Supplementary Information

Maternal polycystic ovary syndrome and offspring's risk of cardiovascular diseases in childhood and young adulthood

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Supplementary Table 1. Hazard ratios and 95% confidence intervals for overall cardiovascular disease in offspring according to maternal polycystic ovary syndrome, by

attained age

Exposure	N	E	HR (95% CI)	
	Number of events	Event rate, per 10,000 person-years	Model 1 ^a	Model 2 b
Attained a	ge ^c <10 years	s (N=6 839 703)		
No PCOS	56 445	8.98	1.0 (Reference)	1.0 (Reference)
PCOS	729	17.10	1.87 (1.74-2.01)	1.22 (1.13-1.31)
10 ≤ Attair	$1 \text{ ed age} \leq 19 \text{ y}$	rears (N=5 619 120)		
No PCOS	74 881	15.71	1.0 (Reference)	1.0 (Reference)
PCOS	376	22.05	1.55 (1.40-1.71)	1.14 (1.03-1.26)
20 ≤ Attair	20 ≤ Attained age ≤ 29 years (N=3 963 638)			
No PCOS	121 440	38.78	1.0 (Reference)	1.0 (Reference)
PCOS	267	49.07	1.32 (1.17-1.48)	1.22 (1.08-1.37)
30 ≤ Attained age ≤ 39 years (N=2 267 578)				
No PCOS	104 457	68.72	1.0 (Reference)	1.0 (Reference)
PCOS	100	76.44	1.14 (0.94-1.39)	1.16 (0.95-1.41)
Attained age \geq 40 years (N=835 515)				
No PCOS	25 559	86.56	1.0 (Reference)	1.0 (Reference)
PCOS	20	136.55	1.60 (1.04-2.48)	1.58 (1.02-2.46)

Abbreviations: PCOS, polycystic ovary syndrome; HR, hazard ratio; CI, confidence interval.

^a Model 1 was unadjusted.

^b Model 2 was adjusted for sex, country and calendar year of birth, maternal country of origin, parity, age, education, and marital status at the time of birth, hypertensive disorders, diabetes, and psychiatric disorders before or during the index pregnancy, and family history of cardiovascular disease.

^c Attained age refers to the age of study participants from their entry into the cohort to their exit from the cohort (i.e., having a CVD diagnosis, death, emigration, or the latest date in our available datasets); i.e. attained age is equivalent to the age at the respective follow-up.

Supplementary Table 2. Sub-analyses of the association between maternal polycystic ovary syndrome and cardiovascular disease in offspring

Exposure	Number	Event rate, per 10 000	HR (95% CI)	
	of events	per 10 000 person- years	Model 1 ^a	Model 2 ^b
Stratified analysis according	to offsprin			
Boy				
No PCOS	189 274	23.03	1.0 (Reference)	1.0 (Reference)
PCOS	791	23.00	1.53 (1.44-1.65)	1.20 (1.11-1.28)
Girl				
No PCOS	193 508	24.89	1.0 (Reference)	1.0 (Reference)
PCOS	701	21.77	1.53 (1.43-1.65)	1.22 (1.13-1.32)
P-value for multiplicative			0.007	0.008
interaction between PCOS				
and sex				
Stratified analysis according	to offsprin	g's country o	f birth	
Denmark		т.	1	
No PCOS	130 768	23.36	1.0 (Reference)	1.0 (Reference)
PCOS	451	20.88	1.50 (1.37-1.65)	1.20 (1.09-1.31)
Sweden				
No PCOS	252 014	24.22	1.0 (Reference)	1.0 (Reference)
PCOS	1041	23.14	1.55 (1.46-1.64)	1.21 (1.13-1.28)
P-value for multiplicative			0.01	0.03
interaction between PCOS				
and country of birth				
Stratified analysis according	to materna	al ART		
Without ART				
No PCOS	380 506	23.96	1.0 (Reference)	1.0 (Reference)
PCOS	1320	22.69	1.57 (1.48-1.65)	1.20 (1.14-1.27)
With ART				
With ART No PCOS	2276	19.75	1.0 (Reference)	1.0 (Reference)
	2276 172	19.75 20.44	1.0 (Reference) 1.09 (0.93-1.27)	1.0 (Reference) 1.06 (0.90-1.24)
No PCOS PCOS				
No PCOS PCOS			1.09 (0.93-1.27)	1.06 (0.90-1.24)
No PCOS PCOS P-value for multiplicative			1.09 (0.93-1.27)	1.06 (0.90-1.24)
No PCOS PCOS P-value for multiplicative interaction between PCOS	172	20.44	1.09 (0.93-1.27) <0.0001	1.06 (0.90-1.24) 0.09
No PCOS PCOS P-value for multiplicative interaction between PCOS and ART	172	20.44	1.09 (0.93-1.27) <0.0001	1.06 (0.90-1.24) 0.09
No PCOS PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with offspring	172 complete da	20.44 ata on matern	1.09 (0.93-1.27) <0.0001 all smoking (N=4 61'	1.06 (0.90-1.24) 0.09
No PCOS PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with CNo PCOS	172 complete d : 163 096 1187	20.44 ata on matern 19.47 21.00	1.09 (0.93-1.27) <0.0001 al smoking (N=4 61' 1.0 (Reference) 1.43 (1.35-1.51)	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27)
No PCOS PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with to PCOS PCOS	172 complete d : 163 096 1187	20.44 ata on matern 19.47 21.00	1.09 (0.93-1.27) <0.0001 al smoking (N=4 61) 1.0 (Reference) 1.43 (1.35-1.51) al body-mass index	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27) (N=3 565 133) d
No PCOS PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with a No PCOS PCOS Restricted to offspring with a Restric	172 complete da 163 096 1187 complete da	20.44 ata on matern 19.47 21.00 ata on matern	1.09 (0.93-1.27) <0.0001 al smoking (N=4 61) 1.0 (Reference) 1.43 (1.35-1.51) al body-mass index 1.0 (Reference)	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27) (N=3 565 133) d 1.0 (Reference)
No PCOS PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with to No PCOS PCOS Restricted to offspring with to No PCOS PCOS	172 complete da 163 096 1187 complete da 273 507 595	20.44 ata on matern 19.47 21.00 ata on matern 25.95 25.43	1.09 (0.93-1.27) <0.0001 al smoking (N=4 61') 1.0 (Reference) 1.43 (1.35-1.51) al body-mass index 1.0 (Reference) 1.57 (1.45-1.70)	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27) (N=3 565 133) d 1.0 (Reference) 1.25 (1.16-1.36)
No PCOS PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with to No PCOS PCOS Restricted to offspring with to No PCOS PCOS PCOS Restricted to offspring born	172 complete da 163 096 1187 complete da 273 507 595	20.44 ata on matern 19.47 21.00 ata on matern 25.95 25.43	1.09 (0.93-1.27) <0.0001 al smoking (N=4 61) 1.0 (Reference) 1.43 (1.35-1.51) al body-mass index 1.0 (Reference) 1.57 (1.45-1.70) and in Sweden since	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27) (N=3 565 133) d 1.0 (Reference) 1.25 (1.16-1.36) 2001 (N=2 765 917)
No PCOS PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with to No PCOS Restricted to offspring with to No PCOS PCOS Restricted to offspring with to No PCOS PCOS Restricted to offspring born in No PCOS	172 complete de 163 096 1187 complete de 273 507 595 in Denmar	20.44 ata on matern 19.47 21.00 ata on matern 25.95 25.43 k since 1995 a 15.51	1.09 (0.93-1.27) <0.0001 lal smoking (N=4 61') 1.0 (Reference) 1.43 (1.35-1.51) lal body-mass index 1.0 (Reference) 1.57 (1.45-1.70) land in Sweden since 1.0 (Reference)	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27) (N=3 565 133) d 1.0 (Reference) 1.25 (1.16-1.36) 2001 (N=2 765 917) 1.0 (Reference)
No PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with on PCOS PCOS Restricted to offspring with on PCOS PCOS Restricted to offspring with on PCOS PCOS Restricted to offspring born No PCOS PCOS	172 complete de 163 096 1187 complete de 273 507 595 in Denmar 49 500 798	20.44 ata on matern 19.47 21.00 ata on matern 25.95 25.43 k since 1995 a 15.51 19.00	1.09 (0.93-1.27) <0.0001 al smoking (N=4 61) 1.0 (Reference) 1.43 (1.35-1.51) al body-mass index 1.0 (Reference) 1.57 (1.45-1.70) and in Sweden since 1.0 (Reference) 1.27 (1.18-1.36)	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27) (N=3 565 133) d 1.0 (Reference) 1.25 (1.16-1.36) 2001 (N=2 765 917)
No PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with on PCOS PCOS Restricted to offspring with on PCOS PCOS Restricted to offspring born No PCOS PCOS Restricted to offspring born No PCOS PCOS Restricted to offspring born No PCOS PCOS Restricted to CVD cases iden	172 complete de 163 096 1187 complete de 273 507 595 in Denmar 49 500 798 ctified from	20.44 ata on matern 19.47 21.00 ata on matern 25.95 25.43 k since 1995 at 15.51 19.00 n national pati	1.09 (0.93-1.27) <0.0001 al smoking (N=4 61) 1.0 (Reference) 1.43 (1.35-1.51) al body-mass index 1.0 (Reference) 1.57 (1.45-1.70) and in Sweden since 1.0 (Reference) 1.27 (1.18-1.36) ient registers	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27) (N=3 565 133) d 1.0 (Reference) 1.25 (1.16-1.36) 2001 (N=2 765 917) 1.0 (Reference) 1.17 (1.09-1.25)
No PCOS P-value for multiplicative interaction between PCOS and ART Restricted to offspring with on PCOS PCOS Restricted to offspring with on PCOS PCOS Restricted to offspring with on PCOS PCOS Restricted to offspring born No PCOS PCOS	172 complete de 163 096 1187 complete de 273 507 595 in Denmar 49 500 798	20.44 ata on matern 19.47 21.00 ata on matern 25.95 25.43 k since 1995 a 15.51 19.00	1.09 (0.93-1.27) <0.0001 al smoking (N=4 61) 1.0 (Reference) 1.43 (1.35-1.51) al body-mass index 1.0 (Reference) 1.57 (1.45-1.70) and in Sweden since 1.0 (Reference) 1.27 (1.18-1.36)	1.06 (0.90-1.24) 0.09 7 257) ° 1.0 (Reference) 1.20 (1.14-1.27) (N=3 565 133) d 1.0 (Reference) 1.25 (1.16-1.36) 2001 (N=2 765 917) 1.0 (Reference)

No PCOS	382 782	23.93	1.0 (Reference)	1.0 (Reference)
<1990	196	30.15	1.17 (1.02-1.35)	1.21 (1.05-1.39)
1990-2003	423	23.02	1.56 (1.42-1.71)	1.23 (1.12-1.35)
>2003	873	20.92	1.75 (1.63-1.87)	1.20 (1.12-1.28)
Imputed data by multiple imputation by chained equations f				
No PCOS	382 782	23.93	1.0 (Reference)	1.0 (Reference)
PCOS	1492	22.41	1.59 (1.52-1.66)	1.20 (1.15-1.26)

Abbreviations: PCOS, polycystic ovary syndrome; ART, assisted reproductive treatment; HR, hazard ratio; CI, confidence interval.

^a Model 1 was unadjusted.

^b Model 2 was adjusted for sex, country and calendar year of birth, maternal origin of country, parity, age, education, and marital status at the time of birth, hypertensive disorders, diabetes, and psychiatric disorders before or during the index pregnancy, and family history of cardiovascular diseases.

^c We further adjusted for maternal smoking in early pregnancy in addition to factors included in Model 2.

^d We further adjusted for maternal body-mass index in early pregnancy in addition to factors included in Model 2.

^e There were 2183 women who had a diagnosis of polycystic ovary syndrome before 1990, 111 23 between 1990 and 2003, and 38 417 after 2003.

^f We imputed missing variables using multiple imputation by the chained equations method to generate five imputations. We used logistic regression to impute the following categorical variables: offspring's sex, maternal origin of country, education, and marital status.

Supplementary Table 3. Hazard ratios and 95% confidence intervals for overall and specific cardiovascular diseases in offspring according to maternal polycystic ovary syndrome in the propensity score matched sub-cohort

Exposure	Number of	Rate, per 10,000	Model 1 ^a	Model 2 ^b		
	events	person-years	HR (95% CI)	HR (95% CI)		
Overall C	VD					
No PCOS	2627	23.74	1.0 (Reference)	1.0 (Reference)		
PCOS	1492	22.41	1.38 (1.29-1.48)	1.19 (1.10-1.27)		
Ischemic h	Ischemic heart disease					
No PCOS	47	0.42	1.0 (Reference)	1.0 (Reference)		
PCOS	20	0.30	1.80 (1.03-3.15)	1.76 (0.98-3.15)		
Acute myo	cardial infarction		·			
No PCOS	18	0.16	1.0 (Reference)	1.0 (Reference)		
PCOS	8	0.12	2.36 (0.98-5.71)	2.51 (1.03-6.16)		
Stroke						
No PCOS	92	0.81	1.0 (Reference)	1.0 (Reference)		
PCOS	44	0.65	1.21 (0.82-1.78)	1.05 (0.70-1.58)		
Haemorrh	agic stroke					
No PCOS	25	0.22	1.0 (Reference)	1.0 (Reference)		
PCOS	13	0.19	1.12 (0.55-2.27)	1.02 (0.48-2.17)		
Ischemic s	troke					
No PCOS	54	0.48	1.0 (Reference)	1.0 (Reference)		
PCOS	29	0.43	1.46 (0.89-2.38)	1.16 (0.39-1.95)		
Heart failu	Heart failure					
No PCOS	38	0.34	1.0 (Reference)	1.0 (Reference)		
PCOS	12	0.18	0.66 (0.33-1.31)	0.72 (0.35-1.49)		
Atrial fibr	illation					
No PCOS	62	0.55	1.0 (Reference)	1.0 (Reference)		
PCOS	18	0.27	0.99 (0.58-1.72)	1.18 (0.68-2.05)		
Hypertensive disorders						
No PCOS	349	3.09	1.0 (Reference)	1.0 (Reference)		
PCOS	146	2.16	1.54 (1.26-1.89)	1.38 (1.11-1.71)		
Peripheral arterial disease						
No PCOS	10	0.09	1.0 (Reference)	1.0 (Reference)		
PCOS	6	0.09	1.46 (0.50-4.27)	1.77 (0.58-5.38)		
A11 '.'	DCCC 1	1 0	1. 1 1.	IID 1 1		

Abbreviations: PCOS, polycystic ovary syndrome; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

^a Model 1 was unadjusted.

^b Model 2 was adjusted for sex, country and calendar year of birth, and maternal age at the time of birth.

Supplementary Table 4. Description of the Danish and Swedish national registers used in our study

in our study		I
Data source	Information retrieved from the register	Period covered
The Danish registers		T
Danish Civil	Sex, birth date, place of birth, vital status,	1968-2016
Registration System	marital status, emigration and immigration,	
	and linkage to relatives	
Danish Integrated	Mother's education level	1980-2016
Database for Labour		
Market Research		
Danish Medical Birth	Birth date, sex, gestational age, birth	1973-2016
Register	weight, singleton status, mother's height,	
	weight, and smoking in early pregnancy,	
	age at delivery and parity	
Danish National	Information on inpatient and outpatient care	Inpatient care: 1977-
Patient Registry	(diagnosis, date)	2016; specialized
2 3		outpatient care and
		emergency
		department contacts:
		1995-2016
Danish Register of	Date of death and cause of death	1970-2016
Causes of Death		1570 2010
The Swedish registers		
Swedish Total	Sex, birth date, place of birth, marital	1968-2014
Population Register	status, migration, and civil status	
Swedish Multi-	Relationships for all residents born since	1961-2014
Generation Register	1932 ^a	
Swedish Register of	Mother's education	1985-2014
Education		
Swedish Medical Birth	Birth date, sex, gestational age, birth	1973-2014
Register	weight, singleton status, mother's height,	
_	weight, and smoking status in early	
	pregnancy, age at delivery and parity, and	
	complications during pregnancy	
Swedish Patient	Information on inpatient and outpatient care	Inpatient care: 1964-
Register	(diagnosis, date)	2020 (its coverage
Č		became nationwide
		since 1987);
		specialized outpatient
		care: 2001-2020
Swedish Cause of	Date and cause of death	1952-2020
Death Register		
	1	1

^a The index persons must have been registered since 1961 in order to be included.

Supplementary Table 5. International Classification of Diseases codes for polycystic ovary syndrome and cardiovascular diseases

ovary syndro	ICD-8	ICD-9	ICD-10
Polycystic ovar			
Denmark	25690		E282
Sweden	25690	256E	E282
Overall cardio	vascular disease	•	
Denmark	390-458		I00-I99
Sweden	390-458	390-459	I00-I99
Ischemic heart	disease		
Denmark	410-414		I20-I25
Sweden	410-414	410-414	I20-I25
Acute myocard	lial infarction		
Denmark	410		I21, I22
Sweden	410	410	I21, I22
Stroke			
Denmark	430, 431, 433, 434, 436		I60, I61, I63, I64
Sweden	430, 431, 433, 434, 436	430, 431, 433, 434, 436	I60, I61, I63, I64
Haemorrhagic	stroke (except subarachn	oid haemorrhage)	
Denmark	431		I61
Sweden	431	431	I61
Ischemic strok	e		
Denmark	433, 434		I63, I64
Sweden	433, 434	433, 434	I63, I64
Heart failure			
Denmark	42709, 42710, 42711,		I110, I130, I132, I50
	42719		
Sweden	427.00, 427.10	428	I11.0, I13.0, I13.2, I50
Atrial fibrillati	on/flutter		
Denmark	42793, 42794		I48
Sweden	427.92	427D	I48
Hypertensive d	lisease		
Denmark	400-404		I10-I15, O10, O11
Sweden	400-404	401-405, 642A, 642B,	I10-I15, O10, O11
		642C, 642H	
Peripheral arte			
Denmark	440, 44399, 445		I70, I739
Sweden	440, 4438, 4439, 445	440, 443W, 443X	I70, I73.9

Abbreviation: ICD, International Statistical Classification of Diseases and Related Health Problems.

Polycystic ovary syndrome diagnoses were extracted from the Danish and Swedish patient registers and the Swedish Medical Birth Register. Overall cardiovascular disease was identified using primary or secondary diagnoses in the national patient registers or from the underlying cause of death in the cause of death register. Ischemic heart disease, stroke, and heart failure were identified based on the primary diagnosis in the national patient registers or from the underlying cause of death in the cause of death register. Hypertensive disease, atrial fibrillation and peripheral artery disease were identified based on the primary or secondary diagnoses in national patient registers.

${\bf Supplementary\ Table\ 6.\ Baseline\ characteristics\ of\ the\ propensity-score-matched\ subcohort}$

Characteristics	Exposure			
	No maternal PCOS	Maternal PCOS		
	(N=51 723)	(N=51 723)		
	N (%)	N (%)		
Characteristics of the of	fspring			
Study country				
Denmark	19 516 (37.3)	20 235 (39.1)		
Sweden	32 207 (62.3)	31 488 (60.9)		
Calendar year of birth				
1973-1978	5252 (10.2)	523 (1.0)		
1979-1984	5631 (10.9)	1088 (2.1)		
1985-1990	6811 (13.2)	2054 (4.0)		
1991-1996	7540 (14.6)	3971 (7.7)		
1997-2002	7137 (13.8)	6428 (12.4)		
2003-2008	8493 (16.4)	13 267 (25.7)		
2009-2016	10 859 (21.0)	24 392 (47.2)		
Sex				
Boy	26 622 (51.5)	26 683 (51.6)		
Girl	25 094 (48.5)	25 040 (48.4)		
Unknown	7 (0.01)	0		
Congenital heart disease				
No	50 890 (98.4)	50 480 (97.6)		
Yes	833 (1.6)	1243 (2.4)		
Preterm birth				
No	46 336 (89.6)	47 536 (91.9)		
Yes	2957 (5.7)	3683 (7.1)		
Unknown	2430 (4.7)	504 (1.0)		
Small for gestational ago	2 a			
No	46 410 (89.7)	47 419 (91.7)		
Yes	5313 (10.3)	4304 (8.3)		
Large for gestational ag	e ^b			
No	46 893 (90.7)	44 900 (86.8)		
Yes	4830 (9.3)	6823 (13.2)		
Maternal characteristics	8			
Country of origin same				
No	10 503 (20.3)	10 550 (20.4)		
Yes	41 217 (79.7)	41 170 (79.6)		
Unknown	3 (0.01)	3 (0.01)		
Age (years) at the time of	f the index birth			
≤19	1672 (3.2)	1488 (2.9)		
20-24	10 689 (20.7)	9699 (18.8)		
25-29	18 333 (35.4)	17 895 (34.6)		
30-34	14 149 (27.4)	15 671 (30.3)		
≥35	6880 (13.3)	6970 (13.5)		
Level of education at the	time of the index birth			
Primary and lower	9820 (19.0)	9931 (19.2)		
secondary				
Upper secondary	22 046 (42.6)	22 076 (42.7)		
Bachelor or higher	19 390 (37.5)	19 240 (37.2)		
Unknown	467 (0.9)	476 (0.9)		

Marital status at the time of	the index birth				
Not married/no registered	26 499 (51.2)	26 554 (51.3)			
partnership					
Married/registered	24 858 (48.1)	24 860 (48.1)			
partnership					
Unknown	366 (0.7)	319 (0.6)			
Parity at the time of the inde	ex birth				
1	28 826 (55.7)	28 453 (55.0)			
_ 2	16 931 (32.7)	16 924 (32.7)			
≥3	5966 (11.5)	6346 (12.3)			
Smoking in early pregnancy	c				
No	31 893 (79.0)	41 577 (83.9)			
Yes	6175 (15.3)	5953 (12.0)			
Unknown	2297 (5.7)	2020 (4.1)			
Body-mass index in early pr	egnancy (kg/m²) ^d				
<18.5	1107 (3.2)	739 (1.64)			
18.5-24.9	17 016 (48.9)	16 424 (36.4)			
25.0-29.9	6819 (19.6)	11 850 (26.3)			
≥30.0	3222 (9.3)	11 264 (25.0)			
Unknown	6615 (19.0)	4806 (10.7)			
Assisted reproductive treatm	nent during index pregnancy	e			
No	28 831 (96.5)	38 028 (82.9)			
Yes	1036 (3.5)	7869 (17.1)			
Diabetes before or during in	Diabetes before or during index pregnancy				
No	48 787 (94.3)	48 460 (93.7)			
Yes	2936 (5.7)	3263 (6.3)			
Hypertensive disorders before or during index pregnancy					
No	47 445 (91.7)	47 779 (92.4)			
Yes	4278 (8.3)	3944 (7.6)			
Psychiatric disorders before or during index pregnancy					
No	45 764 (88.5)	45 804 (88.6)			
Yes	5959 (12.5)	5919 (11.4)			
Family history of cardiovascular disease before the index birth					
No	29 157 (56.4)	28 676 (55.4)			
Yes	22 566 (43.6)	23 047 (44.6)			

Abbreviation: PCOS, polycystic ovary syndrome.

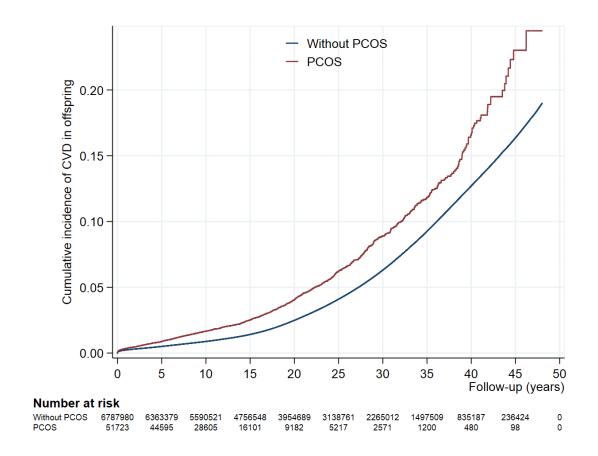
^a Small for gestational age, birth weight below the 10th percentile of the sex-specific standard curve for normal fetal growth.

^b Large for gestational age, birth weight above the 10th percentile of the sex-specific standard curve for normal fetal growth.

^c Maternal smoking was available since 1982 in Sweden and since 1991 in Denmark.

^d Maternal body-mass index has been available since 1982 in Sweden and since 2003 in Denmark.

^e Maternal assisted reproductive treatment has been available since 1994 in Denmark and since 1995 in Sweden.



Supplementary Figure 1. Cumulative incidence of overall cardiovascular disease in offspring according to maternal polycystic ovary syndrome

PCOS, polycystic ovary syndrome.

Supplementary note 1. Description of the source, measurement, and categorization of covariates

1. Offspring characteristics

Sex (boy or girl), calendar year of birth (1973-1978, 1979-1984, 1985-1990, 1991-1996, 1997-2002, 2003-2008, or 2009-2016), gestational age, and birth weight were obtained from the Danish and Swedish Medical Birth Registers. Preterm birth (yes/no) was defined as gestational age < 37 weeks at birth. Birth weight for gestational age was calculated according to the Scandinavian sex-specific reference curve for normal foetal growth, and further categorized into small for gestational age (<10th percentile), appropriate for gestational age (between the 10th and 90th percentile), and large for gestational age (>90th percentile). Diagnoses of congenital heart disease were obtained from the Danish National Patient Register (DNPR) and the Swedish Patient Register (SPR), using the following *International Statistical Classification of Diseases and Related Health Problems* (ICD) codes: 1) in Denmark: ICD-8: 746, 747; ICD-10: Q20-Q27; and 2) in Sweden: ICD-8: 746, 747; ICD-10: Q20-Q27. Diagnoses of diabetes were obtained from the DNPR, and SPR using the ICD codes: 1) in Denmark: ICD-8: 250 and ICD-10: E10-E14; and 2) in Sweden: ICD-8: ICD-8/9: 250 and ICD-10: E10-E14.

2. Maternal characteristics

Information on maternal country of origin (same as the study country or not) and marital status (married/registered partnership versus not) was obtained from the Danish Civil Registration System and the Swedish Total Population Register. Maternal educational level (primary and lower secondary, upper secondary, bachelor, or higher) was extracted from the Danish Integrated Database for Labour Market Research and the Swedish Register of Education.

From the Danish and Swedish Medical Birth Registers, we extracted information on maternal age (\leq 19, 20-24, 25-29, 30-34, or \geq 35 years), parity (1, 2, \geq 3) and assisted reproductive treatment (available since 1994 in Denmark and since 1995 in Sweden) at the time of birth, smoking (available since 1991 in Denmark and since 1982 in Sweden), and body-mass index

(available since 2003 in Denmark and since 1982 in Sweden) in early pregnancy. Body-mass index was further classified as underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5-24.9 \text{ kg/m}^2$), overweight ($25.0-29.9 \text{ kg/m}^2$), and obesity ($\ge 30 \text{ kg/m}^2$).

Maternal comorbidities before or during the index pregnancy, including diabetes, hypertensive disease, and psychiatric disorders, were retrieved from the DNPR and the Swedish Medical Birth Register. Maternal diabetes was identified using the following ICD codes: 1) in Denmark: ICD-8: 249, 250; ICD-10: E10-E14, O24; and 2) in Sweden: ICD-8: 250; ICD-9: 250, 648A, 648W; ICD-10: E10-E14, O24. Maternal hypertensive disease was identified using the following ICD codes: 1) in Denmark: ICD-8: 40009, 40019, 40029, 40039, 40099, 40199, 63700, 63703, 63704, 63709, 63719, 76029; ICD-10: I10, I11, I12, I13, I15, O10, O11, O13, O14, O15, O16; and 2) in Sweden: ICD-8: 400, 401, 402, 403, 404, 63701, 63703, 63704, 63709, 63799, 63710; ICD-9: 401, 402, 403, 404, 405, 642A, 642B, 642C, 642D, 642E, 642F, 642G, 642H, 642X; ICD-10: I10, I11, I12, I13, I15, O10, O11, O13, O14, O15, O16. Maternal psychiatric disorders were identified using the following ICD codes: 1) Denmark: ICD-8: 290-315; ICD-10: F00-F99; and 2) in Sweden: ICD-8: 290-315; ICD-9: 290-319; and ICD-10: F00-F99.

Maternal family history of cardiovascular diseases was defined as a history of cardiovascular diseases among first-degree relatives. A mother's family relatives were identified through the Danish Civil Registration System and the Swedish Multi-Generation Register. We then extracted information on maternal relatives' cardiovascular disease diagnoses (ICD-8/9: 390–459, ICD-10: I00-I99) from the DNPR and SPR.

Supplementary note 2. Description of the mediation analysis

We explored the role of several potential mediators, i.e. preterm birth, small and large for gestational age (SGA and LGA), congenital heart disease, and diabetes in the association between maternal polycystic ovary syndrome (PCOS, the exposure of interest) and cardiovascular diseases (CVD, the outcome of interest) among offspring.

We performed the mediation analysis based on the counterfactual framework, which has been extensively described elsewhere. We obtained the total effect of PCOS on the risk of CVD in offspring by comparing CVD risk among offspring exposed to maternal PCOS with that of unexposed offspring, broken down into direct and mediated effects. The direct effect (DE) represents the effect of maternal PCOS on CVD that was independent of preterm birth, SGA or LGA birth, and congenital heart disease. The mediated effect (ME) reflected the influence of maternal PCOS that could be explained by its influence on mediators. The proportion mediated by each mediator was then estimated as: [DE × (ME-1) / (DE × ME)-1] ×100%, where 0% reflects no mediated effect and 100% reflects no direct effect. We employed the SAS macro *%mediation* developed by Linda Valeri and Tyler Vanderweele² to perform the mediation analysis.

We modelled the exposure-mediator (*i.e.*, maternal PCOS-preterm birth, maternal PCOS-SGA birth, maternal PCOS-LGA birth, maternal PCOS- congenital heart disease, and maternal PCOS-diabetes) using logistic regression. The exposure-outcome (*i.e.*, maternal PCOS-offspring CVD) association was modelled using Cox regression, with an interaction term between the exposure and the mediator. We included the following covariates in the models: offspring's sex, country and year of birth, and maternal country of origin, parity, age, education, and marital status at the time of birth, BMI and smoking in early pregnancy, family history of CVD, hypertensive disease, diabetes, and psychiatric disorders before or during the index pregnancy.

As noted elsewhere,³ the mediation analysis required strong assumptions: 1) no unmeasured exposure-outcome confounding, 2) no unmeasured exposure-mediator confounding, 3) no

unmeasured mediator-outcome confounding, and 4) none of the mediator-outcome confounders being affected by the exposure. Our observational data cannot rule out the possibility of unmeasured confounders, and the assumption of "no unmeasured mediator-outcome confounders" was especially likely to be violated. Therefore, we further examined the impact of unmeasured mediator-outcome confounding by using the sensitivity analysis technique. Using congenital heart disease as an example, we first assumed that the effect of a strong unmeasured confounder U on CVD on the hazard ratio scale was 1.8, that the prevalence of U among offspring with congenital heart disease who were exposed to maternal PCOS was 40%, and that the prevalence of U among unexposed offspring with congenital heart disease was 45%. After introducing the U into the sensitivity analysis, we found that the direct effect was slightly increased (hazard ratio: 1.21, 95% confidence interval: 1.14-1.27), but the mediated effect was reduced and close to null (0.99, 0.98-0.99). We found similar patterns when we performed sensitivity analyses in case of diabetes, preterm birth and SGA or LGA birth.

Supplementary References

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