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RESEARCH ARTICLE

Shared risk and protective factors between Alzheimer’s disease and ischemic stroke: A population-based longitudinal study

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Abstract

Introduction: Stroke, especially ischemic stroke’s (IS) link with Alzheimer’s disease (AD) remains unclear.

Methods: This prospective cohort study included 2459 AD- and cerebrovascular disease-free older adults at baseline (mean age 71.9 ± 10.3 years, Stockholm, Sweden). Using Cox regressions, shared risk factors (SRFs) and shared protective factors (SPFs) between AD and IS were recognized when their hazard ratios in both AD and IS models were significant and in the same direction.

Results: During the follow-up period of up to 15 years, 132 AD and 260 IS mutually exclusive cases were identified. SRFs were low education, sedentary lifestyle, and heart diseases. High levels of psychological well-being, actively engaging in leisure activities, and a rich social network were SPFs. Having ≥1 SPF reduced 47% of AD and 28% of IS risk among people with a low risk profile (<2 SRFs), and 38% of AD and 31% of IS risk with a high risk profile (≥2 SRFs). In total, 57.8% of AD/IS cases could be prevented if individuals have ≥1 SPF and no SRF.

Discussion: AD and IS share risk/protective profiles, and SPFs seem to counteract the adverse effects of SRFs on both AD and IS.

Keywords
Alzheimer’s diseases, Cohort study, Ischemic stroke, Leisure activity, Psychological well-being, Social network, Vascular risk factors

1 | INTRODUCTION

Alzheimer’s disease (AD) has been related to the deposition of amyloid beta (Aβ) peptide plaques in brain tissues that may cause neurodegeneration.1 Stroke, especially ischemic stroke (IS), has been linked to embolism and small-vessel disease.2 Despite the different etiopathogeneses proposed for AD and stroke, clinical studies have shown that the co-existence of AD and stroke occurs more often than expected by chance, indicating a possible relationship between the two disorders.3 However, the link between AD and stroke (particularly IS) has not been fully understood.

Both AD and IS develop as a result of multiple factors rather than a single cause. Evidence has been accumulating suggesting that vascular pathologies (eg, atherosclerosis) are correlated, and interconnected with neurodegenerative pathologies preceding cognitive impairment, AD, and dementia.4 Although pathological confirmation is lacking, stroke-related vascular conditions (eg, hypertension and heart diseases) were found to be associated with AD development.5,6 Yet, the associations between certain vascular risk factors and AD vary by age. That is, middle-life vascular risk factors, such as hypertension, high cholesterol, and obesity, increase late-life AD risk,7,8 but the effect of late-life vascular risk factors on AD tends to be controversial.
Therefore, identifying which are the shared risk factors for both AD and stroke in old age requires further study and would shed light on possible common pathophysiologys.

Many studies have indicated that psychosocial factors, such as social networks, leisure activities, and psychosocial well-being, may reduce the risk of cognitive decline and AD.\(^9\)\(^-\)\(^11\) Likewise, the protective effect of psychosocial factors on stroke has been established.\(^12\) Previous findings indicate that stroke and AD may not only share vascular profiles, but also benefit from similar protective profiles related to psychosocial well-being. Thus, identifying the shared protective psychosocial factors for both AD and stroke will prevent older adults from developing either of the two disorders. Furthermore, it has been hypothesized that protective psychosocial factors in late life may increase the cognitive reserve making the individuals have a high susceptibility to tolerate age-related brain changes or pathology related to AD.\(^11\) Whether these cognitive reserve-related factors can counteract the accumulated harmful effects of the shared risk factors on AD and stroke remains to be elucidated.

AD and IS are associated with multiple lifelong cumulative risk factors. In the current study, we defined "risk" factors as either pathogenic or as negative exposures in early life (eg, genetic risk factors, vascular risk factors, and early life low education level), and "protective" factors are salutogenic and potentially modifiable during late life (eg, psychosocial well-being, rich social network, and vigorous leisure-time activity; Figure S1 in supporting information). The identified shared risk/protective factors will serve as a new tool to be used in interventions designed to reduce the late-life risk of both AD or stroke. Therefore, using a population-based longitudinal cohort of older adults, we sought to (1) identify shared risk and protective profiles for AD and IS and (2) explore whether and to what extent the shared protective profile may decrease the adverse effect of risk factors on AD and IS.

2 | METHODS

2.1 | Study population

Data for this study were derived from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), an ongoing prospective population-based study of the older population (≥60 years) with longitudinal follow-up records. Data collection has been described previously.\(^13\)

In this study, we included up to 15 years of follow-up data from January 2001 until December 2016. At baseline (2001 to 2004), of 3363 participants who were examined, we excluded 528 participants with prevalent dementia (n = 321; prevalent dementia n = 310, missing dementia status n = 11) or history of cerebrovascular diseases (n = 347), and 376 participants who declined to participate in follow-up examinations, leaving 2459 participants who were free from both dementia and cerebrovascular disease in the analytical sample. During the follow-up, 342 developed dementia (132 AD cases without any cerebrovascular diseases), 509 developed cerebrovascular diseases (260 IS cases without AD), and 1738 participants remained free from either dementia or cerebrovascular diseases (Figure S2 in supporting information). Of the cerebrovascular disease and dementia cases developed at follow-up, 520 were with either AD or IS.

2.2 | Data collection

Data collection was conducted through structured assessment by trained physicians, nurses, and psychologists. Information on health...
Vascular risk burden and mental health

Diagnosis of dementia and Alzheimer’s disease

2.3.1 | Diagnosis of dementia and Alzheimer’s disease

Dementia was determined through clinical and cognitive examinations administered according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria (DSM-IV). A three-step procedure was followed, in which two physicians working independently made a preliminary diagnosis and a third opinion was obtained from a senior neurologist whenever a disagreement occurred. For participants who had died before the subsequent follow-up examination, dementia diagnosis was made by reviewing the patient and death registers. AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria.

2.3.2 | Diagnosis of ischemic stroke

Information on cerebrovascular diseases and IS at baseline and during the follow-up period was obtained from clinical examinations in SNAC-K interviews as well as the patient and death registers. Specifically, following the clinical practice routine, the diagnosis of cerebrovascular diseases and IS was made in consideration of clinical manifestations and neuroimaging, which is recorded regularly in the Swedish National Patient Register. If a participant died from acute cerebrovascular diseases or IS-related disorders, the relevant ICD codes were recorded in the Swedish Cause of Death Register. From the records in the registers, we identified participants with cerebrovascular diseases using ICD-10 codes I60-I64, I66, I67, I69, G45, and G46. IS was specifically identified using ICD-10 codes I63 and I64.

2.4 | Demographic factors

Educational level was assessed as maximum years of schooling education, and divided into elementary school, secondary school, or university/above. Occupations were recorded according to the self-reported longest-held occupation in adult life. The occupation was dichotomized as manual workers (blue-collar) versus non-manual workers (white-collar).

2.5 | Apolipoprotein E (APOE) gene

At baseline, genomic deoxyribonucleic acid was obtained from peripheral blood samples. Using a standard polymerase chain reaction procedure, apolipoprotein E (APOE) genotyping was performed by two technicians who were blind to all other data.

2.6 | Vascular risk burden and mental health

2.6.1 | Vascular risk factors

We used information from self-reported questionnaire to assess alcohol consumption, smoking status, and sedentary lifestyle. Specifically, alcohol consumption was quantified as numbers of standard drinks per week, and a standard drink in Sweden contains roughly 12 g of alcohol. Heavy drinking was defined as alcohol consumption per week of >14 standard drinks for males or >7 standard drinks for females. We classified no/light-to-moderate drinking as alcohol consumption per week of ≤14 standard drinks for males or ≤7 standard drinks for females. Smoking status was categorized as never, former, or current smoker. A sedentary lifestyle was defined as no exercise or no regularly health/fitness-enhancing exercise according to the level of exercise.

At baseline, we took non-fasting venous blood samples from participants, and the routine analyses of blood samples were applied at Sabbatsberg Hospital, Stockholm, Sweden. Glycated hemoglobin was measured using the Swedish Mono–S High Performance Liquid Chromatography. Diabetes was ascertained based on self-report, medical records, glycated hemoglobin ≥6.5%, or use of hypoglycemic agents. Arterial blood pressure was measured with a sphygmomanometer, on the right arm in a sitting position. We measured blood pressure twice with a 5-minute interval, and the mean of the two readings was recorded. Hypertensive status was classified into three categories: no hypertension, controlled hypertension (<150/90 mm Hg), and uncontrolled hypertension (≥150/90 mmHg). We measured height and weight of participants when they wore light clothes and no shoes. Body mass index (BMI) was calculated as weight (kilogram) divided by height (meter) squared, and categorized into three groups: <18.5 kg/m², 18.5 to 24.9 kg/m², or ≥25 kg/m². Serum total cholesterol was assessed using standardized enzymatic assay. High cholesterol was defined as non-fasting serum total cholesterol ≥6.22 mmol/L or self-reported use of cholesterol-lowering medications.

2.6.2 | Heart diseases

Heart diseases at baseline were assessed using the ICD codes derived from the physical examination at baseline and integrated with information from the patient registry. The major heart diseases included...

### 2.6.3 Depressive symptoms

Depressive symptoms were assessed at baseline during the medical examinations and defined as present versus absent, according to items from the DSM-5 and DSM-IV-TR, which list nine different symptom domains for depression diagnoses. We further used the Comprehensive Psychopathological Rating Scale (CPRS) to diagnose depression and identified the items from the CPRS that represent each of the nine different symptom domains. Depressive symptoms according to DSM were defined as present or absent based on rating according to the CPRS.

### 2.7 Psychosocial factors

#### 2.7.1 Psychological well-being

The 10-item short version of Positive and Negative Affect Schedule (PANAS) was used to measure the emotional components of well-being. At baseline, participants were asked to report the frequency of specific positive and negative emotional states during the last 12 months. The emotional states included in the PANAS Positive Affect (PANAS-PA) are active, enthusiastic, alert, inspired, and determined. PANAS Negative Affect (PANAS-NA) includes distressed, scared, upset, nervous, and afraid. The response options were “not at all,” “a little,” “somewhat,” “quite a bit,” and “very much,” which were coded from one to five. Using confirmatory factor analysis based on the first-level original scores of the 10 items, a second-level psychological well-being latent score was generated (Figure S3 in supporting information), and further divided into tertiles (low, medium, and high).

#### 2.7.2 Social network index

The social network index was derived from two components, social connections and social support, and it was in agreement with the aforementioned contacts, perceived material and psychological support, sense of affinity with relatives and neighbors, and whether the participant was part of a group of friends. Raw scores on social connections and social support were standardized into z scores and then averaged to create a social connection index and a social support index. The correlation between the social connection index and support index was substantial (0.76); we, therefore, generated a social network index by averaging the two subindices. According to the tertiles of the social network index, we divided participants into three groups (low, moderate, or rich) to reflect their social network levels.

### 2.7.3 Leisure activity

Leisure activity was defined according to a list of 26 predefined activities for which participants reported their engagement and frequency during the past 12 months. Activities were categorized into three groups depending on whether they were predominantly mental, physical, or social. Mental activities included those that require cognitive involvement but not social engagement (ie, playing chess/cards, reading books, listening to music, playing an instrument, using the internet or playing computer games, and creation with clay), and was coded as low (≤1 activity), moderate (2 to 3 activities), or high (≥4 activities). Social activities included those that involve social interactions (ie, cinema/theater/concerts, sports events, museums/art exhibitions, restaurants/bar/cafés, dancing, bingo, church service, traveling, study circles/courses, volunteering, and other social meetings), and was coded as low (0 activities), moderate (1 activity), or high (≥2 activities). Physical activities included light to vigorous exercise (ie, jogging, bicycling, gym/golf/other sports, walking, gardening, strolling through the woods and countryside, picking mushrooms/berries, fishing/hunting, and home repair or car/other repair), and was coded as low (<once/week), moderate (once/week), or high (>once/week).

### 2.8 Statistical analysis

We compared the baseline characteristics by incident AD and IS using t test for continuous variables and chi-squared test for categorical variables. If the continuous variables were not following the normal distribution, Wilcoxon signed-rank tests were applied.

Cox proportional hazards regression models were applied to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of AD or IS in relation to the risk factors and protective factors. Follow-up year was used as the time scale in the model. We calculated the follow-up time from the entry time (the date of the first interview at SNAC-K) until death, stroke diagnosis, AD diagnosis, or last interview date in the SNAC-K data collection, whichever came first. The proportional hazard assumption was tested for all predictors based on the Schoenfeld Residuals.

In order to identify shared risk and protective factors between AD and IS, a statistical threshold of P < .10 was applied in order not to miss any potential factors. Specifically, we included the participants who were free of dementia and cerebrovascular disease at baseline, and two separate Cox regression models were performed to estimate the association of risk/protective factors with (1) incident AD without cerebrovascular diseases and (2) incident IS without AD, after adjusting for demographic factors. With a P-value <.10, a shared risk factor between AD and IS was identified if the HRs in both models were >1.
and a shared protective factor was identified if the HRs in both models were <1. To investigate the dose-response associations of shared risk/protective factors with AD, IS, and AD/IS, aggregated scores were calculated by counting the number of shared risk and protective factors, respectively. The aggregated risk/protective scores were treated as categorical variables (0, 1, and ≥ 2) in the Cox proportional hazards regression models. Population attributable fractions (PAF) were calculated to estimate the magnitude of the protective effect by levels of risk profile, following the formula: \( PAF = \frac{P_x(RR_e - 1)}{1 + P_x[RR_e - 1]} \), where \( P_x \) is the prevalence of exposure and \( RR_e \) is the relative risk of disease because of the exposure. These additional analyses were further conducted: (1) Following different guidelines, we used multiple cut-offs for cardiovascular risk factors to investigate if their associations with AD and IS vary. (2) To detect the influence of age on our results, we conducted stratification analysis by age strata (<75 vs ≥75 years). This is to investigate whether the associations of shared risk and shared protective factors with AD/IS varied by age groups. (3) To explore the role of potential reverse causality, we repeated the main analyses in a sample excluding incident AD and IS cases detected in the first 3-year follow-up period or excluding those who died within 3 years from baseline. (4) To minimize residual confounding, we further adjusted for all the covariates in the model as categorical variables with more than two groups and as continuous variables, respectively. (5) Multiple imputations were conducted to replace the missing covariates. (6) To investigate whether a change of psychosocial well-being would play a critical role and influence its associations with AD and IS, we included PANAS data measured at 3- and 6-year visits and performed an analysis to estimate the effect of changing in psychosocial well-being on AD and IS.

We applied STATA 15.0 (StataCorp, College Station, Texas) and R software (version 3.6.0) for the analyses.

3 | RESULTS

3.1 | Baseline characteristics by incident AD/IS

The average follow-up time was 8.10 years (standard deviation [SD] 3.88 years, range from 0.05 to 15.33 years, 17250.84 person-years in total). Compared to the individuals without dementia or cerebrovascular diseases at follow-up, those who developed incident AD without cerebrovascular diseases were older; more likely to be females, sedentary, underweight, and to have heart diseases or an APOE ε4 allele; but less educated, less likely to be smokers, white collar, to have diabetes, high levels of psychosocial well-being and leisure activities, or a rich social network (Table 1). There was no significant difference between the two groups in the proportion of alcohol consumption, hypertension, cholesterol level, or depression (P > .05). Compared to people without incident IS/AD, participants with incident IS without AD were older; more likely to be sedentary, and to have cardiovascular burden; but less educated, less likely to be heavy drinkers, white collar, engaging in leisure activities; or have a high level of psychological well-being. There was no significant difference between the two groups in terms of sex, smoking status, diabetic status, depression, APOE ε4 status, and social network size (P > .05).

3.2 | Shared risk and protective factors between AD and IS

The shared risk factors between AD and IS were low education, a sedentary lifestyle, and having at least one heart disease (Figure 1). Shared protective factors included high levels of psychological well-being, leisure-time mental activity, and physical activity, and a rich social network.

Apart from the shared risk factors, specific risk factors for AD included current smoking, depression, and positive APOE ε4 status, and specific risk factors for IS were male sex, hypertension (either controlled or not controlled), high cholesterol, and overweight/obesity (Table S1 in supporting information).

3.3 | Aggregated scores of shared risk/protective factors and AD/IS

An aggregated shared risk score (range: 0 to 4) and shared protective score (range: 0 to 4) were generated by counting the number of the shared risk or protective factors at the individual level, respectively. When we scored for heart diseases, a score of 1 was given to those who had only one heart disease, and a score of 2 was given to those who had two or more heart diseases. This is because the estimated risk (HRs) of AD/IS varied by the numbers of heart diseases.

Compared to the group without any shared risk factor, the group with only one shared risk factor did not show significantly increased risk of AD (HR: 1.86, 95% CI: 0.96 to 3.57) or IS (HR: 1.09, 95% CI: 0.74 to 1.59), but the group with two or more shared risk factors showed substantially increased risk of AD (HR: 3.83, 95% CI: 1.94 to 7.53) and IS (HR: 2.20, 95% CI: 1.46 to 3.32; Table 2). Participants were, therefore, classified into two groups: “low risk profile group” (risk index 0 to 1) or “high risk profile group” (risk index ≥2). Compared to the group with low risk profile, the high risk profile group showed a higher risk of AD as well as IS in the multi-adjusted models. Similar associations were observed when either AD or IS were combined as one outcome (Table S2 in supporting information).

Similarly, given that the significant association of protective factors with IS or AS was already observed when one shared protective factor was present, we further categorized participants into two groups: positive protective profile (≥1 protective factor) and negative protective profile (0 protective factors). Compared to the group with negative protective profile, the positive protective profile group displayed significantly reduced risk of AD (HR: 0.56, 95% CI: 0.36 to 0.87) and IS (HR: 0.51, 95% CI: 0.38 to 0.68), and results were consistent between age- and sex-adjusted models and multi-adjusted models. When using AD/IS as a combined outcome, a decrease in the risk of IS/AD of around 50% was observed in the protective profile group (HR: 0.54, 95% CI: 0.44 to 0.66; Table S2).
TABLE 1 Baseline characteristics of participants by incident Alzheimer’s disease or ischemic stroke developed during the 15-year follow-up period

<table>
<thead>
<tr>
<th></th>
<th>No dementia and cerebrovascular disease (n = 1738)</th>
<th>Incident AD without cerebrovascular disease (n = 132)</th>
<th>P-value(^b)</th>
<th>Incident cerebrovascular disease without AD (n = 260)</th>
<th>P-value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>70.40 (10.05)</td>
<td>81.09 (8.19)</td>
<td>&lt;.001</td>
<td>77.03 (9.22)</td>
<td>&lt;.001</td>
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<tr>
<td>Females, n (%)</td>
<td>1083 (62.31)</td>
<td>99 (75.00)</td>
<td>.004</td>
<td>131 (61.92)</td>
<td>.904</td>
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<tr>
<td>Education level, n (%)(^d)</td>
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<tr>
<td>Elementary</td>
<td>217 (12.49)</td>
<td>30 (22.73)</td>
<td></td>
<td>48 (18.46)</td>
<td></td>
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<tr>
<td>Secondary</td>
<td>834 (47.99)</td>
<td>78 (59.09)</td>
<td></td>
<td>144 (55.38)</td>
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<td>University</td>
<td>686 (39.49)</td>
<td>24 (18.18)</td>
<td>&lt;.001</td>
<td>68 (26.15)</td>
<td>&lt;.001</td>
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<tr>
<td>Occupation, n (%)(^d)</td>
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<td>Blue collar</td>
<td>315 (18.25)</td>
<td>42 (32.06)</td>
<td>&lt;.001</td>
<td>78 (30.35)</td>
<td>&lt;.001</td>
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<td>White collar</td>
<td>1411 (81.75)</td>
<td>89 (67.94)</td>
<td></td>
<td>179 (69.65)</td>
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<tr>
<td>Smoking status, n (%)(^d)</td>
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<td></td>
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<td>Never</td>
<td>789 (45.74)</td>
<td>78 (60.00)</td>
<td></td>
<td>127 (48.85)</td>
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</tr>
<tr>
<td>Former</td>
<td>680 (39.42)</td>
<td>34 (26.15)</td>
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<td>108 (41.54)</td>
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<tr>
<td>Current</td>
<td>256 (14.84)</td>
<td>18 (13.85)</td>
<td>&lt;.001</td>
<td>25 (9.62)</td>
<td>&lt;.001</td>
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<td>Heavy drinking, n (%)(^d)</td>
<td></td>
<td></td>
<td></td>
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<td>Never</td>
<td>331 (19.14)</td>
<td>19 (14.39)</td>
<td>.178</td>
<td>34 (13.23)</td>
<td>.022</td>
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<td>Former</td>
<td>443 (25.49)</td>
<td>49 (37.12)</td>
<td>&lt;.001</td>
<td>80 (30.77)</td>
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<td>Diabetes, n (%)(^d)</td>
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<td>Never</td>
<td>160 (9.21)</td>
<td>5 (3.79)</td>
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<td>33 (12.69)</td>
<td>.076</td>
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<td>Former</td>
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<td>&lt;.001</td>
<td>234 (90.00)</td>
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<td>High cholesterol, n (%)(^d)</td>
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<td>Never</td>
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<td>53 (43.09)</td>
<td>&lt;.001</td>
<td>111 (43.53)</td>
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<td>BMI, n (%)(^d)</td>
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<td>&lt;18.5</td>
<td>734 (42.23)</td>
<td>67 (50.76)</td>
<td></td>
<td>98 (11.78)</td>
<td></td>
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<tr>
<td>18.5–24.9</td>
<td>45 (2.59)</td>
<td>6 (4.55)</td>
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<td>1 (0.38)</td>
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<td>≥25</td>
<td>911 (52.42)</td>
<td>43 (32.58)</td>
<td>&lt;.001</td>
<td>147 (56.54)</td>
<td>&lt;.001</td>
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<td>Heart diseases</td>
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</tr>
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<td>0</td>
<td>1470 (84.58)</td>
<td>98 (74.24)</td>
<td></td>
<td>179 (68.85)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>176 (10.13)</td>
<td>22 (16.67)</td>
<td></td>
<td>50 (19.23)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>92 (5.29)</td>
<td>12 (9.09)</td>
<td>.008</td>
<td>31 (11.92)</td>
<td>&lt;.001</td>
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<tr>
<td>APOE ε4 allele, n (%)(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Never</td>
<td>460 (26.47)</td>
<td>54 (40.91)</td>
<td>&lt;.001</td>
<td>63 (24.23)</td>
<td>.609</td>
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<tr>
<td>Former</td>
<td>86 (4.95)</td>
<td>9 (6.82)</td>
<td>.358</td>
<td>9 (3.46)</td>
<td>.484</td>
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<td>Psychological well-being, mean (SD)(^d)</td>
<td>0.07 (0.52)</td>
<td>-0.20 (0.46)</td>
<td>&lt;.001</td>
<td>-0.08 (0.50)</td>
<td>&lt;.001</td>
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<td>Leisure activity, mean (SD)(^d)</td>
<td>2.58 (1.49)</td>
<td>1.85 (1.35)</td>
<td>&lt;.001</td>
<td>2.25 (1.41)</td>
<td>.002</td>
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<td>Social network, mean (SD)(^d)</td>
<td>0.09 (0.53)</td>
<td>-0.09 (0.59)</td>
<td>&lt;.001</td>
<td>0.04 (0.52)</td>
<td>.158</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; APOE, apolipoprotein gene; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

*Participants with incident ischemic stroke in the table did not include those that developed AD, and participants with incident AD did not include those that developed ischemic stroke.

\(^b\)P-value was calculated by comparing the baseline characteristics between the non-demented & non-stroke participants and participants who developed AD.

\(^c\)P-value was calculated by comparing the baseline characteristics between the non-demented & non-stroke participants and participants who developed ischemic stroke.

\(^d\)Missing values: 1 person for education level, 16 for occupation, 15 for smoking status, 12 for heavy drinking, 8 for hypertension, 65 for high cholesterol, 78 for BMI, 15 for depression, 414 for APOE status, 414 for psychological well-being, 327 for leisure activity, and 106 for social network.
FIGURE 1  Hazard ratio (95% CI) of Alzheimer’s disease (AD) and ischemic stroke by shared risk and protective factors. CI, confidence interval; Ref, reference. Notes: Models were adjusted for age, sex, and education. Psychological well-being, leisure activity, and social network were divided into three groups, according to their tertiles. High level of psychological well-being or leisure activity refers to the top tertile group, and low level of psychological well-being or leisure activity refers to the bottom tertile group. Rich social network refers to individuals in the top tertile group, and limited social network refers to those in the bottom tertile group. Table S1 and Table S2 provide detailed information related to each risk and protective factor for incident AD and ischemic stroke. †.05 < P < .10, *.01 < P < .05, ** P < .01
3.4 Counteracting effect of the shared protective profile on AD/IS in relation to levels of the shared risk profile

There was an interaction between the shared risk score and shared protective score on AD ($P = .04$), but not on IS ($P = .38$). A four-category variable of joint exposures was created, by combining the shared risk profile (high vs low) and the shared protective profile (negative vs positive). Figure 2 shows the associations of incident AD and IS with the joint exposures.

Compared to the "high risk and protective (−)" group, only the "low risk and protective (+)" group presented significantly reduced AD risk (Figure 2A), whereas the other three groups all showed substantial reduced IS risk (Figure 2B). The proportion of incident AD cases that could be prevented due to a positive protective profile was 47% (95% CI: 0.22 to 0.64) in participants with a low risk profile and 38% (95% CI: 0.00 to 0.62) in those with a high risk profile. In addition, 28% (95% CI: 0.12 to 0.41) of incident IS cases in participants with a low risk profile and 31% (95% CI: 0.02 to 0.52) of IS cases in participants with a high risk profile were attributable to a positive protective profile. Similar results were obtained when AD and IS were combined (Figure 2C).

The protective profile seemed to reduce the risk of AD/IS by 33% (95% CI: 0.21 to 0.42) among individuals with a low risk profile and by 28% (95% CI: 0.08 to 0.44) among individuals with a high risk profile.

3.5 Population attributable fraction of shared risk and protective factors for AD/IS

The proportions of either AD or IS cases that would be reduced by controlling the shared risk factors and promoting the shared protective factors are shown in Figure 3. Specifically, 26% (95% CI: 0.10 to 0.38)
FIGURE 2  Joint effects of shared risk and protective profiles on incident Alzheimer’s disease (AD) and ischemic stroke. CI, confidence interval; HR, hazard ratio. Notes: P-values were obtained by estimating the effect of the protective profile (positive versus negative) on incident AD (a), incident ischemic stroke (b), and incident AD or ischemic stroke (c) by levels of risk profiles.
of AD/IS cases could be prevented if all individuals in a population had a high level of education, and 42% (95% CI: 0.26 to 0.55) of AD/IS cases could be prevented if all individuals in a population were free from any of the shared risk factors (ie, low level of education, sedentary lifestyle, and heart diseases). In total, 58% (95% CI: 0.42 to 0.69) of AD/IS cases could be prevented by promoting a positive protective profile in individuals free from any of the shared risk factors.

3.6 | Additional analyses

Similar results were observed in the old-old group (>75 years) and the young-old group (<75 years) regarding the association of shared risk/protective factors with AD/IS (Tables S3 and S4 in supporting information). Furthermore, the findings were similar when we applied different cut-offs for cardiovascular risk factors (Table S5 in supporting information), when we removed the incident AD and IS cases detected in the first 3-year follow-up period or those who had died within 3-years from baseline (Table S6 in supporting information), when covariates were adjusted for as either 3 levels of categorical variables or as continuous variables, and when we conducted multiple imputation to replace the missing covariates in the models. Finally, change in psychosocial well-being was not significantly associated with either AD (HR [95% CI] = 0.78 [0.46 to 1.34]) or IS (HR 0.82, 95% CI: 0.60 to 1.13) in our additional analyses.

4 | DISCUSSION

In this population-based long-term follow-up study of Swedish older adults aged 60 years and above, we found that: (1) low level of education, a sedentary lifestyle, and heart diseases are the shared risk factors for AD and IS. High levels of psychological well-being, leisure-time mental and physical activity, and a rich social network are the shared protective factors for AD and IS; (2) a protective profile may decrease 47% of AD and 28% of IS risk among older adults with a low risk profile, and 38% of AD and 31% of IS risk in those with a high risk profile; and (3) more than half of the cases with either AD or IS could be theoretically preventable by controlling the risk profile and promoting the protective profile.

Previous population-based studies have demonstrated that certain risk and protective factors are related to both AD and stroke, including vascular risk factor burden, depression, and social networks.8,9,29-31 When investigating the association of these factors with AD or IS, previous researchers focused exclusively on one of the outcomes, or treated stroke and dementia as a combined outcome. In the current study, we examined AD and IS cases in a mutually exclusive manner, and the shared risk factors identified accordingly may suggest shared pathophysiologicals between AD and IS. To the best of our knowledge, this is the first study attempting to detect shared risk/protective factors for AD and IS, involving a large range of demographic, genetic, vascular, mental, and psychosocial factors.
Several studies have developed scores or indices to predict the risk of stroke or dementia, based on the expected accumulated synergistic effect of multiple risk factors. The Framingham Stroke Risk Score (FSRS) and the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) dementia risk score are two recognized examples. The only overlapping modifiable risk factor between the two scores is high systolic blood pressure. However, the Whitehall II study has revealed that the FSRS is associated with accelerated cognitive decline over 10 years, and another study showed that the FSRS score might even perform better than the CAIDE score in predicting cognitive decline. These findings indicate that the stroke risk–related factors, may play a potential role, either independently or synergistically, in the development of dementia or AD.

Female sex is a well-established risk factor for AD, but sex was not associated with AD in our analyses. The population in the current study consists of a random sample (63.6% females) from central Stockholm (Kungsholmen) during the years 2001 to 2003. Interestingly, females in our sample were more likely to drop out either at baseline or during the follow-up period. Specifically, among those who refused to participate in follow-up interviews, 64.36% were female, and among those who died before the first follow-up interview, 57.39% were female. A lower education level and a higher burden of multimorbidity in females than in males may contribute to the higher attrition rates in females, which may further influence the association between female sex and the risk of AD. The associations of cardiovascular risk factors (eg, high blood pressure, and high total cholesterol level) with AD and IS may vary by age, the presence of frailty, multimorbidities, and treatments. Guidelines for the diagnosis and management of certain cardiovascular risk factors (eg, hypertension and high cholesterol) have been updated recently. In our additional analysis, we have applied multiple cutoffs to cardiovascular measurements in the additional analyses, and the results are consistent with our main findings—cardiovascular measurements (eg, blood pressure and BMI) showed a tendency of protective effect on AD but a risk effect on IS. The reduced hazard of AD as associated with cardiovascular measurements in the additional analyses, and the results are consistent with our main findings—cardiovascular measurements (eg, blood pressure and BMI) showed a tendency of protective effect on AD but a risk effect on IS. The reduced hazard of AD associated with cardiovascular measurements may be driven partially by reverse causality.

In the current study, three major heart diseases (ie, coronary heart disease, atrial fibrillation, and heart failure) were involved in the analysis, and we counted the numbers of heart diseases in each participant as a proxy of aggregation. Yet, future studies need to pay attention when the AD/IS risk was estimated in relation to a distinct combination of two heart diseases, especially when treatments were taken into account. For example, heart failure or atrial fibrillation alone was associated with a higher risk of mortality than coronary heart disease. Co-existence of atrial fibrillation and heart failure may worsen the disease progression and complicate treatments. Subtypes of heart failure (eg, heart failure with preserved ejection fraction and heart failure reduced ejection fraction) are linked to variations in treatments, survival rates, and subsequent stroke risk. In addition, treatments for heart disease (eg, anticoagulant therapy, antiplatelet agents, and statins), could modify the association between burden of heart diseases and AD/IS. Anticoagulation medication in particular may significantly reduce the stroke risk in atrial fibrillation patients; however, there is still debate regarding whether warfarin anticoagulation may increase the risk of all dementia types in atrial fibrillation patients. Therefore, the diverse cardiovascular pathologies, specific aggregations of heart diseases, and treatments are vital factors to consider for future studies when investigating the association of AD/IS with heart diseases.

Moreover, psychosocial factors, such as an active and socially integrated lifestyle, have been suggested to protect older adults from both stroke and dementia/AD. A dose-response association of psychosocial factors with AD has been reported when such factors were aggregated together into a cognitive reserve score, as was the case in our study. We moreover found that a positive protective profile can offset the risk of AD or IS due to shared risk profiles. This is encouraging because, even in older adults with a high risk profile with a low level of education, a sedentary lifestyle, and multiple heart diseases, approximately one third of AD and IS risk, could be counteracted through promoting psychological well-being, leisure activity, and social network.

The Lancet Commission life-course model has demonstrated that up to 35% of dementia cases were potentially preventable if nine life-long factors were diminished, including early life low education, mid-life risk factors (hearing loss, hypertension, and obesity), and late-life risk factors (smoking, depression, physical inactivity, social isolation, and diabetes). The INTERSTROKE study, a world-wide study including 32 countries and focusing on 10 potentially modifiable risk factors (ie, blood pressure, physical activity, apolipoprotein B-to-apolipoprotein A ratio, diet, waist-to-hip ratio, psychological factors, smoking, cardiac events, alcohol consumption, and diabetes), has presented that the 10 factors were collectively linked to about 90% of PAF of IS. In addition, 90% of the PAF of IS was independent with regions, ethnic groups, sex, and age. In the current study, we found that shared risk and protective factors were associated with nearly 60% of PAF of AD/IS. The varied PAF between our study and others may be due to the different age, diversity in the combination of risk/protective factors, and inclusion/exclusion criteria of outcomes.

Vascular dysfunction, atherosclerosis, and deposition of amyloid in cerebral vessels may partially explain the common underlying mechanism between AD and IS. The hypoperfusion and hypoxia caused by atherosclerosis may boost the production of Aβ. The Aβ, in turn, may accelerate the formation of atherosclerotic lesions through endothelial dysfunction or vascular oxidative stress, leading to further vascular damage in the brain. Mitochondrial dysfunction with epigenetic impairment in oxidative respiration appears to be the earliest mechanism in the progression of AD and IS, and they are closely linked to the age-related energy deficits. Certain risk factors, such as peripheral insulin resistance, could largely contribute to this energy deficit and exacerbate Aβ/tau accumulation. Life-long risk factors (eg, low education, sedentary lifestyle, and heart diseases), in theory, may act in different cascades of IS and AD pathologies. For example, one factor may cause oxidative stress and trigger atherosclerosis in middle age, and another factor may lead to the thickening of vascular basement membranes and hypoperfusion in older age. Other pathologies or clinical profiles that are captured by neuroimaging or molecular levels, such as microbleeds and cerebrovascular reactivity, may play an essential role in connecting AD and IS, and may easily be...
influenced by shared risk factors as well. However, it is difficult to speculate the direct causality from the shared risk factors to the common mechanisms, due to lacking neuroimaging and biomarker confirmation, and unmeasured confounding. Moreover, mixed pathologies are frequently observed in AD patients or the aging brain. Specifically, cerebral amyloid angiopathy and small vessel disease are the common vascular pathologies in the aging brain and in AD cases. Certain risk factors, such as heart diseases and cardiovascular risk factors, may give rise to cerebral small vessel disease and consequently, a higher AD or IS risk. The mechanisms in which positive psychosocial factors may lower or compensate the risk of AD and IS are not fully understood. Nevertheless it is plausible to assume that the reduction in AD risk could be achieved through vascular mechanisms that are in part independent of AD pathology. This hypothesis is supported by a recent study displaying that midlife physical activity is associated with a lower incidence of vascular dementia, but not AD. The cognitive reserve concept assumes that individuals with certain lifestyles and psychosocial factors could cope better with increasing brain lesions (eg, AD pathology), reflecting a more flexible or adaptive cognitive network. In the current study, the findings suggest that individuals with more positive psychological profiles tend to have better self-perceptions of aging, which may impact their values, health behaviors, health-care use, and access to instrumental and emotional support. These factors may reduce and/or make people more resilient to psychosocial stress, and therefore improve cardiovascular health by enhancing the immune system or reducing systemic inflammation.

This study has several strengths, including the relatively large study sample with a long follow-up period, the high rate of participation, and the comprehensive diagnoses using multiple resources (eg, physical examination, patient and death registers). The structured SNAC-K interviews provide a wide range of information on demographics, clinical, lifestyle, psychosocial, and behavioral factors. Yet, several limitations need to be pointed out. First, using self-reported questionnaire data on psychosocial factors may introduce measurement bias. This is especially true among older adults who may have cognitive impairment or memory complaints. Second, selection bias may have been introduced by excluding those subjects who did not have any follow-up information or who refused to participate in follow-up interviews, although the proportion of those people was rather small (10.3%). A few factors need to be taken into accounts in future validation studies, such as heart diseases, cancer, and COVID-19. Specifically, when a world pandemic that is associated with elevated mortality in older populations occurs, such as COVID-19, survival bias might be introduced to a study to affect the link of shared risk/protective factors to AD/IS. Third, similar to most observational studies, bias that may be caused by unmeasured confounding factors remains (eg, low-density lipoprotein), even though multiple sensitivity analyses have been carried out in the current study. The factors that we included in this study were from baseline. With a rather long follow-up period in the current study, certain risk or protective factors may vary with time, for instance, the increasing number of heart diseases and reduction in social networks. Furthermore, certain factors, such as the use of medications, treatment of heart diseases, or psychosocial factors, may interact with shared risk factors to influence the AD/IS risk over time. Future studies should further verify the time-varying effect of those factors in relation to both AD and IS. High education is often treated as one of the important cognitive reserve proxies, and showed a protective effect on both AD and IS. The risk factors in our study have been predefined as being either pathogenic or as negative exposures in early life, hence, both low education and sedentary lifestyles are identified as risk factors. However, it is worth investigating the underlying mechanisms of resilience and reserve between AD and IS with respect to the cognitive reserve proxies. Fourth, IS includes a wide range of subtypes, and it can be subdivided into several categories including cardioembolism, small-vessel occlusion, large-artery atherosclerosis, and stroke of undetermined etiology. For example, cardioembolic stroke (embolic events occur in the valve or chambers of the heart) and lacunar stroke (blood vessel occlusion in a perforating artery) are two subtypes of IS. The diverse etiologies and treatments of the two IS categories may display different risk factors; disease burden; comorbidity; and eventually, influence the connection with AD. In the current study, we focused only on general IS without specifying subcategories. Fifth, the AD and IS cases in the current study were based on the clinical diagnosis, which do not represent “pure” AD or “pure” ischemic damage. The advent of molecular neuroimaging techniques enables us to identify the often-combined cerebrovascular disease and AD pathologies in vivo, and more evidence has accumulatively suggested that mixed pathologies are common in aging and important in lowering the threshold for cognitive impairment and dementia. Lack of neuroimaging and biomarkers in this study makes it difficult to relate the shared factors to a “pure” specific pathology. Sixth, although our results display a sufficient reduction in AD/IS risk at the population level by targeting both shared risk and protective factors, proper interpretation is needed at the individual level because PAF does not allow the designation of affected individuals. Finally, our study participants live in central Stockholm and have a relatively higher socioeconomic status and education level than the general older population. Caution is therefore needed when generalizing our findings to other populations.

In conclusion, several shared risk and protective factors between AD and IS were identified among adults aged 60 years and above. Late-life AD and IS risk may be mitigated by targeting multiple lifelong risk/protective factors, including (1) early-life education; (2) midlife lifestyles and risk factors of heart diseases; and (3) late-life psychosocial well-being, social network, and leisure time activity. Moreover, late-life psychosocial factors may even counteract the harmful effect of risk factors that occurred earlier in life on both AD and IS. Our findings support the notion that AD and IS may share pathophysiological mechanisms or mixed pathologies (eg, neurodegenerative and vascular pathologies), which may be the dominant etiology for AD. We, therefore, provide evidence for the implementation of common preventive strategies for both disorders. Future studies are essential to better understand the compensatory mechanisms in AD and IS pathology. Clinical trials may consider using multifactor interventions, such as targeting heart diseases and psychosocial factors, to prevent AD and stroke.
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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

R.W. and W.X. conceptualized and designed the study, R.W. performed the data analysis and drafted the manuscript. C.Q., H.-X.W., C.S.D., Y.S., and A.C.-L. contributed to the data interpretation and revision of the manuscript and approved the final draft. R.W. has the full access to all the data in this study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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