Cardio-metabolic complications of Polycystic Ovarian Syndrome

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Agenda

- General aspects
- Insulin resistance
- Dyslipidemia
- Hypertension
- Metabolic syndrome
- Emerging risk factors
- Cardiovascular disease
- Postmenopausal changes
- Screening
- Recommendations

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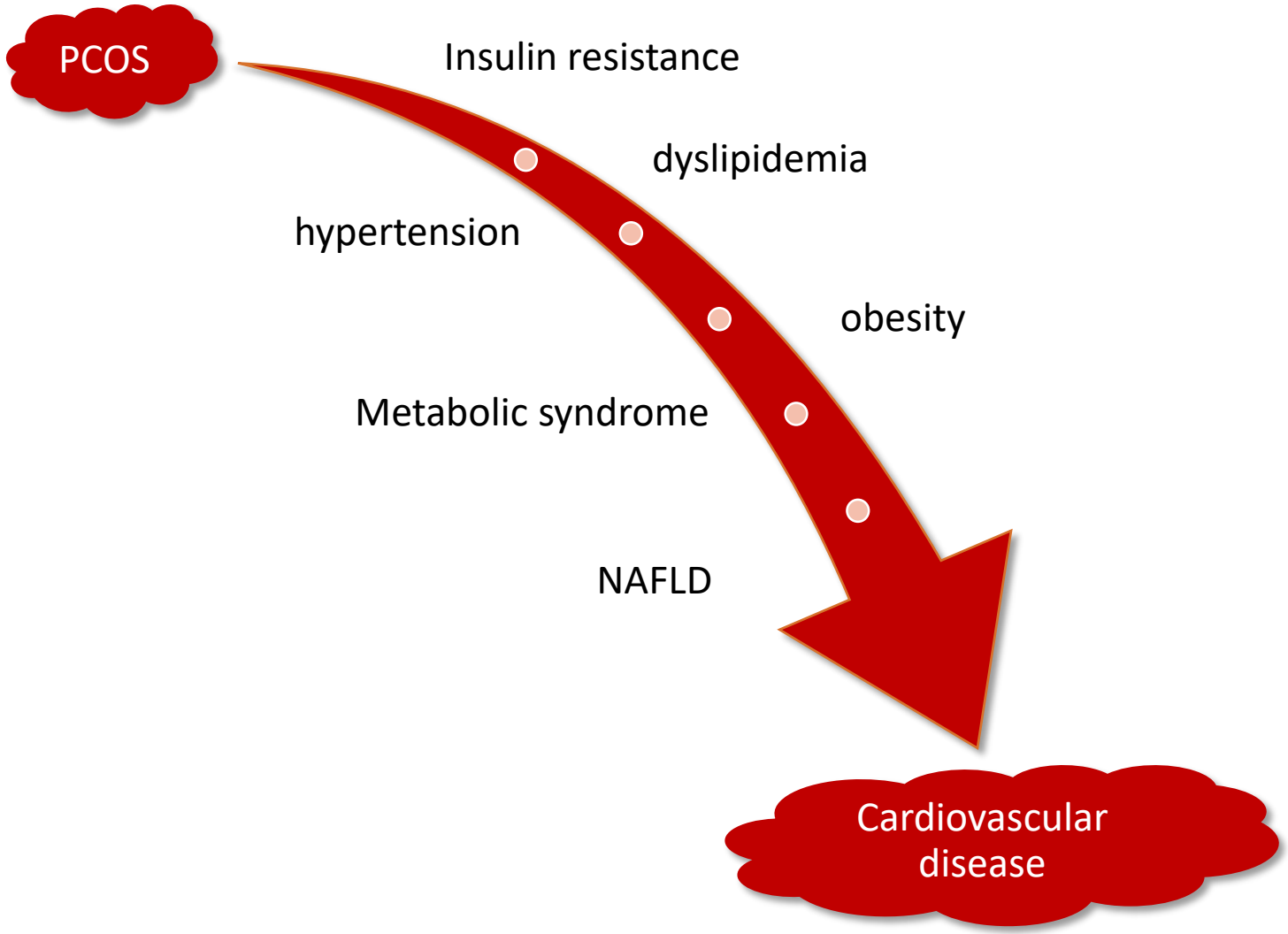
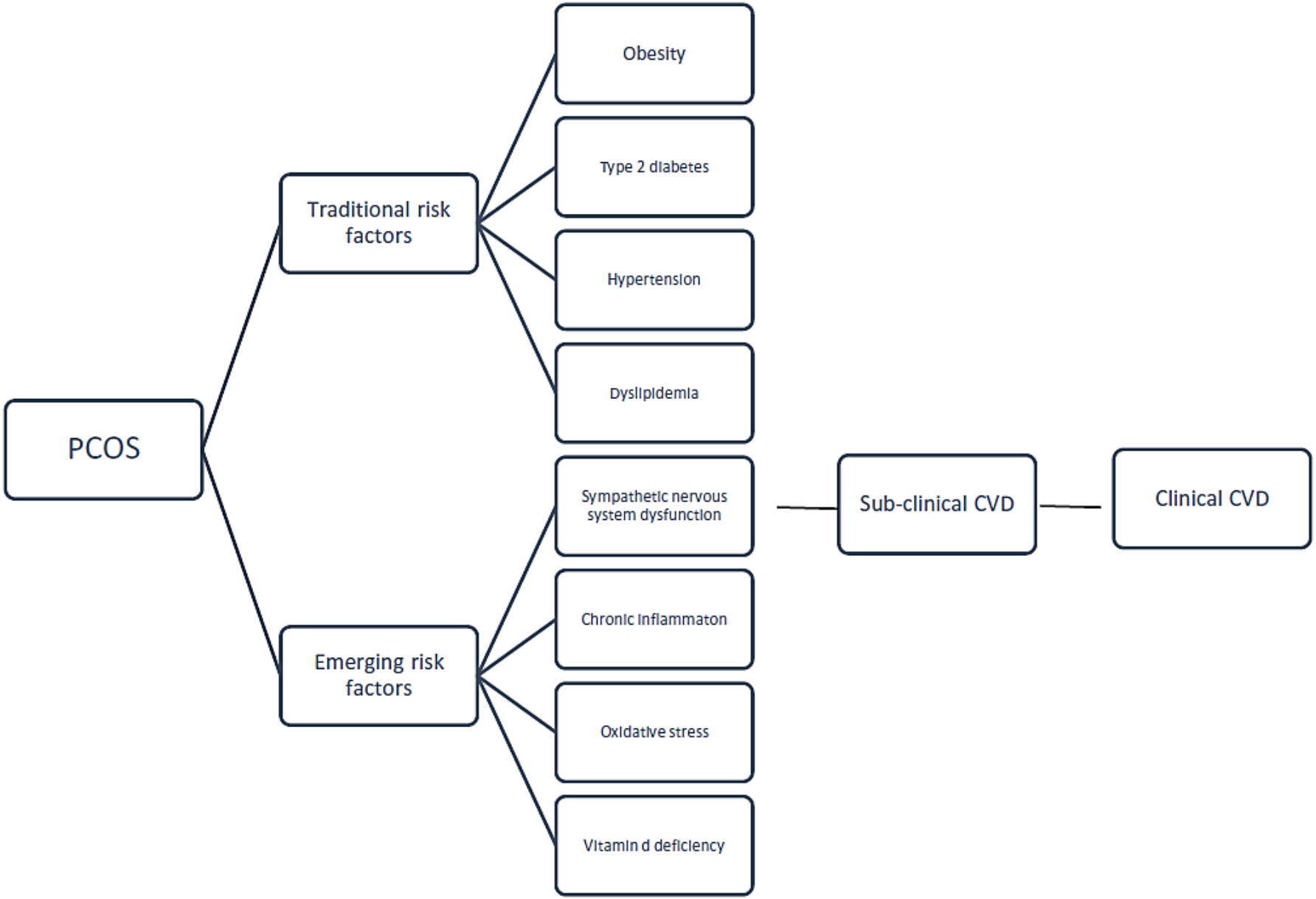
The diagnosis of PCOS per se does not signify an increased CV risk, but rather represents the condition with existing CV risk factors that needs further evaluation, which would provide a more accurate CV risk assessment.

Besides the clinical features of hyperandrogenism (hirsutism, acne, male-type baldness), oligo-/ amenorrhea and impaired fertility, PCOS patients are at risk of cardio-metabolic disorders.


PCOS
Insulin resistance
dyslipidemia
hypertension
obesity
Metabolic syndrome
NAFLD
Cardiovascular disease



Cardiometabolic risk factors in PCOS.

Expert review of endocrinology & metabolism. 2019 Jan 2;14(1):23-33.

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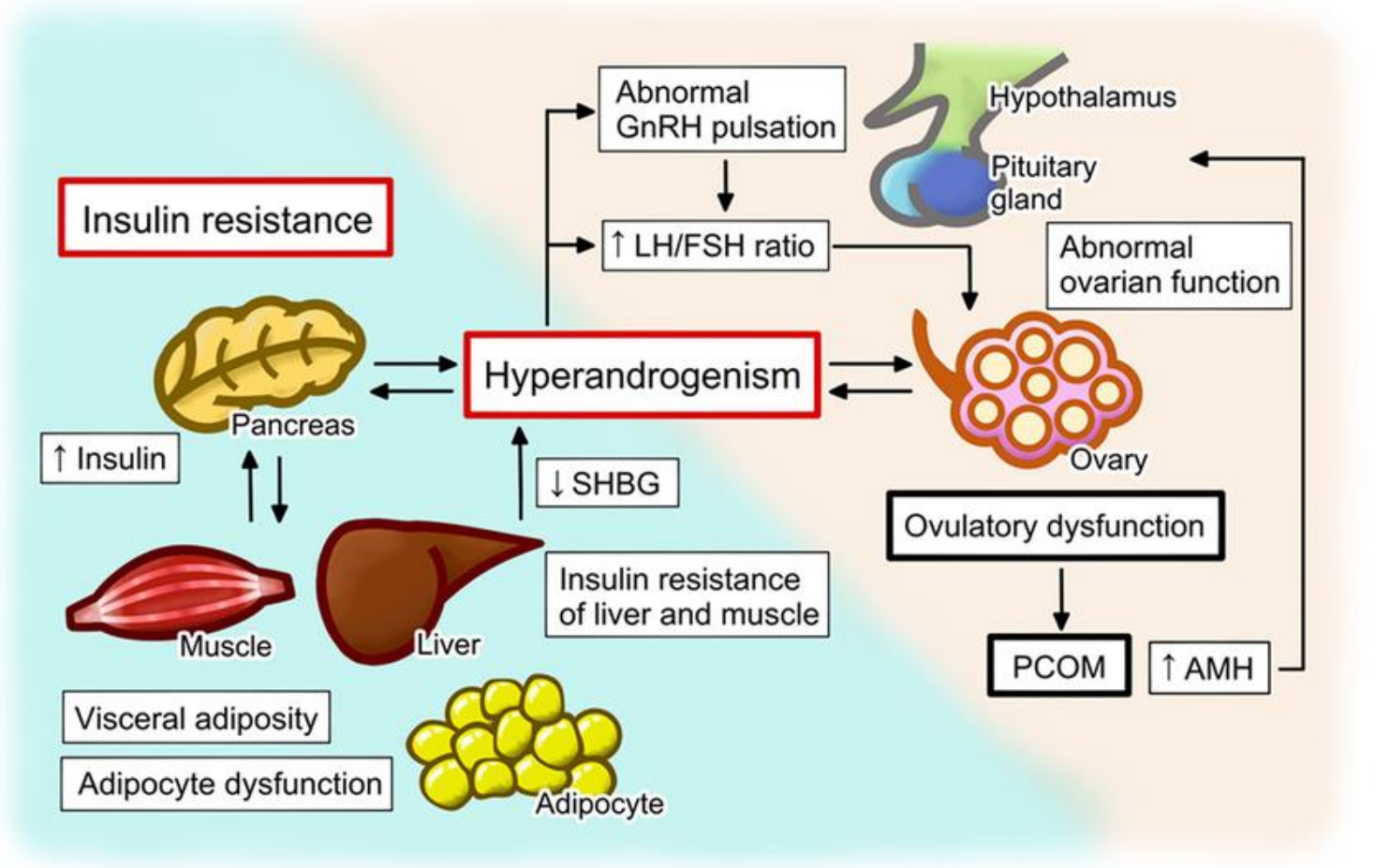
Insulin resistance and diabetes



Reprod Med Biol. 2022;21:e12487.

- IR (detected in 75% of lean women and 95% of overweight/obese women with PCOS).

- Hyperinsulinemia also plays a vital role in the pathogenesis of PCOS.

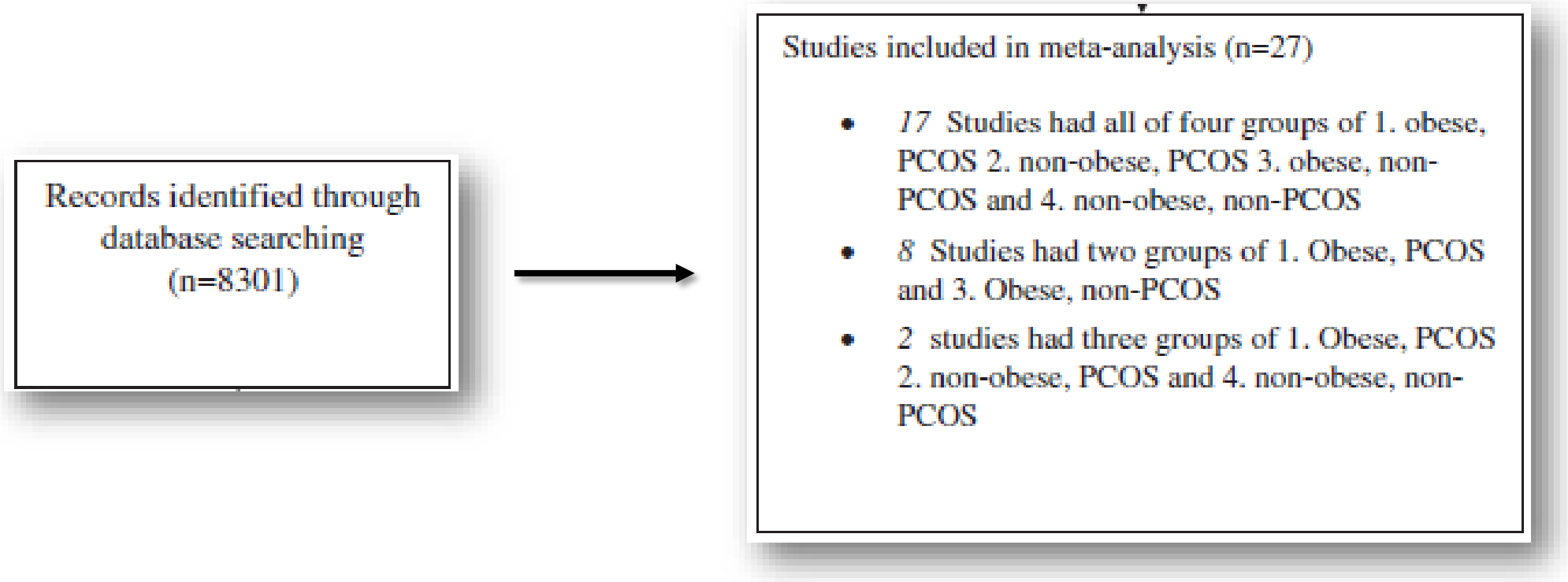
- IR results in the requirement for increased insulin to achieve it’s metabolic action.

- As a consequence, IR is often characterized by increased circulating levels of insulin, both basally and in response to a glucose load, given pancreatic β-cell function is intact.

Human Reproduction, Vol.31, No.11 pp. 2619–2631, 2016

Insulin resistance in obesity and polycystic ovary syndrome: systematic review and meta-analysis of observational studies

Samira Behboudi-Gandevani[1], Fahimeh Ramezani Tehrani[1], Marzieh Rostami Dovom[1], Maryam Farahmand[1], Mahnaz Bahri Khomami[1], Mahsa Noroozzadeh[1], Ali Kabir[3], and Fereidoun Azizi[2]



Gynecological Endocrinology. 2016 May 3;32(5):343-53.

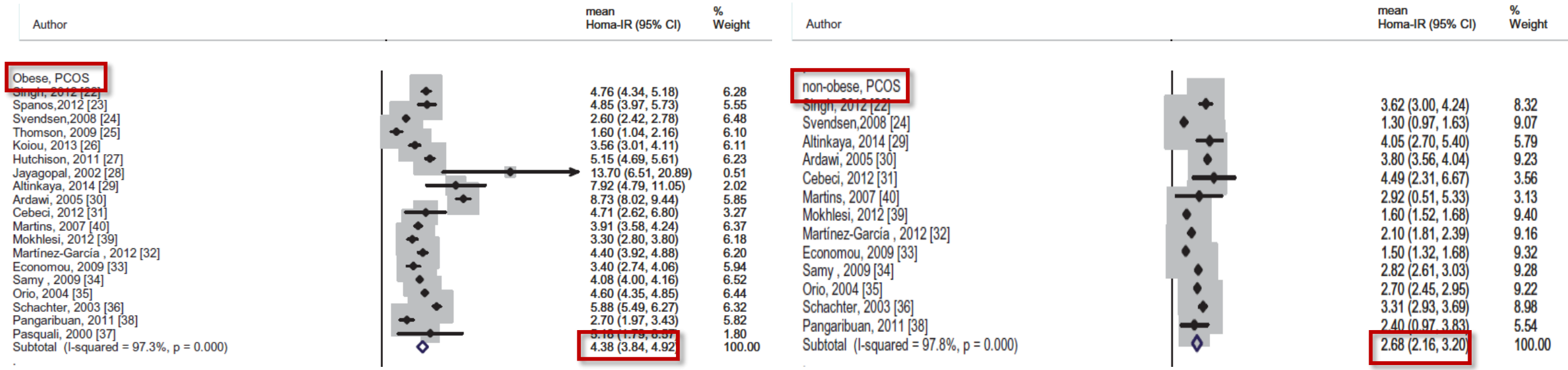


Figure 2. Forest plot of studies reports the IR based on HOMA-IR in different groups.

Gynecological Endocrinology. 2016 May 3;32(5):343-53.

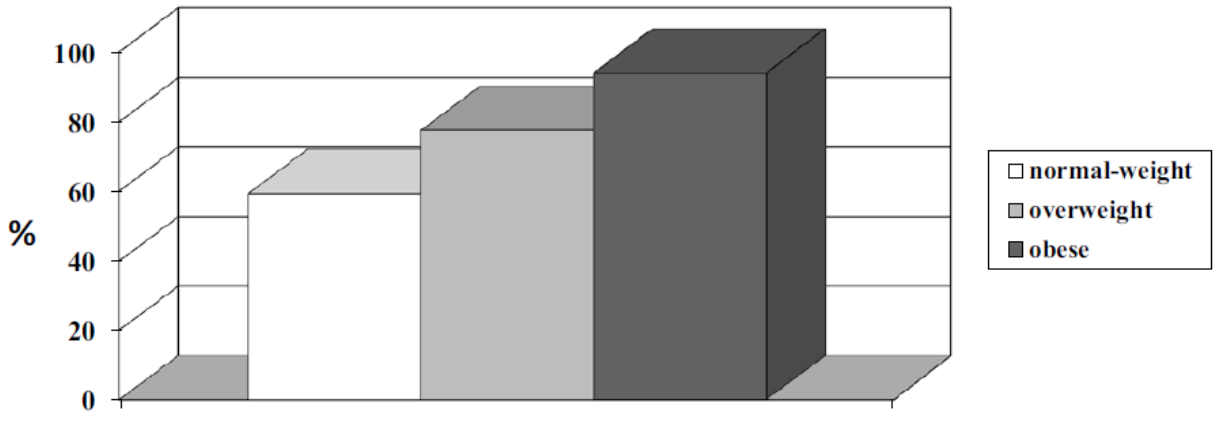


Fig. 2 Frequency of insulin resistance, measured by the hyperinsulinemic euglycemic clamp technique, in women with PCOS of the Verona 3P Study cohort subdivided according to BMI categories

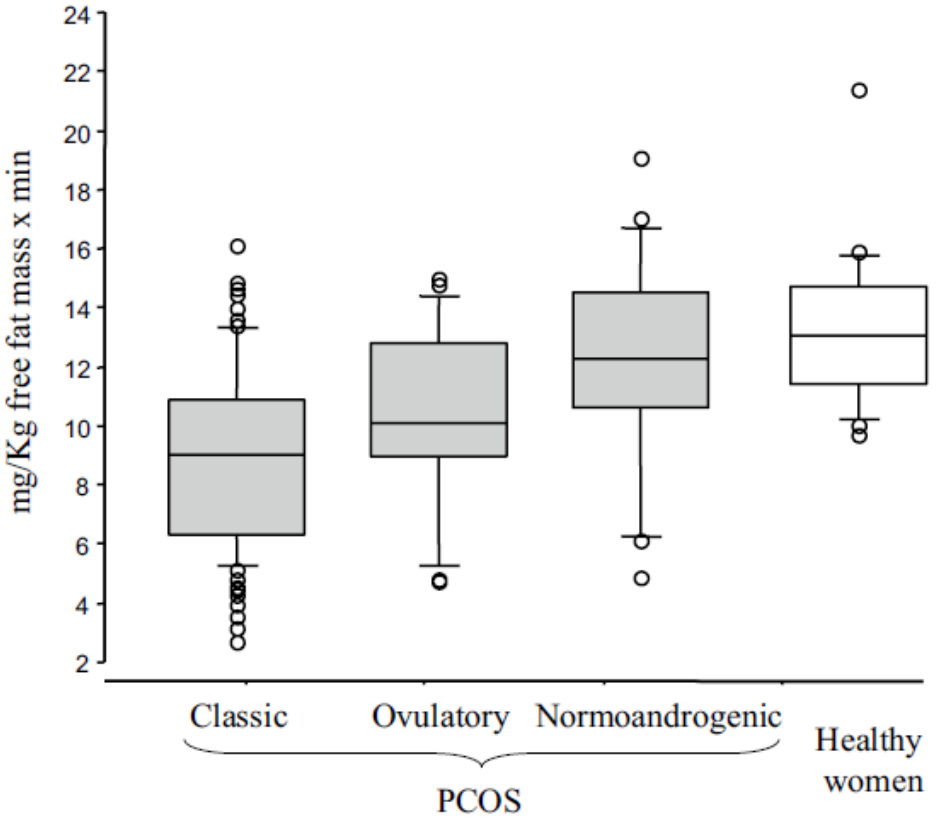


Fig. 1 Insulin-induced glucose utilization during the hyperinsulinemic euglycemic clamp in women with the different clinical phenotypes of PCOS and in control subjects. Reproduced with permission from Moghetti et al. [5]

Journal of endocrinological investigation. 2021 Feb;44:233-44.

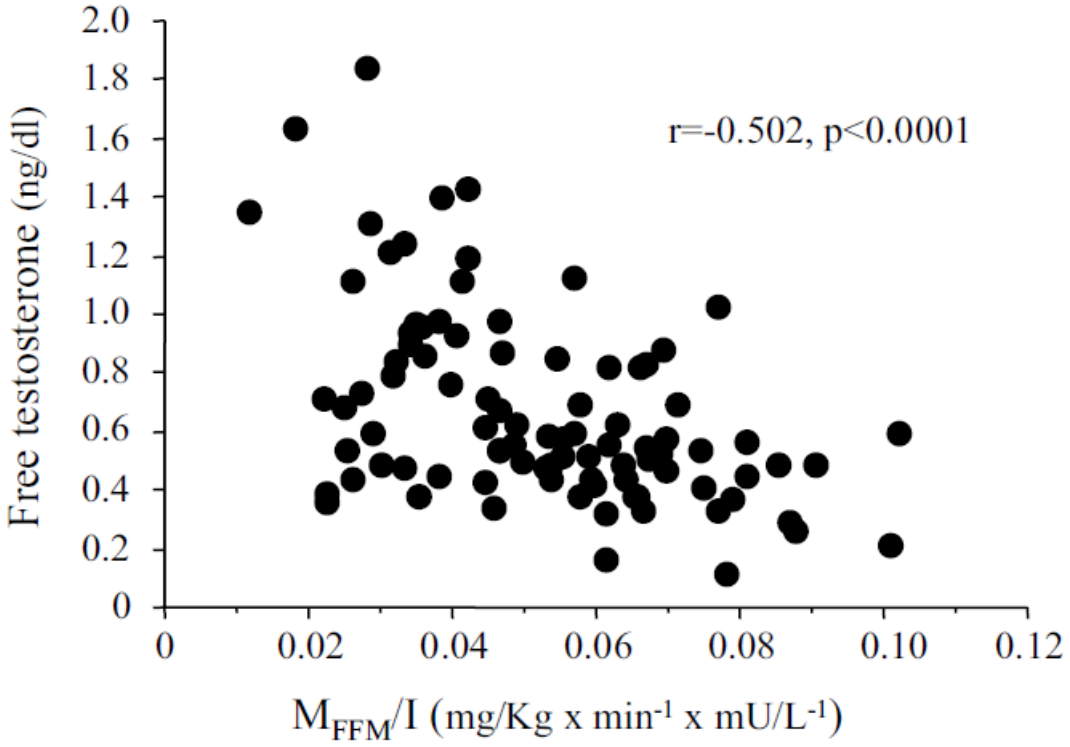


Fig. 3 Relationship between serum free testosterone, as measured by liquid chromatography-mass spectrometry and equilibrium dialysis, and glucose utilization during the hyperinsulinemic euglycemic clamp. Reproduced with permission from Tosi et al. [22]

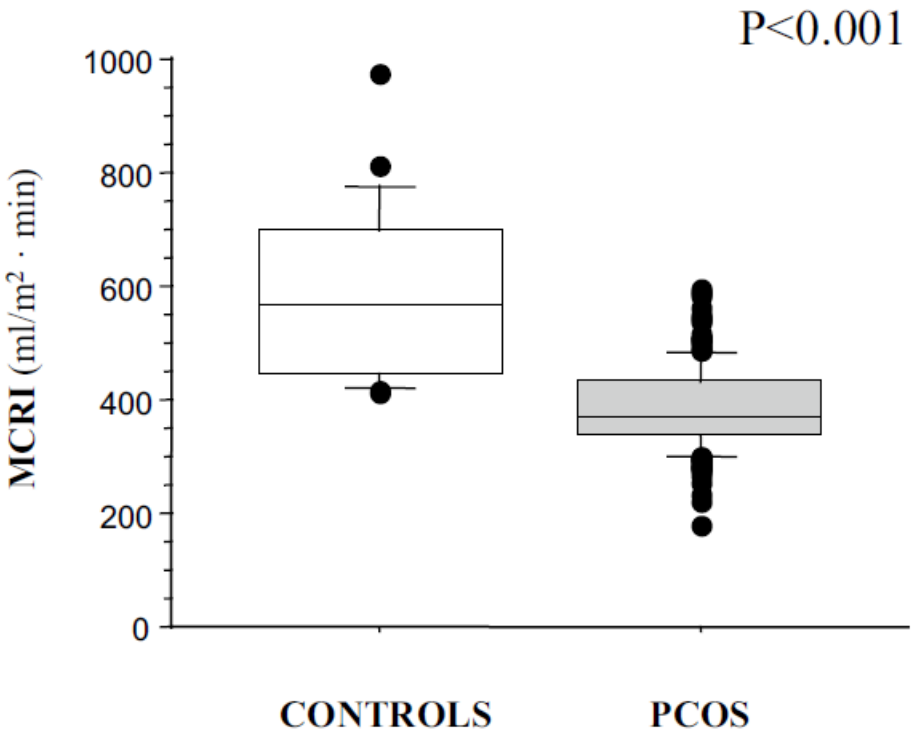


Fig. 4 Comparison of metabolic clearance rate of insulin in women with PCOS and healthy controls. Reproduced with permission from Tosi et al. [33]

Journal of endocrinological investigation. 2021 Feb;44:233-44.

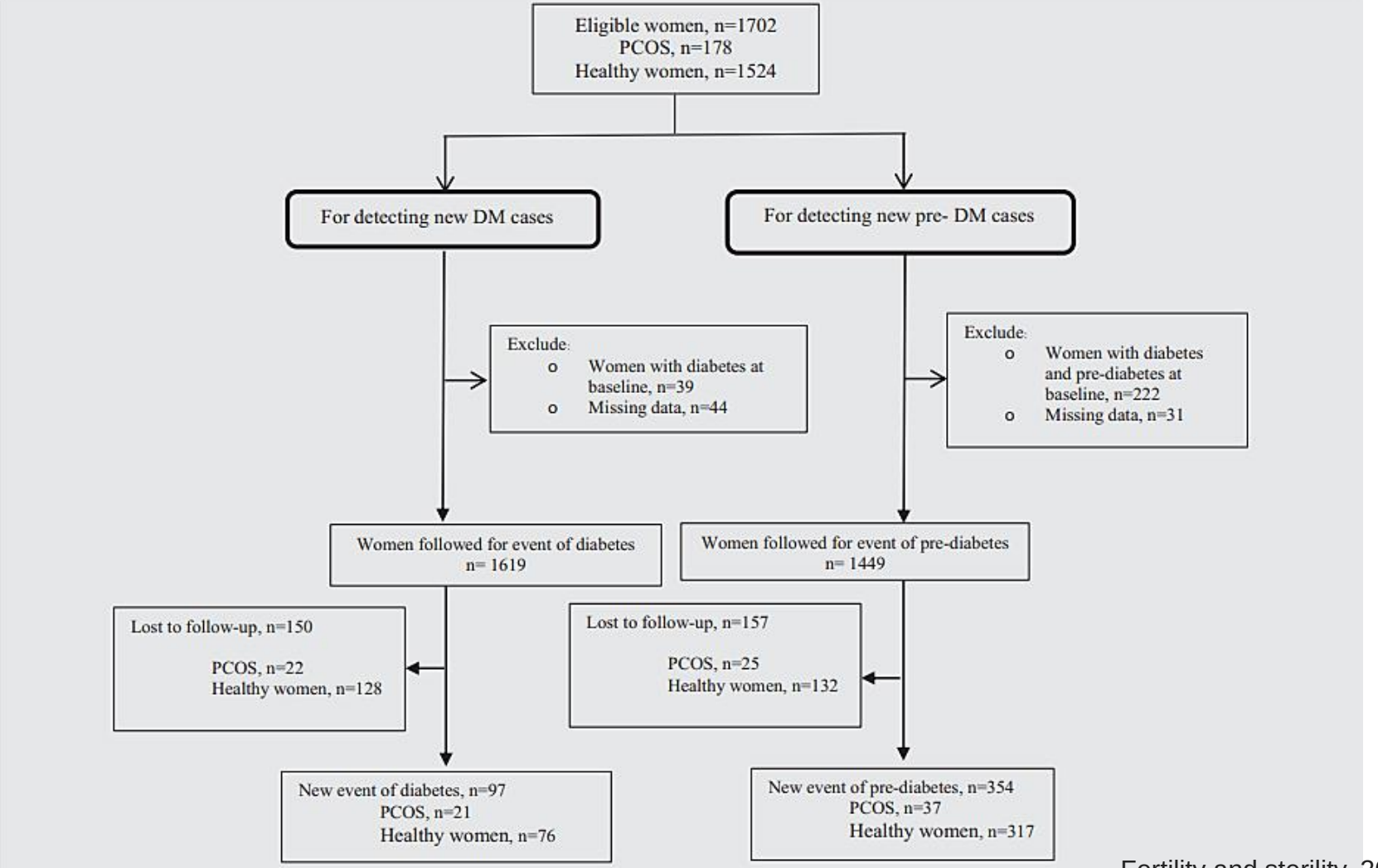
- Studies about the prevalence of IGT and DM2 between women with and without PCOS showed that those with PCOS were about three times more likely to have IGT/DM2, compared to controls.

- Obesity and family history of DM2 are considered independent and additive risk factors, which increase the risk of IGT and DM2 among affected women.

Expert review of endocrinology & metabolism. 2019 Jan 2;14(1):23-33.

Polycystic ovary syndrome is a risk factor for diabetes and prediabetes in middle-aged but not elderly women: a long-term population-based follow-up study

Hadighe Kazemi Jaliseh, Ph.D.,a Fahimeh Ramezani Tehrani, M.D.,b Samira Behboudi-Gandevani, Ph.D.,b Farhad Hosseinpanah, M.D.,c Davood Khalili, M.D., M.P.H., Ph.D.,d,f Leila Cheraghi, M.S.,d and Fereidoun Azizi, M.D.



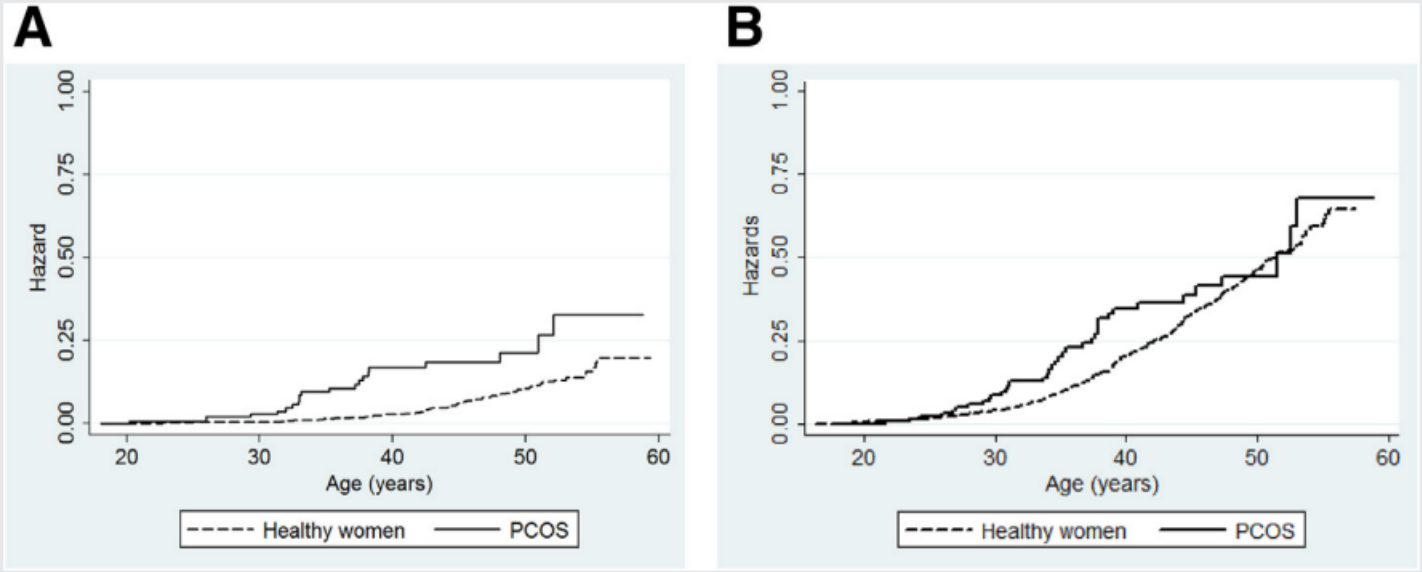
Fertility and sterility. 2017 Dec 1;108(6):1078-84.

Baseline characteristics of case and control groups.

Characteristic	PCOS (n = 178)	Control (n = 1,524)	*P* value
Age (y)	26.4 (8.5)	28.9 (8.6)	.001[a]
BMI (kg/m^2)	26.1 (5.1)	25.4 (4.7)	.062
WC (cm)	82.8 (12.5)	81.7 (11.7)	.281
WHR	0.80 (0.07)	0.80 (0.07)	.802
WHtR	0.52 (0.08)	0.51 (0.07)	.319
SBP (mm Hg)	107.5 (11.7)	108 (12.1)	.272
DBP (mm Hg)	73.1 (9.4)	72.9 (9.2)	.812
TC (mg/dL)	189.9 (44.1)	186.8 (40.04)	.337
TG (mg/dL)[b]	106 (78.7–160.2)	100.0 (73–149)	.75
HDL-C (mg/dL)	44.5 (11.2)	44.4 (10.5)	.975
LDL-C (mg/dL)	119.4 (36.7)	118.2 (34.4)	.667
FBS (mg/dL)	87.2 (9.1)	88.2 (17.2)	.217
BS-2HPP (mg/dL)	107.8 (30.7)	106.3 (35.0)	.617
Prediabetes[c]	22 (12.4)	161 (10.5)	.447
Diabetes[c]	2 (1.1)	37 (2.4)	.084
Family history of diabetes[c]	51 (28.6)	366 (24.01)	.167
Physical activity[c]			.339
Low	92 (51.6)	822 (53.9)	
Moderate	28 (15.7)	248 (16.2)	
High	58 (32.5)	454 (29.7)	

Fertility and sterility. 2017 Dec 1;108(6):1078-84.

FIGURE 2



Kaplan-Meier hazard estimates in incidence rates in women with polycystic ovary syndrome and healthy women. Age is used as the time scale. (**A**) Women with diabetes. (Log-rank test, *P*=.001.) (**B**) Women with prediabetes. (Log-rank test, *P*=.057.)

Kazemi Jaliseh. Prediabetes and diabetes risks in PCOS. Fertil Steril 2017.

Fertility and sterility. 2017 Dec 1;108(6):1078-84.

TABLE 2

Unadjusted and multiple adjusted hazard ratios of incident outcomes by PCOS status.

	PCOS (n = 178)		Healthy women (n = 1,524)		Unadjusted		Multiple adjusted	
Outcome	**Yes**	**No**	**Yes**	**No**	**HR (95% CI)**	***P* value**	**HR (95% CI)[a]**	***P* value**
Diabetes	21	132	76	1,240				
≤40 y	17	78	27	571	6.6 (3.6–12.2)	.001	4.9 (2.5–9.3)	.001
>40 y	4	54	49	669	1.0 (0.3–2.8)	.953	0.8 (0.3–2.3)	.737
Prediabetes	37	92	317	846				
≤40 y	30	59	175	472	1.9 (1.3–2.8)	.001	1.7 (1.1–2.6)	.005
>40 y	7	33	142	374	0.6 (0.1–1.35)	.240	0.5 (0.2–1.2)	.174

Note: Extended Cox proportional hazards regression with age as the time scale were used for analysis. CI = confidence interval; HR = hazard ratio; PCOS = polycystic ovary syndrome.

[a] Baseline fasting blood sugar and body mass index, physical activity, and family history of diabetes were evaluated for confounding.

Kazemi Jaliseh. Prediabetes and diabetes risks in PCOS. Fertil Steril 2017.

Fertility and sterility. 2017 Dec 1;108(6):1078-84.

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- Dyslipidemia in PCOS could occur due to a combination of excess production of triglyceride-rich lipoproteins as well as an increased breakdown of high-density lipoproteins.
- These abnormalities are mostly considered to be a result of IR as well as the impact of excess visceral and hepatic fat.

Expert review of endocrinology & metabolism. 2019 Jan 2;14(1):23-33.

Dyslipidemia

- Types of dyslipidemia in PCOS:
  - Most studies report decreased HDL cholesterol and increased triglyceride levels, the same lipid profile known to be associated with IR.
  - Women with PCOS were found to have higher mean serum triglyceride and very-low-density-lipoprotein (VLDL) levels, but lower HDL values than control women.
  - Some studies demonstrated that women with PCOS exhibited increased TC and LDL levels.

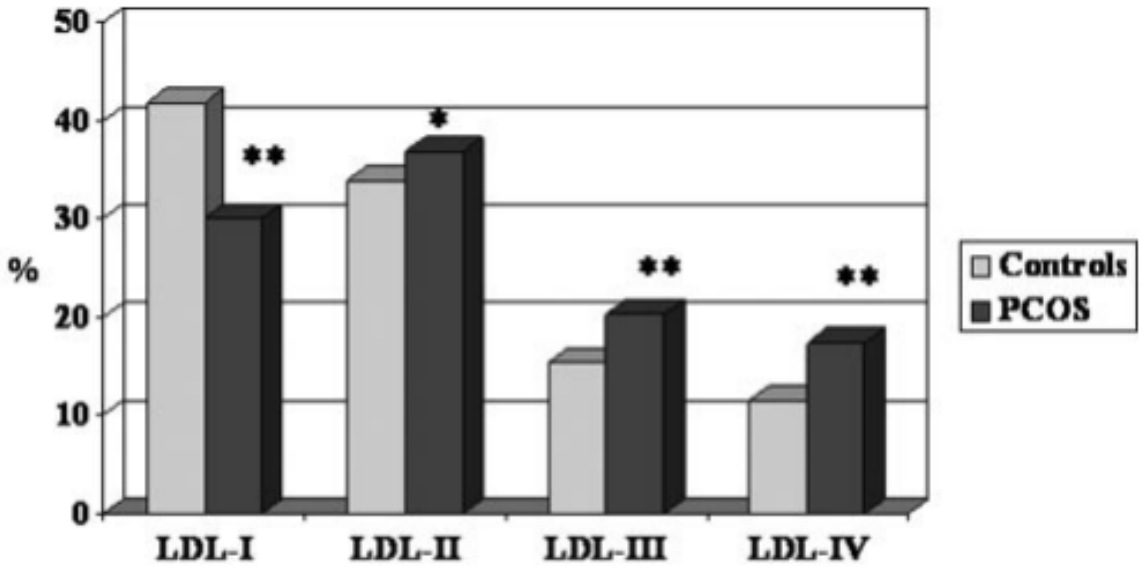
Expert review of endocrinology & metabolism. 2019 Jan 2;14(1):23-33.

Atherogenic Lipoprotein Phenotype and Low-Density Lipoproteins Size and Subclasses in Women with Polycystic Ovary Syndrome

Kaspar Berneis, Manfredi Rizzo, Veronica Lazzaroni, Franca Fruzzetti, and Enrico Carmina

TABLE 1. Clinical data, serum insulin, and plasma lipids in patients with PCOS and in age- and weight-matched controls (mean ± SD)

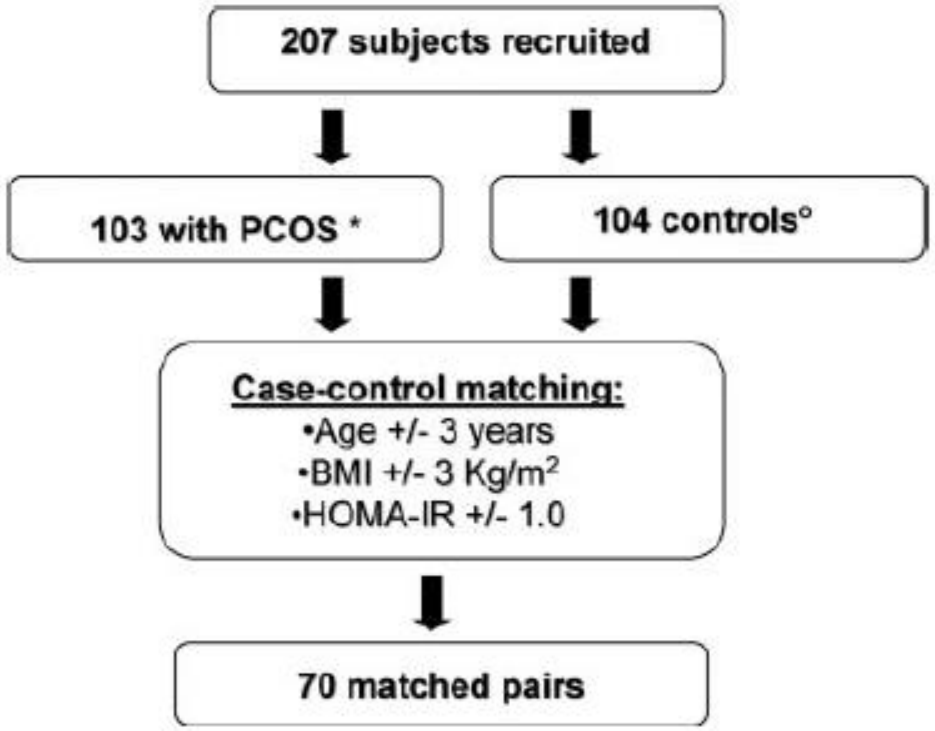
	PCOS (n = 30)	Controls (n = 24)
Age (yr)	25.1 ± 4.2	25.5 ± 3
BMI (kg/m²)	28.4 ± 5.8	28 ± 4.4
Waist circumference (cm)	94 ± 11	89 ± 10
Serum insulin (μU/ml)	18.6 ± 8.7[a]	11.8 ± 5.1
Total cholesterol (mg/dl)	158 ± 23	159 ± 28
Triglycerides (mg/dl)	85 ± 29[a]	61 ± 27
HDL-cholesterol (mg/dl)	47 ± 11[a]	56 ± 14
LDL-cholesterol (mg/dl)	94 ± 32	91 ± 33



The Journal of Clinical Endocrinology & Metabolism; 2006,92(1):186 –189

Lipoprotein Subclass Patterns in Women with Polycystic Ovary Syndrome (PCOS) Compared with Equally Insulin-Resistant Women without PCOS

N. Phelan, A. O'Connor, T. Kyaw-Tun, N. Correia, G. Boran, H. M. Roche, and J. Gibney



J Clin Endocrinol Metab, August 2010, 95(8):3933–3939

TABLE 1. Anthropometric, biochemical, and nutritional characteristics in women with PCOS and normal women

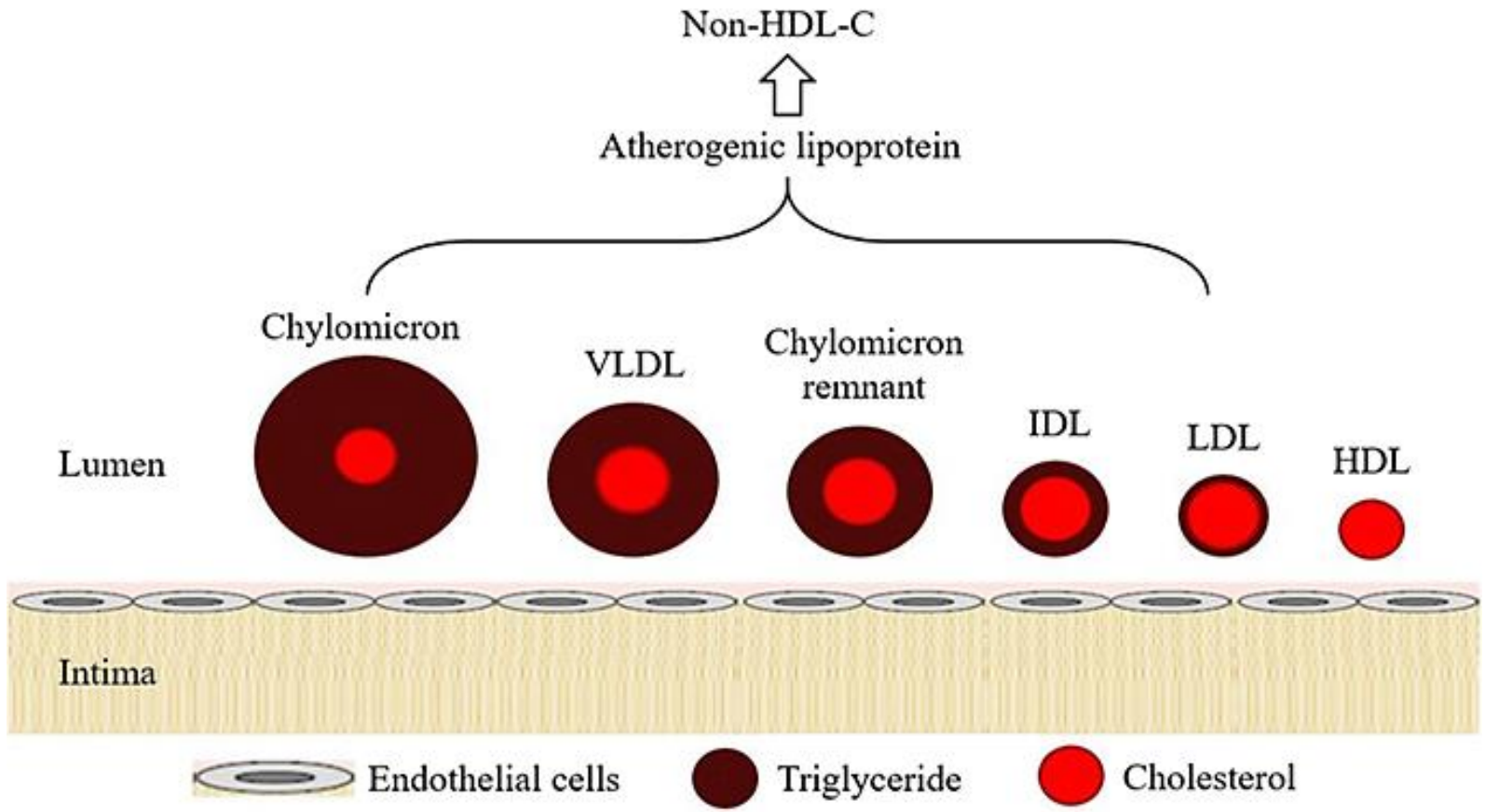
	PCOS	Normal	*P* value[a]
Age (yr)	30.0 ± 5.3	30.0 ± 5.5	ns
BMI (kg/m^2)	31.5 ± 6.9	31.6 ± 5.9	ns
WC (cm)	99.1 ± 15.0	96.5 ± 12.8	ns
Hip circumference (cm)	112.9 ± 12.7	114.7 ± 15.1	ns
Waist to hip ratio	0.87 ± 0.06	0.84 ± 0.07	<0.001
Systolic BP (mm Hg)	122 ± 13	124 ± 14	ns
Diastolic BP (mm Hg)	83 ± 9	83 ± 10	ns
%BF	39 ± 8	40 ± 7	ns
Fasting glucose (mmol/liter)	4.7 ± 0.5	4.7 ± 0.4	ns
Fasting insulin (mU/liter)	12.0 ± 6.6	11.5 ± 7.4	ns
2-h postprandial glucose (mmol/liter)	4.6 ± 1.2	4.6 ± 1.1	ns
2-h postprandial insulin (mU/liter)	32.0 ± 32.7	33.1 ± 39.0	ns
HOMA-IR	2.56 ± 1.49	2.42 ± 1.64	ns
QUICKI	0.16 ± 0.06	0.15 ± 0.07	ns
SiM	5.8 ± 8.4	6.2 ± 7.1	ns
Energy (KJ/d)	1743 ± 458	1756 ± 466	ns
Saturated fat (g/d)	25 ± 10	26 ± 12	ns
Carbohydrate (g/d)	205 ± 68	209 ± 56	ns
Saturated fatty acid (%)	24 ± 11	26 ± 10	ns
Monounsaturated fatty acid (%)	25 ± 4	26 ± 4	ns
Polyunsaturated fatty acid (%)	44 ± 5	43 ± 6	ns
Smokers (%)	18.6	25.7	<0.05
Baecke physical activity score	7.4 ± 0.9	7.7 ± 1.0	ns
Total testosterone (nmol/liter)	2.7 ± 1.2	1.7 ± 8	<0.0001
Free testosterone (nmol/liter)	0.053 ± 0.038	0.028 ± 0.016	<0.0001
Androstenedione (nmol/liter)	16 ± 6	11 ± 4	<0.0001
DHEAS (μmol/liter)	6.3 ± 3.0	5.2 ± 2.4	<0.0001
FAI	14.7 ± 39	4.7 ± 3.2	<0.0001
SHBG (nmol/liter)	37.0 ± 17.8	48.6 ± 23.3	<0.0001

J Clin Endocrinol Metab, August 2010, 95(8):3933–3939

TABLE 2. Lipid profiles and lipoprotein subclasses in women with PCOS and normal women

	PCOS	Control	*P* value
Total cholesterol (mmol/liter)	4.52 ± 0.79	4.49 ± 0.75	0.77
Triglycerides (mmol/liter)	1.12 ± 0.53	1.04 ± 0.66	0.11
HDL-C (mmol/liter)	1.49 ± 0.35	1.57 ± 0.45	0.28
Atherogenic index of plasma [log(TAG to HDL-C ratio)]	−0.15 ± 0.26	−0.21 ± 0.26	0.05
LDL-C (mmol/liter)	2.50 ± 0.70	2.48 ± 0.68	0.89
NEFA (mg/dl)	11.8 ± 5.1	11.7 ± 4.7	0.88
VLDL (%)	16.7 ± 4.2	15.3 ± 3.8	0.03
Large HDL (HDL 1–3) (%)	28.6 ± 9.2	27.5 ± 8.0	0.42
Intermediate HDL (HDL 4–7) (%)	53.5 ± 5.9	54.3 ± 6.4	0.46
Small HDL (HDL 8–10) (%)	17.8 ± 6.8	18.2 ± 5.8	0.79
Large LDL (LDL 1 + 2) (%)	27.8 ± 4.5	27.4 ± 4.4	0.65
Small dense LDL (LDL 3–7) (%)	1.25 ± 1.9	0.75 ± 0.99	0.09
Mean LDL particle size (Å)	271.1 ± 3.2	271.8 ± 1.9	0.36
Non-A LDL pattern (%)	12.9	2.9	0.04*
Apo B (g/liter)	0.84 ± 0.24	0.84 ± 0.23	0.77

J Clin Endocrinol Metab, August 2010, 95(8):3933–3939


Non-HDL-C
Atherogenic lipoprotein
Chylomicron
VLDL
Chylomicron remnant
IDL
LDL
HDL
Lumen
Intima
Endothelial cells
Triglyceride
Cholesterol

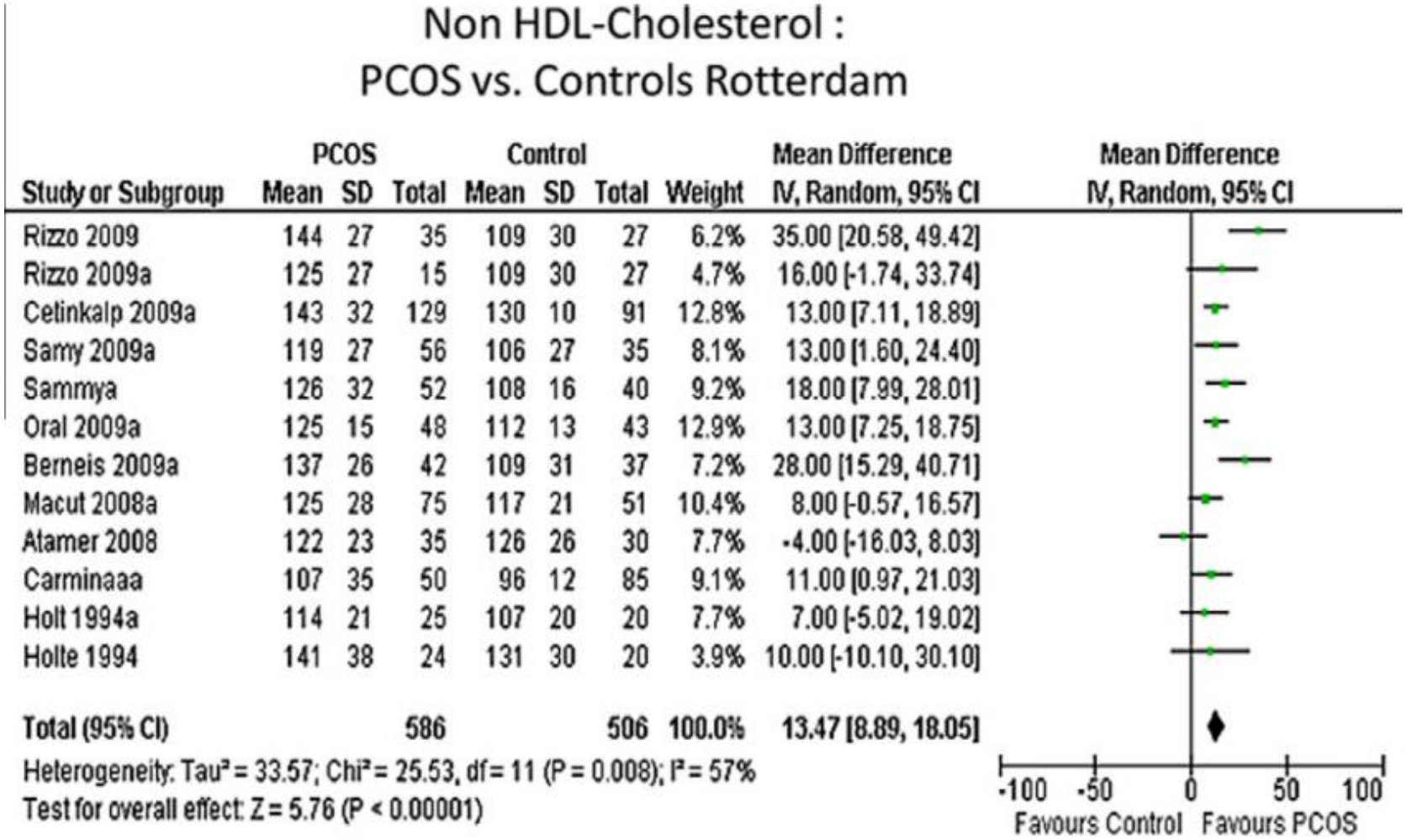


Fig. 4. Non HDL cholesterol in PCOS women vs. non PCOS women – Rotterdam.

Steroids 77 (2012) 295–299

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Hypertension

- Insulin resistance and hyperandrogenism are critical etiological factors underpinning the development of systemic arterial hypertension in PCOS.

- Recent evidence suggests that androgens play only a subtle role in the pathogenesis of hypertension and that this may be more an indirect role through increasing IR.

- Experimental models have postulated that androgen levels may directly control the renin–angiotensin system of the proximal renal tubule and increase reabsorption flow rate, thereby increasing extracellular volume and blood pressure.

- It is also postulated that hyperandrogenism may lead to hypertension by increasing the production of angiotensinogen in the kidneys.

- Visceral adipose cells are characteristically present in higher amounts in the more severe phenotypes of PCOS and release several inflammatory cytokines and adipokines that may inhibit the subcutaneous production of adiponectin, possibly contributing to endothelial dysfunction leading to hypertension.

Risk of hypertension in women with polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression

Mina Amiri[1], Fahimeh Ramezani Tehrani[1*], Samira Behboudi-Gandevani[2], Razieh Bidhendi-Yarandi[3,1] and Enrico Carmina[4]

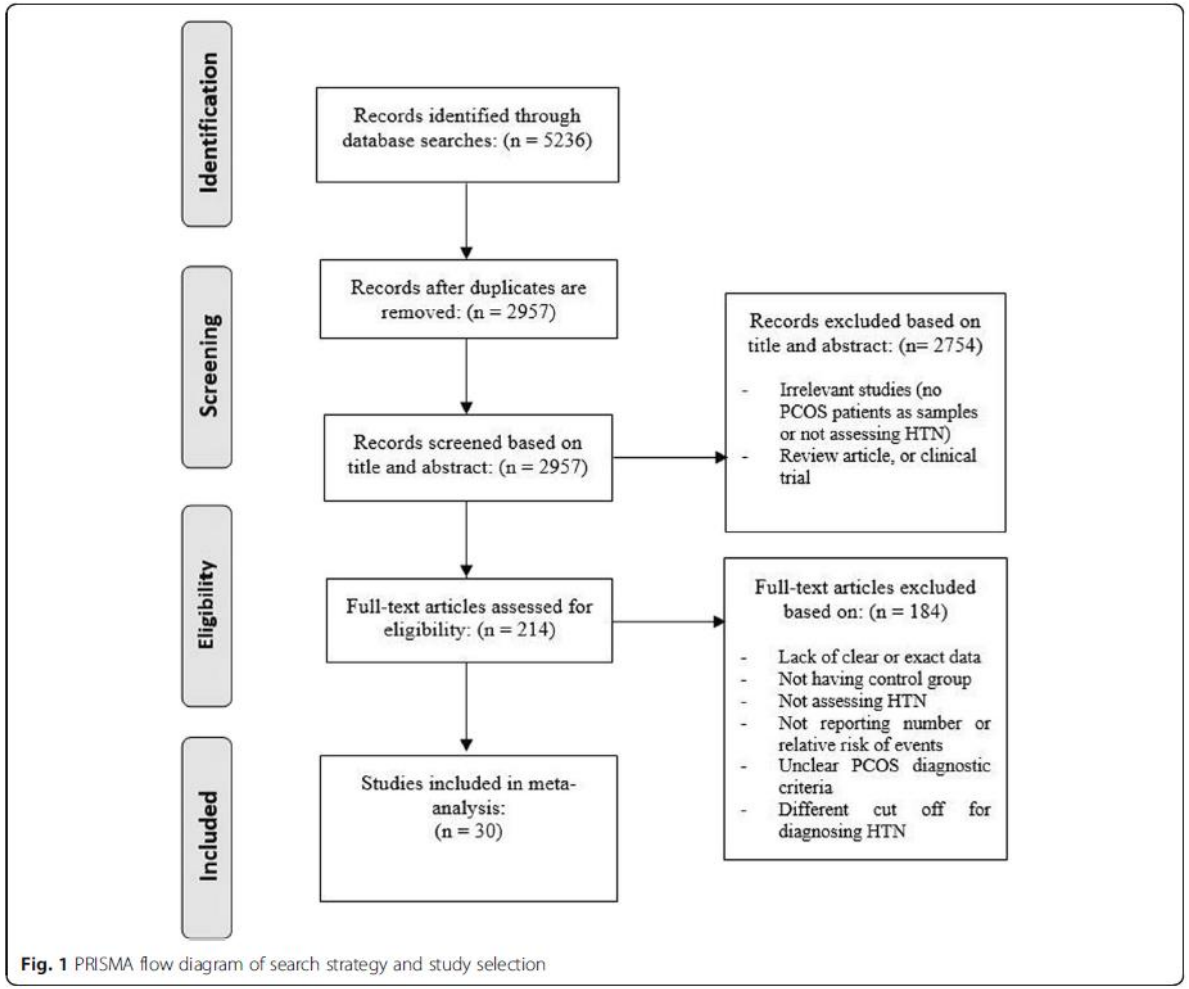

Fig. 1 PRISMA flow diagram of search strategy and study selection

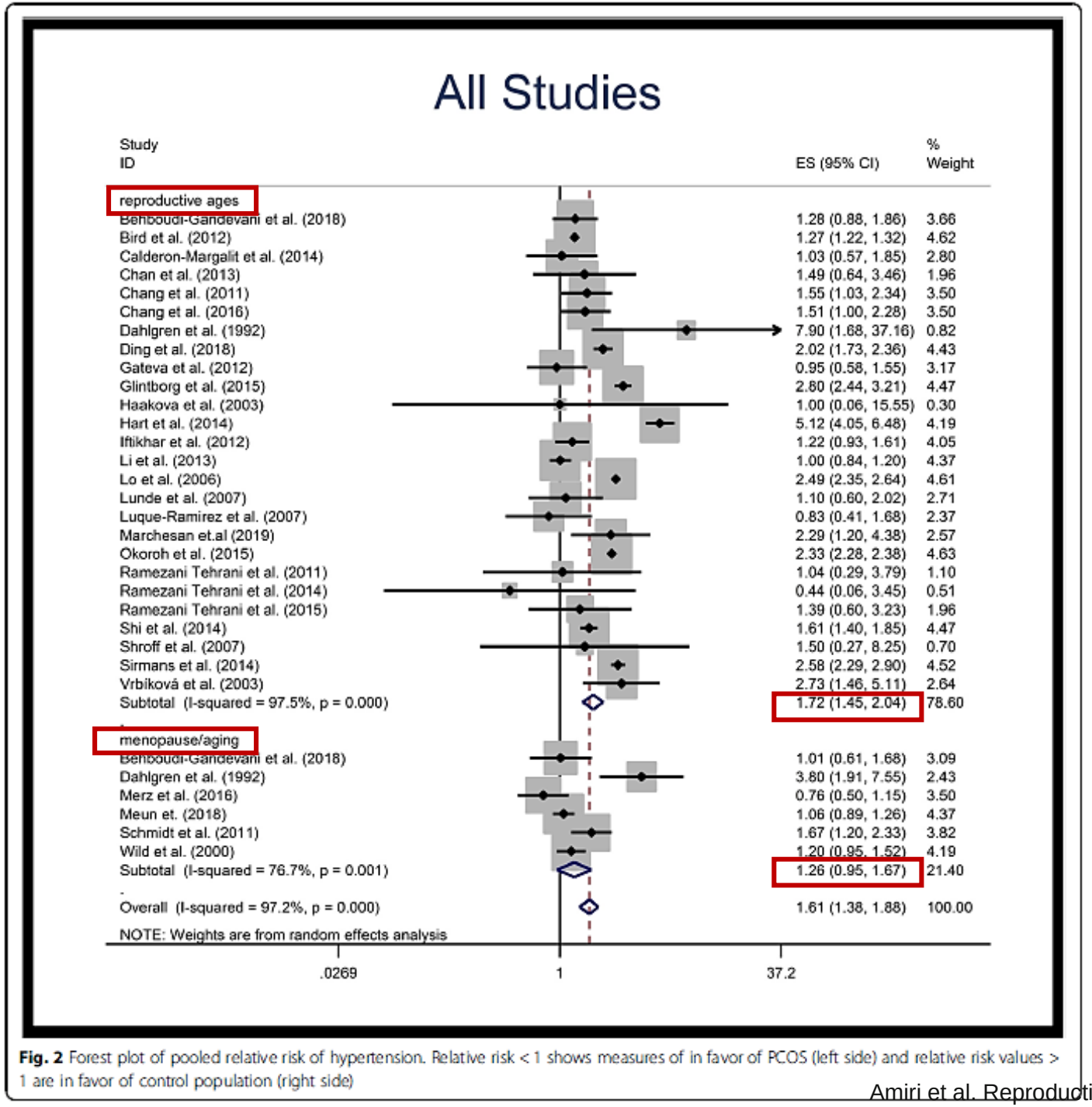

Fig. 2 Forest plot of pooled relative risk of hypertension. Relative risk < 1 shows measures of in favor of PCOS (left side) and relative risk values > 1 are in favor of control population (right side)

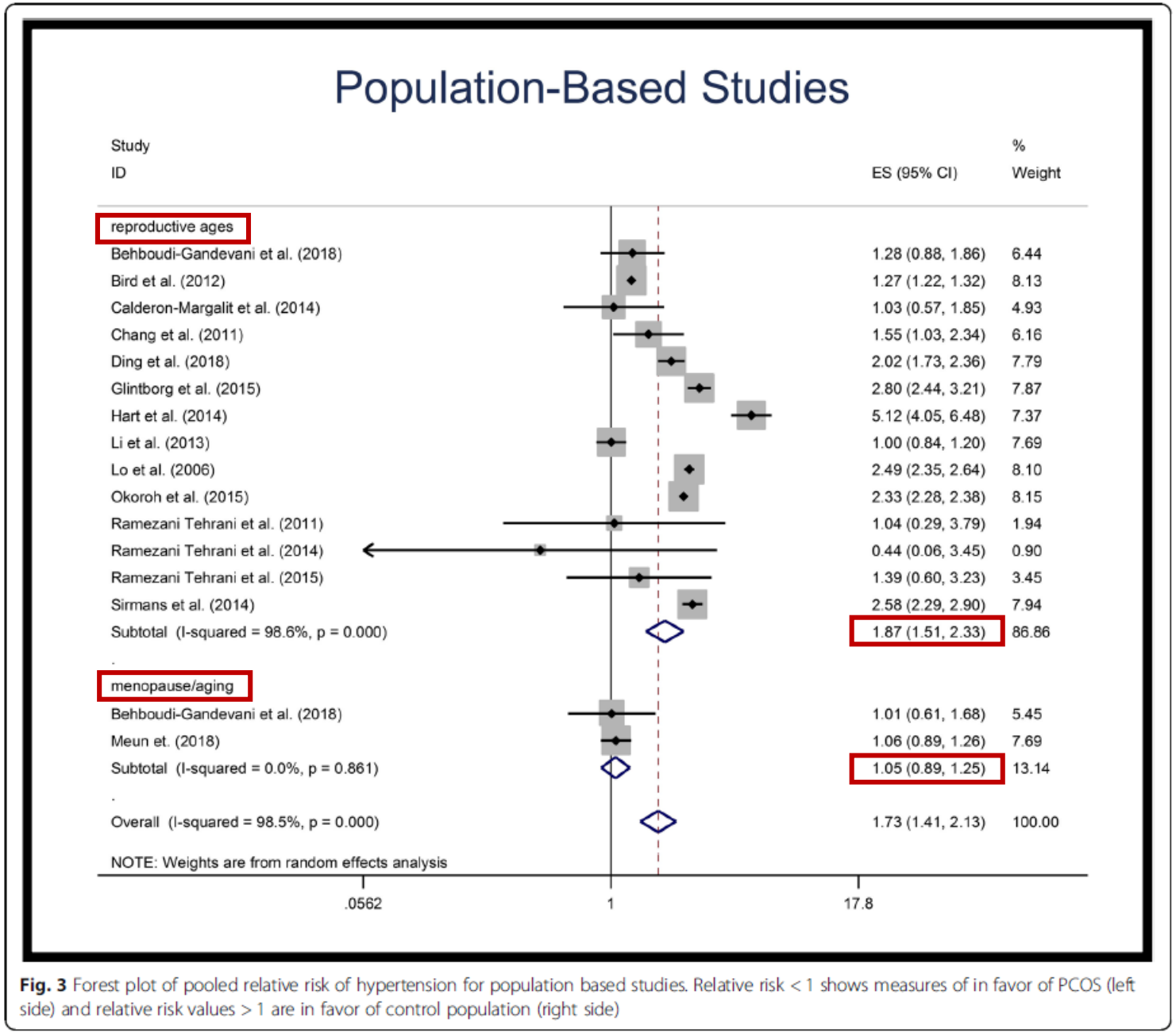

Fig. 3 Forest plot of pooled relative risk of hypertension for population based studies. Relative risk < 1 shows measures of in favor of PCOS (left side) and relative risk values > 1 are in favor of control population (right side)

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Metabolic syndrome

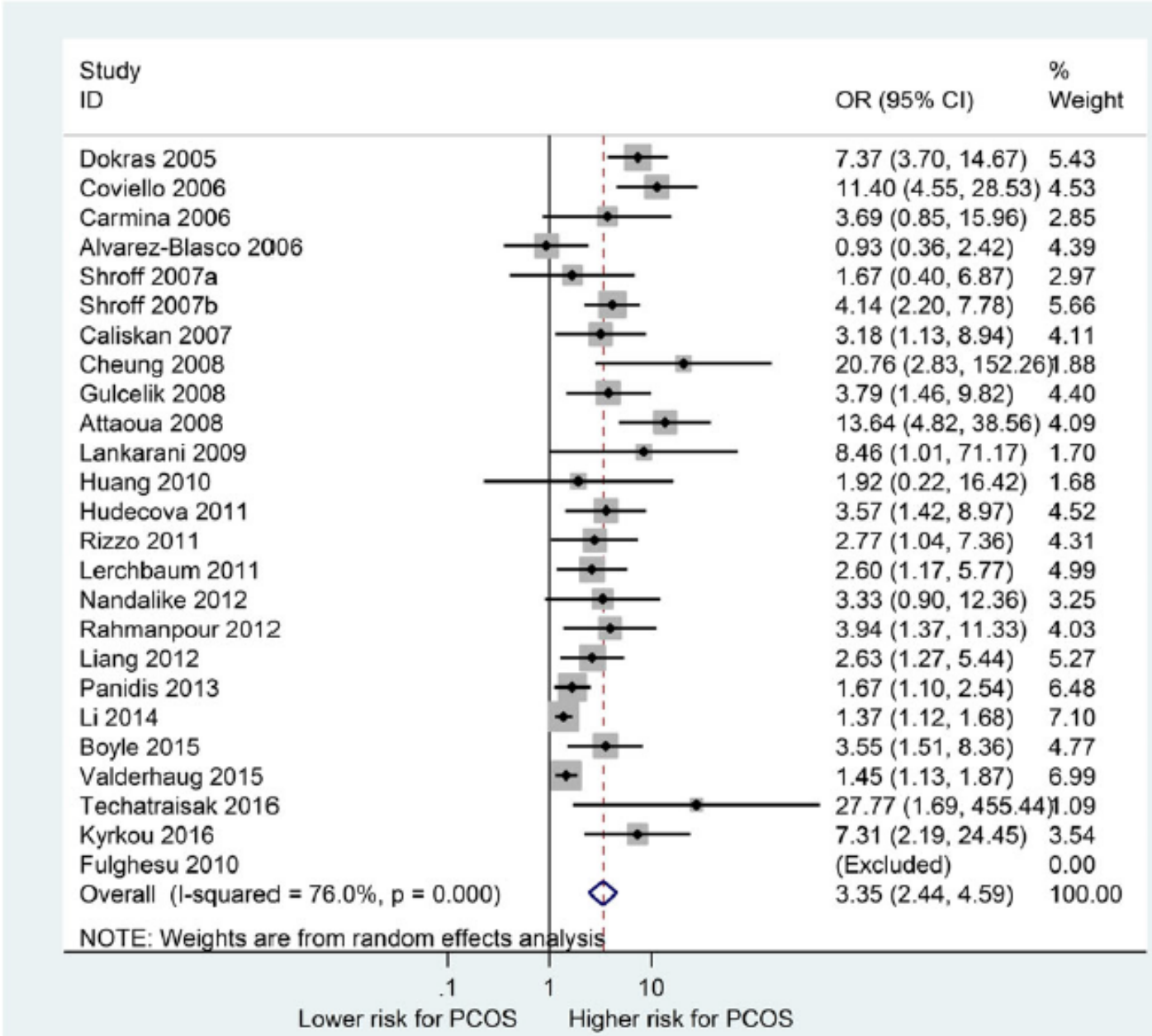
obesity reviews

Obesity Comorbidity

Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression

S. S. Lim[1], N. S. Kakoly[1], J. W. J. Tan[1], G. Fitzgerald[1], M. Bahri Khomami[1], A. E. Joham[1,2], S. D. Cooray[1,2], M. L. Misso[1], R. J. Norman[4], C. L. Harrison[1], S. Ranasinha[1], H. J. Teede[1,2,3] and L. J. Moran[1,4]

Obesity reviews. 2019 Feb;20(2):339-52.



Obesity reviews. 2019 Feb;20(2):339-52.

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1. Sympathetic nervous system :

- Activation of the sympathetic nervous system has an adverse impact on cardiac structure and function among patients with essential hypertension in the general population.

- Studies report an increased production of ovarian nerve growth factor (a marker of sympathetic nervous system (SNS) activity), greater muscle sympathetic nerve activity, reduced sensitivity to catecholamine-induced lipolysis in subcutaneous fat cells and enhanced visceral fat lipolysis among women with PCOS.

- These studies support a possible link between SNS activity with cardiometabolic complications among women with PCOS.

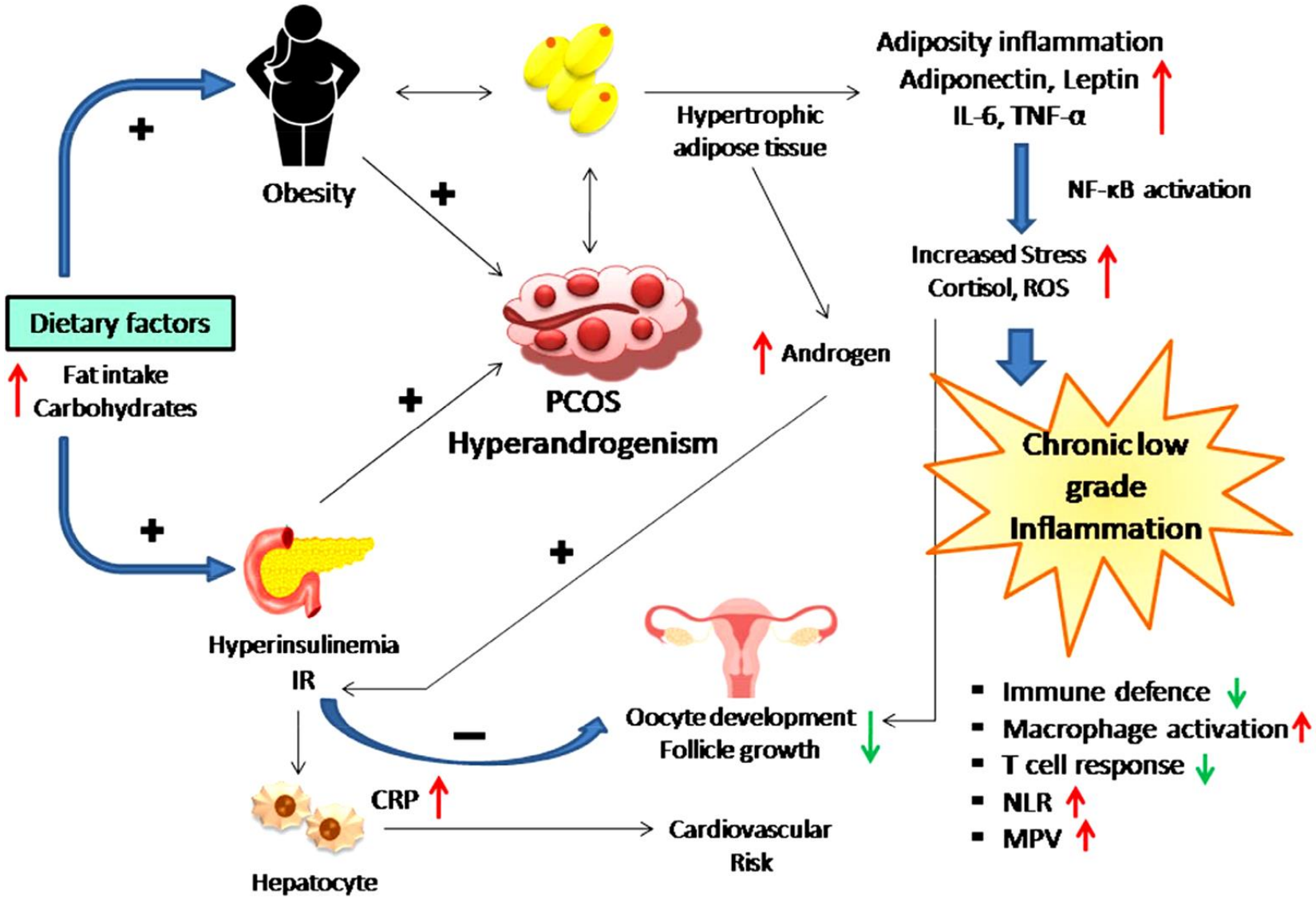
Expert review of endocrinology & metabolism. 2019 Jan 2;14(1):23-33.

2. Chronic inflammation and oxidative stress

- Studies have reported lower levels of anti-inflammatory markers along with an increase in proinflammatory markers such as C-reactive protein (CRP) among women with PCOS compared to controls potentially indicative of a state of chronic inflammation.

- Moreover, direct markers of inflammation such as homocysteine or asymmetric dimethylarginine, associated with cardiovascular morbidity and mortality, have also been identified in association with PCOS.

Expert review of endocrinology & metabolism. 2019 Jan 2;14(1):23-33.



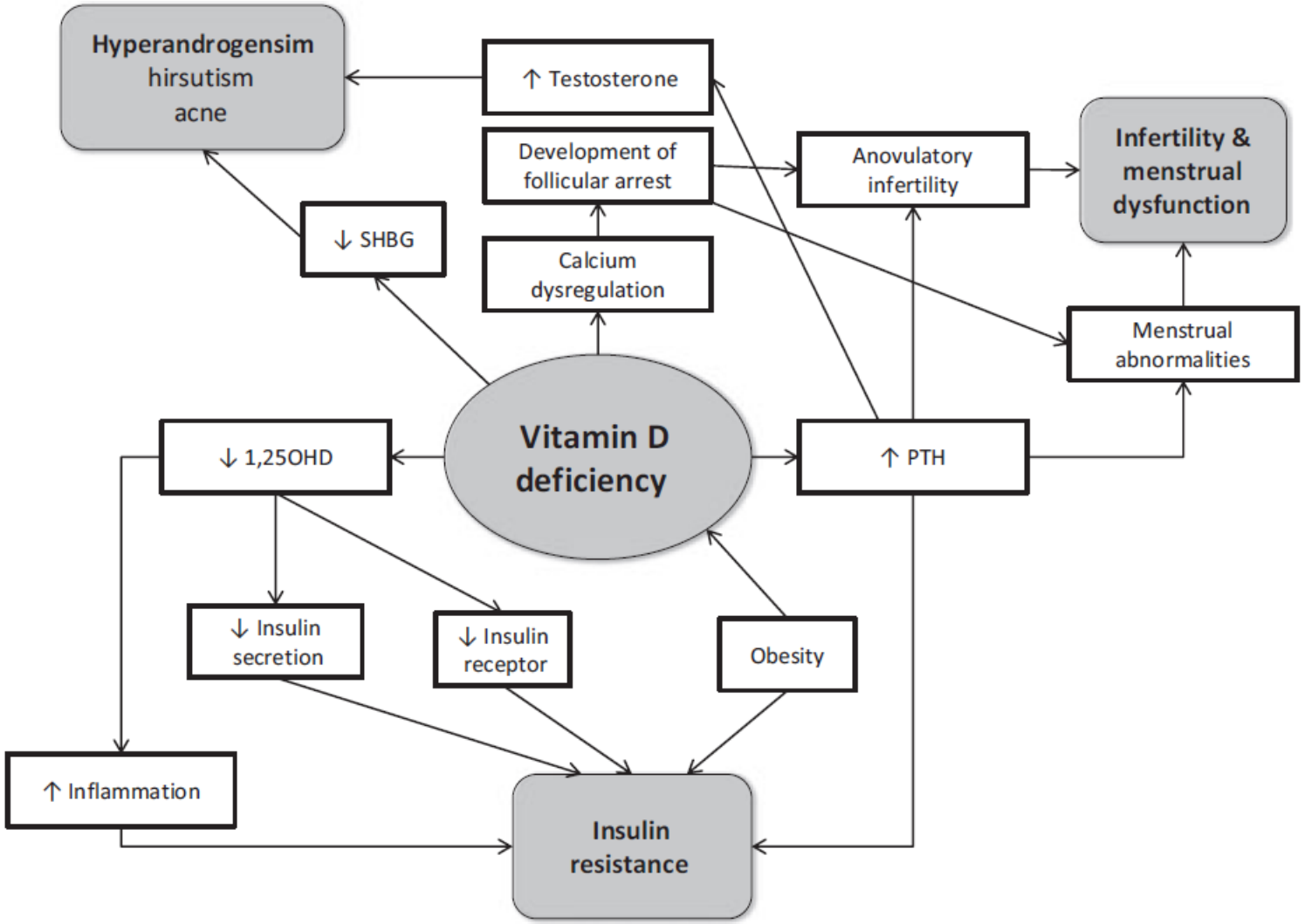
Middle East Fertility Society Journal. 2023 Dec 12;28(1):33.

3. Vitamin D deficiency

- Vitamin D plays a crucial role in the modulation of innate and adaptive immune response in various inflammatory and autoimmune diseases.

- There have also been studies reporting an inverse association of vitamin D and pro-inflammatory markers such as CRP.

Expert review of endocrinology & metabolism. 2019 Jan 2;14(1):23-33.



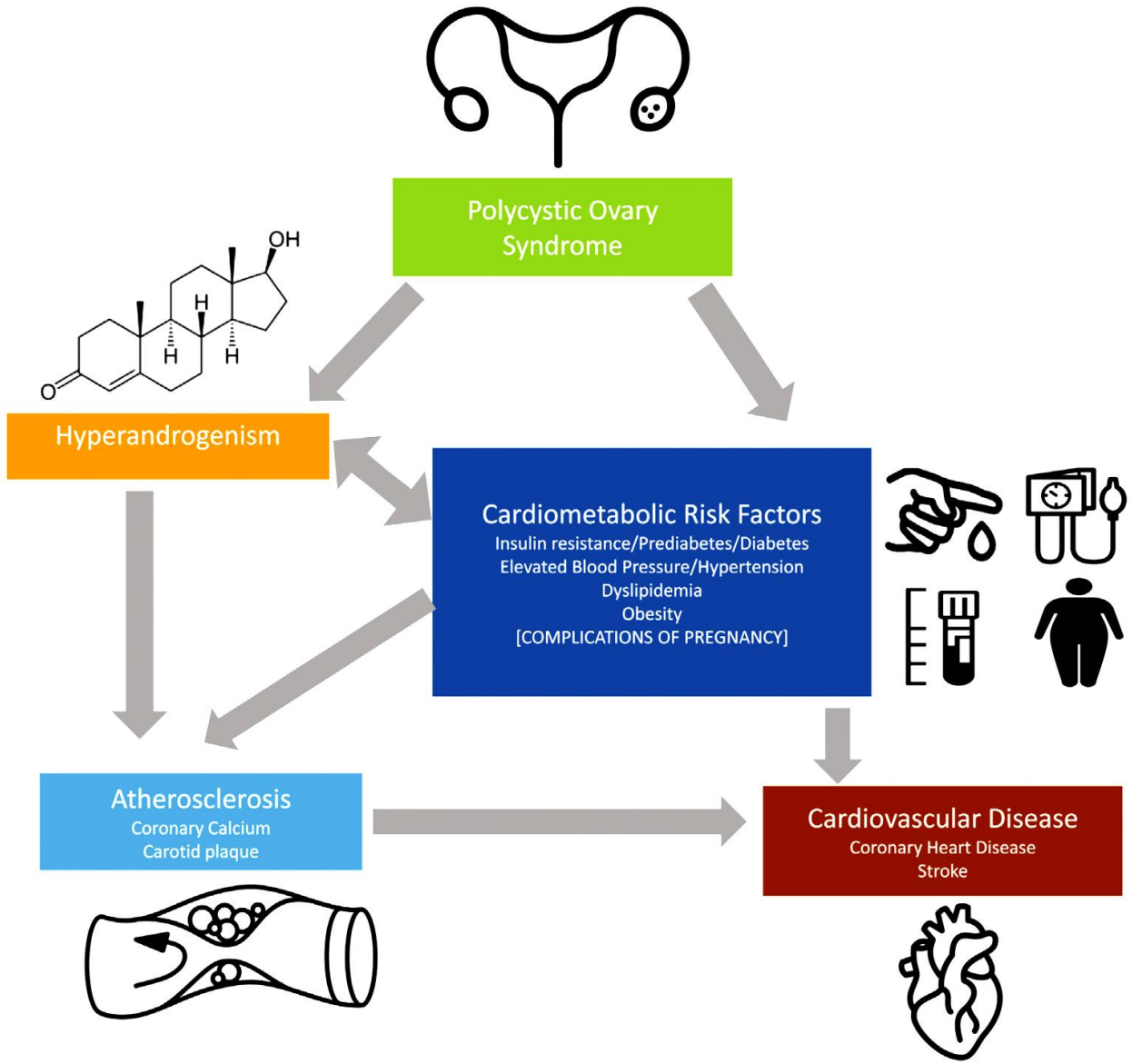
Clinical endocrinology. 2012 Sep;77(3):343-50.

Agenda

- General aspects
- Insulin resistance
- Dyslipidemia
- Hypertension
- Metabolic syndrome
- Emerging risk factors
- Cardiovascular disease
- Postmenopausal changes
- Screening
- Recommendations

- Subclinical CVD:
  - Past studies in premenopausal women have shown that higher free testosterone levels were associated with a greater relative coronary artery calcium (CAC) progression ratio, a measure of subclinical atherosclerosis.
  - Other studies have demonstrated a greater prevalence of CAC and significantly higher CAC score in premenopausal and postmenopausal women with PCOS, even after adjusting for age and BMI.
  - Women with PCOS also have greater carotid intimal medial thickness.

Trends in cardiovascular medicine. 2020 Oct 1;30(7):399-404.


Polycystic Ovary Syndrome
OH
H
H
H
O
Hyperandrogenism
Cardiometabolic Risk Factors
Insulin resistance/Prediabetes/Diabetes
Elevated Blood Pressure/Hypertension
Dyslipidemia
Obesity
[COMPLICATIONS OF PREGNANCY]
Atherosclerosis
Coronary Calcium
Carotid plaque
Cardiovascular Disease
Coronary Heart Disease
Stroke

Challenges in Studying the Association Between PCOS and CVD

1. Using different diagnostic criteria (sometimes self reported)
2. Consider only a single PCOS diagnosis without considering PCOS subtypes.
3. Using a variety of CVD outcomes (even hypertension)
4. Using a range of data sources to ascertain CVD events (including International Classification of Diseases codes, self-reported results, death certificates)
5. The age of the women

Finally, it has been unclear, based on observational studies, whether the association between PCOS and CVD is mediated entirely through traditional risk factors or independently associated with increased risk.

Expert review of endocrinology & metabolism. 2019 Jan 2;14(1):23-33.

Women with PCOS have an increased risk for cardiovascular disease regardless of diagnostic criteria—a prospective population-based cohort study

Meri-Maija Ollila,[1,*] Riikka K. Arffman,[1] Elisa Korhonen,[1] Laure Morin-Papunen,[1] Stephen Franks,[2] Juhani Junttila,[3] and Terhi T. Piltonen[1]

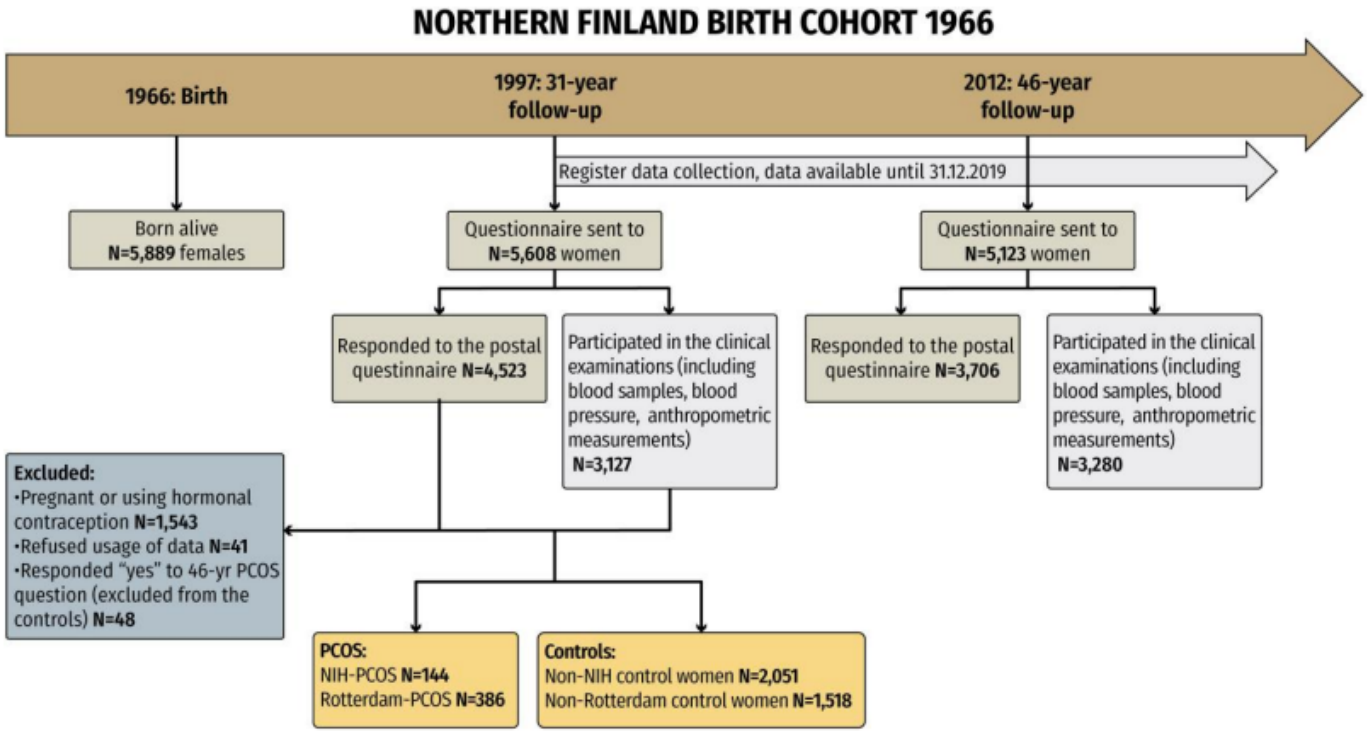


Figure 1. The flowchart of the Northern Finland Birth Cohort 1966.
PCOS, polycystic ovary syndrome, NIH, National Institute of Health.

European Journal of Endocrinology, 2023, 189, 96–105

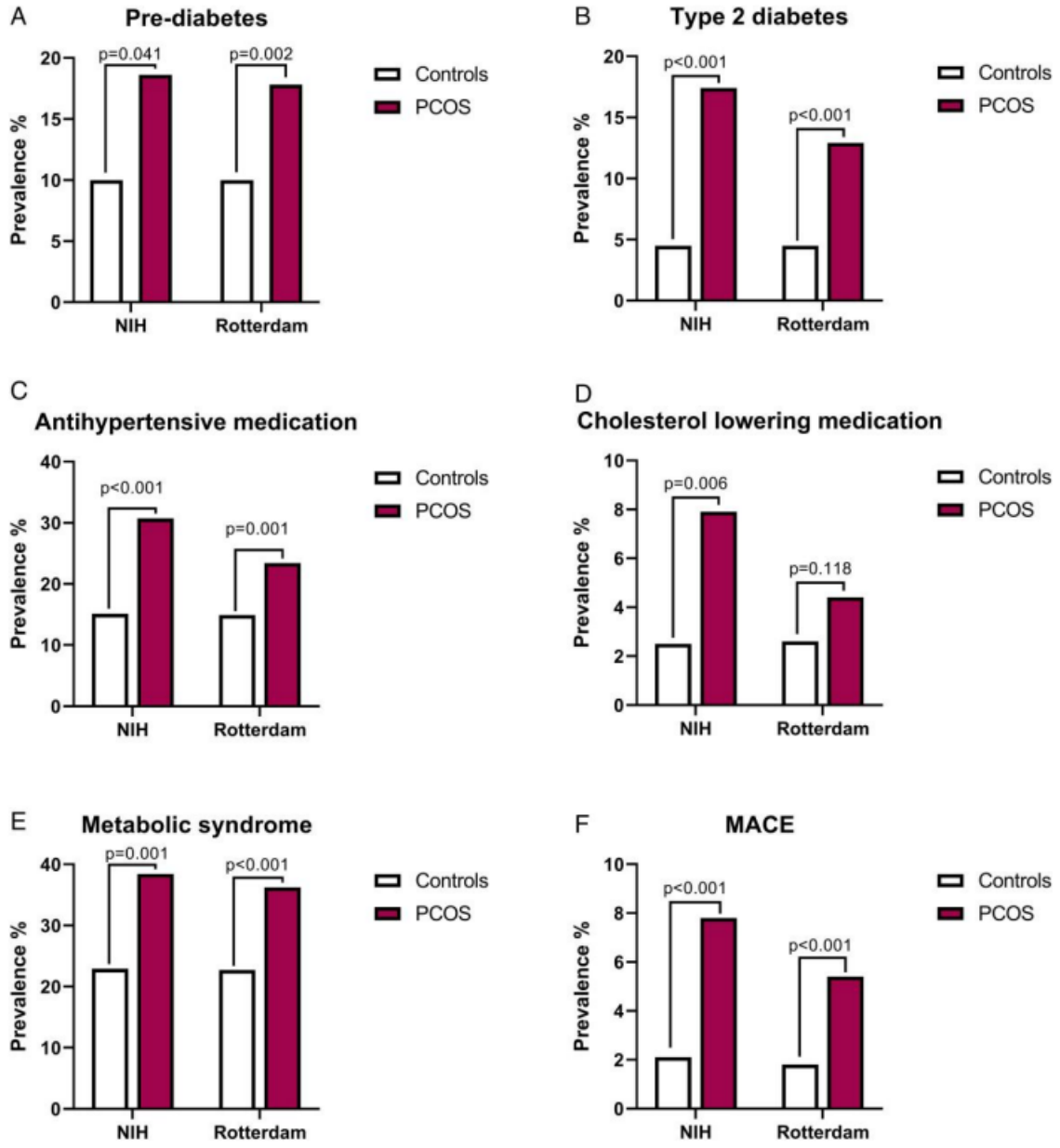
Table 1. Baseline characteristics at age 31 in women with NIH-PCOS, women with Rotterdam-PCOS and control women.

At age 31	Control women (n = 1316-1552)	NIH-PCOS (n = 88-104)	P-value[a]	Control women (n = 934-1122)	Rotterdam-PCOS (n = 261-304)	P-value
Systolic BP (mmHg)	118.78 ± 11.8	124.60 ± 13.6	<.001	118.70 ± 11.5	121.10 ± 13.6	.005
Diastolic BP (mmHg)	74.14 ± 10.1	79.28 ± 12.0	<.001	73.98 ± 10.1	77.10 ± 11.4	<.001
Total cholesterol (mmol/L)	4.81 ± 0.9	4.95 ± 0.9	.129	4.80 ± 0.9	4.95 ± 0.9	.009
LDL (mmol/L)	2.76 ± 0.8	2.95 ± 0.8	.023	2.77 ± 0.8	2.92 ± 0.8	.006
HDL (mmol/L)	1.67 ± 0.4	1.51 ± 0.3	<.001	1.65 ± 0.4	1.58 ± 0.3	.002
Triglycerides (mmol/L)	0.89 ± 0.4	1.14 ± 0.6	<.001	0.90 ± 0.5	1.03 ± 0.6	<.001
Glucose (mmol/L)	4.91 ± 0.5	4.50 ± 0.4	.081	4.91 ± 0.5	4.93 ± 0.4	.400
Insulin (mIU/L)	7.60 ± 3.1	10.15 ± 5.4	<.001	7.68 ± 3.4	8.91 ± 4.9	<.001
HOMA-IR	0.98 ± 0.4	1.31 ± 0.7	<.001	0.99 ± 0.5	1.15 ± 0.6	<.001
HOMA-B	97.48 ± 23.4	111.96 ± 36.0	<.001	98.02 ± 24.3	105.47 ± 31.4	<.001
Alcohol consumption (g/day)	2.20 [0.60; 5.90]	1.75 [0.43; 6.65]	.641	2.30 [0.60; 6.20]	1.70 [0.50; 5.80]	.095
Smoking			.110			.217
Never smoker	40.9% (n = 829)	39.5% (n = 58)		41.9% (n = 631)	39.4% (n = 152)	
Former smoker >6 mo	22.1% (n = 448)	26.5% (n = 39)		22.2% (n = 334)	21.8% (n = 84)	
Former smoker <6 mo	11.9% (n = 241)	6.1% (n = 9)		11.6% (n = 174)	9.6% (n = 37)	
Current smoker	25.1% (n = 508)	27.9% (n = 41)		24.3% (n = 366)	29.3% (n = 113)	
Education			.806			.093
Basic	8.8% (n = 180)	9.6% (n = 14)		8.7% (n = 132)	8.7% (n = 34)	
Secondary	70.6% (n = 1447)	71.9% (n = 105)		69.4% (n = 1053)	74.3% (n = 289)	
Tertiary	20.6% (n = 423)	18.5% (n = 27)		21.9% (n = 333)	17.0% (n = 66)	

Table 3. Hormonal and metabolic parameters at age 46 in women with NIH-PCOS, women with Rotterdam PCOS and control women.

At age 46	Control women (n = 1290-1514)	NIH-PCOS (n = 85-101)	P-value[a]	Control women (n = 910-1085)	Rotterdam-PCOS (n = 256-299)	P-value[b]
Testosterone (nmol/L)	0.85 ± 0.3	0.97 ± 0.3	.001	0.85 ± 0.3	0.92 ± 0.4	.006
SHBG (nmol/L)	54.9 [38.5; 75.7]	48.1 [33.8; 60.9]	.002	55.2 [38.6; 75.4]	48.8 [34.9; 64.8]	<.001
FAI	1.47 [1.04; 2.12]	1.94 [1.51; 2.70]	<.001	1.46 [1.05; 2.08]	1.81 [1.34; 2.46]	<.001
BMI (kg/m^2)	26.3 ± 5.2	28.9 ± 5.7	<.001	26.3 ± 5.2	27.9 ± 5.8	<.001
Waist (cm)	86.5 ± 12.9	92.9 ± 14.2	<.001	86.6 ± 12.9	91.0 ± 14.5	<.001
Systolic BP (mmHg)	119.74 ± 15.5	122.52 ± 16.3	.073	119.44 ± 15.0	122.23 ± 16.0	.005
Diastolic BP (mmHg)	81.83 ± 10.5	84.70 ± 10.3	.005	81.72 ± 10.4	84.03 ± 11.4	.001
Total cholesterol (mmol/L)	5.17 ± 0.9	5.22 ± 0.8	.671	5.22 ± 0.9	5.23 ± 0.9	.621
LDL (mmol/L)	3.23 ± 0.9	3.42 ± 0.8	.047	3.24 ± 0.9	3.38 ± 0.9	.035
HDL (mmol/L)	1.67 ± 0.4	1.53 ± 0.3	.001	1.68 ± 0.4	1.57 ± 0.4	<.001
Triglycerides (mmol/L)	1.08 ± 0.6	1.16 ± 0.5	.224	1.09 ± 0.6	1.15 ± 0.6	.144

At age 46



European Journal of Endocrinology, 2023, 189, 96–105

Table 2. The prevalence as well as the crude and body mass index adjusted Cox regression analysis for cardiovascular disease events in women with NIH-PCOS, Rotterdam-PCOS and respective control women.

	Prevalence and number of events	*P*-value	Crude HR (95% CI)	BMI adjusted HR (95% CI)
Outcome: MACE				
Non-NIH control women	2.2% (43/1973)	<.001	1.00	1.00
NIH-PCOS	7.8% (11/141)		3.49 (1.75-6.96), $P < .001$	2.47 (1.18-5.17), $P = .016$
Non-Rotterdam control women	1.8% (27/1469)	<.001	1.0	1.0
Rotterdam-PCOS	5.2% (20/382)		2.86 (1.58-5.16), $P < .001$	2.33 (1.26-4.30), $P = .007$
Outcome: Myocardial infarction				
Non-NIH control women	0.8% (16/2001)	.010	1.00	1.00
NIH-PCOS	3.5% (5/141)		2.73 (.79-9.35), $P = .111$	2.20 (.60-8.08), $P = .236$
Non-Rotterdam control women	0.7% (10/1469)	.019	1.00	1.00
Rotterdam-PCOS	2.1% (8/382)		2.34 (.85-6.43), $P = .100$	1.85 (.64-5.33), $P = .255$
Outcome: Stroke				
Non-NIH control women	1.1% (23/2001)	.097	1.00	1.00
NIH-PCOS	NA % (<5/141)		2.60 (.89-7.53), $P = .079$	1.81 (.58-5.66), $P = .309$
Non-Rotterdam control women	1.0% (15/1469)	.024	1.00	1.00
Rotterdam-PCOS	2.6% (10/382)		2.76 (1.22-6.20), $P = .014$	2.59 (1.13-5.96), $P = .025$

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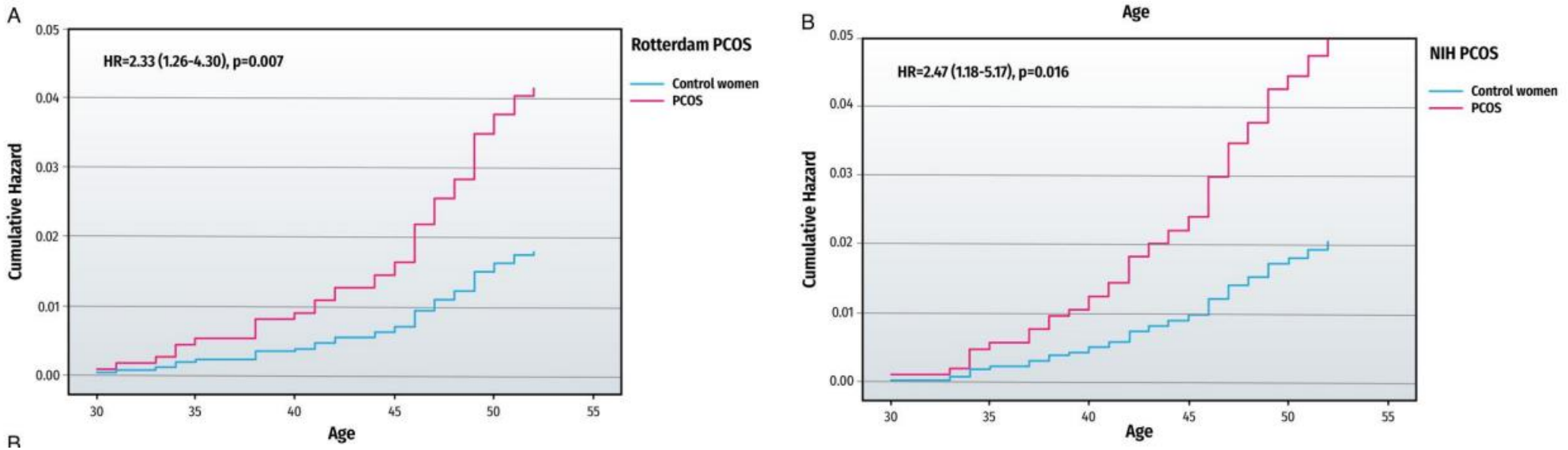

Figure 2. The Cox proportional hazard functions for major adverse cardiovascular events in women with PCOS according to the Rotterdam criteria (A) and NIH criteria (B). PCOS, polycystic ovary syndrome.
The analysis was adjusted by body mass index at age 31.

We also found that the ***risk for MACE*** already started to ***deviate*** from the control women ***during early adulthood*** and that the increased risk of CVD was independent of BMI.
These findings indicate that PCOS should be considered a major risk factor for CVD.

European Journal of Endocrinology, 2023, 189, 96–105

Cardiovascular events among reproductive and menopausal age women with polycystic ovary syndrome: a systematic review and meta-analysis

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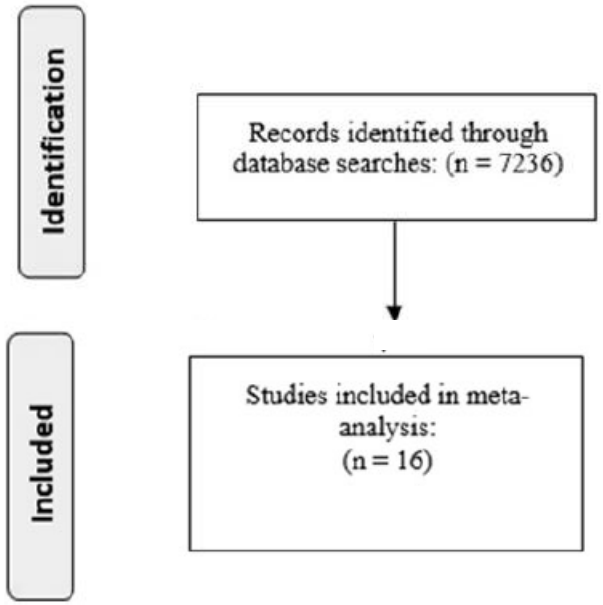
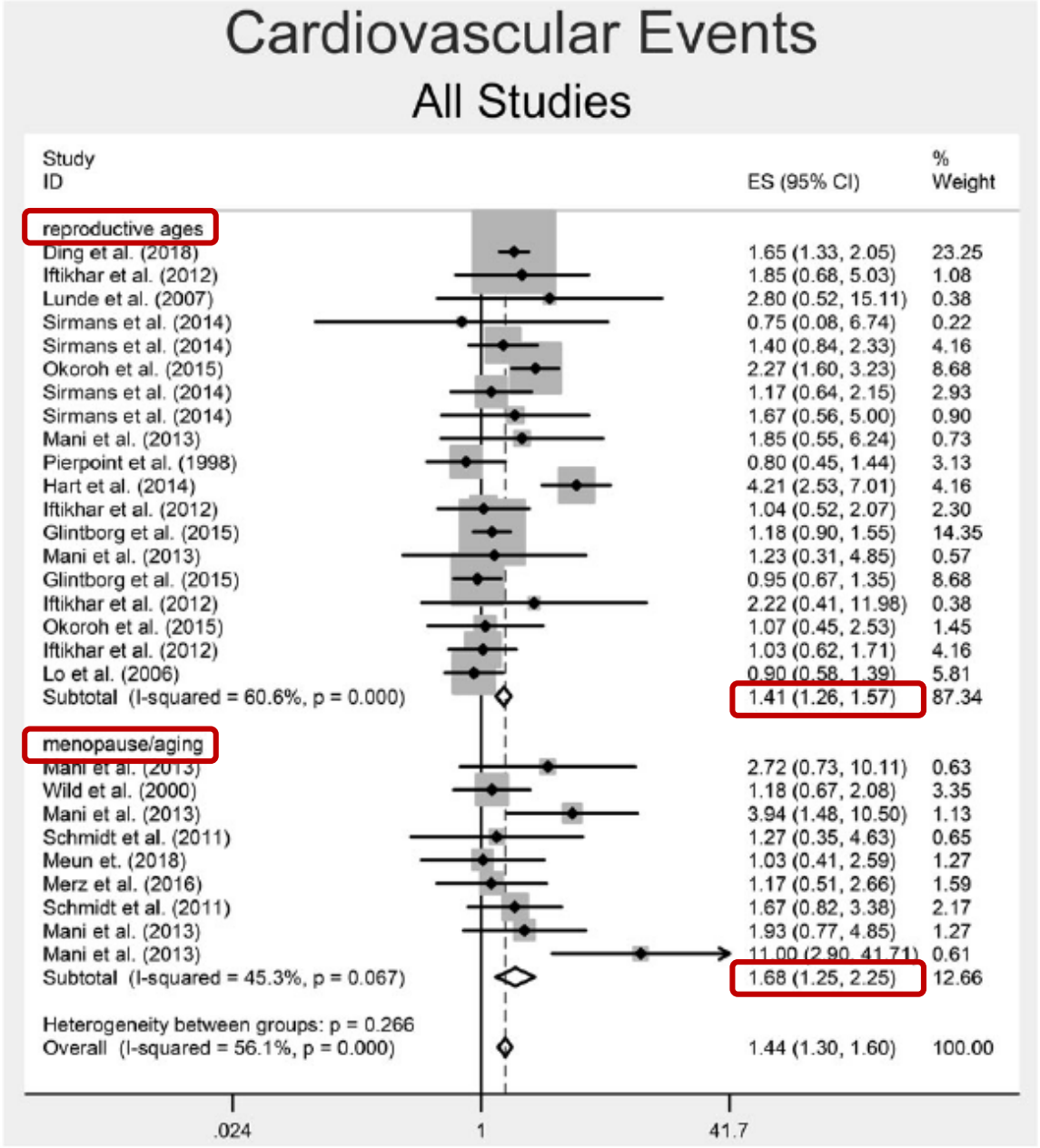
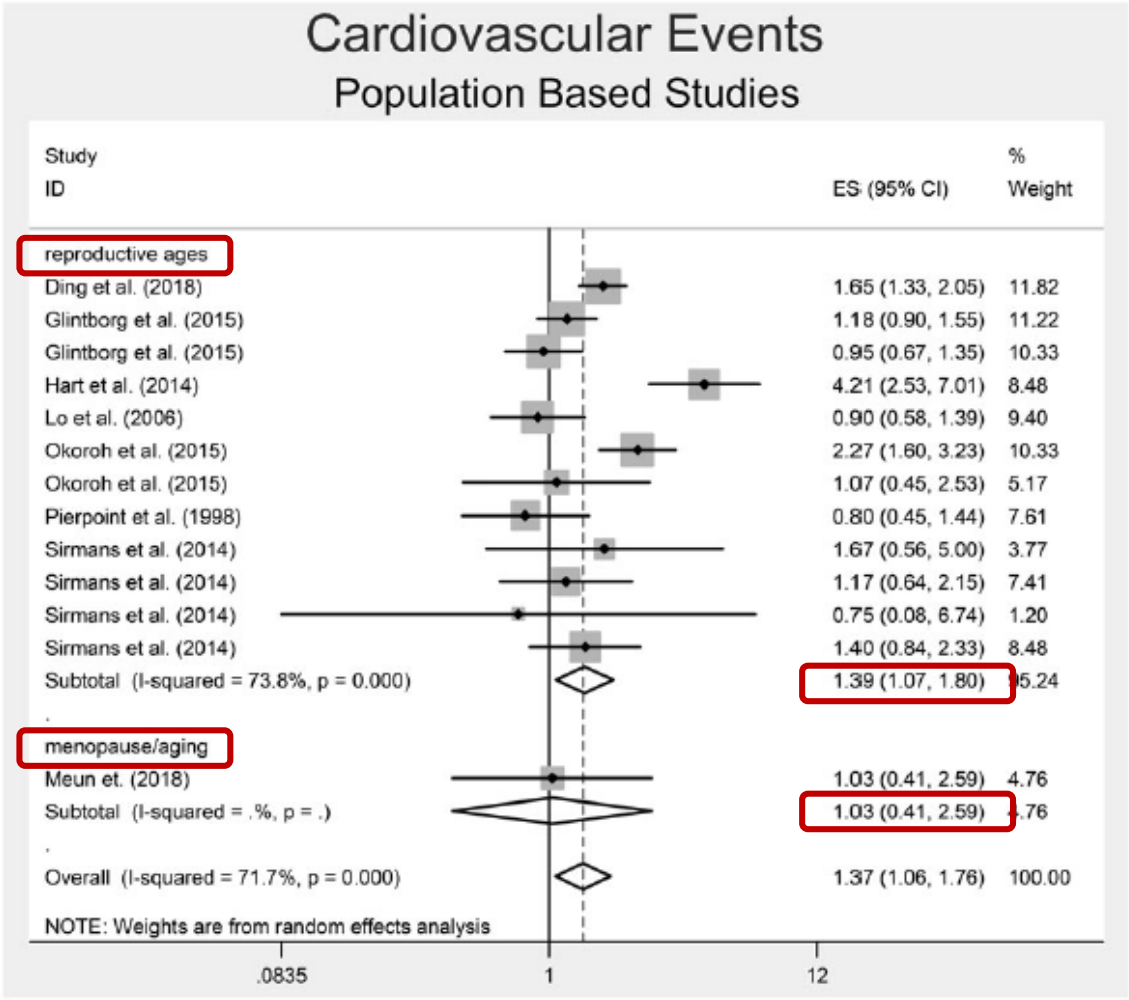


Gynecol Endocrinol. 2020 Jan;36(1):12-23.



Forest plot of pooled hazard ratio of cardiovascular events for all included studies.



Forest plot of pooled hazard ratio of cardiovascular events for population based studies.

Gynecol Endocrinol. 2020 Jan;36(1):12-23.

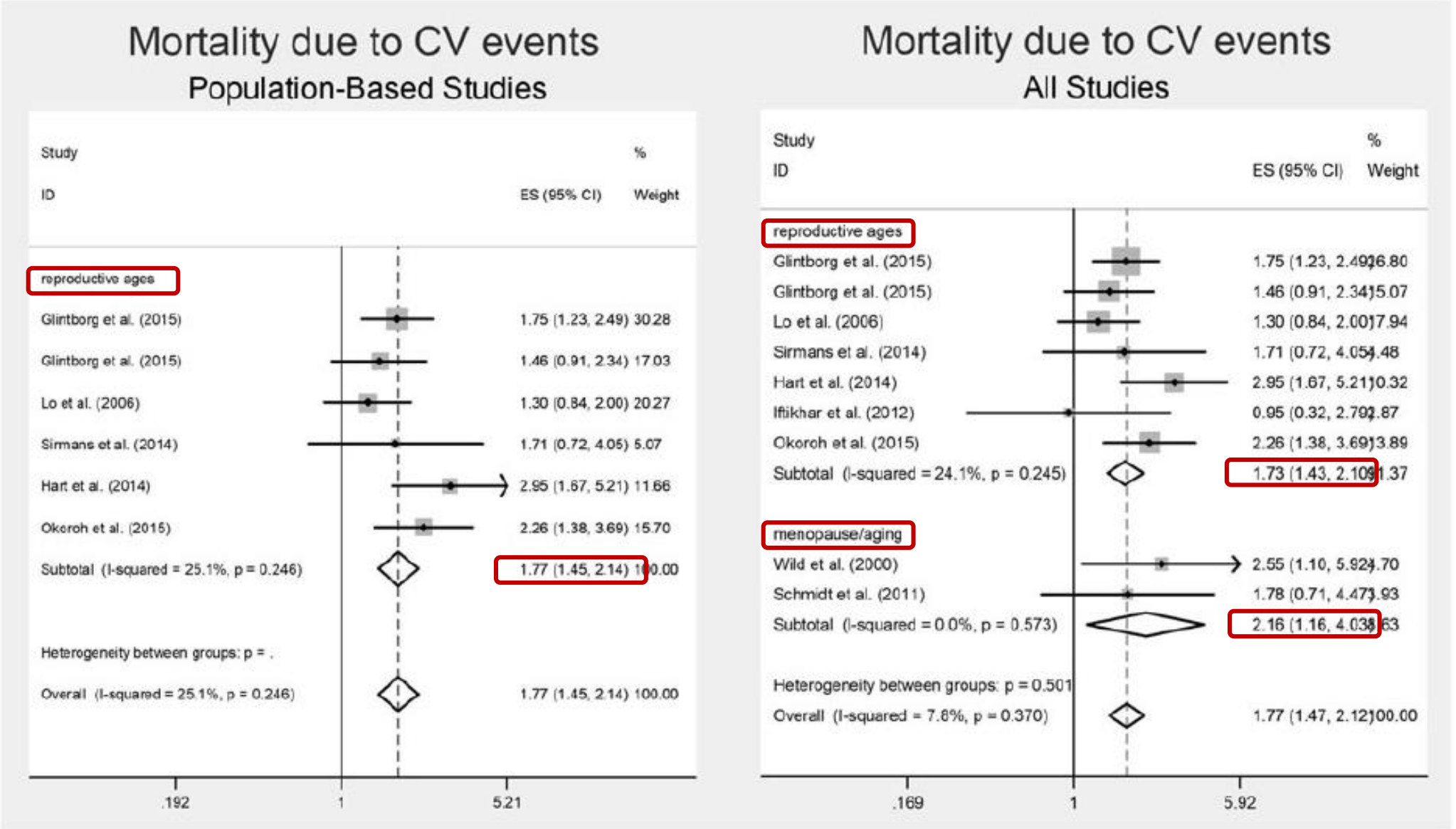
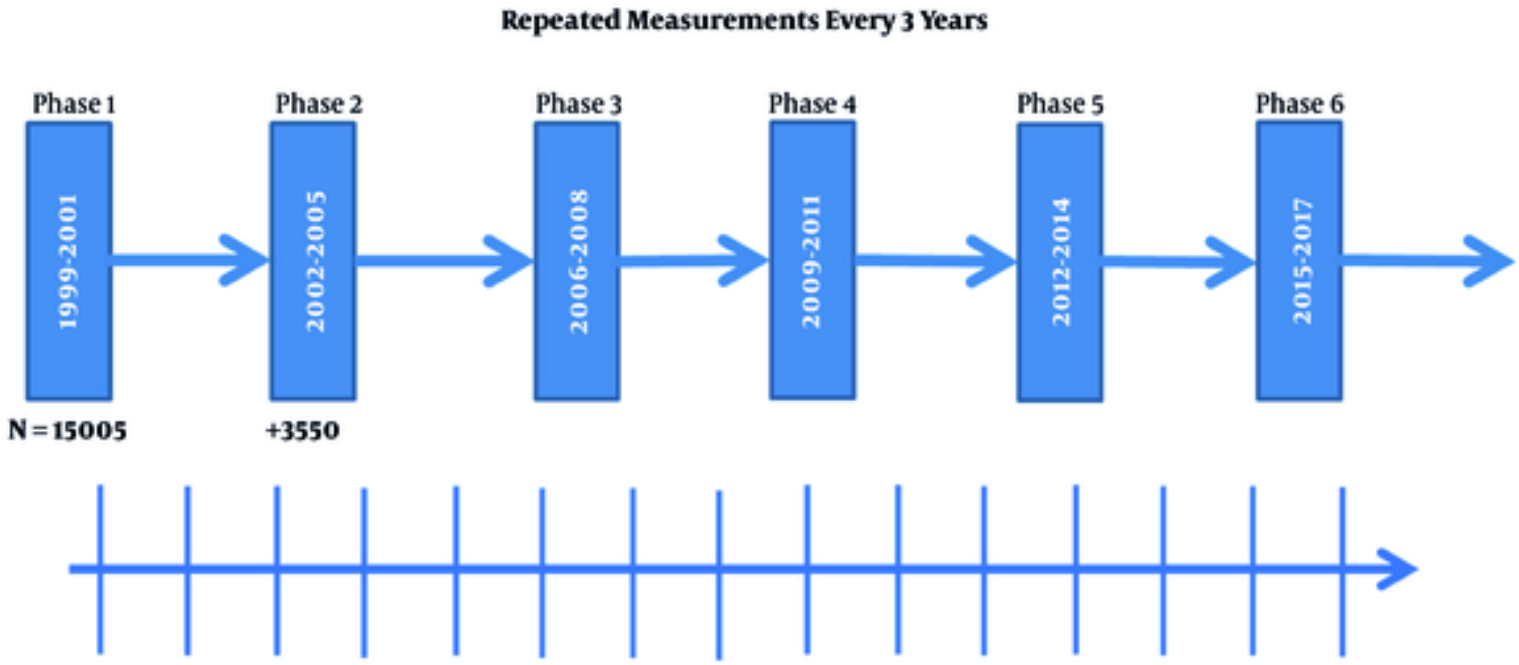


Figure 4. Forest plot of pooled hazard ratio of mortality due to cardiovascular events.

Gynecol Endocrinol. 2020 Jan;36(1):12-23.

The Prevalence of Polycystic Ovary Syndrome, Its Phenotypes and Cardio-Metabolic Features in a Community Sample of Iranian Population: Tehran Lipid and Glucose Study

Mahbanoo Farhadi-Azar1, Samira Behboudi-Gandevani2*, Maryam Rahmati1, Fatemeh Mahboobifard1,3, Ensi Khalili Pouya4, Fahimeh Ramezani Tehrani1 and Fereidoun Azizi



Frontiers in Endocrinology. 2022 Mar 1;13:825528.

TABLE 1 | Comparison the population characteristics of women with PCOS and healthy women.

	PCOS (n = 380)	Healthy women (n = 981)	Unadjusted P-value[¥]	Age and BMI Adjusted P-value[€]
Age, years, mean (SD)	31.1 (7.9)	32.4 (7.6)	0.01	0.002
Adiposity index, mean (SD) or median (25–75%)				
BMI, (kg/m$^{2)}$	26.23 (5.0)	26.20 (4.6)	0.772	0.119
HC, cm	101.1 (8.9)	101.2 (8.6)	0.902	0.307
WC, cm	81.7 (12.1)	81.8 (11.7)	0.921	0.995
WHR	0.81 (0.1)	0.81 (0.1)	0.949	0.648
WHtR	0.51 (0.1)	0.52 (0.1)	0.632	0.383
ABSI	7.3 (7.0–7.7)	7.4 (7.0–7.7)	0.214	0.601
VAI	99.7 (57.9–183.2)	87.0 (54.9–147.1)	**0.021**	**0.041**
LAP	26 (12.0–53.2)	24.2 (13.0–44.2)	0.305	**0.012**
# Hormones, mean (SD) or median (25–75%)				
LH, (mIU/ml)	5.9 (3.8–9.2)	4.7 (3.4–6.4)	<0.001	**0.002**
FSH, (mIU/ml)	7.0 (5.2–9.1)	7.6 (5.6–10)	0.002	**0.022**
17 OH-P, (nmol/L)	1.6 (0.9–2.4)	1.3 (1.0–2.1)	0.265	0.673
TT, ng/dl	0.6 (0.3–0.8)	0.3 (0.1–0.6)	<0.001	**<0.001**
FAI	1.2 (0.6–2.0)	0.5 (0.2–1.0)	<0.001	**<0.001**
A4, ng/ml	1.8 (1.0–2.4)	1.1 (0.9–1.7)	<0.001	**<0.001**
DHEAS, µg/Dl	160.5 (93.7–212.5)	124.8 (67.9–179.3)	<0.001	**<0.001**
SHBG, nmol/L	44.9 (33.4–61.0)	59.7 (44.4–84.4)	<0.001	**<0.001**
# Cardio-metabolic factors, mean (SD) or median (25–75%)				
FBG (mmol/L)	4.7 (4.4–5.0)	4.7 (4.4–5.0)	0.734	0.504
Bs-2hPG (mmol/L)	5.2 (4.4–6.2)	5.1 (4.4–5.9)	0.416	0.575
TC (mmol/L)	4.4 (3.9–5.0)	4.5 (3.9–5.1)	0.668	0.554
TG (mmol/L)	1.1 (0.8–1.8)	1.1 (0.8–1.5)	**0.025**	0.078
HDL-C (mmol/L)	1.1 (0.9–1.3)	1.2 (1.0–1.3)	**0.005**	**0.035**
LDL-C (mmol/L)	2.6 (2.1–3.2)	2.7 (2.2–3.2)	0.304	0.109
SBP (mmHg)	103.6 (12.7)	103.6 (12.1)	0.926	0.903
DBP (mmHg)	68.9 (9.4)	68.8 (9.1)	0.908	0.629
# Comorbidities, n (%)				
Metabolic Syndrome	58 (15.5)	122 (12.7)	0.215	0.066
WC >90, (cm)	87 (24)	194 (20.8)	0.238	0.216
SBP ≥130 (mmHg)	5 (1.3)	28 (2.9)	0.192	0.354
DBP ≥85 (mmHg)	18 (4.8)	38 (3.9)	0.564	0.447
FBS ≥6.1 (mmol/L)	6 (1.6)	31 (3.2)	0.112	0.208
HDL-C <1.03 (mmol/L)	140 (36.9)	274 (28.4)	**0.002**	**0.003**
Lipids disturbances, n (%)				
TG ≥1.7 (mmol/L)	98 (25.8)	184 (19.1)	**0.006**	**0.001**
TC ≥5.02 (mmol/L)	99 (26.0)	252 (26.1)	0.915	0.736
LDL-C ≥3.04 (mmol/L)	112 (31.3)	312 (34.6)	0.382	0.318

TABLE 2 | Features of the participants, classified to 4 phenotypical groups of PCOS and healthy women.

	PCOS Phenotype A(OA + HA + PCOM)(n = 91)	PCOS Phenotype B(OA + HA)(n = 176)	PCOS Phenotype C(HA + PCOM)(n = 82)	PCOS Phenotype D(OA + PCOM)(n = 31)	Healthy women (n = 981)*
Age, year, mean (SD)	31.5 (7.4)	31.1 (8.0)	30.8 (8.1)	30.8 (8.3)	32.4 (7.6)[b]
Adiposity index, mean (SD) or median (25–75%)					
BMI, (kg/m^2)	26.4 (4.4)	26.6 (5.5)	25.8 (4.8)	25.3 (4.0)	26.2 (4.6)[b]
HC, cm	101.0 (8.6)	102.0 (9.7)	100.1 (8.4)	99.2 (7.5)	101.2 (8.6)
WC, cm	82.3 (11.5)	82.1 (13.0)	81.0 (11.5)	79.7 (10.4)	81.8 (11.7)
WHR	0.81 (0.07)	0.80 (0.09)	0.81 (0.07)	0.80 (0.07)	0.81 (0.07)
WHtR	0.52 (0.07)	0.52 (0.09)	0.51 (0.08)	0.50 (0.07)	0.52 (0.07)
ABSI	7.3 (7.0–7.7)	7.3 (6.9–7.7)	7.3 (7.1–7.7)	7.3 (7.0–7.7)	7.37 (7.03–7.7)
VAI	118.8 (60.3–213.1)	98.4 (57.8–175.5)	89.0 (54.4–156.6)	83.2 (60.3–156.9)	87.0 (54.9–147.1)[a,b]
LAP	30.6 (13.8–60.9)	26.7 (11.0–48.6)	19.9 (12.5–43.3)	24.2 (11.3–44.9)	24.2 (13.0–44.2)
#Hormones, mean (SD) or median (25–75%)					
LH, mIU/ml	4.7 (3.1–8.8)	6.3 (3.8–9.2)	6.8 (4.3–10)	4.9 (3.7–6.9)	4.7 (3.4–6.4)[b,c]
FSH, mIU/ml	6.8 (4.8–9.1)	7.3 (5.4–9.1)	7.5 (5.3–9.2)	6.9 (5.3–9.0)	7.6 (5.6–10)[a,d]
17 OH-P, nmol/L	1.3 (0.8–2.1)	1.7 (1.1–2.7)	1.9 (1.4–2.4)	1.5 (1.1–2.2)	1.3 (1.0–2.1)
TT, ng/dl	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.4 (0.3–0.7)	0.3 (0.1–0.5)[a,b,c,d]
FAI	1.2 (0.6–1.9)	1.3 (0.6–2.1)	1.0 (0.5–2.0)	0.8 (0.5–1.4)	0.5 (0.2–0.9)[a,b,c,d]
A4, ng/ml	1.6 (0.9–2.3)	1.8 (1.0–2.4)	1.9 (1.3–2.5)	1.8 (1.1–2.4)	1.1 (0.9–1.7)[a,b,c]
DHEAS, µg/Dl	148 (85.1–225.5)	168.2 (101.2–207.8)	150 (90.7–213.3)	179.7 (118.3–205.5)	124.9 (67.9–179.3)[b,c,d]
SHBG, nmol/L	42.9 (31.5–62.5)	43.6 (31.7–55.6)	45.5 (33.6–55.8)	62.1 (46.8–72.5)	59.7 (44.4–84.4)[a,b,c]
#Cardio-metabolic factors, mean (SD) or median (25–75%)					
FBG (mmol/L)	4.7 (4.4–5.0)	4.7 (4.5–5.0)	4.7 (4.4–5.0)	4.7 (4.4–4.9)	4.7 (4.4–5.0)
Bs-2hPG ;(mmol/L)	5.6 (4.4–6.4)	5.3 (4.4–6.1)	5.0 (4.1–5.9)	5.0 (4.4–5.7)	5.1 (4.4–5.9)
TC (mmol/L)	4.5 (3.9–5.2)	4.4 (3.9–5.2)	4.3 (3.8–4.9)	4.2 (3.8–5.0)	4.5 (3.9–5.1)
TG (mmol/L)	1.4 (0.8–2.2)	1.1 (0.8–1.6)	1.0 (0.8–1.4)	1.2 (0.7–1.8)	1.0 (0.8–1.5)[b]
HDL-C (mmol/L)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.1 (0.9–1.2)	1.1 (0.9–1.3)	1.2 (1.0–1.3)[c]
LDL-C (mmol/L)	2.6 (2.1–3.1)	2.7 (2.1–3.3)	2.6 (2.2–3.1)	2.5 (2.2–3.1)	2.7 (2.2–3.2)
SBP (mmHg)	103.4 (15.5)	104 (12)	102.8 (11.6)	103.8 (10.8)	103.5 (12.1)
DBP (mmHg)	68 (9.5)	69.7 (10.1)	68.6 (7.9)	68.1 (7.9)	68.8 (9.1)
#Comorbidities, n (%)					
Metabolic Syndrome	17 (19.3)	25 (14.4)	12 (15.0)	4 (12.9)	122 (12.7)[a]
WC >90	23 (26.1)	44 (26.2)	15 (19.5)	5 (16.7)	194 (20.8)
SBP ≥130	1 (1.1)	2 (1.1)	2 (2.5)	0	28 (2.9)
DBP ≥85	3 (3.3)	12 (6.9)	2 (2.5)	1 (3.2)	38 (3.9)
FBS ≥6.1	2 (2.2)	3 (1.7)	1 (1.2)	0	31 (3.2)
HDL-C <1.03	30 (33)	66 (37.7)	33 (40.2)	11 (35.5)	274 (28.4)[b,c]
Lipids disturbances					
TG ≥1.7	34 (37.4)	40 (22.7)	16 (19.5)	8 (25.8)	184 (19.1)[a]
TC ≥5.02	28 (30.8)	48 (27.3)	16 (19.5)	7 (22.6)	252 (26.1)
LDL-C ≥3.04	23 (27.1)	58 (34.3)	19 (25.3)	12 (41.4)	312 (34.6)

Agenda

- General aspects
- Insulin resistance
- Dyslipidemia
- Hypertension
- Metabolic syndrome
- Emerging risk factors
- Cardiovascular disease
- **Postmenopausal changes**
- Screening
- Recommendations

Postmenopausal changes in cardiometabolic risks

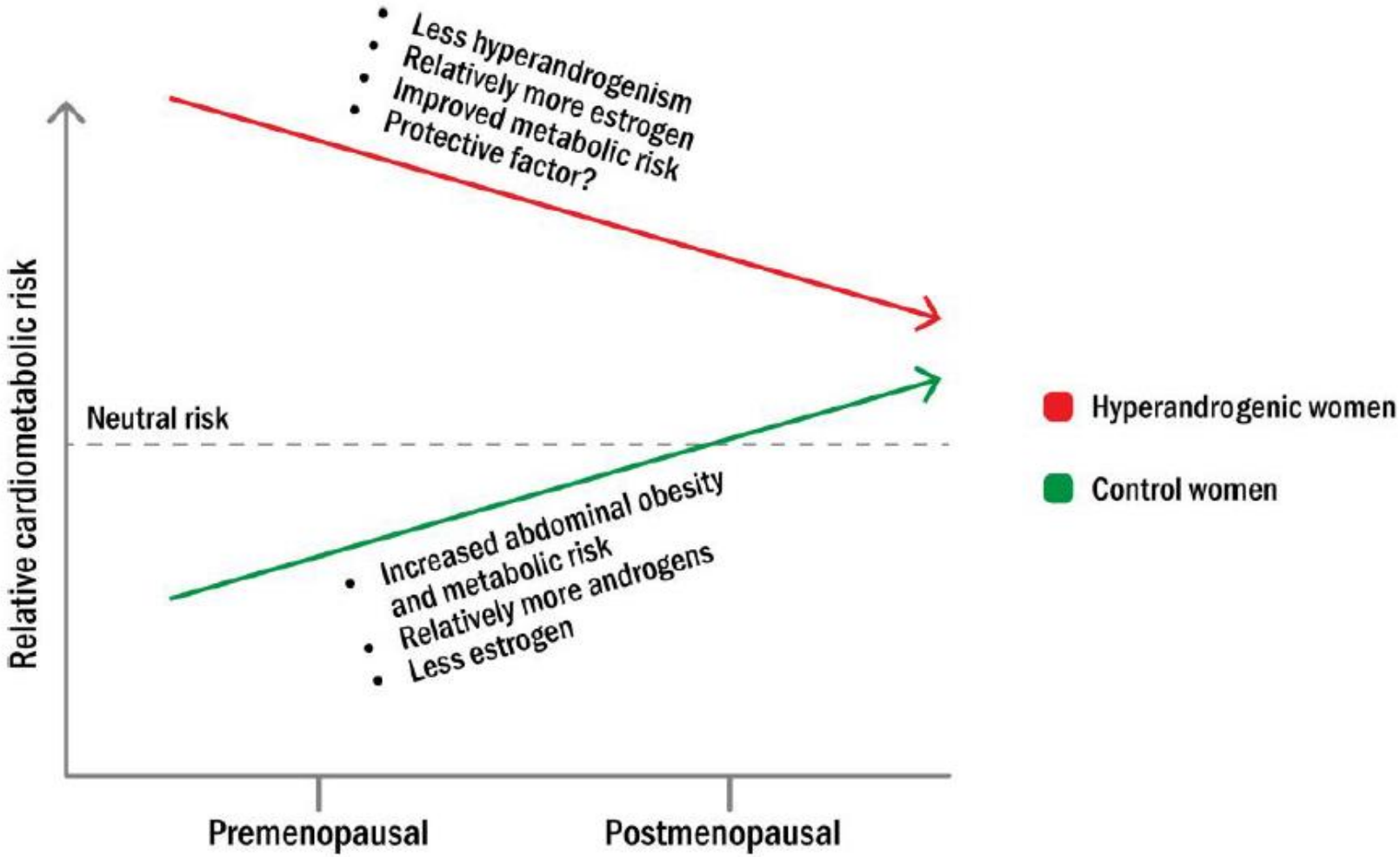
Table 1. Overall estimates of cardiometabolic outcomes in women

Table 2. Evidence of cardiometabolic outcomes in pre- and postmenopausal women with hyperandrogenism (mainly women with PCOS) as based on systematic reviews and meta-analyses

Outcome	Premenopausal nonadjusted for BMI	Premenopausal BMI-adjusted or normal weight groups	Postmenopausal nonadjusted for BMI	Postmenopausal BMI-adjusted
Obesity	+ (64)	----------	+ (9)	----------
Type 2 diabetes	+ (3, 68, 69)	+ (3, 52)	+ (9)	= (9)
Hypertension	+ (65, 69)	+ (65, 66)[a]	+ (9)	= (9, 65)
Dyslipidemia	+ (66, 69)	+ (66)[a]	+ (9)	+ (9)[b]
Metabolic syndrome	+ (52, 67, 70, 71)	+ [a] (67) = (67)[c]	+ (72)	= (72)
Cardiovascular disease	+ (3, 73)	+ (3)	= (9, 73)	= (9)
Coronary artery disease	+ (3)	+ (3)	= (9)	= (9)
Myocardial infarction	+ (3)	+ (3)	+ (9)	= (9)
Stroke	+ (3)	+ (3)	+ (9)	= (9)
Cardiovascular mortality	+ (3, 73)	+ (3)	= (74, 75)[d]	= (74, 75)[d]

Myocardial infarction	OR, 2.50; 95% CI, 1.43-4.38 (3)
Stroke	OR, 1.71; 95% CI, 1.20-2.44 (3)
Cardiovascular mortality	IRR, 1.26; 95% CI, 1.19-1.34 (3)

The Journal of Clinical Endocrinology & Metabolism. 2023 Oct 27



The Journal of Clinical Endocrinology & Metabolism. 2023 Oct 27

Agenda

- General aspects
- Insulin resistance
- Dyslipidemia
- Hypertension
- Metabolic syndrome
- Emerging risk factors
- Cardiovascular disease
- Postmenopausal changes
- Screening
- Recommendations

Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes.

Glycaemic status should be assessed at diagnosis in all adults and adolescents with PCOS.

Glycaemic status should be reassessed every 1-3 years, based on additional individual risk factors for diabetes.

Healthcare professionals, women with PCOS, and other stakeholders should prioritize preventative strategies to reduce type 2 diabetes risk.

Diabetes general population guidelines should consider the inclusion of PCOS as an independent risk factor for diabetes.

Screening for cardiovascular risk factors
(IGT & DM)

Women with type 1 and type 2 diabetes have an increased risk of PCOS, and screening should be considered in individuals with diabetes.

European journal of endocrinology. 2023 Aug;189(2):G43-64.

Screening for cardiovascular risk factors
(Glycemic testing)

Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS, regardless of BMI.

If an OGTT cannot be performed, fasting plasma glucose and/or glycated haemoglobin (HbA1c) could be considered, noting significantly reduced accuracy.

An OGTT should be considered in all women with PCOS and without pre-existing diabetes, when planning pregnancy or seeking fertility treatment. If not performed preconception, an OGTT could be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation.

Insulin resistance is a pathophysiological factor in PCOS; however, clinically available insulin assays are of limited clinical relevance and are not recommended in routine care

European journal of endocrinology. 2023 Aug;189(2):G43-64.

Screening for cardiovascular risk factors
(CVD risk)

Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality, acknowledging that the overall risk of cardiovascular disease in pre-menopausal women is low.

All women with PCOS should be assessed for cardiovascular disease risk factors.

All women with PCOS, regardless of age and BMI, should have a lipid profile (cholesterol, LDL, HDL, and triglyceride levels) at diagnosis. Thereafter, the frequency of measurement should be based on the presence of hyperlipidaemia and additional risk factors or global cardiovascular risk.

All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities.

Cardiovascular general population guidelines could consider the inclusion of PCOS as a cardiovascular risk factor.

European journal of endocrinology. 2023 Aug;189(2):G43-64.

Agenda

- General aspects
- Insulin resistance
- Dyslipidemia
- Hypertension
- Metabolic syndrome
- Emerging risk factors
- Cardiovascular disease
- Postmenopausal changes
- Screening
- Recommendations

Metformin

- Metformin use in obese PCOS women not undergoing lifestyle changes has been shown not to induce or only minimally induce (2.7 kg or 2.9%) weight loss.

- Studies have shown that the combination of metformin and lifestyle changes in obese PCOS women produce slightly more weight loss and a significantly higher reduction in visceral fat than lifestyle changes alone, with the effect of metformin on inducing weight loss being dose dependent.

- Conflicting results exist concerning the effect of metformin on lipid profiles in PCOS patients.

Gynecol Endocrinol. 2018 Feb;34(2):87-91.

The Effect of Metformin on Polycystic Ovary Syndrome in Overweight Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

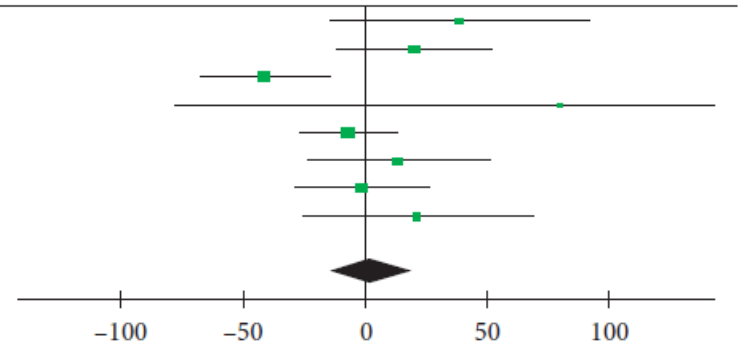
Yuanyuan Guan,[1] Dongjun Wang,[1] Huaien Bu,[2] Tieniu Zhao,[2] and Hongwu Wang[2]

Waist circumference
BMI
Fasting Insulin

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, random, 95% CI
Bonakdaran et al., 2012	98.903	105.17	17	59.899	34.825	16	8.3	39.00 (−13.82, 91.83)
Esfahanian et al., 2012	84.48	54.46	17	63.93	32.59	13	14.8	20.55 (−10.82, 51.92)
Fuxotta et al., 2010	65.61	35.73	15	106.6	37.33	15	16.9	−40.99 (−67.14, −14.84)
Gambineri et al., 2004	153	251	10	73	43	10	1.3	80.00 (−77.83, 237.83)
Gambineri et al., 2006	69.65	34.825	20	76.615	27.86	20	19.8	−6.96 (−26.51, 12.58)
Lord et al., 2006	120.84	61.98	16	106.98	43.87	16	12.6	13.86 (−23.35, 51.07)
Tang et al., 2005	80.7	115	69	81.8	14.723	74	16.4	−1.10 (−28.44, 26.24)
Yarali et al., 2002	94.8	128.4	32	73.2	42	32	9.8	21.60 (−25.21, 68.41)
Total (95% CI)			*196*			*196*	*100.0*	*2.70 (−15.93, 21.33)*

Heterogeneity: tau^2 = 355.80; chi^2 = 15.79, df = 7 (P = 0.03); I^2 = 56%
Test for overall effect: Z = 0.28 (P = 0.78)

Mean difference
Mean difference
IV, random, 95% CI



Favours (experimental) Favours (control)

Test for overall effect: Z = 7.16 (P < 0.00001)

Favours (experimental) Favours (control)

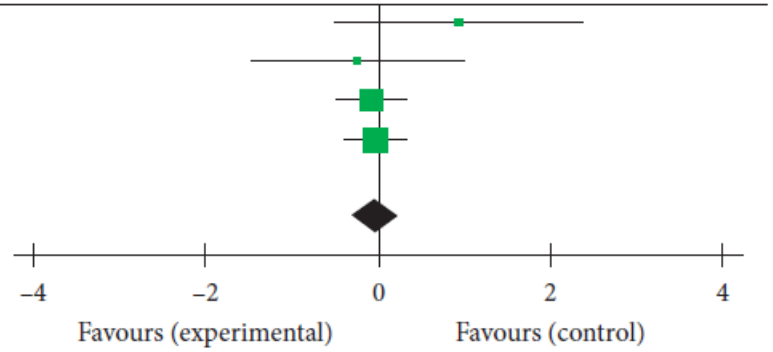
International journal of endocrinology. 2020;2020.

The Effect of Metformin on Polycystic Ovary Syndrome in Overweight Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Yuanyuan Guan,[1] Dongjun Wang,[1] Huaien Bu,[2] Tieniu Zhao,[2] and Hongwu Wang[2]

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, fixed, 95% CI
Esfahanian et al., 2012	3.7	1.79	17	2.75	2.11	13	3.3	0.95 (−0.48, 2.38)
Fuxotta et al., 2010	2.97	1.82	15	3.2	1.6	15	4.4	−0.23 (−1.46, 1.00)
Gambineri et al., 2004	1.05	0.37	10	1.12	0.53	10	41.4	−0.07 (−0.47, 0.33)
Tang et al., 2005	2.04	1.01	69	2.07	1.19	74	51.0	−0.03 (−0.39, 0.33)
Total (95% CI)			*111*			*112*	*100.0*	*−0.02 (−0.28, 0.23)*

Heterogeneity: chi^2 = 1.95, df = 3 (P = 0.58); I^2 = 0%
Test for overall effect: Z = 0.18 (P = 0.86)



International journal of endocrinology. 2020;2020.

Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric and metabolic outcomes including insulin resistance, glucose, and lipid profiles.

Metformin

Where metformin is prescribed, the following need to be considered:

- Active lifestyle intervention should be encouraged. Women should be informed that metformin and active lifestyle intervention have similar efficacy.
- Mild adverse effects, including gastrointestinal side-effects, are generally dose dependent and self-limiting.
- Starting at a low dose, with 500 mg increments 1-2 weekly and extended-release preparations, may minimize side effects and improve adherence.
- Suggested maximum daily dose is 2.5 g in adults and 2 g in adolescents.
- Use may be associated with low vitamin B12 levels, especially in those with risk factors for low vitamin B12 (eg, diabetes, post bariatric/metabolic surgery, pernicious anaemia, and vegan diet), where monitoring should be considered.

European journal of endocrinology. 2023 Aug;189(2):G43-64.

Statins

- Several studies have shown that, in women with PCOS, statins diminish IR and inflammation, lower serum total and free testosterone levels, and improve endothelial dysfunction. However, due to teratogenicity, and contraception is required.
- In selected patients with severe dyslipidemia that is not adequately corrected by lifestyle modification and statins, dual pharmacotherapy may be required.
- Statins combined with a fibrate may be necessary when hypertriglyceridemia and low HDL levels coexist.
- Fenofibrat is preferred because of fewer drug interactions and the decreased risk of myopathy.

- Omega-3 fatty acids (4 g daily, pharmacy grade) are Food and Drug Administration (FDA) approved for serum triglyceride levels greater than 500 mg/dl.

The Journal of Clinical Endocrinology & Metabolism. 2010 May 1;95(5):2038-49.

THE JOURNAL OF
Obstetrics and Gynaecology Research

Original Article

Effect of statins combined or not combined with metformin on polycystic ovary syndrome: A systematic review and meta-analysis

Keyan Miao, Hui Zhou

- Meta-analysis showed significant decline of total testosterone, free testosterone, dehydroepiandrosterone sulphate, androstenedione, luteinizing hormone (LH), LH to follicle-stimulating hormone (FSH) ratio, and prolactin in statin group.
- Our study also demonstrated significant decline of total cholesterol, low-density lipoprotein cholesterol, and triglycerides in statin group.
- Moreover, we found significant decline of fasting glucose, insulin sensitivity index, and high-sensitivity C-reactive protein.

J Obstet Gynaecol Res. 2022 Jul;48(7):1806-1815

Oral contraceptive pills (OCPs)

- OCPs deteriorate the cardiovascular risk and metabolic profile and therefore their use in PCOS women is a matter of concern.

- The impact of OCPs on glucose metabolism depends on several factors: estrogen dose, body type and genetic predispositions of the patient, progestin component of the OCP, environment, and the natural progression of PCOS in each particular patient.

- Estrogen has been shown to impair insulin action in a dose dependent manner.

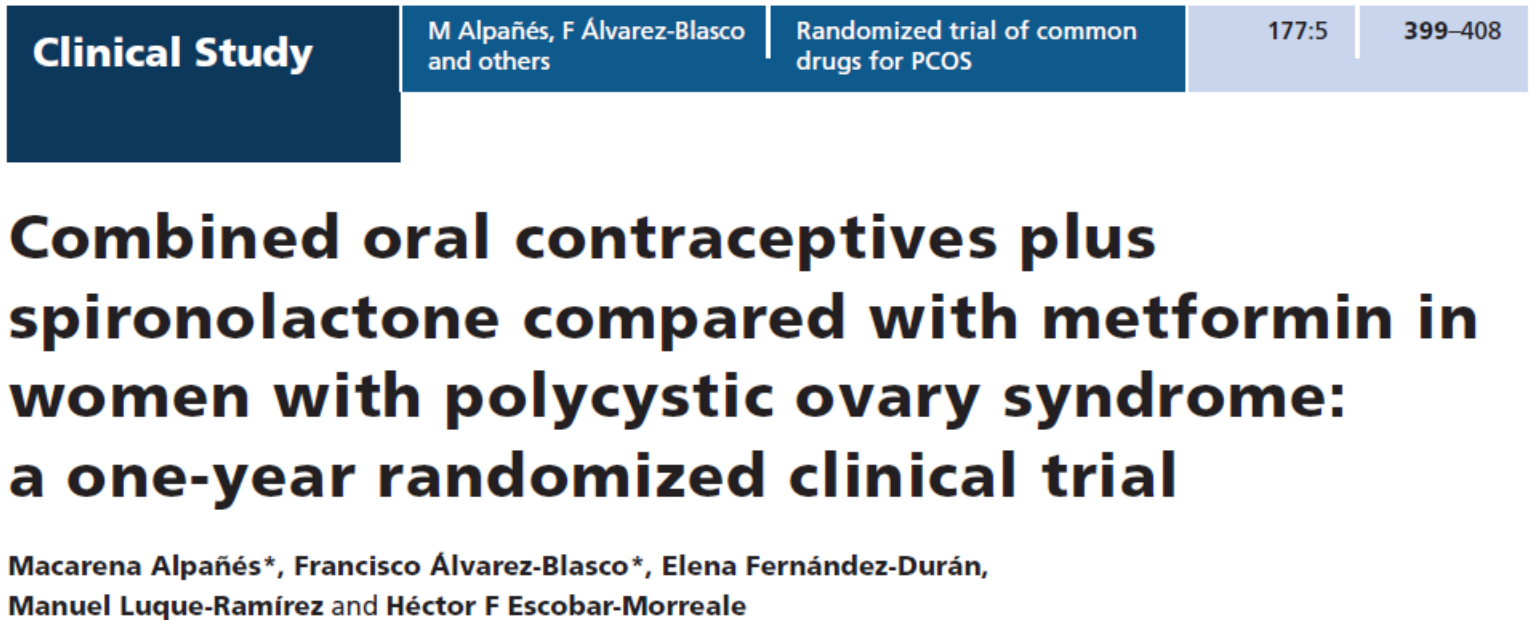
- The nature of the progestin component of an OCP, such as whether it is androgen-like or not, also influences metabolic parameters.

- Studies have shown that those progestins with androgen-like effects increase abdominal visceral fat.
- Considering lipid profile, increased TG levels are the most common side effect of OCP use in women with PCOS, irrespective of age and BM.

- The estrogen component is thought to cause this by lowering TG clearance by the liver.

- However, the estrogen component also has the beneficial effect of raising HDL-C by increasing the hepatic expression of the apoliprotein A–I gene, which in turn enhances HDL-C production.

Anti androgens



Clinical Study | M Alpañés, F Álvarez-Blasco and others | Randomized trial of common drugs for PCOS | 177:5 | 399–408

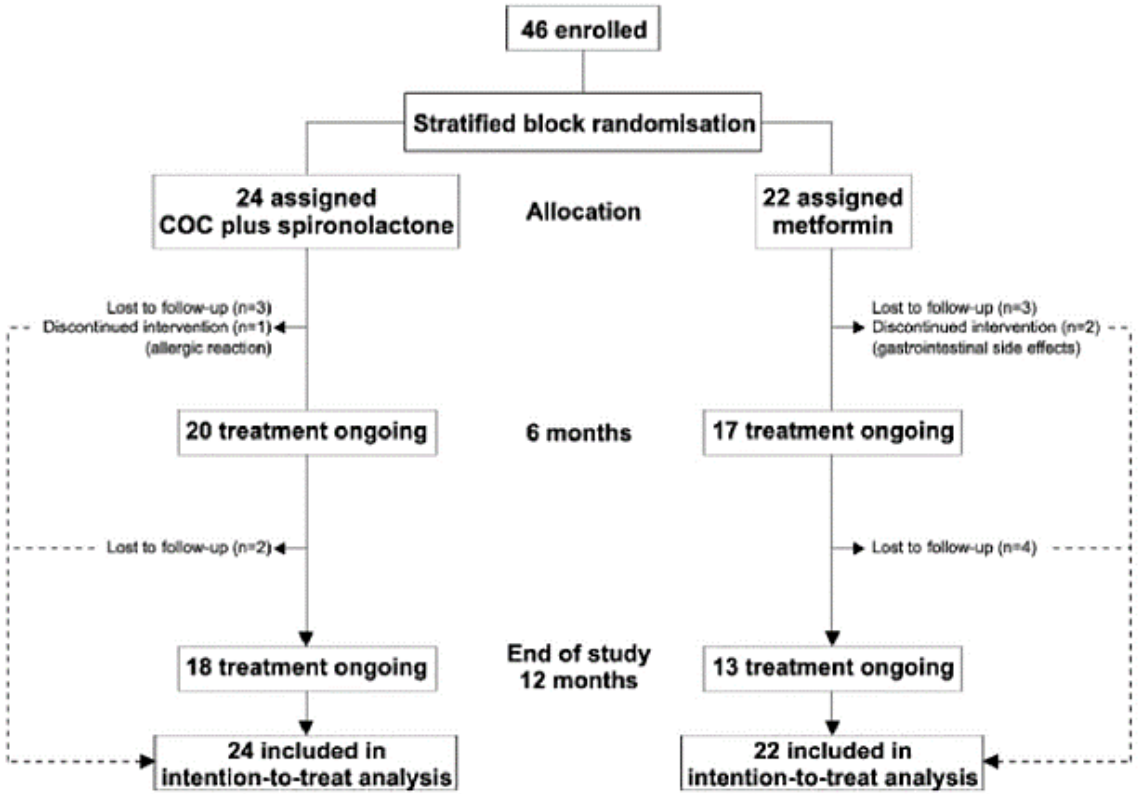
Combined oral contraceptives plus spironolactone compared with metformin in women with polycystic ovary syndrome: a one-year randomized clinical trial

Macarena Alpañés*, Francisco Álvarez-Blasco*, Elena Fernández-Durán, Manuel Luque-Ramírez and **Héctor F Escobar-Morreale**

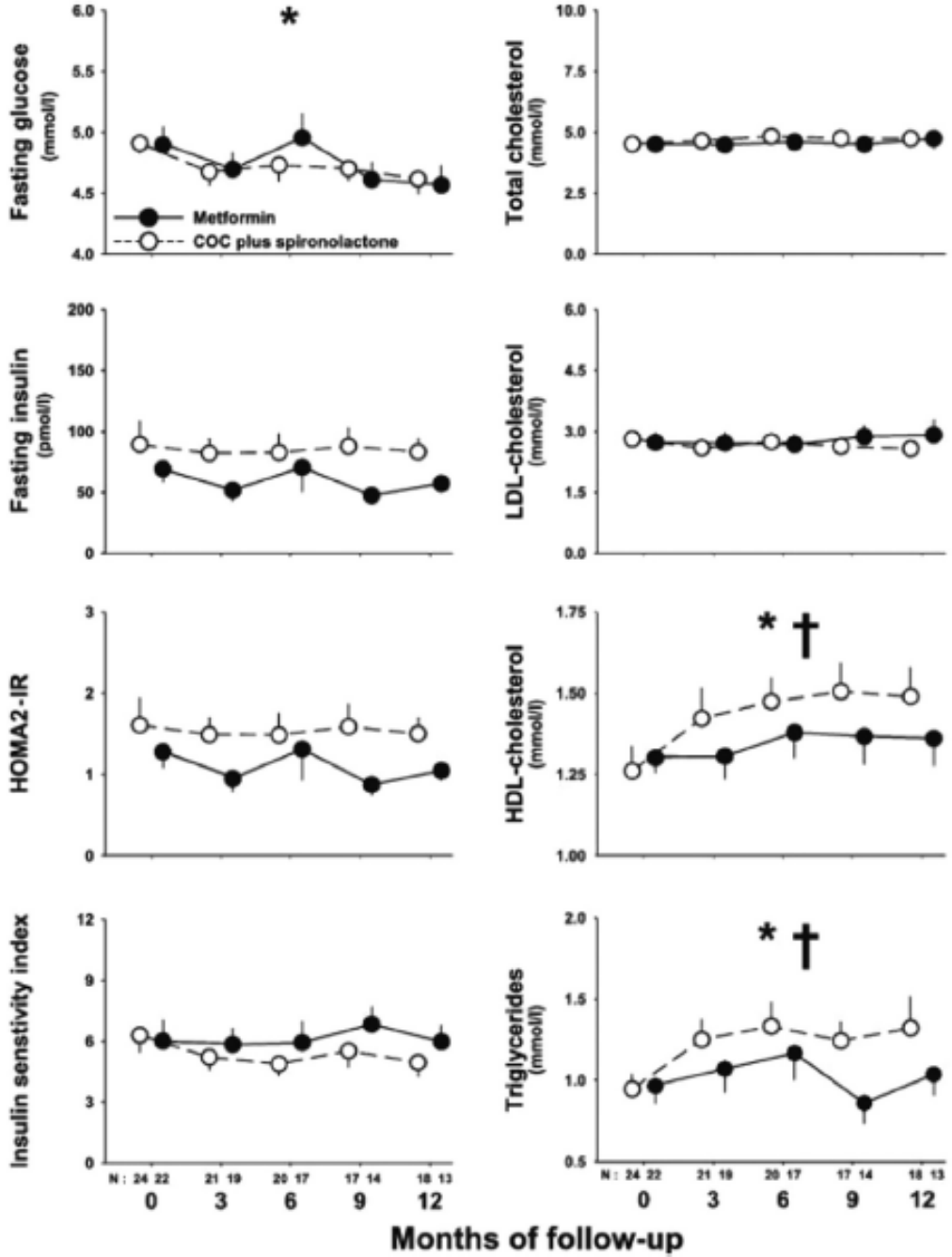
European journal of endocrinology. 2017 Nov;177(5):399-408.

	COC plus spironolactone ($n=24$)	Metformin ($n=22$)
Age (years)	25±5	23±6
Menarche (years)	12±2	12±2
Body mass index (kg/m^2)	30.6±7.9	31.2±9.0
Waist (cm)	87±16	88±18
Waist-to-hip ratio	0.78±0.08	0.78±0.08
Systolic blood pressure (mmHg)	116±11	118±16
Diastolic blood pressure (mmHg)	73±7	77±11
Hirsutism score	10±5	13±7
Total testosterone (nmol/L)	2.6±0.8	2.4±0.8
Free testosterone (pmol/L)	44.9±15.9	46.8±23.5
Sex hormone-binding globulin (nmol/L)	41.4±21.4	32.2±15.7
Androstenedione (nmol/L)	13.8±5.0	13.8±6.4
Dehydroepiandrosterone sulfate (μmol/L)	6.5±2.4	7.2±3.1
Estradiol (pmol/L)	184±121	217±224
Total cholesterol (mmol/L)	4.5±1.0	4.5±1.4
LDL cholesterol (mmol/L)	2.8±0.8	2.7±1.3
HDL cholesterol (mmol/L)	1.3±0.4	1.3±0.2
Triglycerides (mmol/L)	1.0±0.5	1.0±0.5
Fasting insulin (pmol/L)	89±97	69±51
Fasting glucose (mmol/L)	4.9±0.4	4.9±0.7
HOMA2-IR	1.6±1.7	1.3±0.9
Insulin sensitivity index	6.7±5.1	7.0±5.5

HDL, high-density lipoprotein; HOMA2-IR, homeostasis model assessment 2 of insulin resistance; LDL, low-density lipoprotein.



European journal of endocrinology. 2017 Nov;177(5):399-408.



European journal of endocrinology. 2017 Nov;177(5):399-408.

Anti obesity medications

Anti-obesity medications, including liraglutide, semaglutide, and both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.

Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.

Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects.

Different studies have shown improvement in menstural cycles and the rate of natural pregnancies along with positive cardiometabolic effects.

European journal of endocrinology. 2023 Aug;189(2):G43-64.

Sodium glucose cotransporter 2 inhibitors

Journal of
Clinical Medicine

MDPI

Review

The Role of Sodium-Glucose Cotransporter-2 Inhibitors in the Treatment of Polycystic Ovary Syndrome: A Review

Rachel Porth [1,†], Karina Oelerich [1,†] and Mala S. Sivanandy [1,2,*]

J. Clin. Med. **2024**, 13, 1056

Table 1. Key characteristics of the randomized controlled trials that utilized SGLT2 inhibitors in women with PCOS.

	Cai et al. [31]	Elkind-Hirsch et al. [32]	Javed et al. [33]	Tan et al. [34]	Zhang et al. [35]
SGLT2 inhibitor	Canagliflozin 100 mg daily	Dapagliflozin 10 mg daily	Empagliflozin 25 mg daily	Licogliflozin 50 mg three times daily	Canagliflozin 100 mg daily (with Metformin 1000 mg twice a day)
Comparison Arm	M	E, E/D, D/M, P/T	M	P	M
Number of participants	C: 33 M: 35	E: 20 D/E: 20 D: 17 D/M: 19 PH/T:16	EM: 19 M: 20	L: 10 P: 10	C/M: 21 M: 20
Study duration (weeks)	12	24	12	2	12
BMI (kg/m^2)	C: 27.26 (25.55 to 28.99) M: 27.95 (26.22 to 29.69)	E: 38.6 ± 1.1 E/D: 39.9 ± 0.9 D: 38 ± 1.1 D/M: 37.6 ± 1.1 P/T: 38.4 ± 1.1	EM: 37.1 ± 6.2 M: 38.7 ± 7.8	38.1 ± 6.3	C/M: 31.11 ± 3.02 M: 29.33 ± 3.19
Age (years)	C: 28.58 (26.72 to 30.43) M: 27.83 (25.97 to 29.68)	E: 30 ± 1.1 E/D: 31 ± 1.4 D: 28 ± 1.5 D/M: 31 ± 1.6 PH/T: 30 ± 1.5	EM: 26.0 (8.0) M: 31.5 (20.0)	27.6 ± 5.3	C/M: 26.38 ± 5.89 M: 25.5 ± 4.36

Table 2. Comparison of the Changes in Hormonal Parameters in the trials that used SGLT2 inhibitors in women with PCOS.

	Cai et al. [31]	Elkind-Hirsch et al. [32]	Javed et al. [33]	Tan et al. [34]	Zhang et al. [35]
SGLT1/2 inhibitor	Canagliflozin	Dapagliflozin	Empagliflozin	Licogliflozin	Canagliflozin (with Metformin)
Total Testosterone	Pre-treatment: 1.78 ng/mL (1.52 to 2.05) LS mean −0.15 (−0.38 to 0.08)	Pre-treatment: 46 ng/dL ± 5 Post-treatment: 35 ng/dL ± 4.4 (−11) *	Pre-treatment: 1.6 nmol/L ± 0.4 Post-treatment: 1.6 nmol/L ± 0.6	Effect size: 9% decrease in (TR_{LIK066}:TR_{PCB} [TT]: 0.91; 90% CI: 0.77–1.07; p = 0.340)	Pre-treatment: 0.95 ng/mL (0.78–1.08) Post-treatment: 0.53 ng/mL (0.45–0.84) *
Free Androgen Index	n/a	Pre-treatment: 6.7 ± 1.0 Post-treatment: 4.7 ± 0.8 (−2.0) *	Pre-treatment: 10.3 ± 3.0 Post-treatment: 9.4 ± 3.6	n/a	Pre-treatment: 28.62% ± 16.4 Post-treatment: 19.15% ± 13.19 *
DHEAS	Pre-treatment: 261.80 ug/dL (217.77 to 305.83) LS mean −68.96 (−126.36 to −11.55) **	Pre-treatment: 210 mcg/dL ± 22 Post-treatment: 187 mcg/dL ± 24 (−23)	Pre-treatment: 6.1 µmol/L ± 1.6 Post-treatment: 6.2 µmol/L ± 2.1	Effect size: 24% decrease in (TR_{LIK066}:TR_{PCB} [DHEAS]: 0.76; 90% CI: 0.65–0.89; p = 0.008 *	n/a
Androstenedione	Pre-treatment: 4.17 ng/mL (3.53 to 4.81) LS mean −0.48 (−1.04 to 0.09)	n/a	Pre-treatment: 5.7 nmol/L ± 1.4 Post-treatment: 5.7 n µmol/L ± 1.9	Effect size: 19% decrease in (TR_{LIK066}:TR_{PCB} [A4]: 0.81; 90% CI: 0.68–0.99; p = 0.089)	Pre-treatment: 3.57 ng/mL ± 1.29 Post-treatment: 3.22 ng/mL ± 1.35
SHBG	Pre-treatment 33.76 nmol/L (21.64 to 45.89) LS mean −4.82 (−19.40 to 9.75)	Significantly increased *—no data provided by paper	Pre-treatment: 17.3 nmol/L ± 6.4 Post-treatment: 19.2 nmol/L ± 8.5 *	Effect size: 15% increase in (TR_{LIK066}:TR_{PCB} [SHBG]: 1.15; 90% CI: 0.97–1.36; p = 0.173)	Pre-treatment: 13.60 nmol/L (8.55–20.15) Post-treatment: 13.6 nmol/L (9.55–24.10)
Free testosterone	Pre-treatment 2.40 pg/mL (1.92 to 2.88) LS mean 0.30 (−0.30 to 0.89)	n/a	n/a	Effect size: 12% decrease in (TR_{LIK066}: TR_{PCB}[FT]: 0.88; 90% CI: 0.70–1.11; p = 0.353)	n/a

Table 3. Comparison of the changes in anthropometric parameters and BMI in studies that used SGLT2 inhibitors in women with PCOS.

	Cai et al. [31]	Elkind-Hirsch et al. [32]	Javed et al. [33]	Zhang et al. [35]
SGLT2 inhibitor	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin (with Metformin)
BMI (kg/m^2)				
Pretreatment	27.26 (25.55 to 28.99)	38 ± 1.1	37.1 ± 6.2	31.11 ± 3.02
Posttreatment	LS Mean: −1.04 (−1.56 to −0.53)	37.4 ± 1.2 (−0.6) *	36.6 ± 6.0	28.62 ± 2.91 *
Weight (kg)				
Pretreatment	72.94 (67.89 to 77.99)	104 ± 3	102.3 ± 16.6	81.23 ± 9.83
Posttreatment	LS Mean: −2.82 (−3.97 to −1.66)	102.6 ± 4 (−1.4) *	101.5 ± 16.3	75.40 ± 8.68 *
Waist Circumference (cm)				
Pretreatment	92.87 (88.00 to 97.75)	104 ± 3	101.2 ± 9.7	n/a
Posttreatment	LS Mean: −4.05 (−6.18 to −1.91)	101 ± 3.2 (−3)	99.6 ± 9.5 *	
Waist-to-hip ratio				
Pretreatment	0.91 (0.88 to 0.93)	0.81 ± 0.02	n/a	n/a
Posttreatment	LS Mean: −0.02 (−0.04 to 0.00)	0.79 ± 0.017 (−0.02)	n/a	n/a

Table 4. Changes in glycemic indices in the trials that employed SGLT2 Inhibitors in women with PCOS.

	Cai et al. [31]	Elkind-Hirsch et al. [32]	Javed et al. [33]	Zhang et al. [35]
SGLT2 inhibitor	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin (with Metformin)
Hemoglobin A1c (HbA1c)%				
Pretreatment	5.60 (5.37 to 5.83)	n/a	n/a	n/a
Posttreatment	Change from baseline LS mean: −0.26 (−0.43 to −0.09)	n/a	n/a	n/a
HOMA-IR				
Pretreatment	5.33 (3.92 to 6.73)	4.1 ± 0.7	2.6 (2.1)	5.70 (3.38–6.08)
Posttreatment	Change from baseline LS mean: −2.04 (−2.89 to −1.18)	3.4 ± 0.6 (−0.7) *	2.4 (2.7)	3.14 (1.91–4.71) *
FBG				
Pretreatment	5.18 mmol/L (4.99 to 5.38)	98 mg/dL ± 2.3	4.5 mmol/L (0.6)	5.70 mmol/L (5.27–6.02)
Posttreatment	Change from baseline LS mean: −0.23 (−0.40 to −0.06)	93 mg/dL ± 2.1 (−5) *	4.5 mmol/L (0.6)	5.20 mmol/L (4.88–5.35)
FINS				
Pretreatment	22.58 mU/L (16.99 to 28.17)	n/a	12.6 µIU/mL (11.6)	21.5 mU/L (14.35–24.20)
Posttreatment	Change from baseline LS mean: −7.70 (−11.46 to −3.94)	n/a	12.7 µIU/mL (14.4)	12.0 mU/L (8.20–20.15) *

Table 5. Changes in metabolic parameters in the studies that used SGLT2 inhibitors in women with PCOS.

	Cai et al. [31]	Elkind-Hirsch et al. [32]	Javed et al. [33]	Zhang et al. [35]
SGLT2 inhibitor	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin (with Metformin)
Total Cholesterol				
Pretreatment	4.87 mmol/L (4.58 to 5.16)	183 mg/dL ± 6	4.8 mmol/L ± 1.0	4.90 mmol/L ± 0.93
Posttreatment	LS mean: 0.17 mmol/L (−0.05 to 0.39)	186 mg/dL ± 11 (+3.0)	4.7 mmol/L ± 1.1	4.54 mmol/L ± 0.80 *
Triglycerides				
Pretreatment	1.75 mmol/L (1.37 to 2.14)	143 mg/dL ± 21	1.5 mmol/L (1.3)	1.54 mmol/L (1.09–2.01)
Posttreatment	LS mean: −0.36 mmol/L (−0.54 to −0.17)	n/a	1.4 mmol/L (0.9)	1.20 mmol/L (0.84–1.63) *
LDL				
Pretreatment	3.04 mmol/L (2.66 to 3.43)	107 mg/dL ± 6	2.8 mmol/L ± 1.0	3.06 mmol/L ± 0.97
Posttreatment	LS mean: 0.22 mmol/L (0.06 to 0.51)	113.5 mg/dL ± 10 (6.5)	2.7 mmol/L ± 1.1	2.83 mmol/L ± 0.70
HDL				
Pretreatment	1.33 mmol/L (1.12 to 1.54)	44 mg/dL ± 2	1.1 mmol/L ± 0.2	-
Posttreatment	LS mean: 0.02 mmol/L (−0.17 to 0.13)	43 mg/dL ± 2.2 (−1.0)	1.1 mmol/L ± 0.2	-