Cerebral small vessel disease: early life antecedents and long-term implications for the brain, aging, stroke and dementia.

Hypertension

REVIEW

Cerebral Small Vessel Disease: Early-Life Antecedents and Long-Term Implications for the Brain, Aging, Stroke, and Dementia: Dementia Series

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ABSTRACT: Cerebral small vessel disease is common in older adults and increases the risk of stroke, cognitive impairment, and dementia. While often attributed to midlife vascular risk factors such as hypertension, factors from earlier in life may contribute to later small vessel disease risk. In this review, we summarize current evidence for early-life effects on small vessel disease, stroke and dementia focusing on prenatal nutrition, and cognitive ability, education, and socioeconomic status in childhood. We discuss possible reasons for these associations, including differences in brain resilience and reserve, access to cognitive, social, and economic resources, and health behaviors, and we consider the extent to which these associations are independent of vascular risk factors. Although early-life factors, particularly education, are major risk factors for Alzheimer disease, they are less established in small vessel disease or vascular cognitive impairment. We discuss current knowledge, gaps in knowledge, targets for future research, clinical practice, and policy change. ***(Hypertension.* 2023;80:00–00. DOI: 10.1161/HYPERTENSIONAHA.122.19940.)** •

Key Words: cognition ■ education ■ epidemiology ■ policy ■ socioeconomic factors

Cerebral small vessel disease (SVD) refers to a syndrome of clinical and neuroimaging findings in the white and subcortical gray matter resulting from pathologies in the small perforating cerebral arterioles, capillaries, and venules, manifesting on computed tomography or magnetic resonance imaging or pathology examination as white matter hyperintensities (WMHs), small subcortical infarcts, lacunes, enlarged perivascular spaces, microbleeds, and atrophy.[1,2] Clinically, SVD presents as ischemic and hemorrhagic stroke, gait and balance dysfunction, and behavioral and neuropsychiatric symptoms. It is the leading cause of vascular cognitive impairment (VCI), responsible for up to 45% of dementias either as vascular or mixed with Alzheimer disease[3] (AD), affecting all major cognitive domains.[4]

SVD is often attributed to common vascular risk factors, particularly hypertension, smoking, and diabetes,[5] but the proportion of variance of SVD lesion burden explained by these risk factors combined is small (≈2%),[6] and risk factor modification clinical trials have so far had limited effects on preventing recurrent stroke, cognitive decline, and WMH progression (eg, the Secondary Prevention of Small Subcortical Strokes Trial [SPS3] trial[7]). Furthermore, although WMHs are considered a primary pathology in VCI[8] with a dose-dependent effect on cognition, risk of cognitive decline in those with WMHs varies considerably,[9] suggesting other factors contribute to SVD pathology and associated cognitive decline and dementia.

Growing evidence about protective factors for SVD, stroke, and dementia emphasizes a life-course model with a key role for early-life factors. The World Health Organization identified a life-course approach as a priority for policy action in the Health 2020 framework[10] and in their intersectional global action plan for optimizing brain health across the life course.[11] In 2020, reports by the World Health Organization–United Nations Children's

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Nonstandard Abbreviations and Acronyms

AD	Alzheimer disease
SES	socioeconomic status
SVD	small vessel disease
VCI	vascular cognitive impairment
WMH	white matter hyperintensity

Fund (UNICEF) –Lancet Commission and the Lancet Commission on Dementia Prevention highlighted the lifelong, intergenerational benefits of investment in children's health and early development including reducing preterm birth, poor nutrition and growth, prioritizing education for all, and reducing deprivation and inequality.[12,13] The Lancet Commission advocated for an approach to dementia prevention focused on enhancing cognitive resilience in later life by building cognitive reserve earlier in life.[13]

Reserve explains individual differences in clinical status in relation to neuropathology.[14] An individual may be able to sustain cognitive function despite SVD pathology due to a larger brain or synapse count (brain reserve), reduced brain pathology over time (brain maintenance), or more efficient brain networks that are less susceptible to disruption (cognitive reserve).[14] Established determinants of reserve include early-life cognitive ability (IQ), education, and occupation, but other factors operational during childhood, which may impact reserve, include an adverse prenatal environment (eg, due to maternal smoking, preeclampsia, or fetal growth restriction), perinatal brain injury, suboptimal childhood nutrition, a heightened stress environment, and socioeconomic deprivation (Figure).[15,16]

In this review, we summarize current evidence for early-life effects on SVD, stroke, and dementia focusing on epidemiological studies of prenatal nutrition, early-life cognitive ability, education, and childhood socioeconomic status (SES).

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Following several landmark studies, Barker determined that the period from conception to birth, and the first few years of life, is critical in influencing disease susceptibility throughout life. According to the developmental origins of health and disease hypothesis, adverse intrauterine environmental exposures including stress and poor nutrition can induce permanent changes in fetal development, which, in combination with exposures during childhood and adulthood, increase vulnerability to chronic diseases in adulthood.[17]

Direct study of the intrauterine environment is challenging, but birthweight, standardized by gestational age and sex, reflects fetal growth, which is a reliable proxy of favorable or unfavorable conditions. Barker found people with lower birthweight, due to poor fetal growth rather than prematurity, had higher risk of cardiovascular disease and vascular risk factors in adulthood.[18]

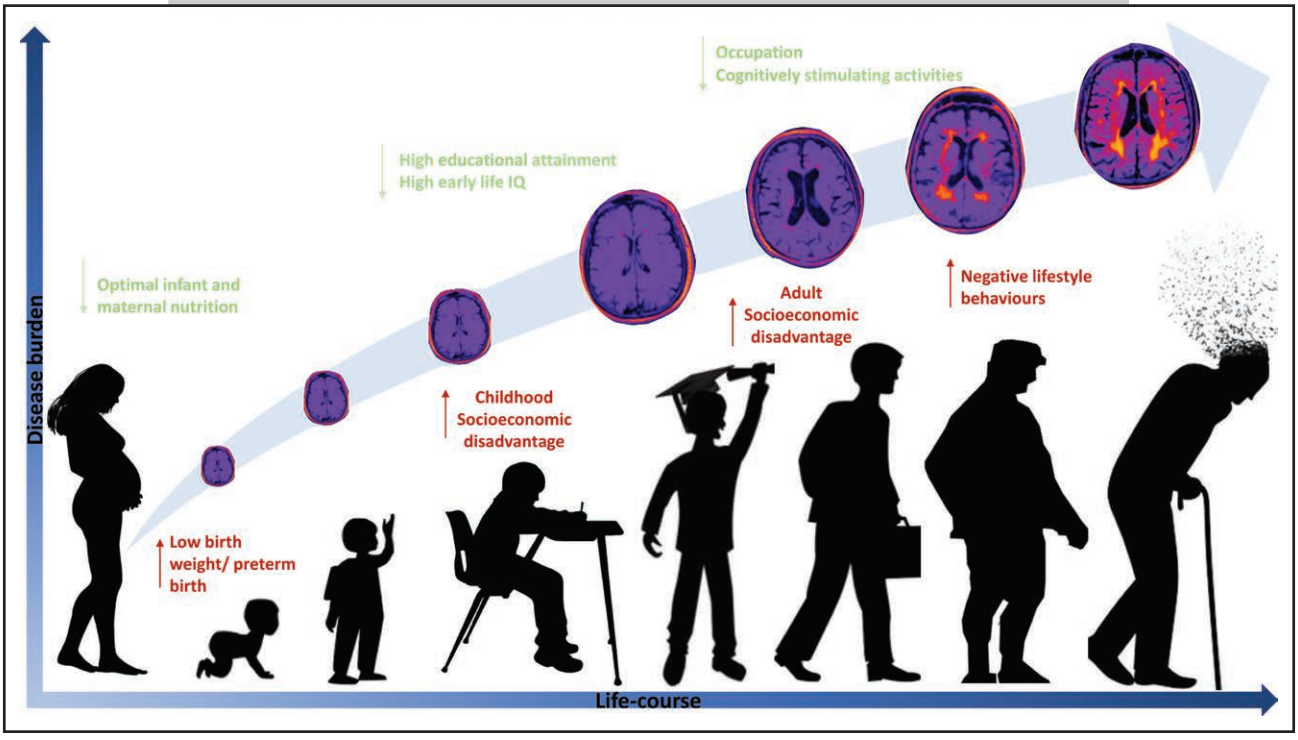

Figure. Protective and susceptibility factors for small vessel disease, stroke, and dementia.

Epidemiological studies have subsequently confirmed these findings, and relations between size at birth and disease in later life, particularly cardiovascular disease, are now well established.

Periods of famine, such as the Dutch famine of 1944 to 1945 and the Chinese great famine of 1959 to 1962, have revealed direct adverse effects of restricted prenatal nutrition on health outcomes including increased vascular risk factors and a higher prevalence of cardiovascular disease.[19]

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE AND CEREBROVASCULAR DISEASE

Stroke

Despite ample evidence for the developmental origins of health and disease hypothesis in respect to cardiovascular disease and vascular risk factors, the potential role of early-life factors in CVD has received relatively little attention.

Large cohort studies report inverse associations between birth weight and stroke incidence and mortality[20–24] with hazard ratios ranging from 0.48 to 0.84 for every 1-kg increase in birth weight (Table 1).[21,22,24] Adjustment for confounders varies widely between studies, and none adjust for all relevant confounders likely to influence later CVD (eg, vascular risk factors, SES, education, and gestational age), meaning that the current findings may be inflated. The largest study (n>70 000) reported an 11% decrease in risk of nonfatal stroke for every 454-g increase in birth weight, independent of vascular risk factors.[20]

In the Dutch famine birth cohort, famine exposure did not increase the prevalence of stroke at 41 years of age[25] or mortality from CVD by 63 years of age.[26] In contrast, those exposed to the Chinese great famine were more than twice as likely to have a stroke by 50 years of age compared with unexposed participants, independent of vascular risk factors.[27] This may be because the Chinese famine was more severe and occurred in a previously undernourished population or may be due to methodological differences between studies.

Importantly, in all of these studies, the participants were relatively young (<65 years) at assessment, yet the median age for stroke is 73 years, and incidence rises with age.[28] Further research is needed to determine whether stroke risk conferred by birthweight increases with advancing age.

Few studies have examined other prenatal exposures such as smoking, alcohol, preeclampsia and gestational diabetes, and later-life CVD. These exposures are associated with smaller brain volumes in children and adults[29] and increased blood pressure and stroke risk in adulthood in some,[30,31] but not all, studies.[32] However associations have not been examined in relation to other markers of SVD.

Small Vessel Disease

Mild variation in birthweight within the normal range, which reflects subtle variations in the intrauterine environment, predicts brain volume (reserve) and cortical configuration across the life course.[33,34] Less is known about the effects of birth weight or prenatal malnutrition on white matter microstructure and SVD in later life. We previously reported that birth weight was positively associated with white matter integrity in the frontal lobes aged 78 years[35] and normal appearing white matter volume,[33] independent of hypertension, but findings are inconsistent.[33,36,37] In community-dwelling older adults aged 59 to 81 years, lacunes, infarcts, and perivascular space severity decreased by 5% to 7% for every 100-g increase in birth weight independent of vascular risk factors, adulthood and childhood SES, education, and gestational age.[36] This is the only study to date to examine birth weight and markers of SVD on magnetic resonance imaging other than WMH burden and brain atrophy.

Brain tissue volume in later life is a product of maximal prior brain size, inferred from intracranial volume, and tissue loss occurring with age. Birth weight positively associates with total brain volume over the age of 50 years independent of body size and vascular risk factors,[33] and total brain volumes at the age of 68 years were smaller in famine-exposed compared with unexposed men.[37] However, these associations are not independent of intracranial volume, suggesting nutritional deficiency or poor fetal growth disrupts brain development in early life, resulting in a smaller peak brain volume, rather than increasing vulnerability to brain tissue atrophy in later life. Intracranial volume negatively associates with risk of mild cognitive impairment, AD, and VCI[38] and is often used as a proxy for brain reserve.[14]

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE, COGNITIVE IMPAIRMENT, AND DEMENTIA

Larger birth weight within the normal range is associated with better cognitive function from infancy through adulthood[39,40] independent of parental social class.[39] A systematic review of birth weight and later-life cognition concluded that effect sizes are small and there is insufficient adjustment for important confounders in several studies,[40] possibly explaining inconsistent findings between small studies[40] and larger population cohorts.[41] In a large Swedish twin study, every 100-g decrease in birth weight increased dementia risk by 2% independent of gestational age, education, and childhood SES, and

Table 1. Overview of the Key Papers Examining Associations Between Birth Factors, Early-Life Cognition, Education, and Childhood SES and Later-Life Stroke, SVD, and Cognitive Impairment

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Birth factors						
Stroke						
Rich-Edwards,[20] Nurses Health Study	Population cohort	n=70 297; 100% female participants; age, 30–55 y	Birth weight	Nonfatal ischemic or hemorrhagic stroke	There was an 11% decrease in risk of nonfatal stroke for every 454-g increase in birth weight*	Age, smoking behavior, hypertension, cholesterol levels, parental history of MI, diabetes, menopausal status, gestational age
Rich-Edwards,[21] Nurses Health Study	Population cohort	n=66 111; 100% female participants; age, 30–55 y	Birth weight	Nonfatal ischemic or hemorrhagic stroke	Higher birth weight associated with decreased risk of total stroke (per 1-kg increase in weight; HR, 0.84 [0.76–0.93]) and ischemic stroke (HR, 0.83 [0.71–0.96]) but not hemorrhagic stroke*	Age, BMI, gestational age
Eriksson (2000)	Hospital birth cohort	n=3639; 100% male participants; age, 45–64 y	Birth weight and length, head circumference	Fatal or nonfatal ischemic or hemorrhagic stroke	Lower birth weight associated with increased risk of fatal and nonfatal stroke (per 1-kg decrease in weight adjusted for head circumference; HR, 1.5). Associations were stronger for hemorrhagic stroke than ischemic stroke*	Adult SES and income, head circumference at birth, gestational age
Hyppönen[22]	Hospital birth cohort	n=10 853; %male/female participants, unclear; age, 67–81 y	Birth weight	Fatal or nonfatal ischemic or hemorrhagic stroke	Higher birth weight associated with decreased risk of stroke (for each 1-kg increase in birthweight and total stroke; HR, 0.59 [0.45–0.83]), occlusive stroke (HR, 0.93 [0.80–1.09]), and hemorrhagic stroke (HR, 0.59 [0.43–0.83])*	Sex, period of birth, social trajectory (consisting of childhood and adult SES), gestational age
Salmi and Hannawi[23]	Population cohort	n=4502; 40% male participants; age, 25+ y	Birth weight	Nonfatal ischemic or hemorrhagic stroke	Higher birth weight was associated with decreased risk of stroke (for 1-kg increase in birth weight; OR, 0.68 [0.48–0.99])*	Age, BMI, physical activity, smoking status, alcohol intake, adult SES
Lawlor et al,[24] Aberdeen Children of the 1950's Cohort	Population birth cohort	n=10 803; %male/female participants, unclear; age, 44–49 y	Birth weight	Fatal or nonfatal ischemic or hemorrhagic stroke	Higher birth weight was associated with decreased risk of stroke (for 1-kg increase in birth weight and stroke; HR, 0.48 [0.30–0.76])*	Age, childhood SES, maternal health factors (age, pregnancy-induced hypertension, antepartum hemorrhage, height), gestational age
Zhou et al,[27] Dutch Famine Birth Cohort	Population cohort	n=12 681; 48% male participants; age, 45+ y	Prenatal famine exposure	Nonfatal ischemic or hemorrhagic stroke	Severe but not less severe prenatal famine exposure associated with increased risk of stroke (vs unexposed OR, 2.87 [1.04–7.95])†	Time, sex, ethnicity, residence, childhood SES, childhood health status
Horenblas et al,[25] Dutch Famine Birth Cohort	Population cohort	n=2155; 50% male participants; mean age, 58 y	Prenatal famine exposure	Nonfatal ischemic or hemorrhagic stroke	No association between famine exposure and stroke‡	Sex
Crump (2021)	Population cohort	n=2 140 866; 54% male participants; age, 18–43 y	Preterm birth	Fatal or nonfatal ischemic or hemorrhagic stroke	HR for stroke and preterm birth (<37 wk), 1.26 (1.12–1.43); early preterm birth (22–33 wk), 1.42 (1.11–1.81); late preterm birth (34–36 wk), 1.22 (1.06–1.40); vs full-term births*	Age, sex, birth year, birth order, parental factors (age, education, birth country, BMI, smoking, hypertension, diabetes)

(*Continued*)

Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Kajantie (2015)	Population cohort	n=19 015; 53% male participants; age, 18–87 y	Preterm birth	Fatal or nonfatal ischemic or hemorrhagic stroke	No association between preterm birth and risk of stroke in adulthood‡	Childhood and adult SES (other covariates not specified)
SVD						
Backhouse et al[36]	Meta-analysis of 4 prospective birth cohorts	n=1993; 44.30% male participants; mean (SD) ages, 59.3 (10.1) to 78.4 (1.5) y	Famine exposure, birth weight	Total SVD burden; WMH; lacunes; PVS; CMBs; brain atrophy	Higher birth weight associated with fewer lacunes (per 100 g; OR, 0.93 [0.88–0.99]), fewer infarcts (OR, 0.94 [0.89–0.99]), and fewer PVSs (OR, 0.95 [0.91–0.99]). No association between famine exposure and SVD*	Age, sex, hypertension, smoking status, adult and childhood SES, education, premorbid IQ, gestational age
Shenkin et al,[35] LBC1921	Community cohort	n=107; 31% male participants; mean (SD) age, 78.4 (5.0, 75–81) y	Birth weight, placental weight, gestational age	Brain tissue volumes and WMH volumes; a gFA and PSMD	Birth weight significantly correlated with frontal FA (r=0.20). Placental weight significantly correlated with PVH (r=−0.24) and DWMH (−0.33), mean diffusivity in the centrum semiovale (r=−0.27) and FA in the frontal lobe (r=0.36)*	Age, sex, disease history, smoking status, blood pressure, HbA1c, cholesterol, triglycerides, gestational age
Muller (2014), AGES-Reykjavik Cohort	Population cohort	n=1254; 42% male participants; mean (range) age, 75 (69–82) y	Birth weight, birth length, ponderal index	Brain tissue volumes and WMH volumes	Lower birth weight, birth length, and ponderal index associated with decreased total brain (per SD decrease β=−13.4 [−6.4 to −8.2]), white matter (β=−5.9 [−2.8 to −4.0]) and gray matter volume (β=−7.2 [−3.4 to −4.2]) but associations lost statistical significance after adjustment for ICV†	Age, sex, education, smoking behavior, alcohol, hypertension, diabetes, hyperlipidemia, coronary artery disease
Wheater et al,[33] LBC1936	Population cohort	n=137; 54% male participants; mean (SD) age, 72.5 (0.7) y	Birth weight	Brain tissue volumes and WMH volumes; a gFA and PSMD	Higher birth weight associated with higher ICV (β=0.17) and higher total (β=0.26), gray matter (β=0.19), and normal appearing white matter volumes (β=0.29). Associations lost statistical significance after adjustment for ICV. No association between birth weight and DTI parameters, cortical thickness, or cortical volume†	Age, sex, ICV
Hulshoff (2000)	Hospital sample of patients with schizophrenia	n=18; 66.7% male participants; mean (SD) age, 51.06 (2.73) y	Famine exposure	WMH burden (not specified)	Prenatal famine exposure associated with increased WMH burden (data not shown)*	None
de Rooij et al,[37] Dutch Famine Birth Cohort	Population cohort	n=118; 44% male participants; mean (range) age, 68 (65–69) y	Prenatal famine exposure	WMH volume; FA, mean diffusivity; brain tissue volumes	In men only exposure to famine in early gestation associated with smaller ICV (vs unexposed males; MD, 50 [2–896] mL), total brain (MD, 57 [17–98] mL), gray matter (MD, 30 [6–53] mL), and white matter volumes (MD, 28 [4–52] mL). Associations lost statistical significance after adjustment for ICV. No association between famine exposure and DTI parameters or WMH volume. Birth weight positively associated with ICV and TBV†	Age, head circumference at birth and at the age of 68 y, ICV

(*Continued*)

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Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Franke et al,[42] Dutch Famine Birth Cohort	Population cohort	n=118; 44% male participants; mean (range) age, 68 (65–69) y	Prenatal famine exposure	BrainAGE: quantifies individual neuroanatomical aging in relation to age-specific atrophy patterns	Prenatal famine exposure in early gestation associated with older appearing brains in males by 4.3 y compared with unexposed males. There was no difference in women†	None
Cognition						
Krishna et al[40]	Systematic review of 11 studies (9 cohorts, 2 community studies)	Sample sizes ranged from 130 to 6875; %male/female participants, unclear; age, 50–89 y	Birth weight	A range of cognitive tests including memory, attention, and verbal fluency	8 studies reported associations between low birth weight and increased risk of cognitive impairment in later life, but effect sizes were small. No meta-analysis was performed*	10 studies adjusted for confounders (2 included age and sex only), of which 6 reported significant effects after adjustment
Mosing et al,[41] the Swedish Twin Registry, the Swedish NPR, the CDR	Population cohort	n=35 191; dementia sample, 47.8% male participants; cognitive impairment sample, 46.9% male participants. Mean (SD, range) age: dementia sample, 69.21 (8.83, 55–89) y; cognitive impairment sample, 68.36 (2.55, 65–74) y	Birth weight, head circumference, birth length, preterm birth	Register-based dementia diagnosis (n=35 191); cognitive impairment diagnosed using a computer-assisted telephone cognitive screening tool (subsample of participants, n=4000)	Those who were smaller at birth had increased risk of dementia diagnosis (low birth weight: HR, 1.22 [1.07–1.40]; birth weight per 100 g adjusted for gestational age: HR, 0.91 [0.85–0.98]; small head circumference for gestational age: HR, 1.65 [1.14–2.39]) and increased cognitive impairment (small for gestational age: OR, 1.73 [1.00–2.99]; small head circumference for gestational age: OR, 2.24 [1.45–3.46]). Twin analysis found no significant differences in effect sizes between monozygotic and dizygotic twins*	Age, sex, parity, age of mother at birth, birth SES, education, gestational age
Raikkonen (2013), Helsinki Birth Cohort	Population cohort	n=931; 100% male participants; mean (SD) age, 67.9 (2.5) y	Birth weight, birth length, head circumference	General cognitive ability: Finnish Defense Forces basic intellectual ability test	Lower birth weight (β=1.04), length (β=0.96), and head circumference (β=0.97) associated with lower cognitive ability (age, 67.9 y) and higher cognitive decline between age 20.1 and 67.9 y (per SD decrease in body size and cognitive decline, β=0.07, β=0.07, and β=0.06, respectively)*	Gestational age, mother's age and height, parity, childhood SES, breastfeeding, education, history of stroke and CHD
de Rooij et al,[43] Dutch Famine Birth Cohort	Population cohort	n=737; 47% male participants; age, 56–59 y	Prenatal famine exposure, birth weight	AH4 test, immediate recall and retrieval, Stroop task	Prenatal famine exposure in early gestation associated with lower scores on the Stroop task (β=−66) and slower response times (β=−0.3)*	Sex
de Groot et al,[45] Dutch Famine Birth Cohort	Population cohort	n=946; 44.70% male participants; mean age, 59 y	Prenatal famine exposure	General cognitive index: composite measure of a battery of cognitive tests	Prenatal famine exposure associated with a decrease of 0.57 (−2.41 to 1.28) points on the cognitive functioning index. Exposure in early gestation resulted in the highest decrease in the cognitive functioning index (4.36 [8.04–0.67] points lower than unexposed individuals)*	Age, hospital of birth, alcohol, smoking, test version
Wang et al,[47] Chinese Famine Studies	Population cohort	n=454; 51.32% male participants; age, 51–56 y	Prenatal famine exposure	MMSE, MoCA, logical memory test, Stroop test	Fetal exposure to famine associated with a 0.638-point decrease in MMSE score (β=−0.638) compared with unexposed participants*	Age, sex, education, lifestyle, medical history (not specified)

(*Continued*)

Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Kang et al[46]	Population cohort	n=6790; 40.9% male participants; mean (SD) age, 53.42 (1.13) y	Prenatal famine exposure	MMSE	Famine-exposed participants had lower scores on the MMSE than unexposed participants, but there was no difference in cognition between those exposed in gestation and those exposed in childhood‡	None
Early life cognition						
Stroke						
McHutchison et al[50]	Systematic review of 13 studies	n=1 209 952; %male/female participants, unclear; age, 33–77 y	Early-life IQ (6 studies) and premorbid IQ (3 studies)	Fatal or nonfatal ischemic or hemorrhagic stroke	Increased risk of stroke with low vs high childhood IQ (HR, 1.17 [95% CI, 1.00–1.37]; MD, 6.83 [95% CI, 2.11–11.55])*	5 studies adjusted for confounders, 1/3 reported associations between childhood IQ and stroke independent of vascular risk factors
Lawlor (2008), Aberdeen Children of the 1950s Cohort	Community cohort	n=11 125; %male/female participants, unclear; age, 56 y	Age 11 IQ	Fatal or nonfatal ischemic or hemorrhagic stroke	Higher early life IQ associated with decreased risk of stroke (HR, 0.68 [95% CI, 0.55–0.84])*	Age
Wennerstad (2010), Swedish Conscription 1951–1976	Population cohort	n=1 135 383; 100% male participants; mean age, 36 y	Early-life IQ	Fatal or nonfatal ischemic or hemorrhagic stroke	Higher childhood IQ associated with decreased risk of stroke (HR, 0.94 [95% CI, 0.92–0.96]).*	Age, childhood SES, BMI, blood pressure
Hemmingsson et al (2007), Swedish Conscription Study 1949–1951	Population cohort	n=44 495; 100% male participants; age, 40–55 y	Early-life IQ	Fatal or nonfatal ischemic or hemorrhagic stroke	No association between early life IQ and risk of stroke‡	Childhood and adult SES, crowded housing in childhood, height, parental CVD mortality, BP, smoking, alcohol consumption, BMI, education
SVD						
Backhouse et al[49]	Systematic review of 4 population studies and 1 community study	n=1512; %male/female participants, unclear; age, 45–84 y	Childhood IQ (4 studies) and premorbid IQ (1 study)	WMH burden (Fazekas or Scheltens scale)	Lower childhood IQ was associated with increased deep (r=−0.066 [0.129–0.003]) and periventricular (r=−0.12 [0.182 to −0.056] and total r=−0.07 [−0.12 to −0.12]) WMH scores*	1 study adjusted for vascular risk factors and reported a significant association
Backhouse et al[36]	Meta-analysis of 4 prospective birth cohorts	n=1993; 44.30% male participants; mean (SD) age, 59.3 (10.1) to 78.4 (1.5) y	Age 11 IQ	Total SVD burden; WMH; lacunes; PVS; CMBs; brain atrophy	Higher childhood IQ associated with lower WMH burden (per IQ point: OR, 0.99 [0.98–0.998]); fewer infarcts (OR, 0.98 [0.97–0.998]), fewer lacunes (OR, 0.98 [0.97–0.999]) and lower total SVD burden (OR, 0.98 [0.96–0.999]). After adjustment for education and childhood SES: total SVD burden OR 0.97–0.997; infarcts OR 0.98, 0.97–1.00.*	Age, sex, hypertension, smoking status, adult and childhood SES, education
Deary et al,[75] LBC1921	Community cohort	n=40; 52.5% male participants; mean age, 83 y	Age 11 IQ	Mean diffusivity, fractional anisotropy	Centrum semiovale FA correlated with age 11 IQ (r=0.37).*	Correlation unadjusted
Shenkin et al,[35] Scottish Metal Survey 1932	Community cohort	n=28; 46% male participants; mean (SD) age, 80 (0.4) y	Age 11 IQ; NART	Mean diffusivity, fractional anisotropy, magnetization transfer ratio	Childhood IQ and estimated premorbid IQ positively correlated with FA in the centrum semiovale.*	Correlation unadjusted

(*Continued*)

Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Wagen (2022), 1946 British Birth Cohort	Population cohort	n=502; 50.7% male participants; mean (SD, range) age, 70.7 (0.7, 69.2–71.9) y	Cognitive ability age 8, 11, or 15 y; educational attainment	Brain predicted age	No association between childhood cognition or education and brain age‡	Sex
Cognition						
Osler et al,[55] Danish Conscripts and Linkage With the Danish Twin Registry	Population cohort	n=666 986; 100% male participants; age, 57–78 y	Cognitive ability age 19 y	First hospital discharge or death from a main diagnosis of dementia	Low early life cognitive ability associated with increased risk of dementia (HR per SD decrease: all-cause dementia, 1.33 [95% CI, 1.31–1.56]; VaD, 1.47 [CI, 1.31–1.56]; AD, 1.07 [CI, 1.03–1.13]). In twin brothers: HR 1.36.*	Height, education, psychiatric hospital admission at conscription
McGurn (2008), 1921 Scottish Birth Cohort	Population cohort	n=173 dementia cases and 173 controls; 40% male participants; age, 66–82 y	Cognitive ability age 11 y	Diagnosis of VaD or AD	Higher childhood IQ associated with decreased risk of late onset VaD (OR, 0.62 [0.41–0.94], for every 10-point increase [0.7 SD] in cognition vs controls) but not AD.*	Participants and controls matched on age, sex, district of birth registration, and father's occupation
Fritsch (2005), CLASS	Population cohort	n=396; 44.9% male participants; mean (SD) age, 75 (1.0) y	Adolescent cognitive ability	MCI or dementia determined from a semistructured interview	Higher adolescent IQ associated with lower risk of dementia (for 1-SD increase in IQ: OR, 0.51 [0.32–0.79]) and MCI (OR, 0.46 [0.24–0.84]).*	Sex, activity level, education level
Huang (2018)	Population cohort	n=85 763; 50.2% male participants; age, 66–73 y	Adolescent cognitive ability	Diagnosis of AD and ARD	Low childhood IQ (men: OR, 1.17 [1.04–1.32]; women: OR, 1.17 [1.04–1.31]) and low general academic aptitude (men: OR, 1.18 [1.05–1.33]; women: OR, 1.19 [1.06–1.33]) were associated with increased risk of ADRD.*	Birth year, race, adolescent SES, region of school and region of residence in later life
Nyberg (2014), Swedish Conscripts	Population cohort	n>1.1 million; 100% male participants; mean age, 60 y	Cognitive ability age 18 y	Early-onset dementia and MCI	Lower early life IQ associated with early onset dementia and MCI (adjusted for covariates and parental education: HR, 4.11 [3.19–5.29] and 3.23 [2.12–4.95]; adjusted for covariates and own education: HR, 3.39 [2.60–4.42] and 2.47 [1.57–3.87]).*	Calendar year, BMI, region, conscription center, parental education, own education
Rantalainen (2018), Helsinki Birth Cohort	Population cohort	n=2785; 100% male participants; mean (SD, range) age, 67.9 (2.5, 64.5–75.7) y	Cognitive ability mean age 20 y	Diagnosis of dementia or AD divided into early onset (<65) or late onset (≥65)	Early life cognition predicted early onset but not late onset dementia or AD. Early onset dementia adjusted for age, father's occupation, mother's age at delivery, birthweight and parity HR 1.77; adjusted for age and education HR 1.47; adjusted for age and diagnosis of stroke or CHD HR 1.85†	Age at testing, birth weight, mother's age at delivery, parity, childhood SES, education, stroke, or CHD diagnosis
Whalley (2000), 1921 Scottish Birth Cohort (Aberdeen)	Community cohort	n=264; %male/female participants, unclear; age, 53–77 y	Cognitive ability age 11 y	Diagnosis of dementia divided into early onset (<65) or late onset (≥65)	Lower childhood IQ associated with late onset dementia (mean MHT, 29.6 [dementia] vs 36.2 [no dementia]) but not early onset dementia†	None
Russ (2017), LBC 1921	Community cohort	n=32 467; 50.4% male participants; age, 66–92 y	Cognitive ability age 11 y	Diagnosis of dementia after the age of 65 y	Low childhood IQ associated with an increased risk of dementia in women but not men (women per SD lower IQ score: HR, 1.13 [95% CI, 1.00–1.18])†	Childhood SES

(*Continued*)

Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Cognitive decline						
Richards et al,[57] The 1946 Birth cohort	Population cohort	n=2058; 48.8% male participants; age, 43 y at baseline	Cognitive ability age 15 y (AH4 test)	Decline in memory between ages 43 and 53 y measured using a word learning list and speed and concentration measured using timed visual search	Higher childhood cognitive ability associated with lower decline in memory (per unit increase in the AH4 men: β=0.16 [0.10–0.22]; women: β=0.15 [0.10–0.20]) and search speed (men: β=0.11 [0.05–0.17]; women: β=0.11 [0.05–0.18])*	Education, occupation, smoking, alcohol consumption, affective state, diastolic blood pressure, forced expiratory volume in 1 s
Staff (2018), Aberdeen Birth Cohorts of 1936	Community cohort	n=388; 49.5% male participants; age, 64 y at baseline	Cognitive ability age 11 y (Moray House Test No. 12)	Cognitive decline using the Rey AVLT	Higher childhood IQ correlated with cognition age 64 y (r=0.38) and was associated with less cognitive decline age 64–77 y (β=0.24) independent of education and childhood SES.*	Age, sex, practice effects on cognitive test, social mobility
Bourne et al,[56] Scottish Mental Health 1932 and 1947 Samples	Population cohort	SMS32: n= 91; 50.6% male participants; age, 77 y at baseline. SMS47: n=349; 47.6% male participants; age, 65 y at baseline	Cognitive ability age 11 y (Moray House Test No. 12)	Cognitive decline between ages 77 and 80 y (SMS32) and ages 65 and 67 y (SMS47) on the MMSE and Raven's progressive matrices	Childhood IQ predicted cognitive change between the 2 follow ups (all participants, β= 0.13). Children with lower IQ experienced cognitive decline between the 2 follow ups but children with higher IQ showed improved cognitive performance.*	Sex, education, occupation
Gow et al,[54] Lothian Birth Cohort 1921 and 1936	Community cohort	LBC1921: n=496; 46% male participants; age, 79 y at baseline. LBC1936: n=1028; 50.2% male participants; age, 70 y	Cognitive ability age 11 y (Moray House Test No. 12)	Cognition age 70 y (LBC1936) and cognitive decline between ages 79 and 87 y (LBC1921) measured using the MHT	Higher early life IQ was associated with cognition in later life but there was no association with cognitive decline.‡	Age, sex, adult SES, education, smoking, alcohol consumption
Ritchie (2016), LBC1921	Community cohort	n=1091; 50.2% male participants; mean (SD) age, 69.53 (0.83) y at baseline	Cognitive ability age 11 y (Moray House Test No. 12)	Wechsler adult intelligence scale age 69–76 y	No association between childhood IQ and later cognitive decline‡	Sex, education, childhood and adult SES, physical fitness, APOE status, vascular risk factors including hypertension and smoking
Gow (2012), Lothian Birth Cohort 1921, NSHD	Population cohort	LBC1921: n=548; 42.6% male participants; mean (SD) age, 79.1 (0.6) y at baseline. NSHD: n=3262; 49% male participants; age, 43 y at baseline	Early-life IQ (Moray House Test: age, 11 y/test of verbal and nonverbal fluency: age, 15 y)	Cognitive decline between ages 43 and 53 y (NSHD) and 79 and 87 y (LBC1921) using a battery of cognitive tests including Raven's progressive matrices	No association between early life IQ and cognitive decline‡	Sex, adult SES, education, smoking, alcohol consumption
Foverskov et al,[60] Danish Registry and Survey of Health, Aging and Retirement in Europe	Population cohort	n=2552 (854 men with early-life cognition data); 45% male participants; age, 63–66 y at baseline	Cognition in youth assessed at the conscript board examination	Cognition: episodic memory (immediate and delayed recall), executive function, and language (verbal fluency test)	Higher early life IQ associated with baseline cognition (β=1.48 [95% CI, 1.23–1.73]) but not rate of change‡	Sex, baseline age, years of follow-up
Education						
Stroke						
McHutchison et al[50]	Systematic review of 79 studies	n=2 881 067; %male/female participants, unclear; age, 33–77 y	Education: years or attainment	Fatal or nonfatal ischemic or hemorrhagic stroke	Less vs more education was associated with increased risk of stroke (OR, 1.35 [95% CI, 1.24–1.48]; MD, 0.66 [95% CI, 0.31–1.01]; HR, 1.33 [95% CI, 1.17–1.53]; RR, 1.35 [95% CI, 1.09–1.67]). This relative increase of 33%–39% was equivalent to an absolute increase in stroke of 3.5/1000*	31 papers reported adjusted results of which 16 adjusted for vascular risk factors. Adjusted studies only: OR, 1.32 (95% CI, 1.09–1.59); adjusted for vascular risk factors: OR, 1.25 (95% CI, 1.04–1.49)

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Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Xiuyun (2020), ARIC Study	Population cohort	n=11 509; 45% male participants; mean (SD, range) age, 54.0 (5.7, 45–64) y	Education: categorized into basic education (less than high school), intermediate education (high school degree or vocational school), and advanced education (attending or completed college or professional school)	Fatal or nonfatal ischemic or hemorrhagic stroke	Advanced education associated with 25% decrease in incident stroke (total stroke: HR, 0.75 [0.62–0.91]; ischemic stroke: HR, 0.73 [0.60–0.90]). No association with hemorrhagic stroke*	Age, race, sex, vascular risk factors including hypertension and diabetes, income
Gao (2021), UK Biobank, Social Science Genetic Association Consortium and META-STROKE Consortium	Population cohort	n=293 723; %male/female participants, unclear; age, >30 y	Education in years	Ischemic stroke	Higher education associated with decreased risk for stroke (for each SD increase in years of education [3.6 y]: OR, 0.54 [95% CI, 0.41–0.71])*	High blood pressure, high cholesterol, BMI, smoking behavior, alcohol consumption, coronary artery disease, type 2 diabetes
SVD						
Backhouse et al[49]	Systematic review of 26 studies	n=1512; %male/female participants, unclear; age, 45–84 y	Education: duration in categories (7 studies); attainment (12 studies), years (7 studies)	WMH burden (16 studies), microbleeds (4 studies), infarcts (4 studies), lacunes (2 studies), combined SVD markers (6 studies).	Fewer years of education was associated with higher WMH burden (OR, 1.24 [1.08–1.44]) and combined SVD markers (OR, 1.17 [95% CI, 1.05–131]) but not lacunes, microbleeds, or infarcts*	3 studies adjusted for vascular risk factors, and 2 of these reported significant effects
Backhouse et al[36]	Meta-analysis of 4 prospective birth cohorts	n=1993; 44.30% male participants; mean (SD) ages, 59.3 (10.1) to 78.4 (1.5) y	Education: divided into low (compulsory education, lower secondary, or ≤11 y) and high (more than compulsory, upper secondary and above, or >11 y)	Total SVD burden, WMH burden, lacunes, PVSs, cerebral microbleeds, brain atrophy	Low education was associated with more microbleeds (OR, 1.90 [1.33–2.72]) after adjustment for childhood IQ and SES (OR, 1.24 [0.71–2.18])*	Age, sex, hypertension, smoking status, adult and childhood SES, education, premorbid IQ, gestational age
Murray (2014), 1936 Aberdeen Birth Cohort	Population cohort	n=227; 47.6% male participants; mean age, 68 y	Educational attainment scored on a 9-point scale ranging from no qualifications (score 1) to professional or higher degree (score 9)	WMH burden (Schelten scale)	Higher educational attainment correlated with WMH (P=−0.17) and periventricular hyperintensities (P=−0.14)*	Correlations unadjusted
Cognition						
Does education modify the association between SVD and cognition?						
Dufouil (2003), The EVA Study	Population cohort of elderly subjects	n=845; 42% male participants; mean (SD, range) age, 68.9 (2.9, 64–76) y	Education: years divided into high education (<11 y) and low education (≥11 y)	SVD: WMH. Cognition: cognitive battery including MMSE and RPM and tests of attention, executive functioning and psychomotor speed.	No association between education and WMH severity but education modified the effect of WMH on cognition in that those with high education were protected against SVD-related cognitive impairment. There was an association between severe WMH and lower cognitive performance on all cognitive tests in those with low but not high education*	Age, sex, occupation, hypertension, alcohol consumption, history of vascular disease
Nebes (2006)	Community sample of older adults	n=141; %male/female participants, unclear; mean (SD, range) age, 73.2 (3.7, 65–80) y	Education: divided into those with a college degree and those without a college degree	SVD: WMH volume. Cognition: Wechsler Adult Intelligence Scale III; N Back test; listening span; Stroop Test	Significant interaction between total WMH volume and education on processing speed (F[2136], 3.20; P=0.04) in that processing speed more strongly negatively associated with WMH severity in less educated participants*	Analysis unadjusted

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Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Brickman (2011), WHICAP	Community sample of older adults	n=717; %male participants; mean (SD) age, 80.02 (5.56) y	Years of education	SVD: WMH volume, total brain volume, ICV. Cognition: large cognitive battery which measured memory, executive functioning/ speed and language.	Those with more education had higher WMH burden when controlling for cognition, suggesting that those with more education were better able to tolerate higher WMH burden than those with less education and that higher education mitigated the impact of WMH on cognition*	Age
Vemuri (2015), MCSA	Population cohort of healthy elderly	n=393; 54.7% male participants; age, 70–90 y	Composite measure of education and occupation	SVD: WMH volume and brain infarcts. Cognition: cognitive battery consisting of 9 cognitive tests assessing 4 cognitive domains (executive function, language, memory, and visuospatial).	Lower education associated with lower baseline cognition (β=0.26) but not cognitive decline. Those with higher education/occupation and SVD pathology performed better on the cognitive tests than those with lower educated/occupation with no pathology. It took 5 y for the cognitive performance of higher educated individual to decline to the baseline performance of a lower educated individual with less pathology*	Age, sex, time (y), amyloid pathway
Farfel (2013), Brazilian Aging, Brain Study Group	Autopsy	n=675; 47.7% male participants; mean (SD) age, 74.0 (11.7) y	Education: divided into those with nonformal education and those with ≥1 y of education	SVD: number/size of lacunar infarcts and SVD severity (assessed in 13 areas using a 4-point scale) identified at autopsy. Cognition: Cognitive ability assessed with the CDR sum of boxes (lower score indicating better cognition)	Each year of education associated with −0.197 unit lower CDR sum of boxes score (better cognition). Education modified the association between lacunar infarcts and cognition such that those with more years of education had lower risk of SVD-related cognitive impairment than those with less education*	Demographic factors including age at death, sex, SES, race, contact with the informant
Jokinen et al,[61] the LADIS Study	Population cohort	n=615; 42.5% male participants; mean (SD, range) age, 73.6 (5.1, 65–84) y	Education in years	SVD: WMH burden (Fazekas scale), lacunar and nonlacunar infarcts and visually rated atrophy. Cognitive battery including the MMSE, VADAS, Stroop test and trail making.	More education associated with higher cognition at baseline (eg, delayed word recall β=−0.20), slower cognitive decline at 3 y follow-up independent of WMH and lacunes (eg, delayed word recall β=−0.12), and sustained functional independence and lower mortality at 7 y follow-up. Education moderated the effect of WMH and lacunes on cognition such that higher education was associated with a weaker effect of WMH and lacunes on cognition at 3- and 7-y follow-up.*	Age, sex, study center, hypertension, diabetes, physical activity
Mungas et al[63]	Population cohort	n=460; 41% male participants; mean (SD) age, 74.5 y at baseline	Education in years	SVD: gray matter volume change. Cognition: SENAS	Brain atrophy had a stronger effect on cognition in those with more vs less education. In those with more education, cognitive decline over the 5-y follow-up was more strongly associated with brain atrophy than in those with less education. The rate of cognitive decline was also slower for those with more education and less atrophy but faster for those with more atrophy†	Age, sex, ethnicity, language of cognitive tests, APOE status

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Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Zahodne et al,[68] Washington Heights Inwood Columbia Aging Project	Community sample of older adults	n=1136; 43.2% male participants; mean (SD) age, 73.9 (5.68) y	Education in years	SVD: WMH volume. Cognition: Episodic memory, immediate and delayed recall and delayed recognition.	Education was not associated with WMH volume. Education attenuated the effect of WMH on cognition in those with less pathology but in those with more pathology, higher education was associated with worse cognition†	Age, age squared, race and ethnicity, chronic disease burden (sum of 13 conditions), APOE-e4 status
Durrani (2022), COMPASS-ND	Memory clinic cohort	n=200; 53% male participants; age, 50–90 y	Educational attainment defined as university degree vs technical school or less combined	SVD: high WMH burden (Fazekas score, 4–6) and brain infarcts. Cognition: cognitive battery including MoCA, and measures of executive functioning, visuospatial ability and verbal fluency	Education and SVD burden had independent noninteractive effects on cognition‡	Age, sex
Cognitive decline						
Zhang (2022)	Hospital cohort of patients with SVD-related cognitive decline	n=116; 48.84% male participants; mean (SD) age, 67.77 (10.11) y	Education in years	Cognition: MoCA	High education was associated with less SVD-related cognitive impairment compared with low education (OR, 0.88 [95% CI, 0.80–0.98])*	Hypertension, Hcy, SVD burden
Staff (2018), Aberdeen Birth Cohorts of 1936	Community cohort	n=388; 49.5% male participants; age, 64 y at baseline	Cognitive ability age 11 y (Moray House Test No. 12)	Cognitive decline between ages 64–77 y using the Rey AVLT	More years of education correlated with cognition age 64 y (r=0.28) and less cognitive decline between ages 64 and 77 y (β=0.84)*	Age, sex, practice effects on cognitive test, social mobility
Hotz (2021), LHAB Database	Population cohort	n=216; 49.1% male participants; mean (SD, range) age, 70.8 (64–87) y at baseline	Education divided into categories: secondary with/without apprenticeship; high schools and secondary technical schools, bachelor master or doctorate degree	Cognition: Global cognition (MMSE) and several measures of processing speed measured between age 70–77 y	University education was associated with higher processing speed at baseline and better performance over time compared with lower education*	Age, sex, antihypertensive medication, statin use, BMI, depressive symptoms
Foverskov et al,[60] Danish Registry and Survey of Health, Aging and Retirement in Europe	Population cohort	n=2552; 45% male participants; age, 63–66 y at baseline	Educational attainment divided into low (first and second stages of basic education), intermediate (upper and post-secondary), and high (first- and second-stage tertiary)	Cognition: episodic memory (immediate and delayed recall), executive function and language (verbal fluency test)	Higher education was associated with better cognition at baseline and slower cognitive decline over 10 y compared with low education (β=0.15 [95% CI, 0.02–0.27]) after adjustment for early-life IQ*	Sex, baseline age, years of follow-up
Zahodne (2015), Washington Heights Inwood Columbia Aging Project	Community sample of older adults	n=3435; 32.5% male participants; mean (SD) age, 76 (7.4) y	Education in years divided into low (0–8 y) and high (9–20 y)	Cognition: detailed cognitive battery assessing memory, language, visuospatial and processing speed	Those with high education had higher cognition at baseline (β=0.70) and slower decline over the 18-y follow-up (β=0.03). Dementia diagnosis was more common in the low education group than the high education group (25.9% vs 12%)*	Baseline age, sex, race, ethnicity, recruitment year, income, health status, depressive symptoms
Marioni (2014)	Population cohort	n=3653; 42.1% male participants; mean (SD) age, 75.3 (6.8) y	Education divided into categories: no education or a nonvalidated primary degree; a validated primary degree up to a nonvalidated secondary degree; a validated secondary degree or higher	Cognition: MMSE divided into 27–30 (no impairment), 23–26 (slight impairment), <23 (moderate/severe impairment)	High education associated with higher baseline cognition (medium vs low education: OR, 0.03 [0.00–0.10]) and lower risk of cognitive decline over 20-y follow-up (high vs low education: HR, 0.50 [95% CI, 0.30–0.70])*	Age, sex, occupation, social engagement

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Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Williams (2021), ELSA	Population cohort	n=5642; 46.3% male participants; mean (SD) age, 73.2 (7.2) y at baseline	Educational attainment: no formal qualifications; high school completion; sixth form completion; non–degree-level higher education; undergraduate degree or above	Cognition: Immediate recall and verbal fluency	Higher educational attainment was associated with higher baseline cognition but not cognitive decline‡	Age, sex, ethnicity
Zahodne (2011), Victoria Longitudinal Study	Population community dwelling	n=1023; 36.5% male participants; mean (SD, range) age, 68.9 (6.9, 55–85) y at baseline	Education in years	Cognition: composite scores of verbal processing speed, episodic memory, working memory.	Higher education associated with better performance on all 4 cognitive domains (eg, verbal fluency was associated with an 11% SD increase for each additional year of education). There was no association between education and the rate of cognitive decline over the 12-y follow-up‡	Sex, age at baseline
Poststroke cognition						
Makin et al,[65] Mild Stroke Study 2	Hospital cohort of stroke patients	n=157; 59% male participants; median (IQR) age, 66 (56–74) y	Education in years; premorbid IQ: NART	Cognition: Addenbrooke's Cognitive Examination-Revised	NART score correlated with cognition 3 mo poststroke (r=0.47). Lower NART score (per 1 point on the NART: OR, 0.91 [95% CI, 0.87–0.95]) and fewer years of education (per year of education: OR, 0.68 [95% CI, 0.48–0.87]) predicted 1-y cognitive impairment better than stroke severity and vascular risk factors*	Age, sex
Ojala-Oksala et al[66]	Hospital cohort of stroke patients	n=486; 50% male participants; median (IQR) age, 72.0 (11) y	Education: divided into 0–6, 7–9, and ≥10 y	Mild or moderate ischemic stroke	More education was associated with less memory impairment (OR, 0.67), aphasia (OR, 0.69) and visuospatial and constructive deficits (OR, 0.70), MMSE (OR, 0.53) and dementia (OR, 0.66), and increased poststroke survival (HR, 0.86)*	Age, sex, marital status, stroke severity, WML
Childhood SES						
Stroke						
McHutchison et al[50]	Systematic review of 10 studies (8 population studies, 1 hospital study, and 1 community study)	n=1 332 172; %male/female participants, unclear; age, 30–80 y	Childhood SES defined as father's occupation, education	Fatal or nonfatal ischemic or hemorrhagic stroke	Lower childhood SES was associated with increased risk of stroke (HR, 1.31 [95% CI, 1.03–1.68]; OR, 1.28 [95% CI, 1.12–1.46]). This was equivalent to an absolute increase of 0.3/1000 strokes*	3 studies adjusted for confounders, 2 adjusted for vascular risk factors of which 1 reported significant results
Zaborenko (2020), Health and Retirement Study	Population cohort	n=12 473; 43% male participants; mean (SD, range) age, 62.76 (0.17, 50–96) y	Childhood SES defined by parental education, paternal occupation, or perception of family finances	Nonfatal stroke	No association between childhood SES and risk of stroke (HR, 0.91 [0.74–1.12])‡	Age, race, marital status, education, wealth in adulthood, smoking status, alcohol intake, physical activity, depressive symptoms, and adult chronic diseases

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Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
SVD						
Murray (2014), 1936 Aberdeen Birth Cohort	Population cohort	n=227; 47.6% male participants; age, 68 y	Childhood SES indicated by parental occupation graded according to the UK Office of Population Statistics classification	WMH burden (Schelten scale)	Correlation between childhood SES and WMH (P=−0.18) and periventricular hyperintensities (P=−0.15)*	Correlations unadjusted
Backhouse et al[36]	Meta-analysis of 4 prospective birth cohorts	n=1993; 44.30% male participants; mean (SD) ages, 59.3 (10.1) to 78.4 (1.5) y	Childhood SES: divided into low (manual parental occupation) and high (nonmanual occupation)	Total SVD burden; WMH burden (Fazeka scale); lacunes; PVS; CMBs; brain atrophy	Low childhood SES associated with fewer lacunes (OR, 0.62 [0.40–0.95])‡	Age, sex, hypertension, smoking status, adult and childhood SES, education, premorbid IQ, gestational age
Cognition						
Lyu (2015), The Health and Retirement Study	Population cohort	n=9407; 41.07% male participants; age, >65 y	Childhood SES ascertained with father's and mother's education, father's occupation, and family financial well-being	Cognition: immediate and delayed free recall	At 12-y follow-up, women whose mother had low education had lower total memory scores (vs high education, β=−0.18). Males whose father had a blue-collar job had lower total memory scores (β=−0.37) at baseline independent of adult SES*	Race, ethnicity, childhood health, marital status, disability status, depression, chronic health conditions, smoking status, alcohol consumption, adult SES
Tsang et al,[84] Whitehall II, Health and Retirement study and the Kame Project	Population cohort	n=5324. %Male participants: Whitehall II, 72.8%; HRS, 41.88%; Kame Project, 43.5%. Mean age at baseline, 50–74.70 y	Parental; education, occupation, unemployment, and family financial hardship	Global cognition measured using the MMSE, TICS-m	Childhood adversity was associated with cognitive trajectory in adulthood. Those with lower childhood SES were more likely to belong to a more rapidly declining group than those with higher childhood SES*	Age, sex, education
Melrose (2014), UC Davis Aging Diversity Cohort	Population cohort	n=333; %male/female participants, unclear; mean (SD) ages, 71.47 (6.46) to 74.93 (6.76) y	Parental educational attainment, complexity of father's job, number of siblings, number of siblings who died before the age of 18 y	The Spanish and English Neuropsychological Assessment scale which measures episodic and sematic memory and executive function.	High vs low childhood SES associated with decreased global cognitive decline (first vs fifth quintile: β=−0.08)*	Ethnicity, education, sex, language of test, APOE status
Moceri et al[83]	Population cohort	n=484; 38.01% male participants; age, >60 y	Father's occupation (manual vs nonmanual), parental age, household size (<7 and ≥7), sibship size (<5 and ≥5), and birth order	Dementia as defined by the DSM III-R and probable AD according to the working group criteria of the NINDs and Stroke/Alzheimer's Disease and Related Disorders Association	Manual father's occupation (OR, 2.0 [1.2–3.3]) and larger household size (OR, 1.5 [0.9–2.4]) associated with increased cognitive decline independent of education*	Age, sex, APOE status, education
Lee (2003), Nurses Health Study	Population cohort	n=15 594; 100% female participants; age, 70–79 y	Father's occupation divided into 9 professional groups	Cognition: TICS, delayed recall, East Boston Memory test, verbal fluency, digit span backwards, global score calculated from these tests	There was a marginal increase in the odds of a low global cognitive function and more global cognitive decline for women whose fathers were farmers (vs white-collar workers: OR, 1.19 and OR, 1.25), independent of education and adult SES*	Age, education, husband's education, household income, vascular risk factors including smoking behavior, blood pressure, and diabetes
Zaninotto (2018), ELSA	Population cohort	n=10 626; 45.6% male participants; mean (SD, range) age: men, 64.6 (9.8, 50–100) y; women, 65.0 (10.2, 50–100) y	Paternal occupation at age 14 y divided into high, intermediate, or low	Battery of cognitive tests assessing memory, processing speed and executive function at baseline and ~8 y follow-up	Low childhood SES associated with lower memory (β=−0.07), executive function (β=−0.12), and lower global cognition (β=−0.08) but not cognitive decline†	Age, adult SES, education, cardiovascular disease, diabetes, physical functioning, BMI, smoking, alcohol, depression

(*Continued*)

Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Ericsson (2016), Swedish Twin Registry	Population cohort	n=859; 40.4% male participants; age, 65 y	Parental occupation classified according to the Swedish socioeconomic index	Cognition: global cognition, memory, language, processing speed, visuospatial ability measured using 8 eight cognitive tests	Childhood social class was associated with global cognition (β=1.55), memory (β=1.51), language (β=1.29), processing speed (β=1.26), and visuospatial abilities (β=0.40) independent of education but not cognitive change†	Sex, birth cohort, education, parental attitudes toward education
Sha (2018), CHARLS	Population cohort	n=10 533; 4706% male participants; mean (SD) age, 58.64 (8.77) y at baseline	Parental education divided into no schooling and capable to read or write; childhood residence divided into village vs town/city; childhood self-evaluated financial status on a 5-point scale	Telephone Interview of Cognitive Status; word recall; picture drawing task measured at baseline and 6 y follow-up	Higher parental education (β=0.17), higher childhood financial status (β=−0.22), childhood city (vs country) dwelling (β=0.69), and having a father not engaged in farming work (β=0.43) were associated with better baseline cognition but not cognitive decline†	Age, sex, marital status, hukou status, smoking, alcohol consumption, adult health status, activities of daily living, depressive symptoms, chronic health conditions
Davis (2017), British Birth Cohort	Population cohort	n=3192; 51% male participants; age, 43 y at baseline	Paternal education divided into ≤primary school vs >primary	Cognition: measures of visual search speed and verbal memory	Higher paternal education associated with higher verbal memory (β=0.52) and processing speed (β=8.35) at baseline but not cognitive decline†	Sex, childhood cognition age at 8 y, educational attainment, adult SES, blood pressure, BMI, diabetes, smoking, cancer, angina
Cermakova (2018), Survey of Health, Ageing and Retirement in Europe	Population cohort	n=20 244; 46% male participants; mean (IQR) age, 71 (8) y at baseline	Household characteristics aged 10 y	Cognition: verbal learning and delayed recall, verbal fluency, and global cognition	Lower childhood SES was associated with lower baseline cognition (global cognition: β=−0.27) but not cognitive decline over 5 y†	Age, sex, country of origin, education, cardiovascular disease, BMI, physical activity, depression, alcohol, smoking, occupation
Rogers (2009), the Aging, Demographics and Memory Study	Population cohort	n=892; %male/female participants, unclear; age, >70 y	Father's or mother's education divided into low (<8 y) and high (≥8 y)	Cognitive impairment or dementia diagnosed according to the DSM III-R by with a battery of neuropsychological tests, a standardized neurological examination and clinical history taken from a proxy informant.	Low maternal education associated with increased risk of dementia (vs high education: OR, 2.0 [1.10–3.80]); however, this lost statistical significance after adjustment for own education (HR, 1.6). No association between paternal education and cognition†	Paternal education, own education, age, APOE status
Gonzales (2013), Health and Retirement Study	Population cohort	n=8833; 40.7% male participants; mean (SD) age, 73.9 (0.1) y	Childhood SEP: father's and mother's education and overall childhood SES (5-point scale: 1, excellent; 5, poor)	Cognition: TICS	Higher childhood SES associated with higher initial cognitive function (eg, financial status: poor vs average, β=0.19). Associations between parental education and cognition lost statistical significance after adjustment for adult SES and health variables. There was no association between childhood SES and cognitive decline†	Age, sex, ethnicity, adult SES, adult health status, and chronic conditions
Maurice (2021), Lothian Birth Cohort 1936	Population cohort	n=519; 50.2% male participants; age, 69.8 (0.90) y at baseline, followed up at 72.8 and 76.7 y	Parental education (low, ≤9 y vs high, >9 y) and occupation (manual vs nonmanual), household crowding (>2 vs <2 occupants per room), and toilet location (exterior vs interior)	Cognition: MMSE	Higher maternal education was associated with lower cognitive decline (β=−0.13) between ages 69.8 and 76.7 y, but after adjustment for adult SES, this lost statistical significance†	Participants' education and occupation
Ritchie (2016), LBC1936	Population cohort	n=1091; 50.2% male participants; age, 70 y at baseline	Father's occupation rated on a 5-point scale from class I (professional) to class V (unskilled)	Cognition: battery of 13 cognitive tests assessing visuospatial ability, processing speed and verbal memory	There was no association between father's occupation and cognitive decline over 6 y‡	Education, adult SES, physical fitness, smoking status, alcohol, BMI, mood

(*Continued*)

Table 1. Continued

Author	Setting	Sample size, sex, and age	Early-life factor	Outcome	Key findings	Covariates
Are associations between childhood SES and cognition mediated by adult SES?						
Beck (2018)	Population cohort	n=1009; 100% male participants; age, 62 y	Parental education (coded on a 1–7 scale) and occupation (coded on a 0–9 scale) assessed individually and together as a SES composite score	Cognition: battery of 13 cognitive tests assessing abstract reasoning, visuospatial ability and verbal fluency and processing speed.	SES predicted cognitive functioning in late middle age (eg, higher SES and general cognition: β=0.08), but these associations were fully mediated by cognitive ability at age 20 y, adult SES, and engagement in cognitively stimulating activities*	Age, ethnicity, APOE status, physical activity, health, education, occupation, early-life cognition
Singh-Manoux et al,[86] Whitehall II Study	Population cohort	n=10 308; 66.89% male participants; age, 46–68 y	Composite measure of SEP measured using father's social class, parental education, and financial difficulties in childhood	Cognition: composite measure consisting of verbal memory, AH4-I, the Mill Hill vocabulary test, verbal fluency	High childhood SEP was associated with better cognitive performance in midlife, but associations were mediated through education and adult SES*	Participant education, occupation, income
Zhang et al,[81] Wisconsin Longitudinal Study	Population cohort	n=5880; 45.7% male participants; mean (SD, range) age, 64.8 (0.7, 63–67) y	Composite measure of parental education and occupation and household income	Cognition: battery of cognitive tests including immediate and delayed recall, verbal fluency and digit ordering.	Although childhood SES had direct and indirect effects on cognition in late midlife (β=0.07; direct effect, β=0.07; indirect effect, β=0.36; total effect, β=0.43), associations were largely mediated by educational attainment and CIQ, ie, childhood SES had a direct effect on adolescent cognition (β=0.07), which in turn had an effect on midlife cognition (β=0.55)†	Age, sex, marital status, number of children
Social mobility						
Faul et al,[85] Health and Retirement Study and ELSA	Population cohort	n=29 237. %Male participants: ELSA, 44.51%; HRS, 43.62%. Mean (SD) age: ELSA, 61.43 (9.37) y; HRS, 63.2 (10.36) y	Composite measure of parental unemployment in childhood, financial difficulty before the age of 16 y, and father's occupation (white collar vs not)	Cognition: episodic memory task	Higher childhood SES was associated with higher cognition at baseline (β=0.87; β=0.20) and cognitive decline (ELSA only; β=−0.10), but these associations lost statistical significance after adjustment for education and wealth. Upward social mobility between childhood and adulthood mitigated the impact of a low childhood SES on cognition*	Age, sex, marital status, race, practice effects, education, adult education, and wealth
Luo and Waite,[82] Health and Retirement Study	Population cohort	n=19 949; 43% male participants; mean (SD) age, 66.87 (10.40) y	Parental education (≥8 y), occupation (white-collar job), and financial situation in childhood	Cognition: TICS total score	Higher SES associated with higher cognitive function scores (β=0.24–0.40) independent of adult SES. Upward social mobility between childhood and adulthood mitigated the impact of a low childhood SES on cognition*	Age, sex, ethnicity, childhood health, adult SES

AD indicates Alzheimer disease; AH4, Alice Heim Test; ARD, Alzheimer disease–related disorder; ADRD, Alzheimer's Disease Related Dementias; AGES-Reykjavik, Age, Gene/Environment Susceptibility study; APOE, apolipoprotein E; ARIC, Atherosclerosis Risk in Communities; AVLT, Auditory-Verbal Learning Test; BMI, base metabolic index; BP, blood pressure; BrainAGE, The Brain Age Gap Estimation; CDR, Cause of Death Register; CHARLS, China Health and Retirement Longitudinal Study; CHD, coronary heart disease; CLASS, Cleveland Longitudinal Aging Studies of Students; CMB, cerebral microbleed; COMPASS-ND, Comprehensive Assessment of Neurodegeneration and Dementia; CIS, childhood IQ; CVD, cerebrovascular disease; DSM III-R, diagnostic and statistical manual of mental disorders volume 3 revised; DTI, diffusion tensor imaging; DWMH, deep white matter hyperintensities; ELSA, English Longitudinal Study of Aging; EVA, Epidemiology of Vascular Aging; FA, fractional anisotropy; gFA, general factor of fractional anisotropy; HbA1c, Hemoglobin A1C; Hcy, homocysteine; HR, hazard ratio; HRS, Health and Retirement study; ICV, intracranial volume; IQR, interquartile range; LADIS, Leukoaraiosis and Disability; LBC, Lothian Birth cohort; LHAB, Longitudinal Health Aging Brain; MCI, mild cognitive impairment; MCSA, Mayo Clinic Study of Aging; MD, mean difference; METASTROKE collaboration, Genetic risk factors for ischaemic stroke and its subtypes; MHT, Moray House Test; MI, myocardial infarction; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; NART, National Adult Reading Test; NIND, National Institute of Neurological Communicative Disorders; NPR, National Patient Register; NSHD, National Survey of Health and Development; OR, odds ratio; PSMD, peak width skeletonized mean diffusivity; PVH, periventricular hyperintensities; PVS, perivascular space; RPM, Ravens Progressive Matrix; SENAS, Spanish and English Neuropsychological Assessment Scales; SEP, socioeconomic position; SES, socioeconomic status; SMS, Scottish Mental Survey; SVD, small vessel disease; TBV, total brain volume; TICS, Telephone Interview of Cognitive Status; TICS-m, Modified Telephone Interview of Cognitive Status; VaD, vascular dementia; VADAS, Vascular Dementia Assessment Scale; WHICAP, Washington Heights/Hamilton Heights Inwood Columbia Aging Project; WML, white matter lesions; and WMH, white matter hyperintensity.

*Findings support an association between the early-life factor and later-life outcome.

†Findings partly support an association.

‡Findings do not support an association.

associations were not due to shared genetic or environmental factors.[41]

At 68 years of age, men, but not women, exposed to the Dutch famine had higher The Brain Age Gap Estimation (BrainAGE) scores, indicating premature brain aging.[42] Individuals exposed to famine also performed worse on selective attention tasks at the age of 56 to 59 years[43] and had more self-perceived cognitive problems at the age of 72 years,[44] but this is not supported by all studies.[45] The Chinese famine studies found prenatal famine exposure increased risk of mild cognitive impairment and dementia[46] and resulted in poorer performance on tasks of visuomotor skills, mental flexibility and attention, and lower general cognition at the age of 51 to 56 years independent of age and education.[47]

There are several plausible biological pathways through which early-life exposures may influence children's neurodevelopment and increase vulnerability to SVD, stroke, and dementia. These include disruption of metabolic processes underlying somatic and neural functioning and growth, altered DNA methylation, impaired white matter myelination and connectivity, fetal growth restriction, suboptimal postnatal nutrition, impaired immune defences, chronic inflammation, and neuroendocrine dysregulation.[48]

Overall, these findings suggest that the prenatal environment is an important contributor to later-life brain health. Birth weight is associated with later-life stroke and cognitive status, but whether these associations are independent of vascular risk factors is unclear. Few studies have examined associations between prenatal factors and SVD as a potential mechanistic pathway, and further studies are needed to clarify these associations.

CHILDHOOD RISK FACTORS FOR COGNITIVE IMPAIRMENT AND DEMENTIA

Early-life IQ, education, and deprivation are determinants of cognitive aging and are associated with general health, longevity, SVD, and stroke.[49,50]

PERINATAL BRAIN INJURY

Around 11% of the global population is born preterm[51] (<37 weeks of gestation). For those born very preterm (<32 weeks), there is a consistent association with a magnetic resonance imaging phenotype that includes diffuse white matter disease, deep gray matter volume reduction, altered cortical configuration, and subsequent neurocognitive deficits and behavioral problems.[52] Atypical brain structure persists into adolescence, and cognitive disadvantage programmed by preterm birth is stable into adulthood.[53] The oldest survivors of very preterm birth are now in their fourth to fifth decades: an important area for research is to determine whether atypical brain development and cognitive disadvantage conferred by preterm birth predict increased prevalence or earlier onset of SVD and other neurodegenerative diseases.

EARLY-LIFE COGNITIVE ABILITY

In general, cognitive ability is stable across the life course; people who score well on cognitive tests in childhood will likely score well into adulthood and old age, with correlations of 0.67 to 0.51 reported between cognition age 11 years and age 70 to 87 years.[54]

Lower early-life cognitive ability increases the risk of all-cause dementia, AD, and VCI independent of education (Table 1).[55] In Danish conscripts (n=666 986), lower early-life intelligence was associated with higher risk of AD (hazard ratio, 1.07) and VCI (hazard ratio, 1.47) by the age of 77 years. Intrasibling and twin analyses attenuated associations, suggesting genetic and environmental factors explain some, but not all, of this association.[55] On the contrary, whether early-life cognition influences cognitive decline is uncertain. In community samples, those with higher childhood IQ decline at a slower rate,[56,57] but this is not supported by all studies,[54] and it is unclear whether these associations are independent of vascular risk factors. In the 1946 British birth cohort, rates of cognitive decline were steeper in individuals with a lower intellectually enriching lifestyle.[58] There was no association between childhood and late-life cognition in those with an intellectually enriching lifestyle, suggesting factors such as education and occupation may modify the effect of early-life IQ on cognitive decline.

EDUCATION

Higher educational attainment is associated with better late-life cognitive functioning and reduced risk and a later onset of dementia. Meta-analysis found a 45% increased risk of dementia with low education and a 7% reduced risk for dementia for each additional year of education, although there was a wide variation of definitions of low education and inconsistent approaches to measuring education between studies.[59]

Higher levels of education predict slower rates of functional and cognitive decline in several,[60,61] but not all,[62] population and SVD cohorts (Table 1) independent of vascular risk factors, including hypertension, and childhood IQ. Although cognition is initially preserved in those with high education, when pathology surpasses a certain threshold, this protective mechanism may no longer be sufficient, and cognition may decline at an accelerated rate. In a 5-year longitudinal study, more years of education were associated with slower cognitive decline in those with low levels of age-related brain atrophy but faster cognitive decline in those with more atrophy.[63] In

patients with mild cognitive impairment and AD, education slows the rate of cognitive decline before diagnosis, delaying diagnosis by ≈9 years, but cognitive decline accelerates following diagnosis.[64] The role of early-life factors in the cognitive trajectories of people with VCI is unclear and has received relatively little attention compared with AD. This is important because premorbid cognition and education are major risk factors for stroke,[50] they predict cognitive impairment at 1 year after stroke better than more commonly included variables like stroke severity and vascular risk factors,[65,66] and account for some differences in VCI unexplained by known risk factors.[66]

Education and SVD may have independent effects on cognition,[67] but several studies suggest that education modifies the impact of SVD on cognition, such that those with more education are protected against SVD-related cognitive deterioration,[9] perhaps because education teaches alternative problem-solving strategies that ameliorate the impact of SVD on executive function. This may explain inconsistent associations between vascular pathology and cognition in some individuals. Jokinen et al[61] showed high education attenuated the association between WMH, lacunes, and cognition and predicted better cognition and slower cognitive decline, sustained functional independence, and lower mortality, independent of WMH volume and vascular risk factors, over a 7-year follow-up. However, in a community-based sample, education attenuated the effect of WMH on memory performance in those with less brain pathology, but it had the opposite effect in those with more pathology,[68] suggesting the protective effect of education on cognition may depend on the severity, type, and stage of the brain pathology.

Educational attainment is a potentially modifiable risk factor for dementia. Raising the school-leaving age has been associated with improved later-life cognition[69] and may partly explain the declining age-specific incident rates of dementia in many high-income countries.[13] Furthermore, older adults who undertake further education found a measurable increase in cognitive reserve,[70] but other studies suggest that additional education after 20 years of age has little effect on later-life cognition.[71]

In summary, higher early-life cognitive ability and more education protect against stroke and SVD independent of vascular risk factors. While these factors are also associated with better later-life cognition, associations with cognitive decline, particularly for early-life cognition, are inconsistent. Some studies suggest that higher education slows the rate of cognitive decline pre-dementia diagnosis and modifies associations between mild or moderate SVD and cognition but has the opposite effect in those with more advanced pathology, but further research, particularly in VCI, is needed to confirm these findings.

HOW MIGHT EARLY-LIFE COGNITIVE ABILITY AND EDUCATION INFLUENCE LATER-LIFE COGNITION?

Highly educated individuals, or those with higher premorbid cognition, may have higher cognitive reserve and be able to tolerate greater neuropathological changes before clinical symptoms occur, perhaps by recruiting alternate neural networks or utilizing existing networks more efficiently. Efficient information processing speed correlates with general intelligence and is thought to rely on the structure of the white matter tracts connecting distal brain areas and myelination.[72] Education predicts fiber tract structure in several brain areas, those with higher levels of education having more richly connected fiber tracts.[73] More years of education is associated with specialized use of neural processing and more efficient brain networks in older adults,[74] and white matter structure at 83 years of age correlates with age 11 IQ.[75]

Premorbid IQ and education may be a marker of brain resistance to age-related pathology such as SVD. Large-scale meta-analyses showed fewer markers of SVD with more education and higher premorbid IQ.[49] Education and early-life cognition could reduce susceptibility to brain pathology through reducing risk factors for disease; however, associations between childhood IQ and SVD were found to be independent of vascular risk factors and adult SES,[36] suggesting an effect of cognitive ability on brain pathology independent of adult vascular risk factors.

High levels of education or cognitive ability may be indicative of more brain reserve, evident in a larger brain or synapse count, which increase the threshold of pathological load required before the disease is clinically evident. Intelligence and brain size show a consistent modest correlation in both children and adults.[76] Age 11 IQ and education duration predict cortical thickness in later life, and age 11 IQ accounts for over two-thirds of the cross-sectional association between cognitive ability and cortical thickness in later life.[77]

CHILDHOOD SES

Socioeconomic disadvantage in childhood shapes neurodevelopmental and health outcomes from birth onward.[78,79] In childhood, brain structure mediates the relationship between SES and measures of function (eg, language, attention, and memory).[80] Children from higher SES households have access to more social and economic resources, which promote healthy development including cognitively stimulating home environments, healthier nutrition, and more stable living conditions.

Few studies have examined childhood SES and risk of stroke and SVD. In a meta-analysis, low childhood SES increases the risk of stroke (10 studies) and SVD (1 study),[49,50] but another study did not find an association

with SVD after adjustment for vascular risk factors and adult SES.[36] Childhood SES is associated with global cognition[81,82] in later life and may predict cognitive decline,[83,84] although findings are inconsistent[85] and few studies adjust for vascular risk factors (Table 1). Associations between childhood SES and late-life cognition may be mediated by educational attainment, early-life cognition, and adult SES[81,86] as early-life cognitive ability and education are closely related to SES, both in childhood and in adulthood,[87] but direct and independent effects of childhood SES on cognition[81,82,85] and cognitive decline[83,84] have been reported. SES is a complex and multidimensional construct that can be described at neighborhood or individual level. Measurement often varies between studies, and if only 1 measurement is considered, it may not always capture the full socioeconomic position of the individual.[79] Furthermore, SES is not stable across the life course, with upward and downward mobility. Socioeconomically disadvantaged children who experience upward mobility in adulthood have better health outcomes than other disadvantaged children with static or downward mobility, suggesting upward mobility can compensate for disadvantage in childhood. Conversely, downward mobility reduces the benefits of higher SES in childhood.[82,85] The effects of adult SES on health were also stronger for people with low compared with high childhood SES.[82]

CONCLUSIONS

SVD is a major cause of stroke, cognitive impairment, and dementia. Current evidence suggests that favorable prenatal and early-life factors related to nutrition, SES, premorbid IQ, and education, can decrease the risk of stroke and SVD and may protect against later development cognitive decline and dementia, but more research is needed, particularly in relation to VCI. As current birth cohorts reach old age, there will be further opportunities to examine early-life factors in relation to stroke and VCI. While associations appear to be independent of vascular risk factors in several studies, inconsistencies between studies in the number and type of covariates included mean that future studies should include mediation analysis of the relationships between early-life factors, vascular risk factors, SVD, and cognition to confirm findings.

SVD increases with age, but there is little information on whether it appears at a younger age in those with adverse early-life factors. However, altered white matter diffusion measures suggesting increased vulnerability to SVD can start in young adulthood in people with high vascular risk (eg, hypertension).[88] Future research should also examine whether early-life factors influence the age of onset of SVD. Positive early-life factors may influence health behaviors and access to socioeconomic resources beneficial to health or may increase brain integrity and resilience, reducing susceptibility of CVD.

Current evidence highlights that identifying modifiable early-life factors as targets for social policy interventions could have long-lasting impacts on health, particularly CVD and dementia. Clinicians caring for adults presenting with neurological diseases may wish to consider early-life circumstances, in addition to current risk factors, when evaluating patients. Health care providers working in pregnancy, childhood, and public health could play a vital role in informing patients and families about life-course brain health, thereby helping deliver these important policy initiatives.

ARTICLE INFORMATION

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Disclosures

None.

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