

REGULAR ARTICLE

Shared unmeasured characteristics among siblings confound the association of Apgar score with stress resilience in adolescence

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ABSTRACT

Aim: We investigated the association between low Apgar score, other perinatal characteristics and low stress resilience in adolescence. A within-siblings analysis was used to tackle unmeasured shared familial confounding.

Methods: We used a national cohort of 527 763 males born in Sweden between 1973 and 1992 who undertook military conscription assessments at mean age of 18 years (17–20). Conscription examinations included a measure of stress resilience. Information on Apgar score and other perinatal characteristics was obtained through linkage with the Medical Birth Register. Analyses were conducted using ordinary least squares and fixed-effects linear regression models adjusted for potential confounding factors.

Results: Infants with a prolonged low Apgar score at five minutes had an increased risk of low stress resilience in adolescence compared with those with highest scores at one minute, with an adjusted coefficient and 95% confidence interval of -0.26 (-0.39 , -0.13). The associations were no longer statistically significant when using within-siblings models. However, the associations with stress resilience and birthweight remained statistically significant in all analyses.

Conclusion: The association with low Apgar score seems to be explained by confounding due to shared childhood circumstances among siblings from the same family, while low birthweight is independently associated with low stress resilience.

INTRODUCTION

The Apgar score was initially developed to assess the potential need for resuscitation. For more than 60 years, it has been used to measure the condition of newborn infants based on heart rate, respiration, colour, muscle tone and reflex irritability (1). Subsequent studies have demonstrated the Apgar score's ability to predict short-term and long-term cognitive outcomes (2,3) as well as developmental impairment (4,5). As an index of early neonatal conditions and health, the Apgar score could, in theory, also be used as a measure of stressful exposures during delivery and early life. Low scores have been associated with perinatal and future potentially stressful medical conditions and procedures such as prolonged labour, emergency caesarean delivery, use of intramuscular injections for intrapartum analgesia, infections and later disease (6). There is evidence, partly

from animal models, that important parameters of the physiological response to stress are set in early life, and poor control of the stress response can persist across life (7). Animal models have demonstrated the importance of very early life exposures and development of the stress response. Such early stressful exposures inhibit expression of glucocorticoid receptors in areas of the brain such as the

Key notes

- Impaired foetal development has previously been associated with increased risk of low stress resilience, but whether there is an independent association is less well established.
- The association with low Apgar score seems to be explained by shared familial childhood circumstances among siblings.
- Low birthweight is independently associated with low stress resilience, signalling the importance of *in utero* influences on development of the ability to cope with stress in later life.

Abbreviations

CI, Confidence interval; OLS, Ordinary least squares linear regression.

hippocampus. The influence on receptor expression results in poor negative feedback control of glucocorticoid stress hormones such as cortisol (7). Poor control of the stress response may further result in a physiological stress arousal of higher magnitude and longer duration, and could therefore increase risk of potentially damaging chronic arousal.

In humans, the inability to cope with stress – low stress resilience – is associated with a raised risk of mental and physical disease in later life (8–10). Identifying possible causes of low stress resilience could help identify intervention targets from an early age. Recent studies have identified associations with early stress in childhood, in form of bereavement (11) and parental cancer (12), and subsequent low stress resilience in young adults. However, whether consequences of early life exposure to stress, signalled by a low Apgar score, are associated with low stress resilience persisting until adolescence has been incompletely described. Previous studies have shown an increased risk of chronic disease in children with low Apgar scores (13–15). A low Apgar score at five minutes is likely to confer a higher risk than a correspondingly low score at one minute, as a prolonged low score is likely to signal more than just transient distress associated with delivery. Therefore, we performed a population-based study to investigate the role of a prolonged low Apgar score, as well as other perinatal characteristics, and subsequent stress resilience in adolescence in a national cohort of conscripts. Family socioeconomic circumstances and impaired foetal growth have previously been linked with stress resilience (16).

METHODS

Swedish register data

This study used data from national registers. The study population was based on men born in Sweden between 1973 and 1992 whose birth was recorded in the Medical Birth Register and with parents identified in the Multi-Generation Register ($n = 1\,055\,980$). Coverage of the Medical Birth Register is high as $<2\%$ of births were not recorded (17), and linkage to parents was successful for 80% of infants born in 1970–1980 and over 95% by 2000. Conscript examinations were obligatory until 2010 when conscription was no longer mandatory. Only a small proportion of men were exempt from the examinations usually due to health reasons. The enrolment rate was high during most of the study period, but declined and relied on volunteers to a greater extent in the later years. A total of 740 661 men in our population were assessed for military conscription between 1987 and 2010. Women were excluded in the study as only a limited number of women undertook the conscription examination. Subjects with invalid data ($n = 1789$) were excluded, as well as men with conscription assessment over age 20 years ($n = 2813$), and men with missing data for variables used in the study (up to $n = 212\,898$), including 10 154 men with missing data for the Apgar score. Many of the exclusions were for men who were unsuitable for military service and did not undertake

these tests (18). The final study population comprised of 527 763 men. The study was approved by the Regional ethics committee in Uppsala, Sweden (DNR 2014/22).

Outcome measure

Stress resilience was assessed as part of the conscription examination to evaluate the potential ability to cope with stress in military service. All men were evaluated by trained military psychologists by combining answers to a semi-structured interview and self-completion questionnaire. The interview covered areas relevant to general everyday life including social maturity, leisure interests, psychological motivation and emotional stability (16,19). The procedure remained relatively unchanged during our study period, with only a minor revision in 1995 (19). Stress resilience on a nine-level normally distributed score (continuous variable with a mean of 4.95 and standard deviation of 1.78) was produced with higher values indicate greater stress resilience, and this measure has been previously used in research. The measure is also known to be relevant to stress-related outcomes arising from nonmilitary conflict situations, as it is associated with diagnoses and treatment for anxiety and depression in later adulthood in this general population-based sample (8–10). The vast majority of the potential conscripts did not experienced military conflict, not even for a short period.

Exposure measure

Since 1973, the Swedish Medical Birth Register has recorded the Apgar score measured at one and five minutes after birth. The score ranges from 0 to 2 in five different aspects of the condition of the newborn, generating a sum of the ratings with a maximum of 10 (range 0–10). Infants born in a better condition have a score of 9–10 at one minute. In this study, infants were classified depending on their Apgar scores at both one and five minutes. We focused on the five-minute score, because a prolonged low score at five minutes is likely to signal more than just transient distress associated with delivery. In the earlier period, 1973–1983, the Apgar variable from five minutes tended to be missing if the infant recorded a high score at one minute. Therefore, we created a combined Apgar score based on the one-minute score which is most complete; all infants already with the highest score (9,10) at one minute stayed in that category. This category was used as the reference. Infants with a score lower than 9 at one minute (0–8) were grouped based on their five-minute score and grouped into the following scores: 0–2, 3–5, 6–8 and 9–10.

Potential confounding measures

Gestational age, birthweight, parental highest social position, maternal education, maternal age at birth and number of older siblings were included as potential confounding factors. Perinatal characteristics were recorded in the Medical Birth Register. Socioeconomic measures were derived from the Total Population Register, the Population and Housing Census 1970–1985 and the Longitudinal Integrated Database for Health Insurance and Labour

Market Studies beginning in 1990. The highest position for the parents from the year closest to the cohort member's birth was defined using an approximation of the European Socioeconomic Classification system. Maternal educational level was derived for the year closest to the cohort member's birth from 1990 to 1995. Year of conscription assessment was also included as a potential confounding factor.

Statistical analysis

To rule out the potential influence of unmeasured confounding by shared familial circumstances among siblings, the association of the Apgar score with subsequent risk of low stress resilience in adolescence was assessed both with standard analyses and also within-siblings analyses (20). The standard analyses used ordinary least squares linear regression (OLS) and within-siblings analyses used fixed-effects (within) linear models. In the OLS regression, the cluster-robust sandwich estimator was used to account for data clustering by family, but it did not influence the results at the level of precision presented. Sibling sets from the same family were identified based on having the same biological mother. Adjustment was for gestational age in five periods, birthweight in fifths, maternal age at birth in seven age groups, number of older siblings (0–3+), maternal education in three categories, head of household's highest social position in three categories and year of conscription in four periods. To examine whether associations were explained by subsequent chronic disease, we performed a sensitivity analysis excluding men with any diagnosis at conscription examination. Analyses were performed using Stata/SE version 14 (StataCorp, College Station, TX, USA). Coefficients were estimated with 95% confidence intervals (CI), and statistical significance was defined as $p < 0.05$.

RESULTS

The total study population comprised of 527 763 men. Mean age at conscription examinations was 18 years (range 17–20). Overall, 619 subjects (0.1%) had an Apgar score of 0–2, 2005 subjects (0.4%) had a score of 3–5, 16 008 subjects (3.0%) had a score of 6–8, and 63 839 subjects (12.1%) had a score of 9–10 at five minutes. The remaining 445 292 subjects (84.4%) had a score of 9–10 at one minute, and these were used as the reference category. Infants with low gestational age, low birthweight, having the oldest and youngest mothers, a high number of older siblings, mothers with low education and low parental socioeconomic position in adolescence were more likely to have low stress resilience (Table 1). When using the chi-square test, all covariates were statistically significantly associated with a low Apgar score (data not shown). Lowest category of gestational age and birthweight, having the oldest and youngest mothers, having three or more siblings or no siblings at all and having mothers with low education were associated with low Apgar score. Less clear differences were observed for parental highest social position.

Table 1 Distribution of stress resilience in adolescence by the Apgar score and the other characteristics

	Stress resilience (1–9) Frequency (mean ± standard deviation)
Apgar score at five minutes	
0–2	619 (4.71 ± 1.77)
3–5	2005 (4.89 ± 1.78)
6–8	16 008 (4.89 ± 1.78)
9–10	63 839 (4.94 ± 1.78)
9–10 (at one minute)	445 292 (4.96 ± 1.78)
Gestational age (weeks)	
22–32	3061 (4.64 ± 1.69)
33–37	49 333 (4.90 ± 1.78)
38–39	177 965 (4.95 ± 1.78)
40–41	243 887 (4.97 ± 1.78)
42–45	53 517 (4.95 ± 1.79)
Birthweight (g)	
276–3150	86 058 (4.81 ± 1.77)
3152–3450	96 269 (4.91 ± 1.78)
3451–3710	109 079 (4.96 ± 1.77)
3711–4000	112 916 (5.01 ± 1.78)
4001–6970	123 441 (5.02 ± 1.79)
Mother's age when giving birth	
Under 18	8597 (4.39 ± 1.79)
18–24	188 683 (4.84 ± 1.77)
25–29	195 574 (5.06 ± 1.77)
30–34	101 694 (5.01 ± 1.77)
35–39	29 470 (4.90 ± 1.78)
40–44	3648 (4.77 ± 1.80)
45+	97 (4.48 ± 1.82)
Number of older siblings	
0	223 384 (5.02 ± 1.77)
1	202 502 (4.97 ± 1.77)
2	77 828 (4.83 ± 1.78)
3+	24 049 (4.55 ± 1.80)
Maternal educational (years)	
≤9	114 103 (4.52 ± 1.74)
10–12	262 982 (4.91 ± 1.75)
13+	150 678 (5.34 ± 1.78)
ESeC, N (%)	
High	174 710 (5.31 ± 1.77)
Intermediate	90 335 (5.10 ± 1.74)
Low	262 718 (4.67 ± 1.75)
Year of conscription	
91/95	178 980 (5.09 ± 1.75)
96/00	151 240 (4.83 ± 1.81)
01/04	130 521 (4.82 ± 1.82)
05/10	67 021 (5.10 ± 1.67)
Diagnosis at conscription	
Yes	321 186 (4.58 ± 1.81)
No	206 577 (5.53 ± 1.57)

ESeC = the European Socioeconomic Classification system of household's highest social position.

Table 2 shows the unadjusted and adjusted coefficients from the OLS and fixed-effects linear models for the association between the Apgar score, other perinatal characteristics and stress resilience. The unadjusted OLS coefficients indicated an increased risk of low stress resilience for infants with the lowest Apgar score (0–2). In this model,

infants with lowest Apgar scores, 0–2 at five minutes, had a statistically significantly risk of developing lower stress resilience in adolescence compared with the reference group with Apgar scores 9–10 at one minute. The coefficient of -0.25 ($-0.39, -0.12$) <0.001 indicates a 0.25 unit lower stress resilience on the scale 1–9. When adjusted for potential confounding factors, the association remained statistically significant. A sensitivity analysis was performed restricted to those without a medical diagnosis by conscription examination in adolescence and thus free of chronic disease (Table 3). Despite the notable reduction in sample size, a statistically significant association with a similar pattern as in main analysis was found. However, in the sensitivity analysis, the association had somewhat higher magnitude estimates. The associations with low Apgar score and stress resilience were of lower magnitude when using within-siblings models and no longer statistically significant (Table 2). Within-sibling analyses estimated the effect of Apgar score on the variation of stress resilience within a set of siblings after taking account for between family variations.

The association with lowest gestational age and stress resilience was statistically significant in all models, but became nonsignificant when adjusted for other confounders in the within-siblings model. Lowest birthweight was independently and statistically significantly associated with low stress resilience in all models, with similar magnitude associations across all adjusted models. As shown in Table 2, the coefficient of -0.15 indicates a 0.15 unit decrease in stress resilience on the scale 1–9 in adjusted within-siblings model. As seen in Table 1, low birthweight infants (276–3150 g) develop, on average, a stress resilience score of 4.81, while the reference category (3451–3710 g) develop a higher stress resilience score on average by 0.15 units.

Those who had lower Apgar scores tended to be less likely to complete the conscription assessment. A comparison of the study population with complete data for all covariates ($n = 527\ 763$) and the broader population with missing data for some covariates ($n = 586\ 096$) indicates that the study population has slightly higher average stress resilience and slightly higher average birthweight, with mean values (and standard deviation) of 4.95 (1.78) compared with 4.93 (1.79); and 3576 g (549), compared with 3571 g (549), respectively. Among those with an Apgar score, the study population has a similar proportion with lowest Apgar score of 0–2 (0.12%) compared with the more complete population (0.12%). Those in the study population had a smaller proportion of parents in the lowest ESeC category (49.78%) compared with the larger population (49.92%). Similarly, a slightly lower proportion of mothers in the study population (21.11%) had the lowest educational level, compared with the wider population (22.62%).

When comparing associations of Apgar score with stress resilience for those with and without missing covariates, the results were almost identical. The coefficients (and 95% CI) from the OLS model for the population with complete data on Apgar and stress resilience ($n = 586\ 096$) are -0.31

($-0.43, -0.18$). The coefficients for the final study population ($n = 527\ 763$) are -0.31 ($-0.44, -0.18$), adjusted for year of conscription, presence of older siblings and mother's age in both populations. The corresponding coefficients from within-sibling analysis are -0.16 ($-0.44, 0.11$) and -0.16 ($-0.41, 0.10$), respectively.

DISCUSSION

This general population-based cohort study of males demonstrated that a low Apgar score is associated with a higher risk of developing low stress resilience using OLS linear models. This association persisted at least until adolescence and did not appear to be explained by the presence of chronic disease. However, the association was eliminated when using within-siblings models that account for confounding that is shared between siblings in the same family, for example cultural, material and parental characteristics or other unmeasured factors (21). Another birth characteristic, low birthweight, was more independently associated with low stress resilience in all models, while the results for younger gestational age were less conclusive.

We are not aware of any previous studies that have studied the association between a low Apgar score and low stress resilience in adolescence. Apart from chronic disease associated with impaired foetal development, the experience of perinatal distress and subsequent medical care may represent a form of stressful exposure relevant to neuroendocrine or cognitive development and future stress resilience. Infants born with a low Apgar score, and thus in a poorer health, have a higher risk of experiencing some stressful exposures including complications during delivery (6), but also later exposures during early childhood. Childhood stressful circumstances could include pain, discomfort and maternal separation due to maternal disease that extends into childhood, or medical procedures of the infant such as being transferred to the intensive therapy unit, a situation that would influence time spent with the mother. There is evidence that early experiences involving some manipulation that results in disruption of the mother–infant relationship can have long-term influences on the behavioural and endocrine responses to stress (22,23). Other psychological consequences for infants born with a low Apgar score include risk of disease in childhood. Children with chronic illnesses are more likely to have emotional, behavioural and psychiatric symptoms than healthy children, and may be psychologically affected by medical treatments (24).

However, adjustment for potential confounders did not markedly change the magnitude of the associations in the OLS models, but socioeconomic characteristics of the family and number of older siblings had the most influence. Number of older siblings may indicate familial social characteristics, but also aspects of personality development and cognitive function (25–27), and has previously been associated with stress resilience in adolescence (28). The hierarchy of siblings can create stressful intersibling interactions and unequal allocation of resources between

Table 2 Coefficients with 95% CIs for the association of Apgar score at birth, and other perinatal characteristics, and stress resilience score in adolescence (n = 527 763)

	OLS linear regression coefficients		Within-siblings coefficients	
	Unadjusted*	Adjusted*	Unadjusted*	Adjusted*
Apgar score at five minutes				
0-2	-0.25 (-0.39, -0.12), <0.001	-0.26 (-0.39, -0.13), <0.001	-0.10 (-0.38, 0.18), 0.495	-0.15 (-0.42, 0.13), 0.308
3-5	-0.07 (-0.15, 0.01), 0.084	-0.02 (-0.10, 0.06), 0.601	0.03 (-0.13, 0.20), 0.714	-0.04 (-0.21, 0.12), 0.604
6-8	-0.07 (-0.10, -0.04), <0.001	-0.04 (-0.07, -0.02), 0.002	0.00 (-0.06, 0.06), 0.920	-0.05 (-0.11, 0.12), 0.113
9-10	-0.01 (-0.03, 0.00), 0.109	-0.02 (-0.04, -0.00), 0.022	0.01 (-0.02, 0.04), 0.522	-0.03 (-0.06, 0.00), 0.065
9-10 (at one minute)	Reference	Reference	Reference	Reference
Gestational age (weeks)				
22-32	-0.33 (-0.39, -0.27), <0.001	-0.10 (-0.17, -0.04), 0.001	-0.24 (-0.39, -0.08), 0.002	-0.10 (-0.26, 0.05), 0.196
33-37	-0.07 (-0.09, -0.06), <0.001	0.09 (0.07, 0.11), <0.001	0.00 (-0.04, 0.04), 0.934	0.10 (0.06, 0.15), <0.001
38-39	-0.02 (-0.03, -0.01), 0.001	0.04 (0.03, 0.05), <0.001	-0.04 (-0.06, -0.01), 0.004	-0.04 (-0.00, 0.05), 0.063
40-41	Reference	Reference	Reference	Reference
42-45	-0.02 (-0.03, 0.00), 0.056	-0.04 (-0.05, -0.02), <0.001	0.07 (0.03, 0.10), <0.001	-0.00 (-0.03, 0.03), 0.896
Birthweight (g)				
276-3150	-0.15 (-0.16, -0.13), <0.001	-0.15 (-0.17, -0.13), <0.001	-0.05 (-0.09, -0.01), 0.007	-0.15 (-0.20, -0.10), <0.001
3152-3450	-0.05 (-0.07, -0.04), <0.001	-0.06 (-0.07, -0.04), <0.001	-0.03 (-0.06, 0.01), 0.072	-0.09 (-0.13, -0.05), <0.001
3451-3710	Reference	Reference	Reference	Reference
3711-4000	0.05 (0.03, 0.06), <0.001	0.05 (0.04, 0.07), <0.001	-0.03 (-0.06, 0.00), 0.066	-0.03 (-0.06, 0.01), 0.097
4001-6970	0.06 (0.04, 0.07), <0.001	0.09 (0.07, 0.10), <0.001	-0.07 (-0.11, -0.04), <0.001	-0.01 (-0.04, 0.02), 0.411
Mother's age when giving birth				
Under 18	-0.67 (-0.71, -0.63), <0.001	-0.42 (-0.46, -0.38), <0.001	0.45 (0.37, 0.53), <0.001	-0.01 (-0.10, 0.09), 0.911
18-24	-0.22 (-0.23, -0.21), <0.001	-0.09 (-0.11, -0.08), <0.001	0.24 (0.22, 0.26), <0.001	0.03 (-0.01, 0.06), 0.102
25-29	Reference	Reference	Reference	Reference
30-34	-0.04 (-0.06, -0.03), <0.001	-0.03 (-0.04, -0.01), <0.001	-0.21 (-0.24, -0.19), <0.001	-0.06 (-0.09, -0.02), 0.001
35-39	-0.15 (-0.18, -0.14), <0.001	-0.07 (-0.09, -0.05), <0.001	-0.35 (-0.40, -0.30), <0.001	-0.09 (-0.16, -0.03), 0.006
40-44	-0.29 (-0.35, -0.21), <0.001	-0.12 (-0.18, -0.07), <0.001	-0.44 (-0.59, 0.28), <0.001	-0.13 (-0.29, 0.03), 0.118
45+	-0.58 (-0.94, -0.22), 0.002	-0.24 (-0.61, 0.12), 0.193	-1.34 (-2.75, 0.08), 0.064	-0.91 (-2.32, 0.51), 0.208
Number of older siblings				
0	Reference	Reference	Reference	Reference
1	-0.05 (0.06, -0.04), <0.001	-0.11 (-0.12, -0.10), <0.001	-0.23 (-0.25, -0.22), <0.001	-0.21 (-0.23, -0.19), <0.001
2	-0.19 (-0.20, -0.17), <0.001	-0.21 (-0.22, -0.19), <0.001	-0.42 (-0.44, -0.39), <0.001	-0.36 (-0.40, -0.32), <0.001
3+	-0.47 (-0.50, -0.45), <0.001	-0.39 (-0.41, -0.36), <0.001	-0.52 (-0.57, -0.48), <0.001	-0.43 (-0.51, -0.36), <0.001
Maternal education (years)				
≤9	-0.82 (-0.84, -0.81), <0.001	-0.54 (-0.55, -0.52), <0.001	-0.68 (-1.54, 0.18), 0.121	-1.10 (-1.96, -0.25), 0.011
10-12	-0.44 (-0.45, -0.43), <0.001	-0.23 (-0.25, -0.22), <0.001	-0.32 (-0.82, 0.20), 0.226	-0.53 (-1.09, -0.02), 0.041
13+	Reference	Reference	Reference	Reference
ESeC				
High	Reference	Reference	Reference	Reference
Intermediate	-0.21 (-0.23, -0.20), <0.001	-0.08 (-0.09, -0.06), <0.001	0.05 (0.00, 0.10), 0.037	0.00 (-0.04, 0.04), 0.961
Low	-0.64 (-0.65, -0.63), <0.001	-0.41 (-0.42, -0.40), <0.001	0.16 (0.12, 0.21), <0.001	0.03 (-0.01, 0.07), 0.138

Adjusted for year of conception, gestational age, birthweight, maternal age at delivery, number of older siblings, maternal education and household's highest social position (ESeC).

*Coefficient (95% CI), p-value.

Table 3 Coefficients with 95% CIs for the association of Apgar score at birth and stress resilience score in adolescence for men without a diagnosis at conscription (n = 206 577)

	OLS linear regression coefficients		Within-siblings coefficients	
	Unadjusted*	Adjusted*	Unadjusted*	Adjusted*
Apgar score at five minutes				
0–2	–0.42 (–0.61, –0.23), <0.001	–0.35 (–0.54, –0.17), <0.001	–0.43 (–0.88, 0.02), 0.063	–0.38 (–0.83, 0.06), 0.091
3–5	–0.08 (–0.12, 0.04), 0.166	–0.06 (–0.17, 0.05), 0.302	–0.03 (–0.38, 0.31), 0.852	–0.15 (–0.49, 0.19), 0.402
6–8	–0.08 (–0.19, 0.03), <0.001	–0.04 (–0.08, –0.00), 0.045	–0.06 (–0.17, 0.05), 0.306	–0.12 (–0.23, 0.01), 0.030
9–10	–0.01 (–0.03, 0.01), 0.444	0.00 (–0.02, 0.02), 0.980	0.03 (–0.03, 0.09), 0.275	–0.00 (–0.06, 0.06), 0.914
9–10 (at one minute)	Reference	Reference	Reference	Reference

*Coefficient (95% CI), p-value.

Adjusted for year of conscription, gestational age, birthweight, maternal age at delivery, number of older siblings, maternal education and household's highest social position (ESeC).

siblings. It is also likely that maternal previous births, that mean having older siblings, could have an influence on the *in utero* environment as foetal characteristics such as gestational age and birthweight have been linked with stress resilience (16). Low birthweight has previously been associated with intellectual performance in adolescence, and cognitive function may also influence stress resilience (8). However, the association with a low Apgar score and stress resilience was little influenced by other birth characteristics.

The within-siblings analyses eliminated the association of low Apgar score with stress resilience, suggesting that shared familial childhood circumstances among siblings could explain the association that was observed in the OLS linear regression analysis. We know family conditions are very important and that siblings share cultural and parental characteristics that influence development. Material and social disadvantage may increase the risk of both low stress resilience and also risk of a low Apgar score. The measure of material and cultural circumstance that we used in this study is relatively imprecise, and further our study lacked information on social interactions within the family. This may be likely to explain that the results from the OLS linear regression suffered from residual confounding. Therefore, it appeared that a low Apgar score do not influence the development of low stress resilience directly, but disadvantaged familial circumstances influence both a low Apgar score at birth and a poorer development of stress resilience. However, we found an independent association between low birthweight and low stress resilience independent of shared familial childhood circumstances, signalling the importance of *in utero* influences on development of the ability to cope with stress as has been demonstrated previously (16).

Strengths and limitations

Our study was based on a large national cohort of more than 500 000 infants, who all survived and participated in conscription assessments at the average age of 18 years. Although the study had relatively few missing data, many of the exclusions were for men who were deemed to be

unsuitable for military service including because of chronic illness, leading to missing values for conscription assessment variables. Infants with low Apgar scores were less likely to be enrolled in the conscription assessment, as were those from more disadvantaged backgrounds. As disadvantage is associated with lower stress resilience (22), it is possible that associations with low stress resilience are somewhat attenuated. However, when we compared associations of Apgar score with stress resilience for those with and without missing data for conscription assessment covariates, the results were almost identical. This was true for both the conventional and within-sibling models.

The study had an opportunity to control for several important potential confounding factors such as socioeconomic characteristics and birthweight (16). Our measure of stress resilience was collected as part of the assessment for compulsory military enlistment in Sweden and was used as an indicator how well the men could cope with daily life and military deployment. This measure was likely to reflect several components such as psychological, social and physiological factors. Stress resilience has been linked with subsequent psychiatric and somatic disease in adulthood (8–10). However, we did not look at the possible processes in childhood that influence low stress resilience, and we only had one measure of stress resilience. Although different measures of stress resilience at conscription have been used during the period relevant for this study, they signal some stability over time. A potential limitation was that we could not be definitive about the biological mechanisms underlying the Apgar score, which may be heterogeneous. Previous studies have suggested interobserver and intra-observer variability in scoring, particularly among preterm infants (29,30). Any measurement error in Apgar score might result in bias towards the null, potentially underestimating the association between Apgar score and stress resilience. In order to compare infants with a prolonged low Apgar score with healthy infants, we used Apgar scores from two time points, one and five minutes. As few women were conscripted at this time, any interpretation may be limited to males only.

CONCLUSIONS

Perinatal characteristics are associated with risk of poor stress resilience in late adolescence. The association with low Apgar score and low stress resilience seems to be explained by confounding due to shared childhood characteristics among siblings from the same family. Low birthweight is independently associated with low stress resilience, signalling the importance of *in utero* influences on development of the ability to cope with stress.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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