

Polycystic ovary syndrome, combined oral contraceptives and the risk of dysglycemia

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Suppl. Table 1: Read codes used in data extraction

Condition	Read Code	Description
Polycystic ovary syndrome	C164.12	Stein - Leventhal syndrome
	C165.00	Polycystic ovarian syndrome
	7E25300	Endoscopic drilling of ovary
Polycystic ovaries	C164.00	Polycystic ovaries
	C164.13	Multi-cystic ovaries
Ovulatory dysfunction	1571	H/O: amenorrhoea
	K590.00	Absence of menstruation
	K590.11	Amenorrhoea
	K590100	Secondary amenorrhoea
	K590z00	Amenorrhoea NOS
	K591.00	Scanty or infrequent menstruation
	K591.11	Infrequent menstruation
	K591000	Hypomenorrhoea
	K591100	Oligomenorrhoea
	K591300	Secondary oligomenorrhoea
	K591z00	Scanty or infrequent menstruation NOS
	K5B0.00	Female infertility of anovulatory origin
	K5B0.11	Anovular cycle
	K5B0100	Secondary anovulatory infertility
	K5B0z00	Female infertility of anovulatory origin NOS
Alopecia	Myu6300	[X]Other androgenic alopecia
	M240.00	Alopecia
	M240z00	Alopecia NOS
	M240H00	Alopecia seborrhoeica
	M240000	Alopecia unspecified
	1N02.00	C/O: hair loss
	M240300	Frontal alopecia of women
	M240012	Hair loss
	M240200	Male pattern alopecia
	M240D00	Marginal alopecia
	22D7.11	O/E – alopecia
	22D4.00	O/E - loss of hair
	Hirsutism	22D8.00
22D8000		O/E - facial hair
M241.00		Hirsutism - hypertrichosis

Suppl. Table 1 (Continued)

Condition	Read Code	Description
Type 2 diabetes mellitus	C106100	Diabetes mellitus, adult onset, + neurological manifestation
	C109611	Type II diabetes mellitus with retinopathy
	C10K000	Type A insulin resistance without complication
	C109.13	Type II diabetes mellitus
	C109.12	Type 2 diabetes mellitus
	C104.00	Diabetes mellitus with renal manifestation
	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
	C10F111	Type II diabetes mellitus with ophthalmic complications
	C109F00	Non-insulin-dependent d m with peripheral angiopath
	C10F911	Type II diabetes mellitus without complication
	C10FA11	Type II diabetes mellitus with mononeuropathy
	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
	C100112	Non-insulin dependent diabetes mellitus
	C107200	Diabetes mellitus, adult with gangrene
	C109500	Non-insulin dependent diabetes mellitus with gangrene
	C10FJ11	Insulin treated Type II diabetes mellitus
	C104.11	Diabetic nephropathy
	C10FR11	Type II diabetes mellitus with gastroparesis
	C10z.00	Diabetes mellitus with unspecified complication
	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
	C10D.00	Diabetes mellitus autosomal dominant type 2
	C10F100	Type 2 diabetes mellitus with ophthalmic complications
	C109F11	Type II diabetes mellitus with peripheral angiopathy
	C10F900	Type 2 diabetes mellitus without complication
	C10FA00	Type 2 diabetes mellitus with mononeuropathy
	C106z00	Diabetes mellitus NOS with neurological manifestation
	C109612	Type 2 diabetes mellitus with retinopathy
	C109511	Type II diabetes mellitus with gangrene
	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
	C109512	Type 2 diabetes mellitus with gangrene
	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
	C10F011	Type II diabetes mellitus with renal complications
C101z00	Diabetes mellitus NOS with ketoacidosis	
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract	

Suppl. Table 1 (Continued)

No.	Read Code	Description
Type 2 Diabetes Mellitus	C10F811	Metabolic syndrome X
	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
	C109400	Non-insulin dependent diabetes mellitus with ulcer
	C105.00	Diabetes mellitus with ophthalmic manifestation
	C10FQ11	Type II diabetes mellitus with exudative maculopathy
	C10F000	Type 2 diabetes mellitus with renal complications
	C109E11	Type II diabetes mellitus with diabetic cataract
	C109E12	Type 2 diabetes mellitus with diabetic cataract
	C106y00	Other specified diabetes mellitus with neurological comps
	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
	C109012	Type 2 diabetes mellitus with renal complications
	C109011	Type II diabetes mellitus with renal complications
	C10FS00	Maternally inherited diabetes mellitus
	C10F311	Type II diabetes mellitus with multiple complications
	C10y.00	Diabetes mellitus with other specified manifestation
	C109H00	Non-insulin dependent d m with neuropathic arthropathy
	C10C.00	Diabetes mellitus autosomal dominant
	C10FC11	Type II diabetes mellitus with nephropathy
	C10zy00	Other specified diabetes mellitus with unspecified comps
	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
	C107400	NIDDM with peripheral circulatory disorder
	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
	C10F300	Type 2 diabetes mellitus with multiple complications
	C10FL11	Type II diabetes mellitus with persistent proteinuria
	C10H.00	Diabetes mellitus induced by non-steroid drugs
	C109H11	Type II diabetes mellitus with neuropathic arthropathy
	C104y00	Other specified diabetes mellitus with renal complications
	C10FC00	Type 2 diabetes mellitus with nephropathy
	C10FJ00	Insulin treated Type 2 diabetes mellitus
	C10FR00	Type 2 diabetes mellitus with gastroparesis
	C10P111	Type 2 diabetes mellitus in remission
	C10F211	Type II diabetes mellitus with neurological complications
	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
	C10FB11	Type II diabetes mellitus with polyneuropathy
	C109700	Non-insulin dependent diabetes mellitus - poor control

Suppl. Table 1 (Continued)

No.	Read Code	Description
Type 2 Diabetes Mellitus	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
	C10N.00	Secondary diabetes mellitus
	C109.00	Non-insulin dependent diabetes mellitus
	C10P100	Type II diabetes mellitus in remission
	C10F200	Type 2 diabetes mellitus with neurological complications
	C109G11	Type II diabetes mellitus with arthropathy
	C109G12	Type 2 diabetes mellitus with arthropathy
	C100z00	Diabetes mellitus NOS with no mention of complication
	C10..00	Diabetes mellitus
	C100100	Diabetes mellitus, adult onset, no mention of complication
	C10FB00	Type 2 diabetes mellitus with polyneuropathy
	C109711	Type II diabetes mellitus - poor control
	C109712	Type 2 diabetes mellitus - poor control
	C109212	Type 2 diabetes mellitus with neurological complications
	C109211	Type II diabetes mellitus with neurological complications
	C10FE00	Type 2 diabetes mellitus with diabetic cataract
	C109J00	Insulin treated Type 2 diabetes mellitus
	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
	C10G.00	Secondary pancreatic diabetes mellitus
	C10F511	Type II diabetes mellitus with gangrene
	C103z00	Diabetes mellitus NOS with ketoacidotic coma
	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
	C10A500	Malnutritn-relat diabetes melitus wth periph circul completn
	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
	C10L.00	Fibrocalculous pancreatopathy
	C10N100	Cystic fibrosis related diabetes mellitus
	C107.00	Diabetes mellitus with peripheral circulatory disorder
	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
	C10FF11	Type II diabetes mellitus with peripheral angiopathy
	C109J12	Insulin treated Type II diabetes mellitus
	C109J11	Insulin treated non-insulin dependent diabetes mellitus
	C10A.11	Jamaica type diabetes
	C10FN11	Type II diabetes mellitus with ketoacidosis
	C10H000	DM induced by non-steroid drugs without complication
	C109B12	Type 2 diabetes mellitus with polyneuropathy
	C10F500	Type 2 diabetes mellitus with gangrene
	C109B11	Type II diabetes mellitus with polyneuropathy
	C108y00	Other specified diabetes mellitus with multiple comps

Suppl. Table 1 (Continued)

No.	Read Code	Description
Type 2 Diabetes Mellitus	C10yz00	Diabetes mellitus NOS with other specified manifestation
	C102.00	Diabetes mellitus with hyperosmolar coma
	C104100	Diabetes mellitus, adult onset, with renal manifestation
	C107.11	Diabetes mellitus with gangrene
	C109111	Type II diabetes mellitus with ophthalmic complications
	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
	C10M.00	Lipoatrophic diabetes mellitus
	C109112	Type 2 diabetes mellitus with ophthalmic complications
	C107.12	Diabetes with gangrene
	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
	C10F411	Type II diabetes mellitus with ulcer
	C103y00	Other specified diabetes mellitus with coma
	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
	C109900	Non-insulin-dependent diabetes mellitus without complication
	C10zz00	Diabetes mellitus NOS with unspecified complication
	C10z100	Diabetes mellitus, adult onset, + unspecified complication
	C10N000	Secondary diabetes mellitus without complication
	C10FE11	Type II diabetes mellitus with diabetic cataract
	C109000	Non-insulin-dependent diabetes mellitus with renal comps
	C10B.00	Diabetes mellitus induced by steroids
	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
	C10F400	Type 2 diabetes mellitus with ulcer
	C104z00	Diabetes mellitus with nephropathy NOS
	C109A11	Type II diabetes mellitus with mononeuropathy
	C109A12	Type 2 diabetes mellitus with mononeuropathy
	C109911	Type II diabetes mellitus without complication
	C109912	Type 2 diabetes mellitus without complication
	C10yy00	Other specified diabetes mellitus with other spec comps
	C109412	Type 2 diabetes mellitus with ulcer
	C109411	Type II diabetes mellitus with ulcer
	C10K.00	Type A insulin resistance
	C10FG00	Type 2 diabetes mellitus with arthropathy
	C10G000	Secondary pancreatic diabetes mellitus without complication
	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
	C10F711	Type II diabetes mellitus - poor control
	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
	C10FH11	Type II diabetes mellitus with neuropathic arthropathy

Suppl. Table 1 (Continued)

No.	Read Code	Description
Type 2 Diabetes Mellitus	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
	C10FP11	Type II diabetes mellitus with ketoacidotic coma
	C10P.00	Diabetes mellitus in remission
	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
	C102z00	Diabetes mellitus NOS with hyperosmolar coma
	C109D11	Type II diabetes mellitus with hypoglycaemic coma
	C10F700	Type 2 diabetes mellitus - poor control
	C100.00	Diabetes mellitus with no mention of complication
	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
	C10y100	Diabetes mellitus, adult, + other specified manifestation
	C109311	Type II diabetes mellitus with multiple complications
	C109312	Type 2 diabetes mellitus with multiple complications
	C106.00	Diabetes mellitus with neurological manifestation
	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
	C10F.11	Type II diabetes mellitus
	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
	C10FN00	Type 2 diabetes mellitus with ketoacidosis
	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
	C10F611	Type II diabetes mellitus with retinopathy
	C107y00	Other specified diabetes mellitus with periph circ comps
	C106.13	Diabetes mellitus with polyneuropathy
	C101.00	Diabetes mellitus with ketoacidosis
	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
	C106.11	Diabetic amyotrophy
	C106.12	Diabetes mellitus with neuropathy
	C10FG11	Type II diabetes mellitus with arthropathy
	C10F.00	Type 2 diabetes mellitus
	C109C11	Type II diabetes mellitus with nephropathy
	C10B000	Steroid induced diabetes mellitus without complication
	C109C12	Type 2 diabetes mellitus with nephropathy
	C10F600	Type 2 diabetes mellitus with retinopathy
	C108z00	Unspecified diabetes mellitus with multiple complications
	44V2.00	Glucose tolerance test impaired
	Impaired glucose regulation	8HIS.00
9NS0400		Referral for impaired glucose tolerance management offered
9mX3.00		Impaired glucose regulation monitoring telephone invitation
9mX4.00		Impaired glucose regulation monitoring verbal invitation
9mX0.00		Impaired glucose regulation monitoring invitation 1st letter
C313500		Glucose intolerance

	9mX2.00	Impaired glucose regulation monitoring invitation 3rd letter
	9mX1.00	Impaired glucose regulation monitoring invitation 2nd letter
	C11y300	Impaired fasting glycaemia
	9mX..00	Impaired glucose regulation monitoring invitation
	C11y200	Impaired glucose tolerance
	R102.11	[D]Prediabetes
	C11y500	Pre-diabetes
	R102.12	[D]Impaired glucose tolerance test
	C11y400	Impaired glucose regulation
	R10E.00	[D]Impaired glucose tolerance
	R10D000	[D]Impaired fasting glycaemia
	R10D011	[D]Impaired fasting glucose

Suppl. Table 2: Risk of type 2 diabetes and dysglycemia (composite outcome combining prediabetes and type 2 diabetes) in women with PCOS compared to population-based controls matched for sex, age, BMI and location of general practice.

	Type 2 Diabetes		Dysglycemia	
	Women with PCOS	Controls	Women with PCOS	Controls
Outcome events, n (%)	1483 (2.32)	1348 (1.09)	2885 (4.51)	2894 (2.34)
Person-years	304379	590335	299,551	585,307
Crude Incidence Rate/10,000 person years	48.7	22.8	96.3	49.4
Follow-up years, Median (IQR)	3.39 (1.34-7.16)	3.47 (1.39-7.18)	3.32 (1.32-7.03)	3.44 (1.38-7.11)
Unadjusted hazard Rate ratio (95% CI)	2.13 (1.98-2.29); p<0.001		1.95 (1.85-2.05); p<0.001	
Adjusted hazard Rate ratio (95% CI)	2.04 (1.89-2.20); p<0.001		1.87 (1.78-1.97); p<0.001	
Adjusted hazard Rate ratio (95% CI)*	1.98 (1.70-2.31); p<0.001		1.95 (1.76-2.16); p<0.001	
Adjusted hazard Rate ratio (95% CI) [†]	2.17 (1.88-2.51); p<0.001		1.93 (1.75-2.13); p<0.001	

Adjustments for age, ethnicity, Townsend deprivation quintile, BMI category, smoking status and baseline diagnosis of hypothyroidism, hypertension and prescription of lipid lowering drugs

*Sensitivity Analysis 1: Analysis of women with incident diagnosis of PCOS and their corresponding controls

[†]Sensitivity Analysis 2: Analysis of women with PCOS-specific diagnosis and their corresponding controls

Suppl. Table 3: Risk factors of type 2 diabetes and dysglycemia (composite outcome combining prediabetes and type 2 diabetes) among women with PCOS (n=64,051).

Risk factors	Type 2 Diabetes	Dysglycemia
Age	1.06 (1.05-1.07); p<0.001	1.06 (1.05-1.06); p<0.001
BMI Categories*		
Underweight/Normal weight	Ref	Ref
Overweight	3.10 (2.41-3.99); p<0.001	2.68 (2.31-3.11); p<0.001
Obese	11.74 (9.46-14.57); p<0.001	7.13 (6.27-8.10); p<0.001
Missing	4.97 (3.85-6.42); p<0.001	3.15 (2.68-3.70); p<0.001
Townsend deprivation score category		
1 (least deprived)	Ref	Ref
2	1.17 (0.97-1.42); p=0.103	1.14 (1.00-1.30); p=0.054
3	1.47 (1.23-1.75); p<0.001	1.27 (1.12-1.44); p<0.001
4	1.54 (1.28-1.84); p<0.001	1.39 (1.22-1.58); p<0.001
5 (most deprived)	1.89 (1.54-2.24); p<0.001	1.67 (1.46-1.91); p<0.001
Missing	1.37 (1.12-1.66); p=0.002	1.28 (1.11-1.46); p<0.001
Smoker categories		
Non-Smoker	Ref	Ref
Discontinued	1.06 (0.91-1.25); p=0.440	1.05 (0.93-1.17); p=0.430
Smoker	1.36 (1.20-1.54); p<0.001	1.30 (1.19-1.42); p<0.001
Missing	0.97 (0.78-1.22); p=0.816	0.86 (0.73-1.02); p=0.093
Ethnicity		
Caucasian	Ref	Ref
Mixed Race	1.75 (1.09-2.81); p=0.019	1.93 (1.40-2.66); p<0.001
Chinese/middle eastern/others	1.27 (0.68-2.37); p=0.456	1.57 (1.04-2.35); p=0.030
Black	1.15 (0.82-1.61); p=0.408	1.66 (1.35-2.05); p<0.001
South Asian	1.92 (1.56-2.37); p<0.001	2.41 (2.09-2.78); p<0.001
Missing	1.00 (0.89-1.11); p=0.945	1.01 (0.93-1.09); p=0.866
Concurrent Conditions at baseline		
Hypothyroidism	1.07 (0.85-1.34); p=0.560	1.17 (1.00-1.37); p=0.056
Hypertension	2.11 (1.79-2.49); p<0.001	1.99 (1.76-2.26); p<0.001
PCOS relevant variables		
Anovulation	1.21 (1.08-1.35); p=0.001	1.17 (1.08-1.27); p<0.001
Hirsutism	1.20 (1.05-1.36); p=0.007	1.15 (1.05-1.27); p=0.004
Hair loss	0.93 (0.77-1.13); p=0.493	0.97 (0.85-1.11); p=0.687
Prescriptions at baseline		
Contraceptives		
No Pill	Ref	Ref
COCP without anti-androgen	0.83 (0.72-0.94); p=0.005	0.77 (0.70-0.85); p<0.001
COCP with anti-androgenic progestin*	0.84 (0.73-0.97); p=0.020	0.85 (0.77-0.94); p=0.002
Single agent anti-androgen therapy^	1.20 (0.84-1.71); p=0.314	0.99 (0.74-1.31); p=0.926
Lipid lowering drugs	1.37 (0.95-1.96); p<0.001	1.35 (1.02-1.77); p=0.036

*Normal/Underweight: <23.5 kg/m² for patients of South Asian ethnicity & <25 kg/m² for patients of all other ethnic groups

Overweight: 23.5-27.5 kg/m² for patients of South Asian ethnicity & 25-30 kg/m² for patients of all other ethnic groups

Obese = ≥27.5 kg/m² for patients of South Asian ethnicity & ≥30 kg/m² for patients of all other ethnic groups

*cyproterone acetate/drospirenone

^cyproterone acetate/flutamide/finasteride

Suppl. Table 4. Risk and protective factors among 2407 women with dysglycemia and 2407 matched controls (n=4814)

Covariates	Adjusted OR (95% CI)
Combined oral contraceptive use	
No COCP	Ref
COCP without anti-androgen	0.72 (0.59-0.87); p<0.001
COCP with anti-androgenic progestin*	0.76 (0.63-0.91); p=0.003
Age	1.05 (0.99-1.12); p=0.106
Smoking Status	
Non-Smoker	Ref
Discontinued Smoker	0.96 (0.79-1.16); p=0.663
Smoker	1.46 (1.25-1.71); p<0.001
Missing	0.93 (0.69-1.24); p=0.613
BMI category*	
Normal Weight	Ref
Overweight	1.45 (0.91-2.31); p=0.118
Obese	1.72 (0.93-3.16); p=0.082
Missing	.
Ethnicity	
Caucasian	Ref
Mixed Race	2.40 (1.33-4.34); p=0.009
Others	1.71 (0.83-3.53); p=0.107
Black	2.03 (1.32-3.12); p<0.001
South Asians	3.39 (2.51-4.59); p<0.001
Missing	0.98 (0.85-1.12); p=0.854
Townsend deprivation score category	
1 (least deprived)	Ref
2	1.19 (0.96-1.46); p=0.111
3	1.40 (1.14-1.73); p=0.001
4	1.41 (1.14-1.74); p=0.001
5 (most deprived)	1.75 (1.39-2.20); p<0.001
Missing	1.53 (1.22-1.92); p<0.001
Concurrent Conditions at baseline	
Hypothyroidism	1.35 (1.09-1.68); p=0.006

Hypertension	2.97 (2.48-3.56); p<0.001
<hr/>	
Prescriptions at baseline	
Metformin	1.50 (1.24-1.81); p<0.001
Single agent anti-androgen therapy [^]	1.74 (0.97-3.13); p=0.063
Lipid lowering medication	1.21 (0.58-2.52); p=0.607

*Normal/Underweight: <23.5 kg/m² for patients of South Asian ethnicity & <25 kg/m² for patients of all other ethnic groups

Overweight: 23.5-27.5 kg/m² for patients of South Asian ethnicity & 25-30 kg/m² for patients of all other ethnic groups

Obese = ≥27.5 kg/m² for patients of South Asian ethnicity & ≥30 kg/m² for patients of all other ethnic groups

*cyproterone acetate/drospirenone

[^]cyproterone acetate/flutamide/finasteride

Suppl. Figure 1: Flowchart

