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CARDIOVASCULAR HEALTH AND BRAIN AGING: A POPULATION-BASED MRI STUDY

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Cardiovascular health and brain aging: a population-based MRI study

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To my family,

Abstract

Deterioration of brain structure and cognitive function occurs as individuals reach advanced age. The former can be observed through various markers of cerebral small vessel disease on magnetic resonance imaging (MRI) scans and the later can be assessed by neuropsychological tests and clinical examinations. In addition, maintaining a favorable cardiovascular health (CVH) status may contribute to delaying brain aging. Having a higher cognitive reserve (CR) capacity may contribute to preserving cognitive function even in the presence of brain damage. In this thesis, we aimed to examine the progression and interrelationships of MRI markers of structural brain aging and the association between the progression of these markers and cognitive decline. Furthermore, we aimed to investigate whether maintaining a favorable CVH status would be related to a slower deterioration of brain structure and whether having a higher CR capacity would be associated with a lower risk of cognitive deterioration and death. Data were derived from the population-based Swedish National study on Aging and Care in Kungsholmen from 2001–2004 to 2016–2019 and the MRI sub-study from 2001–2003 to 2007–2010.

Study I: This six-year follow-up study showed that the progression rate of cerebral small vessel disease markers including expansion rates of white matter hyperintensities (WMHs) and lateral ventricles, incidence of lacunes, and shrinkage rate of gray matter volume, but not the progression rate of perivascular spaces (PVSs), steadily increased with aging ($P < 0.05$). The progression rate of regional WMHs was faster in males than in females and in people without a university degree than those with a degree ($P < 0.05$). In addition, a higher load of microvascular lesions (i.e., WMHs, PVSs, and lacunes) at baseline was related to faster progression of both microvascular lesions (WMHs and lacunes) and gray matter atrophy ($P < 0.05$).

Study II: This follow-up study showed that a greater burden of WMHs at baseline was associated with a faster decline in executive function, letter fluency, perceptual speed, and global cognition over 15 years ($P < 0.05$), but not in episodic or semantic memory. The faster deterioration in category fluency was linked to greater periventricular WMHs at baseline only in people carrying the *APOE*-ε4 allele (multivariable-adjusted β-coefficients and 95% confidence interval [CI]: -0.018, -0.031– -0.004). Accelerated decline in perceptual speed over 15 years was linked to a faster increase in deep and periventricular WMHs during the first six years, and accelerated decline in executive function and global cognition was linked to a faster increase in deep WMHs during the first six years ($P < 0.05$).

Study III: This six-year follow-up study showed that compared to the unfavorable global CVH profile, the intermediate-to-favorable profiles were associated with a slower accumulation of WMHs (multivariable-adjusted β-coefficients and 95% CI: -0.019, -0.035– -0.002 and -0.018, -0.034– -0.001, respectively). Intermediate-to-favorable biological CVH profiles were associated with a slower WMH increase among people aged 60–72 years, but not in those aged 78 years and above. Furthermore, a higher metabolic genetic risk was linked to a faster

accumulation of WMHs in people with intermediate-to-favorable global or behavioral CVH profiles, but not in those with favorable CVH profiles (*P* for both interactions = 0.001).

Study IV: This 15-year follow-up study revealed that a higher composite CR score, which was estimated from early-life education, midlife work complexity, late-life leisure activities, and late-life social network, was associated with a reduced risk of transition from normal cognition to cognitive impairment, no dementia (CIND) (multivariable-adjusted hazards ratio and 95% CI: 0.78, 0.72–0.85) and death (0.85, 0.79–0.93) and from CIND to death (0.82, 0.73–0.91), but not from CIND to dementia neither from CIND to normal cognition (*P* > 0.05). The risk of transitions from normal cognition to CIND or death did not change after controlling for brain aging markers, while the risk of transition from CIND to death became not significant. Furthermore, a higher CR score was associated with a lower risk of transition from CIND to death among people aged 60–72 years (0.65, 0.54–0.77) while not among those aged 78 years and above (0.87, 0.75–1.01) (*P* for interaction = 0.010).

Conclusions: First, the deterioration of brain structure accelerates with advancing age. Cerebral microvascular lesions are associated with accelerated brain atrophy. Second, WMHs are linked to an accelerated decline in multiple cognitive domains except memory. A faster accumulation of WMHs in deep brain regions is associated with an accelerated decline in perceptual speed and executive function. Third, having a favorable CVH profile is associated with a slower progression of structural brain aging attributable to metabolic genetic risk. Finally, having a greater CR capacity might play a crucial role in preserving cognitive health and reducing mortality rate in the prodromal phase of dementia, independent of brain aging markers. The association between higher CR capacity and lower likelihood of transition from CIND to death exists particularly among people in the early stage of older adulthood.

Keywords: structural brain aging, cerebral small vessel disease, cognitive decline, cognitive phenotypes, cardiovascular health, metabolic genetic risk, cognitive reserve, magnetic resonance imaging, population-based study.

Sammanfattning

Försämring av hjärnans struktur och kognitiv funktion inträffar när individer når hög ålder. Den förstnämnda kan observeras genom olika markörer för cerebral småkärlssjukdom på magnetisk resonanstomografi (MRI) och den senare kan bedömas genom neuropsykologiska tester och kliniska undersökningar. Dessutom kan bibehållande av en gynnsam hjärt-kärlhälsa (CVH) bidra till att försena hjärnans åldrande. Att ha en högre kognitiv reserv (CR) kan bidra till att bevara kognitiv funktion även i närvaro av hjärnskador. I denna avhandling syftade vi till att undersöka progressionen och sambanden mellan MRI-markörer för strukturell hjärnåldring och sambandet mellan progressionen av dessa markörer och kognitiv försämring. Dessutom syftade vi till att undersöka om bibehållande av en gynnsam CVH skulle vara relaterad till en långsammare försämring av hjärnstrukturen och om en högre CR skulle vara associerad med en lägre risk för kognitiv försämring och död. Data hämtades från den populationsbaserade svenska nationella studien om åldrande och vård i Kungsholmen från 2001–2004 till 2016–2019 och MRI-understudien från 2001–2003 till 2007–2010.

Studie I: Den sexåriga uppföljningsstudien antydde att progressionshastigheten för markörer för cerebral småkärlssjukdom, inklusive expansionshastigheterna för vita substansens hyperintensiteter (WMHs) och laterala ventriklar, förekomst av lakuner, samt krympningshastigheten för grå substans, med undantag för progressionshastigheten för perivaskulära utrymmen (PVSs), stadigt ökade med åldrandet ($P < 0,05$). Progressionshastigheten för regionala WMHs var snabbare hos män än hos kvinnor och hos personer utan universitetsexamen jämfört med de med universitetsexamen ($P < 0,05$). Dessutom var en högre belastning av mikrovaskulära lesioner (t.ex. WMHs, PVSs och lakuner) vid baslinjen relaterad till snabbare progression av både mikrovaskulära lesioner (WMHs och lakuner) och grå substansatrofi ($P < 0,05$).

Studie II: Den uppföljningsstudien antydde att en större börda av WMHs vid baslinjen var associerad med en snabbare nedgång i exekutiv funktion, bokstavsfluens, perceptuell hastighet och global kognition över 15 år ($P < 0,05$), men inte med episodiskt eller semantiskt minne. Den snabbare försämringen av kategorifluens var kopplad till större periventrikulära WMHs vid baslinjen endast hos personer som bar på *APOE*-ε4-allel (multivariable-justerade β-koefficienter och 95 % konfidensintervall: -0,018; -0,031– -0,004). Accelererad nedgång i perceptuell hastighet över 15 år var kopplad till en snabbare ökning av djupa och periventrikulära WMHs under de första sex åren, och accelererad nedgång i exekutiv funktion och global kognition var kopplad till en snabbare ökning av djupa WMHs under de första sex åren ($P < 0,05$).

Studie III: Den sexåriga uppföljningsstudien visade att jämfört med ogynnsamma globala CVH-profiler var de intermediära-till-fördelaktiga profilerna associerade med en långsammare ansamling av WMHs (multivariable-justerade β-koefficienter och 95% konfidensintervall: -0,019; -0,035– -0,002 respektive -0,018; -0,034– -0,001). Intermediära-till-fördelaktiga biologiska CVH-profiler var associerade med en långsammare ökning av WMHs bland

personer i åldern 60–72 år, men inte hos de som var 78 år och äldre. Dessutom var en högre metabolisk genetisk risk kopplad till en snabbare ansamling av WMHs hos personer med intermediära-till-fördelaktiga globala eller beteendemässiga CVH-profiler, men inte hos de med fördelaktiga CVH-profiler (*P* för båda interaktioner = 0,001).

Studie IV: Den 15-åriga uppföljningsstudien avslöjade att en högre samlad CR-poäng, som beräknades utifrån tidig utbildning, arbetskomplexitet under medelåldern, fritidsaktiviteter senare i livet och socialt nätverk senare i livet, var kopplad till en minskad risk för övergång från normal kognition till kognitiv försämring, ingen demens (CIND) (multivariable-justerad riskkvot och 95 % konfidensintervall: 0,78; 0,72–0,85) och död (0,85; 0,79–0,93), samt från CIND till död (0,82; 0,73–0,91), men inte från CIND till demens eller från CIND till normal kognition (*P* > 0,05). Risken för övergångar från normal kognition till CIND eller död påverkades inte av att kontrollera för markörer för hjärnåldrande, medan risken för övergång från CIND till död inte var signifikant. Dessutom var en högre CR-poäng förknippad med en lägre risk för övergång från CIND till död hos personer i åldrarna 60–72 år (0,65; 0,54–0,77) men inte hos de som var 78 år och äldre (0,87; 0,75–1,01) (*P* för interaktion = 0,010).

Slutsatser: För det första accelererar försämringen av hjärnstruktur med stigande ålder. Cerebrala mikrovaskulära lesioner är kopplade till accelererad hjärnvävnadsatrofi. För det andra är WMHs kopplade till en accelererad nedgång i flera kognitiva områden förutom minnet. En snabbare ansamling av WMHs i djupa hjärnregioner är associerad med en accelererad nedgång i perceptuell hastighet och exekutiv funktion. För det tredje är det att ha en fördelaktig CVH-profil kopplat till en långsammare progression av strukturell hjärnåldrande som kan tillskrivas metabolisk genetisk risk. Slutligen kan en högre CR spela en avgörande roll i att bevara kognitiv hälsa och minska dödligheten i den prodromala fasen av demens, oberoende av markörer för hjärnåldrande. Sambandet mellan högre CR och lägre sannolikhet för övergång från CIND till döden är speciellt tydligt bland personer i tidiga stadiet av äldre vuxenliv.

Nyckelord: strukturellt åldrande av hjärnan, cerebral småkärlsjukdom, kognitiv försämring, kognitiva fenotyper, kardiovaskulär hälsa, metabolisk genetisk risk, kognitiv reserv, magnetisk resonanstomografi, befolkningsbaserad studie.

摘要

脑结构和认知能力的恶化发生在个体的老年时期。前者可以通过磁共振成像（MRI）扫描中的各种脑小血管病标记物来观察，而后者可以通过神经心理学测试和临床检查来评估。此外，保持良好的心血管健康（CVH）状况可能有助于延缓脑老化的过程。拥有更强的认知储备（CR）能力可能有助于在脑病变的情况下维持认知功能。在这项课题中，我们旨在研究结构性脑老化 MRI 标记物的进展和相互之间的关系，以及结构性脑老化标记物的进展与认知衰退之间的关联。此外，我们还旨在探究是否较好的 CVH 状态与延缓的结构性脑老化有关，以及是否更高的 CR 能力与认知状态的转变及死亡有关。数据来自于位于国王岛区域的瑞典国家老龄化与护理研究。 这是一项以人口为基础的队列研究，队列的时间跨度从 2001–2004 年至 2016–2019 年，其中 MRI 研究队列的时间跨度是从 2001–2003 年至 2007–2010 年。

研究一： 此项六年的随访研究发现，脑小血管病标记物的进展速率包括白质高信号区（WMHs）和侧脑室的扩大、腔隙性梗死积累、以及灰质萎缩的速率，随着年龄增长而增加，而血管周围间隙（PVSs）的进展不随年龄的增长而增加；在男性的部分脑区中 WMHs 的进展速率比女性快，在没有大学学位的人群的部分脑区中 WMHs 的进展速率比有大学学位的人群快（$P < 0.05$）。此外，基线期大脑微血管病变（即 WMHs、PVSs 和腔隙性梗死）的负荷与后期微血管病变（WMHs 和腔隙性梗死）和灰质萎缩的快速进展相关（$P < 0.05$）。

研究二：此项随访研究发现，基线时较重的 WMHs 的负荷与执行功能、字母流畅性、感知速度和整体认知能力在 15 年随访期间的快速下降相关（$P < 0.05$），但与情景记忆或语义记忆的变化无关。仅在携带 *APOE*-ε4 等位基因的人群中观察到，基线时较多的脑室周围 WMHs 与类别流畅性的加速下降相关（多变量调整的 β 系数和 95%置信区间：-0.018，-0.031– -0.004）。在随访的 15 年内，感知速度的加速下降与前六年脑深部和脑室周围 WMHs 的快速积累相关，而执行功能和整体认知的加速下降与前六年深部 WMHs 的快速积累相关（$P < 0.05$）。

研究三：此项六年的随访研究发现，相对于不利的综合 CVH 状况，中等至有利的综合 CVH 状态与 WMHs 的延缓进展相关（多变量调整的 β 系数和 95%置信区间分别为：-0.019，-0.035– -0.002 和 -0.018，-0.034– -0.001）。在 60 至 72 岁的人群中，相比于不利的生物学 CVH 状况，中等至有利的生物学 CVH 状况与 WMHs 的延缓进展相关，但在 78 岁及以上的人群中没有此相关性。此外，在中等至有利的综合或行为学 CVH 状况的人群中，较高的代谢遗传风险与 WMHs 的加速进展相关，但在有利的综合或行为学 CVH 状况人群中没有此相关性（交互作用 $P = 0.001$）。

研究四：此项十五年的随访研究发现，从早年教育、中年工作复杂性、晚年休闲活动和晚年社交网络评估得来的较高的 CR 分数与较低的从正常认知到认知障碍，无痴呆（CIND）（多变量调整的风险比：0.78；95% 置信区间：0.72–0.85），以及到死亡

（0.85；0.79–0.93）转变的风险相关，并与较低的从 CIND 到死亡（0.82；0.73–0.91）转变的风险相关，但和从 CIND 到痴呆或从 CIND 到正常认知的转变风险无关。在控制脑老化标志物后，从正常认知到 CIND 或死亡的转变风险没有改变，而从 CIND 到死亡的风险变得不显著。此外，较高的 CR 分数在 60–72 岁的人群中与从 CIND 到死亡的转变风险相关（0.65；0.54–0.77），此关系在 78 岁及以上的人群中不显著（0.87；0.75–1.01）（交互作用 $P = 0.010$）。

结论: 首先，结构性脑老化的进展随着老龄化程度增高而增加。在结构性脑老化中，脑微血管病变与脑萎缩有关。其次，作为结构性脑老化的标志，白质高信号与除了记忆之外的多个认知领域的加速衰退相关。深脑区域白质高信号的快速积累与感知速度和执行功能的加速衰退相关。第三，保持有利的心血管健康状况可以缓解由代谢遗传风险导致的脑结构性老化。最后，较高的认知储备能力可能在痴呆前期起到关键作用，可以保护认知健康并降低死亡率，这与脑老化标志物无关。较高的 CR 能力与较低的从 CIND 转变为死亡的风险之间的关系在处于老年早期的人群中更为明显。

关键词：结构性脑老化，脑小血管病，认知衰退，认知表型，心血管健康，代谢遗传风险，认知储备，磁共振成像，基于人群的研究。

List of scientific papers

I. **Li Y**, Kalpouzos G, Laukka EJ, Dekhtyar S, Bäckman L, Fratiglioni L, Qiu C. Progression of neuroimaging markers of cerebral small vessel disease in older adults: a 6-year follow-up study. Neurobiol Aging. 2022 Apr; 112:204-211. doi: 10.1016/j.neurobiolaging.2022.01.006.

II. **Li Y**, Kalpouzos G, Bäckman L, Qiu C, Laukka EJ. Association of white matter hyperintensity accumulation with domain-specific cognitive decline: a population-based cohort study. Neurobiol Aging. Under revision.

III. **Li Y**, Laukka EJ, Dekhtyar S, Papenberg G, Speh A, Fratiglioni L, Kalpouzos G, Qiu C. Association between behavioral, biological, and genetic markers of cardiovascular health and MRI markers of brain aging: a cohort study. Neurology. 2023 Jan 3;100(1): e38-e48. doi: 10.1212/WNL.0000000000201346.

IV. **Li Y**, Dekhtyar S, Grande G, Kalpouzos G, Laukka EJ, Qiu C. Association of cognitive reserve with transitions across cognitive states and death in older adults: a 15-year follow-up study. Manuscript.

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List of abbreviations

MRI	Magnetic resonance imaging
SVD	Small vessel disease
WMH	White matter hyperintensity
PVS	Perivascular space
GM	Gray matter
FLAIR	Fluid attenuated inversion recovery
STRIVE	STandards for ReportIng Vascular changes on nEuroimaging
SNAC-K	Swedish National study on Aging and Care in Kungsholmen
MMSE	Mini-Mental State Examination
MCI	Mild cognitive impairment
CIND	Cognitive impairment, no dementia
AHA	American Heart Association
CVH	Cardiovascular health
CR	Cognitive reserve
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ATC	Anatomical Therapeutic Chemical
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
SNP	Single-nucleotide polymorphism
HR	Hazards ratio
CI	Confidence interval
SD	Standard deviation

Introduction

The aging process leads to the deterioration of both brain structure and cognitive function (1). Structural brain aging is characterized by specific markers of cerebral small vessel disease on magnetic resonance imaging (MRI) scans, such as white matter hyperintensities (WMHs), perivascular spaces (PVSs), lacunes, and brain atrophy (2). WMHs, PVSs, and lacunes are primarily attributable to microvascular ischemic lesions; brain atrophy indicates mixed cerebral microvascular and neurodegenerative pathology (3, 4). Exploring the relationships between these markers is crucial to understanding brain aging, as they exhibit a reciprocal relationship during the aging process (5, 6). Furthermore, numerous population-based studies have shown that a greater burden of structural brain aging markers, particularly WMHs, is associated with a faster decline in various cognitive domains (7, 8), as well as an increased incidence of dementia (8, 9). It is important to note that structural brain aging is a dynamic process, particularly in later life (10), and thus, changes in structural brain aging markers such as WMHs should be investigated in relation to cognitive decline.

In 2010, the American Heart Association proposed seven cardiovascular health (CVH) metrics aimed at monitoring CVH status and assessing the risk of cardiovascular events (11). The CVH metrics incorporate both behavioral (smoking, diet habit, physical activity, and body mass index) and biological (blood pressure, blood cholesterol, and diabetes) factors (11). Population-based studies have consistently shown that favorable CVH metrics in midlife are associated with a lower risk of cognitive decline and dementia in late life (12, 13). Accordingly, it is plausible to hypothesize that the favorable CVH metrics are also related to a slower progression of structural brain aging. However, there is currently a lack of relevant evidence from population-based studies to support this hypothesis.

Data from population-based studies have consistently indicated that the higher cognitive reserve (CR) capacity is associated with a reduced risk of cognitive decline, mild cognitive impairment (MCI), and dementia in late life (14-17). When examining the transition from normal cognition to the prodromal phase of dementia (e.g., MCI), it is important to recognize that the transition is not unidirectional (18-20). Exploring the potential impact of CR capacity on the dynamic transitions of cognitive states from normal cognition through prodromal phase of dementia to clinical dementia and death can provide valuable insights into the protective effects of CR capacity on brain health. Additionally, given that the associations of individual CR proxies with dementia and MCI may vary depending on age, sex, and genetic susceptibility (e.g., *APOE* genotypes) (21-23), it is also important to examine if the association of CR capacity with transitions across cognitive states and death is influenced by these factors.

In summary, further investigation is warranted to clarify the progression of structural brain aging markers over time and their interrelationships and to examine the association between structural brain aging markers, such as the progression of WMHs, and cognitive decline. In addition, research is warranted to untangle the role of CVH metrics in structural brain aging and the role of CR capacity in cognitive phenotypes.

1 Literature review

1.1 Structural brain aging and cognitive decline

1.1.1 Imaging markers of structural brain aging

Cerebral small vessel disease (SVD) is a pathological process that affects pial and parenchymal circulations (e.g., small arteries, arterioles, venules, and capillaries) of brain. People with cerebral SVD could remain asymptomatic before the onset of clinical stroke, cognitive impairment, dementia, depression, functional dependency, and even death (24). The specific markers of cerebral SVD on structural magnetic resonance imaging (MRI) scans include white matter hyperintensities (WMHs), perivascular spaces (PVSs), lacunes, and brain atrophy (2). Such MRI markers are attributed to cerebral microvascular lesions, neurodegenerative damage, or mixed pathologies (3, 4), and have been extensively utilized as structural indicators of various brain lesions in brain aging research (5, 25).

WMHs present as hyperintense signals on the fluid attenuated inversion recovery (FLAIR) and T2-weighted sequences and hypointense signals on the T1-weighted sequence (2). WMHs on the FLAIR sequence can be quantified via a predefined signal difference between normal white matter tissues and WMHs (26). Several visual rating scales are also available to semi-quantitatively evaluate the load of WMHs, such as the Fazekas scale (27), the Scheltens's scale (28), and the Manolio scale (29). The Scheltens's rating scale divides the entire brain into distinct regions, enabling a detailed depiction of the regional distribution of WMHs (28). Generally, the appearance of WMHs is usually attributed to axonal demyelination, which can be a result of chronic cerebral ischemia (30). Moreover, the dysfunction of blood-brain barrier and amyloid aggregation in brain parenchyma will also contribute to the formation and development of WMHs (31, 32).

PVSs are fluid-filled cavities that mainly surround arterioles and extend from the subarachnoid space into the brain tissue (2). Normally, PVSs are involved in the exchange of cerebrospinal fluid and outflux of metabolic wastes in small vessels and are not visible on MRI scans. The MRI-visible PVSs are mainly due to the dysfunction and dilation of these spaces. These PVSs appear as round cavities with cerebrospinal fluid intensity when imaged perpendicular to their course, displaying a diameter of up to 3 mm, or as linear structures when imaged following the path of the surrounding arterioles (2). The MRI-visible PVSs are predominantly distributed in the basal ganglia and lobar areas, with a few located in the mesencephalon (33, 34). The load of MRI-visible PVSs could be evaluated using visual rating scales. These scales involve reviewing relevant brain regions across multiple slices and recording only the slice with the highest number of PVSs (35-39), or rating the number of PVSs in all slices for certain regions (33, 40, 41). Neuropathological studies have indicated that PVSs in basal ganglia may serve as an indicator of hypertensive arteriopathy, while lobar PVSs are more likely to be associated with the accumulation of cerebral amyloid in small blood vessels (38, 42, 43).

Lacunes presumed to be of vascular origin are commonly observed on the FLAIR sequence. They appear as hypointense signals in the center resembling cerebrospinal fluid, surrounded by

a hyperintense rim. These lacunes typically range from 3 to 15 mm in diameter and are located within the territory of an ischemic or hemorrhagic perforating arteriole (2). The visual rating of lacunes usually follows the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) (2). Lacunes can also be automatically quantified via estimating the intensity and size of possible lacunes near WMHs and other subcortical tissues (44, 45). Lacunes are primarily located in centrum semiovale and basal ganglia. Cerebral hypoperfusion and secondary ischemia in penetrating arterioles may facilitate the formation of lacunes in brain parenchyma (46). In addition, cerebral amyloid angiopathy may drive the formation and development of lacunes (47).

Brain atrophy indicates neuronal loss during the aging process or the end-stage manifestation of cerebral SVD. It usually presents as brain parenchymal loss, ventricular enlargement, and cortical thinning on the T1-weighted sequence (2). Alzheimer's disease-relevant brain atrophy (e.g., medial temporal lobe) reflects the process of neurodegeneration, axonopathy, and tau phosphorylation (48). Several visual rating scales have been proposed to evaluate the global and regional brain atrophy, and some have been used in the auxiliary diagnosis of dementia (49-52). In addition, automated techniques based on spatial normalization and brain segmentation have been frequently used to estimate volumetric changes of global and regional brain tissue (53). Brain atrophy may be secondary to cerebral microvascular lesions. For example, the progressive accumulation of WMHs in brain parenchyma has been associated with the aggregation of tau protein and the formation of neurofibrillary tangles (54). These pathological processes can contribute to cerebral cortical thinning and degenerative changes (55). Moreover, the dilation or dysfunction of PVSs can hinder the clearance of metabolic waste products in the brain, including amyloid-β (56). This impaired clearance mechanism may accelerate the deposition of amyloid-β in cerebral tissues, leading to the synaptic dysregulation and neuronal loss (57).

1.1.2 Progression of structural brain aging

Post-mortem imaging studies have confirmed that the formation of WMHs and lacunes are mainly based on microvascular damage in the brain, while regional and global brain atrophy reflects neurodegenerative or mixed vascular and neurodegenerative pathology (58, 59). The common pathological mechanisms of SVD markers suggest that various SVD markers may be correlated in their development and progression. Studying the progression and interrelationships of these SVD markers could outline the development sequence of brain aging. **Table 1** summarizes the population-based studies that have investigated the interrelationships of various cerebral SVD markers. For example, the cross-sectional population-based Kashima Scan Study in Japan reported a correlation of PVSs in basal ganglia and centrum semiovale with presence of lacunes and greater load of WMHs (60). Apart from the cross-sectional topological associations, cerebral SVD markers may interact to affect the progression of each other. For example, the longitudinal Shanghai Aging Study found that individuals who initially had a higher volume of WMHs experienced a more rapid accumulation of WMHs and PVSs and exhibited an increased risk of developing lacunes over a seven-year period (6). The Icelandic Age, Gene/Environment Susceptibility-Reykjavik Study

Table 1. A summary of population-based studies on the relationships of MRI markers of cerebral small vessel disease

Authors, year, country	Study populations	SVD markers and assessments	Key findings
Cross-sectional studies			
Zhu Y, et al., 2010, France (61)	The Three-City Study, 1818 stroke- and dementia-free subjects, average age: 72.5 years.	PVSs: semiquantitative grade. WMHs: automated estimation. Lacunes: visual assessment.	Higher degree of PVSs is associated with increased WMH volume and more lacunes, but not with brain volumes.
Yakushiji Y, et al. 2014, Japan (60)	The Kashima Scan Study, 1575 neurologically healthy subjects, average age: 57.1 years.	PVSs: semiquantitative grade. WMHs: semiquantitative grade, Fazekas scale. Lacunes: visual assessment.	PVSs in basal ganglia and centrum semiovale are associated with lacunes and severe WMHs.
Gyanwali B, et al., 2019, Singapore (62)	Epidemiology of Dementia in Singapore study, 583 subjects, average age: 70 years.	PVSs: semiquantitative grade. Lacunes: visual assessment. WMHs: automated estimation.	Enlarged PVSs in basal ganglia are associated with higher prevalence of lacunes and higher load of WMHs.
Celle S, et al, 2021, France (63)	The PROgnostic indicator OF cardiovascular and cerebrovascular events study, 315 subjects, average age: 75 years.	WMHs: semiquantitative grade, Fazekas scale. GM: automated estimation.	WMHs are associated with a decrease of GM volume in the middle temporal gyrus, right medial frontal gyrus, and left parahippocampal gyrus.
Longitudinal studies			
Ding J, et al., 2017, Iceland (5)	The Age, Gene/Environment Susceptibility-Reykjavik Study, n=2612; average age:74.6 years; 59% female; follow-up: 5 years.	WMHs: automated estimation. PVSs: visual assessment.	The presence of large PVSs is associated with a faster progression of WMHs volume.
Xia Y, et al. 2020, China (6)	The Shanghai Aging Study, n=191; average years: 68.1 years; 44% female; follow-up: 7 years.	WMHs: automated estimation. PVSs: visual assessment, Potter's scale. Lacunes: visual assessment.	The higher WMH volume is associated with a faster increase of WMHs, PVSs, and lacunes.

***Note**:* Abbreviations: MRI, magnetic resonance imaging; WMHs, white matter hyperintensities; PVSs, perivascular spaces; GM, gray matter.

found that large PVSs (>3 mm) were associated with a faster progression of WMHs over a five-year period (5). However, follow-up data are still sparse on the progression of regular PVSs (<3 mm) and the interrelations between PVSs and other SVD markers in brain aging. In addition, the population-based cross-sectional study of PROgnostic indicator OF cardiovascular and cerebrovascular events has found that the greater burden of WMHs is linked to a reduced gray matter (GM) volume (63). This indicates that microvascular lesions may be connected to advanced and mixed cerebrovascular and neurodegenerative damage. Accordingly, prospective cohort studies are necessary to further elucidate the relationship between imaging markers of microvascular lesions and subsequent mixed cerebrovascular and neurodegenerative changes. Furthermore, the same cerebral SVD marker can reflect varying etiopathological mechanisms depending on their locations (42, 43, 54, 64, 65). For instance, WMHs in the subcortical and deep regions may be due to cerebral arterial dysfunction, whereas WMHs in the periventricular regions are mainly attributable to demyelination (64, 66). Therefore, it is crucial to take into account the regional distribution of SVD markers when examining the interrelationships and progression of these markers.

1.1.3 Cognitive change and phenotypes in aging

Cognitive aging refers to the insidious cognitive deteriorations along with increase in chronological age. Cognitive phenotypes in aging range from the normal age-related cognitive deterioration through mild cognitive impairment (MCI) to dementia. Specifically, the definition of MCI usually requires subjective cognitive complaints or objective cognitive impairment in at least one domain, preserved global cognitive functioning, preserved daily living activity, and free of dementia (67, 68). Individuals with MCI experience cognitive impairment which is greater than what is expected for their age and educational levels but does not meet the criteria for dementia (67, 68). Apart from MCI, a broader definition of cognitive impairment, no dementia (CIND) has been proposed for individuals who meet the criteria for MCI as well as those who are cognitively impaired but do not meet all the criteria for MCI (68). The definition of CIND requires objective impairment in at least one cognitive domain and free of dementia (68). It is possible for individuals with MCI or CIND to reverse to normal cognition or further progress to the clinical stage of dementia later in life (69, 70).

It is worth noting that not all older adults experience significant cognitive impairment or dementia. In fact, many older adults maintain their cognitive abilities well into old age or only experience a minor cognitive decline. To objectively measure cognitive functioning in the cognitively unimpaired population, a comprehensive cognitive test battery is recommended. Brief cognitive tests, such as the Montreal Cognitive Assessment and the Mini-Mental State Examination (MMSE), can be used to evaluate global cognitive function (71). A neuropsychological test battery can be used to evaluate performance in specific cognitive domains, such as memory, executive function, processing speed, and language ability (72). Data from both population-based and clinic-based cohort studies have indicated that the cognitive decline in global and specific domains occurs before the onset of dementia. Moreover, these studies have revealed that different rates of cognitive decline and specific domains exhibiting decline are associated with diverse cognitive outcomes (72-75). For

example, the follow-up data from the Religious Orders Study and the Rush Memory and Aging Project indicated that individuals with amnestic MCI experienced a more rapid global cognitive decline compared to those with non-amnestic MCI (73). Likewise, data from the population-based Swedish National study on Aging and Care in Kungsholmen (SNAC-K) suggested that a faster decline in performance of multiple cognitive tests, including memory, verbal fluency, perceptual speed, and executive function, was related to a higher risk of dementia in six years (75). Furthermore, the clinic-based Amsterdam Dementia Cohort found that the onset of Alzheimer's disease was associated with decline in all examined cognitive domains, including memory, language, attention, executive and visuospatial functioning, and global cognition. On the other hand, the onset of vascular dementia was only associated with decline in attention and executive functioning (74). Therefore, studying performance and changes in various cognitive domains could predict cognitive outcomes and identify individuals at risk of cognitive impairment.

The rates of global and domain-specific cognitive decline among older adults are highly heterogeneous and are influenced by demographic factors and genetic predisposition (e.g., *APOE* genotypes) among older adults (76-79). For example, an Italian cohort comprising two population studies found that global cognitive decline was typically evident after the age of 85 years, and that cognitive decline in executive function and motor speed usually accelerated after the age of 75 years (77). In addition, the Preclinical Alzheimer's Disease consortium analyzed harmonized data from five longitudinal cohort studies and found that the presence of *APOE*-ε4 allele was associated with a faster decline in global cognition, executive function, and episodic memory (78). Therefore, it is necessary to consider these demographic and genetic factors when investigating the decline in various cognitive domains.

1.1.4 Structural brain aging and cognitive decline

Associations of greater burdens of cerebral SVD markers (e.g., WMHs, PVSs, and brain atrophy) with a higher risk of dementia have been frequently reported in cohort studies (8, 80-83). Data from cohort studies have also demonstrated the cognitive influence of cerebral SVD on multiple domains, particularly in processing speed (84, 85). For instance, data from the Lothian Birth Cohort 1936 suggested that a heavier burden of cerebral SVD markers, including WMHs, PVSs, lacunes, and microbleeds was associated with a faster decline in processing speed but not in verbal memory or visuospatial ability (84). Similarly, the data from the multi-center Leukoaraiosis and Disability study suggested that a heavier burden of cerebral SVD, including WMHs and lacunes, was linked to a more pronounced decline in psychomotor functioning and processing speed. However, no association was observed between burden of SVD and deterioration of episodic or working memory (85). Furthermore, given the different neuropathological mechanisms underlying the formation of individual cerebral SVD markers, it is also plausible that these SVD markers might have different impacts on different cognitive domains.

Among the markers of cerebral SVD, WMHs have been most widely examined in the association with cognitive decline and dementia. In terms of the neuropathological mechanism

underlying the development of WMHs, axonal loss and demyelination are usually attributed to cerebral microvascular ischemia, dysfunction of the blood-brain barrier, and cerebral amyloid angiopathy (30-32). Specifically, the underlying etiologies and neuropathological processes leading to WMHs may vary depending on the involved brain regions (64, 66). Consequently, exploring the associations of WMHs across different brain regions with domain-specific cognitive performance could provide valuable insights into the underlying neuropathological mechanisms responsible for decline in those domains. Furthermore, findings from the SNAC-K MRI cohort have suggested that markers of microvascular lesions (e.g., WMHs) are associated with global cognitive decline, and that the presence of *APOE*-ε4 could exacerbate this decline (86). However, the interplay between the burden of WMHs and *APOE* genotypes on domain-specific cognitive changes in the general population has yet to be fully explored.

The dynamic nature of structural brain aging markers, such as WMHs, suggests that their loads can change over time. For example, the progression, relative stability, or even regression of WMHs have been observed over time (4). These dynamic changes of WMHs may be correlated with changes in different cognitive outcomes. A meta-analysis, which synthesized data from population-based cohort studies with follow-up periods shorter than five years, found a correlation between progression of WMHs and accelerated cognitive decline in general intelligence, attention, and executive functioning (87). However, long-term (>10 years) longitudinal relationships between the progression of global and regional WMHs and declines in specific cognitive domains remain to be characterized.

1.2 Cardiovascular health and structural brain aging

1.2.1 Cardiovascular health metrics

The modifiable cardiovascular risk profiles include behavioral risk factors (e.g., heavy alcohol consumption, tobacco use, physical inactivity, imbalanced diet, and obesity), biological risk factors (e.g., high cholesterol level and high blood pressure), and socioeconomic factors (e.g., low education and household income) (88, 89). Over the past decades, numerous population-based studies have linked these modifiable cardiovascular risk factors over the lifespan with dementia (90, 91). Given that these risk factors often coexist in middle-aged and older adults, several composite measures of cardiovascular risk factor burden have been developed and validated for predicting risk of cardiovascular events. For example, the sex-specific Framingham General Cardiovascular Risk Score was initially proposed in 1998 and then updated in 2008 (92, 93). The Cardiovascular Risk Factors, Aging and Dementia score in midlife was introduced in 2006 (94). In 2010, the American Heart Association (AHA) proposed seven cardiovascular health (CVH) metrics that include four behavioral metrics (smoking, physical activity, diet habit, and body mass index) and three biological metrics (total cholesterol, blood pressure, and plasma glucose) for assessing an individual's CVH status. Evidence has emerged that favorable CVH metrics are associated with reduced risks of cardiovascular events and cardiovascular mortality (95, 96). Therefore, the AHA's composite CVH metric approach emphasizes the protective effect of healthy behavioral and biological CVH indicators on late-life health.

1.2.2 Cardiovascular health, genetic susceptibility, and structural brain aging

Having favorable levels of the seven CVH metrics may not only reduce the risk of cardiovascular events, but also promote brain health during the aging process, such as reducing the risk of cognitive decline and dementia (12, 97-99). In terms of the relationship between individual CVH metrics and structural brain aging, previous cohort studies have indicated that healthy behaviors, such as regular physical activity and healthy diet, are associated with a larger brain volume and a lower load of WMHs in older adults (100, 101). In addition, cross-sectional data from the population-based Northern Manhattan Study have shown that adherence to an ideal level across the seven CVH metrics is related to less cerebral microvascular and neurodegenerative lesions, including a lower WMH volume, fewer silent brain infarcts, and a larger cerebral volume (102). Despite the promising findings, evidence is still lacking regarding the longitudinal associations between ideal composite CVH metrics and subsequent structural brain health in older adults, which could provide stronger evidence for the role of favorable CVH metrics in maintaining brain health.

The relationships of CVH metrics with structural brain aging are likely to be affected by demographic and genetic factors. Indeed, evidence from population-based SNAC-K study indicates that the association between favorable CVH metrics and decreased risk of dementia does not appear to remain consistent for individuals in later stage of older adulthood (≥ 78 years) (98). Thus, it is plausible to hypothesize that the relationships between CVH metrics and brain aging differ across various age groups. Furthermore, some susceptibility genes to metabolic risk factors are linked to structural brain aging. For example, the *APOE* gene related to dyslipidemia and the *ACE* gene for hypertension are associated with the development of WMHs (103, 104). Thus, it is reasonable to consider that vascular brain aging may be partly driven by the interplay between metabolic genetic predisposition and CVH metrics. Understanding the interaction between genetic predisposition and modifiable CVH metrics may provide insight into the development of personalized intervention strategies for healthy brain aging.

1.3 Cognitive reserve, brain aging, and cognitive outcomes

1.3.1 Cognitive reserve

A meta-analysis of positron emission tomography imaging studies has indicated that brain amyloid deposition is prevalent in individuals without dementia, and that the initial development of cerebral amyloid aggregation may occur decades before the onset of dementia (105). These findings suggest that certain mechanisms may counterbalance the impact of cerebral amyloid pathology, leading to the proposal of cognitive reserve (CR) to explain such compensatory effects (106). CR refers to the brain's ability to compensate for pathological changes that may lead to cognitive decline (107). Currently, the CR capacity can be measured using either the activity-based method or the residual-based method (15, 107). The activity-based CR capacity can be measured by incorporating the richness of intellectually stimulating activities, such as educational attainment, occupational complexity, social engagement, and mentally demanding activities (107-109). On the other hand, the residual-based CR capacity is

defined as the difference between observed and predicted levels of cognitive functioning, with the latter estimated from age, sex, and the given level of observed brain integrity (15). Strengthening CR capacity could be an important intervention strategy to slow down cognitive decline and delay the onset of dementia.

1.3.2 Cognitive reserve and cognitive phenotypes in aging

Population-based studies have linked the high level of CR capacity with lower risks of MCI and dementia as well as slower cognitive decline in late life (14-17). Most of these studies predominantly investigated the unidirectional cognitive progression from normal cognition to CIND or from non-dementia to dementia in relation to CR capacity. However, prospective cohort studies have recently shown that a substantial proportion of individuals experience fluctuations across cognitive states in the prodromal stage of dementia in late life, particularly between normal cognitive function and MCI (18-20). These dynamic transitions of cognitive states shall be considered when assessing the changes of late-life cognitive health, as they may affect the trajectories of cognitive decline and the potential benefits of CR. In addition, it is also crucial to considering the transition from different cognitive states to death because cognitive impairment or dementia is associated with a higher mortality (110).

Furthermore, the potential relationship between individual CR indicators and cognitive phenotypes might vary by demographic factors and *APOE* genotypes (21-23). For instance, data from the Mayo Clinic Study of Aging indicated that late-life social activities were associated with a lower risk of MCI in individuals carrying the *APOE*-ε4 allele, but not in non-carriers (23). However, the interplay of CR capacity with certain demographic factors and *APOE* genotypes on the transitions across various cognitive states and death remains unclear. Furthermore, data from the Washington Heights/Hamilton Heights Inwood Columbia Aging Project showed that at any given level of domain-specific cognitive performance, individuals with higher CR capacity were able to tolerate more cerebrovascular pathology (i.e., WMHs) compared to those with lower CR capacity (111). In addition, data from the population-based Shandong Yanggu Study of Aging and Dementia indicated that for any given level of global cognition, people with higher level of CR could tolerate more neurodegenerative pathology (i.e., lower hippocampal volume) (112). Therefore, it is worthwhile to investigate whether the relationship between CR capacity and cognitive phenotypes varied by age, sex, or *APOE*-ε4 status, and load of brain pathologies.

1.4 Knowledge gaps

By reviewing the current literature, we identified the following knowledge gaps.

- Is the progression of MRI markers of cerebral SVD varying by demographic factors and are these markers interrelated in their progression in older people?
- Do the severity and progression of WMHs interact with *APOE* genotypes to be differentially associated with the functioning of various cognitive domains?
- Are favorable CVH metrics associated with slow progression of structural brain aging and do favorable CVH metrics counteract the detrimental impact of genetic susceptibility to metabolic risk factors on structural brain aging?

- Is CR capacity associated with transitions across cognitive states and death in older adults while taking into account age, sex, *APOE* genotypes, and structural brain pathologies?

2 Research aims

The overall goal of this doctoral project is to investigate the progression of structural brain aging and its relationship with cognitive decline, and to untangle the role of CVH metrics in structural brain aging and the role of CR capacity in cognitive decline. We will be able to achieve the overall goal by carrying out four individual studies, in which specific aims and research questions are outlined below in Figure 1.

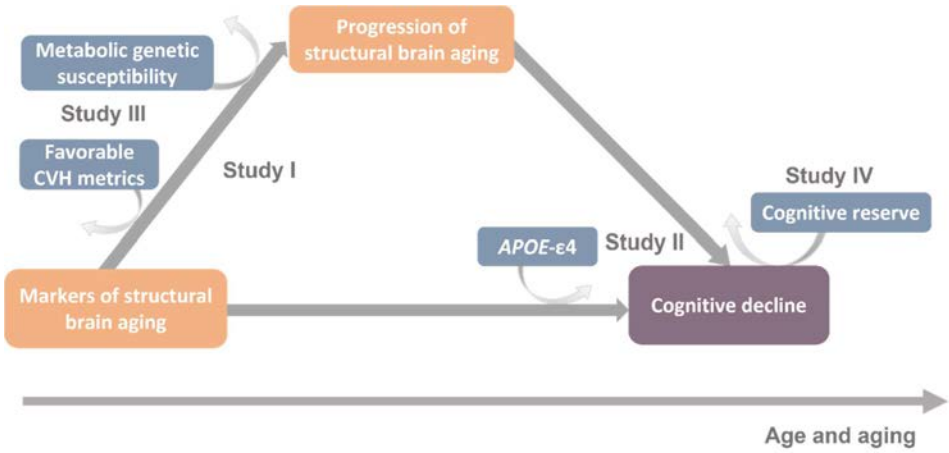

Figure 1. Research aims of the individual studies in the doctoral project.

Note: Abbreviations: CVH, cardiovascular health; CIND, cognitive impairment, no dementia.

- ***Study I****:* We aimed to describe the progression and interrelationships among various MRI markers of cerebral SVD in older adults. Specifically, we sought to describe the progression of WMHs, PVSs, lacunes, and volumes of GM and lateral ventricles over time and investigate whether a heavier load of microvascular lesions at baseline (WMHs, PVSs, and lacunes) would be related to a faster accumulation of microvascular lesions and mixed microvascular and neurodegenerative lesions (GM atrophy and enlargement of lateral ventricles).

- ***Study II:*** We aimed to examine the association of the load and dynamic change of WMHs with decline in multiple cognitive domains. Specifically, we sought to investigate the interaction between baseline load of WMHs and *APOE* genotypes in determining cognitive decline in different domains and whether a faster accumulation of WMHs over time was related to faster decline in specific cognitive domains.

- ***Study III****:* We aimed to explore the interplay of composite CVH metrics with metabolic genetic predisposition on the progression of structural brain aging. Specifically, we sought to investigate whether favorable CVH metrics and lower metabolic genetic risk were associated with a slower accumulation of structural brain aging markers and

whether CVH metrics could interact with metabolic genetic risk to affect the progression of structural brain aging.

- ***Study IV*:** We aimed to investigate the association of lifelong CR capacity with transitions across cognitive states and death in older adults while taking into account age, sex, *APOE* genotypes, and load of pathological brain aging.

3 Materials and methods

3.1 Study population

Data in this doctoral project were derived from the ongoing population-based SNAC-K study and the SNAC-K MRI sub-study (https://www.snac-k.se/) (25). In brief, SNAC-K is a multidisciplinary study of aging and health focusing on people aged 60 years and older in the Kungsholmen district of Stockholm, Sweden. In 2001-2004, 5,111 persons aged 60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and 99 years or older, were randomly selected and invited to participate in the baseline examinations. Out of the 5,111 individuals, 262 could not be contacted, 200 died before the examination, 59 were non-Swedish speakers or deaf, or moved away, leaving 4,590 eligible for the examinations. Out of the 4,590 individuals, 1,227 refused to participate, leaving 3,363 participants (response rate 73.3%) in the baseline examination. The follow-up examinations were performed every six years for participants aged 60–72 years and every three years for those aged ≥78 years, as shown in **Figure 2**. Out of the 3363 participants at baseline, 555 non-institutionalized and MRI-eligible participants (free of disability, claustrophobia, and metallic material in the body) consented to undergo structural brain MRI examinations in 2001–2003, which constituted the SNAC-K MRI cohort (25). The follow-up MRI scans were conducted in 2007–2010 for participants aged 60–72 years and in 2004–2007 and 2007–2010 for those aged ≥78 years, according to the overall follow-up scheme of SNAC-K.

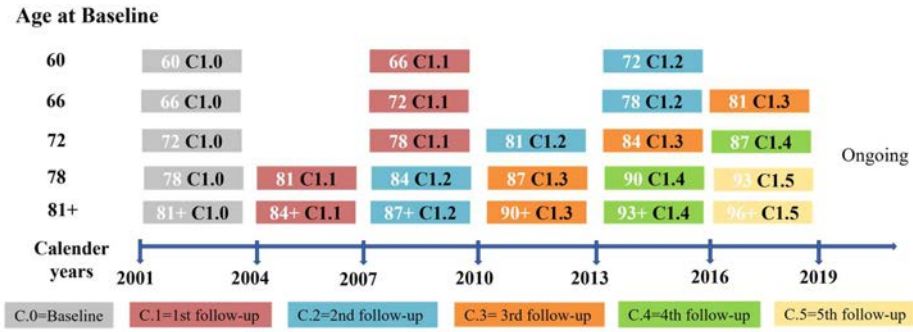

Figure 2. Timeline of data collection in the Swedish National study on Aging and Care in Kungsholmen.

3.2 Analytical samples

Figure 3 shows the flowchart of study participants in the four individual studies included in this doctoral project. Analytical samples for Study I, Study II, and Study III were derived from the SNAC-K MRI cohort. In Study I, a total of 325 participants in the SNAC-K MRI cohort who were dementia-free at baseline were included for analyzing the progression and inter-relationships of MRI markers of brain aging. In Study II, a total of 510 participants who were free of dementia and who had brain MRI data at baseline were included for analyzing the

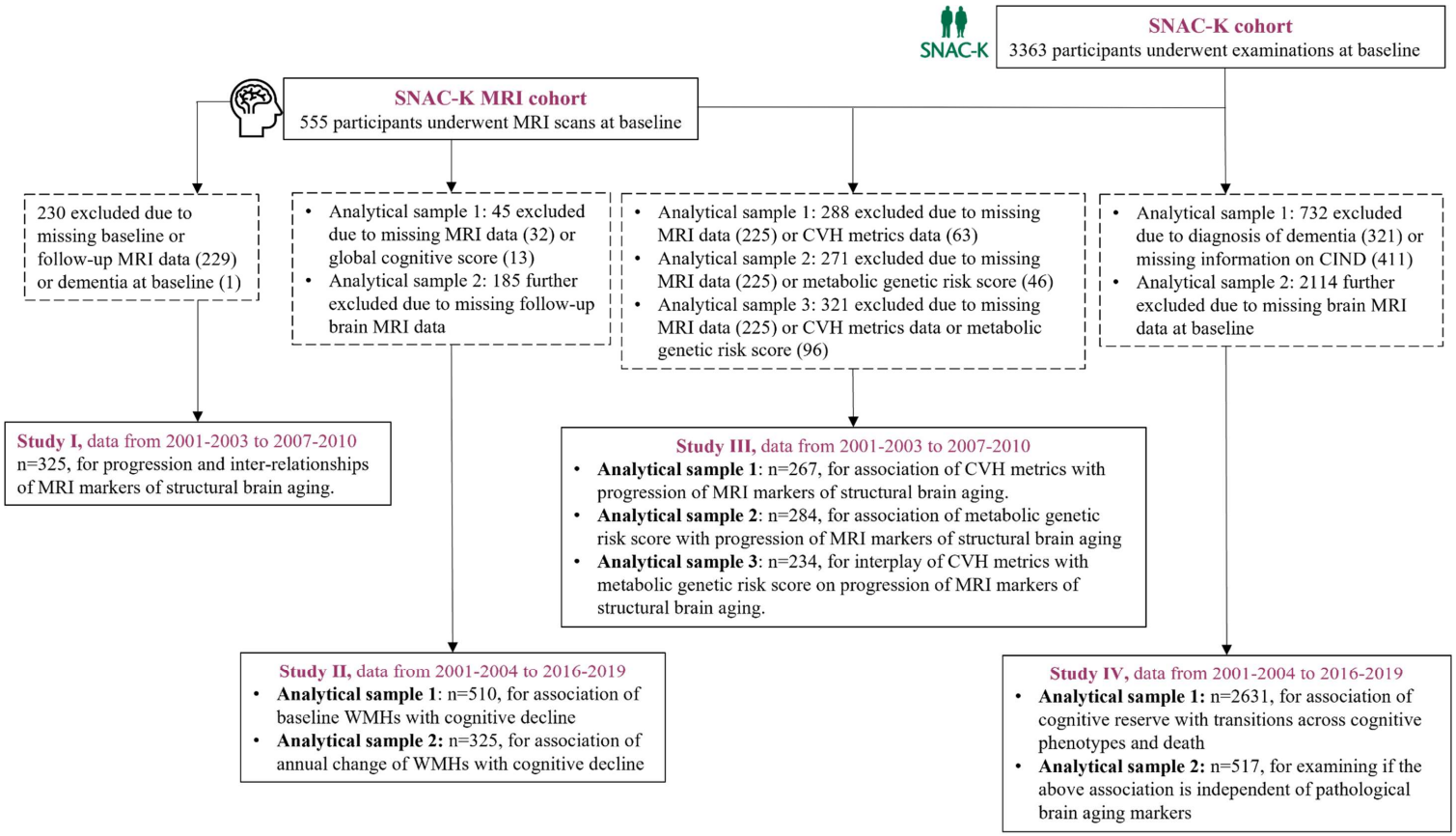

Figure 3. Flowchart of the study samples included in Study I-IV.

Note: Abbreviations: SNAC-K, Swedish National study on Aging and Care in Kungsholmen; MRI, magnetic resonance imaging; CVH, cardiovascular health; CIND, cognitive impairments, no dementia.

relationship between baseline load of WMHs with cognitive decline; and 325 for analyzing the relationship between annual change of WMH loads over the first six-year follow-up period with cognitive decline over the 15-year period. In Study III, a total of 267 participants who were dementia-free and had data on baseline CVH metrics and follow-up brain MRI markers were included, for analyzing the association of CVH metrics with markers of structural brain aging. Likewise, 284 were included for analyzing the association of metabolic genetic risk score with structural brain aging; and 234 for analyzing the interplay of CVH metrics with metabolic genetic risk score on structural brain aging. The analytical samples for Study IV were derived from the combination of the whole SNAC-K study and the SNAC-K MRI sub-study. A total of 2,632 participants were involved for analyzing the association of lifespan CR capacity with transitions across cognitive states and death, while taking into account age, sex, and *APOE* genotypes; out of them, 517 from the SNAC-K MRI cohort were involved for addressing whether the above association was independent of pathological brain aging markers.

3.3 Data collection and assessment

At baseline, we collected data on demographics (e.g., age, sex, years of education, and occupation), lifestyles (e.g., smoking, alcohol consumption, physical activity, diet habits, leisure activity, and social network), cardiovascular risk factors and diseases (e.g., body mass index, blood pressure, blood cholesterol, and ischemic heart disease), MRI markers of structural brain aging, and cognitive functioning through in-person interviews, clinical examinations, testing, laboratory tests, neuropsychological examinations following a structured questionnaire as well as structural brain MRI examinations, as previously described (113, 114).

3.3.1 Brain MRI data

All eligible participants were scanned on a 1.5-Tesla system (Philips Intera, The Netherlands). The core MRI sequences included a 3D axial T1-weighted sequence (resolution: 0.94×0.94×1.5 mm; no gap; repetition time, 15 ms; echo time, 7 ms), a proton-density/T2-weighted sequence (resolution: 0.98×0.98×3 mm; no gap; repetition time, 3995 ms; echo time, 18/90 ms; echo-train length, 6), and a FLAIR sequence (resolution: 0.90×0.90×6 mm; gap between slices: 1mm; repetition time, 6000 ms; echo time, 100 ms; inversion time, 1900 ms; echo-train length, 21). The same scanner, sequences and parameters were used for MRI scans at baseline and follow-up examinations (115).

A neuroimaging analyst (G.K.) manually drew WMHs on FLAIR images and then automatically estimated the global WMH volume through interpolating WMHs on the respective T1-weighted images, using MRIcron (https://www.nitrc.org/projects/mricron) (86). The global WMH volume was log-transformed due to skewed distribution. G.K. preprocessed the T1-weighted images using the Statistical Parametric Mapping 12 (https://www.fil.ion.ucl.ac.uk/spm/), implemented in Matlab R2012b (The MathWorks Inc.) for assessing total GM and total intracranial volumes. G.K. assessed the lateral ventricular volumes using the toolbox of Automatic Lateral Ventricle delineatioN (https://sites.google.com/site/mrilateralventricle/home). The hippocampal volume was automatically assessed in the Freesurfer Version 5.1 (https://surfer.nmr.mgh.harvard.edu/),

using the T1-weighted images (15). The volumes of GM, lateral ventricles, and hippocampus were all adjusted for the total intracranial volume using the linear regression (116).

A trained rater (Y.L.) visually evaluated WMHs, PVSs, and lacunes at baseline and follow-ups, without knowledge of the participants' clinical characteristics. WMHs were identified on FLAIR images as hyperintense signals (2), and scored separately in the frontal lobe, parieto-occipital lobe, temporal lobe, basal ganglia, sub-insular region, mesencephalon, pons, and the frontal and occipital caps, and the bilateral bands of the lateral ventricles in both hemispheres separately, following a modified Scheltens' scale (115). For each of these anatomical areas, WMH scores from both hemispheres were summed. The **lobar WMH score** was calculated as the sum of WMH scores in frontal, parieto-occipital, and temporal lobes (score range: 0–36); the **deep WMH score** as the sum of scores in the basal ganglia (thalamus, internal capsule, globus pallidus, and putamen) and sub-insular territory (external capsule, claustrum, and extreme capsule) (0–24); the **infra-tentorial WMH score** as the sum of scores in mesencephalon and pons (0–12); the **periventricular WMH score** as the sum of scores in the frontal and occipital caps and the bilateral bands of the lateral ventricles (0–12). We did not include infra-tentorial WMH score when analyzing regional WMHs due to the very few WMHs and the skewed distribution (83% had no infra-tentorial WMHs). The **global WMH score** was calculated as the sum of lobar, deep, infra-tentorial, and periventricular WMH scores (0–79). The correlation coefficients between global WMH score (by Y.L.) and global WMH volume (by G.K.) were 0.72 at baseline, 0.77 at the third-year follow-up, and 0.76 at the sixth-year follow-up.

The number of PVSs was counted in each hemisphere separately, following a previously validated protocol (35). For each brain region, PVSs in the slice with the highest numbers were recorded. PVSs on the axial T2-weighted images were counted separately in the frontal lobe, parieto-occipital lobe, cerebellum, mesencephalon, and hippocampus. The counting of PVSs in the basal ganglia and sub-insular region followed the same method, which involved utilizing the axial T1-weighted images rather than the T2-weighted images. It was due to the fact that the T1-weighted images offered a more pronounced contrast between intensities of PVSs and background tissues in comparison to the T2-weighted images, in the basal ganglia and sub-insular region. The **lobar PVS count** was calculated as the sum of PVSs in the frontal and parieto-occipital lobes (count range: 6–136), the **deep PVS count** as the sum of PVSs in the basal ganglia, sub-insular area, and hippocampus (7–64), and the **infra-tentorial PVS count** as the sum of PVSs in mesencephalon and cerebellum (0–11). We excluded the infra-tentorial PVS count from our analysis of regional PVSs due to the limited count of infra-tentorial PVSs and their skewed distribution (84% had infra-tentorial PVS count < 5). The **global PVS count** was calculated as the sum of lobar, deep, and infra-tentorial PVS counts (22–178).

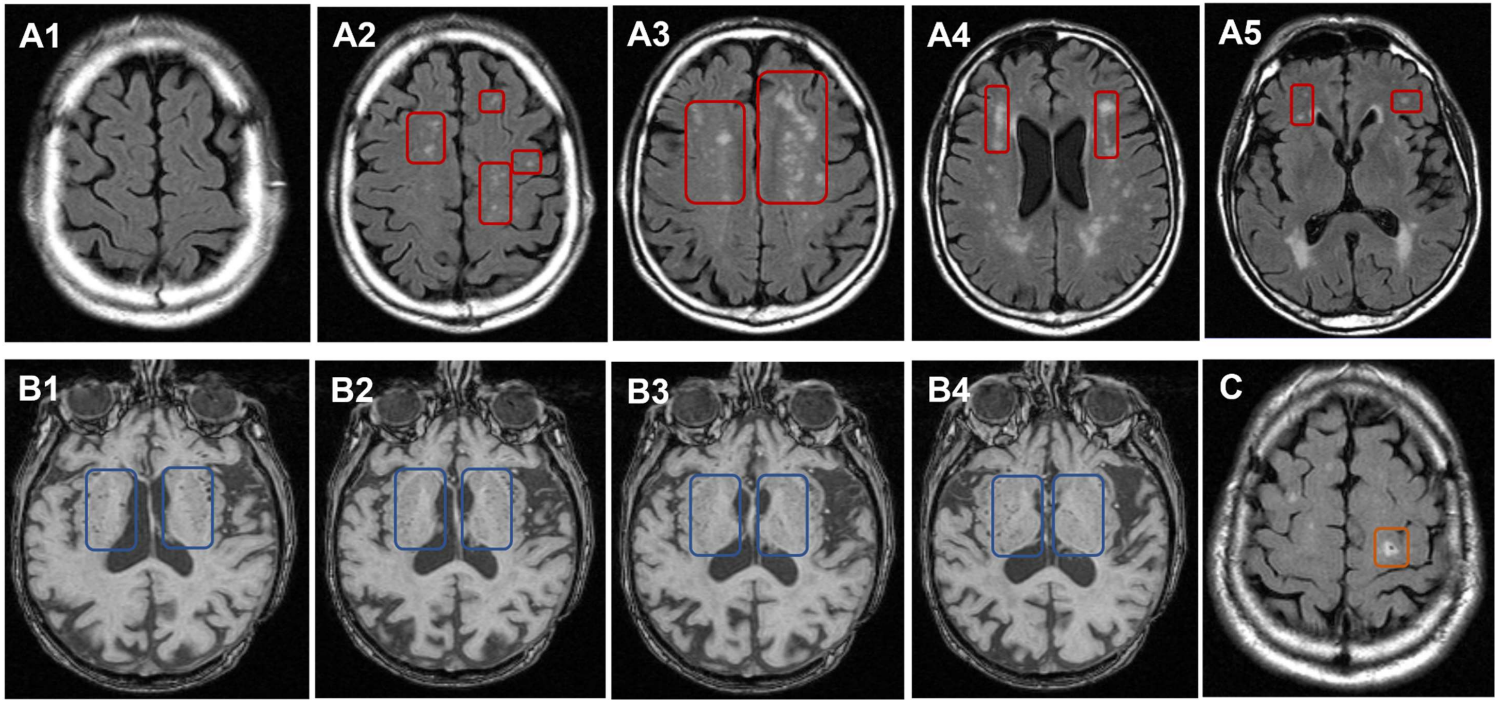

Figure 4. Visual assessments of white matter hyperintensities (A1-A5), perivascular spaces (B1-B4), and lacunes (C) on axial magnetic resonance imaging sequences

Note: A1-A5: White matter hyperintensities in bilateral frontal lobes on the fluid-attenuated inversion recovery images. Visual rating score of white matter hyperintensities: left hemisphere: 5; right hemisphere: 6.

B1-B4: Perivascular spaces in the bilateral basal ganglia on the T1-weighted images. Slice B4 shows the highest number of perivascular spaces in the basal ganglia. Visual count of perivascular spaces: left hemisphere: 16; right hemisphere: 13.

C: One lacune in the right frontal lobe on the fluid-attenuated inversion recovery image.

Lacunes were identified on the FLAIR sequence as a central cerebrospinal fluid-like hypointense signal with a surrounding rim of hyperintense signals (2). Lacunes without a hyperintensity rim were differentiated from PVSs based on the size criteria of 3 mm, as recommended by the STRIVE consortium (2). Both the number and location of lacunes were recorded. We dichotomized lacunes as absence versus presence because the distribution of lacunar count was heavily right skewed (79% had no lacune). We defined prevalent lacune as any lacune identified at baseline. We considered any newly emerged lacune detected on the follow-up images as an incident lacune. **Figure 4** shows the example images for visual assessment of WMHs, PVSs, and lacunes.

The rater (Y.L.) re-evaluated brain images of 30 randomly chosen participants one month after the initial assessment, focusing on WMHs, PVSs, and lacunes. The results showed high correlation coefficients of 0.93 for the global WMH score and 0.91 for the global PVS count. Additionally, the weighted κ value for lacunes was 0.81, indicating good intra-rater reliability.

3.3.2 Assessment of cognitive function

We used a neuropsychological test battery to assess cognitive performance at baseline and follow-ups according to standardized procedures (117). We assessed functioning of the following six cognitive domains: **Episodic memory** was assessed using tests of word recall and recognition. In the free recall test, 16 unrelated words (e.g., carrot, ring, fork) were presented visually and orally to participants. After presentation, participants were asked to recall as many words as possible. The outcome score was the total number of correctly recalled words within 2 minutes. Immediately following free recall, a recognition test was administered. This recognition test involved the presentation of 32 nouns including 16 target words and 16 lures, and participants were asked to determine whether the word had been presented during the free recall test. The outcome score was number of correct recognitions minus number of false recognitions (118). **Semantic memory** was assessed using a 30-item vocabulary task, where participants were instructed to underline the word representing the synonym of each target word. The outcome score was the total number of correct responses within 7 minutes (119). Verbal fluency was assessed by both **letter and category fluency**. Participants were asked to generate as many words as possible cued with a specific letter (“F” and “A”) or category (“animals” and “professions”) within 60 seconds. The outcome scores for letter and category fluency were the total numbers of correct responses. **Perceptual speed** was assessed using tests of digit cancellation and pattern comparison. The digit cancellation task required participants to sequentially go through 11 rows of random digits ranging from 1 to 9 and cross out the target digit “4”. The outcome score was the total number of correct responses within 30 seconds. The pattern comparison task required participants to go through 30 line-segmented patterns and then mark whether the patterns were same or different within 30 seconds. The outcome score was the average number of correct responses across two trials. (98, 120). **Executive function** was assessed with the Trail-Making Test (part B), which required participants to connect 13 encircled digits and letters in alternating order (e.g., 1-A, 2-B, 3-C). The outcome score was the time (seconds) for completing 12 correct connections (121). This score was then reversed, so that higher scores indicated better performance.

The raw scores of these cognitive tests were standardized into z-scores using their baseline mean and standard deviation (SD). If a cognitive domain consisted of multiple tests, a composite score was formed by averaging the z-scores of the tests within that domain. For participants who had cognitive data available for at least three out of the six domains, a composite score for global cognition was computed as the mean value of all the domain-specific cognitive z-scores (98). This was done for baseline and all follow-up examinations.

3.3.3 Diagnosis of dementia and CIND

Dementia was clinically diagnosed according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (122), following a three-step procedure. In brief, two examining physicians independently made the first diagnosis based on information collected during the clinical examination. The cognitive assessment used for diagnosing dementia included the MMSE, the clock drawing test, the forward and backward digit span, and items covering memory, executive functioning, problem solving, orientation, and interpretation of proverbs. For any disagreement in the first diagnosis between the two physicians, a neurologist external to the data collection was consulted and then a final diagnosis was made. The dementia status of deceased participants who had not been diagnosed with dementia was determined by the SNAC-K research group through a review of their medical charts and by cross-referencing with the Swedish Cause of Death Register (123).

We referred to the z-cores of cognitive domains to define CIND. Among dementia-free participants, CIND was defined as scoring at least 1.5 SD below the age group-specific mean in any of the examined cognitive domains (123).

3.3.4 Cardiovascular risk factors and diseases

Smoking status was assessed by asking participants whether and how long they had smoked and how many cigarettes they had consumed every day. We dichotomized smoking status into never or former versus current smoking. Alcohol consumption status was assessed by asking participants whether, how long, and how often they had drunk alcohol. We categorized alcohol consumption into no or light-to-moderate versus heavy alcohol intake (> 14 drinks per week for men or > 7 drinks per week for women) (114).

Diet habits were assessed from a 98-item semi-quantitative food frequency questionnaire. The average frequency of intake over the past year was assessed for each food item using a nine-point scale, which ranged from “never” to “4 times per day or more”. To simplify the analysis, food items were classified as vegetables, fruits, or high-fiber bread (98).

Physical activity was evaluated through questionnaire data by asking participants whether and how often they had participated in any light (i.e., walks, short bike rides, light aerobic activities, gym classes, or golf at least once a week) or moderate-to-intensive activities (i.e., brisk walking, jogging, heavy gardening, long bike rides, intense aerobic activities, gym classes, skating, skiing, swimming, ball games, or similar activities at least once a week). We categorized the intensity of physical activity into physical inactivity (never or ≤ 3 times per

month), light exercise (any light activity > 3 times per month), and moderate-to-intense exercise (any moderate-to-intense activity > 3 times per month) (114).

Body mass index was calculated as measured weight (kg) divided by height (m) squared (114). Arterial blood pressure was measured twice on the left arm in a sitting position using the sphygmomanometer, and the mean of two readings was used for the analysis (114). Non-fasting total serum cholesterol was initially measured, and if the non-fasting total cholesterol was higher than 6.5 mmol/L, then the fasting total cholesterol was measured, and the mean of both measurements was used in the analysis (114). Glycated hemoglobin was measured using the Swedish Mono-S High Performance Liquid Chromatography and added by 1.1% to conform to international values, according to the National Glycohemoglobin Standardization Program (114). We classified all medications according to the Anatomical Therapeutic Chemical (ATC) classification system. We defined hypertension as arterial blood pressure ≥ 140/90 mm Hg or current use of antihypertensive drugs (ATC codes: C02, C03, and C07-C09); diabetes was diagnosed by the examining physician on the basis of history of diabetes, current use of oral hypoglycemic agents or insulin injection (ATC code: A10), records of diabetes in patient register, or glycated hemoglobin ≥6.5%; and high cholesterol level as total cholesterol ≥ 6.22 mmol/L or current use of cholesterol-lowering drugs (ATC code: C10) (115).

All cardiovascular diseases identified by the examining physicians were recorded following the codes of the International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM) (124). Atrial fibrillation was ascertained through electrocardiography and physician's diagnosis (ICD-10-CM code: I48). Heart failure (ICD-10-CM codes: I50, I42, I43, and I255) was identified based on the physician's diagnosis and patient registers (124). The ischemic heart disease was identified via in-person clinical examinations by physicians and through the Swedish National Inpatient Registry from 1969 (ICD-10-CM codes: I20, I25.11, I21, I22, I25.2, Z951, Z955, FNG, FNA, FNB, FNC, FND, HNE, FNF, and HNH) (124).

3.3.5 Cardiovascular health metrics

The definition and categorization of CVH metrics in SNAC-K were previously described in detail (98). Briefly, we defined and categorized each of the seven individual CVH metrics as poor (score = 0), intermediate (score = 1), and ideal (score = 2) levels, respectively, following the Life's Simple 7 approach proposed by the American Heart Association (11). We modified the definitions of smoking status, diet, and blood glucose, according to data available in our project (98), as shown in **Table 2**. We estimated the behavioral metric score (score range: 0–8) by adding up scores of four health behaviors (smoking status, physical activity, diet habits, and body mass index) and the biological metric score (0–6) by adding up scores of three biological health factors (blood pressure, total cholesterol, and blood glucose). The global CVH metric score (0–14) was estimated by adding up scores of both behavioral and biological CVH metrics. Then, we categorized these scores into unfavorable, intermediate, and favorable profiles according to the lower, medium, and upper tertiles in the total sample of SNAC-K.

Table 2. Definitions and scores of cardiovascular health metrics

Metrics	Poor (score = 0)	Intermediate (score = 1)	Ideal (score = 2)
Smoking	Current smoker	Stopped in the last 5 years	Never or stopped >5 year ago
Diet habit	Consumption of fruit and vegetables <2 times per day and no high-fiber bread	Consumption of fruit and vegetables ≥2 times per day or high-fiber bread	Consumption of fruit and vegetables ≥2 times per day and high-fiber bread
Physical activity	Never or ≤2-3 times per month in light and/or moderate/intense exercise	Light exercise >1 time per week	Moderate/intense exercise >1 time per week
Body mass index	≥30 kg/m^2	25–29.9 kg/m^2	<25 kg/m^2
Plasma glucose	Glycated hemoglobin ≥6.5% or self-reported history, hypoglycemic drug use, or diagnosis in the Swedish National Patient Register	Glycated hemoglobin 5.7–6.5% and no diabetes	Glycated hemoglobin < 5.7 %
Total serum cholesterol	≥6.2 mmol/L	<5.2 treated or 5.2-6.2 mmol/L	<5.2 mmol/L untreated
Blood pressure	SBP ≥140 or DBP ≥90 mmHg	Treated SBP <120 and DBP <80 mmHg, or SBP 120-139 mmHg, or DBP 80-89 mmHg	Untreated SBP <120 and DBP <80 mmHg

Note: Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.
Source: *Speh A., et al. J Alzheimers Dis. 2021. doi: 10.3233/JAD-210280.*

3.3.6 Metabolic genetic risk score

Deoxyribonucleic acid was extracted from whole blood samples. Genotyping was performed using analysis of matrix-assisted laser desorption-ionization time of flight on the Sequenom MassARRAY platform at the Mutation Analysis Facility, Karolinska Institutet (118). In total, 103 single-nucleotide polymorphisms (SNPs) that were potentially associated with cognitive phenotypes in aging, cardiovascular risk, and longevity were genotyped in SNAC-K. We selected 15 SNPs from all these SNPs for estimating the metabolic genetic risk score, as shown in **Table 3**. The selected SNPs were related to hypertension, dyslipidemia, and diabetes, which corresponded to the three biological health metrics proposed by AHA. The selection of SNPs was based on findings from previous genome-wide association studies, fine-mapping analyses, or meta-analyses, otherwise from at least two different original studies (i.e., *LIPC* rs1800588 and *LDLR* rs5930 as dyslipidemia susceptibility genes). The distributions of all these genotypes conformed to the Hardy-Weinberg equilibrium ($P > 0.05$). The metabolic genetic risk score was created by adding up the number of risk alleles of these SNPs. The genotype of *APOE* was determined by rs429358 and rs7412 and scored by counting the number of ε4 alleles (score range: 0–2). We categorized the metabolic genetic risk into low, intermediate, and high levels according to tertiles of the total score.

Table 3. Overview of the 15 SNPs related to metabolic risk in the SNAC-K MRI follow-up subsample (n=284)

SNPs	Genotype	Frequency, n (%)	Score	References
Hypertension-related SNPs				
ACE rs1800764	T T	80 (28.17)	0	Chung CM, et al. PLoS One. 2013. DOI:
	C T	142 (50.00)	1	10.1371/journal.pone.005611 9.
	C C	62 (21.83)	2	
ACE rs4343	A A	58 (20.42)	0	Chung CM, et al. PLoS One. 2013. DOI:
	A G	147 (51.76)	1	10.1371/journal.pone.005611 9.
	G G	79 (27.82)	2	
Dyslipidemia-related SNPs				
APOE-ε4 allele	no ε4	208 (73.24)	0	Bennet AM, et al. JAMA. 2007. DOI:
(determined by	ε3ε4/ε2ε4	68 (23.94)	1	10.1001/jama.298.11.1300.
rs429358 & rs7412)	ε4ε4	8 (2.82)	2	
LIPC rs1800588	C C	163 (57.39)	0	Fan YM, et al. Clin Genet. 2009. DOI:
	C T	100 (35.21)	1	10.1111/j.1399-0004.2009. 01180.
	T T	21 (7.39)	2	x; Isaacs A, et al. J Clin Endocrinol Metab. 2004. DOI: 10.1210/jc.2004-0188.
LDLR rs5930	A A	35 (12.32)	0	de Oliveira, et al. J Mol Neurosci. 2020.
	A G	134 (47.18)	1	DOI: 10.1007/s12031-020-015 88-7; Al-
	G G	115 (40.49)	2	Allaf FA, et al. Hum Genome Var. 2014. DOI: 10.1038/ hgv.2014.21.
ADRB3 rs4994	A A	237 (83.45)	0	Ryuk JA, et al. Diabetes Res Clin Pract.
	A G	45 (15.85)	1	2017. DOI: 10.1016/j.
	G G	2 (0.70)	2	diabres.2017.03.034;
TOMM40 rs157580	G G	31 (10.92)	0	Sinnott-Armstrong N, et al. Nat Genet.
	A G	135 (47.54)	1	2021. DOI: 10.1038/s41588 -020-
	A A	118 (41.55)	2	00757-z.
APOA5 rs2266788	A A	244 (85.92)	0	Park S, et al. J Acad Nutr Diet. 2020.
	A G	35 (12.32)	1	DOI: 10.1016/j.jand.2020. 01.009.
	G G	5 (1.76)	2	
APOB rs693	A A	76 (26.76)	0	Niu C, et al. Lipids Health Dis. 2017.
	A G	137 (48.24)	1	DOI: 10.1186/s12944-017-0558-7.
	G G	71 (25.00)	2	
CETP rs5882	G G	27 (9.51)	0	Hellwege JN, et al. Genet Epidemiol.
	A G	113 (39.79)	1	2014. DOI: 10.1002/gepi.21801.
	A A	144 (50.70)	2	
Diabetes-related SNPs				
IDE rs1544210	G G	64 (22.54)	0	Zeggini E, et al. Science. 2007. DOI:
	A G	142 (50.00)	1	10.1126/science.1142364.
	A A	78 (27.46)	2	
LDLC rs4420638	G G	11 (3.87)	0	Sinnott-Armstrong N, et al. Nat Genet.
	A G	82 (28.87)	1	2021. DOI: 10.1038/s41588 -020-
	A A	191 (67.25)	2	00757-z.
PPARG rs1801282	G G	12 (4.23)	0	

	C G	66 (23.24)	1	Sinnott-Armstrong N, et al. Nat Genet.
	C C	206 (72.54)	2	2021. DOI: 10.1038/s41588 -020-00757-z.
PON1 rs662	T T	151 (53.17)	0	Luo JQ, et al. J Cell Mol Med. 2018.
	C T	112 (39.44)	1	DOI: 10.1111/jcmm.13453.
	C C	21 (7.39)	2	

Note: Abbreviations: SNP, single-nucleotide polymorphism; SNAC-K: Swedish National study on Aging and Care in Kungsholmen; MRI, magnetic resonance imaging.

3.3.7 Cognitive reserve

The individual indicators for estimating the lifelong composite CR capacity encompassed early-life education, midlife work complexity, late-life leisure activities, and late-life social network. During the nurse interview, early-life educational data were collected by inquiring about the highest educational degree and the total schooling year. The continuous total schooling year served as a measure of early-life education when assessing the composite CR capacity. Midlife work complexity was collected by inquiring about the five longest-held occupations of participants, which were then ranked based on their substantive complexity using a continuous score ranging from 0.7 to 10. Higher scores were indicative of greater substantive complexity (113).

The late-life leisure activities were evaluated through questionnaire data by asking participants if they had engaged in any of a list of 26 activities and the frequency of their participation in the past year. These activities were grouped into three components: mental (i.e., reading newspapers or books, watching TV, playing chess, cards, musical instruments, or computer games, or listening to music), social (i.e., sport engagement, dance, bingo, travelling, visiting cinema, theater, concert, museum, art exhibition, restaurant, or church, taking course, or participating in non-profit activities or association work), and physical (i.e., gardening, forest roaming, hunting, fishing, knitting, weaving or sewing, painting or drawing, or repairing house, car, or other machine instrument), as previously reported (113). The extent of engagement in the mental and social components was determined by the number of activities participated in and categorized as low (≤ 1 activity), moderate (2-3 activities), or high (≥ 4 activities), with corresponding scores of 0, 1, and 2. The extent of engagement in the physical component was assessed by the frequency of participation and categorized as low (less than once per week), moderate (once per week), or high (more than once per week), with corresponding scores of 0, 1, and 2. The leisure activity score was calculated by summing the scores of the three components, with a range from 0 to 6, where a higher score indicates greater engagement in leisure activities (113).

The size and support of late-life social network were assessed through several indicators. The marital status, living arrangement, number of children, frequency of contact with relatives or friends, and the number of contacts were used to assess the size of late-life social network. In addition, the measures of perceived material and psychosocial support received, satisfaction with social connections, and sense of belonging to social groups were used to assess the support late-life social network. All indicators were standardized into z-scores and averaged to estimate

the size and support of social networks, separately. Finally, the scores of size and support of late-life social network were averaged, resulting in a final score of late-life social network ranging from -2.1 to 1.2. Higher scores indicate a more extensive and supportive social network in later life (113).

The composite lifelong CR capacity was estimated using a structural equation model, incorporating the four aforementioned intellectual activities. To obtain predicted values of the latent variable representing CR, the standardized indicators of the four intellectual activities were multiplied by their corresponding weights and summed together (113).

3.4 Statistical analysis

In the following individual studies, characteristics of study participants at baseline were examined using t-test for continuous variables and $\chi 2$-text for categorical variables. The statistical significance level was set as two-tailed *P*-value < 0.05. Stata Statistical Software: Release 16.0 (StataCorp LLC., College Station, TX, USA) for Windows was used for all the analyses.

Study I: First, we examined the association of demographic factors including age groups (60–72 vs. ≥78 years), sex, and educational degree (with or without university degree) with annual change of continuous SVD measures (i.e., WMH score, PVS count, and GM and ventricular volumes), using the linear mixed-effects model, as well as the association of demographic factors with incidence of lacunes using the Cox proportional-hazards model. Next, for the longitudinal interrelationships of these SVD markers, we used (1) the linear mixed-effects model to investigate the relationship of baseline microvascular lesions (i.e., WMH score, PVS count, and lacunes) with annual change of continuous SVD measures; and (2) the Cox proportional-hazards model to examine longitudinal associations of baseline loads of WMHs and counts of PVSs with the incidence of lacunes. We adjusted for continuous age (years), education (years), current smoking, heavy alcohol consumption, physical inactivity, body mass index, hypertension, diabetes, and high cholesterol, and if applicable, for sex in the above analyses.

Study II: First, we estimated the association of baseline scores of global and regional WMHs with annual average change of cognitive z-scores in the analytical sample 1, using linear mixed-effects models. In addition, we examined the statistical interactions of baseline scores of WMHs with age groups, sex, and *APOE* genotypes (with or without ε4), on annual change of domain-specific cognitive z-scores using the linear mixed-effects models. Next, we examined the association of follow-up time (years) with progression of WMHs (i.e., global and regional WMH scores) over the first 6-year follow-up period using the linear mixed-effects models, in the analytical sample 2. The annual change of WMHs for each person was the sum of the fixed coefficient of follow-up time and the random coefficient for that person. Finally, we examined the association of annual change of WMHs with annual change of cognitive z-scores in analytical sample 2, using linear mixed-effects models. When a significant association was detected, we examined the patterns of WMH progression (defined as no progression, slow progression, and fast progression that corresponded to the lower, medium, and upper tertiles of

annual change of WMH scores, respectively) in association with annual change of cognitive z-scores. We adjusted for age (years), education (years), current smoking, heavy alcohol drinking, physical inactivity, body mass index, hypertension, high cholesterol, diabetes, total intracranial volume, lateral ventricular volume, global count of perivascular spaces, and lacunes at baseline, and if applicable, for sex, *APOE* genotypes, and baseline scores of the corresponding global or regional WMHs.

Study III: In the analytical sample 1, we assessed the associations of CVH profiles (favorable, intermediate, and unfavorable) with annual changes in continuous brain measures (i.e., WMH volume, PVS count, and GM volume) using the linear mixed-effects models. We assessed the associations of CVH profiles with incident lacunes using Cox proportional-hazards models. Then, the three-way interaction of CVH profiles, age groups, and follow-up time (years) on brain measures was tested using the linear mixed-effects models. Likewise, in the analytical sample 2, we examined the associations of the metabolic genetic risk score with annual progression of continuous brain measures using linear mixed-effects models. We assessed the associations of the metabolic genetic risk score with incident lacunes using the Cox proportional hazards models. Next, in the analytical sample 3, we examined the three-way interaction of the metabolic genetic risk score, CVH profiles, and follow-up time on changes of continuous brain measures, using linear mixed-effects models. We adjusted for age (years), sex, and education (years) in the above analyses.

Study IV: First, we examined the relationship of composite CR score with likelihood of transitions across cognitive states (normal cognition, CIND, and dementia) and death using the Markov multi-state model in the analytical sample 1. Next, we examined the statistical interaction of composite CR score with age group, sex, and *APOE* genotypes on the transitions across cognitive states and death. When a statistical interaction was found, we further analyzed the direction and strength of the relationship between composite CR score and transitions across cognitive states or death, stratified by age groups, sex, or *APOE* genotypes. To account for potential confounding factors, we controlled for age (years), current smoking, heavy alcohol drinking, hypertension, high cholesterol, diabetes, body mass index, atrial fibrillation, ischemic heart disease, and heart failure, and if applicable, for sex and *APOE* genotypes, in the aforementioned associations. Finally, we repeated the analysis that examined the association of composite CR score with likelihood of transitions across cognitive states and death using the Markov multi-state model in the analytical sample 2, while additionally adjusting for GM volume, WM volume, hippocampal volume, WMH volume, PVS count and lacunes at baseline.

3.5 Ethical considerations

All phases of data collection for the SNAC-K study received ethical permission from the Ethics Committee at Karolinska Institutet and the Regional Ethical Review Board in Stockholm. The specific reference numbers for these approvals are provided: KI 01-114 (date of approval: 2001-06-18, for wave 1), 04-929/3 (2005-01-19, for wave 2), Ö26-2007 (2007-09-20, for wave 3), 2010/447-31/2 (2010-06-09, for wave 4), 2013/828-31/3 (2013-05-29, for wave 5), and 2016/730-31/1 (2016-02-01, for wave 6) for SNAC-K, and 2009/595-32 (date of approval: 2009-03-30) for the register data.

To ensure the comfort and participation of the study participants, several strategies were implemented. Eligible participants received personalized letters that provided information about the study's objectives, content, duration, and importance. It was explicitly mentioned that participation was voluntary, and they could withdraw from the study at any point. In cases where participants had cognitive impairment, consent was obtained from a proxy, ensuring that their rights were respected. Nurses were responsible for contacting participants who agreed to take part in the study and scheduling the first study visit. Participants were also provided with written reports on their laboratory tests. As part of the informed consent process, participants were assured that their data would be kept confidential and anonymous.

All research activities within the SNAC-K study have been conducted in full compliance with all ethical guidelines, such as obtaining informed consent, ensuring participant comfort, and maintaining confidentiality and anonymity of the collected data.

4 Results

The key results from four individual studies included in the thesis are summarized as follows.

4.1 Progression of MRI markers of structural brain aging (Study I)

Out of the 555 participants who had MRI measures at baseline, the average age was 71.2 years (SD = 9.1), 58.2% were women, and 41.1% held a university degree. Over the course of the study, MRI measures for either the 3-year or 6-year follow-ups were available for 325 individuals, representing 58.6% of the initial MRI cohort. In comparison to people without follow-up MRI measures (n = 230), those with follow-up MRI measures were younger, more likely to have a university degree and to be physically active, while less likely to have hypertension or diabetes ($P < 0.05$). The two groups had no significant difference in body mass index or in the distribution of sex, current smoking, heavy alcohol drinking, or high cholesterol.

During the average of 5.7 years (2.6–7.4) of follow-up, the global WMH score steadily increased over time, with a β-coefficient (95% confidence interval [CI]) being 0.65 (0.54–0.77). Similarly, the global count of PVSs and lateral ventricular volume demonstrated a gradual rise during the follow-up period, while total GM volume experienced a decline ($P < 0.001$). The cumulative incidence of lacunes during the follow-up period was 12.92% (95% CI: 9.68%–17.04%), and the incidence rate (per 100 person-years) was 2.39 (1.77–3.24). Higher age showed a significant correlation with accelerated yearly growth in global, deep, and periventricular WMH scores, as well as ventricular volumes ($P < 0.001$). Additionally, it was linked to a more rapid decline in GM volume and a higher incidence of lacunes ($P < 0.001$). However, age was not significantly associated with the yearly growth in lobar WMHs or the counts of global, lobar, and deep PVSs. Furthermore, males showed a faster progression in lobar WMH scores compared to females (0.17, 0.02–0.32). Individuals without a university degree displayed a more rapid progression of deep and periventricular WMH scores compared to those with a degree (0.14, 0.02–0.27 and 0.07, 0.00–0.14, respectively).

Strong associations were observed between a higher global WMH score at baseline and an accelerated increase in global, deep, and periventricular WMHs and lateral ventricular volumes, as well as a more rapid decrease in GM volume, over the follow-up period ($P < 0.05$, **Table 4**). A higher baseline count of PVSs was significantly associated with an accelerated increase in global and lobar WMH burdens, as well as a decrease in GM volume ($P < 0.05$, **Table 4**). Additionally, the presence of lacunes at baseline showed a significant link to a faster progression of deep and periventricular WMHs, along with accelerated GM atrophy ($P < 0.05$, **Table 4**).

A significant association was observed between elevated scores of global and regional WMHs as well as increased counts of global and deep PVSs at baseline and a greater incidence of lacunes ($P < 0.05$, **Table 5**). After excluding participants with prevalent lacunes at baseline (n = 68), the significant relationships between global and regional WMH scores at baseline with incident lacunes remained. However, the previously observed associations between global and deep PVS counts with incident lacunes were no longer statistically significant (**Table 5**).

Table 4. Associations of global white matter hyperintensities, perivascular spaces, and lacunes at baseline with progression of continuous measures of global and regional cerebral small vessel disease (n=325)

Measures of microvascular lesions at baseline	β-coefficients (95% confidence intervals), annual changes of continuous measures of cerebral small vessel disease								
	White matter hyperintensity score				Perivascular space count			Gray matter volume	Ventricular volume
	Global	Lobar	Deep	Periventricular	Global	Lobar	Deep		
Global WMH score, per 10-point increment	0.15 (0.08–0.22)‡	-0.04 (-0.08–0.01)	0.11 (0.08–0.15)‡	0.02 (0.00–0.04)*	0.08 (-0.05–0.21)	0.03 (-0.07–0.13)	0.05 (-0.01–0.11)	-0.37 (-0.58–-0.16)‡	0.11 (0.03–0.18)‡
Global PVS count, per 10-PVS increment	0.07 (0.03–0.11)‡	0.05 (0.03–0.08)‡	0.01 (-0.02–0.03)	0.01 (-0.01–0.02)	0.02 (-0.07–0.11)	0.00 (-0.07–0.07)	0.01 (-0.03–0.04)	-0.18 (-0.32–-0.04)*	0.02 (-0.03–0.07)
Lacune (n=68)	0.29 (0.00–0.58)*	-0.10 (-0.29–0.09)	0.22 (0.05–0.38)‡	0.10 (0.01–0.18)*	0.43 (-0.11–0.97)	0.36 (-0.07–0.78)	0.07 (-0.18–0.31)	-0.93 (-1.83–-0.03)*	0.23 (-0.09–0.55)

Note: Abbreviations: WMH, white matter hyperintensity; PVS, perivascular space.
The β-coefficients (95% confidence intervals) were adjusted for age (years), sex, education (years), current smoking, heavy alcohol consumption, physical inactivity, body mass index, hypertension, diabetes, and high cholesterol.
*$P \leq 0.05$, ‡$P < 0.001$.

Table 5. Associations of white matter hyperintensities and perivascular spaces at baseline with incident lacunes (n=325)

Measures of cerebral microvascular lesions at baseline	Hazards ratios (95% confidence intervals), incident lacunes	
	Total sample (n=325, 42 with incident lacunes)	People free of lacunes at baseline (n=257, 18 with incident lacunes)
Score of white matter hyperintensities (range 0-79), per 10-point increment		
Global (0-79)	1.78 (1.50–2.10)‡	1.71 (1.30–2.24)‡
Lobar (0-36)	2.72 (2.00–3.69)‡	2.29 (1.47–3.56)‡
Deep (0-24)	3.38 (2.10–5.43)‡	4.47 (1.88–10.63)‡
Periventricular (0-12)	11.52 (4.21–31.47)‡	9.12 (1.83–45.37)†
Count of perivascular spaces (range 22-178), per 10-perivascular space increment		
Global (22-178)	1.14 (1.01–1.28)*	1.09 (0.88–1.34)
Lobar (6-136)	1.08 (0.93–1.26)	0.98 (0.75–1.29)
Deep (7-64)	1.77 (1.28–2.45)‡	2.14 (1.17–3.91)

Note: The hazards ratios and 95% confidence intervals were adjusted for age (years), sex, education (years), current smoking, heavy alcohol consumption, physical inactivity, body mass index, hypertension, diabetes, and high cholesterol.

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

4.2 Association between white matter hyperintensities and cognitive decline (Study II)

In the analytical sample 1 (n = 510), the average follow-up duration was 10.4 years (SD = 3.6) for the cognitive outcomes. The average follow-up time for the structural brain markers was 5.5 years (SD = 1.0). Compared to participants who did not have follow-up WMH measures (n = 185), those who had (n = 325) were younger, more educated, more physically active, less likely to have hypertension and global and periventricular WMHs, and more likely to have smaller lateral ventricles and better performance in executive function, episodic memory, semantic memory, category fluency, and perceptual speed ($P < 0.05$). Notably, the two groups did not differ significantly in terms of global PVS count, lobar and deep WMH scores, total intracranial volume, body mass index, and z-score of letter fluency ($P > 0.05$).

Higher global and regional WMH scores at baseline were all related to a faster decline in letter fluency, perceptual speed, and global cognition ($P < 0.05$, **Table 6**). In addition, the greater global WMH score at baseline was related to a faster decline in executive function ($P = 0.05$, **Table 6**). Higher scores for lobar and deep WMHs at baseline were marginally related to a faster decline in executive function ($P = 0.064$ and 0.054, respectively). Greater baseline periventricular WMHs were linked to a faster decline in category fluency ($P < 0.05$, **Table 6**).

There was a statistical interaction of periventricular WMH score with *APOE*-ε4 allele on annual change in category fluency (P for interaction = 0.046). The significant associations of increased periventricular WMH score with faster decline in category fluency existed only in *APOE*-ε4 carriers (β-coefficient and 95% CI: -0.018, -0.031– -0.004), but not in *APOE*-ε4 non-carriers (-0.005, -0.013–0.003). There was no reliable interaction of WMH scores with sex or age on annual changes in scores of any examined cognitive domains (P for interaction > 0.05).

Faster annual accumulation of deep WMHs during the first six years was associated with a faster decline in executive function and global cognition during the 15-year follow-up period ($P < 0.05$, **Table 7**). Compared to participants with no progression of deep WMHs, those with slow and fast progression of deep WMHs showed a marginally faster decline in executive function, with β-coefficients (95% CI) being -0.018 (-0.049–0.013) and -0.034 (-0.068–0.000), (P for trend=0.053), and a faster decline in global cognition, with β-coefficients (95% CI) being -0.007 (-0.019–0.004) and -0.016 (-0.028– -0.004), respectively (P for trend=0.008). Moreover, faster accumulations of global, deep, and periventricular WMHs were all associated with faster deterioration in perceptual speed ($P < 0.05$). The faster annual accumulation of lobar WMHs was marginally related to faster deterioration in perceptual speed ($P = 0.08$). Compared to people with no progression of WMHs, those with slow and fast progression of global WMHs showed faster decline in perceptual speed, with β-coefficients (95% CI) being -0.010 (-0.026–0.005) and -0.018 (-0.035–-0.002), respectively (P for linear trend = 0.026). The β-coefficients (95% CI) of change in perceptual speed were -0.010 (-0.026–0.006) and -0.017 (-0.033–-0.002) for increase in lobar WMHs (P for linear trend=0.032), -0.006(-0.021–0.010) and -0.016(-0.032–0.001) for increase in deep WMHs (P for linear trend = 0.063), and -0.015 (-0.031–0.001) and -0.016(-0.032–0.000) for increase in periventricular WMHs (P for linear trend = 0.041).

Table 6. Association of white matter hyperintensities at baseline with annual change in cognitive z-scores (analytical sample 1, n=510)

WMH scores at baseline (range)	**Standardized β-coefficient (95% confidence interval), average annual change in cognitive z-scores**						
	Episodic memory [a]	Semantic memory [a]	Category fluency [a]	Letter fluency [a]	Executive function [a]	Perceptual speed [a]	Global cognition
Global (0-79)	-0.003	-0.002	-0.007	-0.015	-0.014	-0.012	-0.010
	(-0.012–0.007)	(-0.009–0.004)	(-0.014–0.004)	(-0.022– -0.008)‡	(-0.028–0.000)*	(-0.018– -0.005)‡	(-0.015– -0.005)‡
Lobar (0-36)	0.002	-0.001	-0.005	-0.013	-0.013	-0.010	-0.008
	(-0.007–0.011)	(-0.008–0.005)	(-0.012–0.002)	(-0.020– -0.006)‡	(-0.026–0.001)	(-0.016– -0.004)†	(-0.013– -0.004)†
Fronto-temporal	0.001	-0.001	-0.005	-0.013	-0.012	-0.009	-0.008
(0-24)	(-0.007–0.010)	(-0.008–0.005)	(-0.012–0.002)	(-0.020– -0.007)‡	(-0.025–0.002)	(-0.015– -0.002)†	(-0.012– -0.003)†
Parieto-occipital	0.003	-0.001	-0.005	-0.010	-0.011	-0.010	-0.007
(0-12)	(-0.006–0.011)	(-0.007–0.006)	(-0.012–0.002)	(-0.016– -0.003)†	(-0.025–0.002)	(-0.016– -0.003)†	(-0.012– -0.003)†
Deep (0-24)	-0.010	-0.004	-0.003	-0.010	-0.016	-0.011	-0.010
	(-0.020–0.000)	(-0.011–0.004)	(-0.011–0.005)	(-0.018– -0.002)*	(-0.033–0.000)	(-0.018– -0.004)†	(-0.015– -0.004)‡
Periventricular	-0.005	-0.003	-0.009	-0.011	-0.007	-0.008	-0.008
(0-12)	(-0.014–0.003)	(-0.010–0.003)	(-0.016–-0.002)*	(-0.018– -0.005)‡	(-0.020–0.006)	(-0.014– -0.002)*	(-0.013– -0.004)‡

Note: Abbreviations: WMH, white matter hyperintensity.

The β-coefficients and 95% confidence intervals were adjusted for age, sex, education, current smoking, heavy alcohol drinking, physical inactivity, body mass index, hypertension, high cholesterol level, diabetes, total intracranial volume at baseline, global count of perivascular space at baseline, lacune at baseline, and *APOE* genotypes.

[a] Of the 510 participants, the number of subjects with missing values was 49 in executive function, 1 in episodic memory, 2 in semantic memory, 2 in category fluency, 1 in letter fluency, and 5 in perceptual speed.

*$P \leq 0.05$, †$P < 0.01$, ‡$P < 0.001$.

Table 7. Association of annual change in white matter hyperintensities with annual change in cognitive z-scores (analytical sample 2, n=325)

Annual change in WMH score, per 1-point increment	**β-coefficient (95% confidence interval) [a], average annual change in cognitive z-scores**						
	Episodic memory [a]	Semantic memory [a]	Category fluency	Letter fluency	Executive function [a]	Perceptual speed [a]	Global cognition
Global (-1.47–3.46)	0.000	0.000	-0.001	0.002	-0.002	-0.012	-0.003
	(-0.012–0.013)	(-0.009–0.009)	(-0.011–0.009)	(-0.007–0.011)	(-0.022–0.017)	(-0.021– -0.003)*	(-0.010–0.004)
Lobar (-1.39–3.22)	-0.004	0.005	0.005	0.004	0.028	-0.013	0.002
	(-0.024–0.016)	(-0.010–0.019)	(-0.011–0.021)	(-0.011–0.019)	(-0.001–0.058)	(-0.027–0.001)	(-0.009–0.013)
Fronto-temporal	-0.023	0.010	-0.002	-0.010	0.045	-0.025	-0.002
(-0.71 –1.72)	(-0.060–0.015)	(-0.016–0.036)	(-0.030–0.027)	(-0.037–0.016)	(-0.011–0.100)	(-0.051–0.002)	(-0.022–0.017)
Parieto-occipital	0.000	0.006	0.009	0.021	0.028	-0.014	0.005
(-1.30–1.35)	(-0.035–0.034)	(-0.018–0.030)	(-0.018–0.036)	(-0.004–0.046)	(-0.028–0.083)	(-0.039–0.012)	(-0.013–0.024)
Deep (-0.18–2.02)	-0.003	-0.008	-0.022	-0.019	-0.061	-0.035	-0.025
	(-0.038–0.032)	(-0.033–0.016)	(-0.049–0.005)	(-0.044–0.007)	(-0.118–-0.004)*	(-0.060– -0.010)†	(-0.043– -0.006)†
Periventricular	0.021	0.013	0.009	-0.034	-0.064	-0.047	-0.021
(-0.72–0.89)	(-0.036–0.078)	(-0.027–0.054)	(-0.034–0.053)	(-0.076–0.007)	(-0.145–0.017)	(-0.088– -0.007)*	(-0.051–0.009)

Note: Abbreviations: WMH, white matter hyperintensity.

The β-coefficients and 95% confidence intervals were adjusted for age, sex, education, current smoking, heavy alcohol drinking, physical inactivity, obesity, hypertension, high cholesterol level, diabetes, total intracranial volume at baseline, global count of perivascular space at baseline, lacune at baseline, *APOE* genotypes, and corresponding global or regional scores of white matter hyperintensity at baseline.

[a] Of the 325 participants, the number of subjects with missing values was 29 in executive function, 1 in episodic memory, 1 in semantic memory, and 4 in perceptual speed.

*P<0.05, †P<0.01, ‡P<0.001.

4.3 Association between cardiovascular health profiles and MRI markers of structural brain aging (Study III)

In the analytical sample 1 (n = 267), there was no significant difference in mean age, female proportion, or years of education among people with different global CVH profiles. The average duration of follow-up was 5.5 years (SD = 0.9). A slower increase in global WMH volume was observed in people with intermediate and favorable (versus unfavorable) global CVH profiles ($P < 0.05$, **Table 8**). The intermediate (versus unfavorable) behavioral CVH profile showed a significant association with a slower progression of WMH volume, whereas the favorable profile did not exhibit the same association ($P < 0.001$, **Table 8**). Neither global nor behavioral CVH profiles showed significant associations with annual changes in PVS count, GM volume, or incidence of lacunes (**Table 8**). People with intermediate or favorable (versus unfavorable) biological profiles experienced a slower GM atrophy. ($P < 0.05$, **Table 8**).

Table 8. Associations of CVH metrics with progression of brain aging markers (analytical sample 1, n=267)

Composite CVH metrics	β-coefficient (95% CI), annual change of brain markers			HR (95% CI), incident lacunes[a]
	WMH volume	PVS count	GM volume	
Global CVH metrics				
Continuous score (2–13), n=267	-0.005 (-0.008– -0.002)†	-0.03 (-0.15–0.09)	0.09 (-0.10–0.29)	1.18 (0.92–1.51)
Categorical (tertiles)				
Unfavorable (2–6), n=59	0 (reference)	0 (reference)	0 (reference)	1 (reference)
Intermediate (7–8), n=103	-0.018 (-0.035– -0.001)*	0.02 (-0.63–0.60)	0.43 (-0.57–1.42)	1.49 (0.30–7.46)
Favorable (9–13), n=105	-0.018 (-0.034– -0.001)*	-0.17 (-0.78–0.44)	0.71 (-0.28–1.69)	2.60 (0.57–11.73)
P for trend	0.063	0.540	0.161	0.138
Behavioral CVH metrics				
Continuous score (1–8), n=267	-0.006 (-0.010– -0.001)†	-0.09 (-0.26–0.07)	-0.03 (-0.29–0.23)	1.20 (0.85–1.70)
Categorical (tertiles)				
Unfavorable (1–4), n=79	0 (reference)	0 (reference)	0 (reference)	1 (reference)
Intermediate (5), n=73	-0.023 (-0.040– -0.007)†	-0.14 (-0.75–0.47)	0.63 (-0.35–1.62)	2.25 (0.43–11.69)
Favorable (6–8), n=115	-0.012 (-0.027–0.002)	-0.37 (-0.91–0.17)	-0.38 (-1.25–0.48)	2.73 (0.61–12.27)
P for trend	0.149	0.170	0.308	0.195
Biological CVH metrics				
Continuous score (0–6), n=267	-0.005 (-0.011–0.000)	0.05 (-0.16–0.26)	0.30 (-0.03–0.63)	1.21 (0.80–1.82)
Categorical (tertiles)				
Unfavorable (0–2), n=116	0 (reference)	0 (reference)	0 (reference)	1 (reference)
Intermediate (3), n=86	-0.014 (-0.028–0.001)	0.15 (-0.39–0.68)	0.94 (0.08–1.80)*	0.74 (0.24–2.25)
Favorable (4–6), n=65	-0.013 (-0.028–0.003)	0.21 (-0.37–0.79)	0.95 (0.02–1.87)*	1.50 (0.52–4.30)
P for trend	0.082	0.459	0.029	0.551

Note: Abbreviations: CI, confidence interval; CVH, cardiovascular health; WMH, white matter hyperintensity; PVS, perivascular space; GM, gray matter; HR, hazards ratio.
The β-coefficients and hazards ratios were adjusted for age (years), sex, and education (years).
[a]31 participants developed incident lacunes among those with CVH metric scores. *$P<0.05$, †$P<0.01$.

We observed a marginally three-way interaction between the biological CVH metric score, age groups, and follow-up time in relation to changes in WMH volume (*P* for interaction = 0.062). Stratifying analyses by age showed that among individuals aged 60–72 years, intermediate and favorable biological CVH profiles were linked with a slower increase of WMH volume compared to the unfavorable profile (**Figure 5**). However, no significant association was observed between biological CVH profiles and WMH increase among people aged ≥78 years.

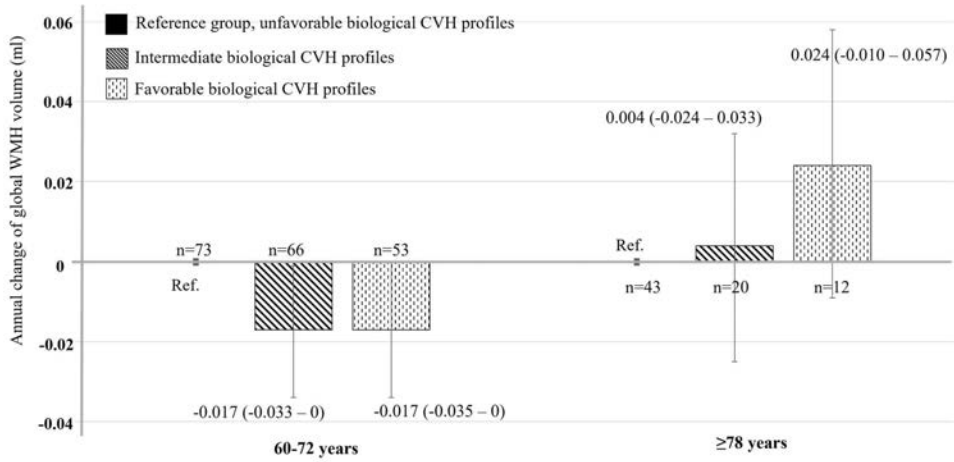

Figure 5. Associations between biological CVH profiles and annual changes of global WMH volume by age groups (analytical sample 1, n=267)
Note: Abbreviations: CVH, cardiovascular health; WMH, white matter hyperintensity. The β-coefficients and 95% confidence intervals were adjusted for age (years), sex, and education (years).

In the analytical sample 2 (n = 284), when dividing the metabolic genetic risk score into tertiles, a high (versus low) genetic risk load was associated with a faster progression of WMHs (*P* for linear trend = 0.002, **Table 9**) compared to a lower genetic risk load. Additionally, the intermediate genetic risk load was also associated with faster GM atrophy ($P < 0.05$, **Table 9**) compared to a low genetic risk load. There were no significant associations between metabolic genetic risk score and progression of PVS count, GM volume, or lacunes (**Table 9**).

In the analytical sample 3 (n = 234), we observed three-way interactions between global and behavioral CVH profiles, metabolic genetic risk score, and follow-up time in relation to the annual progression of WMHs (*P* for both interactions = 0.001). Among individuals with unfavorable and intermediate global CVH profiles, a higher metabolic genetic risk score was associated with a faster progression of WMH. However, this association was not observed among individuals with favorable global CVH profile (**Figure 6A**). Similarly, an increased metabolic genetic risk load was linked to a faster increase in WMH among individuals with unfavorable and intermediate behavioral CVH profiles, but not among individuals with favorable behavioral CVH profile (**Figure 6B**).

Table 9. Associations of metabolic genetic risk score with progression of brain aging markers (analytical sample 2, n=284)

Metabolic genetic risk load (score range)	β-coefficient (95% CI), annual change of brain markers			HR (95% CI), incident lacunes [a]
	Global WMH volume	Global PVS count	Gray matter volume	
Continuous score (6-21), n=284	0.005 (0.003–0.008)[‡]	0.03 (-0.07–0.13)	0.05 (-0.10–0.20)	1.04 (0.86–1.25)
Categorical (tertiles)				
Low (6-11), n=70	0 (reference)	0 (reference)	0 (reference)	1 (reference)
Intermediate (12-13), n=99	0.008 (-0.009–0.024)	0.31 (-0.30–0.92)	0.99 (0.05–1.94)[*]	1.02 (0.32–3.26)
High (14-21), n=115	0.024 (0.008–0.040)[†]	0.08 (-0.51–0.68)	0.26 (-0.67–1.18)	0.88 (0.29–2.71)
P for trend	0.002	0.946	0.886	0.797

Note: Abbreviations: CI, confidence interval; WMH, white matter hyperintensity; PVS, perivascular space.
The β-coefficients and hazards ratios were adjusted for age (years), sex, and education (years).
[a]37 participants developed incident lacunes among those with genetic risk score.
[*]*P*<0.05, [†]*P*<0.01, [‡]*P*<0.001.

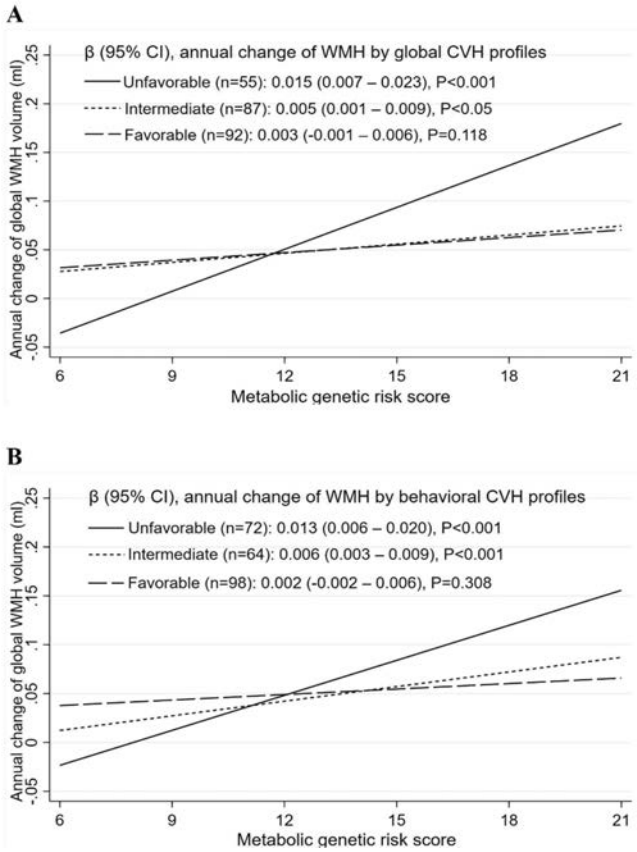

Figure 6. Associations of genetic susceptibility to metabolic risk factors with annual changes of global WMH volume by global (A) and behavioral (B) CVH profile categories (analytical sample 3, n=234)
Note: Abbreviations: WMH, white matter hyperintensity; CVH, cardiovascular health.
The β-coefficients and 95% confidence intervals were adjusted for age (years), sex, and education (years).

4.4 Association between cognitive reserve and transitions across cognitive states, independent of brain pathology (Study IV)

At baseline, compared to people free of CIND (n = 2023), those with CIND (n = 2608) had a lower composite CR score, and were older, more likely to be female, to smoke, to have hypertension, diabetes, ischemic heart disease, and heart failure, and to carry *APOE*-ε4 allele, while less likely to have heavy alcohol consumption or to be engaged in physical activity ($P < 0.02$). Body mass index and prevalence of atrial fibrillation did not differ significantly between the two groups.

In the analytical sample 1 (n = 2631), a higher composite CR score (range: -4.3 to 3.5; median: 0; interquartile range: 1.8) was associated with a ~22% lower risk of transition from normal cognition to CIND and a ~15% lower risk of transition from normal cognition to death, as well as a ~18% lower risk of transition from CIND to death, over the 15 years of follow-up period (**Figure 7A**). Similarly, in the analytical sample 2 (n = 517), a higher composite CR score was linked to a ~24% lower risk of transition from normal cognition to CIND and a ~21% lower risk of transition from normal cognition to death, while no significant association was observed for the transition from CIND to death (**Figure 7B**). There was no association between composite CR score and other transitions across cognitive states and death ($P > 0.05$).

In the analytical sample 1, a statistical interaction was observed between composite CR score and age groups on the likelihood of transition from CIND to death (P for interaction = 0.010); such that a higher composite CR score was significantly associated with a ~35% lower risk of transition from CIND to death in individuals aged 60–72 years, while a ~13% non-significantly lower risk was observed in those aged 78 years and above. There was no statistical interaction of composite CR score with *APOE* genotypes, age groups, or sex on the risk of other transition across cognitive states and death (P for interaction > 0.05).

Table 10. Associations between cognitive reserve and transitions from normal cognition to dementia and from CIND to death by *APOE* genotypes and age groups

	Hazards ratios and 95% confidence intervals			
	n/N	Normal cognition – dementia	n/N	CIND – death
***APOE* genotypes** [a]	93/2466		281/2466	
At least one ε4 allele	60/1744	0.71 (0.48–1.05)	188/1744	0.80 (0.69–0.93)‡
No ε4 allele	33/722	1.07 (0.85–1.34)	93/722	0.72 (0.58–0.91)‡
P-value for interaction		0.051		0.332
Age groups	96/2631		318/2631	
60–72 years	30/1612	0.91 (0.63–1.31)	113/1612	0.65 (0.54–0.77)‡
≥78 years	66/1019	0.93 (0.74–1.18)	205/1019	0.87 (0.75–1.01)
P-value for interaction		0.353		0.010

Note: CIND, cognitive impairment, no dementia.
The hazards ratios and 95% confidence intervals were adjusted for age (years), sex, current smoking, heavy alcohol drinking, hypertension, high cholesterol, diabetes, body mass index, atrial fibrillation, ischemic heart disease, and heart failure, and if applicable, for *APOE* genotypes.
[a] The number of participants with missing value was 165 for *APOE* genotypes. ‡$P<0.001$.

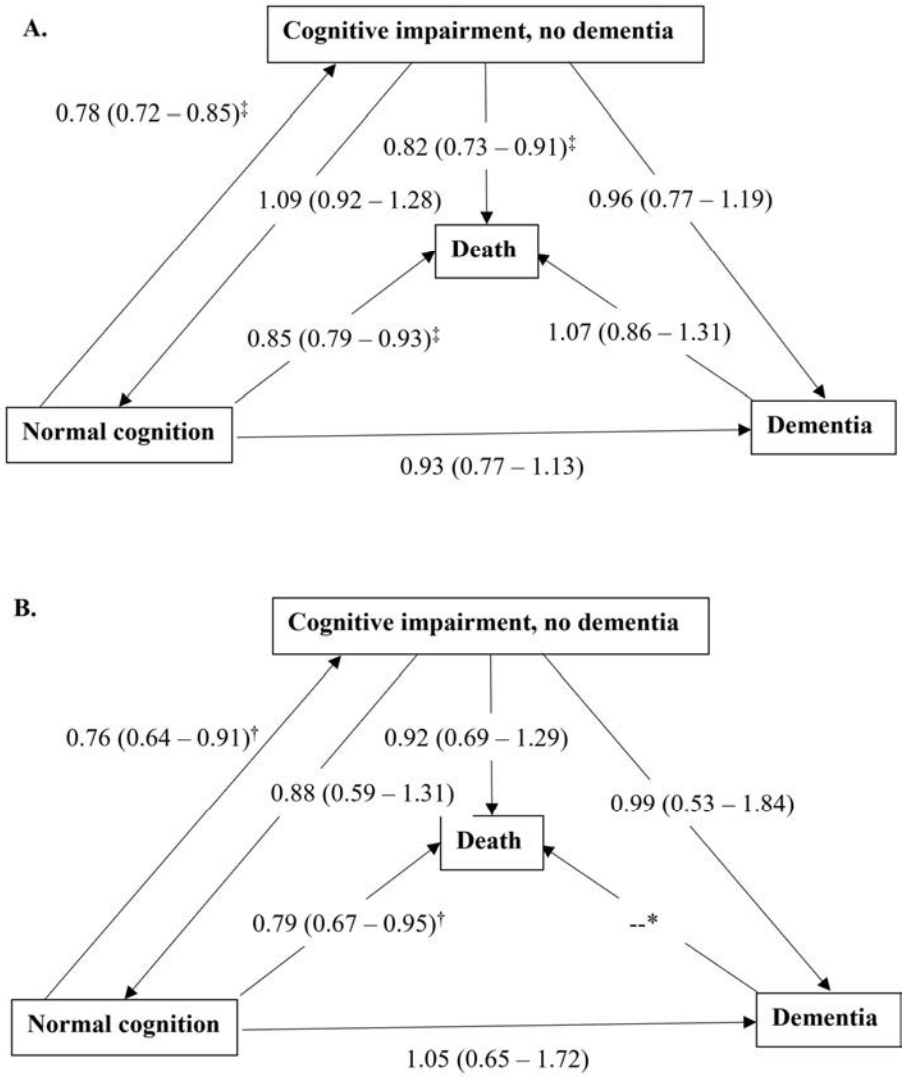

Figure 7. Association of cognitive reserve with transitions across cognitive states and death in the SNAC-K total sample (A) and the SNAC-K MRI subsample (B). Data are hazards ratio (95% confidence interval), derived from the Markov multi-state model.

Note: The hazards ratios and 95% confidence intervals were adjusted for age (years), sex, current smoking, heavy alcohol drinking, hypertension, high cholesterol, diabetes, body mass index, atrial fibrillation, ischemic heart disease, and heart failure, and if applicable, for *APOE* genotypes.

*The parameters were not estimated due to the limited sample size.

†$P<0.01$, ‡$P<0.001$.

5 Discussion

5.1 Summary of the main findings

In this doctoral project, using longitudinal data from the population-based cohort study of Swedish older adults, we sought (1) to investigate the progression and interrelationship of MRI markers of structural brain aging, (2) to explore the relationship of WMHs with domain-specific cognitive decline, (3) to assess the relationship between CVH metrics and structural brain aging, and (4) to examine the association between CR capacity and transitions across cognitive states and death. The main findings from this project are summarized as follows:

I. The progression of cerebral SVD varies by demographics: MRI markers of cerebral SVD, except PVSs, exhibit an accelerated progression with advancing age. Men experience a faster progression of regional WMHs compared to women, and individuals without a university degree demonstrate a swifter progression of regional WMHs than those with a degree. Furthermore, the higher burden of cerebral microvascular lesions is associated with a more rapid progression of cerebral SVD. Specifically, the higher burden of WMHs at baseline is associated with an elevated risk of developing new lacunes, an accelerated accumulation of WMHs, and faster brain shrinkage. Moreover, the greater number of PVSs and prevalent lacunes at baseline are linked to an expedited accumulation of WMHs and faster brain atrophy.

II. The greater burden of WMHs at baseline is associated with a faster decline in executive function, letter fluency, perceptual speed, and global cognition, but not in episodic or semantic memory. Carrying the *APOE*-ε4 allele could exacerbate the deterioration in category fluency due to the greater burden of periventricular WMHs. In addition, the accelerated decline in perceptual speed is linked to a faster accumulation of WMHs in deep and periventricular regions, and the accelerated deterioration in executive function and global cognition is related to a faster accumulation of deep WMHs.

III. The intermediate-to-favorable (versus unfavorable) global CVH profiles are associated with a slower accumulation of WMHs. The intermediate-to-favorable (versus unfavorable) biological CVH profiles are linked to a decelerated progression of global WMHs among people aged 60–72 years, but not in those aged ≥78 years. Moreover, a higher metabolic genetic risk is associated with a faster increase in WMHs. However, this association is evident among people with unfavorable CVH profile, but not in those with favorable global and behavioral CVH profiles.

IV. Higher CR capacity is linked to a reduced risk of transition from normal cognition to CIND or death and from CIND to death. The risk of transition from normal cognition to CIND or death does not change after controlling for brain aging markers, whereas the risk of transition from CIND to death is not evident anymore. No significant association is observed between CR capacity and the transition from CIND to dementia or from CIND to normal cognition. Furthermore, among individuals with CIND at baseline, a higher CR capacity is associated with a lower mortality rate among individuals aged 60–72 years but not among those aged 78 years and above.

5.2 Interpretation and pathological mechanisms

5.2.1 Progression of MRI markers of structural brain aging in old age

Most MRI markers of structural brain aging demonstrate an accelerated progression as individuals age. This phenomenon can be attributed to the age-related deterioration of shared pathological mechanisms and the cumulative effect of risk factors. It has been well established that the blood-brain barrier, which deteriorates with normal aging, is a critical factor in the development of cerebral SVD, particularly WMHs (125). This can result in microvascular wall injury, impaired vasoreactivity, luminal narrowing, and ultimately parenchymal ischemia, all of which can contribute to the pathogenesis of cerebral SVD (125). In addition, population-based studies have found that the impacts of vascular risk factors, such as hypertension, high cholesterol, and diabetes, can accumulate with advancing age (126), and lead to the development of cerebral SVD over time, including WMHs, lacunes, and brain atrophy (127-130). This can partly explain the association between increasing burden of cerebral SVD and advancing age. Despite the faster accumulation of most cerebral SVD markers associated with vascular risk factors, the accumulation of PVSs is not necessarily related to these traditional vascular risk factors in population-based studies (40, 129). This could contribute to the observation that accumulation rate of PVSs does not steadily increase with aging. The lack of a clear association between advancing age and progression of PVSs suggests that other factors may account for the development of PVSs, such as heredity (131). Furthermore, men are usually more likely to be exposed to vascular risk factors and to have a higher ratio of albumin in cerebrospinal fluid to albumin in serum than women, both of which are highly related to the development of WMHs (132, 133). This helps to clarify the sex-specific difference in the accumulation of WMHs observed in our study.

Population-based cohort studies investigating the association between educational attainment and brain aging markers have yielded mixed results. For example, the Epidemiological Clinicopathological Studies in Europe found no direct association between years of education and neurodegenerative or cerebrovascular pathologies (134), whereas the 1936 Aberdeen Birth Cohort study indicated that the lower educational attainment was associated with higher burden of WMHs (135), which aligned with the finding in our study. Education may not have a direct effect on structural brain aging (134). However, it is worth noting that education can potentially influence brain aging indirectly through socioeconomic status (e.g., income, occupation, access to healthcare) and lifestyles (engagement in cognitive and physical activities) related to educational attainment (136-138). Future research is required to assess the multifaceted interactions between educational attainment, socioeconomic status, and lifestyle factors as they collectively contribute to structural brain aging.

5.2.2 Interrelationships between MRI markers of structural brain aging

The association of greater WMHs at baseline with faster progression of cerebral SVD is in line with findings from the population-based Shanghai Aging Study (6). The large autopsy-verified Arizona Study of Aging and Neurodegenerative Disorders has indicated that formation and development WMHs are attributed to the combination of neurodegenerative and vascular causes (139). Furthermore, common vascular risk factors and mechanisms shared among WMHs, lacunes, and brain atrophy could also account for this phenomenon (127-130). From

the perspective of common pathological mechanism, the dysfunction of the blood-brain barrier may result in impaired endothelial junctions. This impairment leads to the leakage of plasma fluid components, which subsequently causes white matter demyelination, arteriosclerosis, perforating arteriolar thrombosis, and the characteristic occurrence of lacunar infarction (4). The dysfunction of blood-brain barrier may also result in the leakage of toxins and subsequent neuronal loss, leading to a reduction in brain volume (125).

The association between greater number of PVSs and faster increase of WMHs is in line with findings from the population-based Age, Gene/Environment Susceptibility-Reykjavik Study (5). We only found the association between higher load of PVSs with subsequent faster progression of WMHs, while not vice versa. It could be explained by the fact that PVSs occur prior to other cerebral SVD markers, including WMHs (140). On the other hand, the PVSs and WMHs share common pathological mechanisms, such as both cerebral amyloid angiopathy and hypertensive angiography which could contribute to the formation of PVSs and WMHs (38, 65). This also explains the close association between PVSs and WMHs.

Previous population-based studies have indicated that cerebral microvascular lesions might accelerate brain atrophy and then further influence cognitive or physical impairment in older adults (25, 141). Our study has provided reliable evidence supporting the temporal sequence of microvascular lesions preceding brain atrophy. In terms of neuropathology, the higher burden of WMHs has been linked to greater accumulation of tau-protein and neurofibrillary tangles (54), both of which can contribute to cortical thinning and degenerative changes in brain parenchyma (55). Moreover, PVSs play a crucial role in clearing interstitial fluid and metabolic waste from the brain, including amyloid-β. When these pathways are dysfunctional, normal clearance may be impaired (56). As a result, the accelerated aggregation of amyloid-β in the brain tissue may lead to an impaired function of synapses and neurons (57). These may partly account for the association observed in Study I and highlight the significance to monitor and control the development of microvascular lesions in old age.

5.2.3 White matter hyperintensity and domain-specific cognitive decline

WMHs, as a typical marker of cerebral microvascular lesions, have been consistently linked to a faster decline in multiple cognitive domains in previous population-based studies (142, 143). The formation and development of regional WMHs have been attributed to multiple potential neuropathological mechanisms, which may contribute to cognitive impairments in specific domains. For example, both cerebral amyloid angiopathy linked to lobar WMHs and cerebral arteriolosclerosis linked to deep WMHs are associated with impaired perceptual speed (144, 145). In addition, evidence from a neuropathological study has indicated that a potential link between WMHs and cortical hypometabolism may lead to executive dysfunction (146). This finding is in line with the modest association observed in Study II, where a higher burden of lobar WMHs is marginally associated with poorer executive function. The limited statistical power resulting from missing values in numerous individuals for the executive function task likely contributes to the non-significant association between regional WMHs and executive dysfunction. Interestingly, although the link between WMHs and impaired memory is suggested by the cross-sectional data from the population-based Age, Gene/Environment Susceptibility-Reykjavik Study (147), our cohort study does not provide convincing evidence

supporting the association between WMHs and subsequent decline in memory. This observation might be partly attributable to the relatively younger and healthier SNAC-K MRI sample compared to the entire population in SNAC-K (86). The former group likely carries a lower burden of WMHs. Moreover, the distinct study designs (cross-sectional design in the Age, Gene/Environment Susceptibility-Reykjavik Study vs. longitudinal design in SNAC-K MRI study) could also potentially account for the observed discrepancies in the findings. Furthermore, memory decline has the least likelihood to be affected by the microvascular lesions compared to language and attention (148), which also makes it difficult to detect a weak-to-moderately strong association between WMHs and changes of memory functioning. Therefore, large-scale prospective cohort studies are necessary to clarify the relationships between global and regional WMHs and memory decline in older adults.

Furthermore, we have found that the decline in category fluency is vulnerable to periventricular WMHs, rather than deep or lobar WMHs. Data from the Mayo Clinic Study of Aging have indicated that periventricular WMHs are related to cerebral amyloid pathology (149). Moreover, data from the Gothenburg H70 Birth Cohort Studies have suggested that cerebral amyloid pathology is associated with worse performance in category fluency (150). These findings support the observed link between higher load of periventricular WMHs and faster decline in category fluency. Notably, we have also identified that individuals carrying the *APOE*-ε4 allele, a genetic risk factor for cerebral amyloid pathology and cognitive decline, experience an exacerbated decline in category fluency in the presence of accumulated periventricular WMHs. This further reinforces the role of cerebral amyloid pathology in the deterioration of category fluency among older adults. It also highlights the importance of monitoring the burden of WMHs for the preservation of cognitive health, particularly in individuals with a higher genetic predisposition to cognitive decline.

Previous population-based studies have linked faster WMH progression with accelerated deterioration of executive function and perceptual speed, despite the relatively shorter follow-up period (<5 years) (87). The study II confirms the phenomenon in a long-term follow-up cohort (mean follow-up time=10.4 years). This finding is significant as it suggests that the detrimental impact on cognitive performance may not only coincide with the development of cerebral microvascular lesions but also manifest several years after structural brain damage (151). Furthermore, we have found that the decline in perceptual speed is related to a more rapid accumulation of both global and regional WMHs. This suggests that the deterioration of perceptual speed may be influenced by multiple neuropathological factors (152). The decline in executive function is specifically associated with a faster progression of deep WMHs, indicating that arteriosclerosis may partly contribute to the deterioration of executive function.

5.2.4 Cardiovascular health and structural brain aging

The proposed reciprocal brain-heart connection in the aging process has prompted numerous investigations into the relationship between CVH and structural or functional brain health (153). In Study III, we investigated the association of CVH metrics with brain aging markers and found that favorable CVH metrics could benefit structural brain health, specifically by slowing down the progression of WMHs in late life. The two-year follow-up data from the

PREVENT-Dementia study show that a higher score of Cardiovascular Risk Factors, Ageing and Dementia risk, which incorporates biological CVH metrics and demographic and genetic metrics, is associated with a faster progression of WMHs, but not associated with the progression of PVSs or lacunes (154). This is partly in accordance with the main finding from our study. Several factors may contribute to the association of CVH metrics with structural brain aging. Firstly, the brain is a highly metabolic organ with a high demand for oxygen and nutrients. Unfavorable CVH is associated with atherosclerosis, which can reduce cerebral blood flow, deprive neurons and oligodendrocytes (myelin sheath) of necessary oxygen and nutrients, and lead to neuronal loss and formation of WMHs over time (155). In addition, unfavorable CVH can also result in dysfunction of the blood-brain barrier and cause inflammation and oxidative stress in the endothelial cells of blood vessels (156). These inflammatory signals can impair the coordinated neurovascular coupling mechanisms that dilate local vessels in response to neural activity. This can lead to exposure of neurons to a relatively ischemic environment, further contributing to brain damage (155).

As people age, the ideal level of CVH profiles may not always be beneficial. Data from community-based studies have shown that lower levels of blood pressure, body mass index, and non-high-density lipoprotein cholesterol in late life are associated with an increased risk of cognitive impairment and dementia (123, 157). Likewise, data from the Clinical Practice Research Datalink have suggested that hypoglycemia is associated with a higher risk of dementia in people with diabetes (158). These findings partly agree with our finding that maintaining ideal biological CVH profiles may not necessarily be beneficial in the late life. Several reasons could explain this phenomenon. First, systematic hypoperfusion due to very low blood pressure may lead to cerebral ischemia and damage to the myelin sheath (159, 160). Second, the non-high-density lipoprotein cholesterol plays a crucial role in maintaining the integrity and function of brain cells and the myelin sheath, and thus the lower level of non-high-density lipoprotein cholesterol might be associated with worsening of brain health (161). Finally, hypoglycemia may influence glucose transport and metabolism, which can result in neuronal damage; hypoglycemia is even associated with stroke (162). Therefore, it is essential to adjust goals of CVH metrics based on the individual's health status and chronological age. Further research is needed to establish CVH goals specified by age, develop guidelines to optimize brain health, and mitigate the risk of cognitive decline and dementia in the older population. Furthermore, we have not observed any significant relationship between favorable biological CVH profile and other markers of brain aging, which strengthens the relatively higher sensitivity of WMHs in response to the different levels of CVH status compared to the other MRI markers of brain aging.

So far, there is no coherent evidence to suggest that individual CVH metrics can modify the genetic risk of brain aging. One longitudinal study found that physical activity could reduce cognitive decline attributable to carrying the *APOE*-ε4 allele (163). However, the follow-up data from the UK Biobank did not support the view (164). Nonetheless, it is important to view CVH metrics as a whole when analyzing their contribution to slowing down brain aging, given the complex interplay between these individual metrics. It is noteworthy that the composite CVH metrics could modify the relationship between metabolic genetic risk and WMH

accumulation. Individuals with favorable CVH profile may have experienced a slower WMH accumulation attributed to high metabolic genetic risk compared to those with unfavorable-to-intermediate CVH profiles. From the public health perspective, this finding highlights the potential impact of promoting and prioritizing an ideal CVH level for people at high risk for vascular brain aging and potential cognitive deterioration.

5.2.5 Cognitive reserve and transitions of cognitive phenotypes

The cognitive benefits of higher CR capacity could be mainly explained from two perspectives: neural reserve and neural compensation (165, 166). Specifically, individuals with higher CR capacity possess a higher intrinsic brain network connectivity (higher neural reserve capacity) and may be better able to tolerate brain pathology without experiencing evident cognitive impairment (166). In addition, individuals with higher CR capacity may exhibit alternative neural pathways that take over the tasks performed by those affected by damage or age-related brain changes. This neural compensation capacity helps to maintain cognitive function in the presence of a great pathological load in the brain (165). The association between higher CR capacity with lower risk of transition from normal cognition to CIND in our study is consistent to the findings in a previous study that greater CR capacity is related to a lower risk of MCI (17). In addition, we found that the cognitive contribution of higher CR capacity appeared to be independent of MRI markers of pathological brain aging, which was overall in line with the finding from the community-based Rush Memory and Aging Project (14). Further research may help clarify whether and to which extent the CR capacity could compensate for the detrimental effects of brain pathology on cognitive function.

Current evidence is still mixed regarding whether the higher CR capacity is no longer cognitively protective after the onset of CIND or MCI. For example, the Nun Study using data on religious sisters (mean age: >75 years, mean follow-up period: 8.6 years), has found that higher CR capacity is associated with a higher likelihood of reversion from MCI to normal cognition than the likelihood of progression from MCI to dementia (18). In addition, data from the population-based Rush Memory and Aging Project (means age: 79 years, mean follow-up period: 5.2 years) have suggested that higher CR capacity is related to a reduced risk of progression from MCI to dementia (14). However, data from the cohort of Biomarkers of Cognitive Decline Among Normal Individuals (mean age: 57 years, mean follow-up period: 12 years) show that higher CR capacity is associated with a faster cognitive decline after the onset of MCI (167). In Study IV, the greater CR capacity is not associated with the slower cognitive decline after the stage of CIND. This phenomenon may be explained by the fact that people with CIND usually display more evident brain atrophy that those with normal cognition (168), and that high CR capacity may not be able to protect against further cognitive decline when the brain pathology reaches a severe stage or threshold (106). Consistent with our finding, data pooled from six cohort studies show that the higher educational attainment, as a CR proxy, is related to a reduced likelihood of transition from normal cognition (MMSE score $\geq$ 27) to mild impairment (23 $\leq$ MMSE score $\leq$ 26). However, there is no significant association between educational attainment and the likelihood of transition from mild impairment to severe impairment (MMSE score $\leq$ 22) (169). Overall, the idea of promoting CR capacity through

lifestyle interventions may be most effective in the early stages of brain aging, emphasizing the importance of early interventions.

Higher CR capacity is related to a reduced risk of transition from normal cognition or CIND to death. Greater levels of CR proxies such as engagement in leisure activities and social networks have been linked to a lower risk of chronic diseases and depression (170, 171), which, in turn, could contribute to a reduced mortality (172). Moreover, emerging evidence from both existing literature and our own study suggests that the higher CR capacity is associated with better cognitive health (173), subsequently reducing the mortality rate (174). In people with CIND, the association of higher CR capacity with lower mortality rate is pronounced among individuals in the earlier stage of old age (60–72 years) but not among those in the later stage of old age (≥78 years). Older individuals compared to younger individuals have usually reached an advanced stage of cognitive impairment, which was demonstrated to be related to a higher mortality (175). It also suggests that the beneficial effects of higher CR capacity on mortality may be more evident in the earlier stages of cognitive decline or impairment. Higher CR capacity may have a diminished impact on mortality outcomes in older people who stay in the prodromal stage of dementia.

5.3 Methodological considerations

This doctoral thesis is based on four population-based observational studies. The methodological considerations in the population-based studies primarily include systematic and random errors. The systematic errors may arise from initial design to data collection and analysis stages, which may affect the validity and reliability of the study findings. It mainly involves selection bias, information bias, and confounding bias. Unlike systematic errors, random errors lead to random data variability, which might be due to the limitations in measurement instruments or sample size.

5.3.1 Selection bias

Selection bias occurs when the study sample is not representative of the target population, as a result, the study sample does not accurately reflect the characteristics of the broader population. It usually happens when the study oversamples a certain subgroup of population to a greater extent. During the initial recruitment stage of the SNAC-K project, our focus was on older adults in the Kungsholmen area of central Stockholm. It is crucial to recognizing that this sample may not be fully representative of the entire older adult population. For example, older adults in the Kungsholmen area differ from those in other regions, in terms of socioeconomic status, access to healthcare, and access to intellectually stimulating activities. This may lead to a discrepancy between the actual and observed cognitive functioning and CR-enhancing activities, and further lead to an underestimated association between brain aging markers and cognitive functioning in Study II and the underestimated association between CR capacity and cognition in Study IV. In addition, the MRI sample is younger, healthier, and less likely to be exposed to vascular risk factors compared with the whole SNAC-K sample, and thus, may have a lower burden of brain aging markers. This may lead to an underestimated progression rate of brain aging markers in Study I, an underestimated association between WMHs and cognitive functioning in Study II, and an underestimated association between CVH metrics and brain

aging in Study III. Finally, during the follow-up period, older adults with more chronic diseases and higher cardiovascular mortality are less likely to be included in the study. Therefore, findings from our study might not be generalizable to older populations residing in various geographical regions or with diverse sociodemographic features. Future studies are warranted to include more heterogeneous populations.

5.3.2 Information bias

Information bias arises when the means for obtaining information are inadequate, leading to the fact that the exposure or outcome variables are not completely true. It includes differential and non-differential misclassifications of variables of interest. The differential misclassification bias is resulted from the non-random classification which is associated with some variables of interest. In this project, this bias may arise when collecting data on lifestyle factors and CR indicators. Specifically, when the trained staff inquired the participants about their lifestyles, which are related to the key variables in Study III and Study IV, those with unhealthy lifestyles such as unbalanced diet, might not have provided accurate information due to some social concerns (176). This potential information bias could result in underestimating the true prevalence of unhealthy lifestyle behaviors in the study sample. To mitigate this bias, researchers could stress the anonymous nature and ensure the confidentiality of the surveys.

Furthermore, the non-differential misclassification bias occurs when the misclassification is not related to any exposure or outcome variables. The collection and assessment of brain aging MRI markers in the project may have led to the non-differential misclassification bias. Specifically, MRI images with sub-optimal quality due to technical issues or insufficient cooperation of the participant (e.g., head motion artifacts), were excluded during the data analysis phase. As a result of this exclusion, these participants with either a healthy brain structure or a pathological brain structure would not be included in the analytical sample. This exclusion would potentially result in a potential misestimation of the actual severity range of structural brain pathology in Study I and Study II. In addition, the unavailability of all metabolism-related genes could have constrained the possibility to detect more robust associations between metabolic genetic risk and structural brain aging in Study III. Furthermore, the assessment of brain aging markers, especially the visual assessment of WMHs, PVSs, and lacunes, might be susceptible to the rater's subjective judgement. However, it is worth noting that the rater has strictly followed the validated criteria and protocols and repeated the assessment work in a random sub-sample, which could minimize the non-differential misclassification bias.

5.3.3 Confounding bias

Confounding bias arises when the relationship between an exposure and an outcome variable is distorted by a factor that affects both the exposure and outcome variables. The variable which is associated with both the exposure and outcome variables, but not a direct result of the exposure variable is usually seen as a confounding variable in statistical analysis. In our project, confounding by socioeconomic status, vascular risk factors, or *APOE*-ε4 is a possibility. Specifically, proxies of socioeconomic status and vascular risk factors were not directly modelled as exposures in Study I and study II; instead, they were adjusted for as covariates (confounders) to limit their potential confounding effect. The *APOE*-ε4 allele was also

considered a confounder in Study II and study IV. In addition, we implemented the analysis stratified by *APOE* genotypes, whenever appropriate, to minimize the impact of confounders.

However, complete avoidance of confounding bias in the project is not possible to achieve due to the imperfect assessment of some confounders and the lack of some potential confounders. For example, some MRI measures of structural brain aging, such as cerebral microbleeds and microinfarcts, are associated with cardiovascular risk factors (177, 178), cognitive decline (178, 179), and MRI markers of structural brain aging which were assessed in our project (6). The lack of these MRI measures may have introduced challenges in accurately assessing the association of WMHs with cognitive decline in Study II, and the role of CR capacity in transitions of cognitive states in Study IV. Future research is warranted to incorporate a broader range of imaging measures of brain aging.

5.3.4 Random errors

Random errors in population-based studies arise from the intrinsic variability in the measurement process. In our project, we have taken several measures to mitigate these errors effectively. First and foremost, we employed a team of highly trained staff dedicated to collecting accurate and precise data. Additionally, a rigorous data quality check procedure was implemented to identify and rectify any potential errors. In cohort studies, the effect of random errors may be reduced by extending the sampling size and prolonging the follow-up period during the initial stages of study design. This may help to enhance the statistical power and generate more reliable results.

6 Conclusions

This doctoral project has provided insights into the progression of structural brain aging and its relationship with cognitive decline and the roles of CVH metrics and CR capacity in brain aging. The main conclusions are summarized below.

- The rate of structural brain aging accelerates with advancing age. Furthermore, cerebral microvascular lesions are associated with accelerated brain atrophy in structural brain aging.
- WMHs, a hallmark of structural brain aging, are linked to an accelerated decline in multiple cognitive domains, except for memory. Faster accumulation of WMHs, particularly in deep brain regions, is associated with an accelerated decline in perceptual speed and executive function.
- The favorable CVH profile is associated with a slower progression of structural brain aging and could mitigate the effects of metabolic genetic risk on structural brain aging.
- Having a great CR capacity could contribute to maintaining cognitive health in the prodromal phase of dementia, regardless of burdens of structural brain aging. In people with CIND, the higher CR capacity is associated with a lower mortality rate in individuals in the earlier stage but not the later stage of old age.

7 Points of perspective

This doctoral project has contributed new knowledge to the current literature regarding the progression of pathological brain aging and the complex interplay among CVH metrics, metabolic genetic risk, and composite CR capacity in structural brain aging and cognitive transition in aging. These findings have potential implications that can inform future directions in research and policy development.

Key findings from this project highlight the importance of CVH profiles and metabolic genetic predisposition in structural brain aging as well as the significance of lifelong CR capacity in late-life cognitive phenotypes. Reducing cerebral microvascular lesions in older individuals by promoting healthier lifestyles becomes crucial for maintaining cognitive function, thus enhancing overall well-being. Moreover, the research findings emphasize the need of enhancing CR capacity from the life-course perspective. This knowledge has implications for policymakers to develop public policy on mental and physical health in old age, to establish health educational programs, and to implement lifestyle interventions. This will eventually help the public to achieve healthy structural brain aging and cognitive health in aging.

These insightful findings also pave the way for future research, in terms of the following aspects:

- Integrating structural brain aging markers with aging biomarkers of peripheral and cerebral neuronal systems (vascular and neurodegenerative pathology) to study brain aging and cognitive outcomes, as well as better understand mechanisms of CR.
- Verification of the findings among diverse populations.
- Exploring the burden and development of certain brain aging markers such as microinfarcts and cerebral microbleeds in relation to cognitive decline or phenotypes in aging.
- Proposing age-specific CVH goals in order to provide valuable insights into maintaining brain and physical health, particularly in the very old population.
- Investigating whether improving CVH status or enhancing CR capacity through lifestyle adjustments can slow down the brain aging process in longitudinal interventional studies.

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to cognitive decline and hippocampal structure and function in healthy aging. Curr Alzheimer Res. 2012; 9:436-46.

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10 Appendix

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991–2023.

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly—Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and

utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia—Pre- and post-death experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.

Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Westerbotn Margareta. Drug use among the very old living in ordinary households- Aspects on well-being, cognitive and functional ability.

Rehnman Jenny. The role of gender in face recognition. (Stockholm University)

Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.

Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.

Livner Åsa. Prospective and retrospective memory in normal and pathological aging.

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.

Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

Svärd Joakim. Emotional facial processing in younger and older adults.

Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.

Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.

Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.

Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.

Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.

Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.

Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.

Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018

Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.

Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.

Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.

Sjöberg Linnea. Using a life-course approach to better understand depression in older age.

Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

2019

Seblova Dominika. Causal effects of education on cognition – How do we generate evidence?

Berggren Rasmus. Cognitive development and educational attainment across the life span.

Vetrano Davide Liborio. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.

Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.

Pan Kuan-Yu. Impact of psychosocial working conditions on health in older age.

Avelar Pereira Bárbara. Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging

Morin Lucas. Too much, too late? Drug prescribing for older people near the end of life.

de Boer Lieke. Dopamine, decision-making, and aging: Neural and behavioural correlates.

Ek Stina. Predictors and consequences of injurious falls among older adults: A holistic Approach.

Ding Mozhu. The role of atrial fibrillation in cognitive aging: a population-based study

2020

Dintica Cristina Silvia. Oral health & olfactory function: what can they tell us about cognitive ageing?

Payton Nicola Maria. Understanding preclinical dementia: early detection of dementia through cognitive and biological markers.

Li Xin. The relation among aging, dopamine-regulating genes, and neurocognition.

Grande Giulia. Development of dementia in older adults: the body-mind connection.

2021

Shang Ying. How can older adults combat diabetes to achieve a longer and healthier life?

Sif Eyjólfsdóttir Harpa. Unequal tracks? Studies on work, retirement and health.

Sundberg Louise. Better all the time? Trends in health and longevity among older adults in Sweden.

2022

Saadeh Marguerita. Enjoying life and living healthier: impact of behavioral and psychosocial factors on physical function in old age.

Naseer Mahwish. Why do older adults seek emergency care? The impact of contextual factors, care, health, and social relations.

Guo Jie. Unraveling the relationship between body mass index and cardiometabolic disease, dementia, and survival in old age.

2023

Wu Jing. Ambient Air Pollution and Transportation Noise: How They Affect Mental Health in Older Adults.

Frisendahl Nathalie. Injurious falls in older adults: early identification of individuals at risk of falls—from observational studies to implementation.