional annual BI change with 1 unit increase in LpPLA2 activity	0.000	-0.001, 0.001	0.9	-0.0001	-0.001, 0.001	0.8	0.000	-0.001, 0.001	0.98
Change in BI score per unit of	--	--	--	0.96	0.44, 1.48	0.0003	1.37	-0.18, 2.92	0.083

mediator									
Additional annual BI change per unit of mediator	--	--	--	-0.38	-0.51, -0.25	<.0001	-0.51	-0.87, -0.15	0.006
Adjusted LpPLA2 activity models:‡									
Annual change in BI	-0.51	-0.83, -0.19	0.002	-0.50	-0.80, -0.19	0.0013	-0.46	-0.77, -0.15	0.004
Change in BI with 1 unit increase in LpPLA2 activity	-0.0004	-0.006, 0.005	0.9	-0.0002	-0.005, 0.005	0.9	-0.001	-0.006, 0.005	0.9
Additional annual BI change with 1 unit increase in LpPLA2 activity	0.000	-0.001, 0.001	0.9	0.000	-0.001, 0.001	0.9	0.000	-0.001, 0.001	0.9
Change in BI score per unit of mediator	--	--	--	1.38	0.81, 1.95	<.0001	1.46	-0.23, 3.15	0.091
Additional annual BI change per unit of mediator	--	--	--	-0.33	-0.47, -0.20	<.0001	-0.37	-0.71, -0.03	0.03

* BI=Barthel index score; WMH=white matter hyperintensity volume; SBI=silent brain infarct; LpPLA2=lipoprotein phospholipase-A2;
†per standard deviation change
‡models are additionally adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, physical activity, alcohol use, body mass index, insurance status, mini-mental state score, depression, and stroke and myocardial infarction occurring during follow-up

Table B18. Models testing mediation of the MRI markers-functional status association by C-reactive protein, new dataset*

	Model without mediator			Model testing mediation with number of lacunar infarcts			Model testing SBI mediation		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted CRP models:									
Annual change in BI	-0.56	-0.65, -0.46	<.0001	-0.49	-0.58, -0.40	<.0001	-0.48	-0.58, -0.39	<.0001
Change in BI with 1 unit increase in CRP	-0.003	-0.05, 0.04	0.9	-0.003	-0.04, 0.04	0.9	-0.005	-0.05, 0.04	0.8
Additional annual BI change with 1 unit increase in CRP	-0.01	-0.02, 0.01	0.2	-0.01	-0.02, 0.005	0.2	-0.01	-0.02, 0.01	0.2
Change in BI score per unit of mediator	--	--	--	0.52	-0.10, 1.14	0.10	1.13	0.12, 2.14	0.03
Additional annual BI change per unit of mediator	--	--	--	-0.23	-0.40, -0.06	0.008	-0.42	-0.68, -0.15	0.002
Adjusted CRP models:‡									
Annual change in BI	-0.47	-0.57, -0.37	<.0001	-0.42	-0.51, -0.32	<.0001	-0.42	-0.51, -0.32	<.0001
Change in BI with 1 unit increase in CRP	0.02	-0.05, 0.08	0.6	0.02	-0.05, 0.08	0.6	0.01	-0.05, 0.07	0.7
Additional annual BI change with 1 unit increase in CRP	-0.01	-0.03, 0.004	0.13	-0.01	-0.03, 0.004	0.13	-0.01	-0.03, 0.004	0.15
Change in BI score per unit of mediator	--	--	--	0.82	0.13, 1.50	0.02	1.60	0.39, 2.82	0.0098
Additional annual BI change per unit of mediator	--	--	--	-0.19	-0.35, -0.03	0.02	-0.31	-0.57, -0.05	0.019
Unadjusted log of CRP models:									
Annual change in BI	-0.53	-0.62, -0.43	<.0001	-0.46	-0.55, -0.37	<.0001	-0.46	-0.55, -0.36	<.0001
Change in BI with 1 unit increase in log of CRP	-0.02	-0.31, 0.27	0.9	-0.02	-0.31, 0.27	0.9	-0.04	-0.33, 0.25	0.8
Additional annual BI change with 1 unit increase in log of CRP	-0.09	-0.17, -0.01	0.02	-0.09	-0.17, -0.02	0.02	-0.08	-0.16, -0.01	0.03
Change in BI score per unit of mediator	--	--	--	0.51	-0.10, 1.12	0.10	1.12	0.11, 2.12	0.03
Additional annual BI change per unit of mediator	--	--	--	-0.23	-0.40, -0.06	0.008	-0.41	-0.67, -0.14	0.002
Adjusted log of CRP									

models:‡									
Annual change in BI	-0.45	-0.54, -0.36	<.0001	-0.39	-0.48, -0.30	<.0001	-0.40	-0.49, -0.31	<.0001
Change in BI with 1 unit increase in log of CRP	0.31	-0.09, 0.71	0.13	0.31	-0.08, 0.71	0.12	0.29	-0.11, 0.69	0.16
Additional annual BI change with 1 unit increase in log of CRP	-0.09	-0.17, -0.02	0.015	-0.10	-0.17, -0.02	0.01	-0.09	-0.17, -0.01	0.02
Change in BI score per unit of mediator	--	--	--	0.82	0.13, 1.50	0.02	1.56	0.36, 2.77	0.01
Additional annual BI change per unit of mediator	--	--	--	-0.19	-0.35, -0.04	0.02	-0.31	-0.57, -0.05	0.02

* BI=Barthel index score; WMH=white matter hyperintensity volume; SBI=silent brain infarct; CRP=C-reactive protein;
‡models are additionally adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, physical activity, alcohol use, body mass index, insurance status, mini-mental state score, depression, and stroke and myocardial infarction occurring during follow-up

Table B19. Models testing mediation of the MRI markers-functional status association by interleukin-6, new dataset*

	Model without mediator			Model testing mediation with number of lacunar infarcts			Model testing SBI mediation		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted IL6 models:									
Annual change in BI	-0.52	-0.65, -0.39	<.0001	-0.45	-0.58, -0.33	<.0001	-0.43	-0.55, -0.30	<.0001
Change in BI with 1 unit increase in IL6	-0.01	-0.10, 0.07	0.7	-0.02	-0.10, 0.07	0.7	-0.01	-0.09, 0.07	0.8
Additional annual BI change with 1 unit increase in IL6	-0.03	-0.07, 0.02	0.3	-0.02	-0.07, 0.02	0.3	-0.03	-0.07, 0.02	0.2
Change in BI score per unit of mediator	--	--	--	0.45	-0.25, 1.15	0.2	1.10	-0.07, 2.27	0.065
Additional annual BI change per unit of mediator	--	--	--	-0.22	-0.42, -0.02	0.03	-0.47	-0.78, -0.16	0.003
Unadjusted log of IL6 models:									
Annual change in BI	-0.53	-0.63, -0.43	<.0001	-0.49	-0.59, -0.38	<.0001	-0.46	-0.56, -0.35	<.0001
Change in BI with 1 unit increase in log of IL6	0.11	-0.31, 0.53	0.6	0.10	-0.33, 0.52	0.6	0.11	-0.31, 0.53	0.6
Additional annual BI change with 1 unit increase in log of IL6	-0.09	-0.20, 0.01	0.09	-0.09	-0.20, 0.02	0.12	-0.10	-0.20, 0.01	0.078
Change in BI score per unit of mediator	--	--	--	0.28	-0.40, 0.95	0.4	0.85	-0.40, 2.10	02
Additional annual BI change per unit of mediator	--	--	--	-0.18	-0.37, 0.02	0.074	-0.44	-0.77, -0.11	0.0097
Adjusted log of IL6 models:‡									
Annual change in BI	-0.45	-0.55, -0.35	<.0001	-0.42	-0.52, -0.31	<.0001	-0.39	-0.50, -0.29	<.0001
Change in BI with 1 unit increase in log of IL6	0.37	-0.15, 0.90	0.16	0.35	-0.17, 0.88	0.2	0.37	-0.15, 0.89	0.16
Additional annual BI change with 1 unit increase in log of IL6	-0.09	-0.21, 0.02	0.11	-0.09	-0.21, 0.03	0.13	-0.10	-0.21, 0.02	0.099
Change in BI score per unit of mediator	--	--	--	0.42	-0.25, 1.10	0.2	1.25	-0.12, 2.62	0.07
Additional annual BI change	--	--	--	-0.13	-0.30, 0.04	0.14	-0.34	-0.66, -0.02	0.037

per unit of mediator									

* BI=Barthel index score; WMH=white matter hyperintensity volume; SBI=silent brain infarct; IL6=interleukin-6;
‡models are additionally adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, physical activity, alcohol use, body mass index, insurance status, mini-mental state score, depression, and stroke and myocardial infarction occurring during follow-up

Table B20. Models testing mediation of the MRI markers-functional status association by tumor necrosis factor receptor-1, new dataset*

	Model without mediator			Model testing mediation with number of lacunar infarcts			Model testing SBI mediation		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted TNFR1 models:									
Annual change in BI	-0.20	-0.56, 0.16	0.3	-0.11	-0.46, 0.24	0.5	-0.09	-0.44, 0.26	0.6
Change in BI with 1 unit increase in TNFR1	-0.50	-1.12, 0.12	0.12	-0.51	-1.12, 0.10	0.099	-0.47	-1.09, 0.14	0.13
Additional annual BI change with 1 unit increase in TNFR1	-0.20	-0.37, -0.03	0.02	-0.20	-0.37, -0.03	0.023	-0.21	-0.38, -0.04	0.018
Change in BI score per unit of mediator	--	--	--	0.96	0.26, 1.67	0.007	1.41	0.26, 2.57	0.017
Additional annual BI change per unit of mediator	--	--	--	-0.35	-0.56, -0.15	0.0007	-0.52	-0.82, -0.21	0.0008
Adjusted TNFR1 models:‡									
Annual change in BI	-0.15	-0.52, 0.22	0.4	-0.08	-0.45, 0.28	0.7	-0.08	-0.44, 0.29	0.7
Change in BI with 1 unit increase in TNFR1	0.19	-0.60, 0.99	0.6	0.15	-0.62, 0.92	0.7	0.20	-0.58, 0.97	0.6
Additional annual BI change with 1 unit increase in TNFR1	-0.18	-0.36, -0.004	0.046	-0.18	-0.36, -0.01	0.042	-0.19	-0.37, -0.01	0.036
Change in BI score per unit of mediator	--	--	--	1.16	0.37, 1.95	0.004	1.75	0.35, 3.15	0.01
Additional annual BI change per unit of mediator	--	--	--	-0.30	-0.49, -0.10	0.003	-0.39	-0.69, -0.09	0.01

*BI=Barthel index score; WMH=white matter hyperintensity volume; SBI=silent brain infarct; TNFR1=tumor necrosis factor receptor-1;
‡models are additionally adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, physical activity, alcohol use, body mass index, insurance status, mini-mental state score, depression, and stroke and myocardial infarction occurring during follow-up

Table B21. Unadjusted and adjusted models of the association between inflammatory biomarkers and MRI findings, original dataset*

	Outcome: SBI			Outcome: WMH		
Inflammatory biomarker	**Odds ratio**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
CRP, unadjusted model	1.00	0.98, 1.03	0.9	-0.00004	-0.0001, 0.00004	0.3
CRP, adjusted model†	1.01	0.98, 1.04	0.6	-0.00002	-0.0001, 0.00007	0.6
TNFR1, unadjusted model	1.14	0.91, 1.44	0.3	0.0006	-0.0001, 0.0014	0.11
TNFR1, adjusted model†	1.05	0.81, 1.36	0.7	0.00005	-0.0007, 0.0008	0.9
IL6, unadjusted model	1	1, 1.001	0.5	-0.0000003	-0.000002, 0.000001	0.7
IL6, adjusted model†	1	1, 1.001	0.6	-0.0000004	-0.000002, 0.000001	0.6
LpPLA2 mass, unadjusted model	1.01	1.00, 1.01	0.1	0.000008	-0.00001, 0.00003	0.5
LpPLA2 mass, adjusted model†	1.01	0.999,1.02	0.10	0.00002	-0.000005, 0.00004	0.12
LpPLA2 activity, unadjusted model	1	0.998, 1.002	0.9	0.000002	-0.000005, 0.000009	0.6
LpPLA2 activity, adjusted model†	1.001	0.998, 1.003	0.7	0.000005	-0.000002, 0.00001	0.15

*SBI=silent brain infarct; WMH=white matter hyperintensity volume; CRP=C-reactive protein; TNFR1=tumor necrosis factor receptor-1; LpPLA2=lipoprotein phospholipase-A2

†models are adjusted for: age, sex, race-ethnicity, diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, smoking, body mass index, marital status, insurance status, mini-mental state score

Table B22. Models assessing the influence of cognition on functional status*

	Entire cohort			MRI cohort		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Model without interaction terms:†						
Annual change in BI	-0.90	-0.97, -0.84	<.0001	-0.55	-0.61, -0.48	<.0001
Change in BI per point of MMSE	0.57	0.42, 0.71	<.0001	0.22	0.08, 0.35	0.0015
Model with time interaction:†						
Annual change in BI	-2.64	-3.24, -2.04	<.0001	-1.65	-2.27, -1.03	<.0001
Change in BI per point of MMSE	0.20	0.05, 0.35	0.0102	-0.09	-0.21, 0.03	0.16
Additional annual change in BI per point of MMSE	0.07	0.04, 0.09	<.0001	0.04	0.02, 0.06	0.0004
Model with time interaction, with MMSE centered:†						
Annual change in BI	-0.94	-1.00, -0.87	<.0001	-0.57	-0.63, -0.50	<.0001
Change in BI per point of MMSE	0.20	0.05, 0.35	0.0102	-0.09	-0.21, 0.03	0.16
Additional annual change in BI per point of MMSE	0.07	0.04, 0.09	<.0001	0.04	0.02, 0.06	0.0004
Model with education term:†						
Annual change in BI	-0.90	-0.97, -0.84	<.0001	-0.55	-0.61, -0.48	<.0001
Change in BI per point of MMSE	0.59	0.44, 0.74	<.0001	0.23	0.09, 0.37	0.001
High school education, versus less than high school education	-0.65	-1.62, 0.33	0.2	-0.47	-1.30, 0.37	0.3
Model with interaction with education:†						
Annual change in BI	-0.90	-0.97, -0.84	<.0001	-0.55	-0.61, -0.48	<.0001
Change in BI per point of MMSE	0.50	0.33, 0.67	<.0001	0.21	0.07, 0.36	0.004
High school education, versus less than high school education	-11.81	-22.05, -1.57	0.02	-3.15	-14.23, 7.94	0.6
Change in BI per point of MMSE in those with high school education	0.41	0.04, 0.78	0.028	0.10	-0.30, 0.49	0.6
Model with interaction with education, with MMSE centered:†						
Annual change in BI	-0.90	-0.97, -0.84	<.0001	-0.55	-0.61, -0.48	<.0001
Change in BI per point of MMSE	0.50	0.33, 0.67	<.0001	0.21	0.07, 0.36	0.004
High school education, versus less than high school education	-1.02	-2.11, 0.07	0.067	-0.58	-1.60, 0.43	0.3
Change in BI per point of MMSE in those with high school education	0.41	0.04, 0.78	0.028	0.10	-0.30, 0.49	0.6
Model with interaction with education and time, with MMSE centered:†						
Annual change in BI	-0.94	-1.00, -0.87	<.0001	-0.57	-0.63, -0.50	<.0001
Change in BI per point of MMSE	0.13	-0.06, 0.31	0.17	-0.09	-0.23, 0.04	0.2
Additional annual change in BI per point of MMSE	0.07	0.04, 0.09	<.0001	0.04	0.02, 0.06	0.0004
High school education, versus less than high school education	-1.11	-2.21, -0.02	0.047	-0.63	-1.66, 0.39	0.2

Change in BI per point of MMSE in those with high school education	0.44	0.06, 0.82	0.025	0.11	-0.29, 0.51	0.6
Model with interaction with education and time and 3-way interaction, with MMSE centered:†						
Annual change in BI	-0.98	-1.06, -0.90	<.0001	-0.56	-0.64, -0.48	<.0001
Change in BI per point of MMSE	0.22	0.04, 0.41	0.016	-0.11	-0.24, 0.02	0.10
Additional annual change in BI per point of MMSE	0.05	0.02, 0.08	0.0002	0.04	0.02, 0.07	0.0013
High school education, versus less than high school education	-1.26	-2.38, -0.14	0.027	-0.62	-1.65, 0.41	0.2
Change in BI per point of MMSE in those with high school education	0.14	-0.25, 0.52	0.5	0.17	-0.18, 0.53	0.3
Additional annual change in BI per point of MMSE in those with high school education	0.06	0.01, 0.11	0.029	-0.01	-0.06, 0.04	0.8

*BI=Barthel index score; MMSE=mini-mental state examination score

†Model additionally adjusted for: age, sex, race-ethnicity, diabetes, hypertension, hypercholesterolemia, physical activity, alcohol use, body mass index, insurance status, and stroke and myocardial infarction occurring during follow-up

Table B23. Models assessing the influence of cognition and silent brain infarct on functional status, original dataset*

Variable	Change in BI score	95% CI	p-value
Model without interaction terms:†			
Annual change in BI	-0.97	-1.13, -0.82	<.0001
Change in BI with SBI	-2.63	-4.87, -0.39	0.021
Change in BI per point of MMSE	0.28	0.06, 0.51	0.015
Model with time interaction, with MMSE centered:†			
Annual change in BI	-1.00	-1.16, -0.83	<.0001
Change in BI with SBI	-2.63	-4.88, -0.39	0.021
Change in BI per point of MMSE	0.08	-0.17, 0.33	0.5
Additional annual change in BI per point of MMSE	0.05	-0.01, 0.10	0.087
Model with time interactions, with MMSE centered:†			
Annual change in BI	-0.87	-1.04, -0.70	<.0001
Change in BI with SBI	1.07	-1.32, 3.45	0.4
Additional annual change in BI with SBI	-0.88	-1.44, -0.32	0.002
Change in BI per point of MMSE	0.08	-0.17, 0.33	0.5
Additional annual change in BI per point of MMSE	0.05	-0.01, 0.10	0.083
Model with 2-way SBI interactions, with MMSE centered:†			
Annual change in BI	-0.85	-1.01, -0.69	<.0001
Change in BI with SBI	1.20	-1.24, 3.64	0.3
Additional annual change in BI with SBI	-0.88	-1.43, -0.32	0.002
Change in BI per point of MMSE	0.35	0.12, 0.59	0.003
Additional change in BI per point of MMSE in those with SBI	-0.48	-1.22, 0.27	0.2
Model with 3-way interactions with time, with MMSE centered:†			
Annual change in BI	-0.89	-1.06, -0.71	<.0001
Change in BI with SBI	0.93	-1.44, 3.29	0.4
Additional annual change in BI with SBI	-0.77	-1.31, -0.24	0.0045
Change in BI per point of MMSE	0.08	-0.17, 0.33	0.5
Additional annual change in BI per point of MMSE	0.07	0.02, 0.13	0.012
Additional annual change in BI per point of MMSE in those with SBI	-0.18	-0.32, -0.04	0.011

*BI=Barthel index score; SBI=silent brain infarct; MMSE=mini-mental state examination score
†Model additionally adjusted for: age at time of MRI, sex, race-ethnicity, diabetes, hypertension, physical activity, alcohol use, body mass index, insurance status, depression, and stroke and myocardial infarction occurring during follow-up

Table B24. Models assessing the influence of cognition and white matter hyperintensity volume on functional status, original dataset*

Variable	Change in BI score	95% CI	p-value
Model without interaction terms:†			
Annual change in BI	-0.98	-1.14, -0.82	<.0001
Change in BI per SD increase in WMH	-2.33	-3.38, -1.27	<.0001
Change in BI per point of MMSE	0.29	0.06, 0.51	0.013
Model with time interaction, with MMSE centered:†			
Annual change in BI	-1.00	-1.17, -0.84	<.0001
Change in BI per SD increase in WMH	-2.32	-3.38, -1.26	<.0001
Change in BI per point of MMSE	0.09	-0.16, 0.34	0.5
Additional annual change in BI per point of MMSE	0.05	-0.01, 0.10	0.09
Model with time interactions, with MMSE centered:†			
Annual change in BI	-1.06	-1.22, -0.89	<.0001
Change in BI per SD increase in WMH	0.53	-0.58, 1.64	0.3
Additional annual change in BI per SD increase in WMH	-0.73	-0.99, -0.48	<.0001
Change in BI per point of MMSE	0.11	-0.14, 0.36	0.4
Additional annual change in BI per point of MMSE	0.04	-0.02, 0.09	0.16
Model with 2-way SBI interactions, with MMSE centered:†			
Annual change in BI	-1.04	-1.20, -0.88	<.0001
Change in BI per SD increase in WMH	0.55	-0.56, 1.66	0.3
Additional annual change in BI per SD increase in WMH	-0.74	-0.99, -0.49	<.0001
Change in BI per point of MMSE	0.27	0.05, 0.50	0.018
Additional change in BI per point of MMSE per SD increase in WMH	0.01	-0.33, 0.35	0.9
Model with 3-way interactions with time, with MMSE centered:†			
Annual change in BI	-1.06	-1.23, -0.89	<.0001
Change in BI per SD increase in WMH	0.50	-0.61, 1.61	0.4
Additional annual change in BI per SD increase in WMH	-0.73	-0.98, -0.48	<.0001
Change in BI per point of MMSE	0.12	-0.13, 0.37	0.3
Additional annual change in BI per point of MMSE	0.03	-0.02, 0.09	0.2
Additional annual change in BI per point of MMSE per SD increase in WMH	-0.04	-0.11, 0.03	0.3

*BI=Barthel index score; SD=standard deviation; WMH=white matter hyperintensity volume; MMSE=mini-mental state examination score

†Model additionally adjusted for: age at time of MRI, sex, race-ethnicity, diabetes, hypertension, physical activity, alcohol use, body mass index, insurance status, depression, and stroke and myocardial infarction occurring during follow-up

Table B25. Models assessing the influence of cognition and silent brain infarct on functional status, new dataset*

Variable	Change in BI score	95% CI	p-value
Model without interaction terms:†			
Annual change in BI	-0.96	-1.12, -0.81	<.0001
Change in BI with SBI	-2.60	-4.51, -0.69	0.0076
Change in BI per point of MMSE	0.24	0.04, 0.45	0.022
Model with time interaction, with MMSE centered:†			
Annual change in BI	-0.99	-1.16, -0.83	<.0001
Change in BI with SBI	-2.61	-4.51, -0.70	0.0075
Change in BI per point of MMSE	0.03	-0.22, 0.27	0.8
Additional annual change in BI per point of MMSE	0.05	-0.004, 0.11	0.07
Model with time interactions, with MMSE centered:†			
Annual change in BI	-0.84	-1.01, -0.67	<.0001
Change in BI with SBI	1.11	-0.98, 3.20	0.3
Additional annual change in BI with SBI	-0.90	-1.43, -0.36	0.001
Change in BI per point of MMSE	0.02	-0.22, 0.27	0.8
Additional annual change in BI per point of MMSE	0.05	-0.004, 0.11	0.068
Model with 2-way SBI interactions, with MMSE centered:†			
Annual change in BI	-0.82	-0.98, -0.66	<.0001
Change in BI with SBI	1.28	-0.83, 3.39	0.2
Additional annual change in BI with SBI	-0.89	-1.42, -0.36	0.001
Change in BI per point of MMSE	0.35	0.13, 0.57	0.0019
Additional change in BI per point of MMSE in those with SBI	-0.58	-1.19, 0.02	0.059
Model with 3-way interactions with time, with MMSE centered:†			
Annual change in BI	-0.86	-1.03, -0.68	<.0001
Change in BI with SBI	0.99	-1.09, 3.06	0.4
Additional annual change in BI with SBI	-0.80	-1.32, -0.29	0.0023
Change in BI per point of MMSE	0.04	-0.20, 0.29	0.7
Additional annual change in BI per point of MMSE	0.07	0.01, 0.13	0.015
Additional annual change in BI per point of MMSE in those with SBI	-0.15	-0.28, -0.02	0.027

*BI=Barthel index score; SD=standard deviation; SBI=silent brain infarct; MMSE=mini-mental state examination score

†Model additionally adjusted for: age at time of MRI, sex, race-ethnicity, diabetes, hypertension, physical activity, alcohol use, body mass index, insurance status, depression, and stroke and myocardial infarction occurring during follow-up

Table B26. Models assessing the influence of cognition and lacunar infarcts on functional status, new dataset*

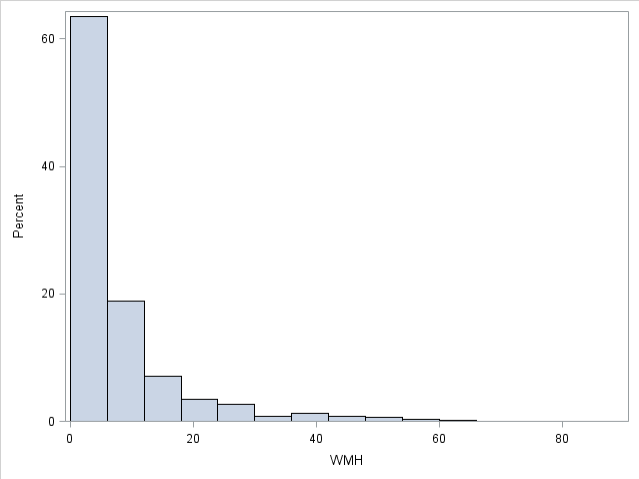
Variable	Change in BI score	95% CI	p-value
Model without interaction terms:†			
Annual change in BI	-0.96	-1.12, -0.80	<.0001
Change in BI with LI	-2.95	-5.03, -0.87	0.0054
Change in BI per point of MMSE	0.24	0.03, 0.45	0.025
Model with time interaction, with MMSE centered:†			
Annual change in BI	-0.99	-1.16, -0.83	<.0001
Change in BI with LI	-2.96	-5.04, -0.89	0.0052
Change in BI per point of MMSE	0.02	-0.22, 0.26	0.9
Additional annual change in BI per point of MMSE	0.05	-0.004, 0.11	0.069
Model with time interactions, with MMSE centered:†			
Annual change in BI	-0.83	-1.00, -0.67	<.0001
Change in BI with LI	1.64	-0.59, 3.86	0.15
Additional annual change in BI with LI	-1.11	-1.70, -0.53	0.0002
Change in BI per point of MMSE	0.03	-0.22, 0.27	0.8
Additional annual change in BI per point of MMSE	0.05	-0.005, 0.11	0.073
Model with 2-way SBI interactions, with MMSE centered:†			
Annual change in BI	-0.81	-0.96, -0.65	<.0001
Change in BI with LI	1.73	-0.49, 3.96	0.13
Additional annual change in BI with LI	-1.11	-1.69, -0.53	0.0002
Change in BI per point of MMSE	0.31	0.09, 0.53	0.0056
Additional change in BI per point of MMSE in those with LI	-0.41	-1.03, 0.22	0.2
Model with 3-way interactions with time, with MMSE centered:†			
Annual change in BI	-0.84	-1.01, -0.68	<.0001
Change in BI with LI	1.49	-0.72, 3.70	0.2
Additional annual change in BI with LI	-1.03	-1.60, -0.46	0.0004
Change in BI per point of MMSE	0.04	-0.20, 0.29	0.7
Additional annual change in BI per point of MMSE	0.07	0.01, 0.13	0.018
Additional annual change in BI per point of MMSE in those with LI	-0.15	-0.29, -0.01	0.037

*BI=Barthel index score; SD=standard deviation; LI=lacunar infarct; MMSE=mini-mental state examination score

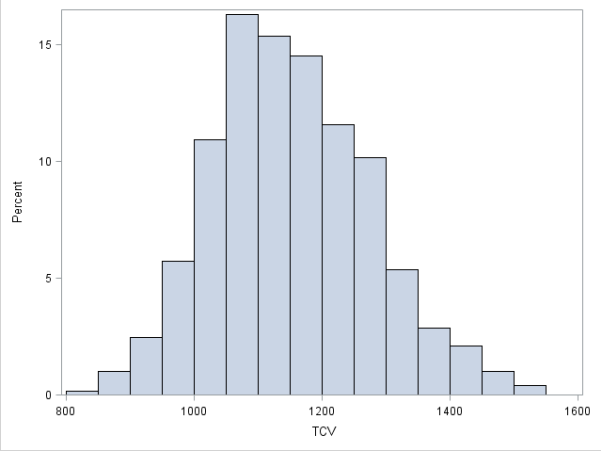
†Model additionally adjusted for: age at time of MRI, sex, race-ethnicity, diabetes, hypertension, physical activity, alcohol use, body mass index, insurance status, depression, and stroke and myocardial infarction occurring during follow-up

Figure B1. Distributions of white matter hyperintensity volume variables

A) white matter hyperintensity volume



B) total cranial volume



Analysis C:

Disability trajectories before and after vascular events: the Cardiovascular Health Study

Abstract

Background: Stroke may contribute to long-term functional decline apart from its acute effects on neurological function. Few studies have compared long-term disability trajectories before and after vascular events or considered the natural history of aging-related decline. We hypothesized that the increase in long-term disability would be steeper post-event than pre-event for stroke but not myocardial infarction (MI).

Methods: In the Cardiovascular Health Study, 5888 Medicare-eligible participants were followed for a mean of 13 years for vascular events and had annual disability assessments with an activities of daily living (ADL) and instrumental ADL scale, modified from the National Center for Health Statistics Supplement on Aging (range 0-12, scored by number of ADLs and IADLs which the participant could not perform, analyzed continuously). During follow-up, 382 participants had ischemic stroke and 395 had MI with $\geq$1 post-event disability assessment. Generalized estimating equations models adjusted for baseline demographics, vascular risk factors, arthritis, cognition, and social support and included a test for different slopes of disability before and after event.

Results: Participants had a mean of 4 disability assessments each pre- and post-stroke and MI. Stroke (0.88, 95% CI 0.57-1.20, p<0.0001) was associated with a greater acute increase in disability than MI (0.20, 0.06-0.35, p=0.006). The annual increase in disability before stroke (0.06 points per year, 0.002-0.12, p=0.04) more than tripled after stroke (0.15 additional points per year, 0.004-0.30, p=0.04). The annual increase in disability before MI (0.04 points per year, 0.004-0.08, p=0.03) did not change significantly after MI (0.02 additional points per year, -0.07-0.11, p=0.7).

Conclusions: In this large population-based study, a trajectory of increasing disability became significantly steeper after stroke but not after MI. This worsening trajectory could be due to delayed cell dysfunction in the brain surrounding stroke, long-term inflammatory profile changes, progressive cardiovascular impairment, or silent recurrent infarcts. Stroke may be considered an ongoing, chronic condition with effects on function instead of a single discrete event.

Introduction

The commonly held view is that stroke is a discrete event and that, following the 3-6 month recovery period after stroke, functional status would remain constant over time if no recurrent events occurred.[34] However, stroke is caused by vascular risk factors such as diabetes and hypertension that have an ongoing and cumulative effect on vessel dysfunction. Also, there are several other biological mechanisms through which ischemic stroke may cause delayed functional decline. One is delayed neuronal death in the ischemic penumbra through apoptosis and necrosis,[210] which may cause delayed functional decline by gradual extension of tissue that is infarcted and not merely at risk of infarction. Furthermore, a single ischemic stroke may cause changes in inflammatory profiles[123] that may have an ongoing deleterious effect on brain structure and function[124] that may persist years after stroke.[125] Another possible mechanism involves progressive cardiovascular impairment and reduced fitness due to static functional impairment after stroke. This cardiovascular, non-neurological impairment adversely effects performance in ADLs.[211] Clinically silent infarcts may also account for long-term decline in function after stroke.

Considering this evidence, stroke may be more effectively considered as an ongoing, chronic condition with effects on function, instead of just a discrete event. We hypothesized that the slope of decline in functional status over the long term is steeper after stroke than before stroke, and that the slope of decline before and after myocardial infarction (MI) is unchanged. There are several reasons for this comparison with MI. MI is a vascular event whose risk factors overlap with those of stroke. It can be considered a type of occlusive, sudden-onset vascular event involving a different area of the body's vasculature than stroke. However, an infarction of cardiac tissue does not result in the kind of impairment that results from an infarction of brain tissue. Also, there is evidence that stroke is not just a "heart attack" of the brain; rather, there are distinct biological properties of the vascular bed of the brain compared to the heart that may have implications for ongoing functional decline.[212] In order to delineate the unique effect of stroke on functional change that results particularly from vascular disease, we used MI as a comparison or control group. We pursued these analyses in the Cardiovascular Health Study (CHS).

Methods

The CHS cohort was recruited from a sex- and age-stratified random sample of Medicare-eligible individuals in North Carolina, California, Maryland, and Pennsylvania.[213] Potential participants were sampled from Medicare eligibility lists in each area. Eligibility criteria included age ≥65 years, not institutionalized, expected to reside in the area for 3 years, and able to provide informed consent. Participants needing a wheelchair or receiving hospice care, radiation treatment, or chemotherapy were excluded. The initial sample of 5,201 participants, recruited from 1989 to 1990, was enriched with the addition of 687 African-American men and women meeting the same eligibility criteria who were recruited from 1992 to 1993, for a combined cohort of 5,888 participants.

Baseline Evaluation

Sociodemographic, functional, and health data were obtained from interviews, clinical examinations, medical record abstraction, and publicly released Medicare claims data, as outlined in previous publications.[213, 214]

Follow-up

CHS has collected data on functional status, extent of social network, cognitive status, and depression annually over 11 years of follow-up through in-person interviews and examinations. Potential events are identified through contact with participants or proxies. Data on incident vascular events such as stroke are collected at local sites, and this abstracted data is reviewed and adjudicated by a centralized cerebrovascular disease endpoint committee. Events are classified as ischemic (lacunar, cardioembolic, atherosclerotic, or indeterminate), hemorrhagic (subarachnoid, intraparenchymal, or indeterminate), or unknown. Since there is no data about stroke severity, we used stroke subtype as a proxy for severity in secondary analysis. Potential MIs occurring during follow-up were reviewed by a specialist outcome committee and included review of clinical history of cardiac symptoms, elevated cardiac enzyme levels, and serial electrocardiographic changes.

Study outcomes

Functional status was measured by the ADL/IADL scale, modified from the National Center for Health Statistics Supplement on Aging[215] and the New Haven Established Populations for Epidemiologic Studies of the Elderly Study.[216] The form assesses general level of physical functioning and mobility, and ability to carry out ADLs and instrumental ADLs (Appendix C1). The scale was scored from 0 to 12 based on the number of ADLs and IADLs with which the participant reported having difficulty or could not perform. The scores were analyzed as a continuous variable as in previous research in this cohort.[214, 217] In secondary analysis, the scale was dichotomized as non-disabled (score of 0) and disabled (score $\geq$1).

Explanatory variables

The course of repeated measures of functional status were modeled, and the primary explanatory variable of interest was time of follow-up assessment in years, ranging from 0 (baseline) to the maximum time of follow-up.

Other covariates were as follows. Demographic variables included age, sex, race-ethnicity, and level of education, defined by self-assessment. Vascular risk factors included hypertension, diabetes mellitus, cardiac disease, hyperlipidemia *(*defined as lipid lowering therapy use or fasting total cholesterol level >240 mg/dL*)*, smoking, alcohol consumption, and physical activity, defined by self-report. The strength of participants' social networks was assessed with the Lubben Social Network Scale,[218] a validated 10-item measure that includes assessments of five aspects of social networks: family networks, friend networks, helping others, confidant relationships, and living arrangements. The total score is a sum of the questions, with scores ranging from 0 to 50. Higher scores indicate larger social networks. The mean total score ranged from 32.34 (SD 7.42) at baseline to 30.73 (SD 7.89) at 11 years of follow-up. Depression was measured by the Centers for Epidemiologic Studies Depression (CES-D) scale,[219] using a cutoff score of >9 for diagnosis of depression. The Mini-Mental State Examination score[220] was assessed at 1 year of follow-up. Personal income was defined as total family income before taxes from all sources in the past 12 months and was selected from a response card as one of the following: under $5000; $5000–$7999; $8000–$11,999; $12000–$15999; $16,000–$24,999; $25,000–$34,999; $35,000–$49,999; over $50,000. For the analyses, income was modeled as an ordinal categorical variable based

on three income groups (<$12,000, $12,000–$34,999, ⩾$35,000), based upon prior analyses in this cohort.[221]

Statistical analysis

The distributions of baseline characteristics were examined. The distribution of follow-up time and the frequencies of occurrence of stroke and cardiac events during follow-up were examined. The frequencies of functional assessments before and after stroke and MI were calculated. The unadjusted distributions of functional scores were summarized among those who had stroke and those who had MI during follow-up.

Stroke cohort The goal of the analysis was to determine whether the slope of functional status was different before and after stroke. For this analysis, only those who experienced ischemic stroke during follow-up and had ≥1 follow-up disability assessment after stroke were included. Due to correlations among repeated measures of outcomes in the same individual, regression models based upon GEE will be used, with an identity link function for continuous variables, and a logit link function for dichotomous variables.

Any assessments of functional status occurring within the 6 months after stroke were ignored, since the course of recovery during this period is well-documented, and our interest is the long-term course of functional status after this initial period of recovery. There were 163 functional assessments within 6 months of stroke. Follow-up was censored at the time of recurrent stroke. The primary covariate of interest was the time of follow-up, and the parameter term associated with this signified the slope of decline in functional status and QOL. The model included a product term (between a dummy variable of post-stroke status, and time of follow-up) that allowed for a different slope before and after stroke, and allowed for a direct test for a significant difference in slope, as follows:

$Y = \text{intercept} + \beta_1 * FU + \beta_2 * FU * \text{poststroke} + \beta_3 * \text{poststroke} + \sum \beta * \text{covariates},$

where FU=follow-up time, poststroke=0 if the time of follow-up was before the stroke, and 1 if after the stroke.

In model building, we sequentially added groups of variables defined by epidemiological relevance. The first model included no covariates, and successive models included demographic

variables, vascular risk factors, social variables, and cognitive and mood factors. These models assessed the relationship between explanatory variables and repeated measurements of functional status. To assess whether the main explanatory variables were associated with the slope of change in outcomes over time, we included interaction terms between time of follow-up assessment and the variable. All significant interactions with time were included in the final model. We used QIC as the model selection criterion after considering candidate final models. Various model diagnostics including residual plots and goodness of fit measures were used to evaluate the final model, including linearity of the time trends. There was no evidence for non-linearity of the time trend. As a working correlation structure we chose the exchangeable (intraclass) structure and compared the QIC obtained with this model with one using the unstructured working correlation structure. We chose the exchangeable model as the final model.

We performed several sensitivity analyses. In one, we did not censor recurrent strokes and included these in the analysis, in order to model the course of function over time while also incorporating the effect of recurrent stroke events. We also performed a sensitivity analyses in which we included measures of stroke severity, using stroke subtype as a proxy for severity.

MI cohort We also conducted an analysis identical to that outlined above, except that the event of interest was MI instead of stroke. Hence, the models assessed functional decline before and after MI in those who had MI during follow-up. We first determined whether a drop in function post-MI occurs as with stroke. The six-month period after MI was not ignored, since the 3-6 month course of recovery documented with stroke does not exist with the same biological implications as with stroke.[222, 223] Follow-up was censored at the time of recurrent MI.

Stroke and MI cohort We also performed another analysis in which we included MI and stroke in the same model, with interaction terms with MI as with stroke above. This allowed a direct comparison between MI and stroke in terms of trajectories of functional status. We used another model in which hospitalization instead of MI was included, in order to directly compare the effect of hospitalization with that of stroke. We used GEE models as above, and limited the cohort to those who had stroke or MI during follow-up. For the determination of events, we considered the 1st stroke or 1st MI only. We included a 3-way interaction term (FUTIME * post-event * type of event [0 if MI/1 if stroke]) to model the

time trend before and after vascular events. We tested 3-way interactions between follow-up time and all covariates and retained variables in the final model that were significant at a p 0.15 threshold (due to decreased power with 3-way interactions).

In secondary analysis, different cutoffs of the functional scale were tested systematically in unadjusted and adjusted models to determine whether there was a cutoff at which a threshold effect could be seen. Also, a dichotomous definition of disability (0 versus any score above 0) was tested according to a similar modeling strategy as above.

In other secondary analyses, models were stratified by presence and absence of depression, as well as by income status (above and below the median income). Also, the pre-stroke trajectory of disability was compared to the trajectory in the whole cohort excluding those who experienced stroke, MI, and both stroke and MI. The slope of change in disability was compared in these 4 groups, in unadjusted and fully adjusted models.

The impact of ischemic stroke subtype on disability trajectories was examined in several ways. First, the fully adjusted model was additionally adjusted for stroke subtype (lacunar, cardioembolic, and "other" subtype as referent). Then, models were stratified by stroke subtype and trajectories of disability were examined before and after stroke. In sensitivity analyses, different cholesterol subtypes (total cholesterol, HDL, LDL, and log of lipoprotein-A) were tested as covariates in separate models.

In order to assess for bias due to differential mortality between MI and stroke, we performed survival analysis of mortality after MI and stroke. With a non-significant log-rank test, it appeared as if the timing of mortality was similar in both groups, hence no significant bias would exist due to differential mortality (Appendix C2). A sensitivity analysis was performed in which the worst possible functional score was assigned at the time of death.

Results

Among the total CHS cohort of 5888 participants, 249 (4.23%) had a history of stroke at study entry and 166 (2.82%) had history of TIA. A history of cardiac and vascular disease was common: 562 (9.54% of 5888) had MI, 964 (16.37% out of 4924) had angina, 275 had CHF (4.67% out of 5888), 1154 (19.6% out of 5888) had coronary heart disease, and 151 (2.56% of 5888) had claudication. The mean of total

follow-up time was 12.87 years (SD 6.20, minimum 0.01, maximum 21.6 years, median 13.17 years). During follow-up, there were 1086 incident first strokes, 885 of which were ischemic (see Appendix C3 [A] for information on stroke subtypes). Among those free of cardiac disease at baseline (n=4734), 850 had an incident MI during follow-up, 758 of which (89.2%) were nonfatal (see Appendix C3 [B] for further information on cardiac events during follow-up).

At the time of analysis, 4637 (78.8%) of the total cohort had died (see Appendix C3 [C] for causes of death). However, despite the large proportion of the cohort who had died at the time of analysis, there was a significant amount of data on functional status before and after vascular events due to the long follow-up in CHS. Out of 415 incident strokes with at least 1 follow-up assessment, 382 were ischemic, all of whom had no history of previous stroke. Among these 382 participants, the average maximum follow-up time was 11.1 (SD 5.0) years (minimum 1.20, maximum 21.5 years). There were an average of 3.7 (SD 2.4) visits before stroke (median 3) and 3.7 (SD 2.3) visits after stroke (median 3). In terms of follow-up time, the minimum was -8.15 years and maximum was 8.91 years (with time centered at the time of stroke; see Appendix C4 for distributions of number of visits before and after stroke). There were 395 incident MIs with at least 1 follow-up assessment. Among these 395 participants, the average maximum follow-up time was 12.4 (SD 5.4) years (minimum 1.4, maximum 21.5 years). There were an average of 3.8 (SD 2.5) visits before MI (median 4) and 3.8 (SD 2.4) visits after MI (median 4). In terms of follow-up time, the minimum was -8.00 years and the maximum was 9.52 years, with time centered at the time of MI.

In the stroke cohort of 382 individuals, 86/319 (63 missing) had incident MI. In the MI cohort of 395 individuals, 89/375 (20 missing) had incident stroke. In the combined dataset of those who had incident ischemic stroke and incident MI, the sample size was 727. During follow-up, 125 individuals had both incident stroke and incident MI: 56 had incident stroke before incident MI; 54 had incident MI before incident stroke; and 15 had incident stroke and incident MI on the same day.

In terms of variable distributions (Table C1), the mean age was similar among the overall cohort, the stroke cohort, and MI cohort. There was a higher proportion of males in the MI cohort. The prevalence of vascular risk factors was higher in the stroke and MI cohorts than in the overall cohort.

The overall functional score increased over follow-up, from a mean of 0.59 (SD 1.13) at year 1, to 1.29 (SD 2.38) at year 5, to 3.51 (SD 3.95) at year 10 (Appendix C5 [A]). The mean of functional scores was <1.0 or close to 1.0 in the years before stroke but increased from 2.00 (SD 2.90) to 4.17 (SD 4.12) from the time of stroke to 9 years after stroke (Appendix C5 [H]). For MI, the mean was <1.00 in the years before MI but increased from 1.32 (SD 2.19) at the time of MI to 2.40 (SD 3.69) at 9 years after MI (Appendix C5 [K]).

When the trajectory of functional status before and after stroke was examined among those who had stroke during follow-up (Table C2), in a fully adjusted model, there was an annual change in disability score before stroke of 0.06 points per year (95% CI 0.002, 0.12) and an additional 0.15 points per year (95% CI 0.004, 0.30) after stroke. There was an average of 0.45 points of change (95% CI -0.05, 0.95) at the time of stroke. In these models, assessments of disability were censored after recurrent stroke.
When both recurrent stroke and incident MI were censored (Table C3), the magnitude and direction of associations was unchanged but the significance levels dropped slightly. There was a similar pattern of associations when a dichotomous definition of disability was used (Appendix C6). Different cutoffs of the functional scale were tested systematically (Appendix C10) in adjusted and adjusted models, and no definite threshold effect was found for a particular cutoff of the functional score.

When a continuous measure of depressive symptoms was used instead of a categorical definition of depression, the relationships between stroke event and trajectories of disability did not change, and disability increased by 0.05 points per point increase in depression score (95% CI 0.01-0.08, p-value 0.007). Models were stratified by presence (n=55) and absence (n=325) of depression (Table C4). Though these models have limited power, several findings emerged. First, in an unadjusted model, the magnitude of pre-stroke increase in disability was higher among those with baseline depression (0.25 points per year, 95% CI 0.07, 0.44) than those without (0.15, 95% CI 0.09, 0.20). A significant additional annual increase in disability was seen in those without depression (0.16 points per year, 95% CI 0.0003, 0.31).

Models were also stratified by income (Table C5). In unadjusted models, among those with income below the median, there was a greater annual increase in disability before stroke (0.21 points per year, 95% CI 0.13, 0.28) compared to those with income above the median (0.08 points per year, 95% CI

0.03, 0.14). Among those with income above the median, there was a trend for an additional annual increase in disability after stroke (0.17 points per year, 95% CI -0.02, 0.36) that was not seen among those with income below the median. There was a greater average increase in disability at the time of stroke among those with income below the median (1.37, 95% CI 0.70, 2.03) compared to those with income above the median (1.05, 95% CI 0.50, 1.60). In a fully adjusted model, there was a significant additional increase in the slope of disability after stroke among those with income above the median of 0.23 points per year (95% CI 0.03, 0.43).

The pre-stroke trajectory of disability was compared, in unadjusted and fully adjusted models, to the trajectory in the whole cohort excluding stroke, MI, and both stroke and MI (Table C6). In unadjusted models, there seemed to be a slightly higher slope of increase in disability pre-stroke in the stroke cohort (0.16 points per year, 95% CI 0.11, 0.21) compared to the whole cohort excluding stroke (0.12, 95% CI 0.11, 0.13), MI (0.14, 95% CI 0.13, 0.15), and stroke and MI (0.12, 95% CI 0.11, 0.13). However, the magnitude of annual change in disability was similar among all cohorts in fully adjusted models.

When trajectories of disability before and after MI were examined (Table C7), there was no difference in slope of change before and after MI in unadjusted or adjusted models with recurrent MI censored; there was, on average, an increase in disability score at the time of MI of 0.34 points (95% CI 0.07 0.61) in a fully adjusted model. With both stroke and recurrent MI censored (Table C8), there was no difference in the slope of change of functional score before and after MI, and there was a trend for increased disability at the time of MI of on average 0.23 points (95% CI -0.04, 0.49).

The trajectories of change in functional score before and after both stroke and MI were further examined in the same model in the entire CHS cohort (Table C9). In unadjusted models, the overall slope of increase in disability was similar both without (0.13 points per year, 95% CI 0.13, 0.14) and with adjustment for stroke and MI (0.12 points per year, 95% CI 0.11, 0.13; and 0.11 points per year, 95% CI 0.10, 0.12). There was a higher magnitude of change at the time of stroke (0.88, 95% CI 0.57, 1.20) than at the time of MI (0.20, 95% CI 0.09, 0.20). Also, there was a greater slope of increase in disability after stroke compared to before stroke (0.14 additional points per year, 95% CI 0.09, 0.20), but no significant difference in pre- and post-MI disability slope (0.01, 95% CI -0.02, 0.04).

The changes in functional score related to stroke and MI were examined in the entire cohort using a single model with terms for both stroke and MI (Table C10). In a fully adjusted model, there was a significant increase in disability at the time of stroke (0.68 points, 95% CI 0.41, 0.96) but not MI (0.03, 95% CI -0.14, 0.19). Also, there was a greater slope of change in disability after stroke compared to before stroke (0.05 additional points per year, 95% CI -0.001, 0.10) but not change pre- and post-MI (0.02, 95% CI -0.02, 0.06).

Table C11 shows a model in which all covariates were included that had significant interactions with time. As with prior models, there was a significant average increase in disability at the time of stroke (0.68 points, 95% CI 0.41, 0.96) but not MI (0.07, 95% CI -0.08, 0.22), and an increased slope of disability after stroke (0.05 additional points per year, 95% CI -0.001, 0.10) but not MI (0.01, 95% CI -0.02, 0.04). In addition, several factors were associated with a higher slope of increase in disability over time: age, education, and diabetes. Higher values of the mini-mental state score and social network score were associated with reduced slope of increase in disability over time.

A sensitivity analysis was performed in which the worst possible functional score was assigned at the time of death (Appendix C7). Results were similar to the primary analysis. Specifically, in a fully adjusted model, there was an average increase in functional score of 0.68 points (95% CI 0.41, 0.96) at the time of stroke but no significant change at the time of MI. There was also an additional increase per year in slope of disability of 0.05 points per year (95% CI -0.001, 0.10) but no additional change after MI.

A model using three-way interaction terms was also used to compare trajectories of disability before and after stroke and MI (Table C12). In a fully adjusted model, stroke was associated with a 0.27 point overall increase in disability compared to MI (95% CI 0.02, 0.52), and there was a 0.19-point-per-year additional increase in disability score after stroke (95% CI 0.10, 0.27) but no change after MI.

In a fully adjusted model with additional adjustment for stroke subtype (using a dummy variable with “other” subtype as referent), the subtype term was not significant. However, the influence of stroke subtype on functional trajectories was explored further. In sensitivity analysis, the trajectories of disability before and after stroke were examined in ischemic stroke subtypes (Appendix C8). Among those with lacunar stroke (n=75), there was no significant change in functional score at the time of stroke (and the magnitude was small), but there was a trend for an additional increase in functional score after stroke

(0.33 additional points per year, 95% CI -0.06, 0.72). For cardioembolic stroke (n=107), there was a large and significant average increase in functional score at the time of stroke (1.52 points, 95% CI 0.67, 2.37), and a trend for an additional increase in disability after stroke (0.25 additional points per year, 95% CI -0.02, 0.53). For "other" ischemic strokes (n=211), there was no significant change in slope of functional change after stroke, but there was an average increase of 1.37 points at the time of stroke (95% CI 0.85, 1.90).

In sensitivity analysis, different cholesterol subtypes were tested in separate models (Appendix C9), but the direction and significance of primary predictors did not change substantively when different subtypes were added (total cholesterol, HDL, LDL, and log of lipoprotein-A levels).

Conclusions for Analysis C

CHS is a large, nationally representative cohort of elderly community-dwelling individuals with long-term follow-up approaching an average of 13 years. There is regular measurement of a sensitive measure of disability including both ADL and IADL items, as well as surveillance and accurate measurement of vascular events such as stroke and MI. Although almost 80% of the cohort had died by the time of analysis, there was a significant amount of data surrounding vascular events to estimate trajectories, with almost 4 annual measurements of disability before and after both stroke and MI. Hence, it is an ideal cohort to estimate disability trajectories before and after stroke and MI.

There were 4 overall groups of analysis in this study: a cohort of those who had stroke during follow-up, a cohort of those who had MI during follow-up, the cohort of those who had either event, and the entire CHS cohort. Among all of these analytic cohorts, a consistent pattern emerged, in which the slope of increase in disability after recovery from stroke was higher compared to before stroke but not different before and after MI. There was a significant increase in disability at the time of stroke and a smaller but also significant increase at the time of MI. Among the cohort of those who had stroke during follow-up, the slope of increase in disability after stroke was more than 2 times the slope before stroke. In all of these models, disability measurements after recurrent stroke were censored, so the estimated disability trajectories were independent of clinical recurrent stroke.

Several factors modified trajectories of disability. Among those with depression, the magnitude of pre-stroke increase in disability was higher compared to those without depression. Among those with lower income, there was a greater annual increase in disability before stroke compared to those with higher income. Among those with higher income, there was an additional increase in the slope of post-stroke stroke, suggesting that there may be more room for disability to occur among those with higher income. Several factors were associated with a higher slope of increase in disability over time: age, education, and diabetes. Better cognitive status and a larger social network were associated with reduced slope of increase in disability over time.

It can be hypothesized that those individuals who eventually have a stroke may have a higher slope of increase in disability before stroke than those who do not eventually have a stroke. However, when we compared pre-stroke trajectories to disability trajectories among those who did not develop stroke, MI, or either event, we found no differences.

Although there was limited power to test subtypes of ischemic stroke, there were no evident differences in slopes of disability among different stroke subtypes. Cardioembolic and "other" subtype strokes were associated with greater average increase in disability at the time of stroke compared to lacunar strokes, reflecting the relatively milder phenotype seen with lacunar strokes.

Further discussion of the findings of this analysis will be found in the concluding chapter.

Table C1. Baseline characteristics of study population

Variable	Entire cohort	First ischemic stroke with ≥1 follow-up assessment	First MI with ≥1 follow-up assessment
Number of participants, No. (%)	5888 (100)	382 (100)	395 (100)
Biological characteristics:			
Age, mean (SD), y	72.8 (5.6)	74.1 (5.7)	73.2 (5.3)
Age at event, mean (SD), y	--	78.3 (5.8)	77.5 (5.7)
Body mass index, mean (SD), kg/m^2	26.7 (4.7)	26.6 (4.4)	26.9 (4.5)
Demographics:			
Male, No. (%)	2495 (42.4)	162 (42.4)	221 (56.0)
Non-Hispanic white, No. (%)	4925 (83.6)	332 (86.9)	351 (88.9)
Non-Hispanic black, No. (%)	924 (15.7)	49 (12.8)	42 (10.6)
American Indian/Alaskan Native, No. (%)	15 (0.3)	1 (0.3)	2 (0.5)
Other race, No. (%)	20 (0.3)	0	0
Non-White, No. (%)	963 (16.4)	50 (13.1)	44 (11.1)
Received at least high school education, No. (%)	3352 (57.1)	234 (61.6)	275 (69.6)
Marital status, No. (%) married	3893 (66.2)	255 (66.9)	249 (63.2)
Yearly income, No. (%)			
<$12,000	1470 (26.7)	118 (32.5)	95 (25.4)
$12,000–$34,999	2779 (50.5)	175 (48.2)	194 (51.9)
≥$35,000	1259 (22.9)	70 (19.3)	85 (22.7)
Yearly income, No. (%)			
<$16,000	2324 (42.2)	182 (50.1)	160 (42.8)
≥$16,000	3184 (57.8)	181 (49.9)	214 (57.2)
Additional health insurance, No. (%)			
None	439 (9.0)	34 (10.3)	31 (8.9)
Private	3507 (71.9)	218 (65.9)	251 (72.3)
Medicaid	258 (5.3)	23 (7.0)	15 (4.3)
Other	675 (13.8)	56(16.9)	50 (14.4)
Vascular risk factors, No. (%)			
Hypertension	3457 (58.8)	281 (73.6)	265 (67.1)
On hypertension medications	2789 (47.4)	244 (58.6)	196 (49.6)
Systolic BP, mean (SD)	136.6 (21.8)	143.2 (24.6)	140.6 (20.3)
Diastolic BP, mean (SD)	70.7 (11.4)	72.1 (12.3)	71.6 (11.7)
Number of alcoholic beverages consumed per week, mean (SD)	2.6 (6.3)	2.3 (5.5)	2.00 (5.5)
Physical activity, mean (SD), kcal	1708.4 (2027.6)	1697.2 (2106.0)	1611.9 (1700.0)
Diabetes mellitus, No. (%)	1739 (29.9)	143 (37.9)	140 (35.6)
Current smoking, No. (%)	601 (11.6)	38 (10.9)	48 (13.2)
Hypercholesterolemia, No. (%)	1241 (21.1)	86 (22.5)	89 (22.5)
Total cholesterol, mean (SD), mg/dL	211.2 (39.3)	215.8 (40.4)	212.6 (38.4)
High-density lipoprotein, mean (SD), mg/dL	54.2 (15.7)	52.7 (17.2)	50.6 (14.2)
Low-density lipoprotein, mean (SD), mg/dL	129.8 (35.7)	133.0 (36.2)	132.9 (34.8)
Atrial fibrillation, No. (%)	236 (5.3)	31 (11.4)	15 (5.1)
History of coronary heart disease, No. (%)	1154 (19.6)	106 (27.8)	76 (19.2)
History of myocardial infarction, No. (%)	562 (9.5)	63 (16.5)	0
C-reactive protein level, mean (SD)	4.8 (8.3)	5.4 (9.0)	5.2 (7.5)
C-reactive protein quartiles: 1st quartile		1.58	

Median 3rd quartile		2.77 5.74	
Lp(a) level, mean (SD)	54.0 (55.8)	54.0 (51.5)	50.0 (48.7)
Log-C-reactive protein level, mean (SD)		1.09 (1.02)	
Log-lipoprotein-A level, mean (SD)		3.48 (1.19)	
Other medical conditions, No. (%)			
Depression	292 (5.4)	31(8.9)	23 (6.2)
CES-D depression scale score, mean (SD)	4.7 (4.60)	5.0 (4.6)	4.7 (4.6)
Depressed (CES-D score >9)	809 (13.8)	55 (14.5)	58 (14.8)
Arthritis	3025 (52.0)	219 (57.9)	231 (58.8)
Mini mental state score, mean (SD)	90.6 (5.7)	89.6 (6.1)	90.2 (5.7)
Ischemic stroke subtype, No. (%)			
Lacunar Cardioembolic Atherosclerotic Hemorrhagic transformation Indeterminate	N/A	75 (19.6) 107 (28.0) 28 (7.3) 4 (1.1) 179 (48.0)	N/A

Table C2. Trajectories of a continuous measure of disability before and after stroke

Variable	Change in functional score	95% confidence limits	p-value
Unadjusted model:			
Annual change before stroke	0.16	0.11, 0.21	<.0001
Additional annual change after stroke	0.09	0.22, 1.24	0.2
Change in functional score at time of stroke	1.21	1.62, 5.75	<.0001
Adjusted for demographics:†			
Annual change before stroke	0.15	0.10, 0.20	<.0001
Additional annual change after stroke	0.12	-0.02, 0.26	0.09
Change in functional score at time of stroke	1.21	0.78, 1.63	<.0001
Adjusted for vascular risk factors:*			
Annual change before stroke	0.15	0.10, 0.20	<.0001
Additional annual change after stroke	0.12	-0.02, 0.26	0.09
Change in functional score at time of stroke	1.21	0.78, 1.63	<.0001
Adjusted for other medical conditions:**			
Annual change before stroke	0.15	0.10, 0.20	<.0001
Additional annual change after stroke	0.12	-0.01, 0.26	0.078
Change in functional score at time of stroke	1.20	0.77, 1.62	<.0001
Adjusted for lipid biomarkers:‡			
Annual change before stroke	0.14	0.09, 0.19	<.0001
Additional annual change after stroke	0.12	-0.02, 0.26	0.09
Change in functional score at time of stroke	1.19	0.75, 1.63	<.0001
Adjusted for cognition:π			
Annual change before stroke	0.09	0.05, 0.13	<.0001
Additional annual change after stroke	0.10	-0.01, 0.21	0.06
Change in functional score at time of stroke	0.64	0.29, 1.00	0.0004
Adjusted for social support: ††			
Annual change before stroke	0.06	0.002, 0.12	0.04
Additional annual change after stroke	0.15	0.004, 0.30	0.04
Change in functional score at time of stroke	0.45	-0.05, 0.95	0.08

†adjusted for age at time of stroke, sex, race, marital status, and income
*no additional adjustment
**additionally adjusted for: arthritis and depression
‡additionally adjusted for log of lipoprotein A levels
πadditionally adjusted for mini-mental state score
†† additionally adjusted for social network score

Table C3. Trajectories of a continuous measure of disability before and after stroke, with recurrent stroke and incident myocardial infarction censored

Variable	Change in functional score	95% confidence limits	p-value
Unadjusted model:			
Annual change before stroke	0.16	0.11, 0.21	<.0001
Additional annual change after stroke	0.09	-0.06, 0.24	0.3
Change in functional score at time of stroke	1.19	0.76, 1.62	<.0001
Adjusted for demographics:†			
Annual change before stroke	0.15	0.11, 0.20	<.0001
Additional annual change after stroke	0.12	-0.03, 0.27	0.1
Change in functional score at time of stroke	1.17	0.73, 1.62	<.0001
Adjusted for vascular risk factors:*			
Annual change before stroke	0.15	0.11, 0.20	<.0001
Additional annual change after stroke	0.12	-0.03, 0.27	0.1
Change in functional score at time of stroke	1.17	0.73, 1.62	<.0001
Adjusted for other medical conditions:**			
Annual change before stroke	0.15	0.10, 0.20	<.0001
Additional annual change after stroke	0.13	-0.02, 0.28	0.1
Change in functional score at time of stroke	1.14	0.70, 1.59	<.0001
Adjusted for lipid biomarkers:‡			
Annual change before stroke	0.14	0.09, 0.19	<.0001
Additional annual change after stroke	0.12	-0.03, 0.27	0.1
Change in functional score at time of stroke	1.13	0.67, 1.59	<.0001
Adjusted for cognition:π			
Annual change before stroke	0.09	0.05, 0.13	<.0001
Additional annual change after stroke	0.09	-0.02, 0.21	0.1
Change in functional score at time of stroke	0.59	0.23, 0.94	0.0012
Adjusted for social support: ††			
Annual change before stroke	0.07	0.01, 0.13	0.02
Additional annual change after stroke	0.13	-0.03, 0.29	0.10
Change in functional score at time of stroke	0.46	-0.07, 0.99	0.09

†adjusted for age at time of stroke, sex, race, marital status, and income
*no additional adjustment
**additionally adjusted for: arthritis and depression
‡additionally adjusted for log of lipoprotein A levels
πadditionally adjusted for mini-mental state score
†† additionally adjusted for social network score

Table C4. Trajectories before and after stroke using a continuous definition of disability, stratified by depression

	With depression (n=55)			Without depression (n=325)		
Variable	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value
Unadjusted model:						
Annual change before stroke	0.25	0.07, 0.44	0.008	0.15	0.09, 0.20	<.0001
Additional annual change after stroke	0.18	-0.25, 0.61	0.4	0.07	-0.08, 0.21	0.4
Change in functional score at time of stroke	1.30	0.20, 2.40	0.02	1.19	0.74, 1.63	<.0001
Fully adjusted model:*						
Annual change before stroke	0.14	-0.06, 0.35	0.2	0.05	-0.01, 0.11	0.096
Additional annual change after stroke	0.04	-0.47, 0.54	0.9	0.16	0.003, 0.31	0.047
Change in functional score at time of stroke	1.01	-0.73, 2.75	0.3	0.39	-0.13, 0.91	0.14

*adjusted for: age at time of stroke, sex, race, marital status, income, arthritis, log of lipoprotein A levels, mini-mental state score, and social network score

Table C5. Trajectories before and after stroke using a continuous definition of disability, stratified by income

	With income below median (n=182)			With income above median (n=181)		
Variable	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value
Unadjusted model:						
Annual change before stroke	0.21	0.13, 0.28	<.0001	0.08	0.03, 0.14	0.005
Additional annual change after stroke	0.03	-0.17, 0.23	0.7	0.17	-0.02, 0.36	0.076
Change in functional score at time of stroke	1.37	0.70, 2.03	<.0001	1.05	0.50, 1.60	0.0002
Fully adjusted model:*						
Annual change before stroke	0.07	-0.04, 0.17	0.21	0.05	-0.02, 0.12	0.1
Additional annual change after stroke	0.06	-0.16, 0.28	0.6	0.23	0.03, 0.43	0.03
Change in functional score at time of stroke	0.56	-0.18, 1.29	0.14	0.38	-0.29, 1.05	0.3

*adjusted for: age at time of stroke, sex, race, marital status, depression, arthritis, log of lipoprotein A levels, mini-mental state score, and social network score

Table C6. Comparing pre-stroke trajectory in stroke cohort to whole cohort trajectories

	Unadjusted models			Fully adjusted models*		
	Annual change in functional score	95% CI	p-value	Annual change in functional score	95% CI	p-value
Pre-stroke trajectory in stroke cohort	0.16	0.11, 0.21	<.0001	0.06	0.002, 0.12	0.04
Trajectory in whole cohort excluding:						
Stroke	0.12	0.11, 0.13	<.0001	0.07	0.07, 0.08	<.0001
Myocardial infarction	0.14	0.13, 0.15	<.0001	0.08	0.07, 0.08	<.0001
Stroke and myocardial infarction	0.12	0.11, 0.13	<.0001	0.07	0.06, 0.08	<.0001

*adjusted for: age at time of stroke, sex, race, marital status, income, arthritis, depression, log of lipoprotein A levels, mini-mental state score, and social network score

Table C7. Trajectories of a continuous measure of disability before and after myocardial infarction (MI), with recurrent MI censored

Variable	Change in functional score	95% confidence limits	p-value
Unadjusted model:			
Annual change before MI	0.13	0.09, 0.18	<.0001
Additional annual change after MI	-0.04	-0.13, 0.04	0.3
Change in functional score at time of MI	0.36	0.11, 0.60	0.004
Adjusted for demographics:†			
Annual change before MI	0.15	0.10, 0.20	<.0001
Additional annual change after MI	-0.03	-0.12, 0.05	0.4
Change in functional score at time of MI	0.35	0.11, 0.60	0.004
Adjusted for vascular risk factors:*			
Annual change before MI	0.15	0.10, 0.20	<.0001
Additional annual change after MI	-0.03	-0.12, 0.05	0.5
Change in functional score at time of MI	0.34	0.10, 0.58	0.006
Adjusted for other medical conditions:**			
Annual change before MI	0.14	0.09, 0.19	<.0001
Additional annual change after MI	-0.03	-0.11, 0.06	0.5
Change in functional score at time of MI	0.35	0.11, 0.59	0.005
Adjusted for inflammatory biomarkers:‡			
Annual change before MI	0.14	0.09, 0.19	<.0001
Additional annual change after MI	-0.03	-0.11, 0.06	0.5
Change in functional score at time of MI	0.35	0.11, 0.60	0.005
Adjusted for cognition:π			
Annual change before MI	0.10	0.05, 0.14	<.0001
Additional annual change after MI	-0.05	-0.12, 0.02	0.16
Change in functional score at time of MI	0.29	0.07, 0.51	0.01
Adjusted for social support: ††			
Annual change before MI	0.04	0.00, 0.08	0.03
Additional annual change after MI	0.02	-0.07, 0.11	0.7
Change in functional score at time of MI	0.34	0.07, 0.61	0.014

MI=myocardial infarction
†adjusted for age at time of MI, sex, race, marital status, and body mass index
*additionally adjusted for diabetes
**additionally adjusted for: arthritis and depression
‡additionally adjusted for log of C-reactive protein levels
πadditionally adjusted for mini-mental state score
†† additionally adjusted for social network score

Table C8. Trajectories of a continuous measure of disability before and after myocardial infarction (MI), with stroke and recurrent MI censored

Variable	Change in functional score	95% confidence limits	p-value
Unadjusted model:			
Annual change before MI	0.14	0.09, 0.19	<.0001
Additional annual change after MI	-0.05	-0.13, 0.04	0.3
Change in functional score at time of MI	0.16	-0.07, 0.39	0.17
Adjusted for demographics:†			
Annual change before MI	0.15	0.10, 0.20	<.0001
Additional annual change after MI	-0.04	-0.13, 0.04	0.3
Change in functional score at time of MI	0.15	-0.08, 0.38	0.2
Adjusted for vascular risk factors:*			
Annual change before MI	0.15	0.10, 0.20	<.0001
Additional annual change after MI	-0.04	-0.12, 0.05	0.4
Change in functional score at time of MI	0.13	-0.09, 0.36	0.2
Adjusted for other medical conditions:**			
Annual change before MI	0.15	0.10, 0.20	<.0001
Additional annual change after MI	-0.04	-0.12, 0.05	0.4
Change in functional score at time of MI	0.14	-0.09, 0.37	0.2
Adjusted for inflammatory biomarkers:‡			
Annual change before MI	0.15	0.10, 0.20	<.0001
Additional annual change after MI	-0.03	-0.12, 0.05	0.4
Change in functional score at time of MI	0.14	-0.09, 0.37	0.2
Adjusted for cognition:π			
Annual change before MI	0.11	0.06, 0.15	<.0001
Additional annual change after MI	-0.05	-0.12, 0.03	0.2
Change in functional score at time of MI	0.12	-0.09, 0.32	0.3
Adjusted for social support: ††			
Annual change before MI	0.05	0.02, 0.09	0.004
Additional annual change after MI	0.02	-0.07, 0.11	0.7
Change in functional score at time of MI	0.23	-0.04, 0.49	0.09

MI=myocardial infarction
†adjusted for age at time of MI, sex, race, marital status, and body mass index
*additionally adjusted for diabetes and coronary heart disease
**additionally adjusted for: arthritis and depression
‡additionally adjusted for log of C-reactive protein levels
πadditionally adjusted for mini-mental state score
†† additionally adjusted for social network score

Table C9. Trajectories of a continuous measure of disability before and after stroke and myocardial infarction in the entire cohort (n=5888), in unadjusted models

Model	Overall change model			Overall change plus average change due to stroke and MI			Pre- and post-stroke and –MI trajectories		
Variable	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value
Annual change	0.13	0.13, 0.14	<.0001	0.12	0.11, 0.13	<.0001	0.11	0.10, 0.12	<.0001
Change in functional score at time of stroke	--			1.65	1.41, 1.89	<.0001	0.88	0.57, 1.20	<.0001
Change in functional score at time of MI				0.27	0.15, 0.39	<.0001	0.20	0.06, 0.35	0.006
Additional annual change after stroke				--			0.14	0.09, 0.20	<.0001
Additional annual change after MI							0.01	-0.02, 0.04	0.4

CI=confidence intervals; MI=myocardial infarction

Table C10. Trajectories of a continuous measure of disability before and after stroke and myocardial infarction in the entire cohort (n=5888), in adjusted models

Variable	Change in functional score	95% confidence limits	p-value
Adjusted for demographics:†			
Annual change	-0.83	-0.98, -0.67	<.0001
Change in functional score at time of stroke	0.86	0.55, 1.17	<.0001
Change in functional score at time of MI	0.22	0.07, 0.36	0.004
Additional annual change after stroke	0.12	0.06, 0.17	<.0001
Additional annual change after MI	0.01	-0.02, 0.04	0.5
Adjusted for vascular risk factors:*			
Annual change	-0.85	-1.01, -0.70	<.0001
Change in functional score at time of stroke	0.85	0.54, 1.17	<.0001
Change in functional score at time of MI	0.11	-0.08, 0.30	0.3
Additional annual change after stroke	0.11	0.06, 0.17	<.0001
Additional annual change after MI	0.01	-0.03, 0.04	0.7
Adjusted for other medical conditions:**			
Annual change	-0.86	-1.02, -0.70	<.0001
Change in functional score at time of stroke	0.84	0.53, 1.16	<.0001
Change in functional score at time of MI	0.14	-0.05, 0.32	0.15
Additional annual change after stroke	0.11	0.06, 0.17	<.0001
Additional annual change after MI	0.01	-0.03, 0.04	0.8
Adjusted for inflammatory biomarkers:‡			
Annual change	-0.87	-1.03, -0.71	<.0001
Change in functional score at time of stroke	0.84	0.52, 1.16	<.0001
Change in functional score at time of MI	0.13	-0.06, 0.32	0.17
Additional annual change after stroke	0.11	0.06, 0.16	<.0001
Additional annual change after MI	0.00	-0.03, 0.04	0.8
Adjusted for cognition:π			
Annual change	0.10	-0.10, 0.31	0.3
Change in functional score at time of stroke	0.76	0.50, 1.03	<.0001
Change in functional score at time of MI	0.16	-0.01, 0.32	0.06
Additional annual change after stroke	0.04	-0.002, 0.09	0.06
Additional annual change after MI	-0.02	-0.05, 0.02	0.3
Adjusted for social support: ††			
Annual change	0.16	-0.08, 0.39	0.19
Change in functional score at time of stroke	0.68	0.41, 0.96	<.0001
Change in functional score at time of MI	0.03	-0.14, 0.19	0.7
Additional annual change after stroke	0.05	-0.001, 0.10	0.056
Additional annual change after MI	0.02	-0.02, 0.06	0.3

†adjusted for age at time of stroke, sex, race, education, income, and interaction terms between time of follow-up and these variables

*additionally adjusted for: diabetes, hypertension, coronary heart disease, and interaction terms between time of follow-up and these variables

**additionally adjusted for: arthritis and depression, and interaction terms between time of follow-up and these variables

‡additionally adjusted for log of C-reactive protein, and interaction terms between time of follow-up and these variables

πadditionally adjusted for mini-mental state score, and interaction terms between time of follow-up and these variables

†† additionally adjusted for social network score, and interaction terms between time of follow-up and these variables

Table C11. Trajectories of a continuous measure of disability before and after stroke and myocardial infarction in the entire cohort (n=5888), in final adjusted model with non-significant interaction terms excluded

	Baseline functional score			Change over time in functional score		
	Difference in baseline functional score	95% CI	p-value	Annual change in functional score	95% CI	p-value
Annual change	0.18	-0.05, 0.42	0.12	--	--	--
Change in functional score at time of stroke	0.68	0.41, 0.96	<.0001	--	--	--
Change in functional score at time of MI	0.07	-0.08, 0.22	0.4	--	--	--
Additional annual change after stroke	--	--	--	0.05	-0.001, 0.10	0.055
Additional annual change after MI	--	--	--	0.01	-0.02, 0.04	0.4
Age at baseline, per yr	0.02	0.02, 0.03	<.0001	0.004	0.002, 0.01	0.0009
Male sex	0.22	0.16, 0.29	<.0001	--	--	--
Non-White race	-0.04	-0.15, 0.06	0.4	-0.02	-0.05, 0.01	0.17
At least high school education level	0.00	-0.09, 0.09	0.99	0.02	0.00, 0.04	0.03
Yearly income of $12000 to $34999	-0.05	-0.13, 0.04	0.3	--	--	--
Yearly income of >=$35000	-0.03	-0.13, 0.06	0.5	--	--	--
Diabetes	0.05	-0.03, 0.13	0.2	0.03	0.01, 0.05	0.005
Hypertension	0.06	-0.0002, 0.11	0.051	--	--	--
Coronary heart disease	0.17	0.06, 0.28	0.002	--	--	--
Arthritis	0.37	0.31, 0.42	<.0001	--	--	--
Depression	0.56	0.44, 0.68	<.0001	--	--	--
Log of C-reactive protein levels	0.09	0.06, 0.13	<.0001	--	--	--
Mini-mental state score	-0.02	-0.02, -0.01	<.0001	-0.004	-0.005, -0.002	<.0001
Social network score	-0.01	-0.01, -0.002	0.003	-0.002	-0.003, -0.0008	0.001

CI=confidence interval

Table C12. Trajectories before and after stroke and myocardial infarction (MI) in the cohort of those with stroke or MI, with 3-way interactions

Variable	Change in functional score	95% confidence limits	p-value
Unadjusted model:			
Annual change before stroke or MI	0.17	0.13, 0.22	<.0001
Overall increase due to stroke, compared to MI	0.28	0.02, 0.55	0.04
Change in functional score at time of stroke or MI	0.74	0.33, 1.14	0.0003
Additional annual change in those with stroke	-0.03	-0.10, 0.04	0.4
Additional annual change after MI	-0.07	-0.14, 0.0009	0.053
Additional annual change after stroke	0.24	0.16, 0.31	<.0001
Adjusted model:*			
Annual change before stroke or MI	0.13	0.07, 0.20	<.0001
Overall increase due to stroke, compared to MI	0.27	0.02, 0.52	0.04
Change in functional score at time of stroke or MI	0.37	-0.01, 0.75	0.059
Additional annual change in those with stroke	-0.11	-0.19, -0.03	0.006
Additional annual change after MI	-0.04	-0.12, 0.04	0.3
Additional annual change after stroke	0.19	0.10, 0.27	<.0001

MI=myocardial infarction

*Adjusted for: baseline age, sex, race, education, income, diabetes, hypertension, coronary heart disease, arthritis, depression, log of C-reactive protein levels, mini-mental state score, and social network score

Integrative concluding chapter

In the previous chapters, several hypotheses were tested related to the conception of cerebrovascular disease as a progressive condition, with chronic effects on disability and functional status. Several main points emerged. In Analysis A, increasing CRP levels were associated with lower overall mean functional score but not with change in slope of function over time. Results were similar for LpPLA2 mass levels. However, for TNFR1, increasing levels were associated not only with overall reduced functional status, but also additional annual decline in function over time. In Analysis B, using different measures of SBI, there was a strong, consistent, independent, and significant effect on accelerated decline in function over time, over and above the annual decline in function due to aging. This pattern was seen with WMHV as well. This pattern of association was seen with MRI imaging markers believed to be caused by vascular impairment (SBI, lacunar infarcts, and WMHV) but not with other MRI structural findings, such as LPVS, which are not believed to be caused directly by a primary vascular pathology. In Analysis C, trajectories of disability were examined not only in relation to baseline predictors but also in relation to vascular events occurring during follow-up. The slope of increase in disability after recovery from stroke was higher compared to before stroke but not different before and after MI. There was a significant increase in disability at the time of stroke and a smaller but also significant increase at the time of MI. Among the cohort of those who had stroke during follow-up, the slope of increase in disability after stroke was more than 2 times the slope before stroke. In all of these analyses, disability measurements after recurrent stroke were censored, so the estimated disability trajectories were independent of clinical recurrent stroke. From these inter-related analyses, a pattern emerges of cerebrovascular disease having a progressive negative influence on functional status in the absence of clinical stroke events, with a strong and reproducible impact of subclinical ischemic brain injury and serum inflammatory biomarkers, especially TNFR1. The following sections will compare these findings to those in previous studies and discuss implications for the design of future studies and treatment paradigms.

Analysis A

C-reactive protein

Many prior studies have examined the association between CRP and vascular outcomes and mortality. Several studies have examined population-based cohorts among those without baseline vascular

disease. In a longitudinal analysis in the prospective cohort of NOMAS, elevated CRP was independently associated with MI and death, but not ischemic stroke.[116] In a meta-analysis of 160,309 individuals without vascular disease from 54 prospective studies,[224] each SD increase in log of CRP levels was independently associated with: coronary heart disease (RR 1.37, 95% CI 1.27–1.48), ischemic stroke (RR 1.27, 95% CI 1.15–1.40), vascular death (RR 1.55, 95% CI 1.37–1.76), and non-vascular death (RR 1.54, 95% CI 1.40–1.68). In addition to those without vascular disease, stroke patients have also been examined. Among 198 young ischemic stroke patients with a mean age of 48 years, higher CRP levels were associated with increased risk of mortality over a mean of 12 years of follow-up.[225] Among 1244 lacunar stroke patients followed for a median of 3 years in the Levels of Inflammatory Markers in the Treatment of Stroke study, higher CRP levels were associated with recurrent stroke, with an adjusted HR of 2.32 for the 4th quartile of CRP levels (95% CI 1.15–4.68), and major vascular events (HR 2.04, 95% CI 1.14–3.67).[226]

In addition to vascular events, disability and functional status have been examined as outcomes in studies of the predictive ability of CRP. For example, among 807 consecutively admitted ICH patients in Finland,[227] elevated CRP levels at admission were associated with worse MRS scores at 3 months. We examined functional status over a longer time period related to ischemic stroke. In the Survey of Midlife Development in the United States (MIDUS) study, a population-based sample of 1255 individuals with data on biomarkers, functional status, and comorbidity were studied.[228] Inflammation, indicated by a latent factor contributed to be CRP, IL6, and fibrinogen, partially mediated the relationship between risk factors and disability. In a cross-sectional analysis using 10 years of data from the National Health and Nutrition Examination Survey (NHANES) among 1729 adults with diabetes,[229] elevated CRP was independently associated with disability in terms of ADL functioning as well as lower extremity mobility. Results were similar when 1403 individuals with cardiovascular disease were examined in NHANES.[139] Among 542 individuals with chronic obstructive pulmonary disease, congestive heart failure, cardiovascular risk, or physical disability, higher CRP and IL6 were associated with less grip strength and poor physical performance independent of demographics.[230]

These associations between CRP and disability have also been found among specific race-ethnic groups. Among 368 African-American individuals, higher levels of CRP and TNFR1 were associated with

multiple measures of increased impairment and disability, including ADLs and IADLs, upper and lower extremity functional impairments, and physical performance.[231] Among 417 Korean acute ischemic stroke patients with CRP measured at admission and 7 days, CRP levels at both time points, but especially at 7 days, was associated with 12-month MRS scores.[232]

In the only known study that has examined change of function over time, among 624 individuals ≥70 years of age in the Einstein Aging Study,[233] elevated CRP was associated with mobility disability in the entire cohort, as well as incident disability and gait speed decline among those without vascular disease, over a median of 2 years of follow-up. In our analysis, we had longer term follow-up and examined a larger cohort with and without vascular disease.

Finally, one study examined the association of CRP with cognitive function. In a cross-sectional analysis of a population-based cohort from Northern Manhattan, 1331 individuals without dementia were studied.[234] Elevated CRP levels were independently associated with impaired memory and visuospatial function.

Interleukin-6

Several previous studies have examined outcomes related to IL6 levels among population-based cohorts. In a prior analysis in NOMAS among 1224 participants,[235] IL6 levels above the median were associated with greater decline in cognitive ability measured by the TICS over a median of 3 years of follow-up. In a cross-sectional meta-analysis of 6 cohorts, levels of circulating biomarkers were tested for associations with measures of physical performance.[236] Higher levels of five inflammatory markers were associated with worse physical performance: IL6, TNFR2, TNFR1, TNFα, and GCSF. Among 2979 individuals aged 70-79 years in the Health, Aging and Body Composition Study,[237] there was a greater risk of incident mobility limitation with higher IL6 (RR 1.19, 95% CI 1.10-2.8), CRP (RR 1.40, 95% CI 1.18–1.68), and soluble TNFR1 levels (RR 1.28, 95% CI 1.04–1.57) over 30 months of follow-up. In the Health Aging and Body Composition study, [238] 2234 elderly individuals were followed for a median of 11.4 years, and higher IL6 levels were associated with the onset of disability and mortality. Higher IL6 levels have also been independently associated with periventricular and deep WMHV among 137 elderly women, suggesting a possible mediating effect between inflammatory states and disability.[239] Also, higher IL6 levels have been

associated cross-sectionally with greater WMHV among 1841 individuals aged 65-80 years but not with WMH progression after 4 years, further complicating the relationship between IL6 and subclinical ischemic brain injury.[240]

The associations between IL6 and outcomes have also been examined in particular subgroups of people. For example, in a meta-analysis of 4112 stroke patients from 20 studies,[241] IL6 was associated with poor outcome, defined as MRS score of >2 or BI score of <85, as well as post-stroke infection. Among 80 individuals with vascular dementia, increasing IL6 levels were independently associated with lower BI scores in a cross-sectional analysis.[242] Among 1727 individuals >70 years of age in the Duke Established Populations for Epidemiologic Studies of the Elderly study,[243] higher IL6 levels were associated with disability and self-rated health, and IL6 levels were associated with cancer, heart attack, and hypertension. Among 3925 men aged 60-79 years, higher IL6 levels were associated with incident mobility limitation over an average of 11.5 years of follow-up.[244]

Tumor necrosis factor receptor-1

In an early cross-sectional analysis in NOMAS among 279 individuals,[245] elevated TNFR1 levels were associated with carotid atherosclerosis among those <70 years of age. In a more recent longitudinal analysis in the NOMAS prospective cohort,[246] 1862 participants were followed for a mean of 8.4 years for mortality and cause of death. Increasing TNFR1 levels were associated with increased risk of all-cause and non-vascular mortality, and the magnitude of association was higher among those with lower socioeconomic status. In the population-based Oxford Vascular Study,[247] 15 biomarkers were tested in 929 patients with minor stroke and TIA. Among the biomarkers tested, 4 were associated with all-cause death: tumor necrosis factor-alpha receptor-1, von Willebrand factor, heart-type fatty-acid-binding protein, and N-terminal pro-B-type natriuretic peptide.

Lipoprotein-associated phospholipase A2

LpPLA2 has been associated with vascular outcomes in previous studies. In a prior NOMAS analysis among 467 individuals with first ischemic stroke, LpPLA2 was independently associated with recurrent

stroke (HR 2.08, 95% CI 1.04-4.18) and the composite outcome of recurrent stroke, MI, or vascular death.[248] CRP was associated with mortality alone. In another NOMAS analysis of 1946 participants in the prospective cohort,[249] LpPLA2 mass levels were associated with the occurrence of large-artery subtype of ischemic stroke among non-Hispanic Whites. In a NOMAS analysis examining WMHV as an outcome,[207] CRP levels were associated with WMHV, as were LpPLA2 levels when 3 biomarkers were examined in the same model (CRP, LpPLA2, and myeloperoxidase).

In a large collaborative study using data from 32 prospective studies and involving 79036 patients,[250] LpPLA2 mass and activity were independently associated with increased risk of vascular events, including MI and stroke, and vascular mortality. In the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, a subset of participants (n=3201) enrolled with stroke or TIA had LpPLA2 activity measured at baseline.[251] Higher LpPLA2 activity levels were independently associated with higher risk of 90-day stroke as well as a composite of ischemic stroke, myocardial infarction, or death, and there was no interaction with treatment assignment. Expert panels have recommended measuring LpPLA2 to improve risk prediction of cardiovascular disease,[252] and the current analyses suggest that it may also be effective to predict functional status.

LpPLA2 activity has also been associated with SBI cross-sectionally in a cohort of 921 stroke-free individuals, but only among women, with OR of 2.14 per 1 SD increase in levels (95% CI 1.31-3.50).[253]

Summary

Multiple prior studies have demonstrated associations between inflammatory biomarkers and vascular outcomes, mortality, and disability measured at single time points. However, the current analysis is the only known analysis, among studies of inflammatory biomarkers, in which both baseline functional status as well as the trajectory of change over time was analyzed, not only disability measured at a single time point. One difficulty in finding biomarkers that can predict outcomes surrounding vascular events is the heterogeneity of events such as stroke and the variety of pathophysiological processes involved in cerebrovascular events. For example, biomarkers originally conceived as representing cardiac pathophysiology have also been associated with subclinical brain injury.[254] One approach to improve the predictive ability of biomarkers is to use a panel of several markers that reflect several of the

pathophysiologic processes that can lead to stroke: coagulative, inflammatory, cardiac, and atherosclerotic.[255, 256] Also, there has been a recognition that biomarkers for Alzheimer's disease change in composition and levels over time, as the disease progresses (Figure D1).[257] Future research will hopefully clarify the mechanisms underlying the progressive decline seen after stroke, which would allow researchers and clinicians to track the progression of biomarkers over time that reflect these processes. Future research would measure biomarkers repeatedly over time through the pre-event and post-event states and enable the identification of those susceptible to accelerated decline over time.

Analysis B

Several previous studies have examined the associations between patient-centered outcomes and brain imaging markers of ischemic and degenerative changes. In a prior analysis in the NOMAS MRI cohort,[258] greater WMHV and smaller TCV were associated with poorer performance in learning a list of words. The current analysis expands upon this previous research by analyzing longitudinal trends of repeated measures of functional status and confirming a long-term effect of SBI and WMHV on functional decline. Prior research on the associations between imaging findings and outcomes has focused on white matter disease, subclinical brain infarcts, and other novel imaging markers.

White matter disease

There have been multiple publications from the Leukoaraiosis and Disability Study (LADIS) on the association between WMHs and outcomes. Overall, individuals aged 65-84 years with any degree of subcortical WMH on MRI and no or mild disability were eligible for the study. In one cross-sectional analysis, increasing leukoaraiosis was associated with increasing disability.[259] Among 619 participants with IADL measured at 1 year,[260] the risk of transition at 1 year to $\geq$2 ADL impairments was higher with a greater degree of WMHV, with an OR of 3.02 (95% CI 1.34-6.78) among those with severe WMHV compared to mild WMHV who were non-disabled at baseline. After a mean of 2.42 years of follow-up, these trends were maintained,[261] with a HR for transition to disability or death of 2.36 (95% CI 1.65-3.81). When gait and balance were examined yearly over 3 years of follow-up, more WMHV predicted decline over time, especially among older ages.[262] In a longitudinal study of cognitive outcomes,[263] those with

subcortical ischemic vascular disease had greater declines in performance on multiple cognitive tests, as well as a threefold increase in risk of developing dementia during follow-up. Results were similar when age-related white matter change was the primary predictor.[264]

Several other studies have examined outcomes among stroke-free individuals with WMH measurements. Among 287 community-dwelling individuals aged 70-90 years,[265] greater WMHV was associated with physical decline over 1 year (defined as being in the top quartile of change in Physiological Profile Assessment scores, with OR 3.02, 95% CI 1.02-8.95), and possibly WMHs in the deep frontoparietal and periventricular parietooccipital regions had the greatest impact on decline. In the population-based Rotterdam Study,[266] 2025 individuals were assessed for change in disability over a mean of 5.7 years. Lower brain volume was associated with greater disability, in terms of overall brain volume as well as gray matter and white matter volumes individually. Greater diffusivity, a marker of brain microstructure, was associated with higher risk of incident impairment. Among 99 individuals 75-89 years of age, global WMHV was associated with urinary incontinence, mobility deficits, and executive dysfunction.[267]

In a prior analysis in CHS,[268] among 3230 individuals without stroke who had MRI and were followed for up to 16 years, 5 clusters of MRI patterns of ischemic injury were identified through a data-driven approach: Normal, Atrophy, Simple Infarct, Leukoaraiosis, and Complex Infarct. Mean years of life, years of healthy life, and years of able life were calculated, and these outcomes were worst among those with Complex Infarct, which had the greatest degree of sickness and disability among the clusters. Among 267 Japanese-American men aged 74-95 years in the Honolulu-Asia Aging Study,[269] cognitive function was measured at baseline and at 5 years, and those with white matter lesions at baseline had twofold higher adjusted odds of having a 1 SD drop in cognitive performance at 5 years.

Besides disability, other patient-centered outcomes have been examined among stroke-free cohorts. In a cross-sectional analysis among 1538 individuals aged 55-72 years in the ARIC study,[270] ventricular size, high-grade WMH, and SBI were associated with worse performance on memory, executive, and language tasks. Among 390 male twins aged 69-80 years in the NHLBI Twin Study, WMHV above the median was associated with a greater drop in Digit Symbol Substitution test scores at 10 years compared to baseline.[271]

The associations between WMHV and outcomes have also been examined in stroke patients. For example, among 408 stroke patients followed at 2 weeks and 1 year from stroke,[272] severe periventricular WMHs were associated with disability at both time points and were associated with poorer recovery at 1 year, but WMHs in deep locations were not associated with these outcomes. Among 101 first ischemic stroke patients followed at 1 year with the MRS,[273] WMHV was associated with greater disability. Three-month outcomes were examined among 185 minor stroke (NIHSS ≤5) patients,[274] and WMHV was associated with 90-day change in NIHSS score and MRS.

Subclinical brain infarcts

Several studies have focused on SBIs as primary predictors of outcomes. In the LADIS study, among 387 individuals with yearly neuropsychological testing and repeat MRI at 3 years,[275] incident lacunes were associated with decline in executive function and speed and motor control. Increase in WMHV was independently associated with executive dysfunction. In CHS, 2450 individuals were followed for a mean of 4 years, and WMHV and brain infarcts were associated with higher incidence of disability and accelerated decline in gait speed.[70] Adjustment for incident stroke and dementia and mini-mental status score did not attenuate associations. Among 350 elderly Japanese individuals without dementia, subclinical white matter lesions were cross-sectionally associated with global cognitive impairment and frontal lobe dysfunction.[276] Finally, among 787 consecutively admitted stroke patients, prior subclinical stroke was associated with higher odds of having a 3-month BI score of ≤60.[277]

Other predictors

In this analysis, there was an association among education, cognitive ability, and functional status. In a previous study, healthy adults ranging in age from 23-84 years, including 28 APOE-E4 carriers, had FDG-PET and MRI.[278] There was an interaction with education, such that APOE-E4 carriers showed an association between higher education and metabolism in the fronto-temporal lobes, which correlated with episodic memory performance. The evidence of higher fronto-temporal metabolism may reflect the strength or density of neural networks and may be one of the biological effects of education. Prior studies have also shown overlap between cerebrovascular disease and neurodegenerative processes. One

hundred eighty-one cognitively normal individuals were followed with yearly MRI and cognitive assessments up to 20 years in the Oregon Brain Aging Study.[279] WMHV increased around 10 years before onset of mild cognitive impairment (MCI), and ventricular size increased approximately 4 years before onset. In 24% of individuals who had MCI and autopsy, there was concomitant Alzheimer's dementia pathology as well as significant cerebrovascular disease. Among 61 patients with subcortical vascular dementia followed annually for 3 years,[280] 11C–Pittsburgh compound B (PiB) PET-positivity at baseline was associated with accelerated decline in attention, visuospatial ability, visual memory, and global cognition. WMHV was associated with similar patterns of decline, but lacunar infarcts and microbleeds were not.

In this analysis, no significant associations were found between measures of perivascular spaces and functional status. In a Japanese population-based study of 1575 neurologically healthy adults who had MRI,[281] basal ganglia perivascular spaces were associated with basal ganglia microbleeds, and centrum semiovale perivascular spaces were associated with lobar microbleeds. There was a common coexistence of perivascular spaces, hypertension, lacunes, and WMHV. However, no functional outcomes were examined in this study and it is difficult to deduct the impact of these findings on functional status. In another study among 31 individuals without dementia who had brain MRI and Pittsburgh compound B-PET imaging,[282] amyloid burden was associated with perivascular spaces in the centrum semiovale. In a study among 201 ICH patients,[283] enlarged perivascular spaces in the centrum semiovale region were associated with small acute DWI-positive lesions, suggesting a possible role of perivascular spaces in vascular risk. The underlying mechanism(s) of which perivascular spaces may be a marker are not well delineated at this time, but these mechanisms may involve neurodegenerative processes.[284]

Summary

Multiple prior studies have shown relationships between subclinical ischemic injury, measured by WMHV and SBI, and patient-centered outcomes. However, a minority of prior studies has examined trajectories of these outcomes over time, delineating not only change between 2 time-points but also slopes of

change over time. More research is needed examining trajectories of cognition and disability over time, possibly in relation to progressive imaging changes on repeated MRIs as well.

The field of neuroimaging is undergoing rapid technological advances, and paralleling these advances has been a reconceptualization of the ways in which subclinical ischemic disease causes pathological effects on function. Recent research suggests that WMHs have different degrees of surrounding tissue that is susceptible to further injury – what has been called the "WMH penumbra" – but that interventions have yet to be found that modify the progression of such regions.[285] Also, WMHV may be caused by ischemic processes but may also be caused by the processes that lead to neurodegenerative diseases such as Alzheimer's dementia. A measure of gray matter integrity, such as cortical thickness, may be a more accurate reflection of the effect of each process.[286] Diffusion tensor imaging can identify impaired fractional anisotropy, and this measure of impaired white matter microstructure has been associated with subsequent risk of Alzheimer's disease in those with mild cognitive impairment.[287] Other studies have found associations between microstructural integrity measured by MRI DWI sequences and subsequent cognitive and functional changes.[288] Future studies may find a similar association between early white matter structural damage and accelerated functional decline after stroke. One issue caused by the advances in imaging technology is heterogeneity in imaging protocols used and definitions used for SBI and WMHs, requiring the development of standard definitions to allow comparison among studies.[289]

Analysis C

Several studies have examined the course of functional outcomes before and after vascular events. In a much earlier publication in CHS of self-rated health with up to 8 years of follow-up,[290] a drop in self-rated health similar to the increase in disability seen in the current analysis was seen at the time of MI. There were significant declines after stroke but not MI, but this analysis was centered on self-rated health and had short follow-up in comparison to the current analysis.

In an analysis in HRS, cognitive function as measured by the modified TICS-m scale was assessed every 2 years over a mean of 4.1 years of follow-up.[159] Compared to Whites, Blacks had greater cognitive decline in adjusted models. Incident stroke caused reduced cognitive function that did

not differ by race, and there were no significant differences in slope of change over time post-stroke. In another analysis in HRS, the course of functional and cognitive impairment was compared before and after stroke (with 432 hospitalizations) and MI (with 450 hospitalizations).[160] Using a combined measure of ADLs and IADLs, there was a greater increase in disability at the time of stroke compared to MI, similar to our findings in CHS. Difference in pre- and post-stroke slopes of change depended on initial impairment levels. Stroke but not MI was associated with higher odds of cognitive impairment.

In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, the course of cognitive function was compared before and after stroke among 515 individuals who had stroke, and 23057 who remained stroke-free, during a mean follow-up of 6.1 years.[161] There was a significantly steeper decline in cognitive function after stroke in the areas of global cognition and executive function. The risk of cognitive impairment was higher after stroke compared to before stroke, with an odds ratio of 1.23 per year (95% CI 1.10-1.38). These findings paralleled our results for the course of disability after stroke.

In HRS, trajectories of biennially measured memory performance were analyzed before and after nonfatal stroke (n=1189), before fatal stroke (n=385), and among 15,766 individuals who did not experience stroke over 10 years of follow-up.[162] Among stroke survivors, the pre-stroke decline in memory performance was greater than among those who remained stroke-free, and those who died of stroke had even greater declines. There was no significant difference in slope of change in memory performance before and after stroke. Limitations of this analysis were the long intervals between memory assessments, the self-report of stroke, and the large amount of missing data regarding stroke timing.

In another analysis among 17341 participants in HRS,[163] there were biennial assessments of a composite memory score over 10 years of follow-up. There were 3 types of individuals: stroke survivors (n=1169), stroke decedents (n=405), and those who did not experience stroke during follow-up (n=15767). As with the prior analysis, stroke was defined by self-report or report of a proxy but not confirmed by specialist review, and there was a significant amount of missing data on month (8.3%) and year (10.5%) of stroke. Also, there was a significant amount of loss to follow-up (37%). Overall, pre-stroke decline in memory performance was greater in older individuals compared to younger individuals. Females had slightly steeper declines in memory performance pre-stroke compared to males, but there

were no significant differences among the stroke-free cohort. For those in the older age stratum, there was a steeper decline in memory performance after stroke compared to before (-0.15 vs. -0.07 points/year, p = 0.003), similar to our findings in CHS.

In the ARIC study,[164] a change score in 3 cognitive measures was calculated over approximately 14 years, and 2 MRIs were performed over a similar time interval (10 years) and scored for presence of infarcts, WMHV, and ventricular size. There was ongoing surveillance for hospitalizations, and type of hospitalization was categorized using ICD-9 codes. For those who were hospitalized during follow-up, there was a decline in performance on the Digit Symbol Substitution Test. When trajectories of change in cognitive performance were compared pre- and post-hospitalization, there was accelerated decline in the Digit Symbol Substitution test after hospitalization, with an additional 0.20 digit-symbol pairs/year (95% CI 0.12–0.27), and accelerated decline in the Word Fluency Test after hospitalization, with an additional 0.09 words/year (95% CI 0.02–0.17). Hospitalized patients had greater development of atrophy. Overall, critical illness and major surgical hospitalizations were associated with greater cognitive decline and MRI changes.

In another ARIC study, trajectories of self-rated health were examined over a median of 17.6 years in 11,188 individuals who remained disease-free, 1071 individuals who developed MI, and 809 who developed stroke.[165] Higher neighborhood income was strongly associated with better self-rated health and less prevalent comorbidities. There was no difference in the slope of change in self-rated health over time before and after stroke in this analysis.

Among 687 community-dwelling elderly individuals assessed for life space mobility, those with surgical hospitalizations had greater drop in mobility at the time of hospitalization compared to those with non-surgical admissions, who had no significant recovery over time.[166]

The concept of frailty may capture some of the observed variation in disability, and previous studies have examined the association between frailty and event-based outcomes. Among 1521 individuals $\leq$65 years of age with first acute MI in 8 Israeli hospitals, the Rockwood frailty index was assessed at baseline and 10-13 years later.[291] The frailest individuals had twice the risk of mortality compared to the least frail group, greater cardiac death, and more hospital admissions.

In the current analysis, male sex was associated with overall worse disability but no difference in slope of change over time. This was true also among 3501 young MI patients (age 18-55 years) with patient-centered outcomes gathered at baseline, 1 month, and 1 year,[222] in whom the trajectory of improvement in QOL and health status was similar among males and females, although females had lower scores in all domains at all time points of follow-up.

We did not find an effect of race-ethnicity on disability trajectories in this analysis. However, in an analysis from the Cooperative Cardiovascular Project,[292] 141095 Medicare beneficiaries, 6.3% of whom were Black, were hospitalized with MI and followed for 17 years. A quarter of the Black patients lived in low-SES areas, compared to 5.7% of White patients, and life expectancy was lower for Black patients. Furthermore, the greatest discrepancy in life expectancy was seen in high- and medium-SES areas. It is possible that this mortality disparity was not paralleled by a disparity in disability. However, further dedicated research in race-ethnic disparities in trajectories of functional status is needed.

Depression was associated with worse overall disability in this analysis. In an early analysis of CHS data with 4 years of follow-up, persistent depression (as compared to temporary depression or no depression) was associated with significantly higher odds of disability, with an adjusted OR of 5.27 (95% CI 3.03-9.16).[217] These findings were confirmed in an analysis of 2102 individuals in the Health, Aging, and Body Composition Study over 9 years of follow-up.[293] Also, among 425 individuals with an acute coronary syndrome, depression symptoms and physical health status were assessed after the event and 12 months later.[294] Persistent depressive symptoms were associated with poorer physical health status. Not only depression but also PTSD is common after sudden health events such as stroke and MI, and PTSD may play a role in social participation in the long term after recovery from events. For example, among 40 MI survivors diagnosed with PTSD 5 months after MI, 2/3 had persistent PTSD more than 2 years after MI.[295] Psychological distress is also common over the long term after stroke, but its effect on trajectories of function is unclear.[296]

Possible mechanisms

Greater knowledge about population trends in disability, as discussed in the above analyses, would inform basic science paradigms about brain injury due to stroke, and specifically would suggest models

that incorporate long-term neurodegeneration or progressive damage into the range of stroke injury. Based on previous studies, there are several mechanisms that could cause the accelerated decline in functional status after stroke seen in the above analyses. Some mechanisms have been discussed above in the opening chapter, and additional mechanisms will be discussed here.

There are several brain structural changes that have been associated with cerebrovascular disease that may have impacts on cognition and functional status. For example, brain infarcts have been associated with smaller hippocampal volumes, which are associated with poorer memory and cognitive function.[297] Silent cerebral infarction has also been associated with reduced grey matter volume and concomitant cognitive deficits.[298] WMHV, SBI, microbleeds, and atrophy have been associated with declines in gait speed, cadence of gait, and length of steps,[299-301] which would affect the mobility aspects of ADL functioning. WMHV and progression of WMHV have been associated with neurological examination findings such as gait and stance abnormalities, upper motor signs, and slowing of fingertaps,[302] and presence and number of neurological deficits have an independent impact on performance of ADLs.[303] Silent deep infarcts and WMHV have been associated with gait variability, which has been associated with falls and disability.[304]

There has been some debate about the pathophysiology of white matter disease, but ischemia and vascular dysfunction have been confirmed to play a major role in the genesis of WMHs. In a study among 5 individuals with moderate to severe WMHV who had weekly MRIs over 16 weeks of follow-up,[305] tiny asymptomatic acute infarcts were identified on repeat scans that eventually resembled WMHs radiographically over follow-up. Vascular risk factors also cause WMHs, which then cause disability and cognitive impairment. For example, in a prior analysis in CHS,[71] hypertension was associated with baseline and incident disability, and WMHV mediated the association between hypertension and disability. Among 976 hypertensive individuals, age, sex, and Framingham cardiovascular risk scores were associated with SBI in a cross-sectional analysis.[306] Not only overt diabetes but also fasting glucose has been independently associated with WMHs and SBI among 172 healthy, non-institutionalized individuals.[307]

Inflammation has also been implicated in the pathophysiology of WMHs, in genetic, epigenetic, and epidemiological studies.[308] Elevated plasma total homocysteine levels have been associated with

reduced brain volume and SBI (but not WMHV) among 1965 healthy individuals in the Framingham Offspring Study, especially among older ages.[309] Endothelial dysfunction has been implicated in the development of WMHV and SBIs, as shown in 2013 stroke-free individuals in the Framingham Offspring Study, in whom asymmetrical dimethylarginine, an inhibitor of endothelial nitric oxide synthase, was associated with subsequent SBIs and WMHV.[310] Hemostatic factors have also been shown to be related to cerebrovascular disease; von Willebrand factor and D-dimer levels were associated with subclinical lacunar infarcts in a case-control analysis of 410 individuals in the ARIC study.[311]

Possible mediators of the relationship between vascular risk factors and trajectories of disability and cognition would need to be clarified in future research. Previous studies have identified possible mediators that could be potential targets for intervention. For example, post-stroke apathy is a less well understood phenomenon that is common, follows variable trajectories, and has an impact on disability and social participation.[312] When 118 individuals with lacunar stroke and WMHs were compared to 398 healthy controls,[313] both apathy and depression were associated with lower QOL. However, impaired white matter structure, as measured by fractional anisotropy, was associated with apathy alone, especially when impaired anisotropy was present in limbic association areas. Further research is needed on conditions such as apathy that are intermediate between brain ischemic damage and disability.

Several studies have suggested a role for socioeconomic status in long-term outcomes, including functional outcomes. For example, all stroke admissions in Denmark from 2003-2012 in those >40 years of age were examined (n=56581, median follow-up 3.1 years), and linkage was performed with national registries with data on income and vital statistics.[314] There was a strong and dose-dependent effect of income on post-stroke mortality, and the relative risk of death in those with the highest income quintile compared to the lowest was 0.70 (95% CI 0.65-0.74). This finding is particularly striking considering that Denmark has free, universal health coverage. In an another analysis of a nationwide registry with 2,397,446 participants over 12 years in the Netherlands,[315] lower socioeconomic status was associated with higher risk of stroke among all ethnic groups, and ethnic groups had higher stroke incidence within strata of income level compared to ethnic Dutch. In an innovative environment-wide association study performed in the National Health and Nutrition Examination Survey, income was significantly associated

with 66 out of 330 tested factors, including infectious, biochemical, physiological, and environmental factors.[316] It is likely that socioeconomic status has multifactorial influences on disability after stroke.

Education has also been shown to have a strong association with outcomes. In an analysis of 851 individuals followed from age 85 to 90 years with 98.7% complete data on disability during follow-up,[317] four trajectories of disability were evident, and education protected against being in the most disabled group. Among 3955 individuals over 10 years of follow-up, those with the most education had a 23-45% reduced chance of disability compared to those with mean levels of education.[318] There was a significant effect of income but with less of a magnitude of effect.

Environmental and social factors may also play a role. Leisure-time physical inactivity is common after MI (up to 37% up to 13 years after MI among 1410 individuals with first MI), and low neighborhood SES predicted low physical activity.[319] Social isolation and changes in caregiver and friend networks during stroke recovery may also play a role in trajectories of performance in ADLs.[320] Even the type of caregiving style may play a role, as suggested by research among TBI patients.[321] Strain on caregiving networks and change in the constitution and effectiveness of these networks over time may play a role in late functional decline.[322]

In the above analyses, baseline depression was associated with subsequent disability, suggesting causal directionality from depression to disability. Several studies have shown an association of depression with disability, but at least one, among 442 Taiwanese elderly individuals with repeated measures of depression and disability over 10 years,[323] has suggested that disability may lead to depression more often than depression leads to disability. Repeated measures of both depression and functional status over time would allow the clarification of this directionality.

It is also unclear whether measures of impairment, such as weakness, or sociodemographic factors are better predictors of functional trajectories. In an analysis of 9471 individuals with 12 years of data from HRS,[324] there were three trajectories of disability, and impairment indicators predicted these trajectories better than sociodemographic characteristics, suggesting that mediators of the relationship between sociodemographics and disability trajectories should be targeted in observational and interventional research. However, further research is needed to clarify these relationships.

Implications for clinical trial design

If there is a progressive decline in functional status in the long-term after stroke that is independent of clinical events such as stroke and MI, the conventional 90-day functional outcome measure after an intervention is likely not adequate to evaluate the effectiveness of a treatment.[325] Figure D2 shows several trajectories of change in functional status that all have the same 90-day functional outcome, each representing a drastically different course of change over time. More data is needed about the expected course of recovery after specific stroke subtypes, or perhaps related to specific locations of infarct. An enhanced ability to predict such trajectories would allow the design of trials of interventions that could modify expected trajectories, not only outcomes at discrete time points such as 90 days.[326] In clinical trials, patient-centered outcomes should be assessed, but the use of standard scales may be limiting. A qualitative study with several interviews over the first year after stroke found that fatigue was common and disabling, although standard scales of physical recovery showed little deficit.[327] Also, a combination of qualitative and quantitative research may be required to develop scales to use in large datasets that are sensitive to the patterns of change in patient-centered outcomes over time.[328, 329]

Biomarkers that represent intermediate processes that occur prior to imaging-confirmed infarct and cerebrovascular disease could be used to identify those at risk as well as a surrogate marker for clinical trials. For example, retinal microvascular abnormalities have been shown to be a powerful predictor of cerebral infarct and WMHV in the ARIC study over a median of 10.5 years of follow-up.[330] The retinal vasculature is an effective marker of cerebrovascular dysfunction because it can be viewed and assessed non-invasively with relatively inexpensive equipment.

Heterogeneous trajectories

Several previous studies have identified distinct trajectories of change in patient-centered outcomes over time, primarily using statistical techniques such as latent class analysis that are tailored to the discovery of groups each with a distinct trajectory. For example, several studies have shown heterogeneous trajectories of disability[331] and cognitive function[332] at older ages that may vary by sex.[333] Almost 1000 African American community-dwelling individuals aged 50-64 years had self-rated health assessed over 9 years of follow-up.[334] Semi-parametric group-based mixture models discovered 4 trajectories of self-rated

health: “persistently good health, good but declining health, persistently fair health, and fair but declining health.”[334] In a study examining psychological symptoms, 444 stroke patients had repeated measures of psychological symptoms over 4 years of follow-up and the Barthel index assessed at the end of follow-up.[335] At first assessment, 21% met criteria for a psychological disorder, but symptoms improved over time and 12% met criteria for a psychological disorder at final follow-up. Four trajectories of change in psychological symptoms were identified over time, and psychological symptoms were associated with subsequent disability. In a Dutch prospective study among 2867 elderly individuals, disability was measured several times over 6 years, and 9 distinct trajectories of disability were identified.[336]

There is heterogeneity in the degenerative processes that accompany chronological aging, and these processes may involve inflammation, impaired coagulation, and endothelial dysfunction. Chronological age is related to these changes but there is not a 1:1 correspondence, and greater knowledge of the factors causing variations among individuals would allow the identification of those more prone to decline. Considering the heterogeneous trajectories that may be seen in functional and cognitive recovery after stroke, different predictive risk factors may exist for each phase of recovery: pre-stroke, acute post-stroke, and chronic post-stroke; further research, with an attention to diverse trajectories of function, is needed to clarify these factors.[337]

Potential interventions to reduce long-term functional decline

Further research is needed that assigns trajectories of functional status as the outcome and tests potential interventions to mitigate this decline. The first step is to identify those at risk of deterioration. Then, several potential approaches may be effective: targeted rehabilitation; continual monitoring of functional status; optimal pharmaceutical secondary prevention strategies; and interventions to reduce social isolation and depression after stroke.[325] For example, an ongoing trial will test whether low-dose aspirin is effective in reducing the progression of SBI and WMH over time.[338] Another ongoing trial will compare whether angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are more effective to reduce progression of subclinical infarcts over 2 years of follow-up.[339]

Other areas of potential intervention are suggested by recent research. Statins and other cholesterol-modifying agents reduce levels of LpPLA2[252] and may play a role in reducing inflammation-

mediated declines in function. Medications specifically targeted to the mechanism of biomarkers, such as darapladib to inhibit the activity of LpPLA2, may also be effective[252]. In addition to medications, diet may have an important impact on cognitive decline. A specific dietary intervention may modify cognitive decline in those susceptible to this.[340] In a large observational analysis of 2 international clinical trials with 27860 patients followed over 56 months,[341] higher diet quality (assessed with the modified Alternative Healthy Eating Index) was associated with lower risk of cognitive decline (HR 0.76, 95% CI 0.66-0.86), independently of baseline cognitive status. Adherence to the Mediterranean diet among 674 elderly individuals with a mean age of 80 years was cross-sectionally associated with less brain atrophy.[342] A recent randomized trial assigned elderly (age 60-77 years) individuals to a multidomain intervention (including diet, exercise, cognitive training, and monitoring of vascular risk factors) or a control group of general health advice, who were followed for change in performance on neuropsychological testing.[343] There was a significantly greater improvement in the intervention arm, ranging from 25-150% improvement on primary and secondary cognitive outcomes. In terms of specific dietary or supplement intake, lower vitamin D levels have been associated with cognitive decline, and further research would clarify whether supplementation modifies trajectories of cognitive change over time.[344]

Traditionally there has been an emphasis on the acute treatment of stroke and rehabilitation targeted to the early period after the event. Indeed, insurance coverage for inpatient and outpatient rehabilitation is limited to the few weeks or months after stroke; stroke specialists have minimal dedicated training in stroke rehabilitation; and a minority of research funding in stroke is targeted to rehabilitation and helping patients deal with the disability effects of stroke.[345] It may be more beneficial to conceive of stroke as a chronic disease that can benefit from ongoing physical rehabilitation over a long time period, since rehabilitative interventions have been shown to be effective even in the chronic phase after stroke.

Rehabilitation may also be effective if it targets cardiorespiratory fitness. Among 565 middle-aged healthy individuals in the Coronary Artery Risk Development in Young Adults Study,[346] cardiorespiratory fitness was measured by a maximal treadmill test duration, and individuals had brain MRI after 5 years. In fully adjusted models, better cardiorespiratory fitness predicted greater brain volume and higher white matter integrity. In the Lifestyle Interventions and Independence for Elders trial,[347] 1635 elderly sedentary individuals were randomized to a physical activity intervention or a health education

intervention and followed for 2.6 years. There was a benefit of the physical activity intervention on prevention of major disability, with a HR of 0.82 (95% CI 0.69-0.98). Alternatively, better control of vascular risk factors may lead to better outcomes. Among 2566 stroke patients in the Fukuoka Stroke Registry, day-to-day blood pressure variability 4-10 days after stroke predicted worse functional outcome at 3 months.[348]

Neurorehabilitation techniques may be beneficial to arrest or reduce functional decline over time, considering the importance of cognitive ability on functional status. Techniques targeting specific cognitive domains or abilities may be useful, but further research is needed.[349] Indeed, cognitive ability and education have been associated with brain health and cognitive reserve that protects against decline. For example, among 1959 subjects who had cortical thickness measurements by MRI, higher education levels were independently associated with mean cortical thickness throughout the brain, as well as in particular brain regions.[350] However, this effect was only seen in older individuals, suggesting that the effect of education may be to reduce atrophy due to effects of aging, which may be a structural manifestation of cognitive reserve. The Austrian Polyintervention Study to Prevent Cognitive Decline after Ischemic Stroke (ASPIS) tested whether a 24-month intervention to enhance compliance reduced post-stroke cognitive decline among 202 individuals.[351] There was no significant effect of the intervention but power was limited. In TBI, environmental enrichment may improve post-injury recovery.[352]

Finally, further elucidation of the early and late inflammatory responses with stroke may identify targeted immune modulatory treatments that were developed for other conditions (such as multiple sclerosis) but may have efficacy to prevent long-term cognitive and functional decline after stroke.[353]

The next step: future studies on trajectories and vascular events

The above analyses suggest several next steps, in terms of hypotheses and study designs, which would elucidate and expand upon the findings discussed above. Some of these steps can leverage data available in existing datasets, but in most cases new data collection would be necessary due to the requirements for accurate repeated measurement of variables over time. For example, in order to clarify the impact of inflammatory and imaging markers on functional trajectories, more formal and thorough mediation analysis would need to be performed. Also, testing for heterogeneous trajectories of functional

change over time is necessary, for example with latent class analysis, in order to better understand the influences on the time course of disability in relation to vascular events. Newer analytic techniques can also statistically estimate the stability of trajectories of disability over time and may useful in future studies.[354]

Repeated measures of not only outcomes but also longitudinal measures of covariates may be necessary, with recent research showing various trajectories of variables such as depression after vascular events such as MI.[355, 356] In the analyses conducted here, most covariates were measured once at baseline, but the status and severity of comorbid conditions is more likely to change over time rather than remain constant as one ages. Many existing longitudinal epidemiological studies do not routinely re-measure comorbidities over follow-up, and most do not measure severity or control of such conditions as hypertension and diabetes, which may have an impact on functional status.

The inflammatory processes surrounding cerebrovascular disease are complex, and likely distinct inflammatory biomarkers vary simultaneously. The variation of a single biomarker is unlikely to effectively capture the predictive potential of a panel of biomarkers varying together. Hence, a future analysis will involve mixtures analysis of multiple biomarkers at once, or other data reduction techniques with even larger numbers of markers. An early attempt at this was made in NOMAS in which the relative levels of CRP and IL6 were analyzed.[201] A 3-level variable was created of CRP-dominant, IL6-dominant, or codominant levels, and there was increased risk of ischemic stroke in the CRP-dominant group and decreased risk in the IL-6–dominant group. A similar approach was used among 718 women followed for 5 years in the Women's Health and Aging Study,[357] in which the combination of low IGF-I levels and high IL6 levels were associated with cross-sectional disability subsequent death and disability. Newer analytic techniques involving clustering and data reduction through machine learning algorithms may have better performance and would be able to incorporate larger numbers of biomarkers simultaneously. Also, even when significant associations between biomarkers and outcomes are found, adding a biomarker to traditional risk factors may not always improve predictive ability of the models,[358] and risk prediction is one important goal of biomarker development.

As imaging technology advances, studies will have to be designed to capture and translate meaningful structural and brain functional data and relate these to trajectories of patient-centered

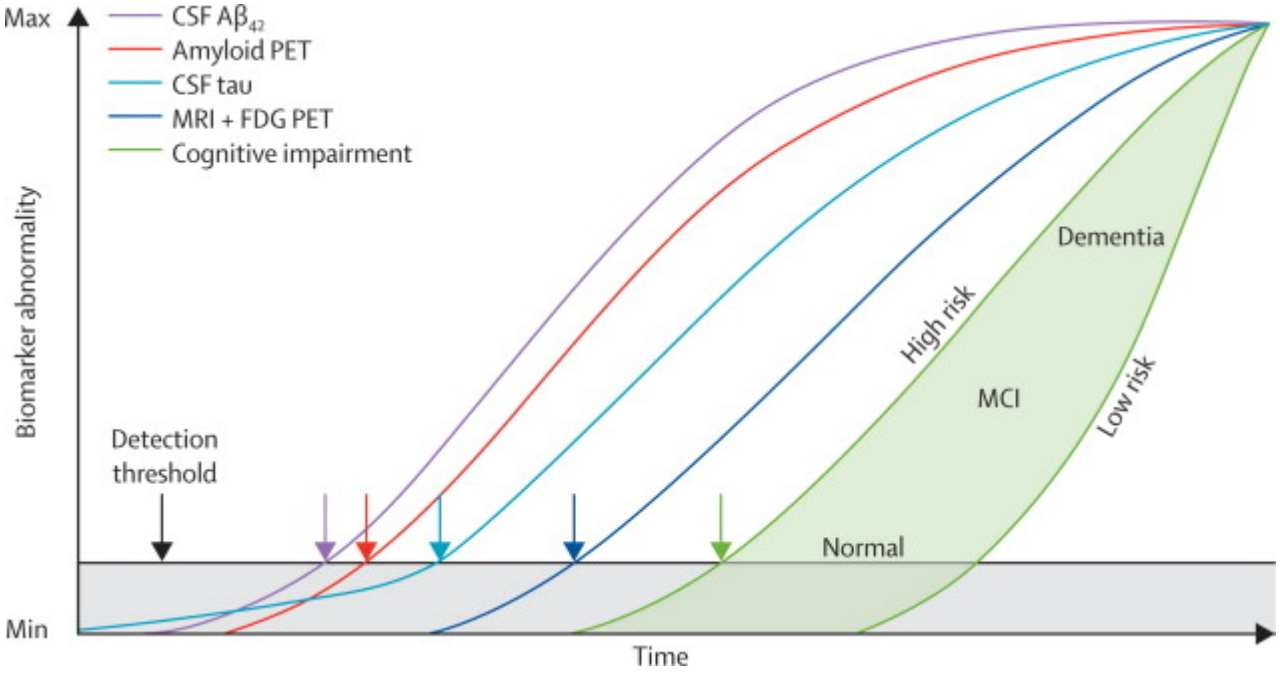
outcomes. For example, longitudinal functional MRI studies conducted in a small number of patients up to 3 months after stroke have shown change in functional networks in brain regions affected by stroke,[359] but longer term follow-up with repeated scans are necessary to elucidate mechanisms of long-term decline. An ongoing study ("CANVAS") will examine whether reduction in brain volume – measured with repeated MRIs over 3 years -- is associated with cognitive decline after stroke.[360]

Conclusions

There are several implications of the research discussed here. One is that if there was an exclusive focus on events as outcomes, which has traditionally been the approach of many observational studies and clinical trials, the long-term declines seen in these analyses would be missed and the burden of disease would be underestimated. These points highlight the importance of measuring patient-centered outcomes, analyzing not only single time-points but trajectories over time, and the use of epidemiologic and not only administrative (claims-based and event-based) data, due to the need to reliably measure outcomes. This research also highlights the likely central role that "subclinical" disease plays in functional ability and health. By identifying subclinical markers (such as SBI and WMHV) and inflammatory biomarkers (such as TNFR1) that have an impact on functional trajectories, these previously ignored or unmeasured elements should move to the forefront of disease prediction, out of the realm of the "subclinical" and into the realm of active and regular use in disease management and prevention.

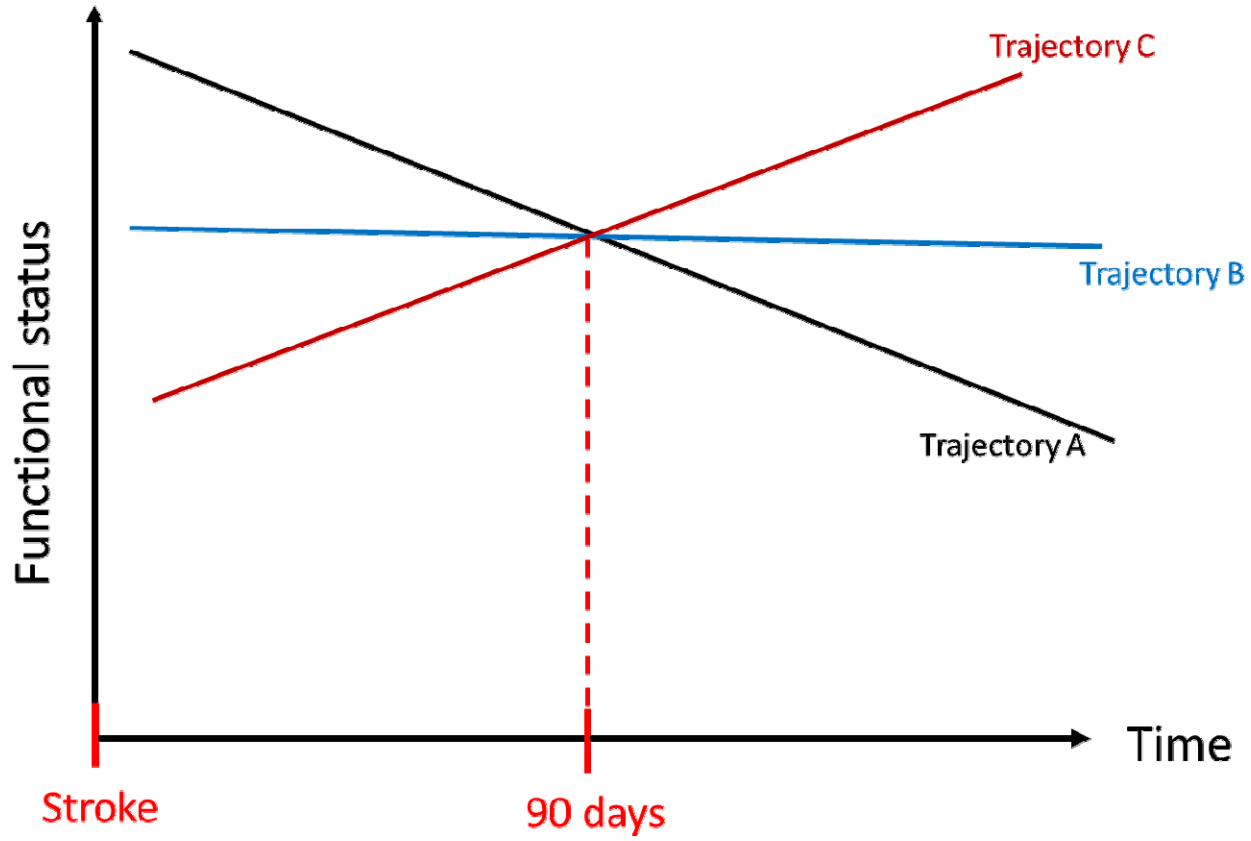
There are several possible future directions. One is that trial outcomes may move from the surveillance of events to the regular measurement of trajectories. In order to increase precision and reduce costs, trials and observational studies may begin to employ novel technologies to repeatedly measure functional outcomes, such as smartphone apps or passive activity trackers.[361] As measurements of subclinical disease become more refined, there should be a greater focus on the detection of previously unseen outcomes. This would hopefully lead to the development of targeted therapeutics and more effective prevention not only of vascular events but also unfavorable functional and cognitive trajectories, which have a large and previously unseen impact on population health.

Figure D1. Model integrating Alzheimer's disease immunohistology and biomarkers (Reproduced from Jack et al.[257])



"The threshold for biomarker detection of pathophysiological changes is denoted by the black horizontal line. The grey area denotes the zone in which abnormal pathophysiological changes lie below the biomarker detection threshold. In this figure, tau pathology precedes Aβ deposition in time, but only early on at a subthreshold biomarker detection level. Aβ deposition then occurs independently and rises above the biomarker detection threshold (purple and red arrows). This induces acceleration of tauopathy and CSF tau then rises above the detection threshold (light blue arrow). Later still, FDG PET and MRI (dark blue arrow) rise above the detection threshold. Finally, cognitive impairment becomes evident (green arrow), with a range of cognitive responses that depend on the individual's risk profile (light green-filled area). Aβ=amyloid β. FDG=fluorodeoxyglucose. MCI=mild cognitive impairment."[257]

Figure D2. Three disparate functional trajectories with the same 90-day outcome



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APPENDICES

Appendix A1. Distribution of Barthel index scores in the entire prospective cohort

Barthel index score	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	182	0.48	182	0.48
5	148	0.39	330	0.87
10	145	0.38	475	1.25
15	125	0.33	600	1.57
20	108	0.28	708	1.86
25	117	0.31	825	2.16
30	137	0.36	962	2.52
35	135	0.35	1097	2.88
40	145	0.38	1242	3.26
45	207	0.54	1449	3.80
50	267	0.70	1716	4.50
55	283	0.74	1999	5.25
60	373	0.98	2372	6.22
65	434	1.14	2806	7.36
70	506	1.33	3312	8.69
75	713	1.87	4025	10.56
80	1032	2.71	5057	13.27
85	1445	3.79	6502	17.06
90	2622	6.88	9124	23.94
95	5923	15.54	15047	39.48
100	23063	60.52	38110	100.00

Appendix A2. Distributions of C-reactive protein and other biomarkers

A) C-reactive protein distributions according to CDC/AHA risk stratification levels

C-reactive protein level	Frequency	Percent	Cumulative Frequency	Cumulative Percent
<1mg/L	524	23.39	524	23.39
1-3 mg/L	710	31.70	1234	55.09
>3 mg/L	1006	44.91	2240	100.00

Frequency Missing = 873

B) CRP-dominant versus IL-6-dominant profiles: conceptual description

		CRP Quartiles			
		Q1	Q2	Q3	Q4
IL6 Quartiles	Q1	Reference	CRP-Dominant	CRP-Dominant	CRP-Dominant
	Q2	IL6-Dominant	Reference	CRP-Dominant	CRP-Dominant
	Q3	IL6-Dominant	IL6-Dominant	Reference	CRP-Dominant
	Q4	IL6-Dominant	IL6-Dominant	IL6-Dominant	Reference

Jorge Luna et al. *Stroke*. 2014; 45: 979-987[201]

C) Frequencies of CRP-dominant versus IL-6-dominant profiles

Dominance profile	Frequency	Percent	Cumulative frequency	Cumulative percent
Reference	593	35.81	593	35.81
IL-6-dominant	561	33.88	1154	69.69
CRP-dominant	502	30.31	1656	100.00

Appendix A3. Associations between log of tumor necrosis factor receptor-1 protein levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-1.03	-1.12, -0.94	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-4.50	-6.18, -2.82	<.0001
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.16	-0.40, 0.09	0.2
Adjusted for demographics:*			
Annual change in BI score	-1.02	-1.11, -0.93	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-2.60	-4.19, -1.01	0.0014
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.11	-0.34, 0.13	0.4
Adjusted for vascular risk factors:**			
Annual change in BI score	-1.03	-1.12, -0.94	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-1.76	-3.35, -0.17	0.03
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.11	-0.35, 0.12	0.3
Adjusted for social variables:†			
Annual change in BI score	-1.02	-1.11, -0.93	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-1.51	-3.11, 0.10	0.066
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.13	-0.37, 0.11	0.3
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.51	-0.73, -0.28	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-1.06	-1.86, -0.25	0.01
Additional annual change in BI score per unit increase in log of TNFR1 levels	0.06	-0.49, 0.61	0.8
Adjusted for stroke and MI:π			
Annual change in BI score	-0.39	-0.61, -0.17	0.0005
Change in BI score per unit increase in log of TNFR1 levels	-1.22	-2.02, -0.42	0.003
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.04	-0.51, 0.42	0.9

TNFR1=tumor necrosis factor receptor-1; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Appendix A4. Associations between log of tumor necrosis factor receptor-1 protein levels and trajectories of functional status; sensitivity analysis with 0 values set to missing

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-1.03	-1.12, -0.94	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-5.30	-6.64, -3.97	<.0001
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.18	-0.43, 0.06	0.15
Adjusted for demographics:*			
Annual change in BI score	-1.03	-1.12, -0.94	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-3.19	-4.58, -1.79	<.0001
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.13	-0.37, 0.11	0.3
Adjusted for vascular risk factors:**			
Annual change in BI score	-1.03	-1.12, -0.94	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-2.36	-3.74, -0.98	0.0008
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.14	-0.38, 0.10	0.3
Adjusted for social variables:†			
Annual change in BI score	-1.02	-1.11, -0.93	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-2.11	-3.50, -0.73	0.003
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.15	-0.39, 0.09	0.2
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.60	-0.80, -0.40	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-0.89	-1.74, -0.05	0.04
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.32	-0.67, 0.03	0.072
Adjusted for stroke and MI:π			
Annual change in BI score	-0.47	-0.67, -0.27	<.0001
Change in BI score per unit increase in log of TNFR1 levels	-1.12	-1.97, -0.27	0.0096
Additional annual change in BI score per unit increase in log of TNFR1 levels	-0.34	-0.67, -0.01	0.046

TNFR1=tumor necrosis factor receptor-1; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Appendix A5. Associations between quartiles of tumor necrosis factor receptor-1 protein levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-0.90	-1.07, -0.73	<.0001
Change in BI score with 2nd quartile of TNFR1 levels€	-1.03	-2.19, 0.14	0.08
Change in BI score with 3rd quartile of TNFR1 levels€	-1.13	-2.35, 0.09	0.07
Change in BI score with 4th quartile of TNFR1 levels€	-5.52	-7.09, -3.94	<.0001
Additional annual change in BI score with 2nd quartile of TNFR1 levels€	0.09	-0.13, 0.31	0.4
Additional annual change in BI score with 3rd quartile of TNFR1 levels€	-0.17	-0.41, 0.07	0.17
Additional annual change in BI score with 4th quartile of TNFR1 levels€	-0.62	-0.92, -0.32	<.0001
Adjusted for demographics:*			
Annual change in BI score	-0.93	-1.10, -0.76	<.0001
Change in BI score with 2nd quartile of TNFR1 levels€	-0.90	-2.22, 0.42	0.18
Change in BI score with 3rd quartile of TNFR1 levels€	-0.04	-1.37, 1.28	0.9
Change in BI score with 4th quartile of TNFR1 levels€	-2.35	-4.03, -0.67	0.006
Additional annual change in BI score with 2nd quartile of TNFR1 levels€	0.11	-0.11, 0.34	0.3
Additional annual change in BI score with 3rd quartile of TNFR1 levels€	-0.12	-0.36, 0.12	0.3
Additional annual change in BI score with 4th quartile of TNFR1 levels€	-0.53	-0.82, -0.23	0.0004
Adjusted for vascular risk factors:**			
Annual change in BI score	-0.94	-1.11, -0.76	<.0001
Change in BI score with 2nd quartile of TNFR1 levels€	-0.67	-2.01, 0.67	0.3
Change in BI score with 3rd quartile of TNFR1 levels€	0.29	-1.04, 1.62	0.7
Change in BI score with 4th quartile of TNFR1 levels€	-0.96	-2.63, 0.71	0.3
Additional annual change in BI score with 2nd quartile of TNFR1 levels€	0.11	-0.11, 0.33	0.3
Additional annual change in BI score with 3rd quartile of TNFR1 levels€	-0.10	-0.34, 0.14	0.4
Additional annual change in BI score with 4th quartile of TNFR1 levels€	-0.54	-0.83, -0.24	0.0004
Adjusted for social variables:†			
Annual change in BI score	-0.92	-1.09, -0.75	<.0001
Change in BI score with 2nd quartile of TNFR1 levels€	-0.44	-1.77, 0.89	0.5
Change in BI score with 3rd quartile of TNFR1 levels€	0.52	-0.81, 1.85	0.4
Change in BI score with 4th quartile of TNFR1 levels€	-0.62	-2.28, 1.04	0.5
Additional annual change in BI score with 2nd quartile of TNFR1 levels€	0.10	-0.12, 0.32	0.4
Additional annual change in BI score with 3rd quartile of TNFR1 levels€	-0.11	-0.35, 0.13	0.4
Additional annual change in BI score with 4th quartile of TNFR1 levels€	-0.56	-0.85, -0.26	0.0002
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.39	-0.61, -0.16	0.0007
Change in BI score with 2nd quartile of TNFR1 levels€	-0.23	-0.90, 0.45	0.5
Change in BI score with 3rd quartile of TNFR1 levels€	0.38	-0.49, 1.25	0.4
Change in BI score with 4th quartile of TNFR1 levels€	-0.21	-1.26, 0.83	0.7

Additional annual change in BI score with 2nd quartile of TNFR1 levels€	0.23	-0.11, 0.58	0.18
Additional annual change in BI score with 3rd quartile of TNFR1 levels€	-0.56	-1.25, 0.12	0.11
Additional annual change in BI score with 4th quartile of TNFR1 levels€	-0.73	-1.38, -0.09	0.03
Adjusted for stroke and MI:π			
Annual change in BI score	-0.21	-0.42, 0.003	0.054
Change in BI score with 2nd quartile of TNFR1 levels€	-0.18	-0.83, 0.47	0.6
Change in BI score with 3rd quartile of TNFR1 levels€	0.28	-0.58, 1.15	0.5
Change in BI score with 4th quartile of TNFR1 levels€	-0.56	-1.60, 0.47	0.3
Additional annual change in BI score with 2nd quartile of TNFR1 levels€	0.13	-0.19, 0.46	0.4
Additional annual change in BI score with 3rd quartile of TNFR1 levels€	-0.65	-1.34, 0.04	0.06
Additional annual change in BI score with 4th quartile of TNFR1 levels€	-0.72	-1.34, -0.10	0.02

TNFR1=tumor necrosis factor receptor-1; BI=Barthel index; MI=myocardial infarction; SD=standard deviation

€compared to the 1st quartile of TNFR1 levels

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Appendix A6. Associations between the highest quartile of tumor necrosis factor receptor-1 protein levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-0.92	-1.01, -0.82	<.0001
Change in BI score with highest quartile of TNFR1 levels€	-4.78	-6.22, -3.33	<.0001
Additional annual change in BI score with highest quartile of TNFR1 levels€	-0.60	-0.87, -0.34	<.0001
Adjusted for demographics:*			
Annual change in BI score	-0.93	-1.02, -0.83	<.0001
Change in BI score with highest quartile of TNFR1 levels€	-2.01	-3.51, -0.50	0.009
Additional annual change in BI score with highest quartile of TNFR1 levels€	-0.53	-0.79, -0.27	<.0001
Adjusted for vascular risk factors:**			
Annual change in BI score	-0.93	-1.02, -0.83	<.0001
Change in BI score with highest quartile of TNFR1 levels€	-0.81	-2.28, 0.66	0.3
Additional annual change in BI score with highest quartile of TNFR1 levels€	-0.55	-0.80, -0.29	<.0001
Adjusted for social variables:†			
Annual change in BI score	-0.92	-1.01, -0.82	<.0001
Change in BI score with highest quartile of TNFR1 levels€	-0.62	-2.09, 0.84	0.4
Additional annual change in BI score with highest quartile of TNFR1 levels€	-0.56	-0.82, -0.30	<.0001
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.43	-0.60, -0.26	<.0001
Change in BI score with highest quartile of TNFR1 levels€	-0.19	-1.20, 0.82	0.7
Additional annual change in BI score with highest quartile of TNFR1 levels€	-0.69	-1.32, -0.06	0.03
Adjusted for stroke and MI:π			
Annual change in BI score	-0.29	-0.46, -0.12	0.0009
Change in BI score with highest quartile of TNFR1 levels€	-0.49	-1.48, 0.51	0.3
Additional annual change in BI score with highest quartile of TNFR1 levels€	-0.64	-1.25, -0.04	0.04

TNFR1=tumor necrosis factor receptor-1; BI=Barthel index; MI=myocardial infarction; SD=standard deviation

€versus all other quartiles

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Appendix A7. Associations between log of interleukin-6 levels and trajectories of functional status; sensitivity analysis with 0 values set to missing

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-0.97	-1.07, -0.88	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.45	-0.88, -0.03	0.04
Additional annual change in BI score per unit increase in log of IL6 levels	-0.13	-0.23, -0.03	0.01
Adjusted for demographics:*			
Annual change in BI score	-0.98	-1.07, -0.88	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.05	-0.47, 0.38	0.8
Additional annual change in BI score per unit increase in log of IL6 levels	-0.13	-0.23, -0.03	0.009
Adjusted for vascular risk factors:**			
Annual change in BI score	-0.98	-1.08, -0.89	<.0001
Change in BI score per unit increase in log of IL6 levels	0.06	-0.37, 0.48	0.8
Additional annual change in BI score per unit increase in log of IL6 levels	-0.13	-0.23, -0.03	0.008
Adjusted for social variables:†			
Annual change in BI score	-0.97	-1.06, -0.88	<.0001
Change in BI score per unit increase in log of IL6 levels	0.07	-0.36, 0.50	0.8
Additional annual change in BI score per unit increase in log of IL6 levels	-0.13	-0.23, -0.03	0.01
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.44	-0.59, -0.29	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.11	-0.37, 0.15	0.4
Additional annual change in BI score per unit increase in log of IL6 levels	-0.06	-0.17, 0.06	0.3
Adjusted for stroke and MI:π			
Annual change in BI score	-0.32	-0.47, -0.16	<.0001
Change in BI score per unit increase in log of IL6 levels	-0.16	-0.42, 0.11	0.2
Additional annual change in BI score per unit increase in log of IL6 levels	-0.09	-0.21, 0.02	0.11

IL6=interleukin-6; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Appendix A8. Associations between dichotomized interleukin-6 levels and trajectories of functional status

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI score	-0.89	-1.01, -0.77	<.0001
Change in BI score with IL-6 levels above median	-1.10	-2.18, -0.02	0.046
Additional annual change in BI score with IL-6 levels above median	-0.20	-0.38, -0.01	0.04
Adjusted for demographics:*			
Annual change in BI score	-0.90	-1.02, -0.78	<.0001
Change in BI score with IL-6 levels above median	-0.12	-1.25, 1.02	0.8
Additional annual change in BI score with IL-6 levels above median	-0.18	-0.36, 0.002	0.052
Adjusted for vascular risk factors:**			
Annual change in BI score	-0.91	-1.03, -0.79	<.0001
Change in BI score with IL-6 levels above median	0.27	-0.86, 1.41	0.6
Additional annual change in BI score with IL-6 levels above median	-0.17	-0.36, 0.01	0.06
Adjusted for social variables:†			
Annual change in BI score	-0.90	-1.02, -0.78	<.0001
Change in BI score with IL-6 levels above median	0.31	-0.81, 1.43	0.6
Additional annual change in BI score with IL-6 levels above median	-0.16	-0.34, 0.02	0.076
Adjusted for mood and cognitive variables:‡			
Annual change in BI score	-0.43	-0.64, -0.22	<.0001
Change in BI score with IL-6 levels above median	-0.31	-0.99, 0.36	0.4
Additional annual change in BI score with IL-6 levels above median	-0.05	-0.40, 0.31	0.8
Adjusted for stroke and MI:π			
Annual change in BI score	-0.19	-0.36, -0.03	0.02
Change in BI score with IL-6 levels above median	-0.41	-1.08, 0.26	0.2
Additional annual change in BI score with IL-6 levels above median	-0.22	-0.55, 0.10	0.2

IL-6=interleukin-6; BI=Barthel index; MI=myocardial infarction

*adjusted for: baseline age, sex, and race-ethnicity

**additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index

†additionally adjusted for: marital status, insurance, number of friends, and years lived in the neighborhood

‡additionally adjusted for: depression, mini-mental state score, and Spitzer quality of life index

πadditionally adjusted for stroke or myocardial infarction occurring during follow-up

Appendix A9. Data on hospitalizations

A) Number of hospitalizations in entire follow-up dataset:

Event: hospitalized since our last contact				
Variable	**Frequency**	**Percent**	**Cumulative frequency**	**Cumulative percent**
Not hospitalized	30119	79.80	30119	79.80
Hospitalized	7625	20.20	37744	100.00

Frequency Missing = 4184

B) Distribution of number of hospitalizations per person:

Number	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	807	24.47	807	24.47
1	711	21.56	1518	46.03
2	591	17.92	2109	63.95
3	406	12.31	2515	76.26
4	289	8.76	2804	85.02
5	179	5.43	2983	90.45
6	124	3.76	3107	94.21
7	77	2.33	3184	96.54
8	45	1.36	3229	97.91
9	31	0.94	3260	98.85
10	19	0.58	3279	99.42
11	12	0.36	3291	99.79
12	2	0.06	3293	99.85
13	2	0.06	3295	99.91
14	2	0.06	3297	99.97
17	1	0.03	3298	100.00

C) Distribution of number of follow-ups per person:

Number	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	127	3.85	127	3.85
2	81	2.46	208	6.31
3	99	3.00	307	9.31
4	104	3.15	411	12.46
5	110	3.34	521	15.80

Number	Frequency	Percent	Cumulative Frequency	Cumulative Percent
6	122	3.70	643	19.50
7	102	3.09	745	22.59
8	92	2.79	837	25.38
9	95	2.88	932	28.26
10	130	3.94	1062	32.20
11	107	3.24	1169	35.45
12	110	3.34	1279	38.78
13	181	5.49	1460	44.27
14	319	9.67	1779	53.94
15	393	11.92	2172	65.86
16	377	11.43	2549	77.29
17	240	7.28	2789	84.57
18	335	10.16	3124	94.72
19	117	3.55	3241	98.27
20	45	1.36	3286	99.64
21	8	0.24	3294	99.88
22	3	0.09	3297	99.97
24	1	0.03	3298	100.00

D) Summary statistics for the ratio of (number of hospitalizations):(number of follow-ups):

Mean	Median	Lower Quartile	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
0.1952870	0.1428571	0.0526316	0.3076923	0.1873152	0	0.9285714	0	3298

E) Amount of time (in years) between post-non-stroke/MI hospitalization assessment and previous assessment (in dataset that excludes stroke and MI hospitalizations)

Mean	Median	Lower Quartile	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
1.0923451	1.0184805	0.9363450	1.1143053	0.5232751	0	11.4934976	32611	5965

F) Amount of time (in years) between post-hospitalization assessment and previous assessment (including stroke and MI hospitalizations and non-"vascular" hospitalizations)

Mean	Median	Lower Quartile	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
1.0508652	1.0130048	0.9144422	1.1088296	0.5442740	0	11.4934976	32611	6304

Appendix A10. Examination of the impact of loss to follow-up and death

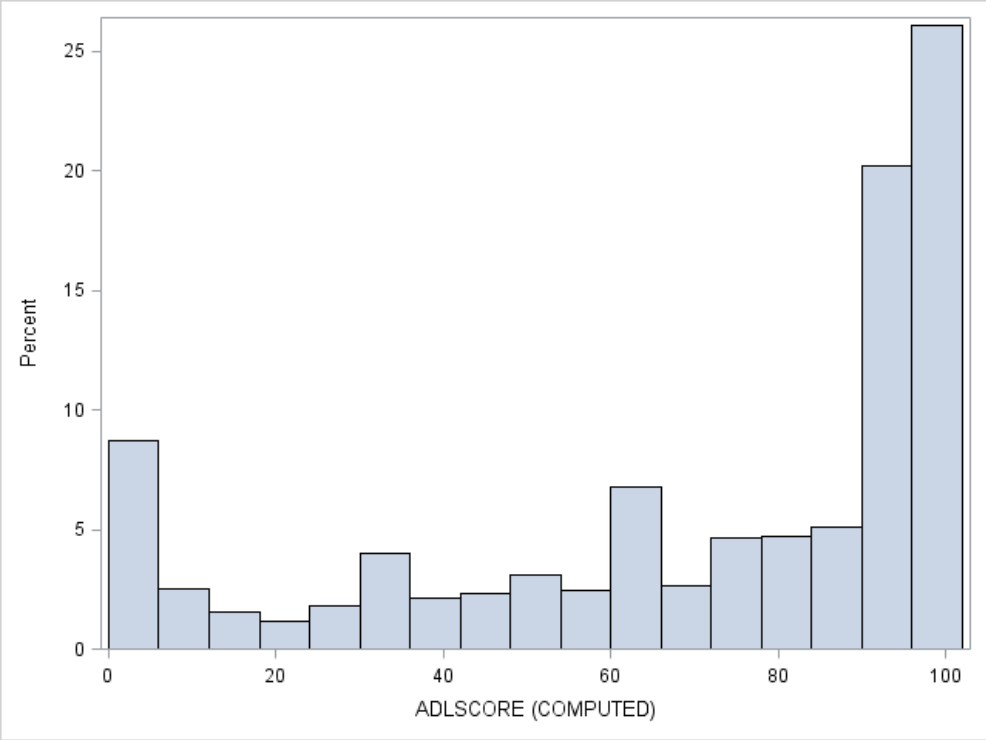
A) Time between last functional assessment and death:

N= 1604
N missing= 11
Mean= 0.74 years
Std dev= 0.76 years
Median= 0.60 years
Max= 7.62 years
Q3 = 0.93 years
Q1 = 0.29 years

B) Distribution of last ADL scores among those who died

ADLSCORE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	90	5.57	90	5.57
5	51	3.16	141	8.73
10	41	2.54	182	11.27
15	25	1.55	207	12.82
20	19	1.18	226	13.99
25	29	1.80	255	15.79
30	31	1.92	286	17.71
35	34	2.11	320	19.81
40	34	2.11	354	21.92
45	38	2.35	392	24.27
50	50	3.10	442	27.37
55	40	2.48	482	29.85
60	55	3.41	537	33.25
65	55	3.41	592	36.66
70	43	2.66	635	39.32
75	75	4.64	710	43.96
80	76	4.71	786	48.67
85	82	5.08	868	53.75
90	147	9.10	1015	62.85
95	179	11.08	1194	73.93
100	421	26.07	1615	100.00

C) Distribution of last ADL scores among those who died

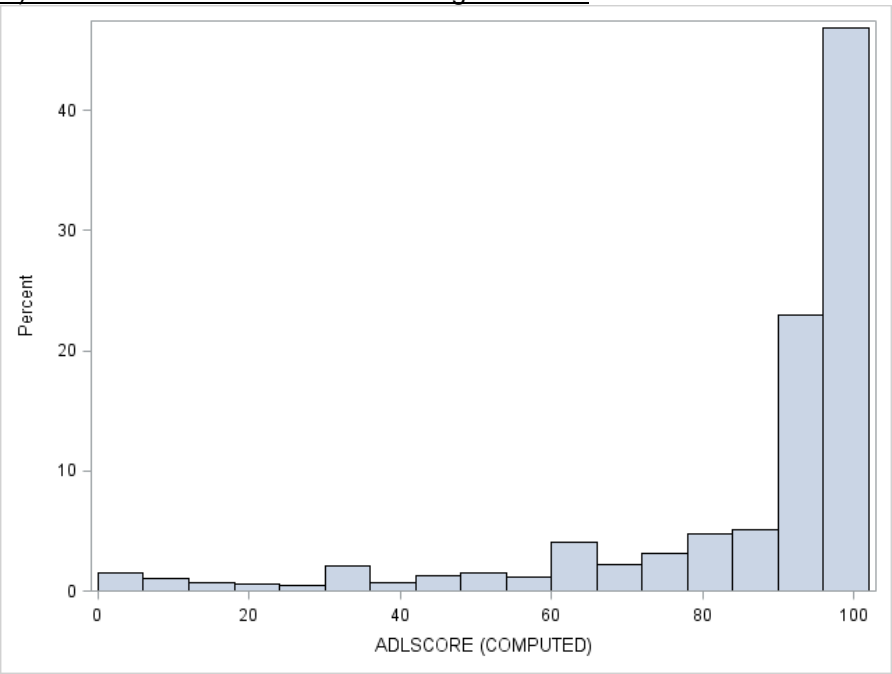


D) Categorization of the interval between last ADL and death, by Barthel index score

Frequency Percent Row Pct Col Pct	BI score	Interval between last ADL and death (yr)				
		<0.5	0.5 - 1	1 - 1.5	>1.5	Total
	<60	295 18.27 61.20 42.45	134 8.30 27.80 22.95	38 2.35 7.88 19.29	15 0.93 3.11 10.79	482 29.85
	60-90	197 12.20 36.96 28.35	221 13.68 41.46 37.84	72 4.46 13.51 36.55	43 2.66 8.07 30.94	533 33.00
	95-100	203 12.57 33.83 29.21	229 14.18 38.17 39.21	87 5.39 14.50 44.16	81 5.02 13.50 58.27	600 37.15

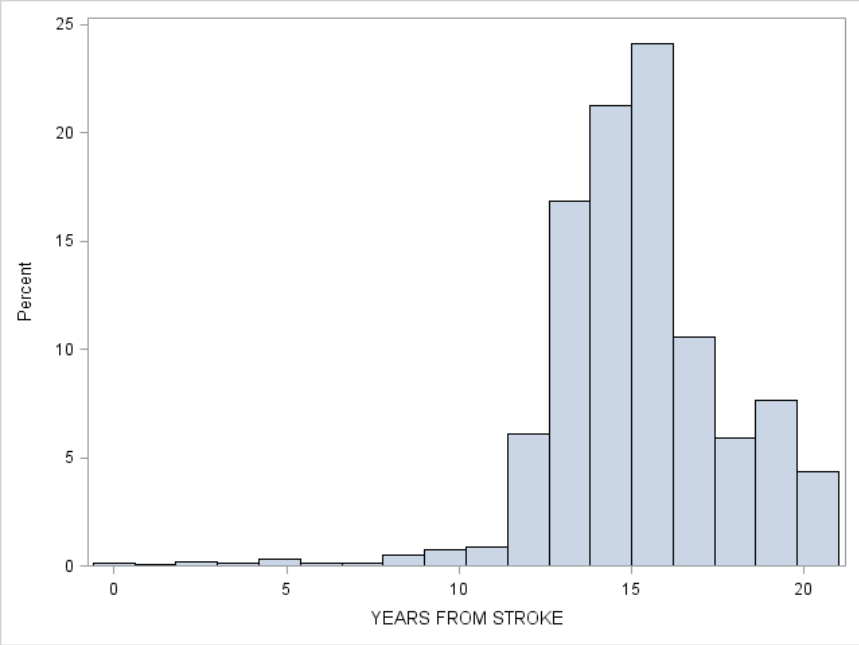
Total	695 43.03	584 36.16	197 12.20	139 8.61	1615 100.00

E) Distribution of last ADL score among survivors:



F) Distribution of maximum follow-up times among survivors:

Mean	Median	Lower Quartile	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
15.1775060	15.0773443	13.5167693	16.3613963	2.5662882	0	20.6160164	1	1683


25
20
15
10
5
0
Percent
0
5
10
15
20
YEARS FROM STROKE

Appendix B1. Location of silent brain infarcts, based on original dataset

A) Brain location of infarcts

Infarct location	Frequency	Percent
Basal ganglia	49	18.4
Brain stem	4	1.5
Caudate	20	7.5
Cerebellum	28	10.5
External capsule	15	5.6
Extreme capsule	8	3.0
Frontal cortex	23	8.6
Frontal white matter	42	15.8
Hippocampus	1	0.4
Internal capsule	12	4.5
Occipital cortex	1	0.4
Occipital white matter	4	1.5
Parietal cortex	11	4.1
Parietal white matter	23	8.6
Posterior cerebral artery territory	2	0.8
Temporal cortex	3	1.1
Temporal white matter	2	0.8
Thalamus	18	6.8

B) Number of superficial/cortical silent brain infarcts (52 missing)

Number	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1133	91.52	1133	91.52
1	89	7.19	1222	98.71
2	11	0.89	1233	99.60
3	4	0.32	1237	99.92
4	1	0.08	1238	100.00

C) Number of non-superficial/subcortical silent brain infarcts (52 missing)

Number	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1128	91.11	1128	91.11
1	88	7.11	1216	98.22
2	19	1.53	1235	99.76
3	3	0.24	1238	100.00

D) Superficial versus non-superficial silent brain infarct location (52 missing)

Location	Frequency	Percent	Cumulative Frequency	Cumulative Percent
None	1045	84.41	1045	84.41
Superficial	83	6.70	1128	91.11
Other	88	7.11	1216	98.22
Both	22	1.78	1238	100.00

Appendix B2. Silent brain infarcts, perivascular spaces, and lacunar infarcts based on new dataset

A) Frequency of silent brain infarcts (lacunar + cortical + cerebellar, 82 missing)

	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No silent brain infarct	964	79.80	964	79.80
Silent brain infarct	244	20.20	1208	100.00

B) Frequency of large perivascular spaces (82 missing)

	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No large perivascular spaces	700	57.95	700	57.95
At least one perivascular space	508	42.05	1208	100.00

C) Number of large perivascular spaces per individual (82 missing)

Number	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	700	57.95	700	57.95
1	255	21.11	955	79.06
2	169	13.99	1124	93.05
3	52	4.30	1176	97.35
4	18	1.49	1194	98.84
5	9	0.75	1203	99.59
6	3	0.25	1206	99.83
8	2	0.17	1208	100.00

D) Frequency of lacunar infarct (82 missing)

	Frequency	Percent	Cumulative Frequency	Cumulative Percent
No lacunar infarct	993	82.20	993	82.20
Lacunar infarct	215	17.80	1208	100.00

E) Distribution of the number of lacunar infarcts (82 missing)

Number	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	993	82.20	993	82.20
1	116	9.60	1109	91.80
2	55	4.55	1164	96.36
3	27	2.24	1191	98.59
4	10	0.83	1201	99.42
5	3	0.25	1204	99.67
6	3	0.25	1207	99.92
7	1	0.08	1208	100.00

F) Total perivascular space score (82 missing)

Score	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	110	9.11	110	9.11
1	34	2.81	144	11.92
2	107	8.86	251	20.78
3	113	9.35	364	30.13
4	193	15.98	557	46.11
5	141	11.67	698	57.78
6	126	10.43	824	68.21

7	84	6.95	908	75.17
8	74	6.13	982	81.29
9	58	4.80	1040	86.09
10	36	2.98	1076	89.07
11	47	3.89	1123	92.96
12	28	2.32	1151	95.28
13	12	0.99	1163	96.27
14	14	1.16	1177	97.43
15	9	0.75	1186	98.18
16	9	0.75	1195	98.92
17	6	0.50	1201	99.42
18	2	0.17	1203	99.59
19	2	0.17	1205	99.75
20	2	0.17	1207	99.92
22	1	0.08	1208	100.00

Appendix B3. Location of lacunar infarct, in new dataset

A) Three-level location variable (83 missing)

Location	Frequency	Percent	Cumulative Frequency	Cumulative Percent
None	2154	85.10	2154	85.10
Subcortical	122	4.82	2276	89.92
Cortical	255	10.08	2531	100.00

B) Four-level location variable (83 missing)

Location	Frequency	Percent	Cumulative Frequency	Cumulative Percent
None	2154	85.10	2154	85.10
Subcortical	109	4.31	2263	89.41
Cortical	255	10.08	2518	99.49
Brainstem and cerebellum	13	0.51	2531	100.00

C) Separate location variables, with number of infarcts in each location

1) Subcortical location (total infarcts=109)

Number of subcortical infarcts	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1203	93.26	1203	93.26
1	70	5.43	1273	98.68
2	13	1.01	1286	99.69
3	3	0.23	1289	99.92
4	1	0.08	1290	100.00

2) Cortical location (total infarcts=255)

Number of cortical infarcts	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1129	87.52	1129	87.52
1	102	7.91	1231	95.43
2	40	3.10	1271	98.53
3	10	0.78	1281	99.30
4	6	0.47	1287	99.77
6	2	0.16	1289	99.92
7	1	0.08	1290	100.00

3) Brainstem location (total infarcts=13)

Number of cortical infarcts	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1277	98.99	1277	98.99
1	13	1.01	1290	100.00

D) Location of silent brain infarcts

Location	Frequency	Percent	Cumulative Frequency	Cumulative Percent
None	1076	83.41	1076	83.41
Cortical	117	9.07	1193	92.48
Subcortical	53	4.11	1246	96.59
Both cortical and subcortical	44	3.41	1290	100.00

Appendix B4. Distribution of time (in years) from baseline enrollment to time of MRI

Mean	Median	Lower Quartile	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
6.0800216	6.2381930	4.2874743	8.2327173	3.4327731	0	14.0177960	0	1290

Appendix B5. Distributions of inflammatory biomarkers in those with MRI data

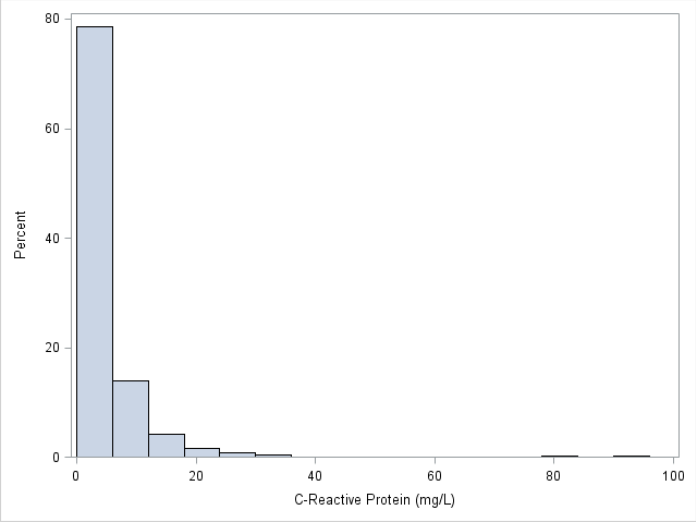
A) Distributions

Variable	Mean	Median	Lower Quartile	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
C-reactive protein	4.46	2.29	0.98	5.48	7.26	0.05	93.40	498	792
Tumor necrosis factor receptor-1	2.23	2.16	1.71	2.65	0.85	0.09	6.40	639	651
Interleukin-6	42.93	1.35	0.81	2.39	451.02	0.00	5000.00	680	610
LpPLA2 activity	301.78	297.64	237.25	361.07	90.06	28.12	888.54	595	695
LpPLA2 mass	116.58	113.38	96.10	136.23	29.03	37.67	216.58	605	685

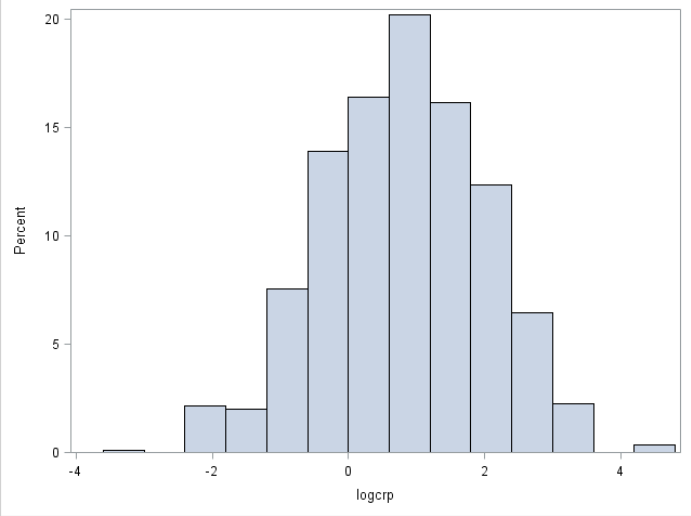
LpPLA2=lipoprotein phospholipase A2

B) Distribution plots of each inflammatory biomarker

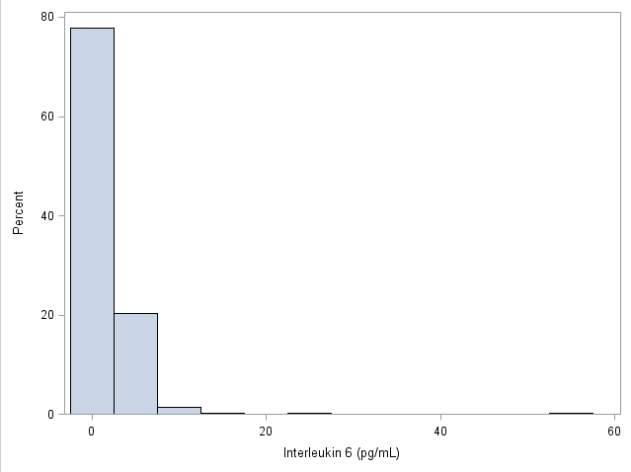
1) C-reactive protein:



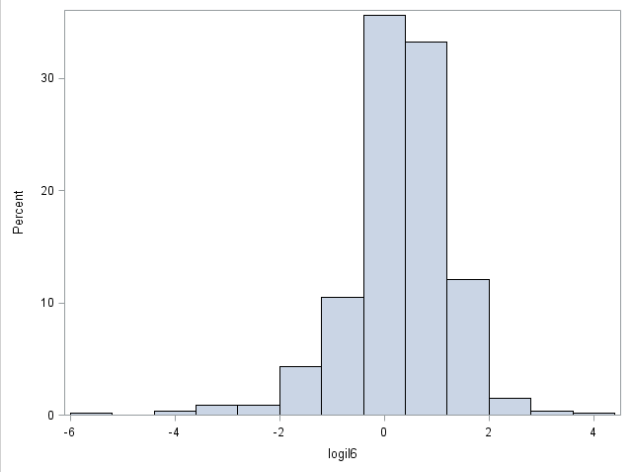
2) log of C-reactive protein values



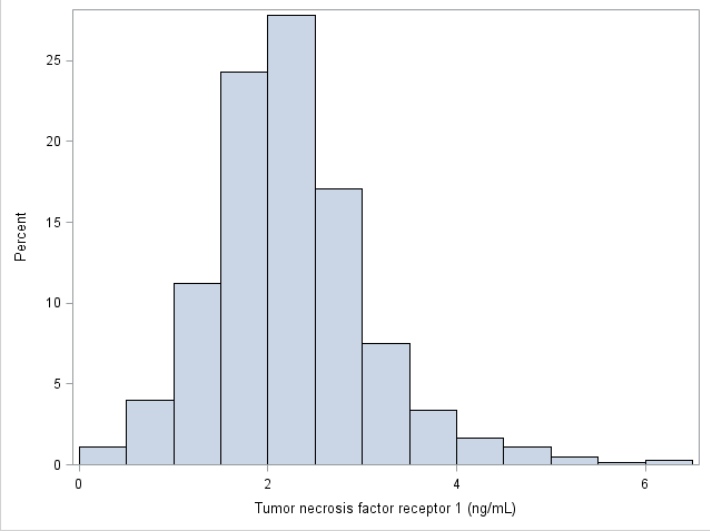
3) Interleukin-6, with 5 values of 5000 set to missing:



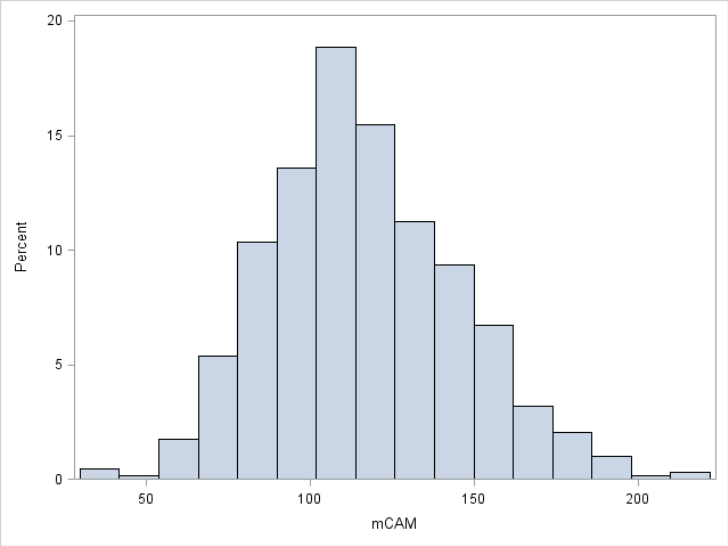
4) log of interleukin-6 levels:



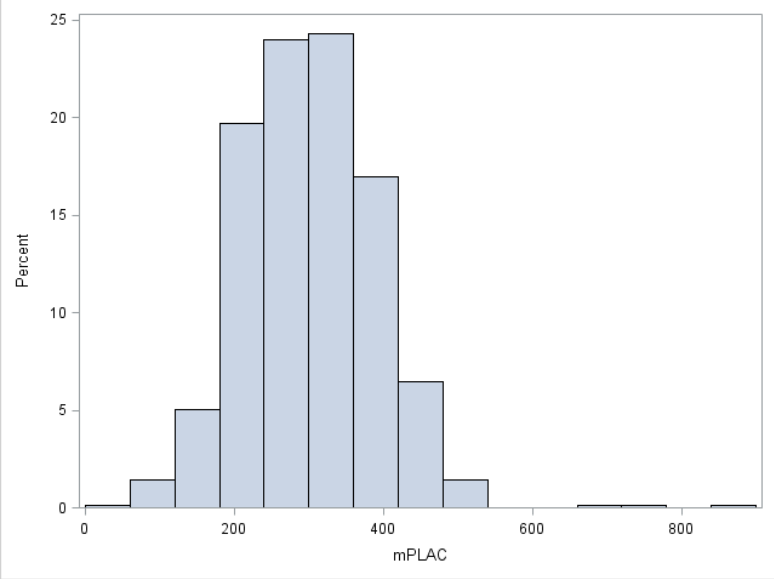
5) Tumor necrosis factor receptor-1:



6) Lipoprotein phospholipase A2 mass:



7) Lipoprotein phospholipase A2 activity:



Appendix B6. Baseline characteristics of the MRI cohort, by availability of inflammatory labs

Variable	Cohort with inflammatory labs	Cohort without inflammatory labs	p-value
Number of participants, No. (%)	911 (70.6)	379 (29.4)	
Biological characteristics:			
Age, mean (SD), y	64.7 (8.1)	64.1 (9.1)	0.3
Body mass index, mean (SD), kg/m^2	28.0 (4.7)	27.6 (5.1)	0.3
Demographics:			
Male, No. (%)	366 (40.2)	144 (38.0)	0.5
Race-ethnicity:			0.9
Non-Hispanic white, No. (%)	134 (14.7)	57 (15.0)	
Non-Hispanic black, No. (%)	159 (17.5)	64 (16.9)	
Hispanic, No. (%)	596 (65.4)	251 (66.2)	
Other, No. (%)	22 (2.4)	7 (1.9)	
Received at least high school education, No. (%)	410 (45.0)	182 (48.0)	0.3
Marital status, No. (%) married	345 (37.9)	198 (52.2)	<0.0001
Health insurance, No. (%)			0.3
Medicaid or no insurance	441 (48.4)	172 (45.4)	
Medicare or private insurance	470 (51.6)	207 (54.6)	
Medicaid health insurance, No. (%)	299 (32.8)	119 (31.4)	0.6
Medicare health insurance, No. (%)	416 (45.7)	181 (47.8)	0.5
Private insurance, No. (%)	373 (40.9)	168 (44.3)	0.3
Vascular risk factors, No. (%)			
Hypertension	626 (68.7)	235 (62.0)	0.02
Systolic BP, mean (SD)	140.6 (19.8)	140.7 (1.5)	0.9
Diastolic BP, mean (SD)	83.8 (10.6)	82.8 (10.6)	0.3
Alcohol consumption	[NR]	[NR]	0.2
Physical activity	[NR]	[NR]	0.8
Diabetes mellitus	168 (18.4)	77 (20.3)	0.4
Smoking:			0.8
Never	437 (48.0)	175 (46.2)	
Former	346 (38.0)	150 (39.6)	
Current	128 (14.1)	54 (14.3)	
Hypercholesterolemia	588 (64.5)	209 (55.2)	0.002
Total cholesterol, mean (SD), mg/dL	202.7 (38.7)	201.0 (36.7)	0.6
High-density lipoprotein, mean (SD), mg/dL	45.7 (14.0)	47.2 (13.4)	0.2
Low-density lipoprotein, mean (SD), mg/dL	130.5 (35.2)	127.0 (32.0)	0.2
History of atrial fibrillation	25 (2.7)	6 (1.6)	0.2
History of coronary heart disease	134 (14.7)	43 (11.4)	0.1
Other medical conditions, No. (%)			
Hamilton depression scale score, mean (SD)	3.2 (3.8)	2.8 (3.8)	0.2
Hamilton depression score $\geq$12			
Chronic bronchitis, asthma, or emphysema	85 (9.4)	35 (9.3)	0.97
Mini mental state score, mean (SD)	26.6 (3.4)	27.0 (3.2)	0.1
History of migraine headaches	171 (18.8)	60 (15.9)	0.2
Spitzer quality of life index score	9.36 (0.99)	9.24 (1.16)	0.2
Social variables, No. (%)			

Number of people known well enough to visit with in their homes:			0.002
None	21 (2.3)	15 (4.0)	
1 or 2	74 (8.1)	50 (13.2)	
3 or 4	178 (19.5)	85 (22.4)	
5 or more	638 (70.0)	229 (60.4)	
Number of times talked to someone on telephone in past week:			0.0003
Not at all	12 (1.3)	12 (3.2)	
Once	54 (5.9)	22 (5.8)	
Two to six times	238 (26.1)	135 (35.6)	
Once a day or more	607 (66.6)	210 (55.4)	
Number of times in past week spent with someone who does not live with you:			0.005
Not at all	158 (17.3)	81 (21.4)	
Once	194 (21.3)	100 (26.4)	
Two to six times	402 (44.1)	127 (33.5)	
Once a day or more	157 (17.2)	71 (18.7)	
Have someone you can trust and confide in	[NR]	[NR]	0.2
Feeling lonely:			0.01
Quite often	130 (14.3)	42 (11.1)	
Sometimes	296 (32.5)	101 (26.7)	
Almost never	485 (53.2)	236 (62.3)	
See relatives and friends	[NR]	[NR]	0.2
Is there someone who would give you help if sick	[NR]	[NR]	0.2
Years lived in community	25.0 (14.9)	26.1 (14.8)	0.2

Appendix B7. Distribution of baseline Barthel index scores

Baseline Barthel index score	Frequency	Percent	Cumulative Frequency	Cumulative Percent
45	3	0.23	3	0.23
55	2	0.16	5	0.39
60	3	0.23	8	0.63
65	5	0.39	13	1.02
70	5	0.39	18	1.41
75	9	0.70	27	2.11
80	20	1.56	47	3.67
85	41	3.20	88	6.88
90	56	4.38	144	11.25
95	267	20.86	411	32.11
100	869	67.89	1280	100.00

Appendix B8. Unadjusted and adjusted models of the association between number of lacunar infarcts (categorical variable) and functional status, using the new dataset

Variable	Change in BI score	95% CI	p-value
Unadjusted model:			
Annual change in BI	-0.86	-1.01, -0.70	<.0001
Change in BI with 1 lacunar infarct, vs. none	1.78	-0.03, 3.58	0.054
Change in BI with 2 lacunar infarcts, vs. none	-2.15	-4.48, 0.18	0.07
Change in BI with 3 lacunar infarcts, vs. none	-4.80	-12.24, 2.63	0.2
Change in BI with >=4 lacunar infarcts, vs. none	-6.64	-20.47, 7.19	0.3
Additional annual change with 1 lacunar infarct, vs. none	-1.12	-1.81, -0.44	0.001
Additional annual change with 2 lacunar infarcts, vs. none	-0.84	-1.58, -0.10	0.03
Additional annual change with 3 lacunar infarcts, vs. none	-2.68	-4.84, -0.51	0.02
Additional annual change with >=4 lacunar infarcts, vs. none	-0.87	-3.70, 1.96	0.5
Adjusted for demographics:†			
Annual change in BI	-0.87	-1.02, -0.72	<.0001
Change in BI with 1 lacunar infarct, vs. none	2.94	0.88, 5.01	0.005
Change in BI with 2 lacunar infarcts, vs. none	-0.35	-2.83, 2.12	0.8
Change in BI with 3 lacunar infarcts, vs. none	-0.91	-9.70, 7.89	0.8
Change in BI with >=4 lacunar infarcts, vs. none	-4.80	-18.43, 8.83	0.5
Additional annual change with 1 lacunar infarct, vs. none	-1.14	-1.84, -0.43	0.003
Additional annual change with 2 lacunar infarcts, vs. none	-0.84	-1.58, -0.10	0.04
Additional annual change with 3 lacunar infarcts, vs. none	-2.97	-5.32, -0.62	0.01
Additional annual change with >=4 lacunar infarcts, vs. none	-0.83	-3.67, 2.02	0.6
Adjusted for vascular risk factors:*			
Annual change in BI	-0.91	-1.08, -0.75	<.0001
Change in BI with 1 lacunar infarct, vs. none	3.20	0.76, 5.64	0.01
Change in BI with 2 lacunar infarcts, vs. none	0.09	-2.48, 2.66	0.9
Change in BI with 3 lacunar infarcts, vs. none	-1.42	-11.15, 8.32	0.8
Change in BI with >=4 lacunar infarcts, vs. none	-5.03	-19.68, 9.62	0.5
Additional annual change with 1 lacunar infarct, vs. none	-1.33	-2.14, -0.52	0.001
Additional annual change with 2 lacunar infarcts, vs. none	-0.70	-1.44, 0.04	0.06
Additional annual change with 3 lacunar infarcts, vs. none	-2.52	-4.79, -0.26	0.03
Additional annual change with >=4 lacunar infarcts, vs. none	-0.41	-3.30, 2.48	0.8
Adjusted for social variables:**			
Annual change in BI	-0.91	-1.08, -0.75	<.0001
Change in BI with 1 lacunar infarct, vs. none	3.28	0.85, 5.71	0.008
Change in BI with 2 lacunar infarcts, vs. none	0.61	-1.99, 3.21	0.6
Change in BI with 3 lacunar infarcts, vs. none	-1.34	-11.21, 8.53	0.8
Change in BI with >=4 lacunar infarcts, vs. none	-5.44	-20.22, 9.34	0.5
Additional annual change with 1 lacunar infarct, vs. none	-1.33	-2.15, -0.52	0.001
Additional annual change with 2 lacunar infarcts, vs. none	-0.70	-1.44, 0.04	0.06
Additional annual change with 3 lacunar infarcts, vs. none	-2.51	-4.76, -0.25	0.03

Additional annual change with >=4 lacunar infarcts, vs. none	-0.41	-3.31, 2.48	0.8
Adjusted for cognition:π			
Annual change in BI	-0.91	-1.08, -0.75	<.0001
Change in BI with 1 lacunar infarct, vs. none	3.31	0.91, 5.72	0.007
Change in BI with 2 lacunar infarcts, vs. none	0.59	-2.05, 3.22	0.7
Change in BI with 3 lacunar infarcts, vs. none	-1.39	-11.27, 8.49	0.8
Change in BI with >=4 lacunar infarcts, vs. none	-5.08	-19.84, 9.68	0.5
Additional annual change with 1 lacunar infarct, vs. none	-1.34	-2.15, -0.52	0.001
Additional annual change with 2 lacunar infarcts, vs. none	-0.70	-1.44, 0.04	0.06
Additional annual change with 3 lacunar infarcts, vs. none	-2.51	-4.76, -0.25	0.03
Additional annual change with >=4 lacunar infarcts, vs. none	-0.43	-3.32, 2.47	0.8
Adjusted for quality of life and depression: ††			
Annual change in BI	-0.92	-1.09, -0.76	<.0001
Change in BI with 1 lacunar infarct, vs. none	3.16	0.71, 5.62	0.01
Change in BI with 2 lacunar infarcts, vs. none	0.58	-2.11, 3.27	0.7
Change in BI with 3 lacunar infarcts, vs. none	-1.41	-11.33, 8.52	0.8
Change in BI with >=4 lacunar infarcts, vs. none	-5.20	-19.90, 9.49	0.5
Additional annual change with 1 lacunar infarct, vs. none	-1.32	-2.13, -0.51	0.001
Additional annual change with 2 lacunar infarcts, vs. none	-0.68	-1.42, 0.05	0.07
Additional annual change with 3 lacunar infarcts, vs. none	-2.48	-4.73, -0.24	0.03
Additional annual change with >=4 lacunar infarcts, vs. none	-0.43	-3.32, 2.47	0.8
Adjusted for stroke and MI: ‡			
Annual change in BI	-0.81	-0.97, -0.65	<.0001
Change in BI with 1 lacunar infarct, vs. none	3.38	0.91, 5.85	0.007
Change in BI with 2 lacunar infarcts, vs. none	1.14	-1.77, 4.05	0.4
Change in BI with 3 lacunar infarcts, vs. none	-1.18	-10.17, 7.81	0.8
Change in BI with >=4 lacunar infarcts, vs. none	-4.61	-17.45, 8.24	0.5
Additional annual change with 1 lacunar infarct, vs. none	-1.27	-2.08, -0.45	0.002
Additional annual change with 2 lacunar infarcts, vs. none	-0.67	-1.33, -0.02	0.04
Additional annual change with 3 lacunar infarcts, vs. none	-2.00	-4.19, 0.19	0.07
Additional annual change with >=4 lacunar infarcts, vs. none	-0.49	-3.34, 2.36	0.7

BI=Barthel index; CI=confidence interval; MI=myocardial infarction

†adjusted for age at time of MRI, sex, race

*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI

**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community

πadditionally adjusted for mini-mental state score

†† additionally adjusted for Spitzer quality of life index and depression

‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Appendix B9. Unadjusted and adjusted models of the association between silent brain infarcts and functional status, stratified by mobility vs. non-mobility domains, using the original dataset

	Mobility domain			Non-mobility domain		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted model:						
Annual change in BI	-0.39	-0.46, -0.32	<.0001	-0.49	-0.59, -0.40	<.0001
Change in BI with SBI	-0.43	-1.38, 0.53	0.4	-0.40	-1.76, 0.95	0.6
Additional annual change with SBI	-0.45	-0.67, -0.23	<.0001	-0.64	-0.99, -0.29	0.0003
Adjusted for demographics:†						
Annual change in BI	-0.40	-0.47, -0.33	<.0001	-0.50	-0.60, -0.41	<.0001
Change in BI with SBI	0.39	-0.61, 1.40	0.4	0.58	-0.87, 2.02	0.4
Additional annual change with SBI	-0.46	-0.68, -0.23	<.0001	-0.64	-1.00, -0.28	0.0005
Adjusted for vascular risk factors:*						
Annual change in BI	-0.40	-0.47, -0.33	<.0001	-0.51	-0.60, -0.41	<.0001
Change in BI with SBI	0.44	-0.56, 1.45	0.4	0.63	-0.82, 2.08	0.4
Additional annual change with SBI	-0.46	-0.68, -0.23	<.0001	-0.64	-1.00, -0.28	0.0005
Adjusted for social variables:**						
Annual change in BI	-0.40	-0.47, -0.33	<.0001	-0.51	-0.60, -0.41	<.0001
Change in BI with SBI	0.50	-0.50, 1.51	0.3	0.70	-0.75, 2.15	0.3
Additional annual change with SBI	-0.46	-0.68, -0.23	<.0001	-0.64	-1.00, -0.28	0.0005
Adjusted for cognition:π						
Annual change in BI	-0.40	-0.47, -0.33	<.0001	-0.51	-0.60, -0.41	<.0001
Change in BI with SBI	0.52	-0.48, 1.53	0.3	0.72	-0.73, 2.17	0.3
Additional annual change with SBI	-0.45	-0.67, -0.22	<.0001	-0.63	-0.99, -0.27	0.0006
Adjusted for quality of life and depression: ††						
Annual change in BI	-0.42	-0.50, -0.35	<.0001	-0.54	-0.64, -0.44	<.0001
Change in BI with SBI	0.34	-0.73, 1.42	0.5	0.56	-1.01, 2.14	0.5
Additional annual change with SBI	-0.43	-0.66, -0.20	0.0003	-0.59	-0.96, -0.22	0.002
Adjusted for stroke and MI: ‡						
Annual change in BI	-0.38	-0.45, -0.30	<.0001	-0.47	-0.57, -0.37	<.0001
Change in BI with SBI	0.43	-0.59, 1.45	0.4	0.68	-0.81, 2.17	0.4
Additional annual change with SBI	-0.37	-0.59, -0.14	0.0016	-0.51	-0.86, -0.15	0.006

BI=Barthel index; CI=confidence interval; SBI=silent brain infarct; MI=myocardial infarction
NOTE: The mobility domain includes transfers, mobility, and stair use; the non-mobility domain includes feeding, bathing, grooming, dressing, bowels, bladder, and toilet use
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Appendix B10. Unadjusted and adjusted models of the association between standardized white matter hyperintensity volume (WMH/TCV), stratified by mobility vs. non-mobility domains, using the original dataset

	Mobility domain			Non-mobility domain		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted model:						
Annual change in BI	-0.49	-0.55, -0.42	<.0001	-0.63	-0.73, -0.54	<.0001
Change in BI with 1 unit increase in WMH	-0.55	-0.98, -0.12	0.013	-0.55	-1.16, 0.06	0.08
Additional annual change with 1 unit increase in WMH	-0.31	-0.41, -0.21	<.0001	-0.49	-0.65, -0.34	<.0001
Adjusted for demographics:†						
Annual change in BI	-0.49	-0.56, -0.43	<.0001	-0.64	-0.74, -0.54	<.0001
Change in BI with 1 unit increase in WMH	0.05	-0.39, 0.49	0.8	0.07	-0.57, 0.71	0.8
Additional annual change with 1 unit increase in WMH	-0.32	-0.42, -0.22	<.0001	-0.50	-0.65, -0.34	<.0001
Adjusted for vascular risk factors:*						
Annual change in BI	-0.51	-0.58, -0.44	<.0001	-0.66	-0.76, -0.55	<.0001
Change in BI with 1 unit increase in WMH	0.16	-0.34, 0.66	0.5	0.13	-0.60, 0.86	0.7
Additional annual change with 1 unit increase in WMH	-0.30	-0.40, -0.19	<.0001	-0.47	-0.64, -0.31	<.0001
Adjusted for social variables:**						
Annual change in BI	-0.51	-0.58, -0.44	<.0001	-0.66	-0.76, -0.55	<.0001
Change in BI with 1 unit increase in WMH	0.18	-0.33, 0.68	0.5	0.16	-0.58, 0.89	0.7
Additional annual change with 1 unit increase in WMH	-0.30	-0.40, -0.19	<.0001	-0.48	-0.64, -0.31	<.0001
Adjusted for cognition:π						
Annual change in BI	-0.51	-0.58, -0.44	<.0001	-0.66	-0.76, -0.55	<.0001
Change in BI with 1 unit increase in WMH	0.17	-0.34, 0.67	0.5	0.14	-0.60, 0.87	0.7
Additional annual change with 1 unit increase in WMH	-0.30	-0.40, -0.19	<.0001	-0.47	-0.64, -0.31	<.0001
Adjusted for quality of life and depression: ††						
Annual change in BI	-0.51	-0.58, -0.44	<.0001	-0.66	-0.77, -0.56	<.0001
Change in BI with 1 unit increase in WMH	0.19	-0.30, 0.68	0.5	0.15	-0.57, 0.88	0.7
Additional annual change with 1 unit increase in WMH	-0.30	-0.40, -0.19	<.0001	-0.47	-0.64, -0.31	<.0001
Adjusted for stroke and MI: ‡						
Annual change in BI	-0.45	-0.52, -0.38	<.0001	-0.58	-0.69, -0.48	<.0001
Change in BI with 1 unit increase in WMH	0.29	-0.18, 0.76	0.2	0.29	-0.38, 0.96	0.4
Additional annual change with 1 unit increase in WMH	-0.28	-0.38, -0.18	<.0001	-0.45	-0.61, -0.30	<.0001

BI=Barthel index; CI=confidence interval; WMH=white matter hyperintensity; TCV=total cranial volume; MI=myocardial infarction

NOTE: The mobility domain includes transfers, mobility, and stair use; the non-mobility domain includes feeding, bathing, grooming, dressing, bowels, bladder, and toilet use
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Appendix B11. Unadjusted and adjusted models of the association between silent brain infarcts and functional status, stratified by mobility vs. non-mobility domains, using the new dataset

	Mobility domain			Non-mobility domain		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted model:						
Annual change in BI	-0.39	-0.46, -0.32	<.0001	-0.47	-0.56, -0.38	<.0001
Change in BI with SBI	-0.72	-1.51, 0.06	0.07	-0.48	-1.61, 0.65	0.4
Additional annual change with SBI	-0.38	-0.58, -0.18	0.0002	-0.61	-0.92, -0.29	0.0002
Adjusted for demographics:†						
Annual change in BI	-0.40	-0.46, -0.33	<.0001	-0.48	-0.58, -0.39	<.0001
Change in BI with SBI	0.0002	-0.84, 0.84	0.99	0.37	-0.85, 1.58	0.6
Additional annual change with SBI	-0.38	-0.58, -0.18	0.0002	-0.61	-0.93, -0.29	0.0002
Adjusted for vascular risk factors:*						
Annual change in BI	-0.41	-0.49, -0.34	<.0001	-0.50	-0.61, -0.40	<.0001
Change in BI with SBI	-0.04	-1.00, 0.91	0.9	0.53	-0.86, 1.91	0.5
Additional annual change with SBI	-0.38	-0.60, -0.17	0.0005	-0.61	-0.95, -0.26	0.0007
Adjusted for social variables:**						
Annual change in BI	-0.41	-0.49, -0.34	<.0001	-0.50	-0.60, -0.40	<.0001
Change in BI with SBI	0.05	-0.91, 1.01	0.9	0.63	-0.77, 2.03	0.4
Additional annual change with SBI	-0.38	-0.60, -0.16	0.0005	-0.60	-0.95, -0.26	0.0007
Adjusted for cognition:π						
Annual change in BI	-0.41	-0.49, -0.34	<.0001	-0.50	-0.61, -0.40	<.0001
Change in BI with SBI	0.05	-0.91, 1.01	0.9	0.63	-0.77, 2.03	0.4
Additional annual change with SBI	-0.38	-0.60, -0.16	0.0005	-0.60	-0.95, -0.26	0.0007
Adjusted for quality of life and depression: ††						
Annual change in BI	-0.42	-0.49, -0.34	<.0001	-0.51	-0.61, -0.41	<.0001
Change in BI with SBI	0.02	-0.94, 0.97	0.97	0.58	-0.83, 1.99	0.4
Additional annual change with SBI	-0.38	-0.59, -0.16	0.0006	-0.60	-0.95, -0.25	0.0007
Adjusted for stroke and MI: ‡						
Annual change in BI	-0.37	-0.44, -0.30	<.0001	-0.45	-0.55, -0.35	<.0001
Change in BI with SBI	0.22	-0.70, 1.14	0.6	0.86	-0.49, 2.20	0.2
Additional annual change with SBI	-0.34	-0.55, -0.12	0.002	-0.55	-0.89, -0.20	0.0018

BI=Barthel index; CI=confidence interval; SBI=silent brain infarct; MI=myocardial infarction
NOTE: The mobility domain includes transfers, mobility, and stair use; the non-mobility domain includes feeding, bathing, grooming, dressing, bowels, bladder, and toilet use
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Appendix B12. Unadjusted and adjusted models of the association between lacunar infarcts and functional status, stratified by mobility vs. non-mobility domains, using the new dataset

	Mobility domain			Non-mobility domain		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted model:						
Annual change in BI	-0.39	-0.45, -0.32	<.0001	-0.47	-0.56, -0.37	<.0001
Change in BI with LI	-0.50	-1.31, 0.31	0.2	-0.24	-1.46, 0.98	0.7
Additional annual change with LI	-0.45	-0.67, -0.24	<.0001	-0.73	-1.08, -0.38	<.0001
Adjusted for demographics:†						
Annual change in BI	-0.39	-0.46, -0.32	<.0001	-0.47	-0.57, -0.38	<.0001
Change in BI with LI	0.33	-0.55, 1.21	0.5	0.72	-0.59, 2.03	0.3
Additional annual change with LI	-0.46	-0.68, -0.24	<.0001	-0.74	-1.10, -0.38	<.0001
Adjusted for vascular risk factors:*						
Annual change in BI	-0.41	-0.49, -0.34	<.0001	-0.50	-0.60, -0.40	<.0001
Change in BI with LI	0.31	-0.69, 1.31	0.5	0.85	-0.65, 2.35	0.3
Additional annual change with LI	-0.46	-0.70, -0.22	0.0001	-0.74	-1.13, -0.34	0.0002
Adjusted for social variables:**						
Annual change in BI	-0.41	-0.48, -0.34	<.0001	-0.50	-0.60, -0.40	<.0001
Change in BI with LI	0.38	-0.63, 1.39	0.5	0.94	-0.58, 2.45	0.2
Additional annual change with LI	-0.46	-0.70, -0.22	0.0001	-0.73	-1.12, -0.34	0.0002
Adjusted for cognition:π						
Annual change in BI	-0.41	-0.49, -0.34	<.0001	-0.50	-0.60, -0.40	<.0001
Change in BI with LI	0.39	-0.61, 1.40	0.4	0.96	-0.55, 2.47	0.2
Additional annual change with LI	-0.46	-0.70, -0.22	0.0001	-0.74	-1.13, -0.35	0.0002
Adjusted for quality of life and depression: ††						
Annual change in BI	-0.41	-0.49, -0.34	<.0001	-0.51	-0.61, -0.41	<.0001
Change in BI with LI	0.36	-0.65, 1.37	0.5	0.91	-0.62, 2.44	0.2
Additional annual change with LI	-0.45	-0.69, -0.22	0.0002	-0.73	-1.12, -0.34	0.0003
Adjusted for stroke and MI: ‡						
Annual change in BI	-0.37	-0.44, -0.30	<.0001	-0.44	-0.54, -0.35	<.0001
Change in BI with LI	0.51	-0.47, 1.48	0.3	1.11	-0.34, 2.56	0.13
Additional annual change with LI	-0.42	-0.65, -0.19	0.0004	-0.68	-1.06, -0.30	0.0005

BI=Barthel index; CI=confidence interval; LI=lacunar infarct; MI=myocardial infarction

NOTE: The mobility domain includes transfers, mobility, and stair use; the non-mobility domain includes feeding, bathing, grooming, dressing, bowels, bladder, and toilet use

†adjusted for age at time of MRI, sex, race

*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI

**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community

πadditionally adjusted for mini-mental state score

†† additionally adjusted for Spitzer quality of life index and depression

‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Appendix B13. Unadjusted and adjusted models of the association between number of lacunar infarcts and functional status, stratified by mobility vs. non-mobility domains, using the new dataset

	Mobility domain			Non-mobility domain		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted model:						
Annual change in BI	-0.41	-0.48, -0.34	<.0001	-0.49	-0.59, -0.40	<.0001
Change in BI with 1 additional LI	-0.50	-1.06, 0.06	0.08	-0.55	-1.41, 0.30	0.2
Additional annual change with 1 additional LI	-0.18	-0.30, -0.06	0.004	-0.33	-0.54, -0.12	0.002
Adjusted for demographics:†						
Annual change in BI	-0.41	-0.48, -0.35	<.0001	-0.50	-0.60, -0.41	<.0001
Change in BI with 1 additional LI	-0.13	-0.73, 0.47	0.7	-0.12	-1.03, 0.79	0.8
Additional annual change with 1 additional LI	-0.18	-0.31, -0.06	0.004	-0.33	-0.54, -0.11	0.003
Adjusted for vascular risk factors:*						
Annual change in BI	-0.44	-0.51, -0.37	<.0001	-0.53	-0.63, -0.43	<.0001
Change in BI with 1 additional LI	-0.18	-0.82, 0.46	0.6	-0.13	-1.13, 0.86	0.8
Additional annual change with 1 additional LI	-0.15	-0.28, -0.03	0.015	-0.29	-0.51, -0.07	0.011
Adjusted for social variables:**						
Annual change in BI	-0.44	-0.51, -0.37	<.0001	-0.53	-0.63, -0.43	<.0001
Change in BI with 1 additional LI	-0.17	-0.82, 0.48	0.6	-0.12	-1.12, 0.89	0.8
Additional annual change with 1 additional LI	-0.15	-0.28, -0.03	0.016	-0.29	-0.51, -0.07	0.011
Adjusted for cognition:π						
Annual change in BI	-0.44	-0.51, -0.37	<.0001	-0.53	-0.63, -0.43	<.0001
Change in BI with 1 additional LI	-0.16	-0.81, 0.49	0.6	-0.10	-1.11, 0.90	0.8
Additional annual change with 1 additional LI	-0.15	-0.28, -0.03	0.015	-0.29	-0.51, -0.07	0.01
Adjusted for quality of life and depression: ††						
Annual change in BI	-0.44	-0.52, -0.37	<.0001	-0.54	-0.64. -0.44	<.0001
Change in BI with 1 additional LI	-0.17	-0.82, 0.48	0.6	-0.12	-1.13, 0.89	0.8
Additional annual change with 1 additional LI	-0.15	-0.28, -0.03	0.016	-0.29	-0.51, -0.07	0.01
Adjusted for stroke and MI: ‡						
Annual change in BI	-0.39	-0.46, -0.32	<.0001	-0.47	-0.57, -0.38	<.0001
Change in BI with 1 additional LI	-0.10	-0.67, 0.48	0.7	-0.02	-0.93, 0.89	0.96
Additional annual change with 1 additional LI	-0.13	-0.25, -0.02	0.03	-0.26	-0.48, -0.05	0.014

BI=Barthel index; CI=confidence interval; LI=lacunar infarct; MI=myocardial infarction
NOTE: The mobility domain includes transfers, mobility, and stair use; the non-mobility domain includes feeding, bathing, grooming, dressing, bowels, bladder, and toilet use
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Appendix B14. Unadjusted and adjusted models of the association between perivascular space score and functional status, stratified by mobility vs. non-mobility domains, using the new dataset

	Mobility domain			Non-mobility domain		
Variable	**Change in BI score**	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Unadjusted model:						
Annual change in BI	-0.39	-0.51, -0.27	<.0001	-0.43	-0.60, -0.27	<.0001
Change in BI with 1 point increase in SPVS	-0.06	-0.14, 0.01	0.11	-0.03	-0.13, 0.08	0.6
Additional annual change with 1 point increase in SPVS	-0.01	-0.03, 0.01	0.19	-0.03	-0.05, 0.002	0.066
Adjusted for demographics:†						
Annual change in BI	-0.39	-0.51, -0.27	<.0001	-0.44	-0.61, -0.27	<.0001
Change in BI with 1 point increase in SPVS	0.01	-0.07, 0.09	0.8	0.05	-0.06, 0.16	0.4
Additional annual change with 1 point increase in SPVS	-0.01	-0.03, 0.01	0.18	-0.03	-0.05, 0.002	0.07
Adjusted for vascular risk factors:*						
Annual change in BI	-0.43	-0.55, -0.30	<.0001	-0.48	-0.65, -0.30	<.0001
Change in BI with 1 point increase in SPVS	0.01	-0.08, 0.11	0.8	0.06	-0.06, 0.18	0.3
Additional annual change with 1 point increase in SPVS	-0.01	-0.03, 0.01	0.3	-0.02	-0.05, 0.01	0.11
Adjusted for social variables:**						
Annual change in BI	-0.43	-0.55, -0.30	<.0001	-0.48	-0.65, -0.30	<.0001
Change in BI with 1 point increase in SPVS	0.01	-0.08, 0.11	0.8	0.06	-0.06, 0.19	0.3
Additional annual change with 1 point increase in SPVS	-0.01	-0.03, 0.01	0.3	-0.02	-0.05, 0.01	0.11
Adjusted for cognition:π						
Annual change in BI	-0.43	-0.55, -0.30	<.0001	-0.47	-0.65, -0.30	<.0001
Change in BI with 1 point increase in SPVS	0.01	-0.08, 0.11	0.8	0.06	-0.06, 0.19	0.3
Additional annual change with 1 point increase in SPVS	-0.01	-0.03, 0.01	0.3	-0.02	-0.05, 0.01	0.10
Adjusted for quality of life and depression: ††						
Annual change in BI	-0.43	-0.55, -0.30	<.0001	-0.47	-0.65, -0.29	<.0001
Change in BI with 1 point increase in SPVS	0.04	-0.05, 0.13	0.3	0.09	-0.03, 0.21	0.14
Additional annual change with 1 point increase in SPVS	-0.01	-0.03, 0.01	0.3	-0.03	-0.06, 0.003	0.078
Adjusted for stroke and MI: ‡						
Annual change in BI	-0.39	-0.51, -0.27	<.0001	-0.42	-0.59, -0.25	<.0001
Change in BI with 1 point	0.05	-0.04, 0.14	0.3	0.10	-0.02, 0.22	0.10

increase in SPVS						
Additional annual change with 1 point increase in SPVS	-0.01	-0.02, 0.01	0.5	-0.02	-0.05, 0.01	0.15

BI=Barthel index; CI=confidence interval; SPVS=score of perivascular spaces; MI=myocardial infarction
NOTE: The mobility domain includes transfers, mobility, and stair use; the non-mobility domain includes feeding, bathing, grooming, dressing, bowels, bladder, and toilet use
†adjusted for age at time of MRI, sex, race
*additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolemia, physical activity, alcohol use, smoking, and body mass index at the time of MRI
**additionally adjusted for: marital status, insurance, number of friends, and years lived in the community
πadditionally adjusted for mini-mental state score
†† additionally adjusted for Spitzer quality of life index and depression
‡ additionally adjusted for stroke and MI occurring during follow-up, as time-varying covariates

Appendix B15. Sensitivity analysis of the association between MRI findings and functional status among those with baseline Barthel index score of 95 to 100, in adjusted models*

	Entire cohort (n=1290)			Among those with BI ≥95 at baseline (n=1136)		
	Change in BI score	**95% CI**	**p-value**	**Change in BI score**	**95% CI**	**p-value**
Models testing SBI, original dataset						
Annual change in BI	-0.85	-1.01, -0.69	<.0001	-0.76	-0.92, -0.60	<.0001
Change in BI with SBI	1.02	-1.38, 3.43	0.4	1.07	-0.95, 3.09	0.3
Additional annual change with SBI	-0.88	-1.44, -0.32	0.0019	-0.79	-1.34, -0.24	0.005
Models testing WMH, original dataset						
Annual change in BI	-1.03	-1.19, -0.87	<.0001	-0.94	-1.10, -0.78	<.0001
Change in BI with 1 SD increase in WMH	0.43	-0.69, 1.55	0.5	1.17	0.14, 2.20	0.026
Additional annual change with 1 SD increase in WMH	-0.73	-0.98, -0.48	<.0001	-0.68	-0.94, -0.41	<.0001
Models testing SBI, new dataset						
Annual change in BI	-0.82	-0.98, -0.66	<.0001	-0.76	-0.92, -0.61	<.0001
Change in BI with SBI	1.01	-1.09, 3.12	0.3	0.77	-1.12, 2.66	0.4
Additional annual change with SBI	-0.90	-1.43, -0.37	0.0009	-0.61	-1.13, -0.10	0.0203
Models testing LI, new dataset						
Annual change in BI	-0.80	-0.96, -0.65	<.0001	-0.76	-0.91, -0.60	<.0001
Change in BI with LI	1.57	-0.66, 3.80	0.2	1.11	-0.90, 3.12	0.3
Additional annual change with LI	-1.12	-1.70, -0.54	0.0002	-0.78	-1.36, -0.21	0.0077
Models testing LPVS, new dataset						
Annual change in BI	-0.92	-1.11, -0.72	<.0001	-0.81	-1.00, -0.62	<.0001
Change in BI with 1 point increase in LPVS	0.65	-0.73, 2.04	0.4	1.03	-0.16, 2.21	0.089
Additional annual change with 1 point increase in LPVS	-0.13	-0.46, 0.19	0.4	-0.16	-0.49, 0.16	0.3

*BI=Barthel index; SBI=silent brain infarct; CI=confidence interval; WMH=white matter hyperintensity volume; SD=standard deviation; LI=lacunar infarct; LPVS=large perivascular space score

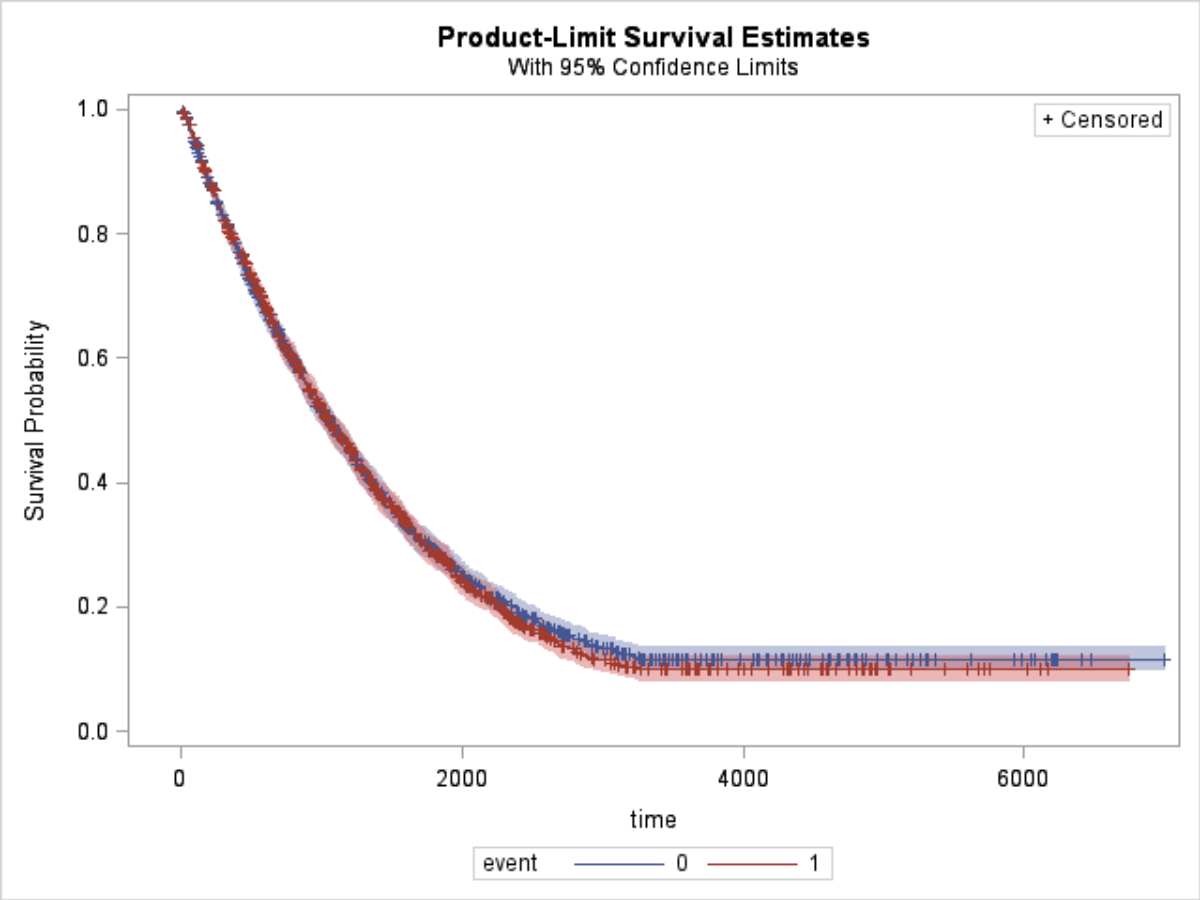
Models are adjusted for: age at the time of MRI, sex, race-ethnicity, diabetes, hypertension, hypercholesterolemia, physical activity, alcohol use, body mass index, insurance status, stroke and myocardial infarction occurring during follow-up, and mini-mental state examination score

Appendix C1. Functional scales in the Cardiovascular Health Study

Activities of daily living: Number of tasks the participant has difficulty with:
-walking around your home
-getting out of bed or chair
-eating including feeding yourself
-dressing yourself
-bathing or showering
-using the toilet

Instrumental activities of daily living: Number of tasks the participant has difficulty with:
-doing heavy housework
-doing light housework
-doing shopping for personal items
-preparing your own meals
-paying bills / managing money
-using the telephone

Appendix C2. Kaplan-Meier survival estimates for MI (event=0) and stroke (event=1)



Log-rank test NS

Appendix C3. Incident events during follow-up

A) INCIDENT STROKE SUBTYPES:

1086 incident first strokes:

- 885 ischemic:
  - 139 lacunar
  - 304 cardioembolic
  - 69 atherosclerotic
  - 26 hemorrhagic transformation
  - 27 unknown
  - 362 indeterminate
  - 18 other

(Note: There were 820 with only one subtype, 58 with 2 subtypes, and 3 with 3 subtypes)

- 121 hemorrhagic:
  - 16 subarachnoid
  - 97 intraparenchymal
  - 6 indeterminate

(Note: There were 117 with only one subtype, 2 with 2 subtypes)

B) CARDIAC EVENTS DURING FOLLOW-UP – whole cohort:

Incident, among whole cohort:

Incident CHD:	1754/4734 (37.1%)
Incident angina:	1395/4924 (28.3%)
Incident angioplasty:	300/5793 (5.2%)
Incident bypass surg:	367/5641 (6.5%)
Incident CHF:	1868/5613 (33.3%)
Incident MI:	1007/5326 (18.9%)
Fatal MI:	119 (11.8% of MI)
Nonfatal MI:	888 (88.2% of MI)
Definite MI:	848 (84% of MI)
Probable MI:	135 (13.4% of MI)
Other MI:	24 (2.4% of MI)

Incident, among those free of CHD at baseline:

Incident CHD:	1754/4734 (37.1%)
Incident angina:	1319/4734 (27.9%)
Incident angioplasty:	216/4734 (4.6%)
Incident bypass surg:	270/4734 (5.7%)
Incident CHF:	1428/4634 (30.8%)
Incident MI:	850/4734 (18.0%)
Fatal MI:	92 (10.8% of MI)
Nonfatal MI:	758 (89.2% of MI)
Definite MI:	718 (84.5% of MI)
Probable MI:	111 (13.1% of MI)
Other MI:	21 (2.5% of MI)

C) DEATHS DURING FOLLOW-UP:

	4637/5888 (78.8%)
Atherosclerotic CHD:	1165/4628 (25.2%)
Cerebrovascular disease:	379/4628 (8.2%)
Other atherosclerotic disease:	105/4628 (2.3%)
Other cardiovascular:	141/4628 (3.1%)
Non-cardiovascular:	2837/4628 (61.3%)
Other:	1/4628 (0.02%)

Appendix C4. Number of assessments before and after stroke

Among cohort with first ischemic stroke and at least one follow-up assessment:

# of visits bfr stroke	Frequency	Percent	Cumulative Freq	Cumulative %
0	46	12.04	46	12.04
1	38	9.95	84	21.99
2	62	16.23	146	38.22
3	48	12.57	194	50.79
4	38	9.95	232	60.73
5	46	12.04	278	72.77
6	42	10.99	320	83.77
7	40	10.47	360	94.24
8	22	5.76	382	100.00

# of visits after stroke	Frequency	Percent	Cumulative Freq	Cumulative %
1	77	20.16	77	20.16
2	69	18.06	146	38.22
3	59	15.45	205	53.66
4	53	13.87	258	67.54
5	39	10.21	297	77.75
6	25	6.54	322	84.29
7	25	6.54	347	90.84
8	20	5.24	367	96.07
9	15	3.93	382	100.00

Appendix C5: distributions of functional outcome scores

A) Distributions of overall functional score:

Variable	Mean	Median	Std Dev	Minimum	Maximum	N Miss
FUNCTN2	0.59	0	1.13	0	8	35
FUNCTN3	0.81	0	1.67	0	12	55
FUNCTN4	1.06	0	2.01	0	12	78
FUNCTN5	1.17	0	2.07	0	12	51
FUNCTN6	1.29	0	2.38	0	12	88
FUNCTN7	1.77	1	2.67	0	12	96
FUNCTN8	2.41	1	3.15	0	12	92
FUNCTN9	2.78	1	3.49	0	12	152
FUNCTN10	3.08	1	3.72	0	12	157
FUNCTN11	3.51	2	3.95	0	12	200

B) Summary statistics of function variable in stroke dataset:

Mean	Lower Quartile	Median	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
1.83	0	1	2	2.90	0	12	346	2469

C) Summary statistics of function variable in MI dataset:

Mean	Lower Quartile	Median	Upper Quartile	Std Dev	Minimum	Maximum	N Miss	N
1.09	0	0	1	2.00	0	12	253	2754

D) Distributions of continuous functional scores by year of follow-up after enrollment:

Year		Score (%)												Missing
	0	1	2	3	4	5	6	7	8	9	10	11	12	
2	231 (66.6)	71 (20.5)	25 (7.2)	9 (2.6)	4 (1.2)	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0	0	35
3	206 (63.0)	67 (20.5)	20 (6.1)	18 (5.5)	7 (2.1)	1 (0.3)	2 (0.6)	2 (0.6)	0	0	1 (0.3)	1 (0.3)	2 (0.6)	55
4	180 (59.2)	61 (20.1)	23 (7.6)	11 (3.6)	7 (2.3)	7 (2.3)	7 (2.3)	2 (0.7)	0	3 (1.0)	0	0	3 (1.0)	78
5	186 (56.2)	67 (20.2)	30 (9.1)	14 (4.2)	7 (2.1)	10 (3.0)	3 (0.9)	3 (0.9)	5 (1.5)	3 (0.9)	1 (0.3)	1 (0.3)	1 (0.3)	51
6	158 (53.7)	70 (23.8)	22 (7.5)	12 (4.1)	6 (2.0)	8 (2.7)	1 (0.3)	5 (1.7)	4 (1.4)	1 (0.3)	1 (0.3)	0	6 (2.0)	88
7	126 (44.1)	70 (24.5)	18 (6.3)	23 (8.0)	13 (4.6)	6 (2.1)	11 (3.9)	3 (1.1)	1 (0.4)	5 (1.8)	3 (1.1)	4 (1.4)	3 (1.1)	96
8	100 (34.5)	66 (22.8)	35 (12.1)	19 (6.6)	17 (5.9)	9 (3.1)	6 (2.1)	7 (2.4)	7 (2.4)	3 (1.0)	12 (4.1)	3 (1.0)	6 (2.1)	92
9	77 (33.5)	50 (21.7)	24 (10.4)	13 (5.7)	9 (3.9)	12 (5.2)	3 (1.3)	10 (4.4)	8 (3.5)	8 (3.5)	4 (1.7)	1 (0.4)	11 (4.8)	152
10	71 (31.6)	42 (18.7)	30 (13.3)	12 (5.3)	14 (6.2)	4 (1.8)	4 (1.8)	10 (4.4)	10 (4.4)	4 (1.8)	7 (3.1)	4 (1.8)	13 (5.8)	157
11	55 (30.2)	32 (17.6)	13 (7.1)	13 (7.1)	11 (6.0)	11 (6.0)	7 (3.9)	7 (3.9)	1 (0.6)	9 (5.0)	4 (2.2)	5 (2.8)	14 (7.7)	200

E) Distributions of categorical functional outcome by year of follow-up after enrollment (Number [%]):

Year	Not disabled (Score=0)	Disabled (Score≥1)	Missing
2	231 (66.6)	116 (33.4)	35
3	206 (63.0)	121 (37.0)	55
4	180 (59.2)	124 (40.8)	78
5	186 (56.2)	145 (43.8)	51
6	158 (53.7)	136 (46.3)	88
7	126 (44.1)	160 (55.9)	96
8	100 (34.5)	190 (65.5)	92
9	77 (33.5)	153 (66.5)	152
10	71 (31.6)	154 (68.4)	157
11	55 (30.2)	127 (69.8)	200

F) Distributions of continuous functional scores by year of follow-up centered on stroke:

Yr	Score (%)													Missing	N
	0	1	2	3	4	5	6	7	8	9	10	11	12		
-8	7 (77.8)	1 (11.1)	0	0	0	0	1 (11.1)	0	0	0	0	0	0	1	9
-7	30 (66.7)	11 (24.4)	2 (4.4)	0	2 (4.4)	0	0	0	0	0	0	0	0	2	45
-6	62 (77.5)	13 (16.3)	3 (3.8)	2 (2.5)	0	0	0	0	0	0	0	0	0	1	80
-5	93 (69.4)	21 (15.7)	7 (5.2)	4 (3.0)	3 (2.2)	3 (2.2)	1 (0.8)	1 (0.8)	1 (0.8)	0	0	0	0	2	134
-4	102 (63.0)	36 (22.2)	11 (6.8)	9 (5.6)	4 (2.5)	0	0	0	0	0	0	0	0	10	162
-3	127 (62.3)	45 (22.1)	12 (5.9)	10 (4.9)	3 (1.5)	3 (1.5)	2 (1.0)	1 (0.5)	0	0	0	0	1 (0.5)	12	204
-2	138 (55.9)	52 (21.1)	21 (8.5)	17 (6.9)	7 (2.8)	3 (1.2)	0	2 (0.8)	4 (1.6)	2 (0.8)	1 (0.4)	0	0	20	247
-1	150 (54.2)	62 (22.4)	27 (9.8)	15 (5.4)	5 (1.8)	5 (1.8)	7 (2.5)	2 (0.7)	0	1 (0.4)	2 (0.7)	1 (0.4)	0	22	277
0	127 (41.5)	68 (22.2)	35 (11.4)	15 (4.9)	11 (3.6)	12 (3.9)	7 (2.3)	11 (3.6)	3 (1.0)	4 (1.3)	3 (1.0)	3 (1.0)	7 (2.3)	47	306
1	93 (34.6)	64 (23.8)	24 (8.9)	15 (5.6)	12 (4.5)	10 (3.7)	9 (3.4)	6 (2.2)	6 (2.2)	9 (3.4)	7 (2.6)	2 (0.7)	12 (4.5)	48	269
2	78 (35.1)	46 (20.7)	20 (9.0)	10 (4.5)	13 (5.9)	8 (3.6)	7 (3.2)	9 (4.1)	7 (3.2)	8 (3.6)	4 (1.8)	4 (1.8)	8 (3.6)	50	222
3	52 (31.1)	35 (21.0)	17 (10.2)	11 (6.6)	10 (6.0)	9 (5.4)	6 (3.6)	4 (2.4)	5 (3.0)	3 (1.8)	3 (1.8)	4 (2.4)	8 (4.8)	39	167
4	32 (26.0)	31 (25.2)	14 (11.4)	9 (7.3)	4 (3.3)	6 (4.9)	1 (0.8)	5 (4.1)	2 (1.6)	4 (3.3)	4 (3.3)	3 (2.4)	8 (6.5)	30	123
5	28 (29.5)	19 (20.0)	8 (8.4)	9 (9.5)	9 (9.5)	2 (2.1)	2 (2.1)	0	4 (4.2)	3 (3.2)	5 (5.3)	1 (1.1)	5 (5.3)	21	95
6	19 (30.0)	11 (17.2)	5 (7.8)	7 (10.9)	3 (4.7)	3 (4.7)	0	2 (3.1)	4 (6.3)	1 (1.6)	1 (1.6)	0	8 (12.5)	21	64
7	14 (37.8)	8 (21.6)	2 (5.4)	0	1 (2.7)	3 (8.1)	1 (2.7)	4 (10.8)	0	1 (2.7)	2 (5.4)	0	1 (2.7)	12	37
8	6 (27.3)	2 (9.1)	6 (27.3)	1 (4.6)	2 (9.1)	1 (4.6)	0	2 (9.1)	0	0	1 (4.6)	1 (4.6)	0	7	22
9	1 (16.7)	0	1 (16.7)	1 (16.7)	2 (33.3)	0	0	0	0	0	0	0	1 (16.7)	1	6

Note: The year includes 6 months before and 6 months after the stated year: for example, year 8 includes values ≥-8.5 and <-7.5

G) Distributions of categorical functional outcome by year of follow-up centered on stroke (Number [%]):

Year	Not disabled (Score=0)	Disabled (Score≥1)	Missing	N
-8	7 (77.8)	2 (22.2)	1	9

-7	30 (66.7)	15 (33.3)	2	45
-6	62 (77.5)	18 (22.5)	1	80
-5	93 (69.4)	41 (30.6)	2	134
-4	102 (63.0)	60 (37.0)	10	162
-3	127 (62.3)	77 (37.8)	12	204
-2	138 (55.9)	109 (44.1)	20	247
-1	150 (54.2)	127 (45.9)	22	277
0	127 (41.5)	179 (58.5)	47	306
1	93 (34.6)	176 (65.4)	48	269
2	78 (35.1)	144 (64.9)	50	222
3	52 (31.1)	115 (68.9)	39	167
4	32 (26.0)	91 (74.0)	30	123
5	28 (29.5)	67 (70.5)	21	95
6	19 (30.0)	45 (70.3)	21	64
7	14 (37.8)	23 (62.2)	12	37
8	6 (27.3)	16 (72.7)	7	22
9	1 (16.7)	5 (83.3)	1	6

Note: The year includes 6 months before and 6 months after the stated year: for example, year 8 includes values ≥-8.5 and <-7.5

H) Summary statistics of continuous functional scores by year of follow-up centered on stroke:

Year	Mean	Lower Quartile	Median	Upper Quartile	Std Dev	Minimum	Maximum	N Miss
-8	0.78	0	0	0	1.99	0	6	1
-7	0.51	0	0	1	0.94	0	4	2
-6	0.31	0	0	0	0.67	0	3	1
-5	0.71	0	0	1	1.48	0	8	2
-4	0.62	0	0	1	1.00	0	4	10
-3	0.77	0	0	1	1.49	0	12	12
-2	1.06	0	0	1	1.82	0	10	20
-1	1.09	0	0	1	1.84	0	11	22
0	2.00	0	1	2	2.90	0	12	47
1	2.66	0	1	4	3.47	0	12	48
2	2.80	0	1	4	3.50	0	12	50
3	2.92	0	1	5	3.53	0	12	39
4	3.20	0	1	5	3.81	0	12	30
5	3.16	0	2	4	3.71	0	12	21
6	3.59	0	2	6	4.14	0	12	21
7	2.86	0	1	5	3.58	0	12	12
8	2.95	0	2	4	3.23	0	11	7
9	4.17	2	3.5	4	4.12	0	12	1

I) Distributions of continuous functional scores by year of follow-up centered on MI:

Yr	Score (%)													Missing	N
	0	1	2	3	4	5	6	7	8	9	10	11	12		
-8	14 (82.4)	1 (5.9)	1 (5.9)	1 (5.9)	0	0	0	0	0	0	0	0	0	0	17
-7	34 (58.6)	15 (25.9)	4 (6.9)	2 (3.5)	1 (1.7)	0	2 (3.5)	0	0	0	0	0	0	1	58
-6	60 (69.8)	16 (18.6)	4 (4.7)	6 (7.0)	0	0	0	0	0	0	0	0	0	3	86
-5	96 (70.6)	20 (14.7)	8 (5.9)	6 (4.4)	2 (1.5)	2 (1.5)	1 (0.7)	1 (0.7)	0	0	0	0	0	2	136
-4	127 (67.9)	28 (15.0)	14 (7.5)	9 (4.8)	7 (3.7)	0	1 (0.5)	0	1 (0.5)	0	0	0	0	8	187
-3	137	47	23	4	6	3	0	1	0	0	0	0	0	13	221

	(62.0)	(21.3)	(10.4)	(1.8)	(2.7)	(1.4)		(0.5)							
-2	171 (62.0)	59 (21.4)	13 (4.7)	15 (5.4)	9 (3.3)	2 (0.7)	2 (0.7)	2 (0.7)	0	1 (0.4)	1 (0.4)	1 (0.4)	0	10	276
-1	173 (57.3)	68 (22.5)	28 (9.3)	14 (4.6)	4 (1.3)	4 (1.3)	4 (1.3)	4 (1.3)	1 (0.3)	1 (0.3)	0	1 (0.3)	0	16	302
0	147 (46.4)	87 (27.4)	34 (10.7)	22 (6.9)	7 (2.2)	2 (0.6)	1 (0.3)	5 (1.6)	4 (1.3)	1 (0.3)	1 (0.3)	4 (1.3)	2 (0.6)	35	317
1	149 (48.5)	90 (29.3)	15 (4.9)	14 (4.6)	15 (4.9)	7 (2.3)	4 (1.3)	1 (0.3)	1 (0.3)	1 (0.3)	4 (1.3)	4 (1.3)	2 (0.7)	46	307
2	121 (52.6)	50 (21.7)	15 (6.5)	9 (3.9)	7 (3.0)	10 (4.4)	4 (1.7)	2 (0.9)	6 (2.6)	2 (0.9)	3 (1.3)	0	1 (0.4)	35	230
3	98 (51.0)	47 (24.5)	16 (8.3)	5 (2.6)	7 (3.7)	3 (1.6)	1 (0.5)	2 (1.0)	4 (2.1)	2 (1.0)	4 (2.1)	3 (1.6)	0	28	192
4	72 (47.7)	39 (25.8)	12 (8.0)	8 (5.3)	7 (4.6)	2 (1.3)	2 (1.3)	1 (0.7)	0	3 (2.0)	3 (2.0)	2 (1.3)	0	24	151
5	55 (48.7)	29 (25.7)	11 (9.7)	8 (7.1)	3 (2.7)	1 (0.9)	0	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	0	10	113
6	36 (51.4)	20 (28.6)	5 (7.1)	3 (4.3)	1 (1.4)	2 (2.9)	0	1 (1.4)	1 (1.4)	0	0	1 (1.4)	0	8	70
7	29 (54.7)	11 (20.8)	4 (7.6)	4 (7.6)	1 (1.9)	0	0	2 (3.8)	0	1 (1.9)	0	0	1 (1.9)	0	53
8	15 (55.6)	3 (11.1)	1 (3.7)	2 (7.4)	0	1 (3.7)	2 (7.4)	0	0	1 (3.7)	2 (7.4)	0	0	3	27
9	5 (50.0)	2 (20.0)	0	0	1 (10.0)	0	0	0	0	2 (20.0)	0	0	0	1	10
10	0	0	0	0	0	0	1 (100.0)	0	0	0	0	0	0	0	1

Note: The year includes 6 months before and 6 months after the stated year: for example, year 8 includes values ≥-8.5 and <-7.5

J) Distributions of categorical functional outcome by year of follow-up centered on MI (Number [%]):

Year	Not disabled (Score=0)	Disabled (Score≥1)	Missing	N
-8	14 (82.4)	3 (17.7)	0	17
-7	34 (58.6)	24 (41.4)	1	58
-6	60 (69.8)	26 (30.2)	3	86
-5	96 (70.6)	40 (29.4)	2	136
-4	127 (67.9)	60 (32.1)	8	187
-3	137 (62.0)	84 (38.0)	13	221
-2	171 (62.0)	105 (38.0)	10	276
-1	173 (57.3)	129 (42.7)	16	302
0	147 (46.4)	170 (53.6)	35	317
1	149 (48.5)	158 (51.5)	46	307
2	121 (52.6)	109 (47.4)	35	230
3	98 (51.0)	94 (49.0)	28	192
4	72 (47.7)	79 (52.3)	24	151
5	55 (48.7)	58 (51.3)	10	113
6	36 (51.4)	34 (48.6)	8	70
7	29 (54.7)	24 (45.3)	10	53
8	15 (55.6)	12 (44.4)	3	27
9	5 (50.0)	5 (50.0)	1	10
10	0	1 (100.0)	0	1

Note: The year includes 6 months before and 6 months after the stated year: for example, year 8 includes values ≥-8.5 and <-7.5

K) Summary statistics of continuous functional scores by year of follow-up centered on MI:

Year	Mean	Lower Quartile	Median	Upper Quartile	Std Dev	Minimum	Maximum	N Miss
-8	0.35	0	0	0	0.86	0	3	0

-7	0.78	0	0	1	1.34	0	6	1
-6	0.49	0	0	1	0.88	0	3	3
-5	0.63	0	0	1	1.28	0	7	2
-4	0.67	0	0	1	1.26	0	8	8
-3	0.68	0	0	1	1.15	0	7	13
-2	0.84	0	0	1	1.61	0	11	10
-1	0.93	0	0	1	1.64	0	11	16
0	1.32	0	1	2	2.19	0	12	35
1	1.35	0	1	1	2.32	0	12	46
2	1.44	0	0	2	2.39	0	12	35
3	1.46	0	0	1	2.56	0	11	28
4	1.48	0	1	2	2.45	0	11	24
5	1.27	0	1	2	2.11	0	11	10
6	1.13	0	0	1	2.01	0	11	8
7	1.32	0	0	1	2.44	0	12	10
8	2.11	0	0	3	3.30	0	10	3
9	2.40	0	0.5	4	3.69	0	9	1
10	6.00	6	6	6	.	6	6	0

Appendix C6. Trajectories before and after stroke using a dichotomous definition of disability

Variable	Odds ratio for change in functional score	95% confidence limits	p-value
Unadjusted model:			
Annual change before stroke	1.22	1.14, 1.30	<.0001
Additional annual change after stroke	0.90	0.82, 0.99	0.04
Change in functional score at time of stroke	1.84	1.42, 2.38	<.0001
Adjusted for demographics:†			
Annual change before stroke	1.24	1.16, 1.32	<.0001
Additional annual change after stroke	0.90	0.82, 0.99	0.03
Change in functional score at time of stroke	1.93	1.47, 2.53	<.0001
Adjusted for vascular risk factors:*			
Annual change before stroke	1.24	1.16, 1.32	<.0001
Additional annual change after stroke	0.91	0.82, 1.00	0.05
Change in functional score at time of stroke	1.88	1.41, 2.51	<.0001
Adjusted for other medical conditions:**			
Annual change before stroke	1.24	1.16, 1.33	<.0001
Additional annual change after stroke	0.91	0.82, 1.00	0.057
Change in functional score at time of stroke	1.91	1.42, 2.57	<.0001
Adjusted for inflammatory biomarkers:‡			
Annual change before stroke	1.24	1.16, 1.33	<.0001
Additional annual change after stroke	0.91	0.82, 1.01	0.06
Change in functional score at time of stroke	1.91	1.42, 2.57	<.0001
Adjusted for cognition:π			
Annual change before stroke	1.23	1.15, 1.32	<.0001
Additional annual change after stroke	0.90	0.81, 1.00	0.056
Change in functional score at time of stroke	1.77	1.30, 2.42	0.0003
Adjusted for social support: ††			
Annual change before stroke	1.23	1.15, 1.32	<.0001
Additional annual change after stroke	0.90	0.81, 1.00	0.056
Change in functional score at time of stroke	1.77	1.30, 2.42	0.0003

†adjusted for age at time of stroke, sex, race, marital status, and body mass index
*additionally adjusted for: coronary heart disease
**additionally adjusted for: arthritis and depression
‡additionally adjusted for log of C-reactive protein levels
πadditionally adjusted for mini-mental state score
†† no additional adjustment

Appendix C7. Trajectories of a continuous measure of disability before and after stroke and myocardial infarction in the entire cohort (n=5888), in unadjusted and adjusted models, with functional score set to worst possible value at death

Variable	Change in functional score	95% confidence limits	p-value
Unadjusted overall change model			
Annual change	0.62	0.61, 0.63	<.0001
Unadjusted overall change plus average change due to stroke and MI model			
Annual change	0.58	0.57, 0.59	<.0001
Change in functional score at time of stroke	2.37	2.14, 2.59	<.0001
Change in functional score at time of MI	1.19	1.02, 1.35	<.0001
Unadjusted pre- and post-stroke and –MI trajectories model			
Annual change	0.55	0.54, 0.56	<.0001
Change in functional score at time of stroke	1.55	1.20, 1.90	<.0001
Change in functional score at time of MI	0.33	0.11, 0.56	0.003
Additional annual change after stroke	0.11	0.08, 0.14	<.0001
Additional annual change after MI	0.13	0.11, 0.15	<.0001
Fully adjusted model:†			
Annual change	0.16	-0.08, 0.39	0.2
Change in functional score at time of stroke	0.68	0.41, 0.96	<.0001
Change in functional score at time of MI	0.03	-0.14, 0.19	0.7
Additional annual change after stroke	0.05	0.00, 0.10	0.056
Additional annual change after MI	0.02	-0.02, 0.06	0.3
Fully adjusted model, with non-significant interaction terms removed:*			
Annual change	0.18	-0.05, 0.42	0.12
Change in functional score at time of stroke	0.68	0.41, 0.96	<.0001
Change in functional score at time of MI	0.07	-0.08, 0.22	0.4
Additional annual change after stroke	0.05	-0.001, 0.10	0.055
Additional annual change after MI	0.01	-0.02, 0.04	0.4

MI=myocardial infarction

†adjusted for: baseline age, sex, race, marital status, education, income, diabetes, hypertension, coronary heart disease, arthritis, depression, log of C-reactive protein levels, mini-mental state score, social network score, and interaction terms between time of follow-up and these variables

*adjusted for: age, sex, race, marital status, education, income, diabetes, hypertension, coronary heart disease, arthritis, depression, log of C-reactive protein levels, mini-mental state score, social network score, and interaction terms between time of follow-up and baseline age, race, education, diabetes, mini-mental state score, and social network score

Appendix C8. Trajectories before and after stroke using a continuous definition of disability, by stroke subtype

Stroke subtype	Lacunar (n=75)			Cardioembolic (n=107)			Other ischemic stroke (n=211)		
Variable	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value
Annual change before stroke	0.19	0.07, 0.31	0.003	0.08	0.01, 0.14	0.03	0.18	0.12, 0.25	<.0001
Additional annual change after stroke	0.33	-0.06, 0.72	0.09	0.25	-0.02, 0.53	0.067	-0.03	-0.18, 0.12	0.7
Change in functional score at time of stroke	0.36	-0.58, 1.30	0.5	1.52	0.67, 2.37	0.0004	1.37	0.85, 1.90	<.0001

Appendix C9. Trajectories before and after stroke using a continuous definition of disability, testing different cholesterol subtypes*

	Model 1: adjusting for TC			Model 2: adjusting for HDL and LDL			Model 3: adjusting for HDL, LDL, and logLPA			Model 4: adjusting for TC, HDL, LDL, and logLPA		
Variable	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value	Change in functional score	95% CI	p-value
Annual change before stroke	0.07	0.01, 0.13	0.02	0.09	0.03, 0.14	0.003	0.07	0.02, 0.13	0.0097	0.07	0.02, 0.13	0.01
Additional annual change after stroke	0.16	0.01, 0.31	0.04	0.14	-0.01, 0.29	0.065	0.13	-0.01, 0.28	0.077	0.13	-0.01, 0.28	0.07
Change in functional score at time of stroke	0.45	-0.05, 0.94	0.079	0.45	-0.05, 0.95	0.076	0.46	-0.05, 0.96	0.076	0.46	-0.04, 0.96	0.07
TC	0.00	0.00, 0.01	0.4	--	--	--	--	--	--	0.01	0.00, 0.02	0.09
HDL	--	--	--	0.01	0.00, 0.02	0.1	0.01	0.00, 0.02	0.16	0.00	-0.01, 0.01	0.6
LDL	--	--	--	0.00	-0.01, 0.00	0.98	0.00	0.00, 0.01	0.7	-0.01	-0.02, 0.00	0.18
logLPA	--	--	--	--	--	--	0.13	0.02, 0.24	0.03	0.14	0.03, 0.25	0.01

*TC=total cholesterol levels, mg/dL; HDL=high-density lipoprotein levels, mg/dL; LDL=low-density lipoprotein levels, mg/dL; logLPA=log of lipoprotein A levels; models are additionally adjusted for: age at time of stroke, sex, race, marital status, income, arthritis, depression, mini-mental state score, and social network score

Appendix C10. Exploring different cutoffs of the functional scale

		Unadjusted model			Model A*			Model B**		
Cutoff (n)	Variable	Odds ratio for change in functional score	95% CI	p-value	Odds ratio for change in functional score	95% CI	p-value	Odds ratio for change in functional score	95% CI	p-value
>0 (n=1310) versus 0 (n=1159)	Annual change before stroke	1.22	1.14, 1.30	<.0001	1.23	1.15, 1.32	<.0001	1.18	1.08, 1.28	0.0002
	Additional annual change after stroke	0.90	0.82, 0.995	0.038	0.90	0.81, 1.002	0.056	0.96	0.85, 1.09	0.5
	Change in functional score at time of stroke	1.84	1.42, 2.38	<.0001	1.77	1.30, 2.42	0.0003	1.93	1.26, 2.96	0.003
>1 (n=785) versus <=1 (n=1684)	Annual change before stroke	1.26	1.16, 1.37	<.0001	1.26	1.16, 1.38	<.0001	1.19	1.06, 1.34	0.003
	Additional annual change after stroke	0.90	0.82, 1.001	0.053	0.9	0.80, 1.005	0.06	0.97	0.83, 1.14	0.7
	Change in functional score at time of stroke	1.98	1.53, 2.55	<.0001	1.93	1.40, 2.66	<.0001	2.15	1.31, 3.55	0.003
>2 (n=570) versus <=2 (n=1899)	Annual change before stroke	1.25	1.13, 1.39	<.0001	1.22	1.10, 1.37	0.0003	1.23	1.04, 1.45	0.01
	Additional annual change after stroke	0.90	0.80, 1.02	0.09	0.93	0.81, 1.07	0.3	0.91	0.73, 1.13	0.4
	Change in functional score at time of stroke	2.37	1.71, 3.28	<.0001	2.5	1.65, 3.80	<.0001	2.31	1.10, 4.84	0.03
>3 (n=435) versus <=3 (n=2034)	Annual change before stroke	1.36	1.16, 1.59	0.0002	1.30	1.11, 1.52	0.001	1.18	0.92, 1.51	0.2
	Additional annual change after stroke	0.82	0.69, 0.97	0.02	0.87	0.73, 1.03	0.1	0.93	0.71, 1.23	0.6
	Change in functional score at time of stroke	2.97	2.00, 4.41	<.0001	3.36	2.04, 5.52	<.0001	4.80	1.79, 12.88	0.002
>4 (n=344) versus <=4 (n=2125)	Annual change before stroke	1.49	1.21, 1.83	0.0001	1.43	1.17, 1.75	0.0006	1.42	1.00, 2.00	0.048
	Additional annual change after stroke	0.73	0.59, 0.90	0.003	0.76	0.60, 0.94	0.01	0.79	0.54, 1.14	0.2
	Change in functional score at time of stroke	3.26	2.09, 5.08	<.0001	3.34	2.02, 5.54	<.0001	3.33	1.03, 10.74	0.045

>5 (n=276) versus <=5 (n=2193)	Annual change before stroke	1.56	1.18, 2.06	0.002	1.46	1.10, 1.93	0.009	1.38	0.90, 2.13	0.14
	Additional annual change after stroke	0.69	0.52, 0.92	0.01	0.74	0.55, 0.99	0.04	0.81	0.51, 1.27	0.4
	Change in functional score at time of stroke	3.73	2.16, 6.46	<.0001	3.79	1.90, 7.55	0.0002	3.11	0.75, 12.88	0.12
>6 (n=232) versus <=6 (n=2237)	Annual change before stroke	1.68	1.22, 2.32	0.001	1.44	1.06, 1.95	0.02	1.48	0.92, 2.40	0.11
	Additional annual change after stroke	0.66	0.48, 0.92	0.01	0.77	0.56, 1.06	0.1	0.76	0.46, 1.25	0.3
	Change in functional score at time of stroke	3.71	1.98, 6.94	<.0001	4.42	1.96, 9.97	0.0003	3.23	0.71, 14.7	0.13
>7 (n=183) versus <=7 (n=2286)	Annual change before stroke	1.62	1.04, 2.50	0.03	1.51	0.89, 2.59	0.13	1.64	0.72, 3.73	0.2
	Additional annual change after stroke	0.68	0.44, 1.06	0.09	0.71	0.41, 1.21	0.21	0.59	0.26, 1.36	0.2
	Change in functional score at time of stroke	4.88	2.24, 10.61	<.0001	5.21	1.98, 13.73	0.0008	4.41	0.77, 25.35	0.097
>8 (n=183) versus <=8 (n=2286)	Annual change before stroke	1.98	1.20, 3.26	0.007	2.37	1.22, 4.61	0.01	3.74	1.11, 12.66	0.03
	Additional annual change after stroke	0.55	0.33, 0.92	0.02	0.44	0.22, 0.86	0.02	0.24	0.07, 0.84	0.03
	Change in functional score at time of stroke	4.66	1.85, 11.72	0.001	3.27	1.09, 9.78	0.03	2.46	0.52, 11.63	0.3
>9 (n=111) versus <=9 (n=2358)	Annual change before stroke	1.75	1.02, 3.02	0.043	1.77	0.98, 3.17	0.055	3.22	0.59, 17.42	0.18
	Additional annual change after stroke	0.64	0.37, 1.11	0.11	0.64	0.35, 1.17	0.14	0.28	0.05, 1.62	0.15
	Change in functional score at time of stroke	6.02	2.27, 15.96	0.0003	3.14	0.77, 12.80	0.11	2.83	0.42, 19.32	0.3
>10 (n=78) versus <=10 (n=2391)	Annual change before stroke	1.17	0.78, 1.77	0.4	1.57	1.23, 1.996	0.0003	1.52	1.02, 2.27	0.04
	Additional annual change after stroke	0.93	0.60, 1.43	0.7	0.69	0.50, 0.947	0.02	0.61	0.35, 1.05	0.07
	Change in functional score at time of stroke	26.05	4.57, 148.7	0.0002	9.98	0.91, 109.3	0.0597	5.90	1.31, 26.6	0.02

*Model A is adjusted for: age at time of stroke, sex, race, marital status, body mass index, coronary heart disease, arthritis, depression, log of C-reactive protein levels, and mini-mental state score

**Model B is adjusted for: age at time of stroke, sex, race, marital status, income, arthritis, depression, log of lipoprotein A levels, mini-mental state score, and social network score