Associations between birth characteristics and eating disorders across the life course: findings from 2 million males and females born in Sweden 1975-1998

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Abstract

Birth characteristics predict a range of major physical and mental disorders, but findings regarding eating disorders (ED) are inconsistent and inconclusive. This total-population Swedish cohort study therefore identified 2,015,862 males and females individuals born 1975-1998, and followed them for anorexia nervosa, bulimia nervosa and ED not-otherwise-specified until end 2010. We examined associations with multiple family and birth characteristics, and conducted within-family analyses to test for maternal-level confounding. In total 1019 males and 15,395 females received an ED diagnosis. Anorexia nervosa was independently predicted by multiple birth (adjusted hazard ratio 1.33 (95% confidence interval 1.15, 1.53) for twin/triplet vs. singleton) and lower gestational age (0.96 (0.95, 0.98) per extra week of gestation, with a clear dose-response pattern). Within-family analyses provided no evidence of residual maternal-level confounding. Higher birthweight for gestational age showed a strong, positive dose-response association with bulimia nervosa (1.15 (1.09, 1.22) per standard deviation increase), again with no evidence of residual maternal-level confounding. We conclude that some perinatal characteristics may play causal, disease-specific roles in the development of ED, including via perinatal variation within the normal range. Further research into the underlying mechanisms is warranted. Finally, several large population-based studies of anorexia nervosa have been conducted in twins: it is possible that these studies considerably overestimate prevalence.

Key Words: eating disorders; life course; birth characteristics; males; females; socioeconomic factors

Abbreviations: AN = anorexia nervosa, BN = bulimia nervosa, ED = eating disorders, EDNOS = eating disorders not-otherwise-specified, ICD = International Classification of Disease.

Introduction

The past two decades have seen substantial research interest in the developmental origins of health and disease, including the impacts of intrauterine conditions across the lifecourse [1]. There is strong evidence that adverse circumstances during pregnancy increase the risk of many leading physical diseases [2-4], and growing evidence that the same applies to several psychiatric disorders [5-9]. This includes some suggestion that the association between early life characteristics and psychiatric disorders is particularly strong among socio-economically disadvantaged groups [5].

Associated with high morbidity and mortality [10, 11], eating disorders (ED) are among the psychiatric conditions which have been linked to adverse birth outcomes. To date, however, studies have been inconsistent and inconclusive. Some report that either higher birthweight or higher birthweight for gestational age predict increased anorexia nervosa (AN) [12] or bulimia nervosa (BN) [13]; others report no association with AN [13-17] and a negative association with BN [17]. Similarly, some studies find that preterm birth or shorter gestational age predict ED [9, 18] or AN [13-15], but others find no association [16, 17, 19]. There are also inconsistent findings with respect to pregnancy or neonatal complications [13-17], with interpretation complicated by the fact that most conditions have been examined in only one study. It is similarly hard to interpret single-study associations between BN and mother's smoking during pregnancy [20] but not with mother's weight gain during pregnancy [17].

These conflicting findings perhaps result from low power in many of these previous studies, which have usually involved relatively small samples (median 73 cases, range 7-1122). Limited power has also

prevented robust comparisons of associations across ED subtypes or between males and females. Using total population data, this study therefore aimed to examine associations between birth characteristics and AN, BN and eating disorder not-otherwise-specified (EDNOS) in two million males and females.

Methods

Study population

We used Swedish register data to create a cohort born between 1975 and 1998, with ethical approval from the Regional Ethics Committee in Stockholm. We restricted our analyses to Swedish-born children of Swedish-born mothers because we lacked emigration data after 2002 and this group has very low emigration rates. This also created a more homogenous sample, reducing the potential for residual confounding. Of 2,135,279 live-born children, we excluded 0.2% who were adopted, 0.8% who died and 0.7% who permanently emigrated before their twelfth birthday. A further 3.9% were excluded due to missing data on explanatory variables, giving a study population of 2,015,862 (49% female). These individuals with complete case data did not differ from those with missing data in the prevalence of ED (e.g. 0.81% vs. 0.83% for lifetime prevalence of any ED, chi-squared p=0.5). For some outcomes our study sample was further restricted to the 2,011,908 individuals still alive and living in Sweden in 1997.

Eating disorder outcome

Using the International Classification of Disease (ICD) [21], we defined AN as ICD-9 code 307.1 (available 1987-1996) and ICD-10 codes F50.0-F50.1 (available 1997-2010); BN as ICD-10 F50.2-F50.3; and EDNOS as ICD-10 F50.4-F50.9. We combined BN and EDNOS for some less well-powered analyses, as these are not distinguished in ICD-9 (combined ICD-9 code 307.5). We excluded EDNOS diagnoses made within 1 year of an AN or BN diagnosis, assuming that these represented the same underlying disorder [11]. Otherwise individuals were allowed to appear as cases for more than one disorder type (e.g. AN at age 14 and BN at age 22); our substantive findings were unchanged in sensitivity analyses which censored individuals after their first ever ED diagnoses.

We identified cases as individuals with a main or secondary ED diagnosis in the Swedish national inpatient, outpatient or death registers. The inpatient register covers public and private hospital facilities and is available from 1969, with high national coverage (>85%) since 1973 and near-complete coverage (>99%) from 1987 [22]. By contrast, the outpatient register is only available from 2001 and has only around 80% coverage [22]. Our findings were very similar in sensitivity analyses restricted to inpatient diagnoses. Previous validation studies of the hospitalisation records have reported positive predictive values of 85-95% for most mental and physical disorders [22], although no validation data are available specifically in relation to ED.

Explanatory variables

Table 1 presents the explanatory variables examined. Parents' highest educational level was identified as the highest ever recorded in the census (1960-1990) or Education register (1985-2001). Parental income used the mean of the mother's and father's age-standardised net household income in the 1990 census. The Swedish Multi-Generation Register provided parents' age, the child's multiple birth status and the child's number of full and half siblings born before 2002. Mother's lifetime ED diagnosis was identified using the register sources described above.

Table 1: Characteristics of Study Population (N= 2,015,862), Born Sweden, 1975-1998

	N	Percent	Mean (standard deviation)
Sex			
Male	1,034,303	51.3	
Female	981,559	48.7	
Birth year			
1975-1979	410,035	20.3	
1980-1984	386,621	19.2	
1985-1989	444,356	22.0	
1990-1994	483,929	24.0	
1995-1998	290,921	14.4	
Mother's highest education level, 2001			
Basic	271,417	13.5	
Higher secondary	1,070,357	53.1	
Tertiary, <3 years	340,782	16.9	
Tertiary, ≥3 years	325,166	16.1	
Post-graduate	8,140	0.4	
Father's highest education level, 2001			
Basic	428,196	21.2	
Higher secondary	1,014,394	50.3	
Tertiary, <3 years	261,931	13.0	
Tertiary, ≥3 years	284,058	14.1	
Post-graduate	27,283	1.4	
Parents' age-standardised household income, 1970 and/or 1990 (SD)	2,015,862		0 (1)
Mother's age at child's birth (years)	2,015,862		28.4 (5.0)
Father's age at child's birth (years)	2,015,862		31.1 (5.6)
Child's number of full siblings, 2002	2,015,862		1.4 (1.0)
Child's number of half siblings, 2002	2,015,862		0.6 (1.2)
Mother diagnosed with ED (1969-2010)			
No	2,009,207	99.7	
Yes	6,655	0.3	
Multiple birth			
Singleton	1,974,275	97.9	
Twin	40,653	2.0	
Triplet or more	934	0.1	
Gestational age (weeks)	2,015,862		39.9 (1.7)
Sex-standardised birthweight for gestational age (SD)	2,015,862		0 (1)
Sex-standardised birth length for gestational age (SD)	2,015,862		0 (1)
Premature rupture of membranes			
No	1,971,521	97.8	
Yes	44,341	2.2	
Delivery method			
Normal vaginal	1,672,845	83.0	
Caesarean	218,355	10.8	
Instrumental [a]	124,662	6.2	
Apgar score at 5 minutes			
0-6	17,833	0.9	
7-10	1,998,029	99.1	
Cephalohematoma			
No	1,984,374	98.4	
Yes	31,488	1.6	
Other birth trauma involving head/neck / central nervous system			

	N	Percent	Mean (standard deviation)
No	1,997,664	99.1	
Yes	18,198	0.9	
Mother's smoking in early pregnancy [b]			
None	1,016,821	76.1	
1-9 cigarettes/day	199,724	14.9	
10+ cigarettes/day	120,119	9.0	
Mother's pre- pregnancy weight status [c]			
Underweight	53,229	5.4	
Normal	720,343	73.3	
Overweight	162,419	16.5	
Obese	47,091	4.8	
Mother's weight gain in pregnancy relative to BMI$			
Inadequate	186,353	25.9	
Appropriate	296,388	41.2	
Excessive	236,255	32.9	

BMI=body mass index, ED = eating disorder, SD=standard deviations. Most correlation coefficients between these explanatory variables were <0.1 and all r≤0.7. †Forceps delivery in 5% of instrumental deliveries, suction in 95%.
[a] Only available for 66% of sample, [b] Only available for 49% of sample. [c] Only available for 34% of sample.

The Medical Birth Register provided information on birth characteristics. We calculated sex-standardised birthweight and birth length for gestational age using all live births 1973-1998 as our reference group. Among all potential pregnancy complications, we selected cephalohematoma and premature rupture of the membranes for inclusion as specific disorders, because these had showed trends towards associations with AN in previous Swedish studies [14, 15]. The Web appendix provides the ICD codes which defined these outcomes and also the other (non-cephalohematoma) birth traumas. Mother's smoking was measured at the first antenatal visit (usually at 8-12 weeks gestation [23]), as was the mother's self-reported height and usual weight, which we used to define pre-pregnancy weight status as underweight (body mass index <18.5kg/m^2), normal (18.5-24.9kg/m^2), overweight (25-29.9kg/m^2) or obese (≥30kg/m^2). Mother's weight gain during pregnancy was classified as 'inadequate', 'appropriate' or 'excessive' using Institute of Medicine guidelines [24].

Statistical analysis

We used Cox regression to calculate hazard ratios, starting follow-up when the child turned 12 or, for BN and EDNOS, on 1st January 1997, whichever was latest. We continued follow-up until 31st December 2010 or until death, emigration or first diagnosis for the outcome in question, whichever was earliest. We entered continuous variables as linear terms unless entering quadratic terms provided evidence (P<0.05) of non-linearity in adjusted analyses. All explanatory variables had complete data except mother's smoking, pre-pregnancy weight status and weight gain, which were only collected in some years. We therefore analysed associations with these variables separately, restricting analyses to individuals with observed data. All analyses used Stata 12 (Statacorp, Brownsville Texas).

Parental age and the birth characteristics are primarily properties of individual children, permitting within-family comparisons. To do this we created 'between-mother' variables representing the average across all the mother's offspring (e.g. their mean gestational age) and 'within-mother' variables representing the departure of each individual from that mean (e.g. the cohort member's own gestational age minus the mother's average: equations in the Web Appendix). We then used Wald tests to compare the effect sizes of these two variables when entered simultaneously into Cox regression analyses: if they

differed significantly we interpreted this as evidence of residual maternal-level confounding [25]. If associations were entirely the product of such confounding, one would expect the within-mother effect to be (i) significantly weaker than the between-mother effect and (ii) not significantly different from zero. For illustrative purposes, we also present comparisons between cohort members according to both their own status (e.g. preterm vs. non-preterm) and that of their siblings (e.g. any sibling preterm vs. no sibling preterm). If associations were the product of maternal confounding, one would expect the risk associated with having a preterm sibling to be similar to the risk associated with being preterm oneself.

Results

Between 1987 and 2010, 1019 males and 15,395 females received a diagnosis of ED (0.10% and 1.6%, respectively). This included 420 males and 6931 females diagnosed with AN (assigned between 1987-2010), 63 males and 2741 females diagnosed with BN (assigned 1997-2010) and 640 males and 9768 females diagnosed with EDNOS (assigned 1997-2010). At all ages, rates of first ED diagnosis were 15-20 times higher in females (Figure 1, part A) than males (Figure 1, part B).

Figure 1: Rates of first diagnosis with eating disorders in inpatient and outpatient registers, among Swedish females and males born 1975-1998 and followed to end 2010

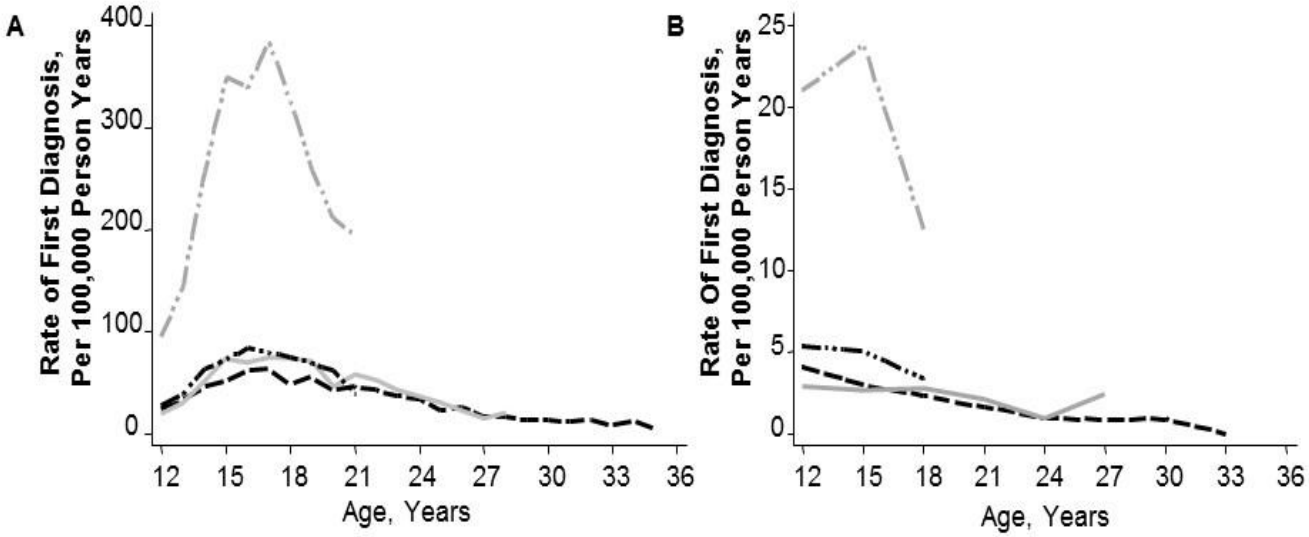


Figure part A = eating disorders in females. Figure part B = eating disorders in males. Grey dot-dash lines show rates among those born 1989-98 using the combined inpatient and outpatient registers. Black dot-dash line shows rates among those born 1989-98 using the inpatient registers. Grey solid line shows rates among those born 1982-88 using the inpatient registers. Black dotted line shows rates among those born 1975-81 using the inpatient registers.

Associations with family characteristics

Higher mother's and father's education showed a dose-response association with all three ED outcomes, while income showed no independent associations (Table 2). For EDNOS these associations differed by sex, with EDNOS in males showing no association with parental education but being associated with lower income (all $P \leq 0.004$ for sex interactions in adjusted analyses). No other explanatory variable in Table 2 showed evidence of a sex interaction at the 1% significance level (see Web Tables 1 and 2 for sex-stratified results in full).

Table 2: Family And Birth Predictors of ED, Combining Males and Females (Born Sweden, 1975-1998): Hazards Ratios and 95% Confidence Intervals

	Anorexia nervosa (follow-up 1987-2010)				Bulimia nervosa (follow-up 1997-2010)				Eating disorder not-otherwise-specified (follow-up 1997-2010)			
	Minimally-adjusted [d]		Adjusted [e]		Minimally-adjusted [d]		Adjusted [e]		Minimally-adjusted [d]		Adjusted [e]	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Female (vs. male) child sex	17.48	15.84, 19.29[c]	17.53	15.89, 19.35[c]	46.11	35.92, 59.20[c]	46.03	35.85, 59.09[c]	14.04	12.89, 15.29[c]	14.05	12.90, 15.31[c]
Mother's education												
Basic	1[c]		1[c]		1[c]		1[c]		[1[c]]		[1[c]]	
Higher secondary	1.11	1.02, 1.20	1.06	0.98, 1.15	1.09	0.97, 1.23	1.09	0.97, 1.23	[1.04]	[0.97, 1.11]	[1.04]	[0.97, 1.12]
Tertiary, <3 years	1.52	1.39, 1.66	1.30	1.18, 1.42	1.40	1.22, 1.60	1.34	1.16, 1.54	[1.18]	[1.08, 1.27]	[1.15]	[1.06, 1.25]
Tertiary, ≥3 years	1.78	1.63, 1.94	1.36	1.24, 1.50	1.53	1.34, 1.75	1.38	1.19, 1.60	[1.26]	[1.16, 1.37]	[1.18]	[1.08, 1.29]
Post-graduate	2.50	1.91, 3.28	1.58	1.19, 2.09	1.18	0.65, 2.16	0.92	0.50, 1.71	[2.01]	[1.54, 2.62]	[1.72]	[1.31, 2.27]
Father's education												
Basic	1[c]		1[c]		1[c]		1[c]		[1[c]]		[1[c]]	
Higher secondary	1.15	1.07, 1.22	1.13	1.05, 1.20	1.07	0.97, 1.18	1.04	0.94, 1.15	[1.05]	[0.99, 1.12]	[1.05]	[0.99, 1.12]
Tertiary, <3 years	1.53	1.41, 1.66	1.39	1.27, 1.51	1.26	1.11, 1.44	1.17	1.02, 1.34	[1.16]	[1.08, 1.26]	[1.15]	[1.06, 1.24]
Tertiary, ≥3 years	1.90	1.76, 2.05	1.58	1.45, 1.72	1.41	1.26, 1.59	1.23	1.07, 1.41	[1.30]	[1.21, 1.40]	[1.25]	[1.15, 1.35]
Post-graduate	2.53	2.18, 2.95	1.97	1.68, 2.32	1.91	1.48, 2.46	1.63	1.25, 2.14	[1.59]	[1.35, 1.88]	[1.43]	[1.20, 1.70]
Parental income: change per standard deviation	1.02	1.01, 1.02[c]	1.01	0.99, 1.02	1.01	1.00, 1.03	1.00	0.96, 1.04	[1.01]	[0.99, 1.02]	[0.99]	[0.96, 1.02]
Mother's age: change per decade	1.28	1.23, 1.34[c]	1.04	0.97, 1.11	1.15	1.07, 1.24[c]	1.05	0.94, 1.17	1.05	1.00, 1.09[a]	0.93	0.88, 1.00[a]
Mother's age: change per decade	1.20	1.15, 1.25[c]	1.09	1.03, 1.16[b]	1.10	1.03, 1.17[b]	1.00	0.91, 1.09	1.07	1.03, 1.11[b]	1.06	1.00, 1.12[a]
No. full siblings: change per sibling	0.98	0.96, 1.00	0.96	0.93, 0.98[b]	0.99	0.95, 1.02	1.00	0.96, 1.04	0.96	0.94, 0.98[c]	0.97	0.95, 1.00[a]
No. half siblings												
0-1	1[a]		1		1[a]		1[c]		1[c]		1[c]	
2-3	0.92	0.85, 0.99	0.95	0.88, 1.02	1.14	1.03, 1.27	1.21	1.08, 1.35	1.17	1.10, 1.25	1.18	1.11, 1.27
4-5	0.85	0.74, 0.98	0.89	0.77, 1.04	1.23	1.02, 1.48	1.33	1.10, 1.62	1.30	1.16, 1.46	1.32	1.18, 1.49
6+	0.93	0.71, 1.22	1.00	0.76, 1.31	1.02	0.70, 1.51	1.14	0.77, 1.69	1.25	0.99, 1.57	1.28	1.02, 1.61
Eating disorder in mother (yes vs. no)	1.93	1.43, 2.61[c]	2.03	1.51, 2.75[c]	1.80	1.02, 3.17[a]	1.83	1.04, 3.24[a]	1.65	1.21, 2.25[b]	1.63	1.19, 2.22[b]
Multiple birth (yes vs. no)	1.49	1.30, 1.70[c]	1.33	1.15, 1.53[c]	0.77	0.57, 1.05	0.81	0.59, 1.11	1.05	0.91, 1.23	1.04	0.89, 1.22
Gestational age: change per week	0.96	0.94, 0.97[c]	0.96	0.95, 0.98[c]	1.00	0.98, 1.02	1.00	0.98, 1.02	0.98	0.97, 0.99[a]	0.98	0.97, 0.99[a]
Birthweight for gestational age: change per (sex-standardised) standard deviation	1.02	1.00, 1.04	1.00	0.97, 1.04	1.11	1.07, 1.15[c]	1.15	1.09, 1.22[c]	1.04	1.01, 1.06[b]	1.04	1.01, 1.07 [a]
Birth length for gestational age: change per (sex-standardised) standard deviation	1.03	1.00, 1.05[a]	1.02	0.98, 1.05	1.05	1.01, 1.09[b]	0.95	0.89, 1.00	1.03	1.00, 1.05[a]	1.00	0.97, 1.03

Premature rupture of membranes (yes vs. no)	1.16	0.99, 1.35	1.05	0.89, 1.23	1.26	0.95, 1.66	1.25	0.94, 1.66	1.05	0.89, 1.23	1.00	0.85, 1.17
Delivery method												
Normal vaginal	1[c]		1		1		1		1		1	
Caesarean	1.19	1.11, 1.28	1.08	1.01, 1.17	1.05	0.93, 1.18	1.06	0.94, 1.20	1.02	0.95, 1.10	0.99	0.92, 1.07
Instrumental	1.07	0.97, 1.18	1.04	0.94, 1.15	0.85	0.71, 1.01	0.86	0.72, 1.03	1.03	0.93, 1.13	1.01	0.92, 1.12
Normal Apgar (7-10 vs. 0-6)	1.00	0.77, 1.29	1.08	0.83, 1.41	1.23	0.78, 1.93	1.20	0.76, 1.88	1.01	0.79, 1.31	1.04	0.81, 1.34
Cephalohematoma (yes vs. no)	1.04	0.86, 1.27	1.06	0.87, 1.29	0.77	0.54, 1.10	0.80	0.56, 1.15	1.13	0.94, 1.36	1.13	0.94, 1.36
Other birth trauma (yes vs. no)	1.32	1.05, 1.66[a]	1.28	1.02, 1.62[a]	1.01	0.69, 1.47	1.04	0.71, 1.52	1.06	0.83, 1.36	1.04	0.81, 1.33

CI=confidence interval, HR=Hazard ratio. [a] $P<0.05$, [b] $P<0.01$, [c] $P<0.001$. [d] Minimally-adjusted analyses adjust for child's sex and birth year. [e] Adjusted models additionally adjust for all variables shown in the column. Variables in square brackets showed evidence at the 1% level of an interaction with sex: see text for details and Web Tables 1 and 2 for sex-stratified results.

Adjusting for socio-economic characteristics, there was little evidence of an independent association with mother's age. Higher father's age did remain independently associated with AN, but this was only seen in between-mother analyses (Table 3). As such, this association seemed more likely to reflect residual maternal/family-level confounding factors than a causal effect. An increased number of full siblings independently predicted a lower rate of AN and EDNOS, while an increased number of half siblings predicted a higher rate of BN and EDNOS (Table 2). The association with full siblings was particularly strong if the siblings were older (i.e. suggesting a protective effect of higher birth order), while the association with half siblings was observed regardless of the half-siblings' age or sex (Web Table 3). All outcomes were associated with an ED diagnosis in the mother.

Table 3: Comparison of Between-Mother and Within-Mother Associations, for Characteristics Independently Associated with ED and Varying Between Siblings, among Males and Females Born 1975-1998 in Sweden

Outcome	Explanatory variable	Mutually adjusted [a]		Further adjusted [b]	
		HR	95%CI	HR	95%CI
AN	Father's age (change per decade)				
	Between-mother [c]	1.26	1.21, 1.31	1.12	1.05, 1.18
	Within-mother [d]	0.97	0.89, 1.06	0.91	0.82, 1.02
	P value [e]	<0.001		<0.001	
AN	Multiple birth (binary)				
	Between-mother [c]	1.54	1.31, 1.81	1.37	1.16, 1.62
	Within-mother [d]	1.36	1.03, 1.80	1.22	0.91, 1.62
	P value [e]	0.47		0.50	
AN	Gestational age (change per week)				
	Between-mother [c]	0.96	0.94, 0.97	0.96	0.95, 0.98
	Within-mother [d]	0.95	0.93, 0.97	0.96	0.94, 0.98
	P value [e]	0.58		0.79	
AN	Caesarean delivery (yes vs. no)				
	Between-mother [c]	1.22	1.13, 1.32	1.11	1.02, 1.20
	Within-mother [d]	1.07	0.91, 1.24	0.98	0.84, 1.15
	P value [e]	0.12		0.17	
AN	Other birth trauma (yes vs. no)				
	Between-mother [c]	1.53	1.14, 2.07	1.43	1.06, 1.93
	Within-mother [d]	1.08	0.77, 1.53	1.11	0.78, 1.56
	P value [e]	0.12		0.25	
AN	Mother smoking in pregnancy (any vs. none)				
	Between-mother [c]	0.70	0.65, 0.76	0.85	0.78, 0.91
	Within-mother [d]	1.14	0.94, 1.39	1.19	0.97, 1.46
	P value [e]	<0.001		<0.001	
AN (females only)	Mother pre-pregnancy BMI (change per unit)				
	Between-mother [c]	0.95	0.94, 0.96	0.95	0.94, 0.97
	Within-mother [d]	1.01	0.96, 1.06	0.98	0.93, 1.04
	P value [e]	0.02		0.24	
BN	Birthweight for gestational age (change per SD)				
	Between-mother [c]	1.11	1.07, 1.16	1.15	1.09, 1.22
	Within-mother [d]	1.11	1.03, 1.20	1.15	1.06, 1.25
	P value [e]	0.99		0.96	
BN + EDNOS	Excessive mother's weight gain (binary)				
	Between-mother [c]	1.13	1.05, 1.21	1.14	1.06, 1.23
	Within-mother [d]	1.05	0.90, 1.24	1.06	0.90, 1.25
	P value [e]	0.47		0.42	

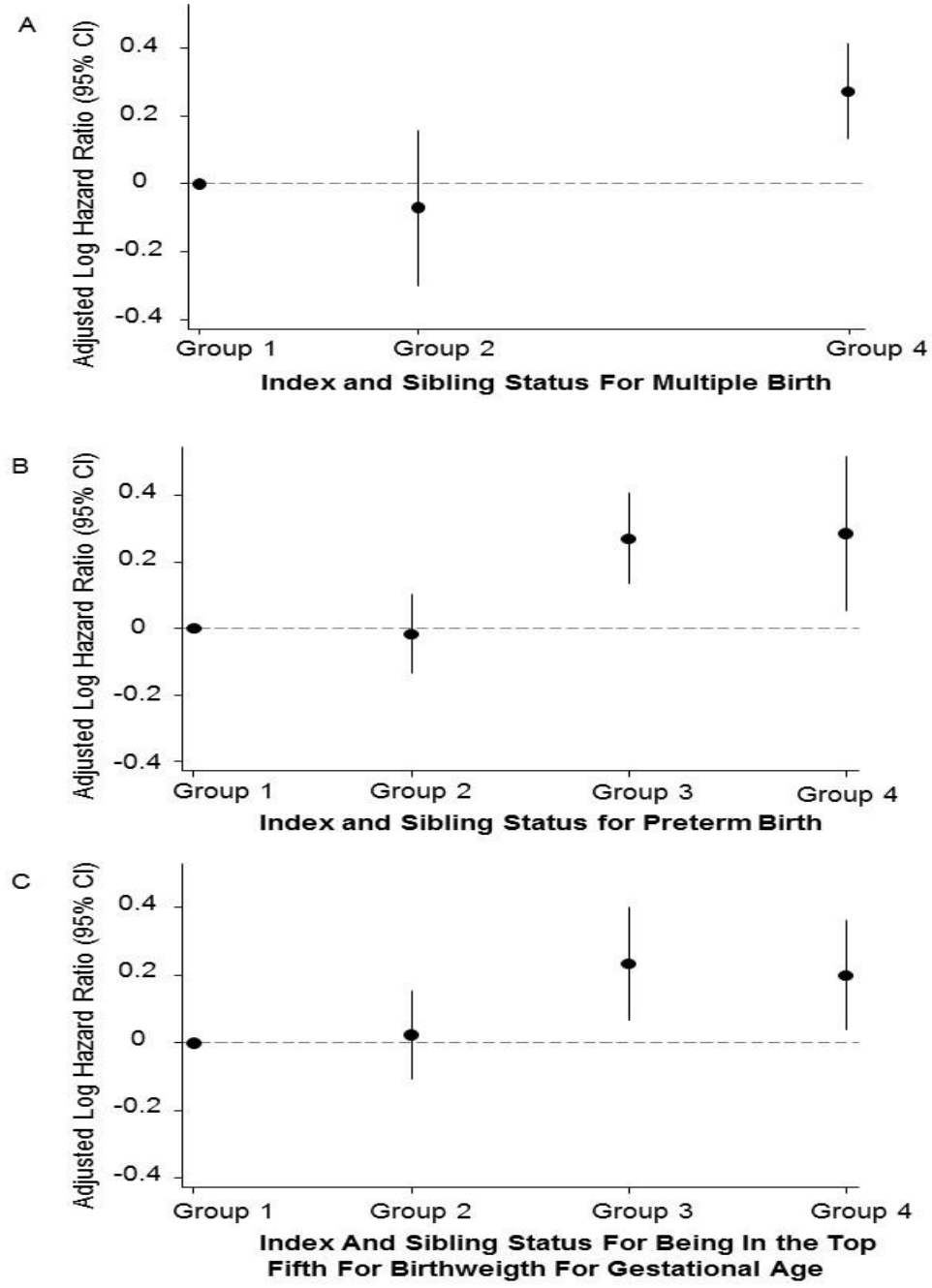
CI=confidence interval, AN=anorexia nervosa, BMI=body mass index, BN=bulimia nervosa, ED=eating disorder, SD=standard deviation. [a] Mutually-adjusted analyses adjust for the between- and within-mother variables in question, plus the child's sex and birth year. [b] Further adjusted models additional adjust for the child's family and birth characteristics shown in Table 2. [c] 'Between-mother' variables represent the average across all the mother's offspring. [d] 'Within-mother' variables represent the departure of each individual cohort from that mean (see Web Appendix for equations). [e] *P*-values are Wald tests for equality of between-mother and within-mother coefficients.

Associations with birth characteristics

Multiple birth and gestational age; Twin/triplet status and lower gestational age independently predicted AN (Table 2), and these associations were significant in both sexes (Web Tables 1 and 2). Gestational age showed a clear dose response relationship with AN, with a gradient even observed within term births (adjusted P=0.008 for difference between those born at 37-38 versus 39-41 weeks: see also Web Figure 1). There was likewise a non-significant trend towards a higher rate in triplets than twins (Web Figure 1). There was no evidence of any interaction between gestational age and either parental education or income (all P>0.4 in adjusted analyses).

Both of these associations with were largely specific to AN, and were not observed in the maternal siblings of twins or preterm individuals (Figure 2 parts A and B). Instead the between-mother and within-mother coefficients for multiple birth and gestational age were very similar, thereby providing no evidence of residual confounding (Table 3). Here and below, these associations were all very little changed after additional adjustment for the mother's smoking status, pre-pregnancy weight status or weight gain in subset analyses restricted to individuals with complete data for those additional maternal characteristics (Web Table 4).

Figure 2: Within-family comparisons of the effect of selected characteristics upon ED, among Swedish males and females born 1975-1998 and followed to end 2010



CI=confidence interval. Figure part A = anorexia nervosa according to multiple birth status of index child and sibs. Figure part B = anorexia nervosa according to preterm status of index child and sibs. Figure part C = bulimia nervosa according to whether the index child and their siblings are in the top fifth in terms of birthweight for gestational age. In each figure part, Group 1 (the reference category) = index child does not have the risk factor in question and nor do any siblings (e.g. the index child is not preterm and nor are any of their siblings). Group 2 = index child does not have the risk factor but one or more of their siblings does. Group 3 = index child has the risk factor but none of their siblings do. Group 4 = index child has the risk factor and at least one sibling does too. All analyses are adjusted for the child's family and birth characteristics shown in Table 2, and were restricted to cohort members with at least one maternal sibling in the cohort from a separate maternal pregnancy.

Mother's pre-pregnancy weight status: There was a progressive association between increased weight status in the mother and a lower risk of AN in the daughter. In adjusted analyses the hazard ratio was 1.30 (95% confidence interval 1.15, 1.48) for daughters of

underweight vs. normal weight mothers; 0.82 (0.73, 0.91) for daughters of overweight vs. normal mothers; and 0.70 (0.56, 0.87) for daughters of obese vs. normal mothers (Web Table 6). Within-family comparisons were not fully conclusive, but suggested that this may reflect residual confounding or a maternal-level effect rather than a causal, pregnancy-level effect. There was no evidence that mother's weight status predicted AN in boys (p=0.91 for adjusted association, p<0.001 for sex interaction), nor evidence of an association with BN, EDNOS or a combined category of 'non-anorexia ED' (all *P*>0.05; Web Tables 5 and 7).

Mother's smoking; There was a strong negative association between mother's smoking and AN in minimally-adjusted analyses, but this was substantially attenuated upon adjusting for parental characteristics, particularly parental education (Web Tables 5 and 6). Moreover, the association was only seen in between-mother comparisons; the within-mother coefficient showed a non-significant trend in the opposite direction (Table 3). These findings were therefore most compatible with an interpretation of residual confounding by maternal characteristics. Smoking showed no association with BN, EDNOS or a combined category of 'non-anorexia ED' (all *P*>0.15; Web Tables 5 and 7).

Birthweight for gestational age and maternal weight gain; Higher birthweight for gestational age showed no independent association with AN, a weak association with EDNOS, and a strong, dose-response association with BN (Table 2 and Web Figure 1). This association was only observed in females but there was no evidence of a sex interaction (*P*=0.25), indicating that the null finding in males may simply reflect the particularly small number of male BN cases (N=63). Within-family analyses provided no evidence of residual maternal-level confounding (Figure 2 part C and Table 3).

There was also a trend towards increased BN and EDNOS (but not AN) among mothers who gained excessive weight during pregnancy (adjusted hazards ratio 1.12 (95% confidence interval 1.04, 1.20) for BN and EDNOS combined: point estimates very similar when analysed separately, see Web Tables 5 and 7). Our within-family analyses were, however, inconclusive as to how far this may reflect residual confounding, perhaps reflecting the substantially reduced sample size for this variable.

Other birth characteristics; There was little or no evidence that AN, BN or EDNOS were independently associated with delivery method, birth length for gestational age, Apgar score, cephalohematoma, other birth traumas or premature rupture of the membranes. The only possible exceptions were that caesarean delivery and other (non-cephalohematoma) birth trauma showed marginally-significant associations with AN. Within-family analyses suggested, however, that these associations were compatible with an interpretation of mother-level confounding. In the context of multiple testing it is also plausible that these two associations are chance findings.

Discussion

In this total-population cohort of two million Swedish males and females, shorter gestational age and multiple birth status independently predicted anorexia nervosa (AN), while higher birthweight for gestational age predicted bulimia nervosa (BN). These two associations with AN were significant in both sexes; the association of birthweight with BN was not, but this plausibly reflected low power in males. All of these associations showed dose-response relationships, persisted after extensive adjustment, and were equally strong in within-family comparisons. As such, all three were consistent with a causal interpretation. By contrast,

although mother's smoking predicted reduced AN, this seemed to reflect maternal-level confounding. Similarly, although lower mother's weight predicted AN in daughters (but not sons) and excessive mother's weight gain during pregnancy predicted increased BN and EDNOS, there was not strong evidence that this reflected a causal, pregnancy-level effect. There was no convincing evidence of associations with birth length for gestational age, premature rupture of the membranes, delivery method, Apgar score or birth trauma.

Strengths and limitations

Study strengths include the total population design, the use of multiple prospectively-collected characteristics with high data completeness, the use of within-family comparisons, and the inclusion of 7 to 1000 times more ED cases than previous studies [9, 12-20]. One important limitation is that we only captured ED diagnoses recorded in hospitalisation records, although we did improve upon previous Swedish studies [14, 15] by including outpatient cases. We believe selection bias with respect to explanatory variables is unlikely to explain our results, given that our key findings persist in within-family comparisons. It is, however, unclear whether our findings would generalise to milder community cases, particularly given previous suggestions that birth characteristics may most strongly predict chronic or severe ED [13, 26]. Another limitation is that our within-family comparisons could only seek to control for confounding at the mother/family level, and not at the pregnancy or child level. We therefore cannot exclude the possibility that some observed effects reflect confounding by unmeasured individual-level factors (e.g. maternal stress during that particular pregnancy). A third limitation is that we lacked information on established risk factors which might mediate the observed relationships (e.g. temperament [27] or early feeding habits [28]) or interact with birth outcomes to determine which individuals are at most risk (e.g. stressful life events [29]). Similarly, we did not adjust for other mental disorders such as bipolar disorder among our cohort members, which might possibly mediate some of the observed association with eating disorders [30, 31]. Clarifying the mechanisms underlying the observed associations is one priority for future research.

Meaning of the study

Unlike some previous, smaller Swedish studies [14, 15] we found that the association between gestational age and AN was not confined to very preterm infants. This is consistent with growing recognition that effects of gestational age operate across the full range [32, 33], and makes it unlikely that the explanation involves preterm-specific factors such spending time in neonatal intensive care. One ED-specific pathway could involve early feeding problems, which are associated with both shorter gestation [32] and subsequent ED [16, 34]. Alternatively or additionally, earlier gestation could impair the development of the brain and associated neuro-endocrinological stress responses [9, 27, 35], thereby increasing subsequent vulnerability to ED [36, 37]. This second, more generalised mechanism is perhaps more consistent with recent reports of a graded association between gestational age and other major psychiatric disorders in overlapping Swedish cohorts [5, 9]. Notably, however, we did not replicate the finding that high socio-economic position reduces the magnitude of the negative association between shorter gestational age and non-ED psychiatric disorders [5]. This may be because ED is unusual in itself being associated with socio-economic advantage [38].

An independent significant association between multiple birth status and AN has not previously been reported and is somewhat unexpected given the association, reported here and previously [38], between having more full siblings and having a lower rate of ED. It is also

somewhat unexpected given that, after adjusting for gestational age, twins are similar to singletons for most outcomes [39-41]. This includes similarity with respect to mental health [40], although one Danish study (which did not adjust for other perinatal factors) has indicated higher hospitalisations for psychiatric disorder [42]. Factors specifically related to multiple birth status include a lower likelihood of being breastfed [43, 44] and lower levels of parent-infant interaction and communication [41, 45]. It is possible that one or both of these factors could impair maternal-child attachment bonding and so contribute to an increased risk of AN [46, 47], although it is unclear to us whether such effects could plausibly account in full for the 1.5-fold difference in AN rate observed between twins and singletons. Replication of this finding is therefore warranted, perhaps using register data from other Nordic countries. If replicated, this finding is noteworthy as many of the large community-based studies of ED prevalence have been conducted in twins [48-51]. Our findings suggest the possibility that such studies substantially overestimate ED prevalence.

We hypothesise that the association between high birthweight for gestational age and BN (but not AN) reflects the influence of birthweight on childhood obesity [52] and of obesity on BN (but again, not AN) [34, 53]. To the extent that the association between excessive maternal weight gain and BN is causal, this could also be mediated via its effect on childhood obesity [54]. Alternatively, genetic susceptibility is a possible confounder for this latter association, given evidence in a large recent study that BN predicts excessive weight gain in pregnancy [55]. By contrast, genetic confounding cannot readily explain the other observed associations, as large studies indicate no associations between maternal AN and gestational age [56-58] or between maternal BN and birthweight [56, 57]. As for the weaker associations between gestational age, birthweight and EDNOS, we suggest these may reflect the presence of unrecognised or subclinical cases of AN or BN.

We failed to replicate associations with instrumental delivery, birth trauma and premature rupture of membranes, which were reported in previous analyses of a subset of our study population [14, 15]. Given that these previously-reported associations were generally non-significant or at most weakly significant in adjusted analyses ($P \geq 0.02$), they may simply have reflected chance findings. By contrast, our findings regarding family correlates of ED closely replicate those recently reported in relation to a slightly younger cohort from Stockholm [38], and also extend these previous findings by comparing associations across types of ED. This included demonstrating that an increased number of half siblings specifically increases rates of BN and EDNOS, perhaps reflecting the influence of family discord or poor parent-child relationships [34, 53]. We likewise extend the recent Stockholm study [38] in finding that maternal ED and higher parental education are generally associated to a similar degree with *all* types of ED, with the notable exception of an absence of association between parental education and EDNOS in males. We also echo a previous, questionnaire-based Portuguese study [59], in reporting a sex-specific association between lower maternal weight status and increased AN risk in daughters. The sex-specificity of this effect is intriguing; possible mechanisms could include sex-specific genetic contributors to AN, or alternatively a greater social modelling of mothers by their daughters than by their sons. Further research into the mechanisms underlying all these associations is warranted, as is research into the parental or family factors which may be upstream determinants of the birth characteristics considered in this paper. Such research may inform the design of preventive interventions or help to identify children particularly at risk.

Conclusion

Genetic influences on ED susceptibility are well-established, as are proximate environmental factors such as critical comments about eating, weight and body shape [34, 60]. This paper complements these findings by providing the strongest evidence to date that a small number of perinatal outcomes play a causal, disease-specific role in the development of anorexia and bulimia nervosa. Notably, these associations could not simply be explained as responses to extreme perinatal adversity, but instead were observed across the normal range for gestational age and birthweight. As such even the modest effect sizes may translate non-trivial population health impacts [61]. These findings therefore support the utility of the developmental origins concept with respect to ED, and highlight the importance of taking a lifecourse perspective in laying the foundation for healthy eating and healthy weight [4]. Through further investigation into underlying mechanisms, including potential interactions with other genetic and environmental risk factors, we hope these findings will help understand the aetiology of this important disease and identify targets for public health prevention.

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Competing interests

None

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Web appendix

Supplementary methodological information

ICD codes used to define birth traumas and premature rupture of membranes

We defined birth traumas as diagnoses beginning with 772 in ICD-8, 767 in ICD-9 and P10, P11, P12, P13, P14 and P15 in ICD-10. We followed Cnattingius *et al.* [1] in excluding fractures of the clavicle, arm and leg (ICD codes 772.20-772.23, ICD-9 codes 767.2 and 767.3, ICD-10 codes P13.2-P13.9), in order to focus on head and neck injuries or traumas with central nervous system symptoms. We also followed Cnattingius *et al*. in examining cephalohematoma (the most common birth trauma) separately, defining cephalohematoma as ICD-8 code 772.31, ICD-9 code 767.19, and ICD-10 P12.0. We defined premature rupture of the membranes as ICD-8 codes 635.95 or 661.0, ICD-9 codes 658.1, 658.2 or 761.1, and ICD-10 codes O42.0, O42.1, O42.9, O75.6 and P01.1.

Comparison of between-mother and within-mother effects

Among our explanatory variables, parental age and the birth characteristics are primarily properties of individual children not families. This allowed us to make within-family comparisons for these characteristics, and so examine whether any associations we saw might reflect residual confounding by parental or family characteristics. To do this we created two variables to enter into Cox proportional hazards models, a 'between-mother' variable representing the average characteristics of all the offspring of each mother (e.g. their mean gestational age) and a 'within mother' variable representing the departure of each individual cohort from that mean:

$$h_{jk}(t) = h_0(t) \exp\left(\beta_1 \bar{y}_j + \beta_2 (y_{jk} - \bar{y}_k) + \alpha_1 Z_{1jk} + \alpha_2 Z_{2jk} + \ldots\right)$$

where '$h_{jk}(t) = h_0(t) \exp(...)$' is the standard expression for fitting a Cox model to estimate the hazard in the jth child of the kth mother; $\bar{y}_k$ is the average value of y (the variable of interest) across the kth mother's offspring; $(y_{jk} - \bar{y}_k)$ is the departure of the jth child of the kth mother from that average; and $\alpha_1 Z_{1jk} + \alpha_2 Z_{2jk}$ are other variables adjusted for in the model and their associated coefficients. In this model, β_1 therefore captures the between-mother effect of y and β_2 captures the within-mother effect.

To test for residual confounding we compared the estimated effects of the between-mother and within-mother variables, that is tested whether $\beta_1 = \beta_2$. If the within-mother effect was significantly different from the between-mother effect we interpreted this as evidence of residual maternal-level confounding [2]. If maternal-level confounding were generating spurious associations, then one would expect the within-mother effect (β_2) to be weaker than the between-mother effect; if maternal-level confounding were the entire explanation for any association, one would expect β_2 to be non-significant.

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Web Table S1: Family and birth predictors of ED subtypes among females: hazards ratios and 95% CIs

			Anorexia nervosa (follow-up 1987-2010)		Bulimia nervosa (follow-up 1997-2010)		Eating disorder not-otherwise-specified (follow-up 1997-2010)	
			Minimally-adjusted	**Adjusted**	**Minimally-adjusted**	**Adjusted**	**Minimally-adjusted**	**Adjusted**
Family characteristics	Mother's education	Basic	1***	1***	1***	1***	1***	1***
		Higher secondary	1.09 (1.01, 1.18)	1.04 (0.96, 1.13)	1.10 (0.97, 1.24)	1.10 (0.97, 1.24)	1.06 (0.98, 1.14)	1.06 (0.98, 1.14)
		Tertiary, <3 yrs	1.51 (1.38, 1.65)	1.28 (1.17, 1.41)	1.39 (1.21, 1.59)	1.33 (1.15, 1.53)	1.21 (1.11, 1.32)	1.17 (1.07, 1.28)
		Tertiary, ≥3 yrs	1.78 (1.63, 1.94)	1.35 (1.22, 1.49)	1.53 (1.34, 1.75)	1.37 (1.18, 1.59)	1.30 (1.19, 1.41)	1.21 (1.10, 1.32)
		Post-graduate	2.54 (1.93, 3.34)	1.59 (1.20, 2.12)	1.21 (0.66, 2.21)	0.93 (0.50, 1.72)	1.98 (1.49, 2.62)	1.66 (1.24, 2.22)
	Father's education	Basic	1***	1***	1***	1***	1***	1***
		Higher secondary	1.15 (1.08, 1.24)	1.13 (1.06, 1.21)	1.06 (0.96, 1.17)	1.04 (0.94, 1.15)	1.06 (1.00, 1.13)	1.06 (0.99, 1.12)
		Tertiary, <3 yrs	1.55 (1.42, 1.68)	1.40 (1.28, 1.53)	1.26 (1.10, 1.43)	1.17 (1.02, 1.33)	1.20 (1.10, 1.29)	1.17 (1.08, 1.27)
		Tertiary, ≥3 yrs	1.94 (1.80, 2.10)	1.61 (1.48, 1.76)	1.41 (1.25, 1.59)	1.23 (1.07, 1.41)	1.32 (1.23, 1.43)	1.26 (1.16, 1.37)
		Post-graduate	2.56 (2.19, 2.99)	1.98 (1.68, 2.34)	1.95 (1.51, 2.51)	1.67 (1.27, 2.18)	1.65 (1.39, 1.95)	1.48 (1.23, 1.77)
	Parental income	Change per standard deviation	1.02 (1.01, 1.02)***	1.01 (0.99, 1.02)	1.01 (1.00, 1.03)	1.00 (0.97, 1.04)	1.01 (1.00, 1.02)	1.00 (0.98, 1.02)
	Mother's age	Change per decade	1.28 (1.22, 1.34)***	1.04 (0.97, 1.11)	1.16 (1.08, 1.25)***	1.05 (0.94, 1.18)	1.05 (1.00, 1.10)*	0.93 (0.87, 0.99)*
	Father's age	Change per decade	1.19 (1.14, 1.24)***	1.08 (1.02, 1.15)*	1.10 (1.03, 1.18)**	1.00 (0.91, 1.10)	1.07 (1.03, 1.11)**	1.06 (1.00, 1.12)*
	No. full siblings	Change per sibling	0.98 (0.96, 1.01)	0.96 (0.93, 0.98)**	0.99 (0.95, 1.02)	1.00 (0.96, 1.04)	0.96 (0.94, 0.99)**	0.98 (0.95, 1.00)*
	No. half siblings	0-1	1**	1	1***	1***	1***	1***
		2-3	0.90 (0.84, 0.97)	0.93 (0.86, 1.01)	1.15 (1.03, 1.28)	1.21 (1.08, 1.35)	1.16 (1.09, 1.24)	1.18 (1.10, 1.27)
		4-5	0.83 (0.71, 0.96)	0.88 (0.75, 1.02)	1.24 (1.03, 1.49)	1.34 (1.10, 1.63)	1.27 (1.13, 1.43)	1.30 (1.15, 1.47)
		6+	0.89 (0.67, 1.18)	0.96 (0.72, 1.28)	1.05 (0.71, 1.54)	1.17 (0.79, 1.73)	1.24 (0.98, 1.57)	1.29 (1.01, 1.63)
	ED in mother	Yes (vs. no)	1.88 (1.37, 2.57)***	1.97 (1.44, 2.70)***	1.84 (1.04, 3.24)*	1.88 (1.06, 3.31)*	1.53 (1.09, 2.14)*	1.51 (1.08, 2.12)*
Birth characteristics	Multiple birth	Yes (vs. no)	1.43 (1.25, 1.65)***	1.28 (1.10, 1.48)**	0.73 (0.53, 1.01)	0.77 (0.55, 1.07)	1.02 (0.87, 1.20)	1.02 (0.86, 1.20)
	Gestational age	Change per week	0.96 (0.95, 0.97)***	0.96 (0.95, 0.98)***	1.00 (0.98, 1.02)	1.00 (0.97, 1.02)	0.98 (0.97, 1.00)**	0.98 (0.97, 0.99)**
	Birthweight for gestational age	Change per (sex-standardised) SD	1.01 (0.99, 1.04)	1.00 (0.97, 1.04)	1.12 (1.08, 1.16)***	1.16 (1.10, 1.22)***	1.04 (1.02, 1.07)**	1.04 (1.01, 1.08)*
	Birth length for gestational age	Change per (sex-standardised) SD	1.02 (1.00, 1.05)	1.01 (0.98, 1.05)	1.05 (1.01, 1.10)**	0.94 (0.89, 1.00)	1.03 (1.01, 1.06)*	1.00 (0.97, 1.04)
	Premature rupture of membranes	Yes (vs. no)	1.12 (0.94, 1.32)	1.02 (0.86, 1.20)	1.29 (0.97, 1.70)	1.28 (0.96, 1.70)	1.09 (0.93, 1.28)	1.04 (0.88, 1.23)
	Delivery method	Normal vaginal	1***	1			1	1
		Caesarean	1.18 (1.10, 1.27)	1.08 (1.00, 1.16)	1.04 (0.92, 1.17)	1.05 (0.93, 1.19)	1.00 (0.93, 1.08)	0.98 (0.91, 1.06)
		Instrumental	1.06 (0.96, 1.18)	1.03 (0.93, 1.15)	0.84 (0.70, 1.01)	0.86 (0.71, 1.03)	1.01 (0.91, 1.12)	0.99 (0.89, 1.10)
	Normal Apgar	7-10 (vs. 0-6)	1.02 (0.77, 1.34)	1.10 (0.83, 1.45)	1.26 (0.79, 2.01)	1.22 (0.77, 1.94)	0.98 (0.76, 1.27)	1.00 (0.77, 1.29)
	Cephalohematoma	Yes (vs. no)	1.05 (0.86, 1.29)	1.07 (0.87, 1.32)	0.77 (0.53, 1.11)	0.80 (0.55, 1.16)	1.18 (0.98, 1.42)	1.18 (0.98, 1.43)
	Other birth trauma	Yes (vs. no)	1.28 (1.00, 1.63)*	1.25 (0.98, 1.59)	0.96 (0.65, 1.43)	0.99 (0.67, 1.48)	1.03 (0.79, 1.33)	1.01 (0.77, 1.31)

*p<0.05, **p<0.01, ***p<0.001. ED=eating disorder, SD=standard deviation, Minimally-adjusted analyses adjust for child's birth year, adjusted models additionally adjust for all variables shown in the column.

Web Table S2: Family and birth predictors of ED subtypes among males: hazards ratios and 95% CIs

			Anorexia nervosa (follow-up 1987-2010)		Bulimia nervosa (follow-up 1997-2010)		Eating disorder not-otherwise-specified (follow-up 1997-2010)	
			Minimally-adjusted	**Adjusted**	**Minimally-adjusted**	**Adjusted**	**Minimally-adjusted**	**Adjusted**
Family characteristics	Mother's education	Basic	1	1	1	1	1	1
		Higher secondary	1.43 (1.00, 2.04)	1.48 (1.03, 2.11)	0.99 (0.45, 2.19)	0.97 (0.43, 2.17)	0.80 (0.63, 1.02)	0.86 (0.67, 1.10)
		Tertiary, <3 yrs	1.71 (1.15, 2.53)	1.65 (1.10, 2.49)	1.83 (0.77, 4.33)	1.85 (0.75, 4.54)	0.81 (0.60, 1.08)	0.91 (0.66, 1.24)
		Tertiary, ≥3 yrs	1.82 (1.23, 2.69)	1.65 (1.07, 2.52)	1.66 (0.69, 3.96)	1.81 (0.70, 4.69)	0.85 (0.63, 1.15)	0.96 (0.69, 1.34)
		Post-graduate	1.81 (0.44, 7.53)	1.27 (0.29, 5.56)	[no cases]	[no cases]	2.31 (1.01, 5.28)	2.89 (1.19, 7.01)
	Father's education	Basic	1	1	1	1	1	1
		Higher secondary	1.02 (0.78, 1.33)	1.04 (0.79, 1.35)	1.29 (0.66, 2.53)	1.24 (0.62, 2.44)	0.97 (0.78, 1.20)	1.02 (0.82, 1.27)
		Tertiary, <3 yrs	1.27 (0.91, 1.77)	1.21 (0.85, 1.71)	1.69 (0.73, 3.93)	1.49 (0.62, 3.61)	0.78 (0.57, 1.06)	0.85 (0.62, 1.17)
		Tertiary, ≥3 yrs	1.28 (0.93, 1.78)	1.14 (0.80, 1.64)	1.59 (0.70, 3.60)	1.35 (0.54, 3.38)	1.03 (0.78, 1.37)	1.12 (0.82, 1.53)
		Post-graduate	2.18 (1.16, 4.11)	1.91 (0.97, 3.76)	[no cases]	[no cases]	0.91 (0.42, 1.95)	0.83 (0.37, 1.87)
	Parental income	Change per standard deviation	0.98 (0.86, 1.11)	0.93 (0.81, 1.08)	0.88 (0.59, 1.30)	0.79 (0.51, 1.21)	0.80 (0.70, 0.92)**	0.82 (0.71, 0.94)**
	Mother's age	Change per decade	1.39 (1.15, 1.67)**	1.02 (0.78, 1.33)	0.89 (0.53, 1.47)	0.83 (0.39, 1.78)	1.05 (0.89, 1.24)	1.02 (0.81, 1.28)
	Father's age	Change per decade	1.39 (1.19, 1.62)***	1.30 (1.04, 1.61)*	0.88 (0.56, 1.38)	0.91 (0.47, 1.77)	1.06 (0.92, 1.22)	1.02 (0.84, 1.24)
	No. full siblings	Change per sibling	0.94 (0.85, 1.03)	0.92 (0.83, 1.03)	1.03 (0.81, 1.31)	1.03 (0.79, 1.33)	0.93 (0.86, 1.02)	0.96 (0.88, 1.05)
	No. half siblings	0-1	1	1	1	1	1*	1
		2-3	1.22 (0.92, 1.61)	1.14 (0.84, 1.54)	1.06 (0.51, 2.24)	1.11 (0.51, 2.42)	1.28 (1.01, 1.63)	1.17 (0.91, 1.51)
		4-5	1.30 (0.78, 2.18)	1.20 (0.70, 2.05)	0.93 (0.23, 3.84)	0.99 (0.23, 4.22)	1.74 (1.17, 2.58)	1.52 (1.01, 2.30)
		6+	1.74 (0.72, 4.20)	1.55 (0.63, 3.83)	[no cases]	[no cases]	1.36 (0.56, 3.28)	1.13 (0.46, 2.77)
	ED in mother	Yes (vs. no)	2.73 (1.02, 7.31)*	2.88 (1.07, 7.71)*	[no cases]	[no cases]	2.97 (1.33, 6.65)**	2.81 (1.26, 6.30)*
Birth characteristics	Multiple birth	Yes (vs. no)	2.40 (1.53, 3.76)***	2.22 (1.36, 3.64)**	2.82 (0.88, 8.98)	2.54 (0.72, 8.99)	1.48 (0.91, 2.40)	1.29 (0.77, 2.15)
	Gestational age	Change per week	0.92 (0.88, 0.97)**	0.95 (0.90, 1.00)*	0.99 (0.86, 1.14)	1.02 (0.89, 1.19)	0.94 (0.91, 0.99)**	0.95 (0.90, 0.99)*
	Birthweight for gestational age	Change per (sex-standardised) SD	1.11 (1.01, 1.23)*	1.06 (0.92, 1.22)	0.93 (0.73, 1.20)	0.95 (0.66, 1.38)	1.00 (0.92, 1.08)	1.03 (0.91, 1.16)
	Birth length for gestational age	Change per (sex-standardised) SD	1.13 (1.03, 1.25)*	1.10 (0.95, 1.27)	0.96 (0.74, 1.23)	1.02 (0.70, 1.48)	0.98 (0.90, 1.07)	0.98 (0.87, 1.11)
	Premature rupture of membranes	Yes (vs. no)	1.69 (1.02, 2.78)*	1.44 (0.86, 2.41)	[no cases]	[no cases]	0.60 (0.30, 1.20)	0.52 (0.26, 1.05)
	Delivery method	Normal vaginal	1	1	1	1	1	1
		Caesarean	1.41 (1.08, 1.85)	1.19 (0.90, 1.59)	1.57 (0.79, 3.10)	1.53 (0.75, 3.11)	1.26 (0.99, 1.61)	1.15 (0.89, 1.49)
		Instrumental	1.17 (0.81, 1.68)	1.12 (0.77, 1.63)	0.98 (0.35, 2.71)	0.89 (0.31, 2.53)	1.24 (0.92, 1.68)	1.30 (0.95, 1.77)
	Normal Apgar	7-10 (vs. 0-6)	0.77 (0.32, 1.86)	0.94 (0.38, 2.28)	0.67 (0.09, 4.82)	0.77 (0.11, 5.65)	1.71 (0.55, 5.31)	1.97 (0.63, 6.15)
	Cephalhematoma	Yes (vs. no)	0.93 (0.44, 1.96)	0.94 (0.44, 2.00)	0.78 (0.11, 5.64)	0.81 (0.11, 5.95)	0.70 (0.33, 1.47)	0.68 (0.32, 1.44)
	Other birth trauma	Yes (vs. no)	1.90 (0.90, 4.02)	1.76 (0.82, 3.75)	2.41 (0.59, 9.88)	2.39 (0.57, 10.01)	1.51 (0.71, 3.18)	0.86 (0.67, 1.10)

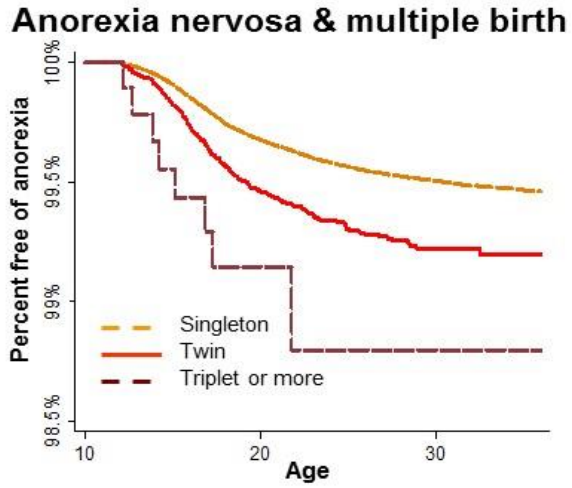
*p<0.05, **p<0.01, ***p<0.001. ED=eating disorder, SD=standard deviation, Minimally-adjusted analyses adjust for child's birth year, adjusted models additionally adjust for all variables shown in the column.

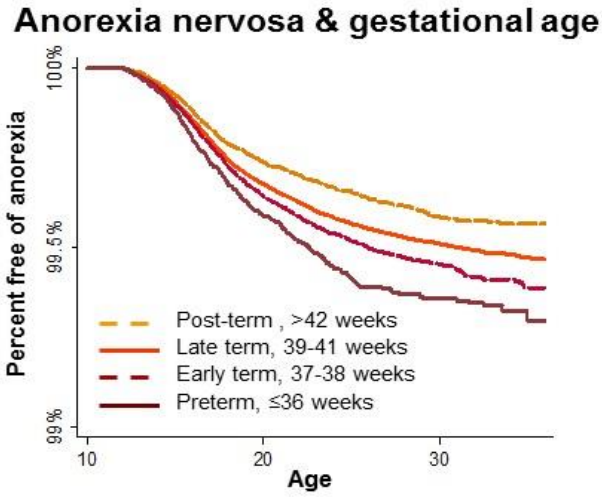
Web Table S3: Association between sibling type and a) anorexia nervosa, b) non-anorexia ED (follow-up 1987-2010), among Swedish males and females born 1975-1998: hazards ratios and 95% CI

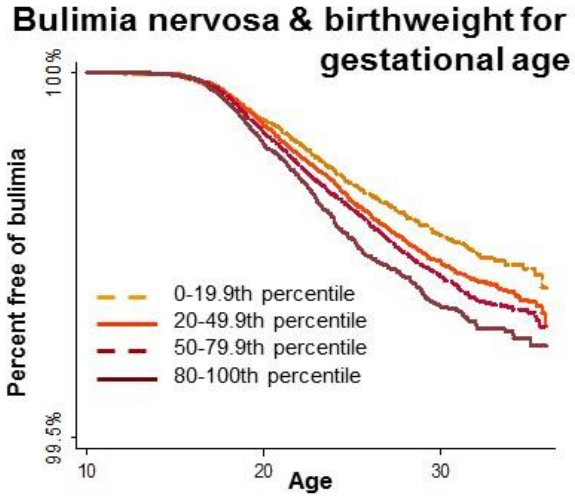
		Anorexia nervosa		Non-anorexia ED†	
		Minimally-adjusted	Adjusted	Minimally-adjusted	Adjusted
Full siblings	Older brothers	0.95 (0.91, 0.98)**	0.90 (0.86, 0.94)***	0.94 (0.91, 0.97)***	0.94 (0.91, 0.98)**
	Older sisters	1.00 (0.96, 1.04)	0.95 (0.91, 0.99)*	1.00 (0.97, 1.04)	1.01 (0.97, 1.04)
	Younger brothers	0.97 (0.94, 1.01)	0.98 (0.93, 1.02)	0.97 (0.94, 1.00)	0.98 (0.95, 1.02)
	Younger sisters	1.01 (0.97, 1.05)	1.01 (0.97, 1.05)	0.99 (0.96, 1.03)	1.01 (0.97, 1.04)
Half siblings	Older brothers	0.98 (0.94, 1.02)	0.97 (0.92, 1.02)	1.10 (1.06, 1.14)***	1.08 (1.04, 1.12)***
	Older sisters	0.97 (0.92, 1.01)	0.95 (0.90, 1.00)	1.09 (1.06, 1.13)***	1.06 (1.02, 1.11)**
	Younger brothers	0.93 (0.88, 0.98)**	1.00 (0.95, 1.07)	1.11 (1.07, 1.15)***	1.11 (1.07, 1.16)***
	Younger sisters	0.92 (0.88, 0.98)**	1.00 (0.94, 1.07)	1.07 (1.03, 1.11)**	1.04 (1.00, 1.09)*

*p<0.05, **p<0.01, ***p<0.001. ED=eating disorder, Minimally-adjusted analyses adjust for child's sex and birth year (as linear plus quadratic terms), adjusted models additionally adjust for all variables shown in the column and in Table S1.
†Bulimia nervosa and EDNOS combined to increase power; results similar in analyses predicting each separately

Web Figure S1 Survivor functions for selected associations between early life characteristics and eating disorders, conducted on the full sample of males and females







Web Table S4: Comparison of estimated effect sizes of family and birth predictors of ED, before and after adjustment for mother's smoking in pregnancy, pre-pregnancy weight status and weight gain: hazards ratios and 95% CIs

			Anorexia nervosa (follow-up 1994-2010) N= 678,736		Bulimia nervosa (follow-up 1997-2010) N=678,541		Eating disorder not-otherwise-specified (follow-up 1997-2010) N=678,541	
			Adjusted 1	**Adjusted 2**	**Adjusted 1**	**Adjusted 2**	**Adjusted 1**	**Adjusted 2**
Family characteristics	Mother's education	Basic	1	1	1	1	1	1
		Higher secondary	1.06 (0.92, 1.21)	1.04 (0.91, 1.19)	1.14 (0.92, 1.41)	1.15 (0.92, 1.43)	1.05 (0.94, 1.19)	1.06 (0.94, 1.20)
		Tertiary, <3 yrs	1.26 (1.08, 1.46)	1.22 (1.04, 1.42)	1.57 (1.22, 2.00)	1.59 (1.24, 2.04)	1.22 (1.06, 1.40)	1.24 (1.08, 1.43)
		Tertiary, ≥3 yrs	1.37 (1.17, 1.60)	1.32 (1.13, 1.55)	1.56 (1.20, 2.01)	1.59 (1.23, 2.06)	1.28 (1.10, 1.48)	1.29 (1.12, 1.50)
		Post-graduate	1.11 (0.66, 1.87)	1.06 (0.63, 1.79)	0.53 (0.13, 2.20)	0.55 (0.13, 2.27)	2.12 (1.41, 3.19)	2.17 (1.44, 3.27)
	Father's education	Basic	1	1	1	1	1	1
		Higher secondary	1.21 (1.08, 1.35)	1.20 (1.07, 1.34)	0.88 (0.74, 1.04)	0.88 (0.75, 1.04)	1.02 (0.93, 1.13)	1.02 (0.93, 1.13)
		Tertiary, <3 yrs	1.53 (1.33, 1.76)	1.49 (1.30, 1.71)	1.08 (0.87, 1.35)	1.10 (0.88, 1.37)	1.12 (0.98, 1.27)	1.12 (0.98, 1.27)
		Tertiary, ≥3 yrs	1.75 (1.53, 2.01)	1.69 (1.47, 1.95)	1.17 (0.94, 1.46)	1.19 (0.95, 1.48)	1.29 (1.13, 1.47)	1.29 (1.14, 1.48)
		Post-graduate	2.14 (1.64, 2.79)	2.05 (1.57, 2.68)	1.39 (0.87, 2.22)	1.41 (0.88, 2.26)	1.62 (1.24, 2.11)	1.62 (1.24, 2.12)
	Parental income	Change per standard deviation	0.99 (0.95, 1.04)	0.99 (0.95, 1.04)	1.01 (0.97, 1.05)	1.01 (0.97, 1.05)	0.98 (0.93, 1.03)	0.98 (0.93, 1.03)
	Mother's age	Change per decade	1.08 (0.97, 1.21)	1.10 (0.98, 1.22)	1.06 (0.88, 1.27)	1.06 (0.88, 1.27)	0.88 (0.79, 0.97)	0.89 (0.80, 0.98)
	Father's age	Change per decade	1.09 (0.99, 1.19)	1.09 (0.99, 1.20)	0.93 (0.80, 1.09)	0.93 (0.80, 1.09)	1.07 (0.98, 1.16)	1.07 (0.98, 1.17)
	No. full siblings	Change per sibling	0.95 (0.91, 0.99)	0.95 (0.91, 0.99)	1.02 (0.96, 1.09)	1.02 (0.96, 1.09)	0.98 (0.94, 1.02)	0.99 (0.95, 1.02)
	No. half siblings	0-1	1	1	1	1	1	1
		2-3	0.86 (0.75, 0.98)	0.87 (0.76, 0.99)	1.38 (1.15, 1.66)	1.36 (1.13, 1.64)	1.07 (0.96, 1.20)	1.06 (0.95, 1.19)
		4-5	0.79 (0.62, 1.02)	0.81 (0.63, 1.04)	1.22 (0.85, 1.73)	1.20 (0.84, 1.71)	1.22 (1.01, 1.49)	1.21 (1.00, 1.48)
		6+	0.62 (0.35, 1.10)	0.64 (0.36, 1.13)	0.90 (0.40, 2.03)	0.89 (0.40, 2.00)	1.42 (0.98, 2.04)	1.41 (0.98, 2.03)
	ED in mother	Yes (vs. no)	1.38 (0.78, 2.44)	1.37 (0.78, 2.42)	1.82 (0.75, 4.38)	1.86 (0.77, 4.48)	1.24 (0.72, 2.14)	1.25 (0.72, 2.15)
Birth characteristics	Multiple birth	Yes (vs. no)	1.55 (1.23, 1.95)	1.53 (1.21, 1.94)	0.76 (0.42, 1.37)	0.73 (0.41, 1.32)	0.81 (0.60, 1.10)	0.77 (0.56, 1.04)
	Gestational age	Change per week	0.96 (0.94, 0.98)	0.96 (0.94, 0.99)	1.01 (0.97, 1.05)	1.01 (0.96, 1.05)	0.98 (0.96, 1.00)	0.97 (0.95, 1.00)
	Birthweight for gestational age	Change per (sex-standardised) SD	0.99 (0.93, 1.04)	0.99 (0.94, 1.05)	1.11 (1.01, 1.21)	1.10 (1.00, 1.21)	1.04 (0.98, 1.09)	1.03 (0.97, 1.08)
	Birth length for gestational age	Change per (sex-standardised) SD	1.04 (0.98, 1.10)	1.04 (0.98, 1.09)	0.94 (0.86, 1.03)	0.94 (0.86, 1.03)	1.01 (0.96, 1.07)	1.01 (0.96, 1.07)
	Premature rupture of membranes	Yes (vs. no)	0.88 (0.66, 1.16)	0.89 (0.67, 1.17)	1.25 (0.80, 1.95)	1.24 (0.79, 1.93)	0.99 (0.77, 1.28)	0.99 (0.77, 1.28)
	Delivery method	Normal vaginal	1	1	1	1	1	1
		Caesarean	1.11 (0.99, 1.26)	1.13 (1.00, 1.27)	1.15 (0.93, 1.41)	1.14 (0.93, 1.40)	1.07 (0.95, 1.20)	1.06 (0.94, 1.20)
		Instrumental	0.95 (0.80, 1.12)	0.95 (0.80, 1.12)	0.89 (0.66, 1.19)	0.88 (0.66, 1.18)	1.05 (0.90, 1.22)	1.04 (0.89, 1.21)
	Normal Apgar	7-10 (vs. 0-6)	0.75 (0.51, 1.10)	0.74 (0.50, 1.09)	2.16 (0.69, 6.71)	2.17 (0.70, 6.74)	1.14 (0.72, 1.81)	1.14 (0.72, 1.82)
	Cephalhematoma	Yes (vs. no)	0.94 (0.68, 1.31)	0.94 (0.68, 1.31)	0.65 (0.34, 1.26)	0.65 (0.33, 1.25)	1.15 (0.87, 1.52)	1.15 (0.87, 1.52)
	Other birth trauma	Yes (vs. no)	1.47 (1.01, 2.16)	1.48 (1.01, 2.16)	1.28 (0.66, 2.48)	1.28 (0.66, 2.48)	0.75 (0.46, 1.23)	0.75 (0.46, 1.23)

ED=eating disorder, SD=standard deviation, Adjusted 1 models adjust for child's birth year plus all variables shown in the column; adjusted 2 models additionally adjust for the mother's smoking in pregnancy, pre-pregnancy weight status and weight gain

Web Table S5: Smoking, maternal pre-pregnancy weight status and maternal weight gain as predictors of ED subtypes, among males and females born 1982-1998: hazards ratios and 95% CIs

		Anorexia nervosa (follow-up 1994-2010)		Non-anorexia ED† (follow-up 1994-2010)	
		Minimally-adjusted	**Adjusted**	**Minimally-adjusted**	**Adjusted**
Mother's smoking in early pregnancy (no. cigarettes/day)	None	1***	1***	1	1
	1-9 per day	0.79 (0.73, 0.86)	0.92 (0.85, 1.00)	0.96 (0.90, 1.02)	1.03 (0.96, 1.10)
	10+ per day	0.66 (0.60, 0.74)	0.81 (0.73, 0.91)	0.97 (0.89, 1.05)	1.05 (0.97, 1.14)
Mother's pre-pregnancy weight status	Underweight	[1.23 (1.09, 1.39)]	[1.28 (1.13, 1.45)]	0.96 (0.85, 1.07)	0.97 (0.86, 1.09)
	Normal	[1]	[1]	1	1
	Overweight	[0.79 (0.71, 0.87)]	[0.84 (0.76, 0.93)]	0.95 (0.87, 1.03)	0.97 (0.89, 1.06)
	Obese	[0.65 (0.53, 0.80)]	[0.72 (0.59, 0.89)]	0.88 (0.75, 1.03)	0.92 (0.79, 1.08)
Mother's weight gain in pregnancy relative to BMI	Inadequate	0.99 (0.90, 1.08)	0.99 (0.90, 1.09)	0.97 (0.89, 1.05)	0.97 (0.90, 1.05)
	Appropriate	1	1	1**	1**
	Excessive	0.95 (0.87, 1.04)	0.99 (0.91, 1.08)	1.10 (1.02, 1.18)	1.12 (1.04, 1.20)

*p<0.05, **p<0.01, ***p<0.001. BMI=body mass index. Minimally-adjusted analyses adjust for child's sex and birth year (as linear plus quadratic terms), adjusted models additionally adjust for all variables shown in Table 2 of the main text. For no variable was there was evidence (p<0.01) of an interaction with sex, except with regard to mother's weight status in predicting AN (p<0.001 for interaction): see below for sex-stratified models. †Bulimia nervosa and EDNOS combined to increase power.

Web Table S6: Smoking, maternal pre-pregnancy weight status and maternal weight gain as predictors of anorexia nervosa, stratified by sex: hazards ratios and 95% CIs

		Males		Females	
		Minimally-adjusted	**Adjusted**	**Minimally-adjusted**	**Adjusted**
Mother's smoking in early pregnancy (no. cigarettes/day)	None	1	1	1***	1**
	1-9 per day	0.84 (0.60, 1.16)	0.90 (0.64, 1.27)	0.79 (0.73, 0.86)	0.92 (0.85, 1.01)
	10+ per day	0.63 (0.39, 1.00)	0.69 (0.43, 1.12)	0.67 (0.60, 0.74)	0.82 (0.73, 0.92)
Mother's pre-pregnancy weight status	Underweight	0.78 (0.40, 1.53)	0.87 (0.44, 1.71)	1.25 (1.10, 1.42)	1.30 (1.15, 1.48)
	Normal	1	1	1***	1***
	Overweight	1.14 (0.80, 1.62)	1.11 (0.78, 1.59)	0.77 (0.69, 0.85)	0.82 (0.73, 0.91)
	Obese	1.05 (0.55, 2.01)	1.04 (0.54, 1.99)	0.62 (0.50, 0.78)	0.70 (0.56, 0.87)
Mother's weight gain in pregnancy relative to BMI	Inadequate	0.85 (0.56, 1.28)	0.88 (0.58, 1.33)	0.99 (0.91, 1.09)	1.00 (0.91, 1.10)
	Appropriate	1	1	1	1
	Excessive	0.83 (0.58, 1.21)	0.83 (0.57, 1.21)	0.96 (0.88, 1.05)	1.00 (0.91, 1.10)

*p<0.05, **p<0.01, ***p<0.001. BMI=body mass index. Minimally-adjusted analyses adjust for child's sex and birth year (as linear plus quadratic terms), adjusted models additionally adjust for all variables shown in Table 2 of the main text.

Web Table S7: Smoking, maternal pre-pregnancy weight status and maternal weight gain as predictors of non-anorexia ED, stratified by sex: hazards ratios and 95% CIs

		Males		Females	
		Minimally-adjusted	**Adjusted**	**Minimally-adjusted**	**Adjusted**
Mother's smoking in early pregnancy (no. cigarettes/day)	None	1	1	1	1
	1-9 per day	0.98 (0.76, 1.27)	0.90 (0.69, 1.17)	0.96 (0.89, 1.02)	1.04 (0.97, 1.11)
	10+ per day	1.13 (0.84, 1.52)	0.98 (0.72, 1.34)	0.96 (0.88, 1.04)	1.05 (0.97, 1.15)
Mother's pre-pregnancy weight status	Underweight	1.08 (0.68, 1.71)	1.02 (0.65, 1.62)	0.95 (0.84, 1.07)	0.97 (0.86, 1.09)
	Normal	1	1	1	1
	Overweight	0.87 (0.64, 1.20)	0.89 (0.65, 1.23)	0.95 (0.87, 1.04)	0.98 (0.90, 1.07)
	Obese	1.21 (0.75, 1.96)	1.25 (0.76, 2.03)	0.85 (0.72, 1.01)	0.89 (0.75, 1.06)
Mother's weight gain in pregnancy relative to BMI	Inadequate	0.77 (0.54, 1.10)	0.72 (0.50, 1.03)	0.98 (0.90, 1.06)	0.99 (0.91, 1.07)
	Appropriate	1*	1*	1*	1*
	Excessive	1.20 (0.91, 1.60)	1.24 (0.93, 1.66)	1.09 (1.01, 1.18)	1.11 (1.03, 1.20)

See notes to Table S6.