Supplementary Appendix

Leone M, Kuja-Halkola R, Leval A, Butwicka A, Skov J, Zhang R, Liu S, Larsson H, Bergen SE. Genetic and environmental contribution to the co-occurrence of endocrine-metabolic disorders and depression: a nationwide Swedish study of siblings

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Methods S1.

We used structural equation modeling (SEM) to estimate the contribution of genetic, shared-, and non-shared environmental factors to the co-occurrence of depression and endocrine-metabolic disorders. SEM is a statistical method combining factor and regression analyses used to describe the relative contribution of the latent (unmeasured) constructs that are assumed to underpin the observed data (1).

SEM can be applied to analyze categorical traits by using liability threshold models. In this model, the associations between binary traits are modelled as tetrachoric correlations, i.e., the observed binary trait is assumed to be underpinned by a normal distribution of liability in the population. Individuals whose disease risks exceeded a given threshold on this liability distribution are cases, and those below are non-cases. The level of the threshold is given by the life-time prevalence of the disorder in the population (2).

A SEM model may be fitted using different optimization techniques, mainly maximum likelihood and weighted least squares (WLS). In this study, similar estimates were obtained when comparing these two approaches, although we encountered convergence issues when estimating 95% CIs using maximum likelihood; on the contrary, WLS was found to be faster (less than 3 minutes per analysis, compared to approximately 17 minutes when using maximum likelihood) and stable during optimization.

In order to avoid possible introduction of biases, we only used ACE models and did not test other submodels (e.g. by excluding C). In fact, given that our results showed a small contribution of C to the co-occurrence of depression and endocrine-metabolic disorders, excluding this parameter would have necessarily increased (biased upwards) the A (3).

Table S1. Sibling pairs characteristics

	Full cohort (n=2 263 311)	Female (n=1 105 301; 48.8) [a]
Full siblings		
Unique individuals	1 615 237 (71.4)	458 087 (41.4)
Sibling pairs	1 207 943	286 123
Familial co-aggregation pairs [b]	2 415 886	572 246
Quantitative genetic modelling pairs [c]	691 499	211 178
Maternal half-siblings		
Unique individuals	240 938 (10.6)	69 280 (6.3)
Sibling pairs	173 934	42 128
Familial co-aggregation pairs [b]	347 868	84 256
Quantitative genetic modelling pairs [c]	86 948	29 418
Paternal half-siblings		
Unique individuals	246 886 (10.9)	72 705 (6.6)
Sibling pairs	186 374	44 913
Familial co-aggregation pairs [b]	372 748	89 826
Quantitative genetic modelling pairs [c]	NA	NA

Abbreviations: NA, not applicable.

Data is presented as number (%) of individuals.

[a] Female-female pairs were used when investigating polycystic ovarian syndrome.

[b] In the familial co-aggregation analyses, all possible combinations of sibling pairs were identified, with each individual contributing at least once as an index person and once as a sibling.

[c] In the quantitative genetic modelling, only full- and maternal half-sibling pairs were included and, within each family, only the oldest pair of siblings was selected to avoid dependency between sibling pairs from the same family and increase the precision of the estimates.

Table S2. Diagnostic classification of endocrine-metabolic disorders considered in this study

Type of disease	ICD Version	Diagnostic code
Autoimmune disorders		
Autoimmune hypothyroidism [a]	ICD-8	244.09
	ICD-9	244W, 244X, 245C
	ICD-10	E03.4-E03.9, E06.3
Graves' disease	ICD-8	242.00-242.09
	ICD-9	242A
	ICD-10	E05.0
Type I diabetes [b]	ICD-8	250.00-250.09
	ICD-9	250A-X
	ICD-10	E10
Non-autoimmune disorders		
Type II diabetes [c]	ICD-8	250.00-250.09
	ICD-9	250A-X
	ICD-10	E11
Polycystic ovarian syndrome [d]	ICD-8	256.90
	ICD-9	256E
	ICD-10	E28.2
Obesity	ICD-8	277.99
	ICD-9	278A
	ICD-10	E66

Abbreviations: ICD-8, International Classification of Diseases, 8th revision; ICD-9, Swedish version of the International Classification of Diseases, 9th revision; ICD-10, International Classification of Diseases, 10th revision.

[a] The definition of autoimmune hyperthyroidism was based upon consultation with Swedish endocrinologists as well as on prior literature.(4)

[b] When using ICD-8 and ICD-9, we restricted T1D measure to individuals with a diagnosis of diabetes between 7 months and 18 years of age because these earlier versions of the ICD do not distinguish between type 1 and type 2 diabetes. This definition of T1D was based on prior evidence showing that: 1) The majority (98-99%) of Swedish children who are 0-18 years of age at diagnosis of diabetes have type 1 diabetes;(5) 2) Onset of diabetes before the age of 6 months tends to be indicative of neonatal diabetes with monogenic etiology.(6)

[c] When using ICD-8 and ICD-9, we restricted T2D measure to individuals with a diagnosis of diabetes after the age of 18 years because these earlier versions of the ICD do not distinguish between type 1 and type 2 diabetes. It is important to note that only 877 (13.5%) individuals were diagnosed with diabetes after age 18 using ICD-8 and ICD-9.

[d] As polycystic ovarian syndrome is a condition affecting women's ovaries, this diagnosis was applicable only to female individuals in our study.

Table S3. Diagnostic classification of depression

Psychiatric Disorders	ICD Version	Diagnostic Code
Depression	ICD-8	300.4
	ICD-9	296B, 311
	ICD-10	F32-F33

Note: For each individual, the first recorded primary or secondary diagnosis of depression from an inpatient (i.e., hospitalization) or outpatient (i.e., specialist care) contact during the follow-up period was included.

Table S4. Sex-specific prevalence of endocrine-metabolic disorders among individuals with and without a depression diagnosis

Endocrine and metabolic disorder	Sex	No Depression 2 145 260 (94.8)	Depression 118 051 (5.2)
Autoimmune disorders			
Any autoimmune disorder	Female	24 925 (66.1)	3688 (78.1)
	Male	12 808 (33.9)	1032 (21.9)
Autoimmune hypothyroidism	Female	15 606 (86.7)	2574 (89.0)
	Male	2387 (13.3)	318 (11.0)
Graves' diseases	Female	4071 (82.2)	422 (86.3)
	Male	880 (17.8)	67 (13.7)
Type 1 diabetes	Female	7399 (42.3)	1017 (58.5)
	Male	10 108 (57.7)	720 (41.5)
Non-autoimmune disorders			
Any non-autoimmune disorder	Female	41 424 (74.1)	6447 (79.8)
	Male	14 501 (25.9)	1633 (20.2)
Type 2 diabetes	Female	2465 (45.4)	615 (58.6)
	Male	2966 (54.6)	434 (41.4)
Obesity	Female	29 190 (70.7)	4825 (78.8)
	Male	12 115 (29.3)	1301 (21.2)
Polycystic ovarian syndrome [a]	Female	12 397 (100) [a]	1675 (100) [a]

Data is presented as number (%) of individuals.

[a] As polycystic ovarian syndrome is a condition affecting women's ovaries, this diagnosis was applicable only to female individuals in our study.

Table S5. Prevalence of endocrine-metabolic disorders in individual with and without depression among sibling cohorts

	Individuals with at least one full-sibling 1 615 237 (71.4)		**Individuals with at least one maternal half-sibling** 240 938 (10.6)		**Individuals with at least one paternal half-sibling** 246 886 (10.9)	
	Depression 80 454 (5.0)	No depression 1 534 783 (95.0)	Depression 19 462 (8.1)	No depression 221 476 (91.9)	Depression 18 224 (7.4)	No depression 228 662 (92.6)
Autoimmune disorders						
Any autoimmune disorder	3 133 (3.9)	26 337 (1.7)	738 (3.8)	3 875 (1.7)	685 (3.8)	3 948 (1.7)
Autoimmune hypothyroidism	1 920 (2.4)	12 488 (0.8)	432 (2.2)	1 857 (0.8)	408 (2.2)	1 916 (0.8)
Graves' diseases [a]	321 (0.4)	3 421 (0.2)	92 (0.5)	552 (0.2)	87 (0.5)	562 (0.2)
Type 1 diabetes	1 157 (1.4)	12 295 (0.8)	282 (1.4)	1 764 (0.8)	252 (1.4)	1 755 (0.8)
Non-autoimmune disorders						
Any non-autoimmune disorder	5 153 (6.4)	37 363 (2.4)	1 528 (7.9)	7 969 (3.6)	1 371 (7.5)	7 518 (3.3)
Type 2 diabetes	617 (0.8)	3 355 (0.2)	202 (1.0)	642 (0.3)	168 (0.9)	613 (0.3)
Obesity	3 857 (4.8)	27 066 (1.8)	1 202 (6.2)	6 410 (2.9)	1 067 (5.9)	5 954 (2.6)
	Females with at least one full-sister 458 087 (41.4) [b]		**Females with at least one maternal half-sister** 69 280 (6.3) [b]		**Females with at least one paternal half-sister** 72 705 (6.6) [b]	
	Depression 30 015 (6.6)	No depression 428 072 (93.4)	Depression 7 073 (10.2)	No depression 62 207 (89.8)	Depression 6 896 (9.5)	No depression 65 809 (90.5)
Polycystic ovarian syndrome [b]	652 (2.2)	5 313 (1.2)	170 (2.4)	780 (1.3)	166 (2.4)	842 (1.3)

Data is presented as number (%) of individuals.

[a] Because the prevalence of Graves' disease was too low in the sibling cohorts, this disorder was not included in the quantitative genetic analyses.

[b] As polycystic ovarian syndrome is a condition affecting women's ovaries, this diagnosis was applicable only to female individuals in our study.

Table S6. Prevalence of individuals with and without depression having a full-, maternal half-, or paternal half-sibling diagnosed with an endocrine-metabolic disorder

	Individuals with at least one full-sibling 1 615 237 (71.4)		**Individuals with at least one maternal half-sibling** 240 938 (10.6)		**Individuals with at least one paternal half-sibling** 246 886 (10.9)	
	Depression 80 454 (5.0)	No depression 1 534 783 (95.0)	Depression 19 462 (8.1)	No depression 221 476 (91.9)	Depression 18 224 (7.4)	No depression 228 662 (92.6)
Sibling autoimmune disorders						
Any autoimmune disorder	2 644 (3.3)	39 668 (2.6)	619 (3.2)	5 906 (2.7)	548 (3.0)	6 336 (2.8)
Autoimmune hypothyroidism	1 409 (1.8)	19 610 (1.3)	318 (1.6)	2 939 (1.3)	296 (1.5)	3 249 (1.4)
Graves' diseases [a]	327 (0.4)	5 162 (0.3)	90 (0.5)	885 (0.4)	69 (0.4)	942 (0.4)
Type 1 diabetes	1 110 (1.4)	18 112 (1.2)	268 (1.4)	2 596 (1.2)	255 (1.4)	2 678 (1.2)
Sibling non-autoimmune disorders						
Any non-autoimmune disorder	4 274 (5.3)	58 045 (3.8)	1 294 (6.6)	12 387 (5.6)	1 166 (6.4)	12 251 (5.4)
Type 2 diabetes	445 (0.6)	5 335 (0.3)	112 (0.6)	1 129 (0.5)	112 (0.6)	1 150 (0.5)
Obesity	3 229 (4.0)	42 302 (2.8)	1 070 (5.5)	9 969 (4.5)	921 (5.1)	9 766 (4.3)
	Females with at least one full-sister 458 087 (41.4) [b]		**Females with at least one maternal half-sister** 69 280 (6.3) [b]		**Females with at least one paternal half-sister** 72 705 (6.6) [b]	
	Depression 30 015 (6.6)	No depression 428 072 (93.4)	Depression 7 073 (10.2)	No depression 62 207 (89.8)	Depression 6 896 (9.5)	No depression 65 809 (90.5)
Polycystic ovarian syndrome [b]	617 (2.1)	6 859 (1.6)	126 (1.8)	1 043 (1.7)	140 (2.0)	1 096 (1.7)

Data is presented as number (%) of individuals.

[a] Because the prevalence of Graves' disease was too low in the sibling cohorts, this disorder was not included in the quantitative genetic analyses.

[b] As polycystic ovarian syndrome is a condition affecting women's ovaries, this diagnosis was applicable only to female individuals in our study.

Table S7. Prevalence of individuals with and without depression having a full- or maternal half-sibling diagnosed with an endocrine-metabolic disorder (using only one pair of siblings per family)

	Individuals with a full-sibling 1 382 998		**Individuals with a maternal half-sibling** 173 869	
	Depression 68 868 (5.0)	No depression 1 314 130 (95.0)	Depression 14 356 (8.2)	No depression 159 540 (91.8)
Sibling autoimmune disorders				
Any autoimmune disorder	1 569 (2.3)	24 194 (1.8)	321 (2.2)	3 085 (1.9)
Autoimmune hypothyroidism	843 (1.2)	11 894 (0.9)	165 (1.1)	1 525 (1.0)
Graves' diseases [a]	NA	NA	NA	NA
Type 1 diabetes	636 (0.9)	10 896 (0.8)	141 (1.0)	1 353 (0.8)
Sibling non-autoimmune disorders				
Any non-autoimmune disorder	2 525 (3.7)	34 200 (2.6)	678 (4.7)	6 373 (4.0)
Type 2 diabetes	274 (0.4)	3 345 (0.3)	62 (0.4)	615 (0.4)
Obesity	1 892 (2.7)	24 599 (1.9)	550 (3.8)	5 063 (3.2)
	Females with at least one full-sister 422 356 [b]		**Females with at least one maternal half-sister** 58 836 [b]	
	Depression 27 669 (6.6)	No depression 394 687 (93.4)	Depression 6 110 (10.4)	No depression 52 726 (89.6)
Polycystic ovarian syndrome b	459 (1.7)	5 106 (1.3)	92 (1.5)	722 (1.4)

Data is presented as number (%) of individuals.

[a] Because the prevalence of Graves' disease was too low in the sibling cohorts, this disorder was not included in the quantitative genetic analyses.

[b] As polycystic ovarian syndrome is a condition affecting women's ovaries, this diagnosis was applicable only to female individuals in our study.

Table S8. Association and familial co-aggregation of depression and endocrine-metabolic disorders using logistic regression model

Endocrine-metabolic disorder	Within-individuals			Full-siblings			Maternal half-siblings			Paternal half-siblings		
	OR (95% CI)	*P* Value	Bonferroni [a]	OR (95% CI)	*P* Value	Bonferroni [a]	OR (95% CI)	*P* Value	Bonferroni [a]	OR (95% CI)	*P* Value	Bonferroni [a]
Autoimmune disorders												
Any disorder	2.05 (1.99-2.12)	<0.001	Significant	1.24 (1.19-1.29)	<0.001	Significant	1.17 (1.07-1.27)	<0.001	Significant	1.06 (0.97-1.16)	0.22	Not significant
Autoimmune hypothyroidism	2.34 (2.25-2.44)	<0.001	Significant	1.31 (1.24-1.39)	<0.001	Significant	1.22 (1.08-1.38)	0.001	Significant	1.03 (0.91-1.18)	0.62	Not significant
Graves' disease	1.43 (1.30-1.57)	<0.001	Significant	1.15 (1.02-1.29)	0.02	Not significant	1.17 (0.93-1.46)	0.18	Not significant	0.92 (0.70-1.20)	0.53	Not significant
Type 1 diabetes	1.88 (1.79-1.98)	<0.001	Significant	1.16 (1.08-1.24)	<0.001	Significant	1.11 (0.97-1.27)	0.11	Not significant	1.12 (0.98-1.28)	0.11	Not significant
Non autoimmune-disorders												
Any disorder	2.33 (2.28-2.39)	<0.001	Significant	1.39 (1.34-1.44)	<0.001	Significant	1.18 (1.11-1.25)	<0.001	Significant	1.18 (1.11-1.26)	<0.001	Significant
Type 2 diabetes	3.48 (3.25-3.72)	<0.001	Significant	1.53 (1.37-1.69)	<0.001	Significant	1.08 (0.88-1.33)	0.44	Not significant	1.21 (0.99-1.47)	0.06	Not significant
Obesity	2.44 (2.37-2.50)	<0.001	Significant	1.44 (1.39-1.50)	<0.001	Significant	1.20 (1.13-1.29)	<0.001	Significant	1.17 (1.09-1.25)	<0.001	Significant
Polycystic ovarian syndrome [b]	1.79 (1.70-1.88)	<0.001	Significant	1.25 (1.14-1.36)	<0.001	Significant	1.06 (0.88-1.29)	0.54	Not significant	1.22 (1.02-1.46)	0.03	Not significant

Abbreviations: OR, Odds Ratios.

[a] Bonferroni-corrected significance level of $P < 0.005$, accounting for the 11 main analyses.

[b] As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Table S9. Association and familial co-aggregation of depression and endocrine-metabolic disorders using hazard proportional hazards regression model, and modelling depression as the outcome disorder

Endocrine-metabolic disorder	Within-individuals			Full-siblings			Maternal half-siblings			Paternal half-siblings		
	HR (95% CI)	*P* Value	Bonferroni [a]	HR (95% CI)	*P* Value	Bonferroni [a]	HR (95% CI)	*P* Value	Bonferroni [a]	HR (95% CI)	*P* Value	Bonferroni [a]
Autoimmune disorders												
Any disorder	1.79 (1.72-1.86)	<0.001	Significant	1.20 (1.14-1.26)	<0.001	Significant	1.18 (1.07-1.31)	0.001	Significant	1.07 (0.96-1.20)	0.21	Not significant
Autoimmune hypothyroidism	1.85 (1.75-1.97)	<0.001	Significant	1.30 (1.20-1.41)	<0.001	Significant	1.31 (1.12-1.53)	<0.001	Significant	1.06 (0.89-1.26)	0.53	Not significant
Graves' disease	1.43 (1.27-1.61)	<0.001	Significant	1.22 (1.05-1.42)	0.01	Not significant	1.15 (0.88-1.51)	0.32	Not significant	0.83 (0.60-1.15)	0.26	Not significant
Type 1 diabetes	1.85 (1.76-1.95)	<0.001	Significant	1.13 (1.05-1.21)	0.001	Significant	1.11 (0.96-1.28)	0.17	Not significant	1.11 (0.96-1.28)	0.16	Not significant
Non autoimmune-disorders												
Any disorder	2.10 (2.04-2.18)	<0.001	Significant	1.39 (1.33-1.45)	<0.001	Significant	1.17 (1.08-1.27)	<0.001	Significant	1.15 (1.06-1.25)	0.001	Significant
Type 2 diabetes	2.88 (2.63-3.16)	<0.001	Significant	1.42 (1.23-1.64)	<0.001	Significant	1.01 (0.76-1.34)	0.95	Not significant	1.06 (0.81-1.40)	0.67	Not significant
Obesity	2.20 (2.11-2.28)	<0.001	Significant	1.43 (1.35-1.50)	<0.001	Significant	1.22 (1.12-1.33)	<0.001	Significant	1.15 (1.04-1.26)	0.01	Not significant
Polycystic ovarian syndrome [b]	1.69 (1.57-1.82)	<0.001	Significant	1.34 (1.19-1.52)	<0.001	Significant	1.00 (0.77-1.31)	0.98	Not significant	1.17 (0.91-1.50)	0.22	Not significant

Abbreviations: HR, Hazard Ratios.

[a] Bonferroni-corrected significance level of $P < 0.005$, accounting for the 11 main analyses.

[b] As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Table S10. Association and familial co-aggregation of depression and endocrine-metabolic disorders using hazard proportional hazards regression model, and modelling depression as the exposure disorder

Endocrine-metabolic disorder	Within-individuals			Full-siblings			Maternal half-siblings			Paternal half-siblings		
	HR (95% CI)	*P* Value	Bonferroni [a]	HR (95% CI)	*P* Value	Bonferroni [a]	HR (95% CI)	*P* Value	Bonferroni [a]	HR (95% CI)	*P* Value	Bonferroni [a]
Autoimmune disorders												
Any disorder	2.13 (2.03-2.23)	<0.001	Significant	1.30 (1.22-1.39)	<0.001	Significant	1.12 (0.97-1.30)	0.12	Not significant	1.05 (0.91-1.21)	0.52	Not significant
Autoimmune hypothyroidism	2.18 (2.07-2.29)	<0.001	Significant	1.28 (1.19-1.39)	<0.001	Significant	1.09 (0.92-1.30)	0.31	Not significant	0.99 (0.83-1.18)	0.91	Not significant
Graves' disease	1.19 (1.04-1.37)	0.01	Not significant	1.02 (0.85-1.21)	0.86	Not significant	1.10 (0.77-1.57)	0.61	Not significant	1.00 (0.66-1.51)	1.00	Not significant
Type 1 diabetes	1.47 (1.29-1.67)	<0.001	Significant	1.27 (1.10-1.45)	0.001	Significant	1.13 (0.85-1.50)	0.41	Not significant	1.12 (0.86-1.46)	0.39	Not significant
Non autoimmune-disorders												
Any disorder	2.13 (2.07-2.20)	<0.001	Significant	1.33 (1.27-1.39)	<0.001	Significant	1.14 (1.05-1.23)	0.002	Significant	1.16 (1.07-1.27)	<0.001	Significant
Type 2 diabetes	3.45 (3.16-3.78)	<0.001	Significant	1.60 (1.39-1.84)	<0.001	Significant	1.20 (0.91-1.58)	0.20	Not significant	1.36 (1.05-1.77)	0.02	Not significant
Obesity	2.28 (2.20-2.37)	<0.001	Significant	1.39 (1.32-1.47)	<0.001	Significant	1.14 (1.04-1.25)	0.004	Significant	1.15 (1.05-1.26)	0.004	Significant
Polycystic ovarian syndrome [b]	1.56 (1.46-1.67)	<0.001	Significant	1.14 (1.02-1.27)	0.03	Not significant	1.07 (0.83-1.38)	0.61	Not significant	1.21 (0.95-1.54)	0.12	Not significant

Abbreviations: HR, Hazard Ratios.

[a] Bonferroni-corrected significance level of $P < 0.005$, accounting for the 11 main analyses.

[b] As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Table S11. Univariate ACE models with 95% confidence intervals calculated using weighted least squares

Disorder	A	C	E
Depression	0.39 (0.30-0.48)	0.03 (-0.01-0.07)	0.58 (0.53-0.63)
Autoimmune disorders			
Any disorder	0.54 (0.33-0.74)	0.01 (-0.09-0.11)	0.45 (0.35-0.56)
Autoimmune hypothyroidism	0.57 (0.24-0.90)	0.02 (-0.14-0.18)	0.41 (0.24-0.58)
Graves' disease [a]	NA	NA	NA
Type 1 diabetes	0.70 (0.40-1.00)	0.02 (-0.12-0.17)	0.28 (0.12-0.43)
Non-autoimmune disorders			
Any disorder	0.60 (0.46-0.73)	0.01 (-0.06-0.07)	0.40 (0.32-0.47)
Type 2 diabetes	0.70 (-0.07-1.46)	0.01 (-0.37-0.38)	0.30 (-0.10-0.69)
Obesity	0.68 (0.53-0.82)	0.02 (-0.05-0.09)	0.31 (0.23-0.39)
Polycystic ovarian syndrome [b]	0.28 (-0.09-0.66)	0.17 (-0.01-0.35)	0.55 (0.35-0.75)

Abbreviations: A, additive genetic factors; C, shared environmental factors; E, non-shared environmental factors; NA, not applicable.

[a] Because the prevalence of Graves' disease was too low in the sibling cohorts, this disorder was not included in the quantitative genetic analyses.

[b] As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Table S12. A, C, and E correlations with 95% confidence intervals calculated using weighted least squares

Disorder	r_{ph}	r_A	r_C	r_E
Autoimmune disorders				
Any disorder	0.15 (0.14-0.16)	0.09 (-0.14-0.32)	1.00 (-4.44-6.44)	0.17 (0.06-0.29)
Autoimmune hypothyroidism	0.17 (0.16-0.18)	0.13 (-0.17-0.42)	1.00 (-4.15-6.15)	0.19 (0.03-0.35)
Graves' disease [a]	NA	NA	NA	NA
Type 1 diabetes	0.11 (0.10-0.13)	-0.01 (-0.28-0.26)	1.00 (-3.23-5.23)	0.24 (0.03-0.44)
Non-autoimmune disorders				
Any disorder	0.19 (0.18-0.20)	0.23 (0.05-0.40)	1.00 (-3.25-5.25)	0.13 (0.04-0.23)
Type 2 diabetes	0.22 (0.20-0.23)	0.31 (-0.09-0.71)	-1.00 (-29.93-27.93)	0.17 (-0.10-0.45)
Obesity	0.19 (0.18-0.20)	0.21 (0.03-0.39)	1.00 (-1.66-3.66)	0.14 (0.02-0.26)
Polycystic ovarian syndrome [b]	0.11 (0.09-0.13)	0.34 (-0.32-0.99)	-0.02 (-0.79-0.74)	0.02 (-0.17-0.21)

Abbreviations: r_{ph}, phenotypic correlation (tetrachoric correlation); r_A, genetic correlation; r_C, shared environmental correlation; r_E, non-shared environmental correlation; NA, not applicable.

[a] Because the prevalence of Graves' disease was too low in the sibling cohorts, this disorder was not included in the quantitative genetic analyses.

[b] As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Table S13. Bivariate heritability explained by A, C, and E with 95% confidence intervals calculated using weighted least squares

	Bivariate heritability [a]		
Disorder	**A**	**C**	**E**
Autoimmune disorders			
Any disorder	0.28 (-0.44-1.01)	0.12 (-0.22-0.46)	0.60 (0.20-0.99)
Autoimmune hypothyroidism	0.34 (-0.47-1.15)	0.13 (-0.25-0.51)	0.53 (0.09-0.97)
Graves' disease [b]	NA	NA	NA
Type 1 diabetes	-0.06 (-1.31-1.20)	0.22 (-0.37-0.81)	0.84 (0.15-1.52)
Non-autoimmune disorders			
Any disorder	0.58 (0.13-1.03)	0.08 (-0.12-0.29)	0.34 (0.09-0.58)
Type 2 diabetes	0.74 (-0.19-1.66)	-0.07 (-0.50-0.37)	0.33 (-0.18-0.84)
Obesity	0.56 (0.08-1.04)	0.12 (-0.10-0.34)	0.32 (0.05-0.59)
Polycystic ovarian syndrome [c]	0.93 (-0.85-2.71)	-0.03 (-0.86-0.81)	0.10 (-0.88-1.07)

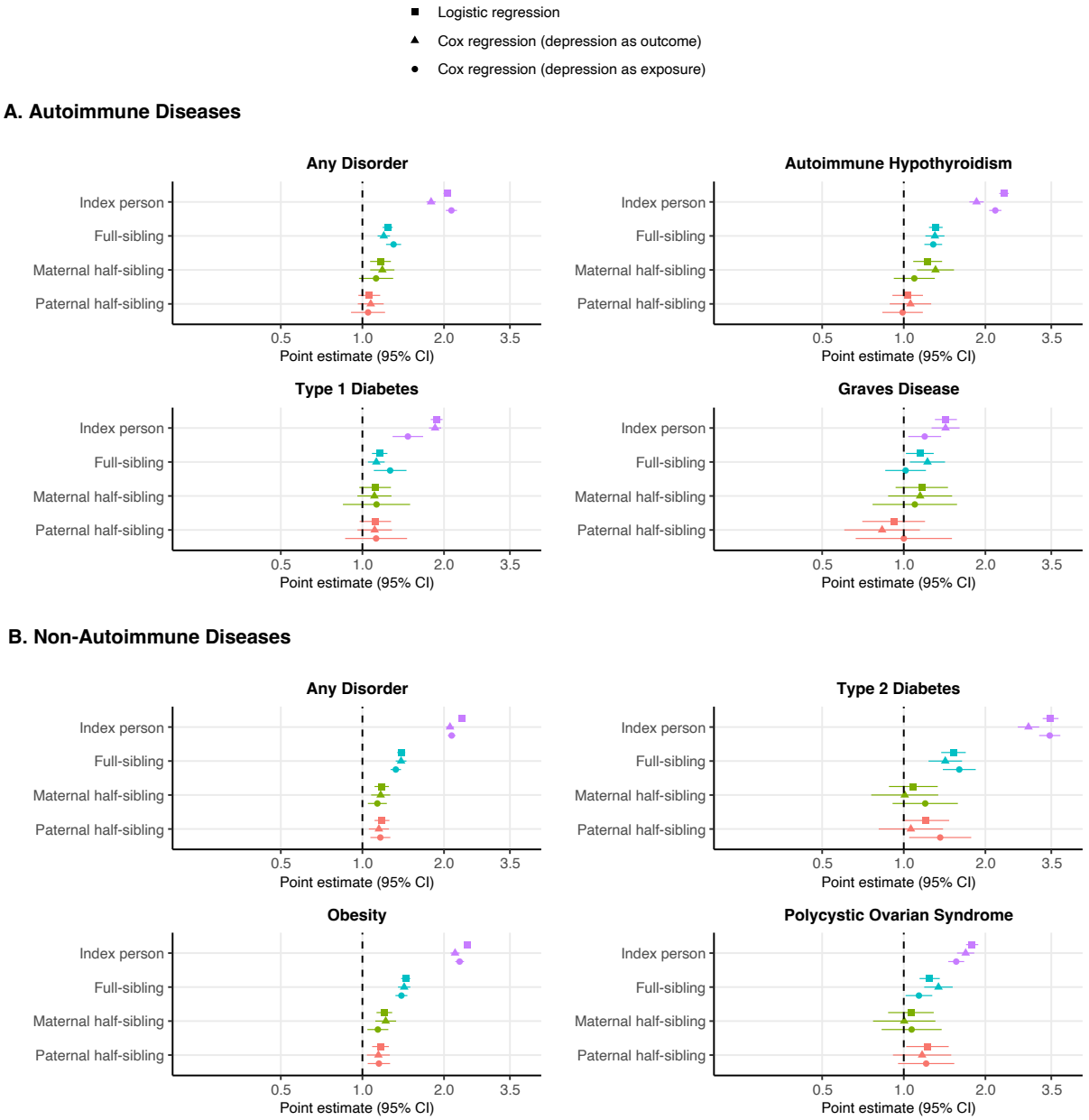
Abbreviations: A, additive genetic factors; C, shared environmental factors; E, non-shared environmental factors; NA, not applicable.

[a] Bivariate heritability is the fraction of the phenotypic correlation (tetrachoric correlation) explained by genetic and environmental factors.

[b] Because the prevalence of Graves' disease was too low in the sibling cohorts, this disorder was not included in the quantitative genetic analyses.

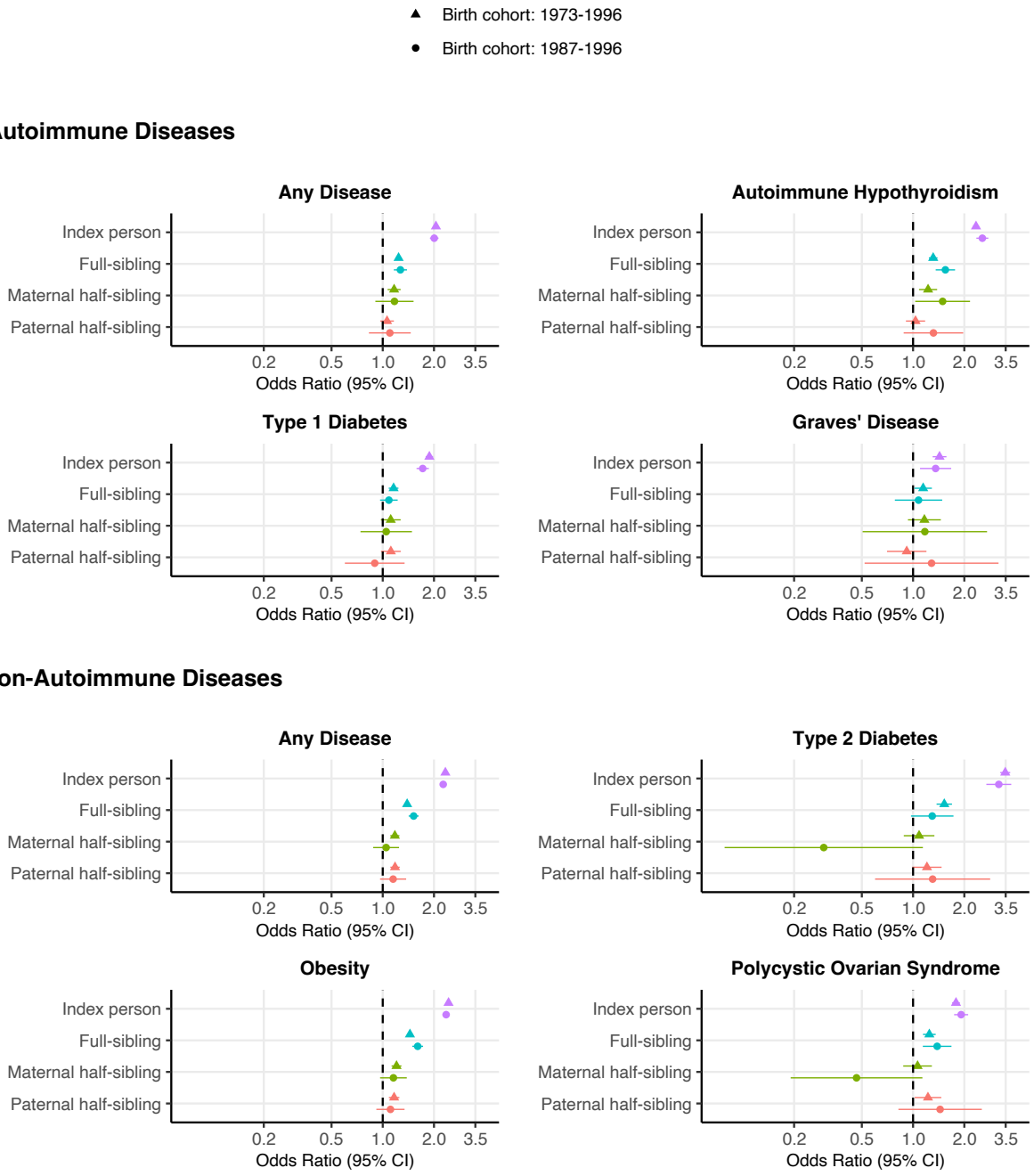
[c] As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Figure S1. Association and familial co-aggregation of depression and endocrine-metabolic disorders, grouped as autoimmune and non-autoimmune conditions: Comparison of logistic regression and Cox proportional hazard regression models



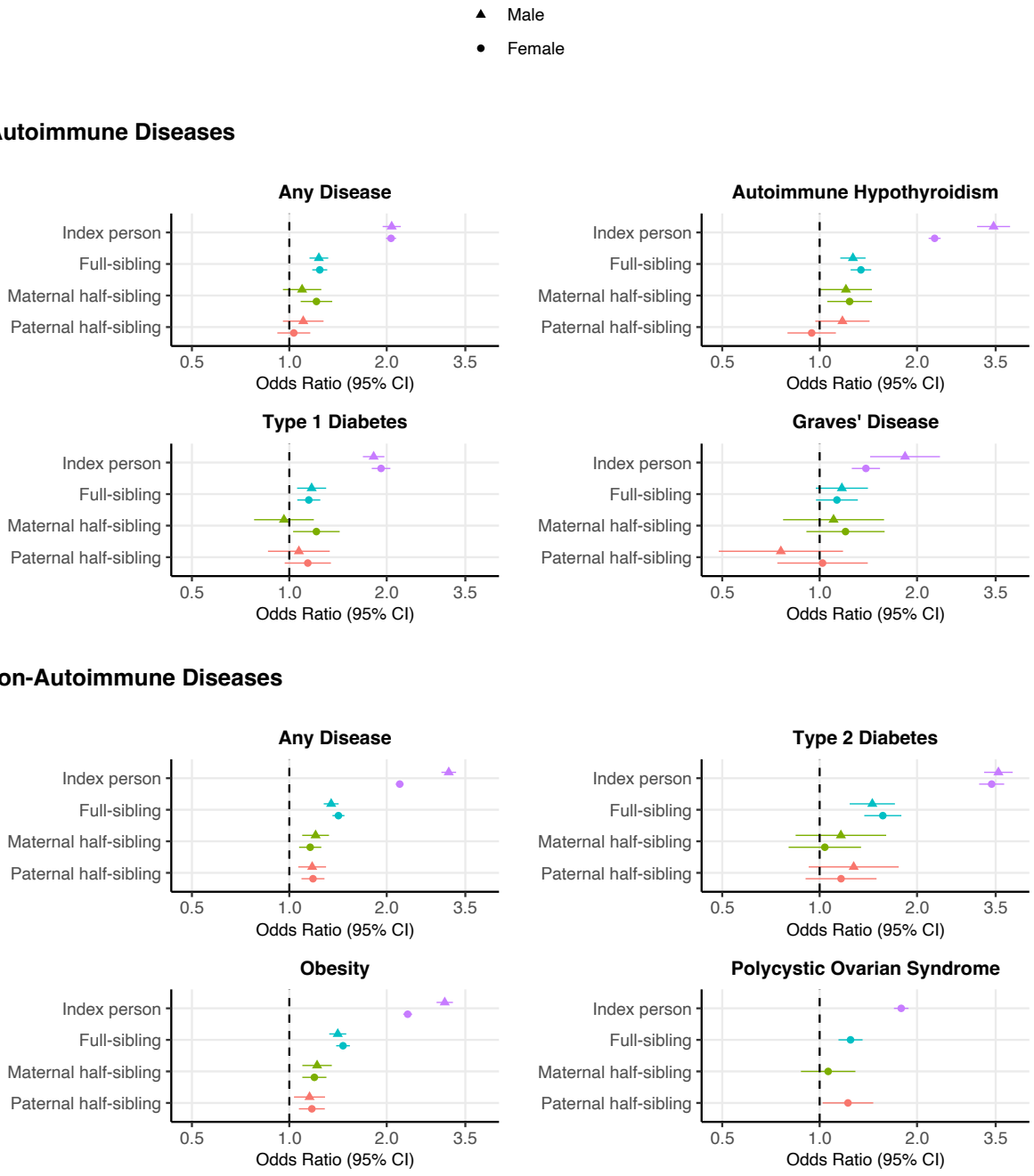
Note: As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Figure S2. Association and familial co-aggregation of depression and endocrine-metabolic disorders, grouped as autoimmune and non-autoimmune conditions: Comparison of original vs restricted birth cohort



Note: As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

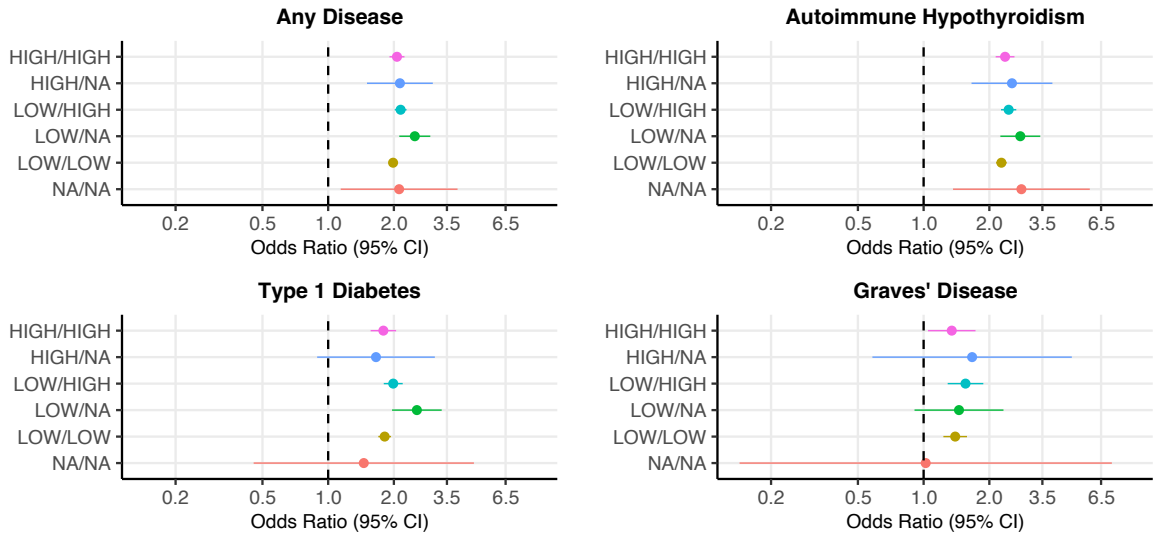
Figure S3. Association and familial co-aggregation of depression and endocrine-metabolic disorders, grouped as autoimmune and non-autoimmune conditions: Comparison of male and female



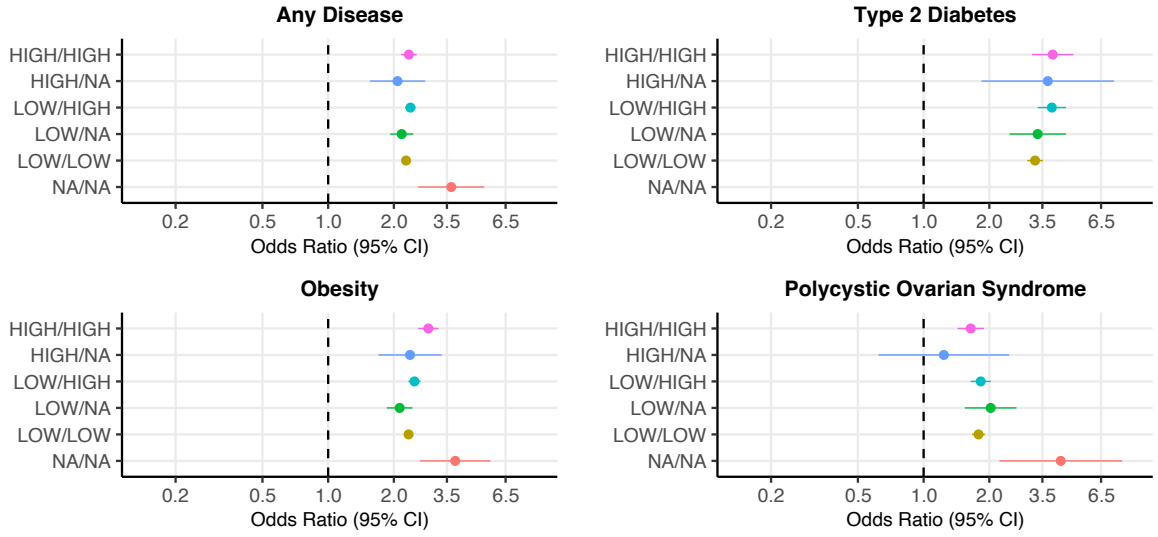
Note: As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Figure S4. Association and familial co-aggregation of depression and endocrine-metabolic disorders, across parental educational levels

A. Autoimmune Diseases



B. Non-Autoimmune Diseases



NA: Not applicable

Note: As polycystic ovarian syndrome is a condition affecting women's ovaries, only female individuals were included in the analyses when exploring this disorder.

Both maternal and paternal educational levels were measured, defined as low (primary school, lower and upper secondary school) or high (≥1 year of university).

Labels explanation:

- HIGH/HIGH = both parents had high educational level
- HIGH/NA = one parent had high educational level, while the other parent had missing information

- LOW/HIGH = one parent had low educational level, while the other parent high educational level
- LOW/NA = one parent had low educational level, while the other parent had missing information
- LOW/LOW = both parents had low educational level
- NA/NA = both parents had missing information

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