Polycystic Ovary Syndrome & Cardiometabolic Risk

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Disclosures

Grant funding – NIH

Consultant - Medtronic, AbbVie, Ferring

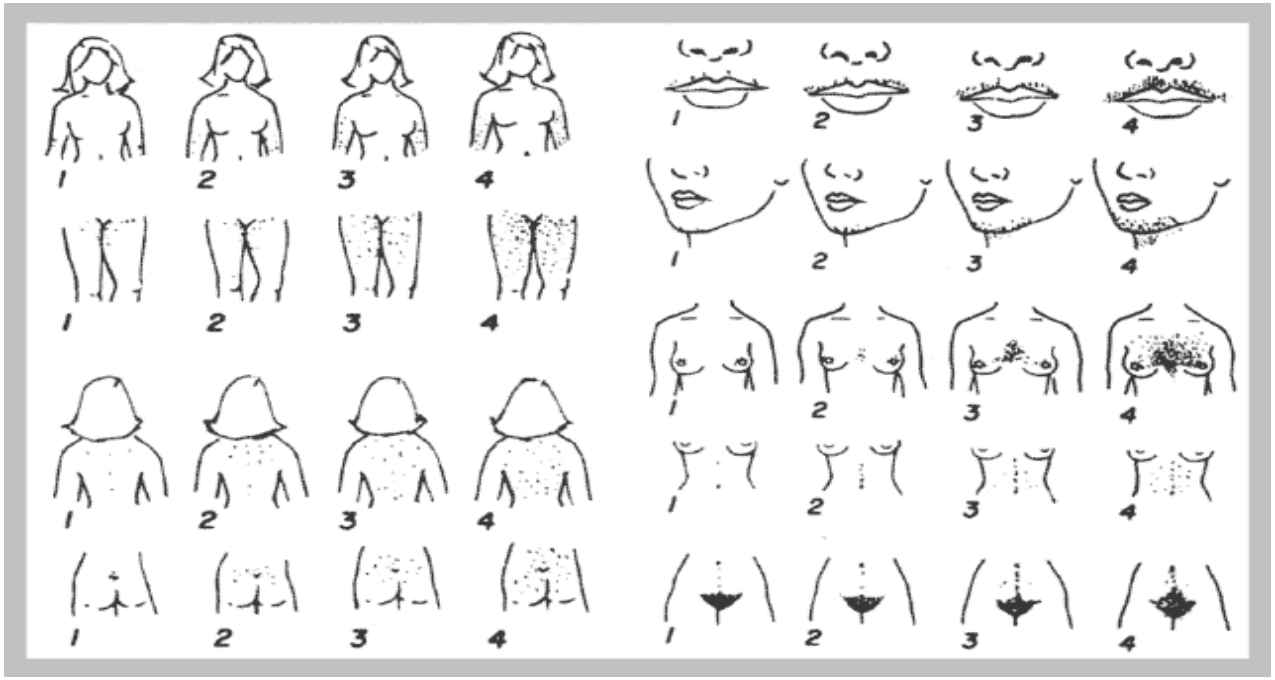
Rotterdam Criteria

1. Oligo-ovulation or anovulation
2. Clinical or biochemical signs of hyperandrogenism
3. Polycystic ovaries on ultrasound

any two of above three
(exclusion of TSH, Prolactin, 17 OH progesterone, DHEAS)

Most common endocrine disorder in reproductive age women
8-13%

Human Reproduction 2018 Sep 1;33(9):1602-1618
Fertil Steril 2018 Aug;110(3):364-379.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2
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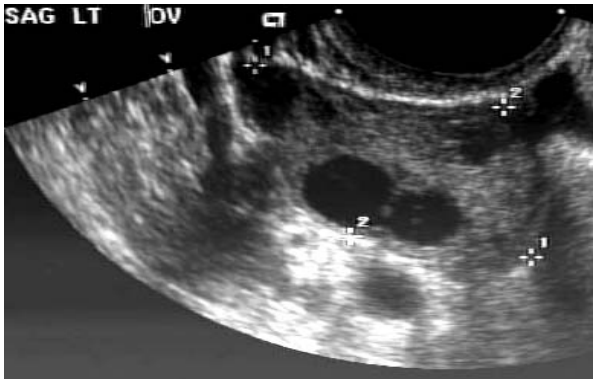
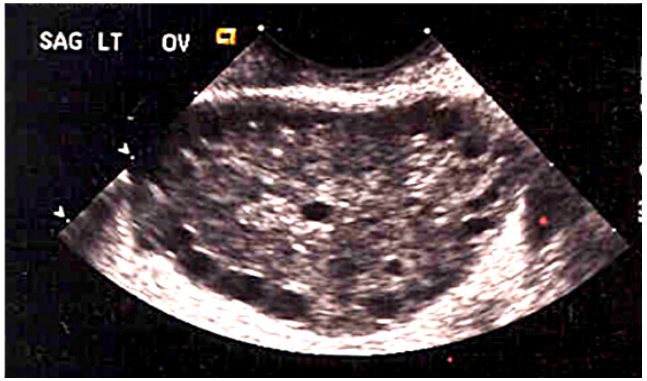
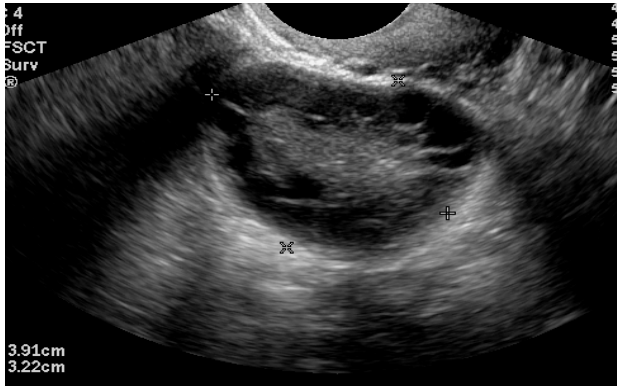
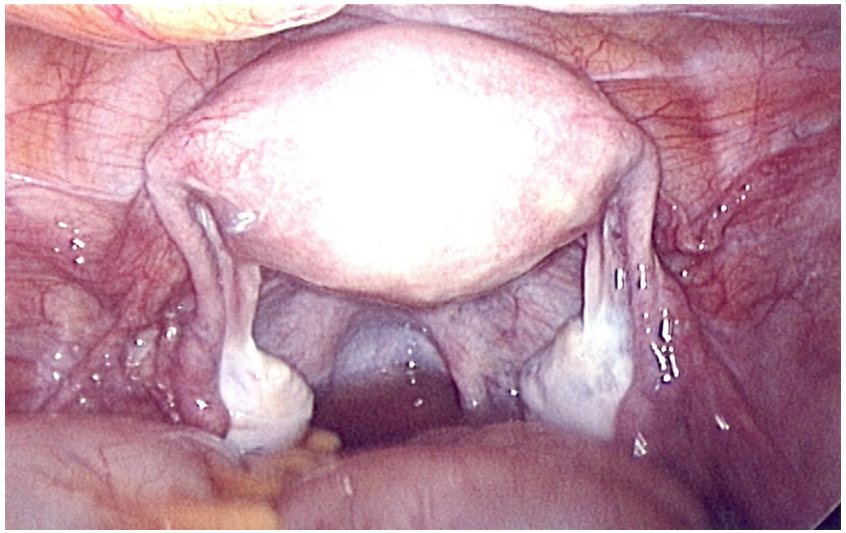
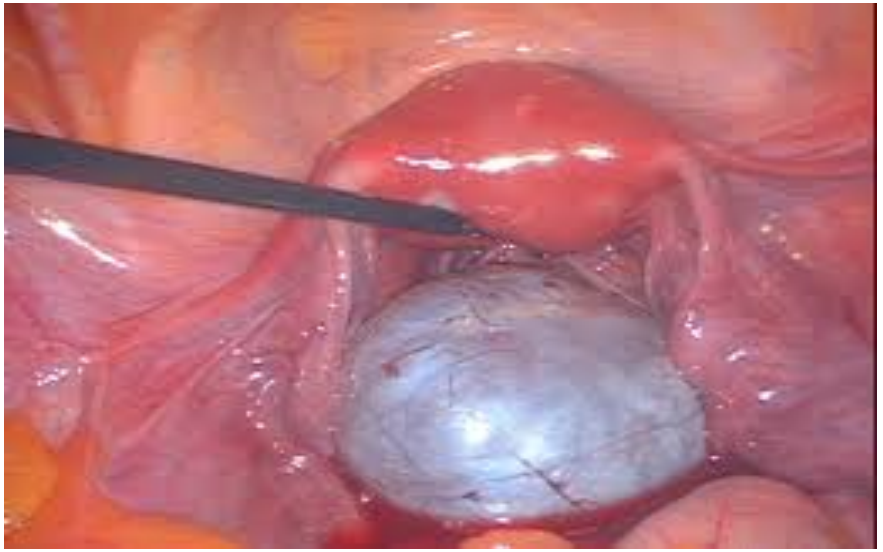
Ultrasound Morphology of Ovaries





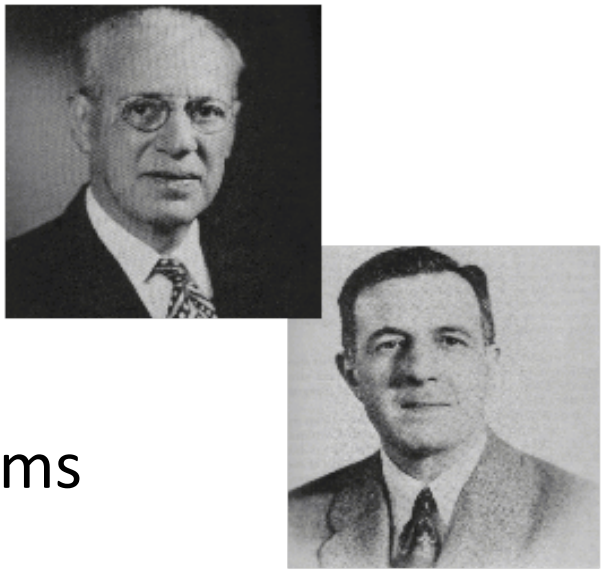






THERE IS NO OVARIAN CYST!

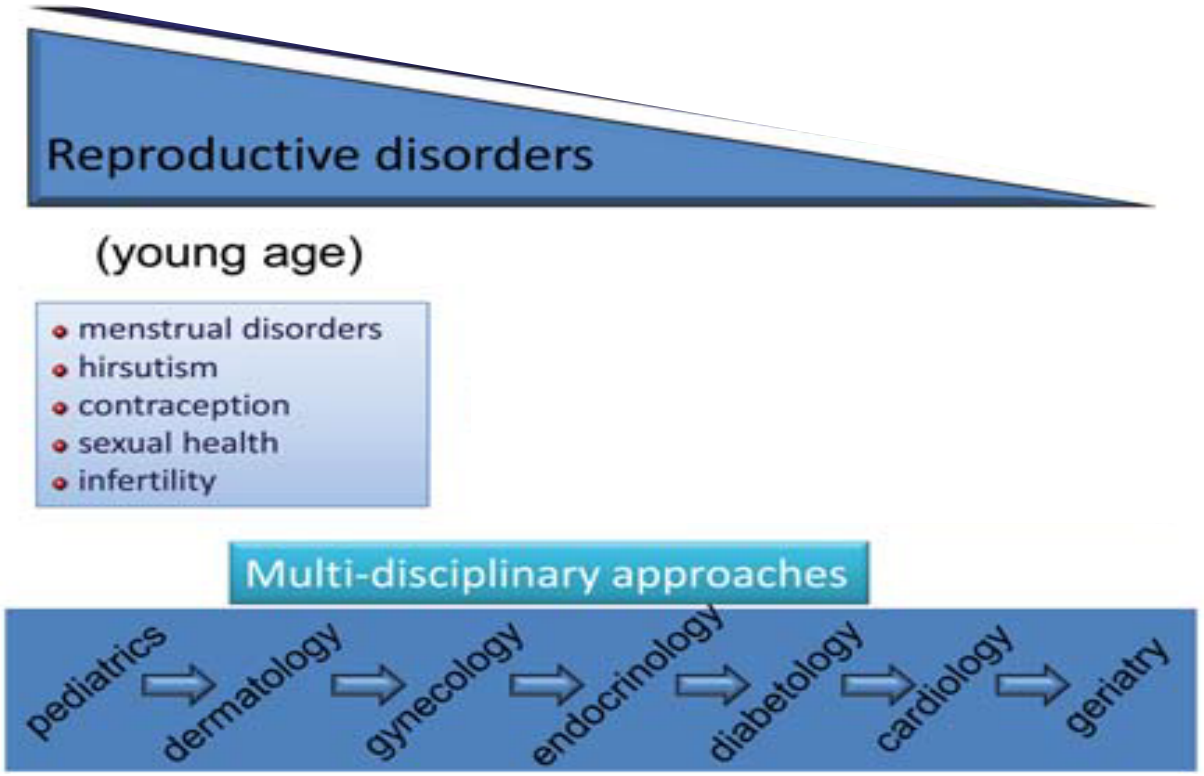
Diagnostic Dilemmas



- Changing definitions
- Heterogeneous - phenotypes
- Age of diagnosis - changing symptoms
- Race/Ethnicity

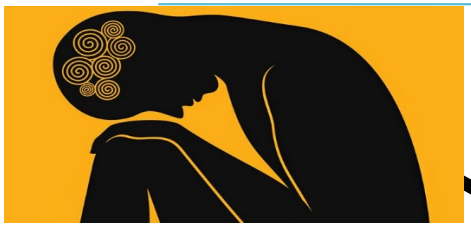
Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol, 1935; 29: 181-91.

A Changing Paradigm in PCOS



Human Reproduction 27:14-24 (2012)

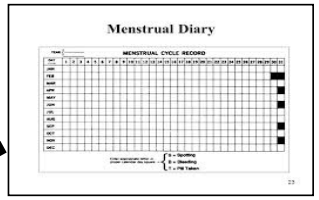
Mood disorders



Infertility

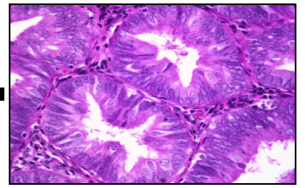
Hirsuitism

Oligomenorrhea



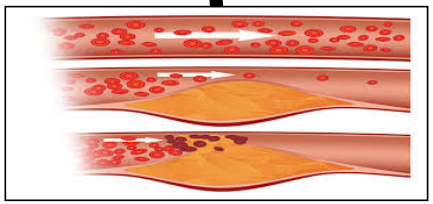
OBESITY

Preeclampsia

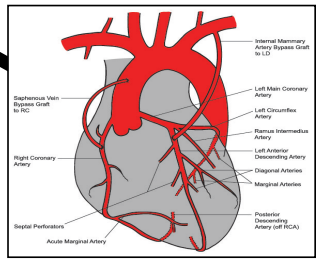


Endometrial hyperplasia

Glucose intolerance

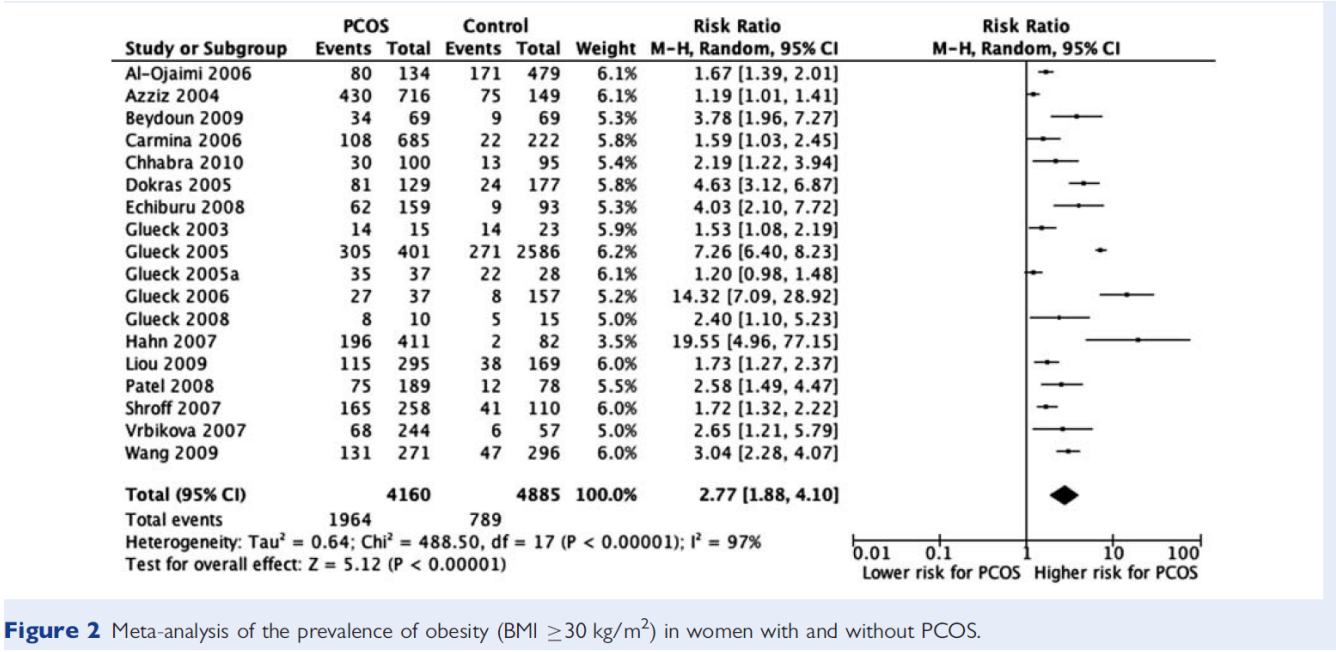


Hyperlipidemia



Cardiovascular disease risk

Obesity Increased in PCOS



Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Ojaimi 2006	80	134	171	479	6.1%	1.67 [1.39, 2.01]
Azziz 2004	430	716	75	149	6.1%	1.19 [1.01, 1.41]
Beydoun 2009	34	69	9	69	5.3%	3.78 [1.96, 7.27]
Carmina 2006	108	685	22	222	5.8%	1.59 [1.03, 2.45]
Chhabra 2010	30	100	13	95	5.4%	2.19 [1.22, 3.94]
Dokras 2005	81	129	24	177	5.8%	4.63 [3.12, 6.87]
Echiburu 2008	62	159	9	93	5.3%	4.03 [2.10, 7.72]
Glueck 2003	14	15	14	23	5.9%	1.53 [1.08, 2.19]
Glueck 2005	305	401	271	2586	6.2%	7.26 [6.40, 8.23]
Glueck 2005a	35	37	22	28	6.1%	1.20 [0.98, 1.48]
Glueck 2006	27	37	8	157	5.2%	14.32 [7.09, 28.92]
Glueck 2008	8	10	5	15	5.0%	2.40 [1.10, 5.23]
Hahn 2007	196	411	2	82	3.5%	19.55 [4.96, 77.15]
Liou 2009	115	295	38	169	6.0%	1.73 [1.27, 2.37]
Patel 2008	75	189	12	78	5.5%	2.58 [1.49, 4.47]
Shroff 2007	165	258	41	110	6.0%	1.72 [1.32, 2.22]
Vrbikova 2007	68	244	6	57	5.0%	2.65 [1.21, 5.79]
Wang 2009	131	271	47	296	6.0%	3.04 [2.28, 4.07]
Total (95% CI)		**4160**		**4885**	**100.0%**	**2.77 [1.88, 4.10]**
Total events	1964		789			

Heterogeneity: $Tau^2 = 0.64$; $Chi^2 = 488.50$, df = 17 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 5.12$ ($P < 0.00001$)

Figure 2 Meta-analysis of the prevalence of obesity (BMI $\geq$30 kg/m^2) in women with and without PCOS.

OR 2.77 (95%CI 1.88-4.1)

Lin et al, HRU, 2012

Obesity High in PCOS Adolescents

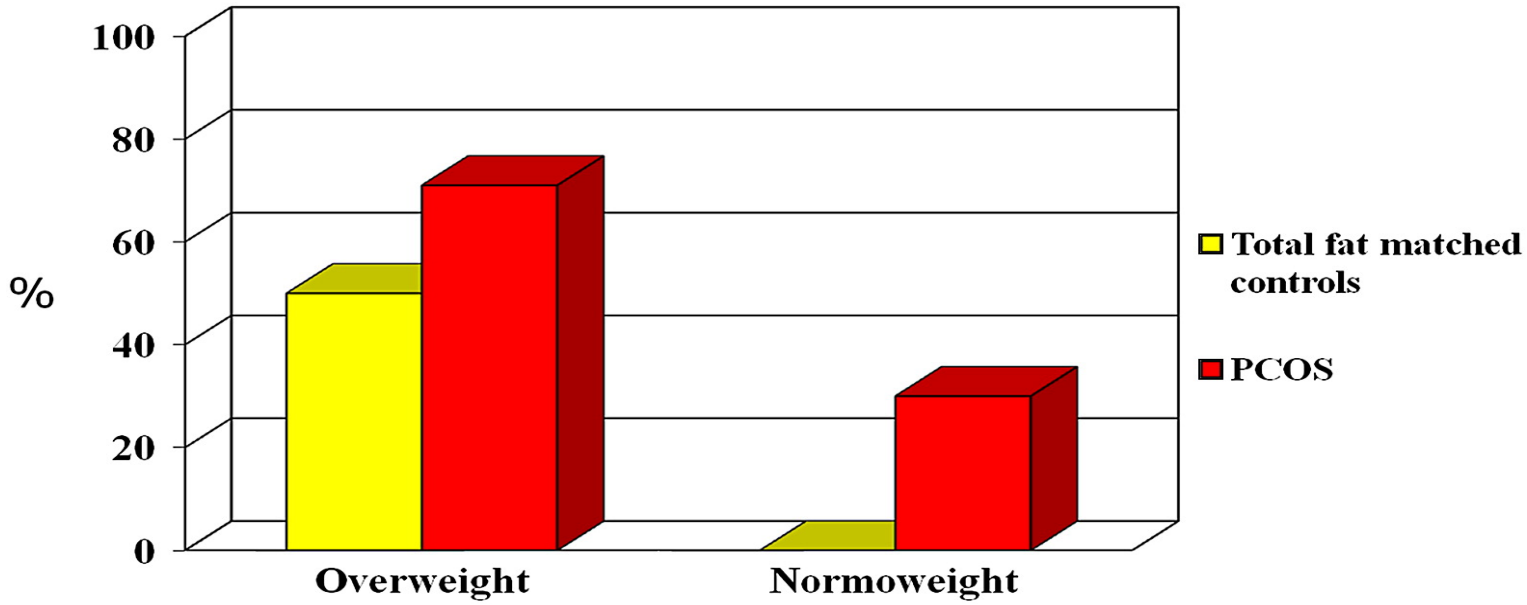
Table I Features of PCOS in adolescence according to three international adult diagnostic criteria (Hickey, 2009).

	All	PCOS-R[a]			PCOS-N[a]			PCOS-AES[a]		
	n = 232	No (*n* = 179)	Yes (*n* = 48)	*P*	No (*n* = 216)	Yes (*n* = 10)	*P*	No (*n* = 216)	Yes (*n* = 11)	*P*
Current age (years)	15.2 (0.48)	15.2 (0.43)	15.4 (0.62)	0.099	15.2 (0.45)	15.7 (0.72)	0.001	15.2 (0.43)	15.9 (0.89)	*<0.001*
Age at menarche (years)	12.5 (1.2)	12.6 (1.2)	12.4 (1.1)	0.361	12.5 (1.2)	11.9 (1.4)	0.165	12.6 (1.2)	11.8 (1.3)	*0.112*
Months since menarche	32.2 (15.0)	31.3 (15.0)	35.4 (15.0)	0.092	31.8 (15.0)	46.1 (17.0)	0.026	31.5 (14.4)	48.4 (17.8)	*0.010*
BMI (kg/m^2)	22.7 (3.8)	22.3 (3.0)	24.5 (5.7)	<0.001	22.4 (3.4)	29.4 (6.8)	<0.001	22.5 (3.4)	28.8 (6.7)	*<0.001*
BMI (z-score)	0.54 (0.8)	0.48 (0.8)	0.77 (0.9)	0.026	0.50 (0.8)	1.45 (0.9)	0.008	0.50 (0.8)	1.37 (0.9)	*0.009*
BMI, *n* (%)										
Normal	163 (70.3)	134 (74.9)	26 (54.2)	<0.001	157 (72.7)	2 (20.0)	<0.001	153 (70.8)	3 (27.3)	*<0.001*
Overweight	48 (20.7)	37 (20.7)	10 (20.8)		44 (20.4)	3 (30.0)		44 (20.4)	3 (27.3)	
Obese	19 (8.2)	7 (3.9)	11 (22.9)		13 (6.0)	5 (50.0)		13 (6.0)	5 (45.5)	

Hickey et al, 2011, Hum Reprod

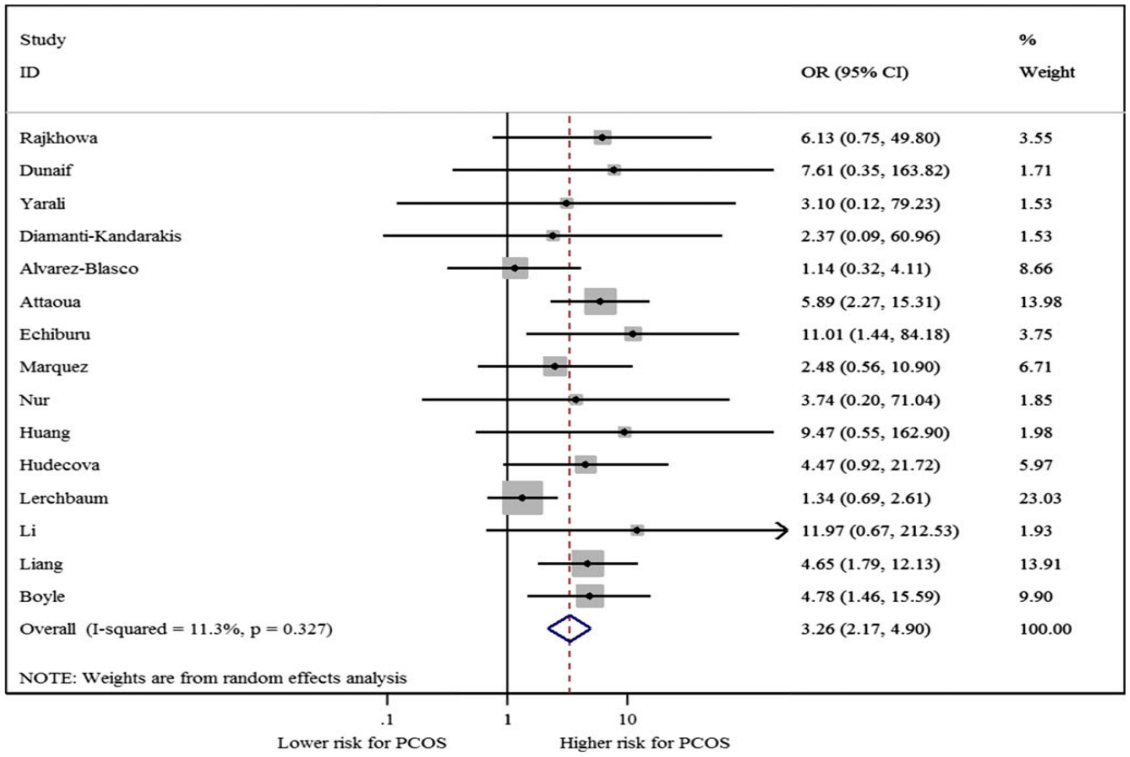
Abdominal Adiposity in PCOS

Prevalence of abdominal adiposity in
normal and overweight women



Jovanovic et al. Fert Steril 2010 Aug

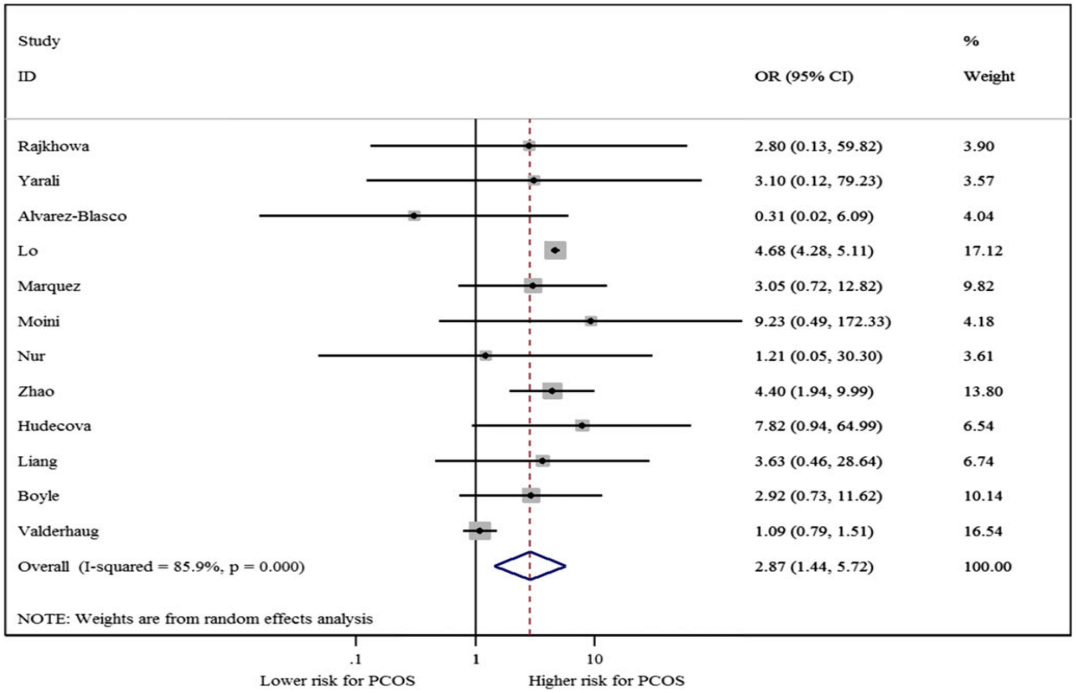
PCOS – Impaired Glucose Tolerance



OR 3.26 (2.17-4.9) Prevalence 6-35%

Kakoly et al, 2018, Hum Reprod

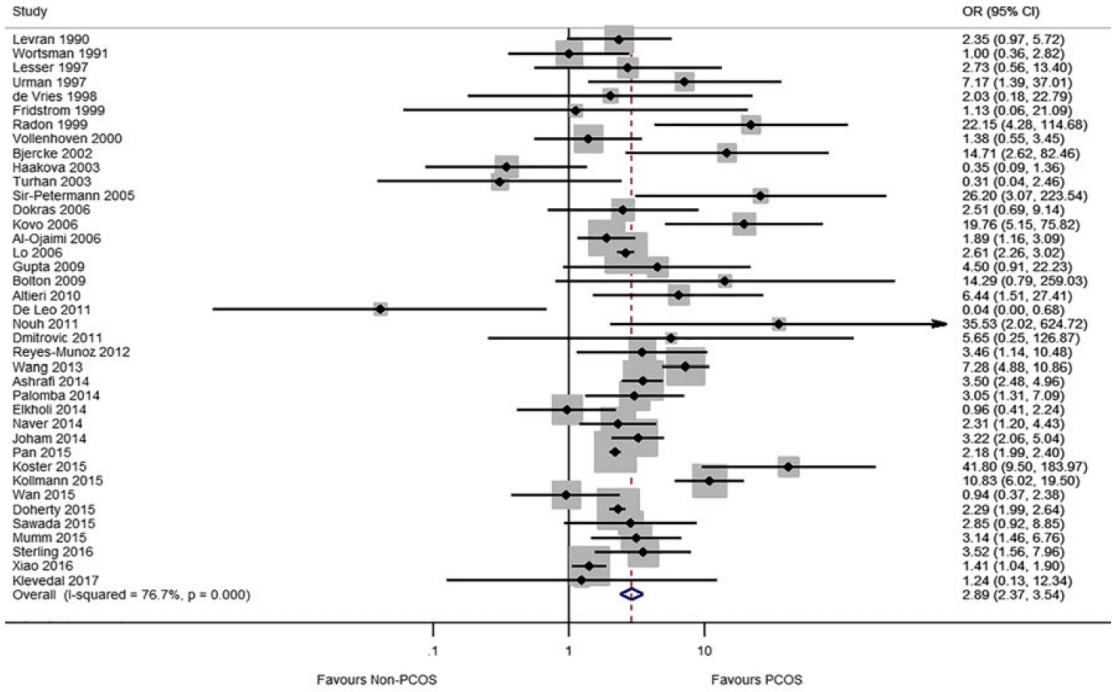
PCOS - Type 2 Diabetes



OR 2.87 (1.44-5.72) Prevalence 2-10%

Kakoly et al, 2018, Hum Reprod

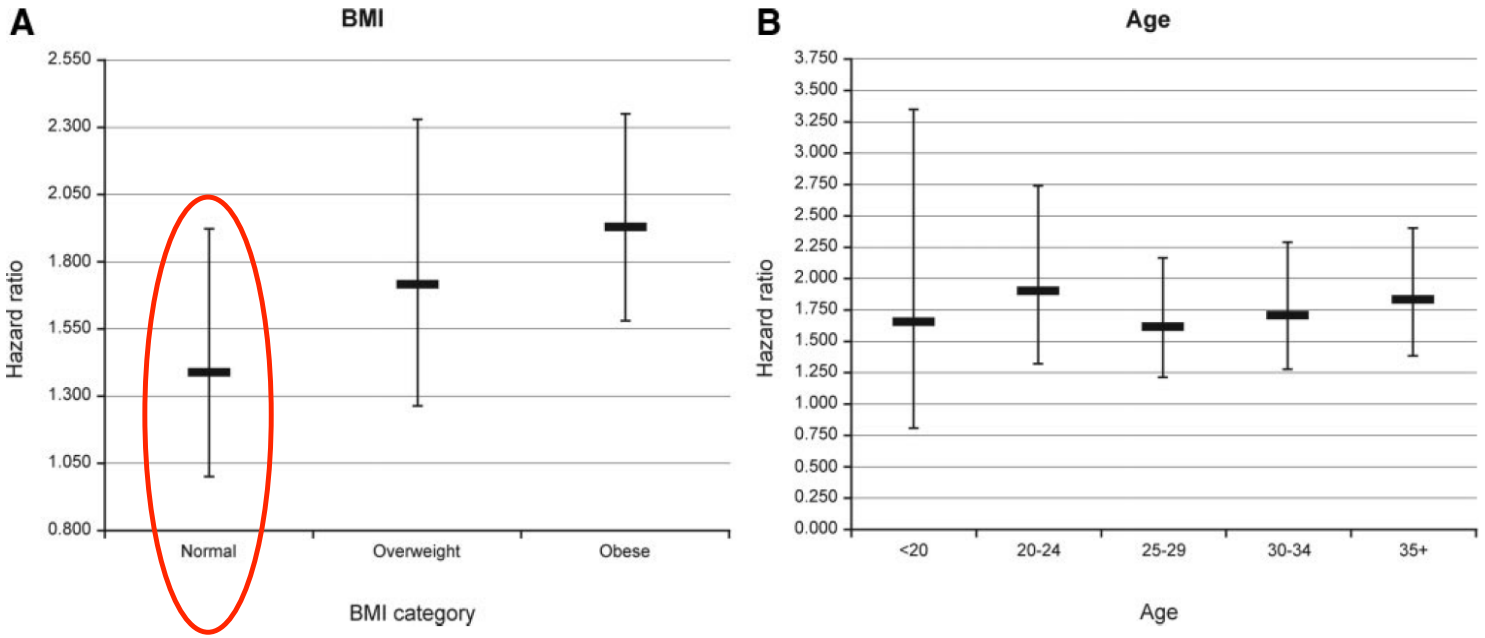
PCOS - Gestational Diabetes



OR 2.89 (95% CI 2.37 – 3.54)

Khomami et al, Obesity Rev, 2019

Diabetes Risk is Independent of Age and BMI



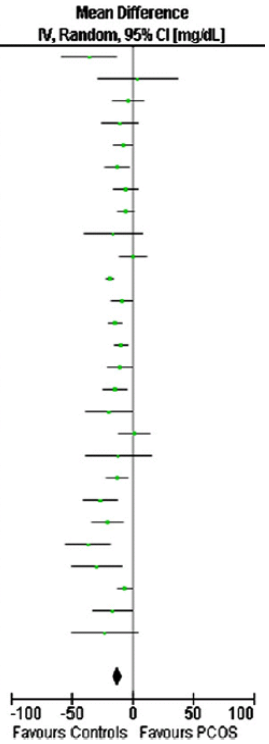
HR 3.07 (95% CI 2.7-3.3)

Morgan et al, 2012, JCEM

Dyslipidemia in PCOS - LDL-C

Study or Subgroup	Controls Mean [mg/dL]	Controls SD [mg/dL]	Controls Total	PCOS Mean [mg/dL]	PCOS SD [mg/dL]	PCOS Total	Weight	Mean Difference IV, Random, 95% CI [mg/dL]
Rizzo 2009	101	47	27	137	39	35	1.6%	-36.00 [-57.94, -14.06]
Rizzo 2009abc	105	62	27	101	47	15	0.8%	4.00 [-29.36, 37.36]
Moran 2009a	125	27	27	129	35	80	3.4%	-4.00 [-16.75, 8.75]
Roa-Barrios 2009a	106	35	48	117	47	62	2.7%	-11.00 [-26.33, 4.33]
Cetinkalp 2009a	110	29	91	118	29	129	5.4%	-8.00 [-15.78, -0.22]
Samy 2009a	97	15	40	110	32	52	4.5%	-13.00 [-22.86, -3.14]
Samyab	96	24	35	102	22	56	4.5%	-6.00 [-15.82, 3.82]
Oral 2009ab	93	22	43	99	7	48	5.9%	-6.00 [-12.87, 0.87]
Berneis 2009a	105	62	37	121	43	42	1.4%	-16.00 [-39.84, 7.84]
Macut 2008ab	101	23	53	101	39	79	4.2%	0.00 [-10.60, 10.60]
Valkenburg 2008	106	19	295	125	25	557	7.6%	-19.00 [-22.00, -16.00]
Hahn 2007	112	37	82	121	38	411	4.9%	-9.00 [-17.81, -0.19]
Carmina 2005	96	12	85	111	36	204	6.5%	-15.00 [-20.56, -9.44]
Carmina 2005a	101	8	42	111	36	204	6.5%	-10.00 [-15.50, -4.50]
Carminaac	96	12	85	107	35	50	4.4%	-11.00 [-21.03, -0.97]
Vryonidou 2005	104	24	55	119	35	75	4.4%	-15.00 [-25.15, -4.85]
Chekir 2005	104	24	45	124	45	25	2.0%	-20.00 [-38.98, -1.02]
Yildirim 2003ab	108	28	30	107	23	30	3.4%	1.00 [-11.97, 13.97]
Christian 2003a	99	62	71	111	71	36	1.1%	-12.00 [-39.31, 15.31]
Legro 2001a	117	23	35	130	33	153	4.7%	-13.00 [-22.24, -3.76]
Legroab	98	26	27	115	32	42	3.1%	-27.00 [-40.78, -13.22]
Tiras 1999a	93	22	35	114	33	35	3.3%	-21.00 [-34.14, -7.86]
Meirow 1996	111	27	20	148	39	31	2.1%	-37.00 [-55.12, -18.88]
Von Eckardstein 1996	111	27	26	141	46	26	1.8%	-30.00 [-50.50, -9.50]
Talbott 1995	111	35	206	118	32	206	6.1%	-7.00 [-13.48, -0.52]
Wild 1992	105	28	16	122	32	47	2.5%	-17.00 [-33.49, -0.51]
Wild 1985	96	38	29	119	64	30	1.1%	-23.00 [-49.75, 3.75]
Total (95% CI)			**1612**			**2760**	**100.0%**	**-12.60 [-15.69, -9.51]**

Heterogeneity: Tau² = 30.14; Chi² = 62.11, df = 26; I² = 58%
Test for overall effect: Z = 7.99



LDL-C levels were higher by 12.6mg/dl (%95 CI 9.5-16.5)

Wild et al, Fertil Steril, 2012

Reverse Cholesterol Transport & Efflux

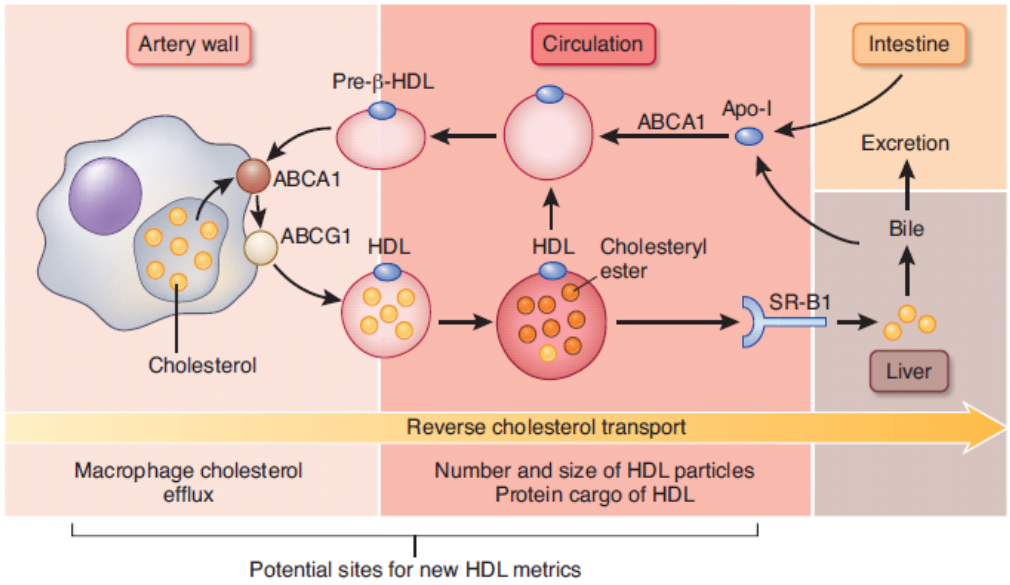


Figure 1 Overview of reverse cholesterol transport by HDL. Potential sites for new HDL metrics are indicated.

Cholesterol Efflux Capacity & Coronary Artery Disease

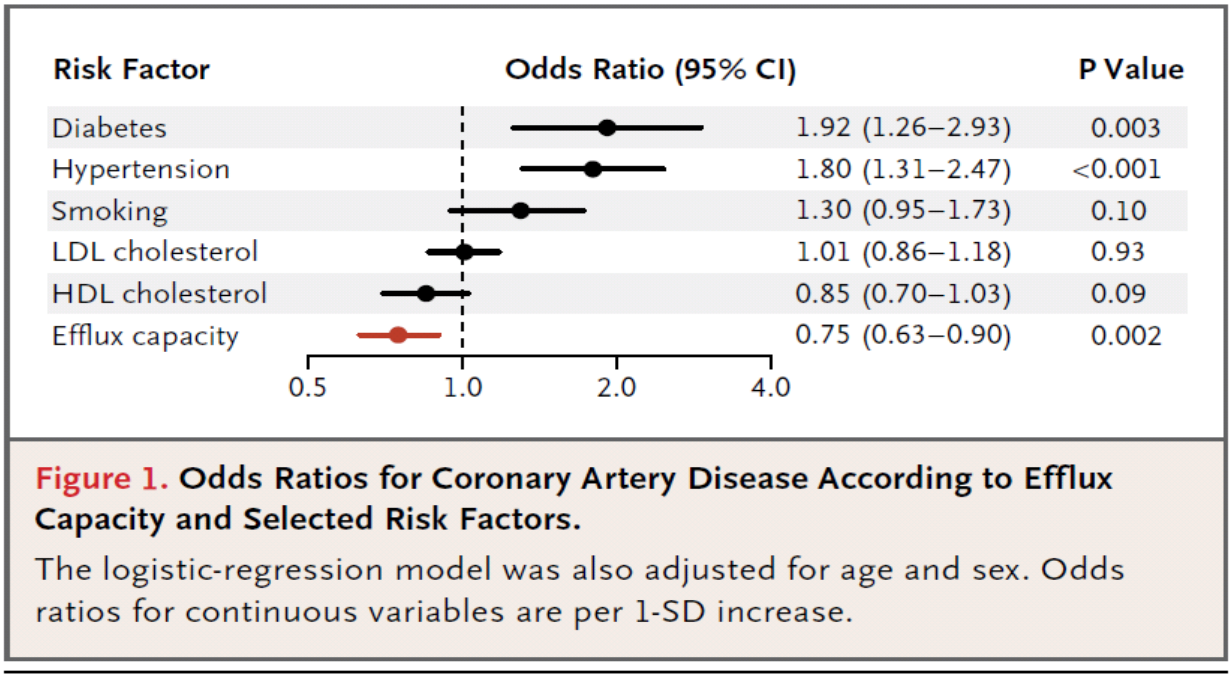


Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.

The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

Khera et al, NEJM, 2013

Decreased cholesterol efflux capacity and atherogenic lipid profile in young women with PCOS

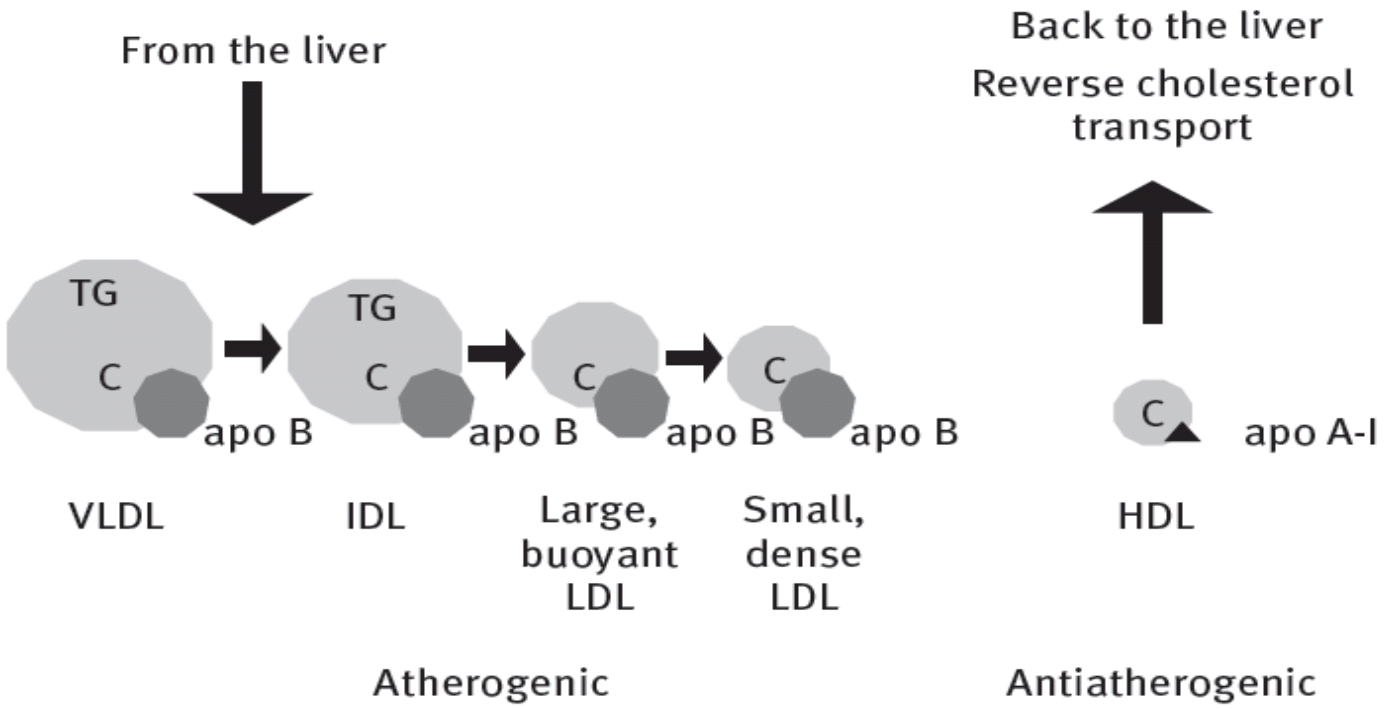
Andrea Roe, MD,[1], Jennifer Hillman, MD, Samantha Butts, MD, MSCE[1], Mathew Smith, BS,[1] Daniel Rader, MD[2], Martin Playford, PhD,[3], Nehal N Mehta, MD, MSCE[3] and Anuja Dokras, MD., PhD[1]

	PCOS n=124	Controls n=67
Total Cholesterol mg/dL)	192.5±37.9	189.7±34.5
HDL-C (mg/dL)	54.7 ±16.1	57.5± 17.9
Non-HDL Chol	137.7 ±38	124.9 ± 44
LDL-C mg/dl	167.1± 50.8	154.9 ±43.9
TG mg/dl	146.5± 92.9	112.2 ±69.9**
Lipid lowering therapy	2/125 (1.6%)	1/65 (1.5%)
Apo A1 mg/dl	161.1 ±38.2	174.4 ±35.5**
Apo B mg/dl	84.8±23.3	79.1±19.3
Apo B /A1	0.55 0.2	0.47 0.16**
HDL function# Cholesterol efflux capacity	**0.96 (IQR 0.86-1.06)**	**1.05 (0.91-1.18)***

Roe et al, 2014, JCEM

Women with PCOS had an 11% decrease in normalized cholesterol efflux capacity

Lipid Profile Overview



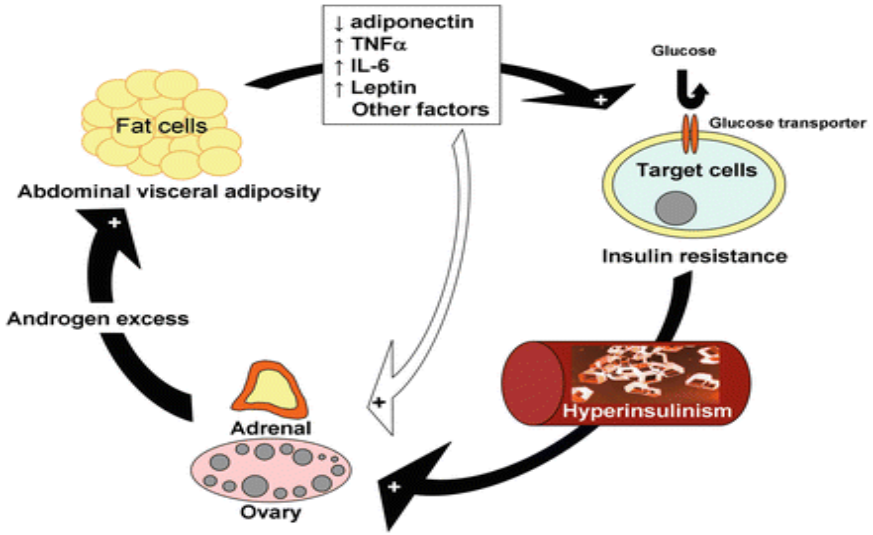
Atherogenic Lipoprotein Particles – NMR Spectroscopy

Particle concentration	PCOS (n=124)	Controls (n=68)
Total VLDL and Chylomicrons nmol/L	51.44±24.16	45.73±17.56
Large VLDL and Chylomicrons nmol/L	4.04±3.7	2.37±1.73 **
Medium VLDL nmol/L	18.36±12.64	15.27 ± 7.62
Small VLDL nmol/L	29.55 ± 14.54	29.16± 14.19
Total LDL nmol/L	1067.76±391.75	919.57± 300.34 *
IDL nmol/L	201.01± 125.31	253.85 ±181.39
Large LDL nmol/L	200.94± 143.27	203.07 ± 147.08
Small LDL nmol/L	652.91 ±367.95	434.33± 280.17 **
Total HDL umol/L	39.09 ±9.14	35.64 ± 7.83 **
Large HDL umol/L	6.77 ±4.44	7.68± 3.77
Medium HDL umol/L	14.39 ±7.62	12.77± 6.4
Small HDL umol/L	18.32 ±5.96	16.21± 5.37 *
Particle Size nm VLDL	49.58±6.04	46.78± 5.28 **
LDL	21.03 ±5.73	20.67± 0.65
HDL	9.34 ±0.49	9.55 ± 0.44 **

**p<0.01, *p<0.05

Roe et al, 2014, JCEM

Risk of Metabolic Syndrome



Adults OR 3.35 (95% CI 2.44-4.59)

Lim et al, Obesity Rev 2018

Adolescents OR 2.69 (1.29, 5.60)

Fazleen et al, Diabet Metab Syn 2018

Non Obese Women with PCOS have increased Cardio Metabolic Risk

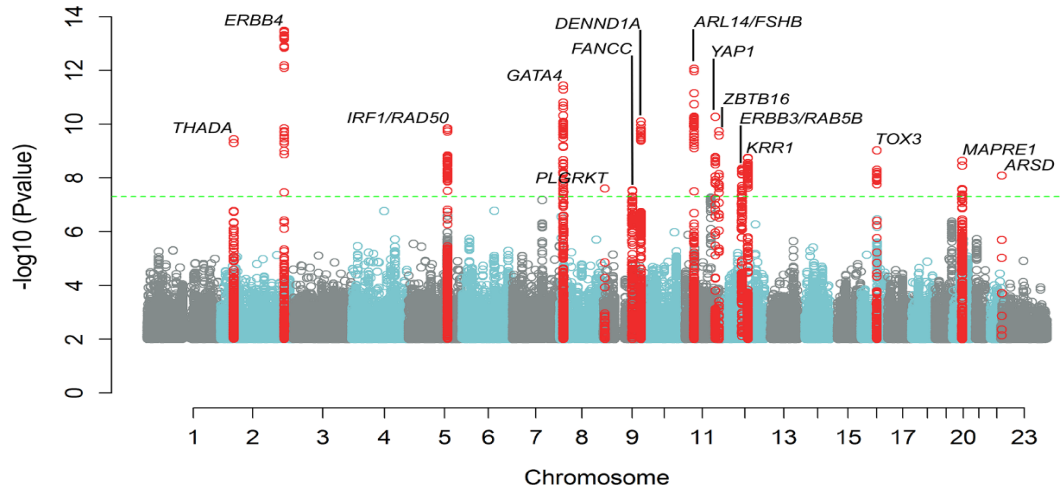
Meta-analysis results for glucose metabolic disturbances and cardiovascular disease risk factors.

Outcome	No. of studies	Effects model	OR (95%CI)	*P* value	Heterogeneity P_h value	Heterogeneity I^2 (%)
Comparison in glucose metabolism disturbances						
HIN	1		36.27 (1.76, 747.12)			
IR	3	Random	5.70 (1.46, 22.32)	.012	0.005	81.1
IFG	4	Random	1.08 (0.46, 2.53)	.864	0.109	50.4
IGT	4	Fixed	3.42 (1.56, 7.52)	.002	0.310	16.3
Pre-DM	3	Fixed	1.39 (0.73, 2.63)	.317	0.459	0
T2DM	5	Fixed	1.47 (1.11, 1.93)	.007	0.555	0
T2DM cohort	3	Fixed	1.48 (1.12, 1.95)	.007	0.245	29
Comparison in CVD risk factors						
Dyslipidemia	2	Fixed	1.87 (0.85, 4.13)	.121	0.913	0
high-TC	1		5.78 (0.31, 107.92)			
high-TG	2	Fixed	10.46 (1.39, 78.56)	.022	0.554	0
low-HDL	2	Fixed	4.03 (1.26, 12.95)	.019	0.626	0
Hypertension	3	Random	2.44 (0.80, 7.43)	.117	0.117	53.3

Note: CI = confidence interval; CVD = cardiovascular disease; high-TC = hypercholesterolemia; high-TG = hypertriglyceridemia; HIN = hyperinsulinemia; IFG = impaired fasting glucose; IGT = impaired glucose intolerance; IR = insulin resistance; low-HDL = low high-density lipoprotein; Pre-DM = IGT plus IFG; OR = odds ratio; T2DM = type 2 diabetes mellitus.

Zhu. Metabolic disturbances in non-obese PCOS. Fertil Steril 2018.

Genetic Correlations with Metabolic Phenotype



Phenotype	Genetic Correlation	SE	Z	P-value
Body mass index	0.34	0.039	8.60	8.21×10^{-18}
Childhood obesity	0.34	0.066	5.17	2.40×10^{-7}
Fasting insulin levels	0.44	0.087	5.01	5.33×10^{-7}
Type 2 diabetes	0.31	0.068	4.47	7.84×10^{-6}
High-density lipoprotein levels	-0.23	0.059	-3.96	7.40×10^{-5}
Menarche	-0.16	0.042	-3.76	1.71×10^{-4}
Triglyceride levels	0.19	0.052	3.61	3.05×10^{-4}
Coronary artery disease	0.23	0.069	3.32	8.86×10^{-4}
Depression	0.205	0.0582	3.5203	0.0004
Menopause	-0.014	0.0183	-0.762	0.4461
Male pattern balding	0.0149	0.0168	0.8861	0.3756

https://doi.org/10.1371/journal.pgen.1007813.t004

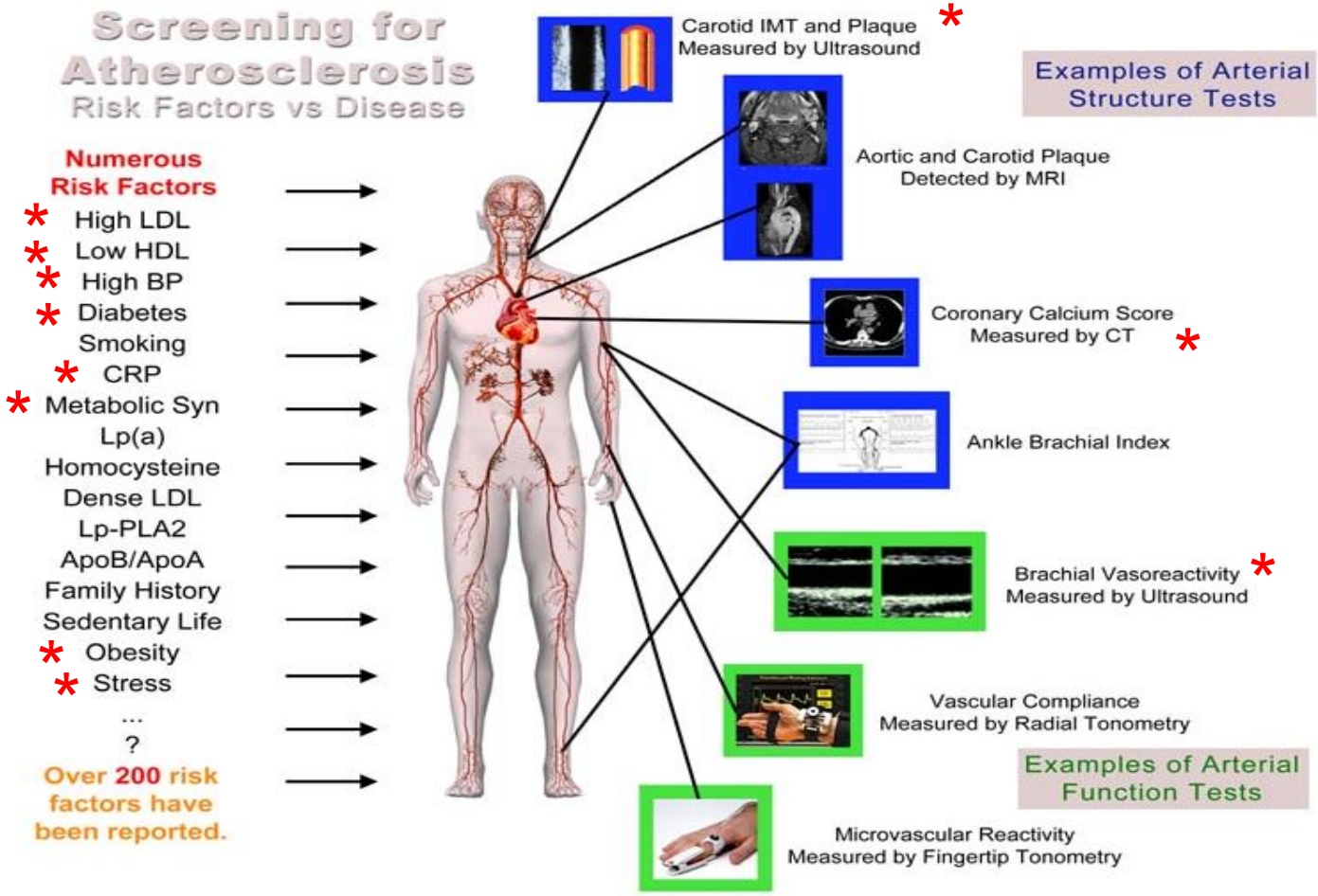
Day et al, PCOS 2018

Family Members have Increased Metabolic Risk

- Mothers – metabolic syndrome, dyslipidemia
- Fathers – metabolic syndrome, dyslipidemia, hypertension
- Brothers – hypertension
- Sisters - hypertension, metabolic syndrome

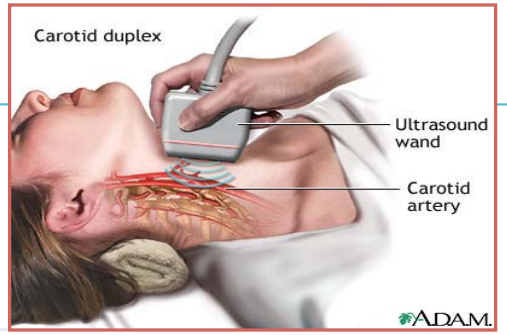
Yilmaz et al, Fert Steril 2018

PCOS and Subclinical Atherosclerosis



Carotid artery intima-media thickness in polycystic ovary syndrome: a systematic review and meta-analysis

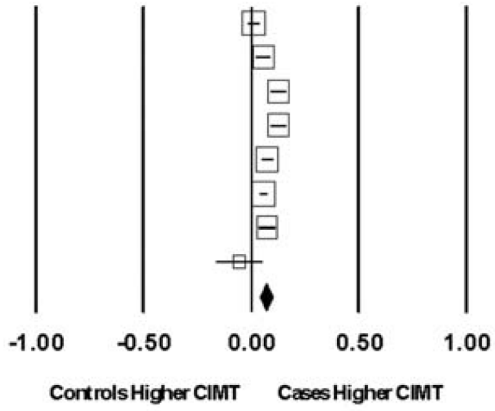
Michelle L. Meyer [1,*], Angela M. Malek [2], Robert A. Wild [3], Mary T. Korytkowski [4], and Evelyn O. Talbott [2]



A

Study name	Difference in means	Lower limit	Upper limit	p-Value	Cases	Controls
Talbott 2000 30-44 y	0.010	-0.024	0.044	0.564	78	82
Talbott 2000 >=45 y	0.060	0.019	0.101	0.004	47	60
Orio 2004	0.140	0.097	0.183	0.000	30	30
Vural 2005	0.138	0.093	0.183	0.000	43	43
Cascella 2008	0.080	0.046	0.114	0.000	200	100
Heutling 2008	0.060	0.036	0.084	0.000	83	39
Carmina 2009	0.080	0.032	0.128	0.001	95	90
Pepene 2011	-0.063	-0.187	0.061	0.320	64	20
	0.072	0.040	0.105	0.000	640	464

Statistics for each study | Sample size | Difference in means and 95% CI

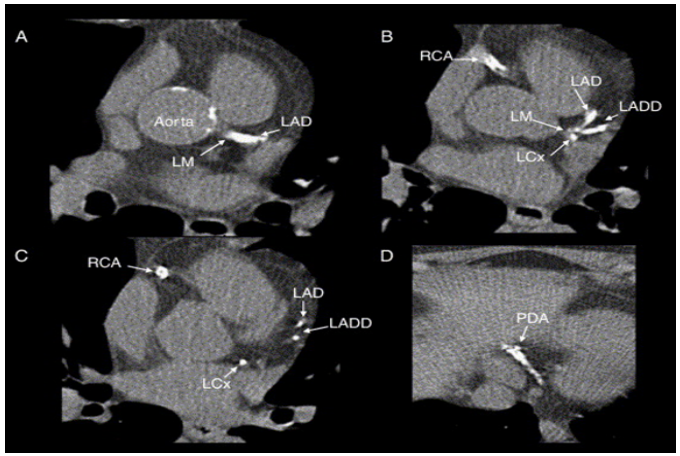


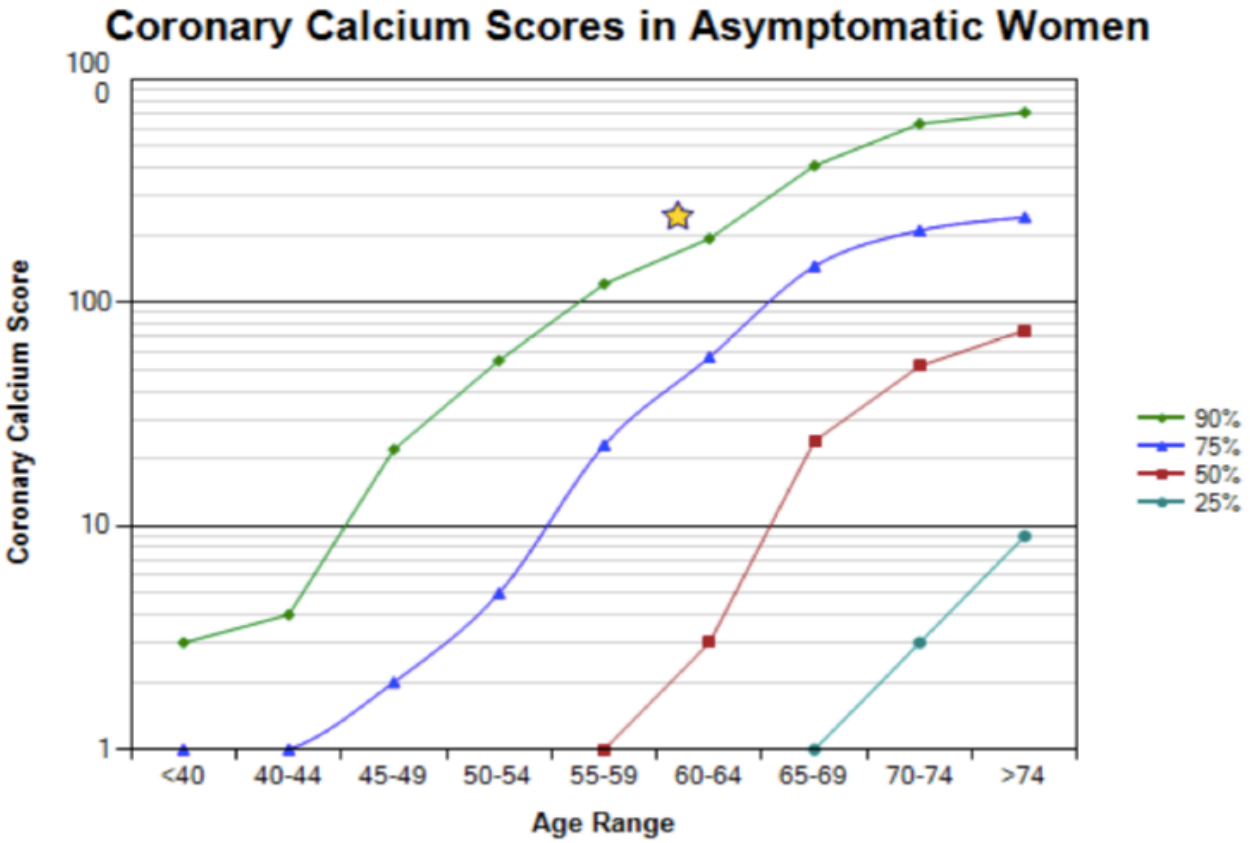
PCOS 1123, Controls 923

Human Reprod 2012

Coronary Artery Calcification & PCOS

Author Year	n	Study Population/ Study Design	Outcome Measure/ Results
Shroff, 2007	24 cases 24 24 controls	Obese, premenopausal [cross-sectional]	Prevalence of CAC (>0) **OR=5.5 (1.03, 29.45) p<0.03**
Christian, 2003	36 cases 71 controls	Premenopausal, age 30-45 [cross-sectional]	Prevalence of CAC (>0) OR=1.99 (0.68,5.82) p=0.21 (NS)
Talbott, 2004	61 cases 85 controls	BMI < 35 [prospective] Age 40-61	Prevalence of CAC (>0) **OR=2.31 (1.00, 5.33) p=0.049**
Talbott, 2008	149 cases 166 controls	All BMI [cross-sectional]	Prevalence of CAC >10 **OR=1.90 (1.04, 3.48) p=0.037**
Chang, 2011	144 PCOS 170 controls	Age 37-45years Cross sectional	Prevalence of CAC (>10) PCOS 5.4% controls 6.3% p=0.74
Calderon-Margalit 2014	55 PCOS 668 controls	Mean age 45.3	Prevalence of CAC (>0) **OR 2.7 (1.37-5.25)**




Coronary Calcium Scores in Asymptomatic Women
100
0
100
10
1
Coronary Calcium Score
<40
40-44
45-49
50-54
55-59
60-64
65-69
70-74
>74
Age Range
90%
75%
50%
25%

CVD in a Danish Population of Young Women with PCOS

Table 1 Event rates of CVD in PCOS OUH, PCOS Denmark and controls

	PCOS OUH (N = 1159)		PCOS Denmark (N = 17,995)		Controls (N = 52,329)		P^a	P^b
	N (%)	IR	N (%)	IR	N (%)	IR		
CVD events	264 (23)	22.6	3970 (22)	22.0	7344 (14)	13.2	< 0.001	0.54
CVD (HT and DL excluded)	71 (6)	5.4	1290 (7)	6.4	2678 (5)	4.5	< 0.001	0.16
ICD10 CVD, total	121 (10)	9.5	1727 (10)	8.7	3089 (6)	5.2	< 0.001	0.31

Glintborg et al, Cardiovasc Diabetol 2018

Risk of coronary heart disease and risk of stroke in women with polycystic ovary syndrome: A systematic review and meta-analysis

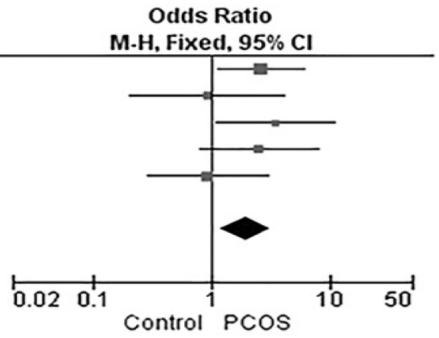
Sarah A. Anderson, John A. Barry, Paul J. Hardiman *

Institute for Women's Health, University College London, London WC1E 6HX, United Kingdom

Non fatal stroke

Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Wild 2000	10	319	13	1060	28.3%	2.61 [1.13, 6.00]	2000
Lunde 2007	2	131	12	723	17.6%	0.92 [0.20, 4.15]	2007
Cheang 2008	5	24	11	158	11.1%	3.52 [1.10, 11.22]	2008
Schmidt 2011	6	32	8	95	15.9%	2.51 [0.80, 7.89]	2011
Iftikhar 2012	5	309	6	343	27.1%	0.92 [0.28, 3.06]	2012
Total (95% CI)		**815**		**2379**	**100.0%**	**1.94 [1.19, 3.17]**	
Total events	28		50				

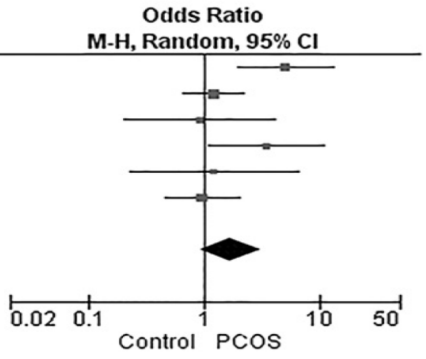
Heterogeneity: Chi² = 4.11, df = 4 (P = 0.39); I² = 3%
Test for overall effect: Z = 2.65 (P = 0.008)



Non fatal CHD

Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Cibula 2000	6	28	38	752	18.1%	5.12 [1.96, 13.38]	2000
Wild 2000	15	319	42	1060	25.0%	1.20 [0.65, 2.19]	2000
Lunde 2007	2	131	12	723	10.9%	0.92 [0.20, 4.15]	2007
Cheang 2008	5	24	11	158	15.0%	3.52 [1.10, 11.22]	2008
Schmidt 2011	2	32	5	95	9.3%	1.20 [0.22, 6.51]	2011
Iftikhar 2012	13	309	15	343	21.8%	0.96 [0.45, 2.05]	2012
Total (95% CI)		**843**		**3131**	**100.0%**	**1.70 [0.92, 3.11]**	
Total events	43		123				

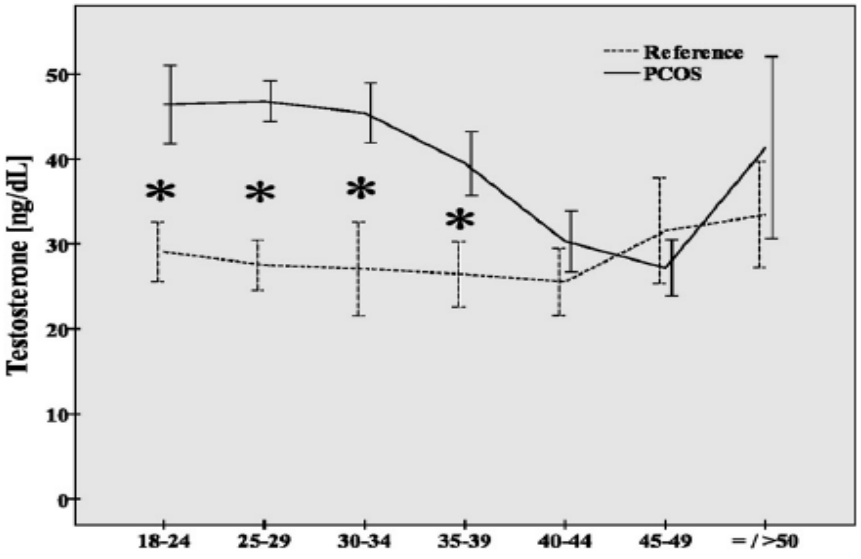
Heterogeneity: Tau² = 0.29; Chi² = 10.90, df = 5 (P = 0.05); I² = 54%
Test for overall effect: Z = 1.71 (P = 0.09)

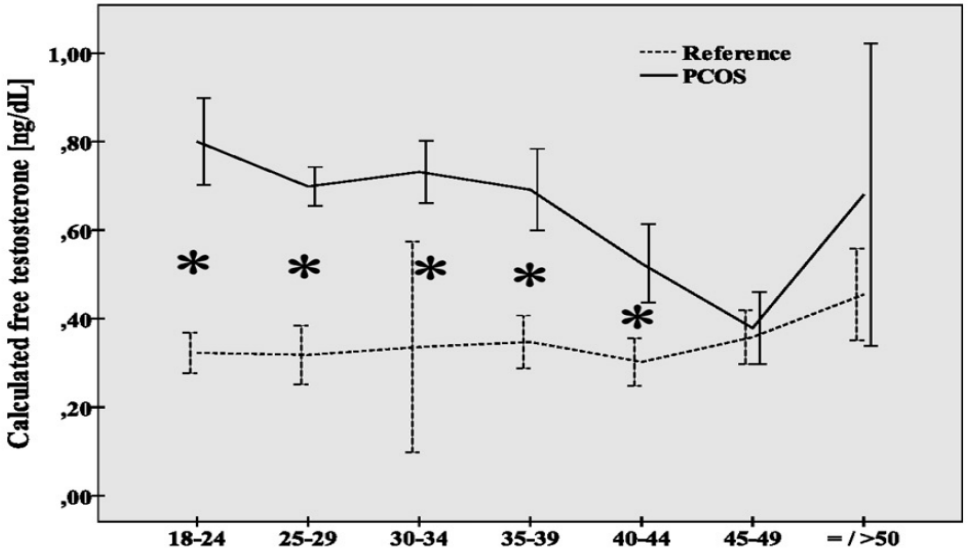


Int J Card , 2014

Androgen Profile Through Life in Women With Polycystic Ovary Syndrome: A Nordic Multicenter Collaboration Study

PCOS n=681, controls n=230

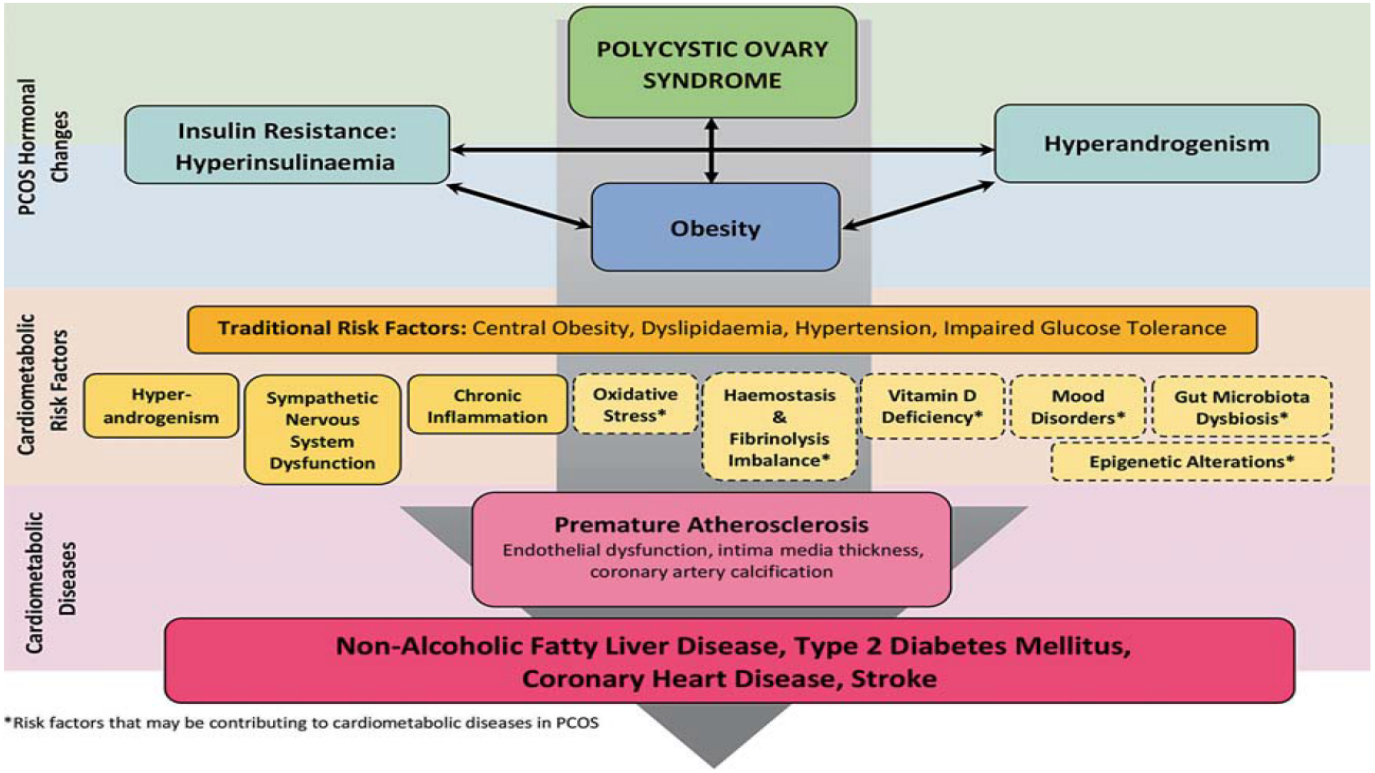




Age in years

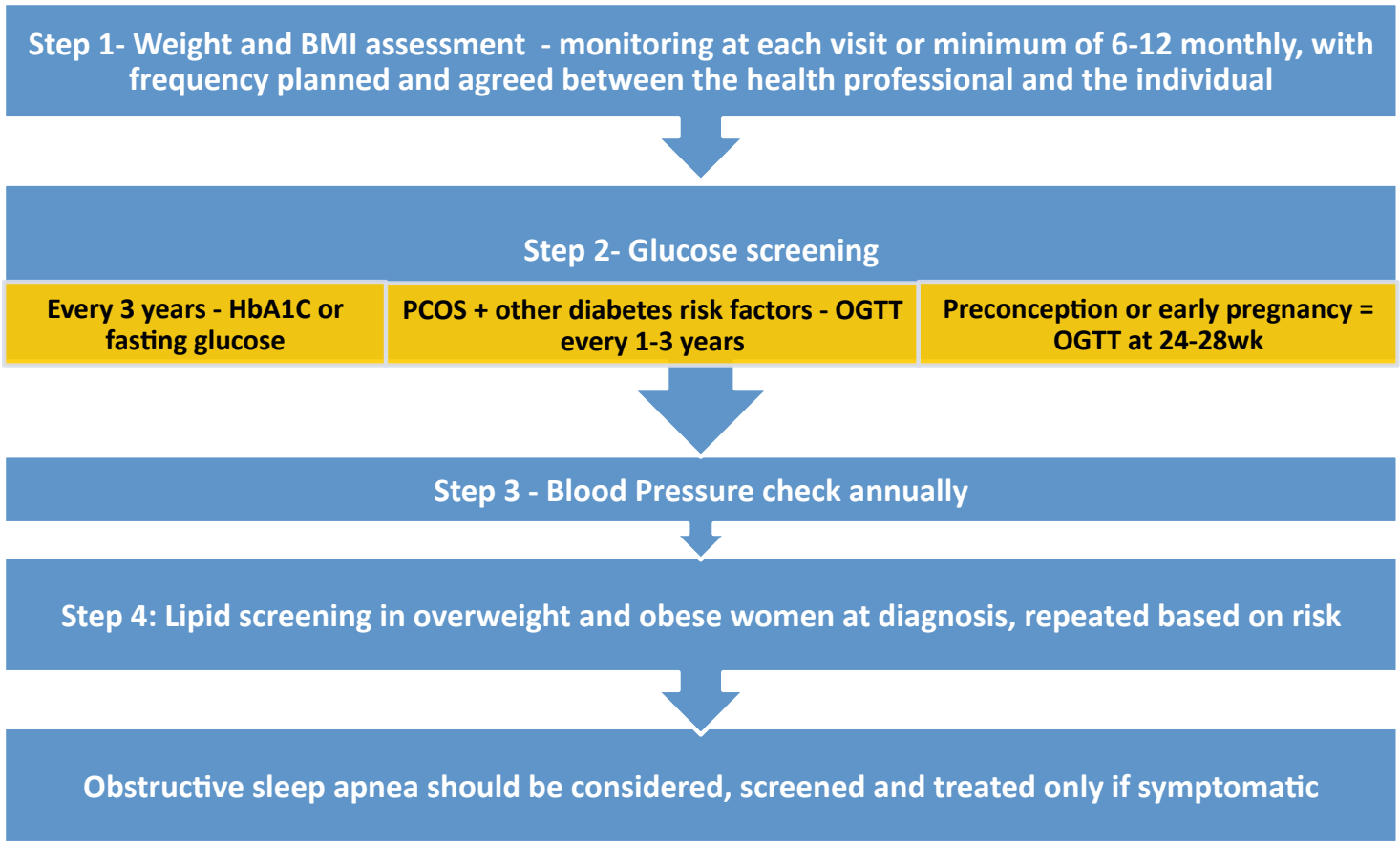
Pinola et al, JCEM , 2015

Does the CVD Risk Persist in the Menopause?



Hypothesis – older women with PCOS should have an increased risk of CVD

Metabolic Risk Screening for Primary Prevention of CVD



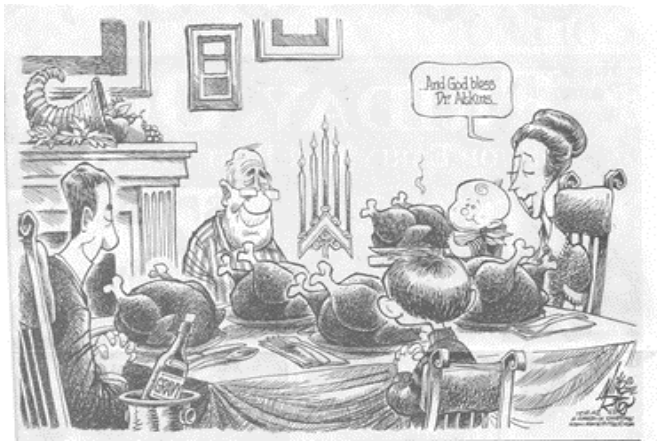
Human Reproduction 2018 Sep 1;33(9):1602-1618
Fertil Steril 2018 Aug;110(3):364-379

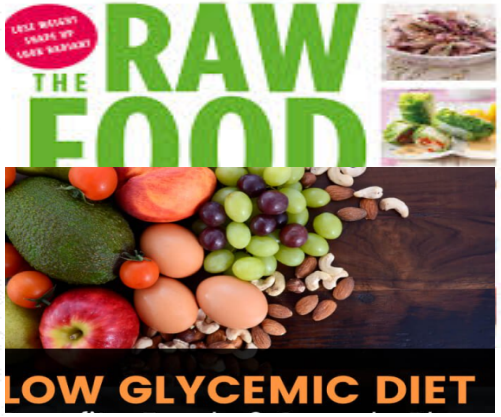
Metformin & Lifestyle Changes

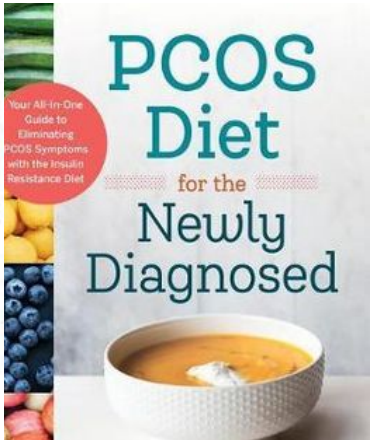
4.4.1	EBR	Metformin in addition to lifestyle, could be recommended in adult women with PCOS, for the treatment of weight, hormonal and metabolic outcomes.	❖❖❖ ⊕⊕◯◯
4.4.2	EBR	Metformin in addition to lifestyle, should be considered in adult women with PCOS with BMI ≥ 25kg/m2 for management of weight and metabolic outcomes.	❖❖❖ ⊕⊕◯◯
4.4.3	EBR	Metformin in additional to lifestyle, could be considered in adolescents with a clear diagnosis of PCOS or with symptoms of PCOS before the diagnosis is made.	❖❖❖ ⊕⊕◯◯
4.4.4	CPP	Metformin may offer greater benefit in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups (see 1.6.1).	
4.4.5	CPP	Where metformin is prescribed the following need to be considered: • adverse effects, including gastrointestinal side-effects that are generally dose dependent and self-limiting, need to be the subject of individualised discussion • starting at a low dose, with 500mg increments 1-2 weekly and extended release preparations may minimise side effects • metformin use appears safe long-term, based on use in other populations, however ongoing requirement needs to be considered and use may be associated with low vitamin B12 levels • use is generally off label and health professionals need to inform women and discuss the evidence, possible concerns and side effects.	

Human Reproduction 2018 Sep 1;33(9):1602-1618
Fertil Steril 2018 Aug;110(3):364-379

What Diet is the Best for PCOS?







- No specific diet, general energy deficit -30%
- Behavioural; SMART
  Specific, Measurable, Activating, **Realistic**, Timely
- Psychological wellbeing to promote healthy lifestyle

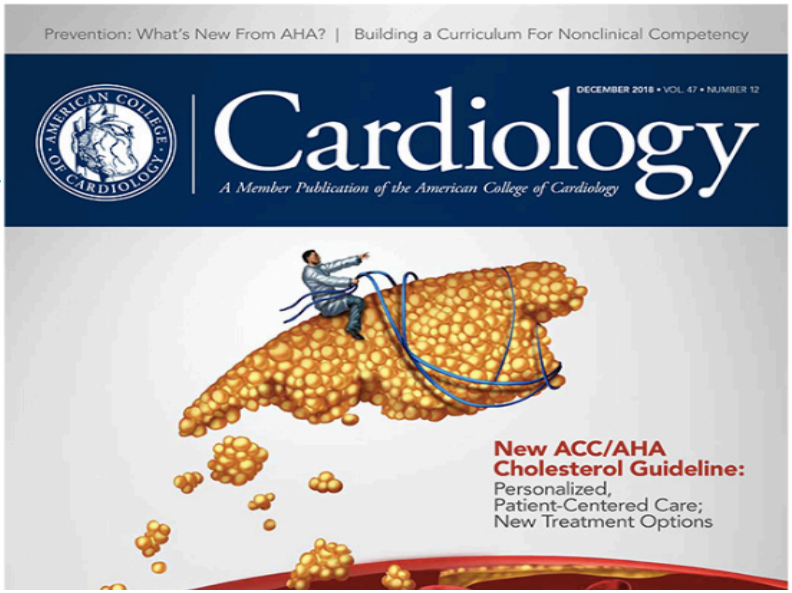


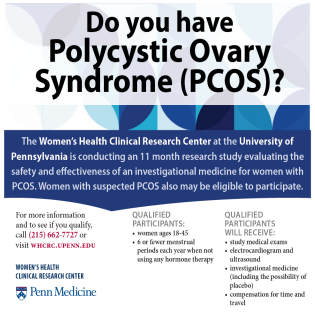
TABLE 2 Risk-Enhancing Factors for Clinician–Patient Risk Discussion (10)

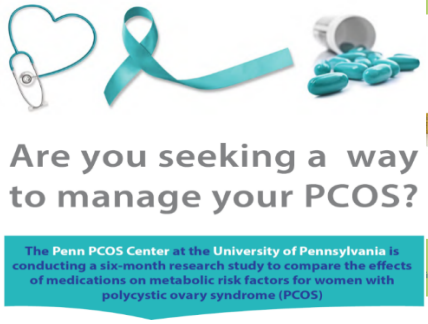
Risk-Enhancing Factors

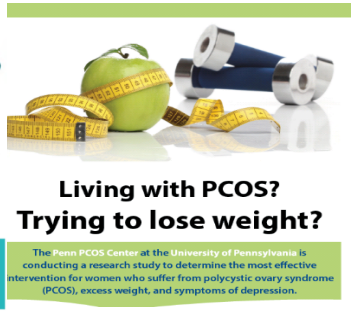
- **Family history of premature ASCVD** (males, age <55 y; females, age <65 y)
- **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non-HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>150 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
- **High-risk race/ethnicities** (e.g., South Asian ancestry)
- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  - If measured:
    - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    - **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
    - **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
    - **ABI** <0.9

PENN PCOS CENTER

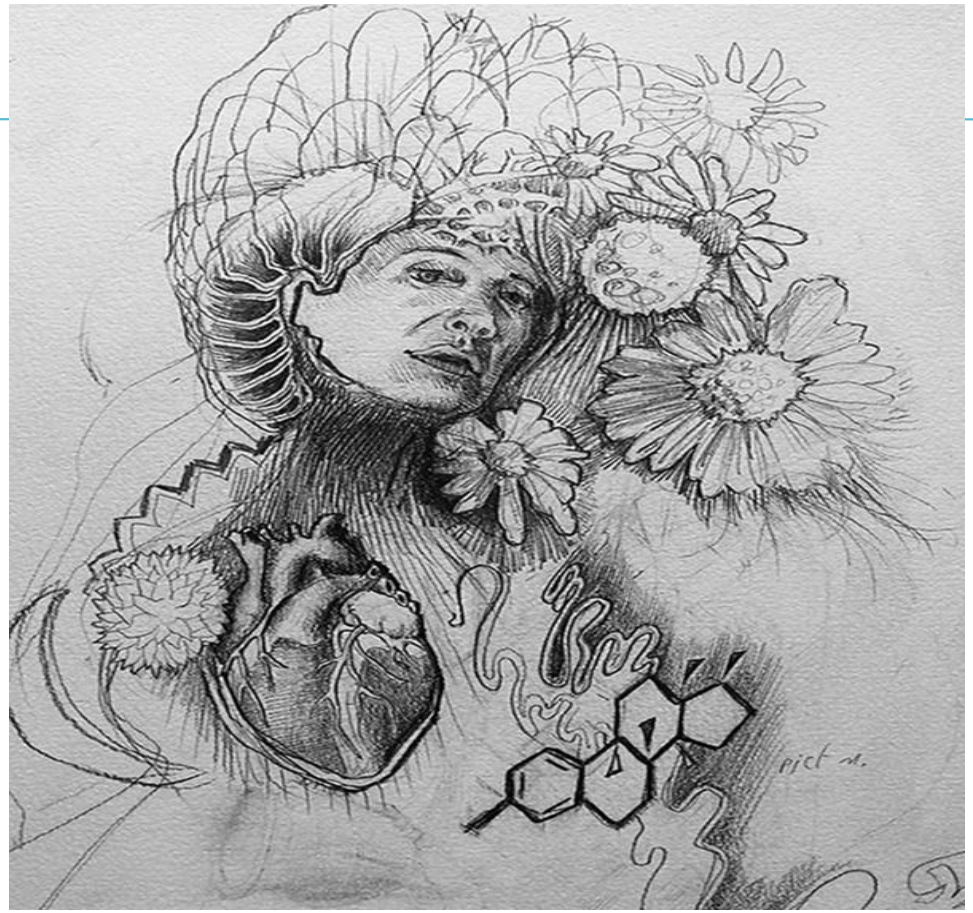
- Reproductive Endocrinologist
- Nurse Practitioner
- Clinical Nutritionist
- Dermatologist
- Psychiatrist/Clinical Psychologist
- Weight management
- Research Coordinator





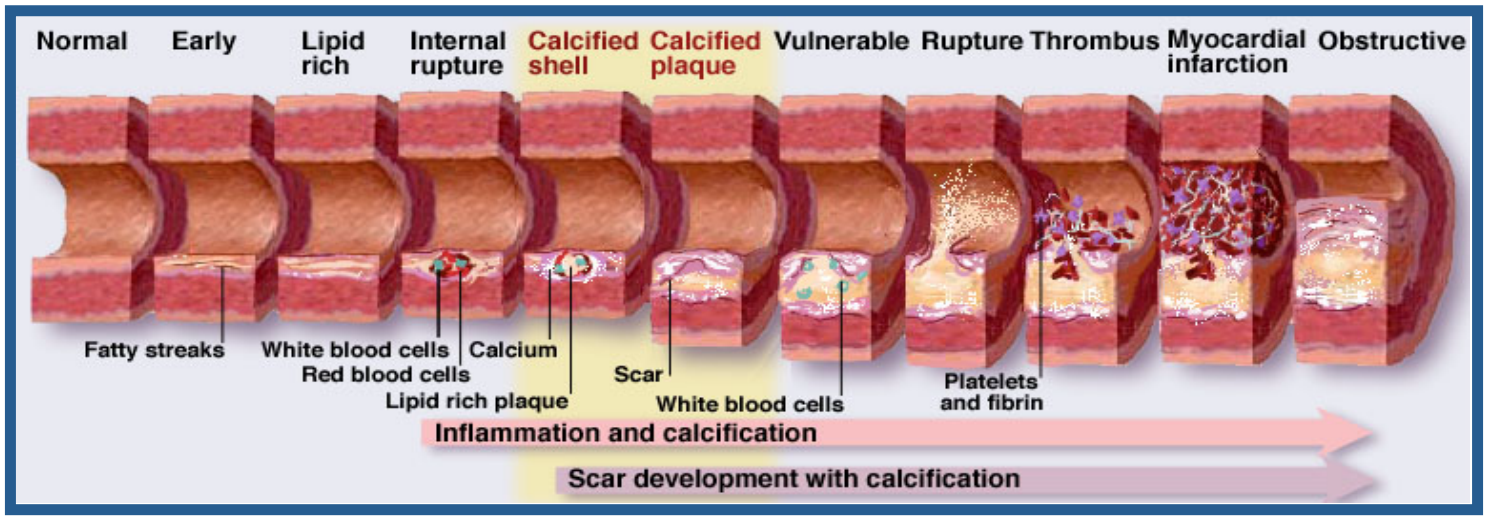



PCOS Challenge
The National Polycystic Ovary Syndrome Association
Iconic Landmarks Around the World Light Up Teal for PCOS Awareness Month
#PCOS
#WorldPCOSDay
#PCOSChallenge
#TurnItTeal
#CystersUnited
PCOSAwarenessMonth.org
PCOSChallenge.org



Cardiovascular risk factors and disease in women. Art work by Piet Michiels, Leuven, Belgium.

Coronary Artery Disease Timeline



Atypical presentations and expanded spectrum of Ischemic Heart Disease (coronary microvascular dysfunction, vasomotor abnormalities, spontaneous coronary artery dissection and stress induced cardiomyopathy) in women

PREVALENCE OF PCOS

Country	Prevalence NIH	Prevalence Rotterdam
Australia	8.6-15.3%	9-21.3%
Brazil	NA	8.5%
China	2.2-7.1%	5.6-11.2%
Denmark	NA	16.6%
Greece	6.8%	NA
Iran	4.8-7.1%	14.1-15.2%
Italy and Spain	5.4%	NA
Mexico	6%	NA
Sri Lanka	NA	6.3%
Turkey	6.1%	19.9%
UK	8%	NA
USA	4-13%	NA

Lizneva et al, Fertil Steril. 2016 May 24.

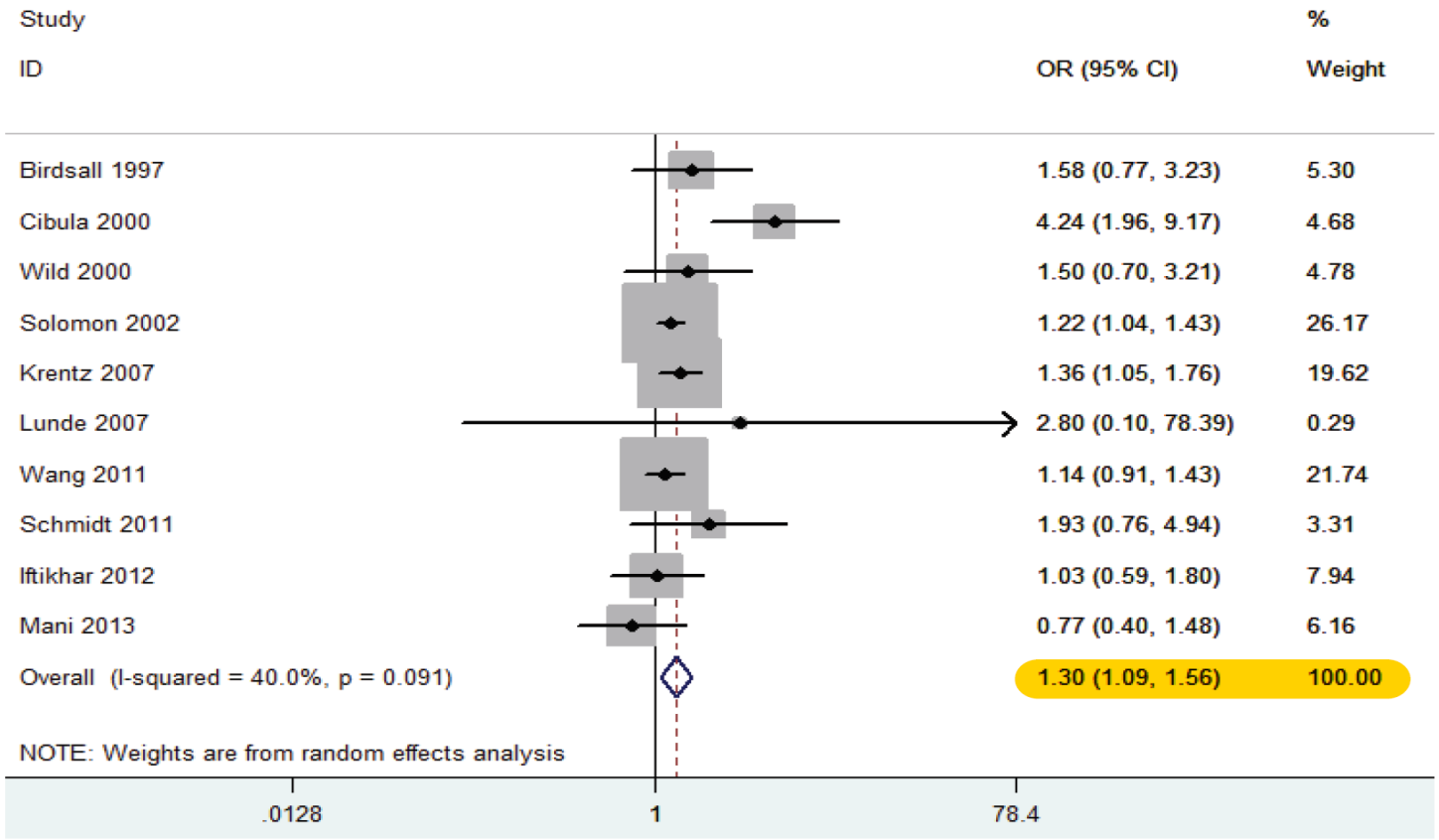
Impact of Race on Metabolic Risk

PCOS	US White	US Black	India	Brazil	Finland	Norway
n	186	101	220	238	94	287
Metabolic Syndrome	52 (28%)	**52 (51.5%)**	65 (29.6%)	70 (29.4%)	26 (27.7%)	106 (26.5%)
BMI criterion	89 (47.9%)	**74 (73.3%)**	82 (37.3%)	100 (42%)	**45 (47.9%)**	135 (47%)
TG criterion	38 (20.4%)	10 (9.9%)	**59 (26.8%)**	**64 (26.9%)**	11 (11.7%)	58 (20.2%)
BP criterion	68 (36.6%)	**59 (58.4%)**	37 (16.8%)	83 (34.9%)	34 (36.2%)	**131 (45.6%)**
Glucose criterion	22 (11.8%)	22 (21.8%)	**63 (28.6%)**	42 (17.7%)	16 (17%)	**75 (26.1%)**
HDL criterion	77 (41.4%)	**72 (71.3%)**	**214 (97.3%)**	**142 (59.7%)**	**41 (43.6%)**	**161 (56.1%)**

Chan et al, AJOG, 2017

Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): a meta-analysis

Luqian Zhao[1], Zhigang Zhu[1], Huiling Lou[1], Guodong Zhu[1], Weimin Huang[1], Shaogang Zhang[1] and Feng Liu[1]

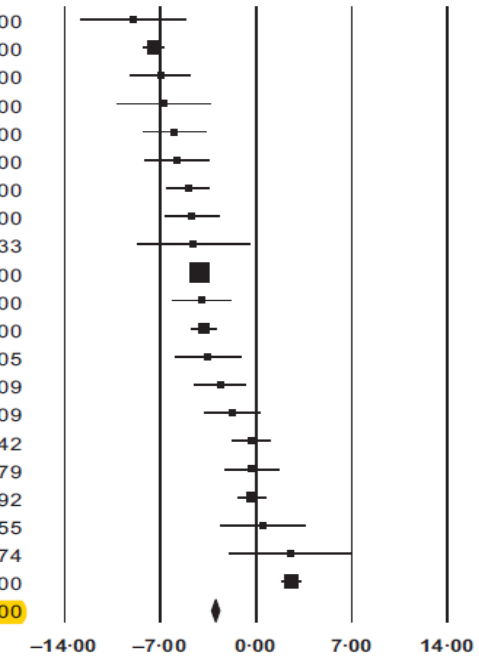


Oncotarget , 2016

Endothelial function measured using flow-mediated dilation in polycystic ovary syndrome: a meta-analysis of the observational studies

PCOS 908
Controls 566

Study	Age	BMI	Statistics for each study			
			Difference in means	Lower limit	Upper limit	*P*-Value
Sorensen	33·000	25·000	−9·010	−12·939	−5·081	0·000
Battaglia	25·000	25·000	−7·500	−8·322	−6·678	0·000
El-Kannishy	25·000	23·000	−7·000	−9·281	−4·719	0·000
Pepene	26·000		−6·750	−10·245	−3·255	0·000
Alexandraki	25·000	27·000	−5·990	−8·359	−3·621	0·000
Diamanti-Kandarakis	26·000	29·000	−5·790	−8·209	−3·371	0·000
Kravarti	23·000	25·000	−4·960	−6·585	−3·335	0·000
Tarkun	24·000	24·000	−4·670	−6·689	−2·651	0·000
Soyman	24·000	23·000	−4·560	−8·751	−0·369	0·033
Cascella	24·000	29·000	−4·100	−4·644	−3·556	0·000
Cussons	31·000	24·000	−3·970	−6·204	−1·736	0·000
Orio	22·000	22·000	−3·800	−4·787	−2·813	0·000
Meyer	33·000	37·000	−3·540	−6·010	−1·070	0·005
Carmina	25·000	29·000	−2·600	−4·560	−0·640	0·009
Moran	34·000	36·000	−1·700	−3·782	0·382	0·109
Soares	25·000	23·000	−0·350	−1·824	1·124	0·642
Mather	33·000		−0·300	−2·391	1·791	0·779
Mancini	25·000	29·000	−0·300	−1·397	0·797	0·592
Brinkworth		36·000	0·500	−2·641	3·641	0·755
Arikan	23·000	21·000	2·530	−2·007	7·067	0·274
Beckman			2·600	1·846	3·354	0·000
			−3·021	−3·315	−2·727	0·000



Sprung et al, Clin Endo 2013