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A registry study on nonsyndromic craniosynostosis: Long-term associations with academic achievement

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Summary *Objective:* To assess the association between nonsyndromic craniosynostosis (NSC) and academic achievement.
Methods: Registry data were analyzed on demographic background, presence of craniosynostosis and other comorbidities, grades, and results on national standardized tests (NSTs) across primary and upper secondary school, as well as the presence of academic degrees. The analysis used regression modeling on a sample of N = 1110 individuals with NSC and a matched cohort of N = 10,654 individuals.
Results: There was a significant negative association between NSC and NST scores in third grade for both mathematics (aOR 0.76, 95% CI 0.60–0.99, p = .020) and Swedish (aOR 0.69, 95% CI 0.54–0.89, p = .004). The association seemed to primarily be carried by females with NSC (aORs for the interaction term 0.26–0.45, all ps < .05). Further, a slightly stronger negative association was observed in individuals with psychiatric comorbidities (aOR 0.44, 95% CI 0.22–0.90, p = .025 for mathematics; aOR 0.45, 95% CI 0.21–0.98, p = .045 for Swedish). No statistically significant association was found between NSC and NST scores or grades in later school years, or with academic degrees.
Conclusions: There is evidence for a limited temporary negative association between NSC and academic achievement. A stronger negative association between NSC and academic achievement seems to be present in girls, and for individuals with psychiatric comorbidities. This has important implications for clinical management and provision of support in educational contexts.

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Craniosynostosis (CS) is a congenital condition that involves premature fusion of the sutures of the cranial bones in the infant, which influences the growth of the skull in a variety of ways.[1] The condition is relatively rare, occurring in approximately one in every 2000 to 2500 births[2-5] and can be categorized into single-suture or complex CS depending on the number of affected sutures.

CS leads to skull deformity and may restrict the space available for the growth of the infant's brain as it develops and expands in size during the first years of life, prompting surgical intervention in most cases. However, no definitive link has been established between single-suture non-syndromic CS (NSC) and delayed cognitive development.[6-9] The significance of factors such as age at surgery on cognitive prognosis in NSC is also not yet established.[10]

Although deficits in general cognitive ability may not be pronounced in NSC, subtle deficits in specific functions may persist into school age, resulting in an increased prevalence of various psychiatric comorbidities such as attention-deficit/hyperactivity disorder (ADHD) and learning disorders, which are known to have adverse effects on academic achievement.[11-14] However, with a few notable exceptions,[12,15] long-term longitudinal studies examining the effect of NSC on academic achievement are lacking. The interplay of NSC with other demographical characteristics such as sex in relation to academic achievement is also under-researched.[16]

A registry study on a Swedish cohort suggests an increased prevalence of several neuropsychiatric conditions in the NSC population, which are negatively associated with academic achievement.[17] Further, a US-based longitudinal study found specific, albeit comparatively small, effects on math computation and some other aspects of academic achievement in NSC individuals using standardized testing[15] while a Finnish cohort study did not find impairment in school grades compared to healthy controls.[18] A recent study on a Canadian cohort found small albeit changing effects over time, with average overall grade scores but with a trend of improving scores in math and worsening scores on reading and writing.[19]

This study aims to further investigate the relationship between NSC and academic achievement using registry data and a matched comparison sample, controlling for confounders such as the influence of parental demographic factors and psychiatric comorbidity, which is usually not possible in this field due to sample size restrictions. We also attempted to test for a moderating effect of age at surgery in patients with sagittal NSC operated on before versus after six months of age. Based on previous findings and known effects of demographic factors on academic achievement, we hypothesized that:

- The presence of NSC would be associated with poorer academic achievement in comparison to individuals without NSC.
- This effect would be moderated by sex and psychiatric comorbidity.
- In individuals with sagittal NSC, older age at primary surgery for the condition would be associated with poorer academic achievement.

Methods

Data sources

Data were obtained from the National board of Health and Welfare in Sweden and Statistics Sweden. The 10-digit National Registration Number was used to link registries. Data were drawn from the Swedish Medical Birth Register (MBR), the National Patient Register (NPR), the Swedish Cause-of-Death Register, the Register of Total Population, the Multi-generational Register, the Migration Register, the Census of the population and housing, the longitudinal integration database for health insurance and labor market studies (LISA), and the Swedish School-Grade Register (SGR).[20-24] The registers are further described in Appendix 1.

Participants

Through MBR and NPR, we identified N = 1110 individuals with NSC born in Sweden between January 1, 1973 and December 31, 2004 who received their diagnosis prior to age 5 years as recorded in the NPR. A comparison group from the population was created by randomly including 10 individuals without NSC for each participant with NSC (n = 10,654) matching for month and year of birth, sex, and county of birth.

For all analyses of achievements in Swedish throughout the educational system, we excluded children that followed the curriculum of Swedish as their secondary language. All subjects were observed from their date of birth until outcome, emigration, death, or end of the study until December 31, 2012, whichever occurred first.

NSC exposure was defined as having an ICD-8 (used in Sweden 1969–1986) or ICD-10 (fully implemented in Sweden from 1997 to the end of the study period) diagnosis of NSC (756.00 or Q75.0) while at the same time having a code of craniofacial surgery, either 0202 (ICD-8) or AAK20/30 (ICD-10).[25] Codes from ICD-9 (used in Sweden 1987–1996) were not used since the diagnostic code of NSC under this system was also used to denote several genetic syndromes with craniosynostosis.[17] No data identifying sutural subtypes were available. Sagittal cases were identified by the proxy of having the AAU00 surgical code for extraction of surgical springs (ICD-10) before age 5 years in addition to an NSC code, resulting in a sagittal subgroup of 221 individuals.

Table 1 Data matrix for comparison of grades across years.

Calculated grade value	1973-1994	1994-2011	2012-2013
1	1	Not passed	F
2	2 and 3	Pass	E and D
3	4	Pass with distinction	C and B
4	5	Pass with excellence	A

Outcome measures

We utilized results from national standardized tests (NSTs) and grades in the ninth school year and in upper secondary school for both mathematics and Swedish as well as having a university degree as the outcome measures. We estimated the proportion of passed tests among NSTs in mathematics and Swedish, based on up to seven different tests in mathematics and up to eight different tests in Swedish for each individual in the cohorts and then investigated odds ratios for passed tests. The various procedures for NSTs and the systems for reporting grades in Sweden used across the study period are further described in Appendix 2.[26]

The process for reporting NSTs for year 6 changed from 2012 to 2013, and the 2013 tests were only reported as a final grade of test instead of passed subtests. Because of these changes, we decided to exclude the results from the 2013 NSTs in school year 6.

The Swedish compulsory school grading system has been revised several times across the time periods under study. To enable a direct comparison between these different time periods, the grade outcome variables were translated using the data matrix depicted in Table 1. We also identified all individuals born before 1990 who had obtained a university degree.

Covariates

Multivariable analyses adjusted for potential confounders, including perinatal complications, somatic indicators, year and season of birth, sex, known genetic syndromes, parental psychiatric morbidity, and parental sociodemographic factors.

Perinatal variables were collected from the MBR, including gestational age at birth, which was dichotomized ($<37/\geq37$ gestational week). Small for gestational age was defined as having a body length of less than -2 standard deviations. Birth weight was defined as low if <2500 g. Low Apgar score was defined as <7 at 5 min after birth. A binary variable was created for any perinatal complication (preterm, SGA, low Apgar, or low birth weight) and was used in the models.

Information on psychiatric diagnoses of the participants was extracted from the NPR with ICD codes 290–315 (ICD-8), 290–319 (ICD-9), and F00-F98 (ICD-10). Information on suicide attempts was also extracted from the NPR using the codes E950-E959 (ICD-8 and ICD-9) and X60-X84 (ICD-10). Data on psychiatric diagnoses of the participants were only extracted if they occurred before the time of outcome.

Age of the parents at the time of birth was identified and we used the mean age of the parents or the age of one parent if the other parent's age was missing for the multivariable analyses.

Data on maternal country of birth from the MBR were aggregated across regions: Sweden, other Nordic countries, and other countries. Information on parental educational attainment was retrieved from the LISA database and entered into the model as a categorical variable using four categories according to the Swedish Education Terminology: 0–9 years, 10–11 years, 12–14 years, and >14 years (university). The highest level of education obtained by either of the parents was used in the analyses.

Parental psychiatric morbidity was defined as having at least one psychiatric diagnosis (codes 290–315 in ICD-8, 290–319 in ICD-9, and F00-F98 in ICD-10) in the NPR, or a suicide attempt (codes E950-E959 in ICD-8 and ICD-9 and X60-X84 in ICD-10) in the NPR, or a death by suicide in the Cause-of-Death Register. This ordinal variable took a value of 0 if none of the parents had psychiatric morbidity, 1 if only one parent had psychiatric morbidity, and 2 if both parents had psychiatric morbidity. The variable was treated as time varying in the analyses.

Statistical analysis

Data were analyzed using STATA 17 Basic Edition.[27] We analyzed academic achievement at five different time points throughout the school years and early adulthood for the NSC group, using a separate subgroup analysis within people with psychiatric disorders to compare the academic achievement of participants with NSC to those without NSC. Due to lacking coverage in psychiatric outpatient setting in the databases used in the study, we did not perform separate analyses for those without a registered psychiatric diagnosis.

Binominal regression with logit link function and cluster robust standard errors were used to investigate odds ratios for the proportion of succeeded NST subtests in mathematics and Swedish. We used ordinal regression with cluster robust standard errors to investigate odds ratios for grades in mathematics and Swedish when finishing compulsory school and at upper secondary school. Conditional logistic regression with robust standard errors was used to investigate the odds ratio of the binary outcome of achieving a university degree or not among individuals with NSC compared to unaffected individuals.

The child's birth year was either excluded, included as a categorical variable (outcomes for school years 3 and 5), or modeled as a restricted cubic spline with three knots. To examine a possible moderating effect of sex, we estimated separate models where an interaction term of sex and the exposure of NSC regardless of psychiatric morbidity were modeled separately.

Results

The descriptive demographic characteristics for NSC individuals and the comparison cohort are presented in Table 2. The NSC individuals had a higher prevalence of perinatal complications, their parents were slightly older,

Table 2 Descriptive characteristics of NSC cases and matched comparison cohort.

Descriptive	NSC	Comparison cohort	p[a]
Total sample (Males n, %)	1110 (736, 66.3%)	10,689 (7131, 66.7%)	.77
Year of birth			.76
1965–1974	68 (6.1%)	680 (6.4%)	
1975–1984	323 (29.1%)	3230 (30.2%)	
1985–1994	87 (7.8%)	862 (8.1%)	
1995-	632 (56.9%)	5917 (55.2%)	
Perinatal complications	159 (15.8%)	916 (9.6%)	< .001
Mean age parents, m (sd)	31 (5.34)	30.4 (5.17)	< .001
Maternal region of birth			.039
Sweden	920 (87.2%)	8708 (85.2%)	
Other Nordic country	47 (4.5%)	405 (4.0%)	
Outside Nordic countries	88 (8.3%)	1105 (10.8%)	
Unknown	55 (5.0%)	471 (4.4%)	
Parental education (years)			.025
0–9	57 (5.2%)	584 (5.5%)	
10–11	285 (25.9%)	2534 (24.0%)	
12–14	393 (35.7%)	4068 (38.5%)	
> 14	365 (33.2%)	3371 (31.9%)	
Unknown	10 (1.0%)	130 (1.2%)	

[a] P-values denote results from chi-square tests.

and were to a larger extent born in Sweden or other Nordic countries. The groups were comparable on all other demographic measures. Among NSC individuals, the presence of psychiatric comorbidity was 14.6%, compared to 7.3% in the comparison cohort. The three most common psychiatric comorbidities were intellectual disability, language disorder, and anxiety disorders. For a more thorough review of these comorbidities, refer to Tillman et al., 2020.[17]

Descriptive data and results from the main analysis of the effect of NSC on academic achievement in the full sample are presented in Table 3. A negative association between NSC and NST scores in year 3 was observed for both mathematics and Swedish. No other significant effects were found across outcomes.

Results from the main analysis on the effect of NSC on academic achievement in the subgroup with psychiatric

Table 3 Adjusted odds ratios for the association between NSC status and various academic outcomes, for the full sample.

Academic outcomes	NSC cohort	Comparison cohort	aOR	95% CI	p
Mathematics	*% passed tests*	*% passed tests*			
[a]Year 3, National tests (N = 4155)	88.9%	92.8%	0.76	0.60–0.99	.020
[a]Year 5 or 6, National tests (N = 1053)	88.7%	91.6%	0.70	0.40–1.23	.238
	% with high achievement[d]	*% with high achievement*[d]			
[b]Year 9, Final grade (N = 5209)	37.1%	36.8%	1.09	0.90–1.32	.440
[b]Year 12, Upper secondary school grade (N = 1656)	47.0%	49.3%	0.90	0.67–1.22	.440
Swedish	*% passed tests*	*% passed tests*			
[a]Year 3, National tests (N = 3713)	91.0%	92.8%	0.69	0.54–0.89	.004
[a]Year 5 or 6, National tests (N = 993)	89.2%	89.5%	1.00	0.57–1.74	.953
	% with high achievement[d]	*% with high achievement*[d]			
[b]Year 9, Final grade (N = 5011)	39.3%	39.8%	1.02	0.84–1.24	.919
[b]Year 12, Upper secondary school grade (N = 1672)	47.5%	47.1%	1.13	0.83–1.55	.469
Higher education	*% with degree*	*% with degree*			
[c]Having a university degree (N = 4994)	19.5%	20.5%	0.82	0.61–1.10	.186

Models were adjusted for perinatal complications, sex, year of birth, parental age, maternal country of birth, parental psychiatric disorders, and education level.

[a] The outcome measure is the proportion of passed subtests; binominal regression derived adjusted odds ratios (aOR) express the odds to pass a subtest among the exposed compared to the unexposed.

[b] The outcome measure is final grade in ordinal scale; ordinal logistic regression derived aORs express the odds for higher grade among the exposed compared to the unexposed.

[c] Outcome is having a university degree; conditional logistic regression derived aORs express the odds for a university degree among exposed compared to unexposed.

[d] High achievement is defined as getting a grade 3 or 4 in a grade scale 1–4.

Table 4 Adjusted odds ratios for the association between NSC status and various academic outcomes, for the subgroup with psychiatric comorbidity.

Academic outcomes	NSC cohort	Comparison cohort	aOR	95% CI	*p*
Mathematics	*% passed tests*	*% passed tests*			
[a]Year 3, National tests (N = 212)	71.8%	87.9%	0.44	0.22–0.90	.025
[a]Year 5 or 6, National tests (N = 57)	62.5%	82.3%	CNA[5]	CNA[5]	-
	% with high achievement[d]	*% with high achievement*[d]			
[b]Year 9, Final grade (N = 171)	29.7%	19.4%	1.70	.68-4.26	.260
[b]Year 12, Upper secondary school grade (N = 65)	45.5%	44.4%	0.73	0.14–3.88	.713
Swedish	*% passed tests*	*% passed tests*			
[a]Year 3, National tests (N = 198)	81.2%	95.5%	0.45	0.21–0.98	.045
[a]Year 5 or 6, National tests (N = 55)	87.5%	89.8%	.241	0.04–1.67	.150
	% with high achievement[d]	*% with high achievement*[d]			
[b]Year 9, Final grade (N = 163)	42.9%	33.6%	2.48	1.08–5.70	.033
[b]Year 12, Upper secondary school grade (N = 64)	30.0%	50.0%	0.68	0.15–3.15	.624
Higher education	*% with degree*	*% with degree*			
[c]Having a University degree (N = 361)	7.8%	7.0%	CNA[e]	CNA[e]	-

Models were adjusted for perinatal complications, sex, year of birth, parental age, maternal country of birth, parental psychiatric disorders, and education level.

[a] The outcome measure is the proportion of passed subtests; Binominal regression derived adjusted odds ratios (aOR) express the odds to pass a subtest among the exposed compared to the unexposed.

[b] The outcome measure is the final grade in ordinal scale; ordinal logistic regression derived aORs express odds for higher grade among the exposed compared to unexposed.

[c] Outcome is having a university degree; conditional logistic regression derived aORs express the odds for a university degree among exposed compared to unexposed.

[d] High achievement is defined as getting a grade 3 or 4 in a grade scale 1-4.

[e] CNA = Convergence not achieved

comorbidity are presented in Table 4. Similar associations as those found in the total sample were observed in this subgroup, though numerically stronger. There was also a significantly positive association of NSC on final grade in Swedish in year 9 in this subgroup.

Stratified analyses comparing the three different grading systems employed during the study period are presented in Table 5. There were no significant effects of grading systems and due to selective attrition in the data set, only academic achievement from year 9 could be compared.

When the interaction effect of sex was included in analyses, no main effects (i.e., NSC in males) remained significant for the full NSC sample and the point estimates were mostly attenuated toward the null. Additionally, significant negative effects were found for the interaction term (i.e., NSC interacted with female sex) on NST scores in year 5 or 6 for mathematics and in year 3 for Swedish, indicating that the association between NSC and academic achievement was present in females only. These results are shown in Table 6.

Analyses regarding the influence of age at surgery in individuals with sagittal NSC treated before versus after six months of age with springs could not be performed due to insufficient cases with outcome data.

Discussion

The present study investigated the association between non-syndromic craniosynostosis (NSC) and academic achievement across childhood and early adulthood in a

Table 5 Association between NSC status and academic outcomes, stratified across grading systems.

Academic outcomes	1973-1993				1994-2011				2012-2013			
Mathematics	*n*	*aOR*	*95% CI*	*p*	*n*	*aOR*	*95% CI*	*p*	*n*	*aOR*	*95% CI*	*p*
[a]Year 9, Final grade	1095	1.43	0.91-2.24	.121	3271	1.03	0.81-1.31	.811	843	1.06	0.69-1.63	.421
Swedish	*n*	*aOR*	*95% CI*	*p*	*n*	*aOR*	*95% CI*	*p*	*n*	*aOR*	*95% CI*	*p*
[a]Year 9, Final grade	1051	1.13	0.65-1.94	.668	3167	1.01	0.80-1.29	.912	793	0.97	0.63-1.47	.789

Models were adjusted for perinatal complications, sex, year of birth, parental age, maternal country of birth, parental psychiatric disorders, and education level.

[a] The outcome is the final grade in ordinal scale; ordinal logistic regression derived aORs express the odds for higher grade among the exposed compared to the unexposed.

Table 6 Effect modification by sex for the association between NSC status and academic outcomes.

Academic outcomes	NSC status (Effect in males)			Interaction NSC*female (How the NSC effect differs in females compared to males)		
Mathematics	*aOR*	*95% CI*	*p*	*aOR*	*95% CI*	*p*
[a]Year 3, National tests (N = 4155)	0.92	0.67–1.25	.58	0.64	0.40–1.02	.061
[a]Year 5 or 6, National tests (N = 1053)	1.13	0.55–2.32	.730	0.26	0.08–0.80	.020
[b]Year 9, Final grade (N = 5209)	1.02	0.82–1.28	.847	1.25	0.82–1.90	.294
[b]Year 12, Upper secondary school grade (N = 1656)	0.84	0.58–1.21	.341	1.30	0.70–2.40	.401
Swedish	*aOR*	*95% CI*	*p*	*aOR*	*95% CI*	*p*
[a]Year 3, National tests (N = 3713)	0.88	0.64–1.20	.418	0.45	0.27–0.75	.002
[a]Year 5 or 6, National tests (N = 993)	1.15	0.62–2.12	.662	0.50	0.14–1.78	.284
[b]Year 9, Final grade (N = 5011)	1.05	0.84–1.32	.653	0.90	0.59–1.38	.625
[b]Year 12, Upper secondary school grade (N = 1672)	1.13	0.77–1.66	.521	1.00	0.52–1.92	.999
Higher education	*aOR*	*95% CI*	*p*	*aOR*	*95% CI*	*p*
[c]Having a University degree (N = 4994)	0.94	0.66–1.35	.758	0.70	0.39–1.26	.236

Models were adjusted for perinatal complications, sex, the interaction of female sex and NSC, year of birth, parental age, maternal country of birth, parental psychiatric disorders, and education level.

[a] The outcome measure is the proportion of passed subtests; binominal regression derived adjusted odds ratios (aOR) express the odds to pass a subtest among females compared to males in the exposed group.

[b] The outcome measure is the final grade in ordinal scale; ordinal logistic regression derived aORs express the odds for higher grade among the exposed compared to the unexposed.

[c] The outcome is having a university degree; conditional logistic regression derived aORs express the odds for a university degree among exposed compared to unexposed.

large sample of operated patients in Sweden. Overall, small negative associations with academic achievement were found in early primary school. There was some evidence for a mediating influence of psychiatric comorbidity and the majority of the associations were carried by females with NSC. Overall, the results are in line with previous studies showing relatively small negative associations between NSC and academic achievement.[15,19]

The significant effects found in primary school seemed to become less pronounced during the later school years. One possible explanation for this is that the cognitive effects of NSC, which might be attributed to skull growth restrictions, are most prominent early in life and then lessen as neural plasticity improves cognitive networks in the brain as the child ages.

A second possible explanation is that the negative association between NSC and academic achievement in the early school years prompted provision of special educational support, which may have improved academic achievement over time. Unfortunately, we do not have data regarding such special educational support to investigate this hypothesis further.

A third explanation might be that a substantial proportion of the cognitive effects in NSC is manifested by an increased prevalence of intellectual disability, with a prevalence of 3.6% among NSC cases in a previous study on the same data set.[17] In Sweden, this diagnosis gives access to special schools under a different curriculum where grades are not issued and NSTs not undertaken. This means that follow-up outcome data from these individuals may not have been available simply because these individuals never took the tests constituting our outcomes.

Additionally, it is important to note that while our results for later time points are non-significant, and the point estimates are attenuated toward the null, the confidence intervals are not tight enough to warrant a claim of equivalence for NSC versus not NSC during the later school years.

Overall, the additive effects of psychiatric comorbidity on academic achievement were relatively limited and less pronounced than expected. Again, it is possible that provision of special supports might account for these limited associations given that the subgroup with NSC and psychiatric comorbidity would likely be identified as having the greatest need for special schooling. This may also in part explain the unexpected positive association found between NSC and grades for the 9th school year in this subgroup.

The significant negative effect on academic achievement in females with NSC was similarly unexpected, running counter to previous findings of more substantial cognitive difficulties in boys with NSC.[16] However, these findings are in line with other research on individuals with neurodevelopmental disorders showing a higher burden of disease in females that meet diagnostic thresholds.[28,29] Additionally, gender differences among NSC subtypes, with an overrepresentation of girls with the unicoronal subtype as noted in previous studies on Swedish NSC patient populations, might contribute to this association.[4] Regardless, these results are important to consider in the assessment of girls with NSC during preschool and early school years.

We believe our results align with the scarce previous findings and our own clinical experience of relatively mild effects of NSC on academic achievement. However, the results also point to the importance of identifying individuals at risk of exhibiting academic difficulties already before school age, given that effects seem to be most pronounced during the first school years. Additionally, the

academic deficits found specifically in females warrant attention given to girls with NSC in referral for special support in academic settings.

Strengths and limitations

To the best of our knowledge, this study is the largest to date investigating the link between NSC and academic achievement. Additionally, the study investigates real-world outcomes such as grades and NST scores of particular importance to long-term prognosis in terms of higher educational attainment and later life course. The study was also able to consider and statistically control for a large set of confounders, though as is common in observational studies we still cannot rule out unmeasured confounding.

However, despite its substantial sample size, the present study was not sufficiently large for all planned subanalyses to be performed such as age at surgery in sagittal NSC due to selective data attrition and modeling issues. Additionally, several factors such as the provision of special educational support was beyond the scope of the data making us unable to perform analyses that might have shed light on some of the possible explanations of our results. Future studies taking such factors into consideration might hopefully be able to address these issues.

The present study also relied on registry data of NSC, which does not consider the fact that genetic studies have made significant advances during recent decades identifying more individuals with genetic syndromes previously identified as nonsyndromic. As described under our methods, we have taken steps to account for this confounder as far as our dataset allowed, though the possibility of confounding based on genetic syndromes cannot be ruled out completely.

Conclusion

This study has shown some but relatively mild and temporal associations between NSC and academic achievement, primarily in the early school years. There was some evidence for a more substantial association in those with psychiatric comorbidity and in females. The results have clinical significance in terms of identifying children with NSC in need of referral for special support in educational contexts. The results also acknowledge that in the long run, surgically treated children with NSC often perform equally well in school as children without NSC, which is an important message to parents of children with NSC.

Ethical approval

Data were pseudonymized and collected under approval by the Uppsala Ethics Committee (Reg. No. 2012/363).

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Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bjps.2024.11.014.

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