Late Preterm Birth and Neurocognitive Performance in Late Adulthood: A Birth Cohort Study

Kati Heinonen, PhD[a], Johan G. Eriksson, MD, DMSc[b,c,d,e,f], Jari Lahti, PhD[a], Eero Kajantie, MD, PhD[b,g,h], Anu-Katriina Pesonen, PhD[a], Soile Tuovinen, PhD[a], Clive Osmond, PhD[i], Katri Raikkonen, PhD[a]

abstract

OBJECTIVES: We studied if late preterm birth (34 weeks 0 days–36 weeks 6 days of gestation) is associated with performance on the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) in late adulthood and if maximum attained lifetime education moderated these associations.

METHODS: Participants were 919 Finnish men and women born between 1934 and 1944, who participated in the Helsinki Birth Cohort Study. They underwent the CERAD-NB at a mean age of 68.1 years. Data regarding gestational age (late preterm versus term) were extracted from hospital birth records, and educational attainment data were gathered from Statistics Finland.

RESULTS: After adjustment for major confounders, those born late preterm scored lower on word list recognition (mean difference: −0.33 SD; $P = .03$) than those born at term. Among those who had attained a basic or upper secondary education, late preterm birth was associated with lower scores on word list recognition, constructional praxis, constructional praxis recall, clock drawing, Mini–Mental State Examination, and memory total and CERAD total 2 compound scores (mean differences: >0.40 SD; P values <.05), and had a 2.70 times higher risk of mild cognitive impairment (Mini–Mental State Examination score: <26 points) ($P = .02$). Among those with tertiary levels of education, late preterm birth was not associated with CERAD-NB scores.

CONCLUSIONS: Our findings offer new insight into the lifelong consequences of late preterm birth, and they add late preterm birth as a novel risk factor to the list of neurocognitive impairment in late adulthood. Our findings also suggest that attained lifetime education may mitigate aging-related neurocognitive impairment, especially among those born late preterm.

FREE

WHAT'S KNOWN ON THIS SUBJECT: More than 70% of all preterm deliveries are late preterm (34–36 weeks of gestation). Existing evidence suggests that compared with those born at term, those born late preterm score lower on neurocognitive tests in childhood and young adulthood.

WHAT THIS STUDY ADDS: The effect of late preterm birth on neurocognitive performance persists up to late adulthood, especially among those who have only a basic or upper secondary level of education. Late preterm birth is also associated with a risk of memory impairments.

[a]*Institute of Behavioural Sciences and* [e]*Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland;* [b]*National Institute for Health and Welfare, Helsinki, Finland;* [d]*Vasa Central Hospital, Vasa, Finland;* [e]*Unit of General Practice, Helsinki University Central Hospital, Helsinki, Finland;* [f]*Folkhälsan Research Centre, Helsinki, Finland;* [g]*Children's Hospital, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland;* [h]*Department of Obstetrics and Gynecology, Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland; and* [i]*MRC Lifecourse Epidemiology Unit (University of Southampton), Southampton General Hospital, United Kingdom*

Dr Heinonen conceptualized and designed the study, conducted the analyses, interpreted the data, drafted the initial manuscript, and revised the manuscript; Dr Eriksson, Dr Lahti, Dr Kajantie, Dr Pesonen, Ms Tuovinen, and Dr Osmond conceptualized and designed the study, interpreted the data, and critically reviewed the manuscript; Dr Räikkönen conceptualized and designed the study, interpreted the data, drafted the initial manuscript, and revised the manuscript; and all authors approved the final manuscript as submitted.

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Every 10th birth worldwide is preterm (<37 weeks' gestation [≥37–42 weeks of gestation are term]).[1] Preterm birth is associated with a severe risk of early mortality and morbidity, as well as a risk of neurocognitive deficits.[2–11] The majority of the existing evidence has been derived from studies comparing premature infants born at the most severe end of the gestational age or birth weight distribution versus those born at term.[4,7,10,12] However, >70% of all preterm deliveries are late preterm, defined as a delivery at 34 weeks 0 days through 36 weeks 6 days of gestation.[13–15] Those born late preterm (and not only those born at the most severe end of the preterm births) are also at an increased risk for neonatal mortality; these infants more often experience complications of immaturity[16–18] than their term peers. The last weeks of gestation before term also represent a critical period for brain development.[19] At 34 weeks, the brain weight is only ~65% of that of the term brain, cortical volume increases by 50% between 34 and 40 weeks of gestation, and significant changes in gray and white matter volumes occur.[19–21] Surprisingly, however, little is known about the longer term neurocognitive consequences of late preterm births.

Studies conducted up until childhood and young adulthood suggest that individuals born late preterm may be at an increased risk of neurodevelopmental disabilities (eg, mental retardation, cerebral palsy),[22–24] they more often experience school-related problems,[22,25–28] and they perform poorer on academic achievement and neurocognitive tests.[22,26,27,29–36] The literature is not entirely consistent: some studies have found no differences in neurocognitive performance between those born late preterm and term.[30,31,37–39] However, it remains unknown if the effects of late preterm birth on neurocognitive performance persist to late adulthood. Accordingly, we tested if late preterm birth is associated with performance on the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) in subjects in their late 60s. Moreover, we have recently shown that late preterm birth is associated with lower lifetime attained level of education.[5] Because lower level of education is a risk factor for aging-related neurocognitive impairment,[40] we also tested whether education level moderated these associations.

METHODS

The Helsinki Birth Cohort Study comprises 13 345 singleton live births (100% white; 6975 men) in Finland between 1934 and 1944.[6] In 2001–2003, a randomly selected subsample of 2003 individuals of the initial population participated in a clinical follow-up. In 2005–2011, a total of 1377 (68.7%) of those who participated in the clinical follow-up were still traceable and living <100 km from Helsinki. Of these, 1109 (80.5%) (487 men) underwent the CERAD-NB (mean ± SD age: 68.2 ± 2.9 years; range: 61.2–77.0 years). A total of 153 (13.8%) participants were excluded who were born <34 weeks 0 days or >41 weeks 6 days of gestation or had inaccurate gestation data; also excluded were preterm participants with a disproportionally large birth weight for length of gestation (>2 SDs [probably errors]).[4] We also excluded 30 participants with a history of stroke, 6 with Parkinson's disease, and 1 who discontinued the CERAD-NB (n = 37 [3.3%]). The analytic sample thus comprised 919 (82.9%) participants.

Those subjects included in the randomly selected clinical follow-up sample but who dropped out or were excluded from the present study (n = 1084 [54.1%]) had a longer gestational age (mean difference: 3.19 days; SE difference: 0.59) (F[11 935] = 29.1, P < .001), earlier year of birth (mean difference: 0.13; F[12 002] = 5.9, P = .02), lower educational attainment (64.3% vs 57.7%, basic/upper secondary; (χ^2[1] = 9.2, P = .002), and were more likely to be men (48.5% vs 43.7%; χ^2[1] = 4.6, P = .03).

The Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District approved the study. Register data were linked with permission from the Ministry of Social and Health Affairs. Participants provided written informed consent.

Gestational Age

Length of gestation was calculated by using the mother's last date of menstruation, as recorded in the birth records.[5]

Neurocognitive Functioning

A trained master's level psychology student or research nurse performed the CERAD-NB. Subtests are presented in Supplemental Table 3. Subtests are used to measure cognitive performance in domains, including memory, language, visuospatial ability, and executive functioning. In addition to subtest scores, 3 compound scores were calculated. The memory total compound score was calculated by summing the word list recall, word list recognition (correct-positive + correct-negative recognitions), and constructional praxis recall subtest scores.[40] The memory total compound score combines subscales measuring delayed memory; it is a global score for episodic memory. The CERAD total compound score was computed by using 2 methods presented in earlier studies.[40–42] First, 7 of the 9 subtest raw scores (excluding clock drawing and the Mini–Mental State Examination [MMSE]) were summed for total score 1. Second, the sum of these raw scores when standardized (mean: 0; SD: 1), thus giving each equal weight, generated total score 2. Furthermore, mild cognitive impairment (MCI) in 4 subtests and in 1 compound score were defined by

using country-specific clinical cutoff scores as presented in Table 1.

Covariates, Confounders, and Moderators

Data regarding gender, date of birth, maternal age at delivery (years), parity, and height and weight before delivery (from which BMI was calculated) were extracted from birth records. Fathers' occupational status in childhood (manual worker/junior clerical/senior clerical/other) was extracted from birth, child welfare clinic, and school health care records. Systolic and diastolic blood pressures and BMI were measured at a clinical visit in 2001 through 2003. Maximum educational attainment in adulthood (1970–2000) was obtained from Statistics Finland and coded as basic/upper secondary versus tertiary.

TABLE 1 Sample Characteristics According to Late Preterm (34 Weeks 0 Days–36 Weeks 6 Days of Gestation) and Term (37 Weeks 0 Days–41 Weeks 6 Days of Gestation) Births

Characteristic	Late Preterm (n = 47)	Term (n = 872)	P (t test or χ^2)
	n (%) or Mean ± SD	n (%) or Mean ± SD	
Men	21 (44.7)	381 (43.7)	.89
Length of gestation, d	251.4 ± 5.60	278.34 ± 8.40	<.001
Gestational week			<.001
34 wk 0 d to 34 wk to 6 d	8 (17.0)		
35 wk 0 d to 35 wk to 6 d	12 (25.5)		
36 wk 0 d to 36 wk to 6 d	27 (57.4)		
37 wk 0 d to 37 wk to 6 d		85 (9.7)	
38 wk 0 d to 38 wk to 6 d		131 (15.0)	
39 wk 0 d to 39 wk to 6 d		232 (26.6)	
40 wk 0 d to 40 wk to 6 d		266 (30.5)	
41 wk 0 d to 41 wk to 6 d		158 (18.1)	
Birth weight, g	2857.3 ± 416.4	3422.5 ± 448.1	<.001
Relative birth weight, SD	−0.31 ± 0.96	0.09 ± 0.97	.01
Year of birth			.63
1934–1939	11 (23.4)	232 (26.6)	
1940–1944	36 (76.6)	640 (73.4)	
Mother's age at delivery, y	29.8 (5.72)	28.7 (5.39)	.19
Mother's BMI before delivery	26.36 (2.50)	26.46 (2.60)	.79
Parity			.20
First	27 (57.4)	395 (45.3)	
Second	20 (42.6)	460 (52.8)	
Third or more	0	17 (1.9)	
Father's occupation in subject's childhood			.82
Manual worker	27 (57.4)	528 (60.6)	
Junior clerical	13 (27.7)	203 (23.3)	
Senior clerical	7 (14.9)	132 (15.1)	
Other	0	9 (1.0)	
Maximum attained level of education			.20
Basic or upper secondary	28 (59.6)	502 (57.6)	
Lower tertiary (polytechnic, vocational, bachelor's degree)	9 (19.1)	250 (28.7)	
Upper tertiary (master's or higher)	10 (21.3)	120 (13.8)	
Late adulthood blood pressure, mm Hg			
Systolic blood	147.69 ± 23.22	143.27 ± 19.60	.14
Diastolic blood	89.56 ± 10.50	88.05 ± 9.91	.31
BMI	27.05 ± 4.58	27.36 ± 4.25	.63
Age at CERAD-NB testing	68.8 ± 2.86	68.1 ± 2.90	.11
MCI[a]			
Verbal fluency, <18 points	3 (6.5)	107 (12.4)	.23
Word list memory (learning), <18 points	9 (19.1)	82 (9.5)	.03
Word list recall, <5 points	4 (8.5)	46 (5.3)	.35
MMSE, <26 points	10 (21.3)	129 (14.8)	.23
Memory total score, <29 points	1 (2.1)	20 (2.3)	.93
CERAD total score 1, <74 points	0	14 (1.6)	.38

All participants had full data on the MMSE; in the term group, in each CERAD-NB subtest 8 to 9 participants had missing information; and in the late preterm group, 1 participant had missing information in verbal fluency and in CERAD total score.
[a] Country-specific clinical cutoff scores.[40,42]

Statistical Analysis

Differences between those born late preterm and term were tested by using multiple linear (continuous variables) and logistic (dichotomous variables) regression analyses. Of the CERAD compound and subtest scores, verbal fluency, Boston naming test, word list recognition, constructional praxis, and constructional praxis recall were skewed, and square root transformation was performed to attain normality. All CERAD scores were then standardized (mean: 0; SD: 1) to facilitate interpretation. We adjusted for age at testing and gender (model 1) and for maternal age, BMI before delivery, parity, fathers' occupational status in childhood, and subject's maximum attained education (model 2); we further adjusted for systolic and diastolic blood pressures and BMI in late adulthood (model 3). The interaction term "late preterm/term birth × education" tested effect modification according to education level, and analyses were also run separately in the education groups. Analyses were performed by using SPSS version 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

RESULTS

Table 1 and Supplemental Table 4 display the sample characteristics according to late preterm and term birth. Higher age was associated with lower scores on all CERAD-NB scales (r values > |0.07|, P values <.05), except on verbal fluency (r = –0.06, P = .07), word list recognition (r = –0.02, P = .56), and clock drawing (r = –0.004, P = .91). After adjustments for age at testing and gender, lower level of education was related to lower scores on all CERAD-NB scales (F values [1905–1907] > 12.9, P values <.001), except clock drawing (F[1907] = 2.1, P = .15).

After adjustments (models 1 and 2), those born late preterm had

significantly lower scores on word list recognition, and they tended to score lower on memory total compound than those born at term (Table 2).

Figure 1A shows that after model 1 adjustments, among those who had lower attained education level, late preterm birth was associated with lower scores on word list recognition, constructional praxis, clock drawing, and on memory total compound; after model 2 adjustments, it was also associated with lower scores on constructional praxis recall, MMSE, and total score 2 and a higher risk for MMSE-defined MCI (late preterm, n = 10 [35.7%]; term, n = 96 [19.1%]; model 1, odds ratio: 2.13 [95% confidence interval: 0.94 to 4.84]; P = .07; model 2, odds ratio: 2.70 [95% confidence interval: 1.14 to 6.38]: P = .02). Among those who had higher attained education level, late preterm birth was not associated with CERAD-NB scores (Fig 1B). Results of interaction analyses are also shown in Fig 1. These results remained significant after further adjustments for systolic and diastolic blood pressures and BMI measured in late adulthood (model 3; data not shown).

DISCUSSION

To our knowledge, this study is the longest follow-up investigation of neurocognitive performance of individuals born late preterm and the first to show that late preterm birth is associated with poorer episodic memory performance in late adulthood. When these associations were examined according to maximum lifetime educational attainment, we found that among those who had attained lower levels of education, late preterm birth was associated with lower scores for episodic memory, executive functioning, visual reproduction, and for general neurocognitive functioning, and they had a higher risk of MMSE-defined MCI. Among those who had higher attained education, late preterm birth was not associated with performance on the CERAD-NB.

Our findings are consistent with earlier studies showing that late preterm birth is associated with lower performance on neurocognitive tests in general[22,26,27,29–36] and on tests measuring visuospatial abilities and executive functioning in particular.[30,32] All of these studies except for 1 trial[36] were conducted in samples of children. The only study that we are aware of that has extended the follow-up to young adulthood found that at 18 years of age, military conscripts who were born late preterm had lower mean intelligence test scores than those born between 39 and 41 weeks of gestation. Although our new finding related to poorer episodic memory functioning among those born late preterm may reflect aging-related impairment in neurocognitive processes, we cannot rule out that the previous findings in children and young adults and our findings in early old age lay in a continuum (different neurocognitive manifestations of late preterm birth at different stages of the life span). Interestingly, a recent study found that lower general cognitive ability at age 11 years predicted lower immediate and delayed memory and MMSE scores at age 90 years.[43]

Despite our study being the longest follow-up of the neurocognitive consequences of late preterm birth conducted thus far, the participants were still relatively young and hence only a few subjects met the criteria for MCI. However, it has been shown that impairment in the level of episodic memory may especially characterize prodromal states of Alzheimer's disease (AD),[40] and it may be effective in identifying those with a family history of AD.[44] Moreover, a neurocognitive profile characterized by pronounced deficits in executive functioning along with poor episodic memory (eg, recognition memory impairment) is typical in patients with early-onset AD. Furthermore, visual reproduction may be sensitive in detecting early AD. Although differentiation between the various types of dementia (particularly in the earlier stages of disease) can be difficult, the cognitive profile of those born late preterm may be closer to that of patients with AD than that of patients with other types of dementia, such as

TABLE 2 Mean Differences in CERAD-NB Subtests and Compound Scores Between Those Born Late Preterm and Term

CERAD-NB Scale	Late Preterm Versus Term,[a] B (95% CI), P	
	Model 1	Model 2
Verbal fluency[b]	0.21 (–0.08 to 0.50), .15	0.22 (–0.06 to 0.51), .13
Boston naming test[b]	0.04 (–0.24 to 0.32), .78	0.06 (–0.22 to 0.34), .68
Word list memory (learning)	−0.22 (–0.50 to 0.06), .12	−0.19 (–0.46 to 0.08), .17
Word list recall	−0.14 (–0.42 to 0.14), .33	−0.11 (–0.39 to 0.17), .44
Word list recognition[b,c]	−0.35 (–0.64 to –0.07), .02	−0.33 (–0.61 to –0.04), .03
Constructional praxis[b]	−0.22 (–0.52 to 0.08), .16	−0.21 (–0.50 to 0.09), .17
Constructional praxis recall[b]	−0.16 (–0.45 to 0.12), .26	−0.15 (–0.43 to 0.13), .30
Clock drawing[b]	−0.20 (–0.49 to 0.09), .18	−0.20 (–0.49 to 0.09), .18
MMSE	−0.16 (–0.46 to 0.13), .28	−0.16 (–0.44 to 0.13), .29
Memory total score[d]	−0.27 (–0.55 to 0.01), .06	−0.24 (–0.51 to 0.04), .09
CERAD total score 1[e]	−0.10 (–0.39 to 0.18), .47	−0.07 (–0.34 to 0.20), .59
CERAD total score 2[f]	−0.17 (–0.45 to 0.12), .25	−0.13 (–0.41 to 0.14), .33

[a] Mean differences (B) and 95% confidence interval (CIs) are presented. Model 1 denotes adjustments made for age at testing and gender. Model 2 denotes further adjustments made for maternal age, BMI before delivery, parity, fathers' occupational status in childhood, and subject's maximum attained education.

[b] Square-root-transformed values. All values are standardized scores (mean: 0; SD: 1).

[c] Correct-positive – false-positive recognitions.

[d] Word list recall + word list recognition (correct-positive + correct-negative recognitions) + constructional praxis recall.

[e] Summation of subtest raw scores (except clock drawing and MMSE).[5]

[f] Summation of standardized subtest scores (except clock drawing and MMSE).

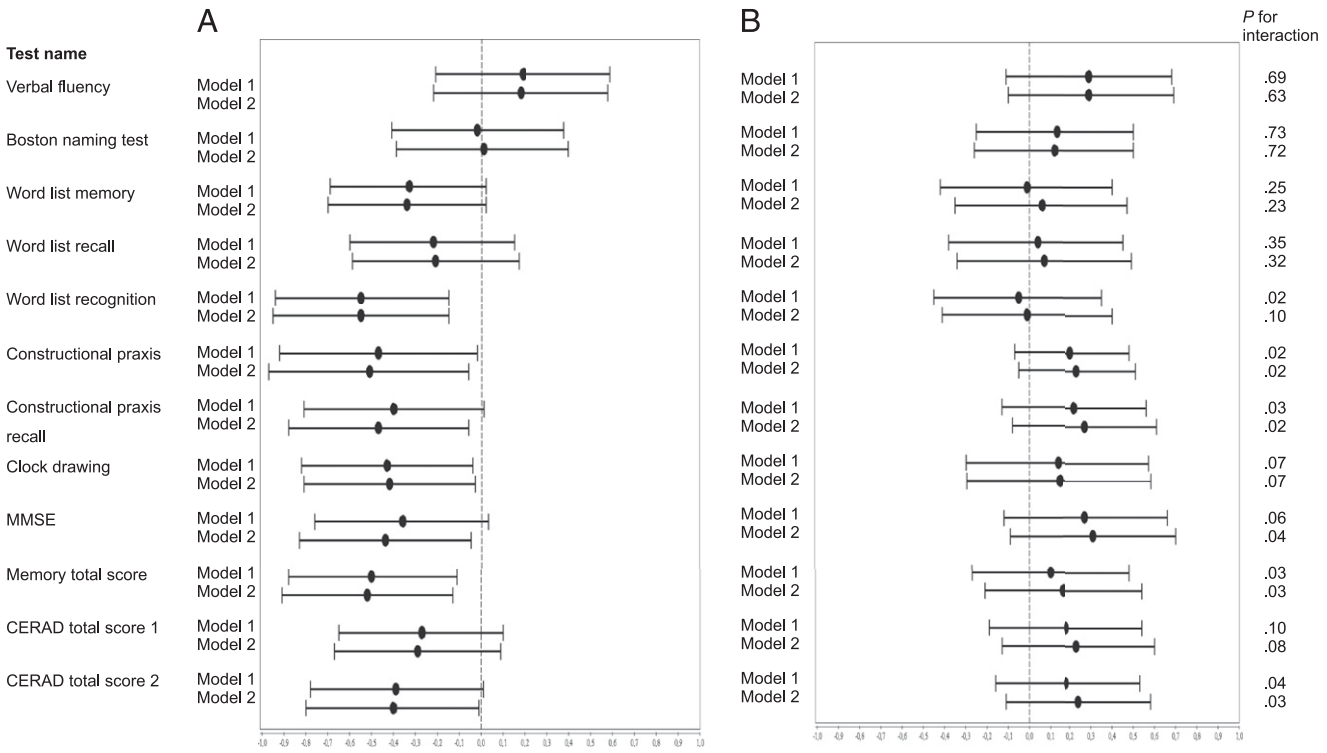

FIGURE 1

Differences between the late preterm and term groups on the CERAD-NB according to education level attained. Forest plots present the mean differences and 95% confidence intervals among those with (A) basic or upper secondary education and (B) tertiary education. Model 1 denotes adjustments made for age at assessment and gender, and model 2 denotes further adjustments made for maternal age, BMI before delivery, parity, and fathers' occupational status.

frontotemporal dementia, which is characterized by more impaired spontaneous word generation task and lesser deficits in tests on memory and visuospatial abilities.[45,46] In the present study, we excluded subjects with a history of stroke or other brain injury and made adjustments for blood pressure. Hence, our sample most likely did not include those with early stages of vascular dementia. Thus, individuals born late preterm may be at an increased risk of MCI and dementia, especially those subjects who have attained lower levels of education. Additional studies are needed to clarify if the dementia risk pertains specifically to AD.

Our findings relating to achieved education may reflect attained neurocognitive reserve.[42] Higher educational attainment has been shown to be related to later onset of AD[44] and to modify the association between AD-related neuropathology and neurocognitive functioning.[47] The finding that late preterm birth was not associated with performance on the CERAD-NB among those who had attained tertiary levels of education may indicate that their higher neurocognitive reserve mitigates the aging-related neurocognitive impairment.

Several mechanisms could underlie the associations between late preterm birth and neurocognitive impairment.[21] First, substantial brain development occurs during the last weeks of pregnancy,[19–21] and late preterm birth may affect these neurodevelopmental processes. Second, neonatal morbidity associated with late preterm birth may add to the risk of brain injury and later neurocognitive impairment. Those born late preterm have an increased risk for impairments (eg, neonatal hypoglycemia, hyperbilirubinemia, sepsis),[17,18] which, in turn, are known to be associated with an increased risk for neurologic sequelae.[48–52] Third, the primary cause of preterm labor may also underlie. Pregnancy disorders (eg, preeclampsia, hypertension), intrauterine growth restriction, and maternal smoking are more common among those born late preterm than among those born at term.[53–56] These factors, in turn, have been shown to be related to a child's neurocognitive impairment.[57–60] Finally, a common genetic basis may also be involved.

There are several strengths to our study. We used a well-known standardized neurocognitive performance battery in late adulthood, and the educational attainment levels and gestational age were derived from registers, which all exclude the possibility of self-reporting bias. We were also able to account for many perinatal (ie, birth

order) and parental (ie, maternal age and BMI, fathers' occupational status) variables, as well as late adulthood variables (ie, lifetime educational attainments, blood pressure, BMI), relating to preterm birth and/or risk for aging-related neurocognitive impairment.

However, there were also some limitations. Birth registers of individuals born between 1934 and 1944 lack detailed information on potential impairments and complications associated with preterm birth. Furthermore, at that time period, gestational age could only be defined based on the last menstrual date of the mother. To minimize the misclassification of term birth to preterm birth, preterm participants with disproportionally large birth weight for length of gestation were excluded. In addition, the context in which births of the Helsinki Birth Cohort Study participants occurred several decades ago differs from that of today. Although the majority of the births in the Helsinki area in 1934–1944 occurred in hospitals, and preterm infants were generally treated at pediatric wards,[61] neonatal mortality was still ∼40%.[62] Moreover, induction of delivery was rare, and participants in our cohort represent mainly spontaneous preterm births. Accordingly, a limited number of participants in the Helsinki Birth Cohort Study born before 34 weeks of gestation with CERAD-NB were available for our study (n = 12), thus restricting the analyses to those born ≥34 weeks' gestation. Furthermore, smoking among women was rare; although there are no numerical data from the 1930s or 1940s, historical data indicate that women's smoking habits gradually increased from the 1950s onward (although it was only 13% in the 1960s).[63] During World War II, although Helsinki was never occupied by the enemy, there were food shortages, and many fathers of the participants served in the army, potentially compromising the fathers' occupational attainments. However, Finland changed rapidly toward a modern welfare state after the war, indicating more equal education opportunities for the participants in the present study. The educational level of our cohort participants is still lower than that of more current cohorts in most of the developed countries, however. Thus, due to considerable improvements in prenatal and neonatal care and increased affluence over the last few decades, the present findings may not be generalizable to cohorts born more recently in high-resource settings; they may, however, be more relevant to cohorts born in today's low-resource settings. These are unavoidable limitations that cannot be overcome in the near future when studying cognitive aging in those born late preterm.

CONCLUSIONS

Our study contributes significantly to the scientific literature by offering insight into the lifelong consequences of late preterm birth, suggesting that it is a novel risk factor for neurocognitive impairment in late adulthood. Moreover, our findings also suggest that maximum attained lifetime education may mitigate aging-related neurocognitive impairment, especially among those born late preterm.

Address correspondence to Kati Heinonen, PhD, Institute of Behavioural Sciences, PO Box 9, 00014 University of Helsinki, Helsinki, Finland. E-mail: kati.heinonen@helsinki.fi

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