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Longitudinal trajectories of cognitive decline and cerebral blood flow abnormalities in octogenarian men with normal global cognition

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ABSTRACT

Aims: Cognitive and perfusion changes have been previously observed in older men with Mini Mental State Examination scores>24 points. We aimed to investigate time change in cognitive domains in a cohort of non-demented men between age 68 and 82, and how they are expressed in regional defects estimated by Cerebral Blood Flow (rCBF).

Methods: 103 men at age 81 with MMSE scores >24 (mean 28.4 ± 1.7), no dementia or stroke, were examined with the same cognitive test battery at age 68 and age 81: Synonyms (SRB-1), Block design (SRB-3), Paired Associates, Digit Symbol Substitution and Benton Visual Retention test. rCBF was estimated using ^{99mTc}-HMPAO SPECT at age 82.

Results: Between ages 68 and 82 we observed a relative decline (Δ%) of cognitive test scores: SRB-3 and Benton tests, -33.7 % (SD 16,8) and -25.8 % (SD 23.9) respectively, followed by Digit Symbol test: -22,6 % (SD 15,6). The cluster of men (46 %) could be detected, grouped on the largest test score decline and highest overall test predictors' importance in decreasing order: Δ% SRB-3, Δ% Paired Associates, Δ% Digit Symbol, Δ% Benton VR and Δ% SRB-1. Compared to the cluster with stable cognitive functions, it expressed lower rCBF in frontal and parietal lobes, and in subcortical areas.

Conclusion: Nearly half of the studied, community-dwelling cohort of non-demented, octogenarian men with MMSE > 24, had a combination of decreasing visuospatial ability and episodic memory during preceding years, expressed by widespread rCBF changes in fronto-subcortical areas.

Introduction

We have previously shown that in older men with MMSE scores of at least 25 points, MMSE scores were very sparsely correlated with regional Cerebral Blood Flow (rCBF). Instead, lower scores on visuo-spatial tests and tests of verbal fluency were associated with decreased rCBF in frontal and temporal-parietal lobes [1]. A cluster of low achievers at age 81 with the highest discriminating importance of lower scores on tests of verbal fluency (Srb-1) and of Digit Symbol had lower rCBF in all cortical and subcortical brain areas. The long-term rate of cognitive decline and the onset of accelerated decline is dependent on many factors, such as gender, education, genetics, neuropathology, personality, and a level of previous general mental ability, which is especially associated with the preservation of verbal memory in aging [2,3]. Our study aimed to analyze the rate and characteristics of a cognitive decline during the preceding 14 years in 81-years-old men without dementia and with MMSE scores >24, and their correlation with changes rCBF and mortality.

Methods

Study sample

A prospective population sample study, "Men born in 1914", included all men born in the even months of 1914 in the city of Malmö, Sweden. When they were 68 years old, five hundred of them agreed to participate. The most recent follow-up of the cohort started when the subjects reached 81 years of age, and 281 men were found to be still

Abbreviations: ROIs, Regions of interest; rCBF, Regional cerebral blood flow; SPECT, Single-photon emission computed tomography; MMSE, Mini mental state examination.

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alive. (Fig. 1). Of these, 185 agreed to take part (66 %) in a new investigation, including both physical and neuropsychological examinations. Clinical examination and neuropsychological data were available from 171 of them at the ages of 68 and 81. At the recent follow-up at age 81, possible dementia was classified according to the DSM-IV criteria, and one subject was diagnosed as being demented. The Mini-Mental State Examination (MMSE) was performed on 171 men, giving a mean value of 27.7 (SD $\pm$ 3.5). Eight subjects had MMSE scores $<$ 25. During the following year after the last clinical examination, all survivors and those who accepted the invitation were invited to a rCBF measurement. After the exclusion of eight stroke sufferers, one demented subject according to the DSM-IV, and those with MMSE score $<$25, 103 men who completed rCBF measurement and all cognitive tests were defined as the study population [4]. Mortality data has been available until 2012.

Cerebral blood flow estimation

Each subject received an intravenous injection of 800 MBq 99mTc-HMPAO (Ceretec; Amersham Inc., Little Chalfont, Buckinghamshire, UK). The acquisition was performed under resting conditions on a triple-headed gamma camera system (Siemens Multispect 3, Siemens, Chicago, IL, USA) with fan beam low-energy collimators and in 360° rotation (64 views, 20 s/view, in a 128 · 128 matrix, and a zoom factor of 1.23). The energy window used had a 15 % window centered over the 140 keV peak. Image processing included reconstruction of 10 transaxial 1 cm-thick slices, from 1 cm below the orbitomeatal line and upwards. Regions of interest (ROIs) were delineated in each slice and defined as lobular ROIs in each hemisphere. The value measured in each ROI was expressed as a percentage of the mean cerebellar count density [4].

Tests of cognitive function

The same psychological investigation was performed both at age 68 and at age 81 by one clinical psychologist according to the previously published protocol [5,6], including five tests on cognitive ability:

- Srb-1, Test of Synonyms

A test on general verbal ability. The individual is presented with a list of 30 words, each followed by five words of which one should be chosen as the correct synonym for the first word (maximum score: 30).

- Srb-3, Block design test

A Swedish test of visuospatial and constructional ability is very similar to the block design, which is part of the Wechsler adult intelligence scale. A printed design is shown to the individual whereupon he is

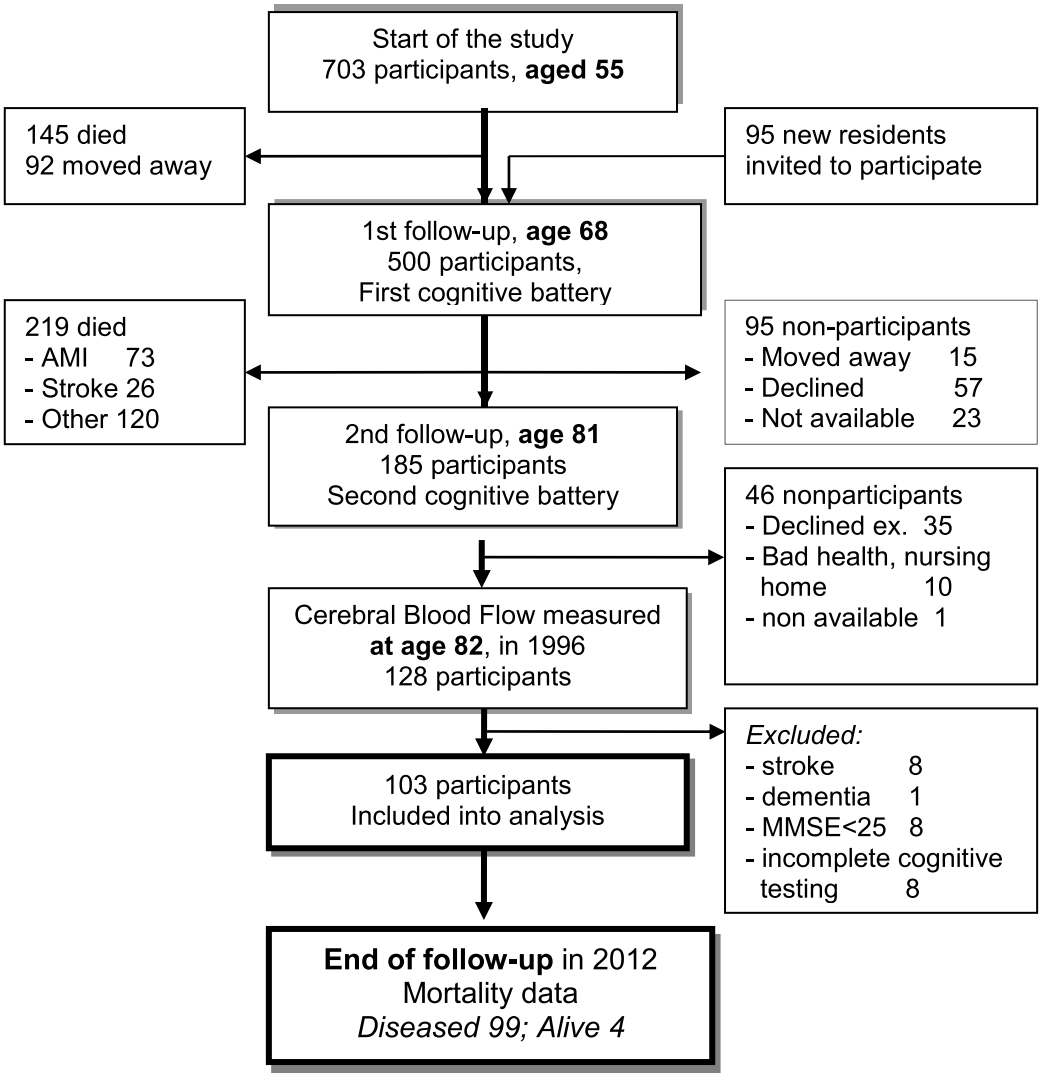

Fig. 1. Flowchart of the cohort study "Men born in 1914".

asked to assemble wooden blocks to produce a pattern identical to the printed design (maximum score: 42).

- Paired associates test

A Swedish version of the Wechsler original Verbal Paired Associates, of verbal, immediate memory, where the subject is read a list of paired associates which he can also see written on paper. When the paper has been removed, the subject is given a word from the list and is asked to present the correct associated word. Maximum score: 30.

- Digit Symbol Substitution test

A test is measuring psychomotor speed, visual-motor coordination, concentration, and cognitive flexibility (12). The participant is asked to copy symbols that are paired with digits according to a coding key, which can be seen throughout the test. The individual is asked to copy as many as possible in 90 s (maximum score: 90).

- Benton Visual Retention test

A test often used to estimate immediate, visual, spatial memory. Ten drawings of geometrical design are shown to the individual for ten seconds each. All correctly copied designs from the memory are scored as correct versus incorrect (maximum correct score: 10).

Theory/calculation

Background data are expressed as means ± standard deviation or frequencies (%). Relative changes in cognitive test scores (Δ%) were calculated as (test score at 81 – test score at 68)* 100 / test score at 68. Spearman test was used to test the correlation between cognitive tests and rCBF. All five tests' Δ% were used for classification using TwoStep Cluster Analysis, to reveal natural groupings within a dataset of neuropsychological tests. The likelihood measure has been estimated for a probability distribution on the variables. The number of clusters was determined automatically. The difference in rCBF between the two clusters has been calculated using *t*-test. Mortality data were available until 2012. Survival analysis has been performed using Cox regression with clusters as categorical covariates. A two-tailed *p*-value of less than 0.05 was considered statistically significant. All data analyses and statistical calculations were performed using the SPSS (SPSS Inc., Chicago, USA) data package.

Ethical approval

The Ethics Committee at Lund University approved the study (LU 111–82), and informed consent was obtained from all participants.

Results

Baseline cognitive data from the survey at age 68 and 82 are presented in Table 1. The z-scores of test results collected at age 68 were compared between *cases*, i.e. subjects who survived to the next survey, completed SPECT examination at age 68, and achieved MMSE score ≥25, and a *baseline group*, i.e. subjects who died before the last survey or declined the examinations at age 81–82 (table 2). The difference was explicitly largest for SRB-1 test, followed by SRB-3, Digit Symbol, Benton, and Paired Associates test. In the *case* group, during 14 years of follow-up, we observed a decline in mean scores on all tests. Verbal test scores (SRB-1 and Paired Associates test) were most stable at a group level, with a mean relative decline compared to age 68ys., at −9.00 % (SD 17.0 %) and −16.5 % (SD 27.6 %) respectively, showing both decreasing and increasing individual tests values over time. Other tests showed a dominant decreasing score pattern: SRB-3 and Benton tests scores showed the largest relative decline, −33.7 % (SD 16,8), −25.8 % (SD 23.9), respectively, followed by Digit Symbol test: −22,6 % (SD 15,6).

At age 68, mainly scores of Digit Symbol and SRB-3 test scores were correlated with rCBF values estimated 14 years later (table 3). Relative change in test scores between age 68 and 81 (Δ%) correlated with rCBF in as follows: strongest positive correlations were observed between Δ% of SRB-3, and of Paired Associates tests and rCBF in parietal, frontal, and occipital lobe and in subcortical areas (table 3), while Δ% of Digit Symbol test with rCBF in both frontal lobes, left temporal and parietal lobe, as well as in subcortical areas.

Upon completing the TwoStep Cluster Analysis procedure, which included Δ% of each of the five cognitive tests, the silhouette measure of cohesion and separation suggested the best cluster quality for a two-cluster solution, with a ratio of sizes 1.17, and with a fair average silhouette of 0.4. The two clusters were defined on the predictors of overall importance as follows: Δ% SRB-3 had the highest importance of 1.0, followed by Δ% Paired Associates (importance 0.41), Δ% Digit Symbol (importance 0.37), Δ% Benton VR (importance 0.29) and finally Δ% SRB-1 tests (importance 0.14) (table 4). The cluster which comprised study subjects with the largest relative decline of these test scores (lowest negative values of Δ%) was defined as *Decliners,* while the cluster expressing a moderate relative decline was defined as *Stables.* Mann-Whitney test analysis showed highly significant differences for four of the tests, with Z-values in the same decreasing order as the tests' overall importance in the cluster analysis (table 4). The clusters did not differ concerning baseline test scores at age 68 (table 4). When comparing rCBF of both clusters, *Decliners* showed lower rCBF mostly in frontal and parietal lobes, and in subcortical areas (table 5).

Until 2012, 99 men were diseased with a median survival time of 110 months (SE 9.7) since CBF examination. Survival analysis did not show a difference in mortality between *Decliners* and *Stables* (HR= 0.84; 95 %CI = 0.55 - 1.29; *p*= *.427*).

Table 1
Background cognitive data of a population-based cohort of men ($n = 103$) at age 68 and 81 years.

mean scores (SD)	Age 68 years	Age 81 years
Srb-1	22.0 (5.4)	20.0 (5.4)
Srb-3	22.9 (5.4)	15.3 (5.6)
Digit Symbol	38.2 (11.1)	29.3 (9.4)
Paired Associates	19.0 (5.1)	15.9 (6.0)
Benton VR	6.1 (1.4)	4.5 (1.5)

Table 2
Mean z-scores of each cognitive test examined at age 68 in a case group (MMSE >24) and in a baseline group (MMSE <25 at age 81, absent for survey or dead before the survey at age 82).

		Mean	SD	Mean difference	t	*p*
z-score SRB1	case group	.304	.8677	1.881	17.48	<0.001
	baseline group	−1.577	.0287			
z-score SRB3	case group	.533	.8189	.725	7.07	<0.001
	baseline group	−0.192	1.0194			
z-score PairedA	case group	.240	.9204	.362	3.22	.003
	baseline group	−0.122	1.0227			
z-score Benton	case group	.408	.8246	.579	5.59	<0.001
	baseline group	−0.171	1.0261			
z-score DigitS	case group	.391	.9447	.596	5.19	<0.001
	baseline group	−0.205	.9750			

Table 3
Correlation coefficients between regional rCBF at age 81 and raw scores of the neuropsychological test at age 68, and between rCBF and relative change in test scores (Δ%) between ages 68 and 81.

rCBF at area:	SRB-1 at 68ys.	Δ%	SRB-3 at 68ys.	Δ%	DigitSymbol at 68ys.	Δ%	PairAssoc at 68ys.	Δ%	Benton VR at 68ys.	Δ%
Frontal R	.147	.048	0.54	.198*	.172	.191*	.093	.312**	.029	.150
L	.171	.048	0.61	.125	.175	.171*	.104	.258**	.022	.119
Tempor R	.141	.122	.029	.132	.263*	.068	.192*	.056	.111	−0.014
L	.172	.118	.030	.188	.173	.157*	.164	.066	.115	.001
Parietal R	.132	.088	.043	.274**	.203*	.232*	.192*	.206*	.066	.109
L	.090	0.127	−0.003	.242*	.143	.219*	.153	.191*	−0.008	.133
Occipital	.149	.022	.158	.180	.275*	−0.039	.212*	.037	.120	.064
Bas Nuc R	.191*	.055	.148	.055	.222*	.084	.131	.129	.135	.007
L	.142	.049	.153	.055	0.271*	.051	.132	.079	.061	.015
Thalam R	.181	.059	.149	.124	.213*	.045	.122	.104	.104	.053
L	.227*	.082	.216*	.081	.370**	.060	.237**	.105	.070	.039
Subcortical	.229*	.056	.083	.251*	.188	.226*	.171	.214*	.095	.165

* $p < .05$.
** $p < .005$; R: right: L: left.

Table 4
Two clusters of study subjects and their (a) predictors ordered in decreasing overall importance of each test Δ% between ages 68 and 81, and (b) raw scores of baseline test results at age 68.

	Cluster 1 *Decliners group* (46 %) *Median (range)*	Cluster 2 *Stables group* (54 %) *Median (range)*	Z	*p*
a. Δ% tests, 82–68ys				
Δ% SRB-3	−45.4 (−82.6-[−15.0])	−23.8 (−48.5-[−3.7])	−6.69	<0.00005
Δ% Paired Assoc.	−25.0 (−93.7–25.0)	−6.7 (−33.3–63.6)	−5.26	<0.00005
Δ% Digit Symbol	−27.3 (−59.6-[−4.6])	−15.7 (−43.7–27.8)	−4.26	<0.00005
Δ% Benton VR.	−33.3 (−80.0–25.0)	−14.3 (−55.5–20)	−4.48	<0.00005
Δ% SRB-1	−10.0 (−50.0–42.8)	−4.5 (−30.8–36.4)	−2.58	.010
b. test scores, 68ys				
SRB-3	23 (12–32)	23 (9–38)	−0.58	.557
Paired Assoc.	20 (10–29)	19 (7–29)	−0.23	.814
Digit Symbol	37 (21–63)	37 (15–63)	−0.45	.654
Benton VR.	6 (3–10)	6 (3–9)	−0.307	.759
SRB-1	23 (7–30)	23 (9–30)	−0.09	.926

Table 5
Differences in regional Cerebral Blood Flow between the two clusters of study subjects based on Δ% of five cognitive tests: *Decliners* and *Stables*.

Regions of CBF measurement	Clusters	Mean rCBF	SD	T	*P*
Frontal R	Decliners	78.3	5.89	−3.308	.001
	Stables	82.3	5.75		
Frontal L	Decliners	78.4	6.01	−2.259	.026
	Stables	81.2	5.64		
Temporal R	Decliners	78.1	4.89	−1.678	.097
	Stables	79.9	5.38		
Temporal L	Decliners	76.9	5.09	−1.879	.064
	Stables	78.8	4.37		
Parietal R	Decliners	78.8	6.14	−2.794	.006
	Stables	82.2	5.16		
Parietal L	Decliners	78.1	6.75	−2.510	.014
	Stables	81.3	4.86		
Occipital	Decliners	87.4	6.13	−2.195	.031
	Stables	90.1	5.59		
Basal Nuc R	Decliners	91.8	7.29	−1.118	.267
	Stables	93.5	6.55		
Basal Nuc L	Decliners	90.3	7.69	−1.089	.279
	Stables	91.9	6.11		
Thalamus R	Decliners	91.9	7.69	−1.585	.117
	Stables	94.6	8.35		
Thalamus L	Decliners	92.0	8.60	−0.416	.678
	Stables	92.7	7.36		
Subcortical	Decliners	61.3	6.76	−3.434	.001
	Stables	66.0	6.27		

p: level of significance; t: t-value of the *t*-test.

Discussion

Our study population includes selected subjects with normal MMSE scores [7], mainly because demented subjects died between the follow-ups or declined to participate [8], and also due to predetermined selection which was an objective of the study. The remaining cohort reached a high age with good cognition despite that several of the subjects had lower scores on several neuropsychological tests already at age 68, which was reflected by SPECT findings 14 years later. It means that either the decrement of cognitive state was milder compared to the unselected general populations, or the selection process in our cohort excluded fatal cardio/cerebrovascular emergencies. The association between test scores at age 68 and rCBF might be explained by a natural trajectory of cognitive decline in subjects with mild pathology and non-developing dementia, indicating speeded performance as the most sensitive and more specific to discovering early organic brain pathology [9]. During the follow-up of this cohort, the largest relative decline was observed for two visuospatial tests, while the results of the verbal capacity test were best preserved in the senescence, and with a mild decline during the follow-up time. Visuospatial skills have been previously shown to be the most impaired cognitive subdomain in older adults with Mild Cognitive Impairment, and have been related to thinning of the lateral temporal cortices and impaired functional connectivity within the visuospatial network [10]

Cluster analysis allowed an identification of a large subgroup of subjects with MMSE >24 at age 81, who had a combination of cognitive decline mostly in domains of visuospatial ability and episodic memory, even if, at age 68, their test scores were similar to the subgroup of cognitively stable men. It supports previous observations that cognitive

status measures and domain-specific measures might not be equally appropriate for examining changes over time [11]. Perfusion/metabolic defects seen in our study were not only located in the right parietal lobe, as observed in previous visuospatial test studies, but more widespread, as it was suggested that broader regions are recruited to perform on the block design test, and that the block design test is not only associated with visuospatial functioning but more complex planning and organization [12]. It has also been revealed that decreased eye fixation strategies in older adults are related to increasing cognitive demand and delays in both the eye and the hand [13].

Multiple articles report that white matter changes in the frontal region are significantly associated with longitudinal declines in executive function and executive memory [14]. The combination of visuospatial and episodic memory decline in a substantial part of our cohort and their perfusion defects dominantly in frontal and subcortical areas resemble also the concept of frontal-subcortical syndrome, either as a part of subcortical ischemic microangiopathy [15] or in neurodegenerative diseases [16,17]. The disruption of the fronto-subcortical circuit was also observed and suggested as an explanatory mechanism in subthreshold concepts or diagnoses such as Motoric-Cognitive Risk Syndrome [18], Mild Cognitive Impairment [19] or Mild Behavioral Impairment [20]. In our study, even if a non-demented cohort of *decliners* shares a common neuropsychological time-variability profile, it can still comprise men with different mechanisms of cerebral aging. The median relative decline in this cohort was between 25 and 45 % in all tests except verbal capacity, which expresses a mixed profile of cognitive decline in our subjects. As stroke patients have been excluded, the possible mechanism of cognitive decline might be early neurodegenerative or subcortical vascular one. The disruption of the structural connectivity network of prefrontal, parietal, and subcortical areas, mainly in anterior thalamic radiation and forceps minor, has been previously observed in non-demented older adults with subcortical ischemic vascular cognitive impairment [21,22]. Our results suggest that not only single neuropsychological tests but also grade, and combined decline of cognitive domains over 14 years, could separate individuals with substantial perfusion deficits. Decliners did not have increased mortality and median survival time showed an exceptionally long-living cohort, suggesting that cognitive decline without signs of dementia at age 82, despite cerebral perfusion changes, is not a mortality risk in men. These results should be however confirmed in larger cohorts.

The main strength of our study is that the group was randomly selected, and community-dwelling. Subjects were born the same year and were of the same gender, which could allow a fair longitudinal design without these confounders. During both surveys, the psychological interview was performed by the same clinical neuropsychologist. As in each longitudinal cohort we deal with a large survival bias losing subjects with extended vascular risk factors and high genetics risk. Some of the disabled elderly chose not to join the re-examination or were not capable of being examined due to disabilities, explaining the low prevalence of dementia and stroke at the last follow-up. Elderly with cognitive decline could also be more likely to decline participation. The choice of rCBF measurement may to some extent influence the results. We have chosen the ROI approach with reference region in the cerebellum as a semi-quantitative method. An alternative, statistically parametric mapping, was not possible due to technical reasons, but the difference between these methods should be negligible due to an automatic delineation of ROI.

Conclusion

In non-demented men at age 82 ys., mean scores of all cognitive tests decreased during the preceding 14 years, with the largest difference for visuospatial test: SRB-3 and Benton, followed by psychomotor speed test, Digit Symbol, while verbal tests were most stable. We could identify a cluster of men (46 %) with the largest combined relative test score decline and highest predicting importance in decreasing order: Δ% SRB-3, Δ% Paired Associates, Δ% Digit Symbol, Δ% Benton VR, and Δ% SRB-1. Compared to the rest of the cohort, with stable cognitive functions, this subgroup expressed lower rCBF in frontal and parietal lobes, and in subcortical areas. Older men with normal general cognition might present a combination of decreasing visuospatial ability and episodic memory, expressed by widespread rCBF changes.

CRediT authorship contribution statement

Arkadiusz Siennicki-Lantz: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Lena André-Petersson:** Conceptualization, Data curation, Investigation. **Sölve Elmståhl:** Software, Resources, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

None

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Declaration of Generative AI and AI-assisted technologies in the writing process

Statement: During the preparation of this work the authors used Grammarly tool in order to review spelling, grammar and punctuation in the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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