

PCOS

Cardiovascular Health

(Post-Reproductive Life)

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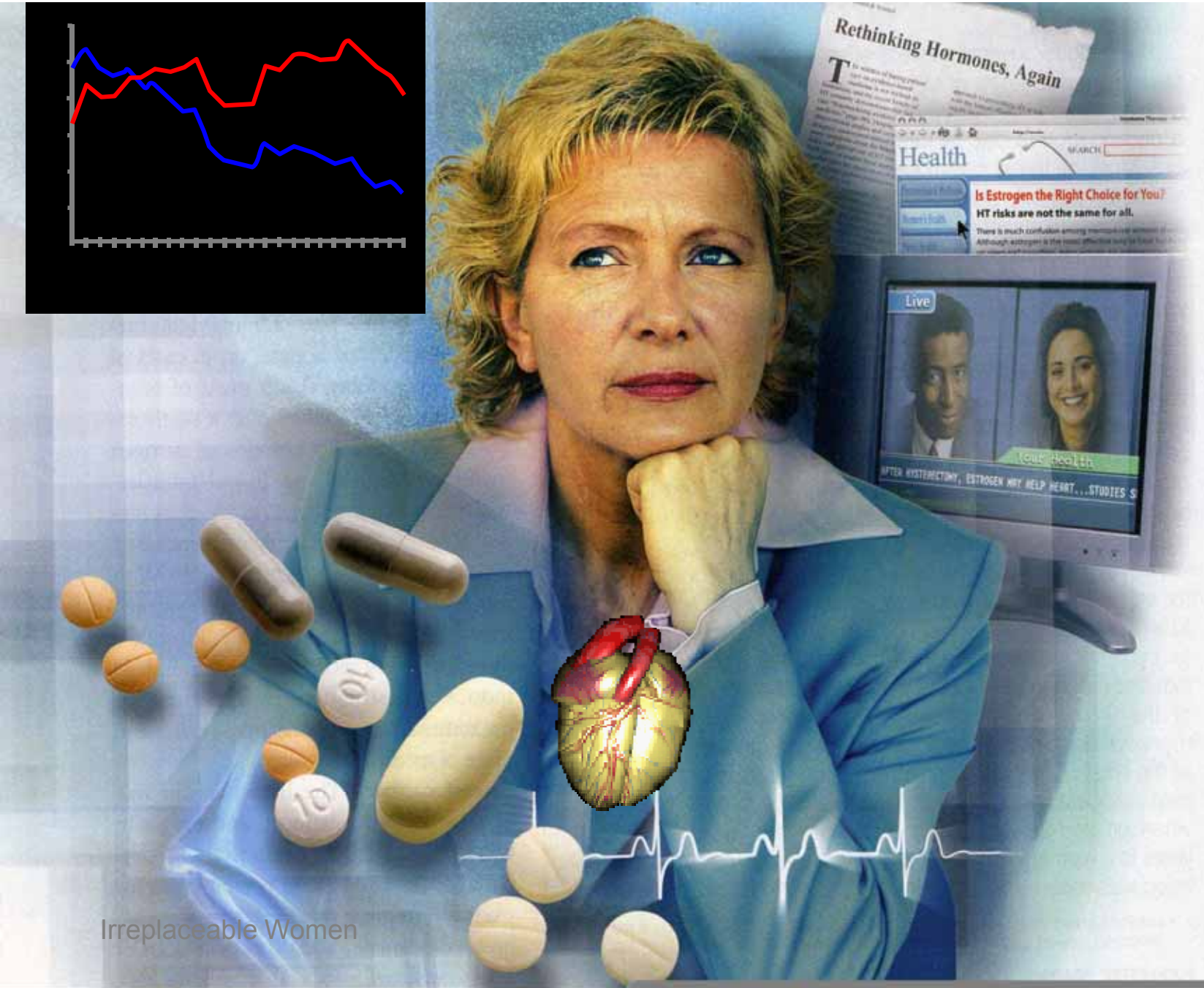
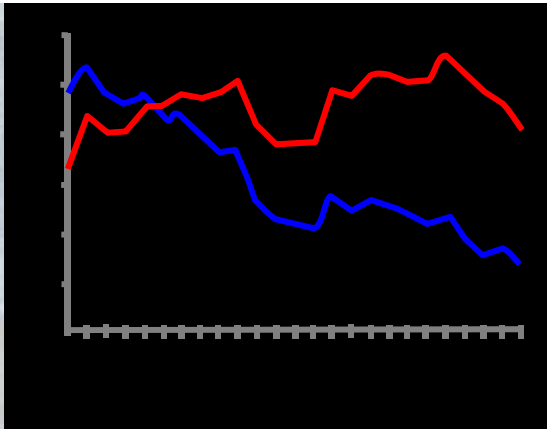
Women's health aspects of PCOS ESHRE Campus symposium
Amsterdam, The Netherlands
18 November 2010

Conflicts

- none

Objectives

- Attendee become familiar with the evidence for the major risk factors for CVD
- Attendee will become familiar with the evidence for major CVD risk factors in women with PCOS
- Attendee will become familiar with recommendations in the AE-PCOS Consensus guidelines for CVD risk for women with PCOS



Irreplaceable Women

INTERHEART study: case-control study
9 risk factors accounted for
94% of the Population Attributable Risk
for myocardial infarction

Risk	Odds	Protective Odds
• Smoking	2.86 (2.36–3.48)	Fruits/Vegs 0.58 (0.48–0.71)
• Diabetes	4.26 (3.51–5.18)	Alcohol 0.41 (0.32–0.53)
• Hypertension	2.95 (2.57–3.39)	Exercise 0.48 (0.39–0.59)
• Abdominal obesity	2.26 (1.90–2.68)	
• Psycho/Social	3.49 (2.41–5.04)	
• ApoB/ApoA1	4.42 (3.43–5.70)	

PCOS

Fruits and Vegetables



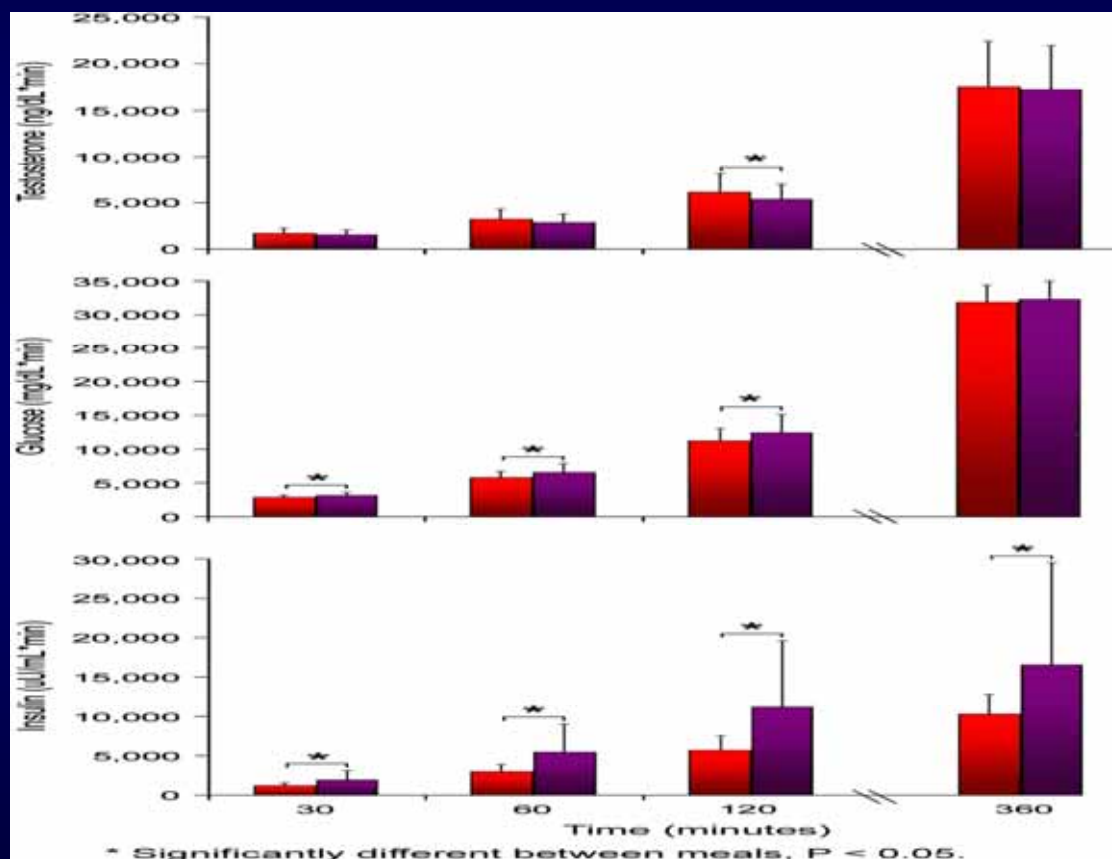
Difference in dietary intake between women with polycystic ovary syndrome and healthy controls

Variable	Control	PCOS	<i>P</i> value
Cola beverages	4.1 ± 7.9	2.9 ± 4.2	.50
White bread	5.5 ± 2.9	7.9 ± 4.4	.02
Fried potatoes	0.4 ± 0.7	1.0 ± 1.5	.07
Cooked potatoes	2.9 ± 3.3	2.8 ± 2.7	.86
White rice	1.1 ± 1.9	1.2 ± 1.7	.77
Pasta	2.6 ± 2.5	2.5 ± 2.8	.92

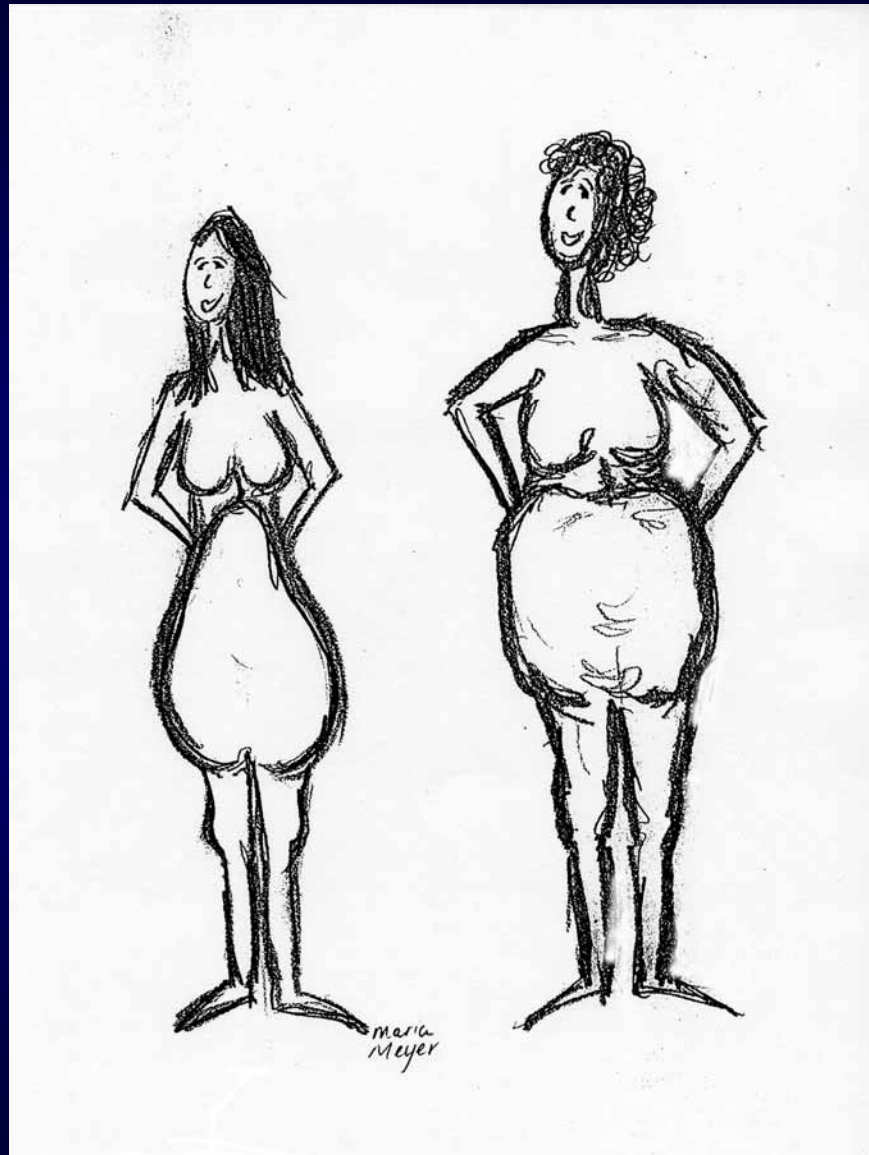
4 day diet recall 30 PCOS
and 27 controls

Douglas, C. et al
2006

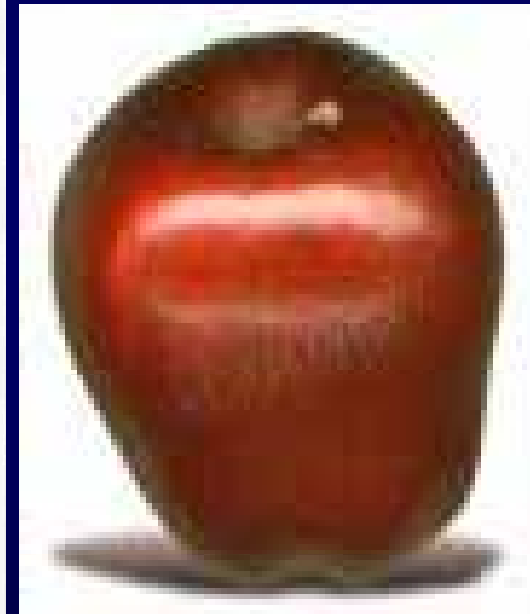
Comparison of hormonal and metabolic markers after a high-fat, Western meal versus a low-fat, high-fiber meal in women with polycystic ovary syndrome



The Pear



The Apple



Waist Circumference < 35 inches (88cm)

Abdominal Obesity and Waist Circumference Thresholds

	Men	Women
Europid	≥ 94 cm (37.0 in.)	≥ 80 cm (31.5 in)
South Asian	≥ 90 cm (35.4 in.)	≥ 80 cm (31.5 in)
Chinese	≥ 90 cm (35.4 in.)	≥ 80 cm (31.5 in)
Japanese	≥ 85 cm (33.5 in.)	≥ 90 cm (35.4 in)

Current NCEP ATP-III criteria

>102 cm (>40 in) in men, >88 cm (>35 in.) in women

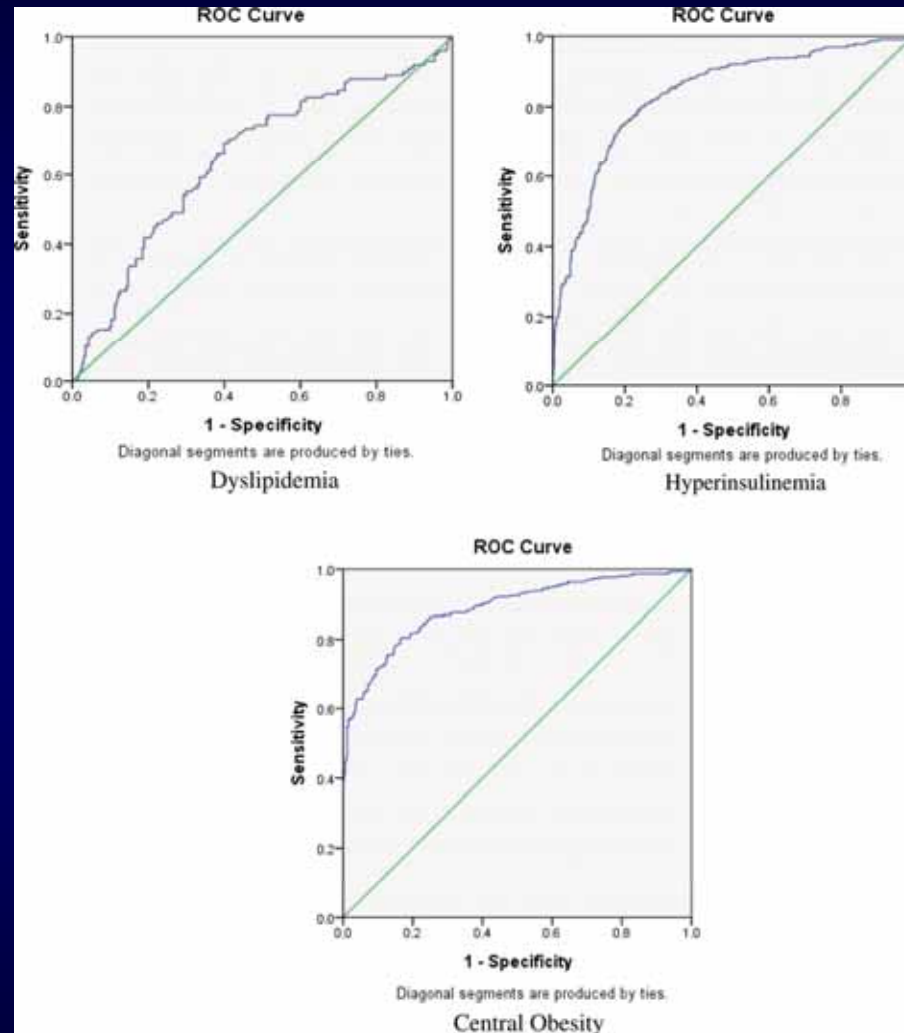
**Appropriate BMI levels for PCOS
patients in Southern China
n=(999) PCOS vs. (922 controls)**

BMI

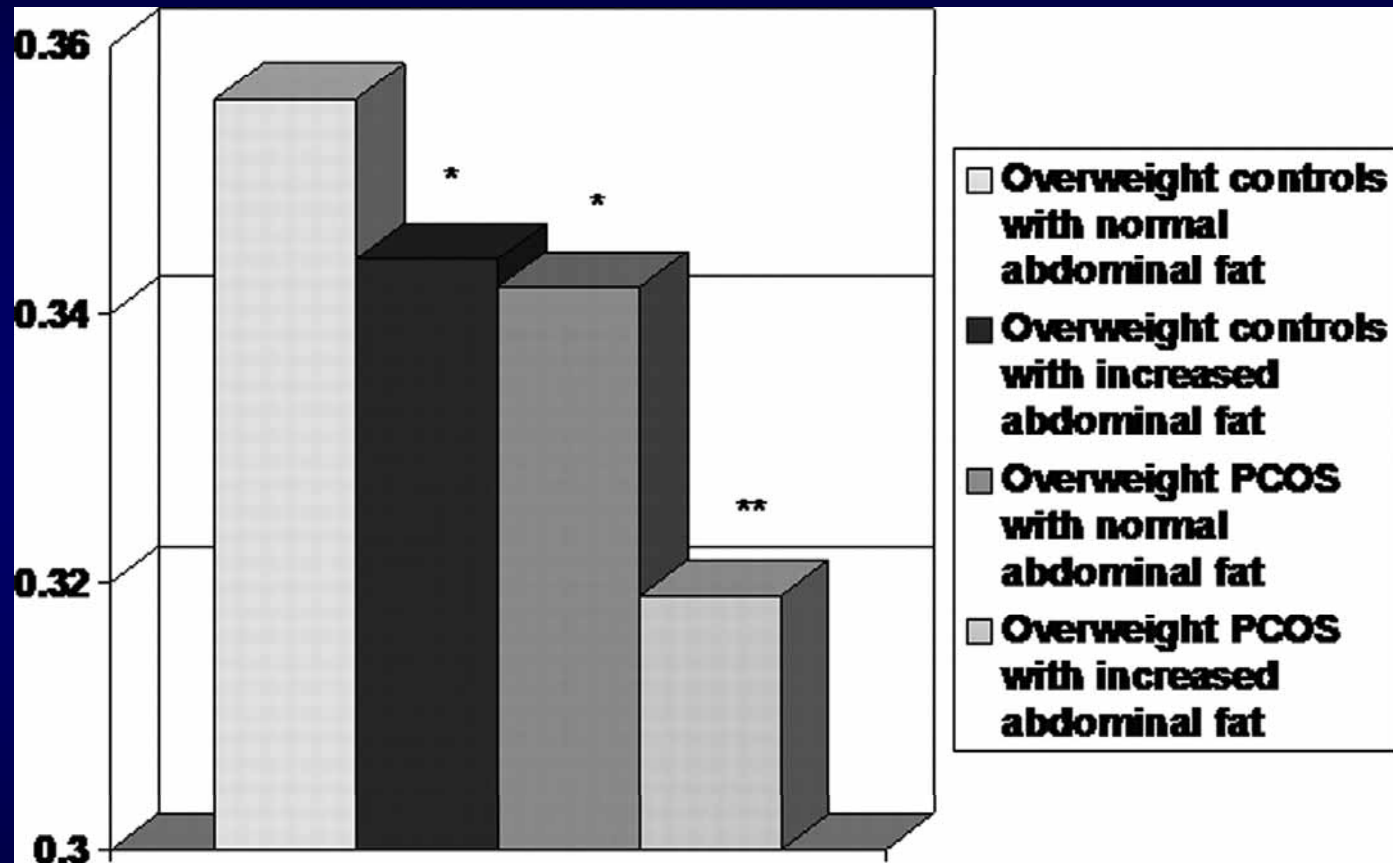
OR dyslipidemia

- | | |
|--|------------------|
| • $<18.5\text{kg/m}^2$ (6.62%) | 2.51(1.02-6.16) |
| • ≥ 18.5 & $<23\text{Kg/m}^2$ (11.7%) | 4.10((2.45-6.85) |
| • ≥ 23 and $<25\text{ Kg/m}^2$ (29%) | 2.22(1.19-4.15) |
| • $\geq 25\text{ Kg/m}^2$ (39%) | 1.36(0.74-2.47) |

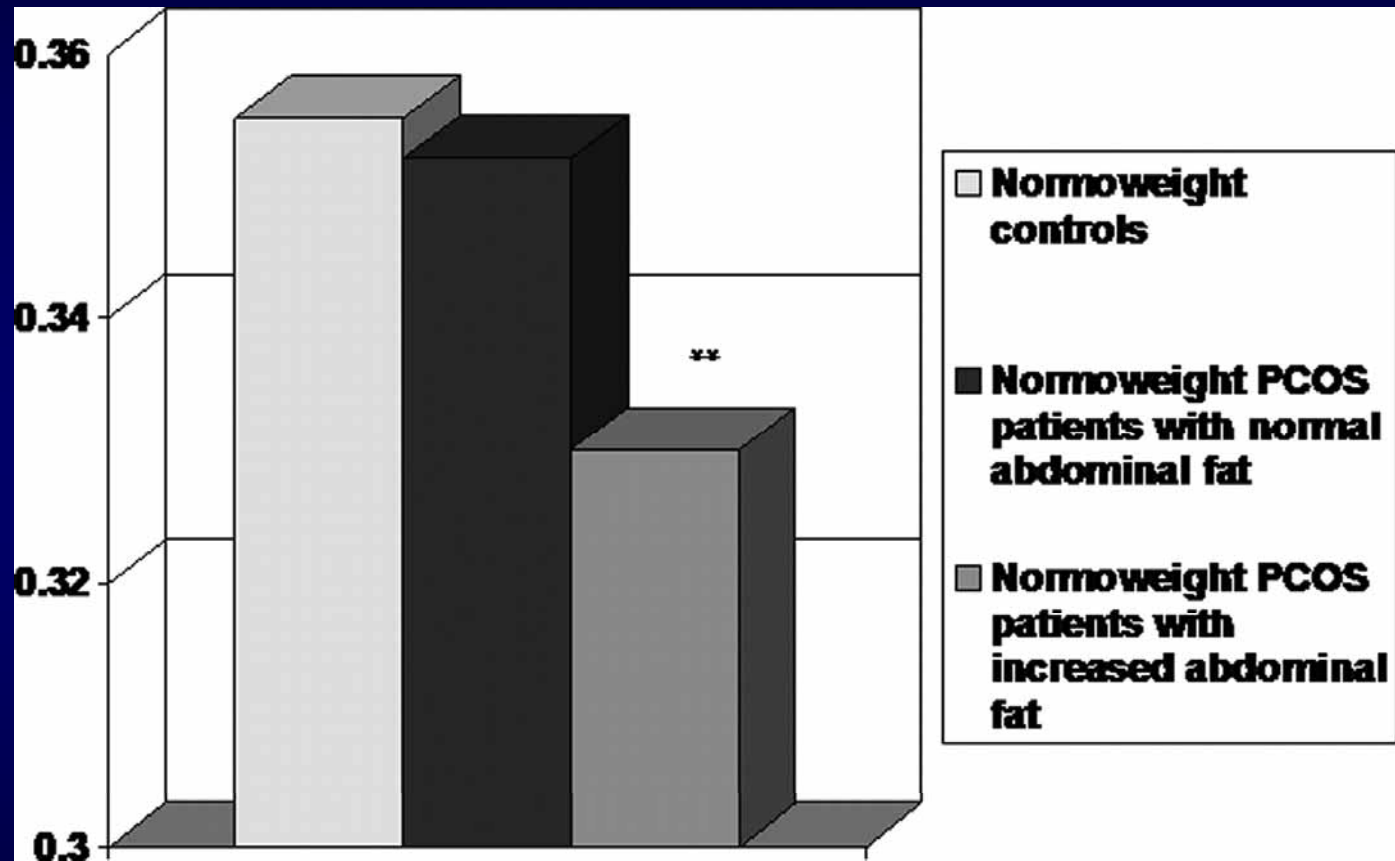
**ROC curves for detecting metabolic syndrome (MetS)(3 or more)
In Chinese PCOS (n=999) BMI 23 Rotterdam**



Insulin sensitivity (calculated by QUICKI) in PCOS patients and controls



Insulin sensitivity in normoweight PCOS patients and controls NIH



Association of biochemical hyperandrogenism with type 2 diabetes and obesity in Chinese women with polycystic ovary syndrome median age 26 vs. 30 in controls

Definition	N(%)	BMI>25 or W:Hip >=.8	BMI>=25	W:Hip >=.8
HA	719 (81.4%)			
Oligo-anovul	850 (96.3%)			
PCO	798 (90.4%)			
Rotterdam	883 (100%)	371 (42%)	173(20%)	203(31%)
NIH	686(77.7%)	311(45%)	149(22%)	167(31%)
PCOS-AES	719(81.4%)	322(45%)	151(21%)	176(23%)
Rotterdam (non HA)	164(18.6%)	49(30%)	22(14%)	162(30%)
Control	717		63(8.8%)	

Variation in metabolic and cardiovascular risk with different polycystic ovary syndrome phenotypes

Parameter	PCOS (n=195)	H+PCO (n=195)	Hirsute (n=68)	Controls (n=25)		P value BMI adjusted
Age (y)	22.31 ± 6.7 ^a	25.89 ± 7.56 ^b	24.73 ± 8.35 ^{ab}	29.68 ± 4.29 ^b	<.001	—
BMI (kg/m ²)	31.06 ± 7.98 ^a	26.96 ± 6.38 ^b	26.91 ± 7.48 ^b	26.97 ± 3.64 ^b	<.001	—
Waist circum- ference (cm)	93.79 ± 18.81 ^a	83.42 ± 13.37 ^b	84.07 ± 16.92 ^b	79.83 ± 8.37 ^b	<.001	.019
SBP (mm Hg)	123.09 ± 16.92 ^a	114.73 ± 21.02 ^b	116.33 ± 15.30 ^b	115.21 ± 9.51 ^b	.002	.24
DBP (mm Hg)	78.9 ± 12.29 ^a	73.48 ± 12.84 ^b	74.22 ± 13.10 ^b	73.6 ± 8.27 ^{ab}	.005	.41

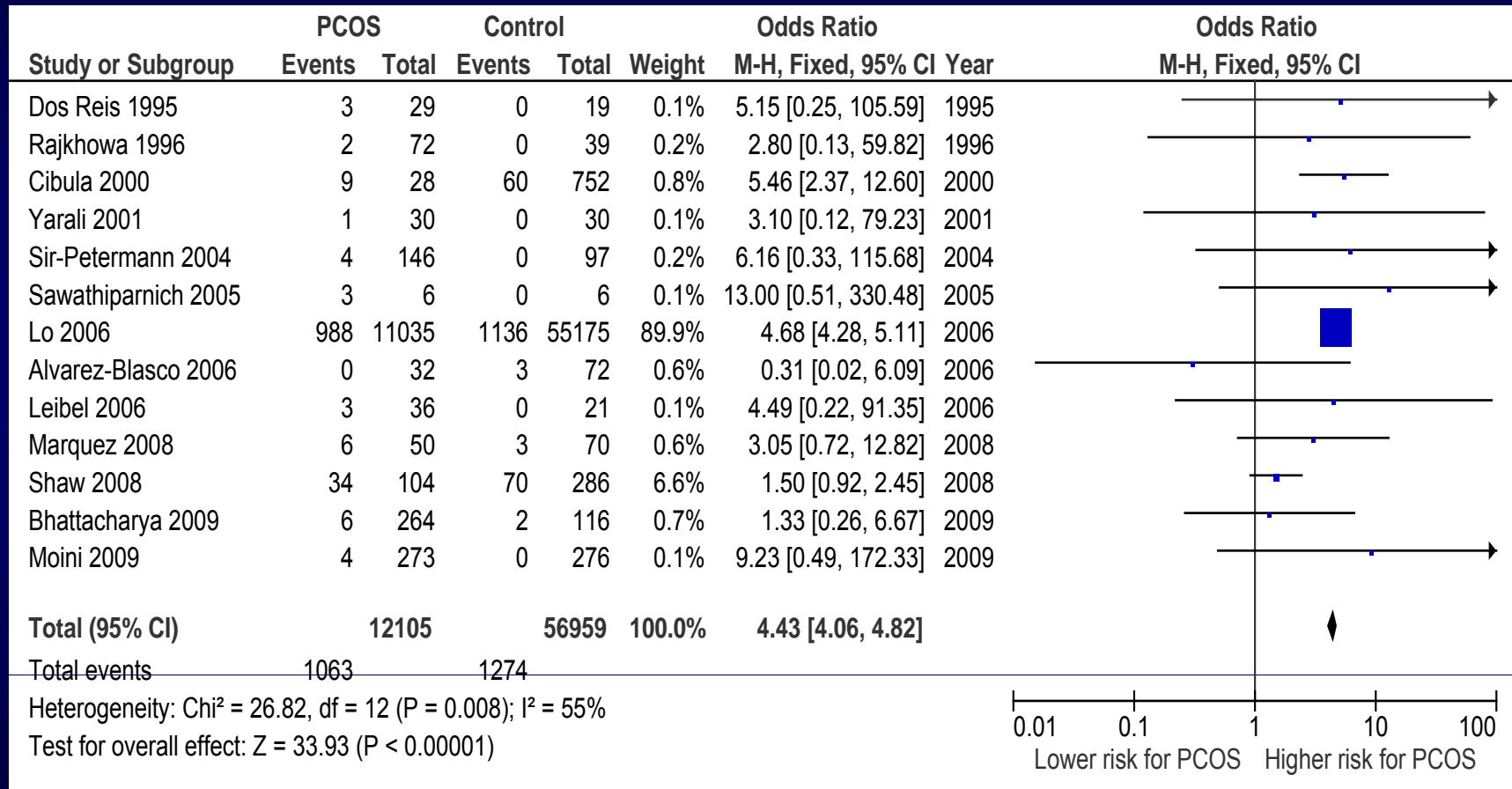
Variation in metabolic and cardiovascular risk with different polycystic ovary syndrome phenotypes

Parameter	PCOS (n=195)	H+PCO (n=195)	Hirsute (n=68)	Controls (n=25)		P value BMI adjusted
Metabolic syndrome ^e (%)	31.3 ^a	11.9 ^b	9.0 ^b	0 ^b	<.001	—
Metabolic syndrome ^e ow/obese (%)	42.9 ^a	20.8 ^b	18.8 ^b	0 ^c	<.04	—
Waist >88 cm (%)	59.9 ^a	33.3 ^b	34.3 ^b	16 ^b	<.001	—
BP ≥130/≥85 mm Hg (%)	40.2 ^a	28.9 ^{ab}	20.3 ^b	13.0 ^b	.003	—

Wiltgen et al 2010

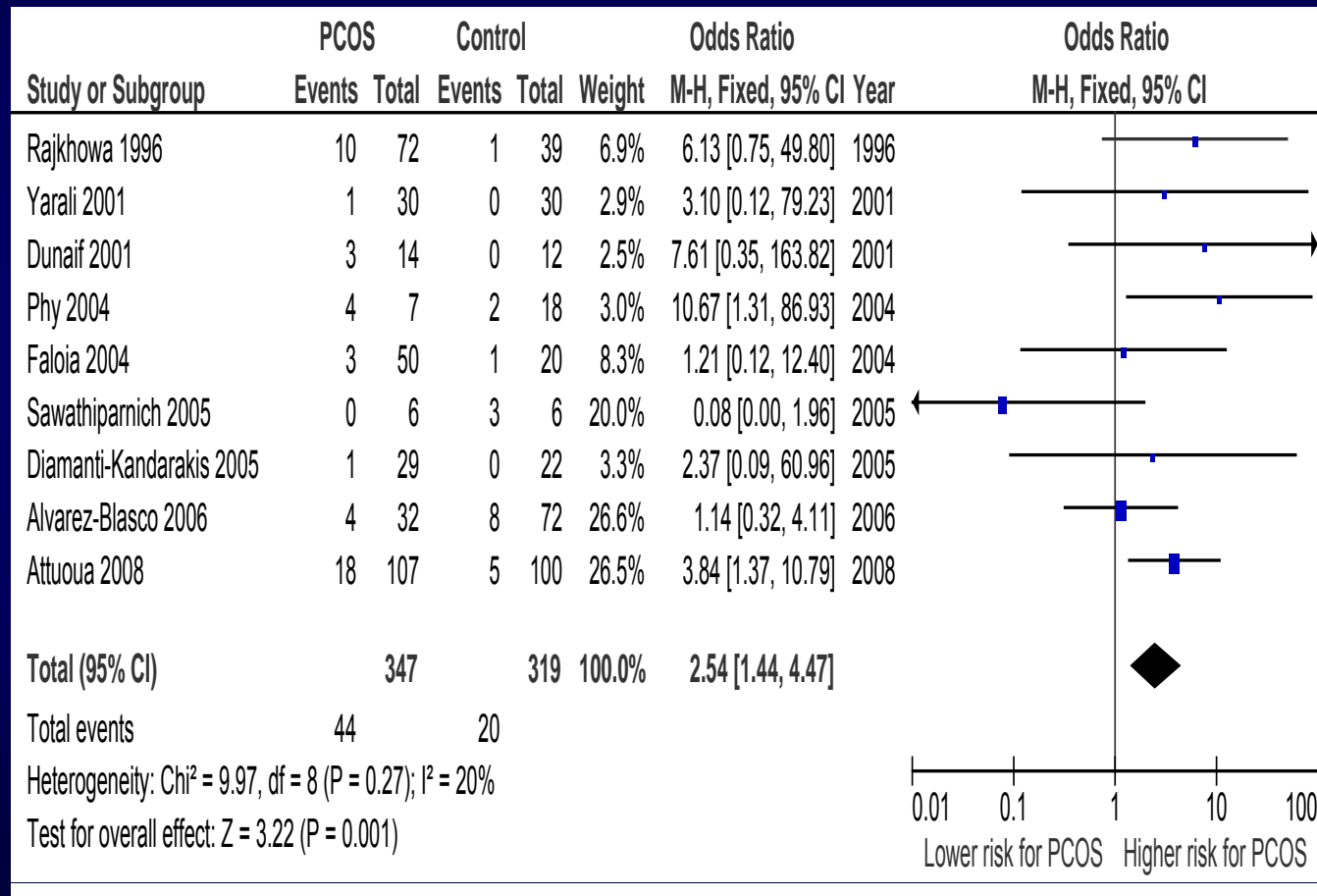
T2DM & PCOS

Prevalence of T2DM in PCOS vs. Controls



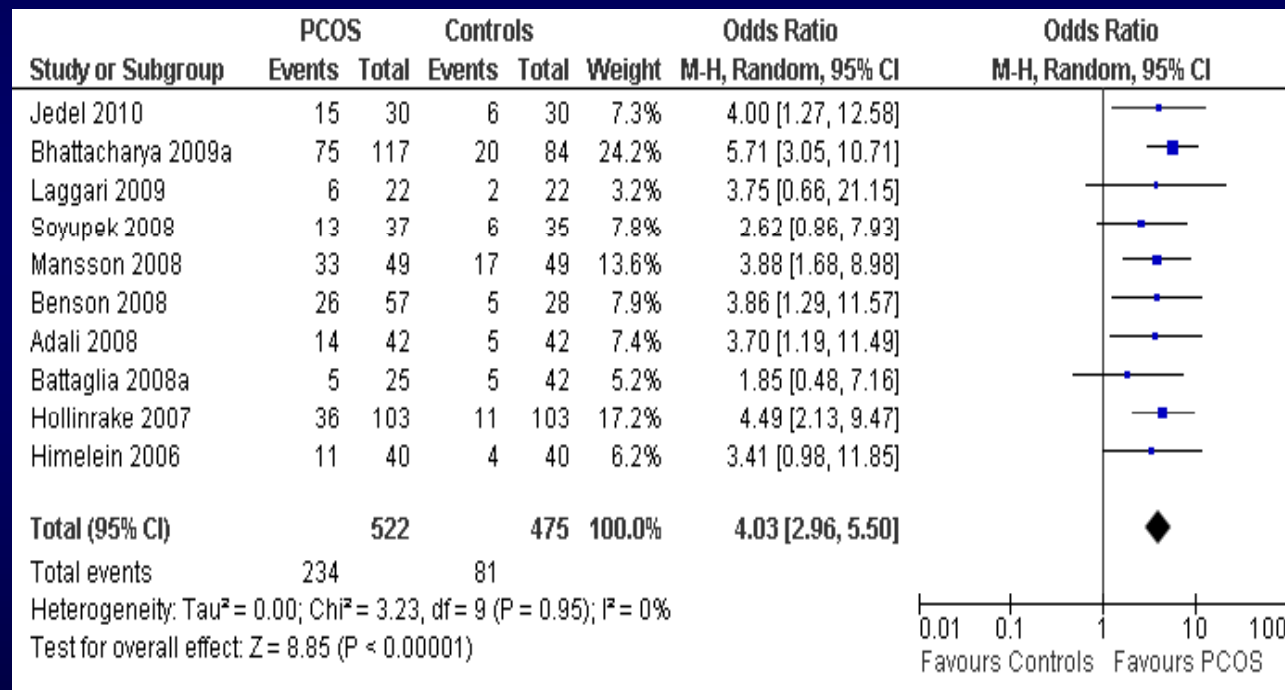
Moran , L. et al. 2010

Prevalence of T2DM in PCOS vs. Controls (BMI matched)



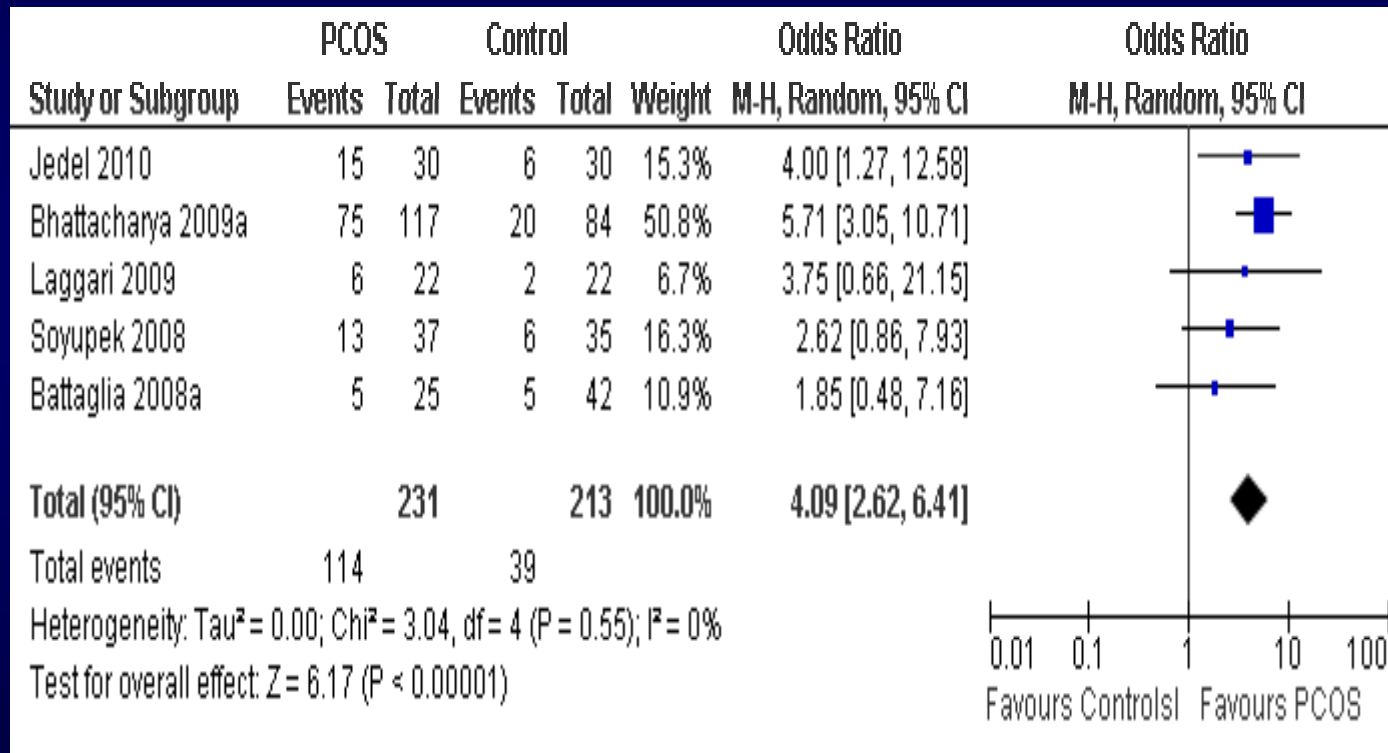
PCOS & Psycho/Social Factors

Odds of Positive Depression Screen in Women with PCOS vs. Controls



Dokras et al 2010

Odds of Depression Score Positive PCOS vs. Controls BMI Matched



Dokras et al 2010

PCOS

&

Dyslipidemia

Lipid and apolipoprotein abnormalities in hirsute women

PCOS (n=47)

- 31 years
- Waist 94.7 cm
- BMI = 33.9
- Higher Trig, lower HDL-cholesterol, higher non HDL cholesterol,
- higher APO CIII*

Non PCOS (n=15)

- 32 years
- Waist 68.9cm
- BMI = 21.6

Wild RA 1992

More Atherogenic Serum Lipoprotein Profile Is Present in Women with Polycystic Ovary Syndrome: A Case-Control Study

**PCOS (n=577) 29 yrs
BMI 27**

**Non PCOS (n=295) 33 years
BMI 24.4**

TG (mg/dL)	95
Cholesterol (mg/dL)	196
*HDL-Chol (mg/dL)	45
+LDL-Chol (mg/dL)	125
**Non HDL Chol (mg/dL)	151
*Apo- AI (mg/dL)	118
Apo B (mg/dL)	81
*Apo B/Apo A	.69

TG (mg/dL)	82
Cholesterol (mg/dL)	178
HDL-Chol(mg/dL)	56
LDL-Chol (mg/dL)	106
Non HDL Chol (mg/dL)	123
Apo- AI (mg/dL)	146
Apo B (mg/dL)	79
Apo B/Apo A	.55

+Calculated
LDL

Valkenburg R et al 2008

Lipids and lipoprotein subfractions in women with PCOS: relationship to metabolic and endocrine parameters

PCOS (n=52)

- BMI = 29.4 matched
- Age = 28.2 yrs
- Waist = 88 cm
- FAI = 8.8
- *Triglycerides (mg/dL)=1.3
- HDL Cholesterol = 1.19

- ***Hepatic lipase (mmol FA/ml/h)= 14.3**

- ***LDL III (mg/dL) 38**

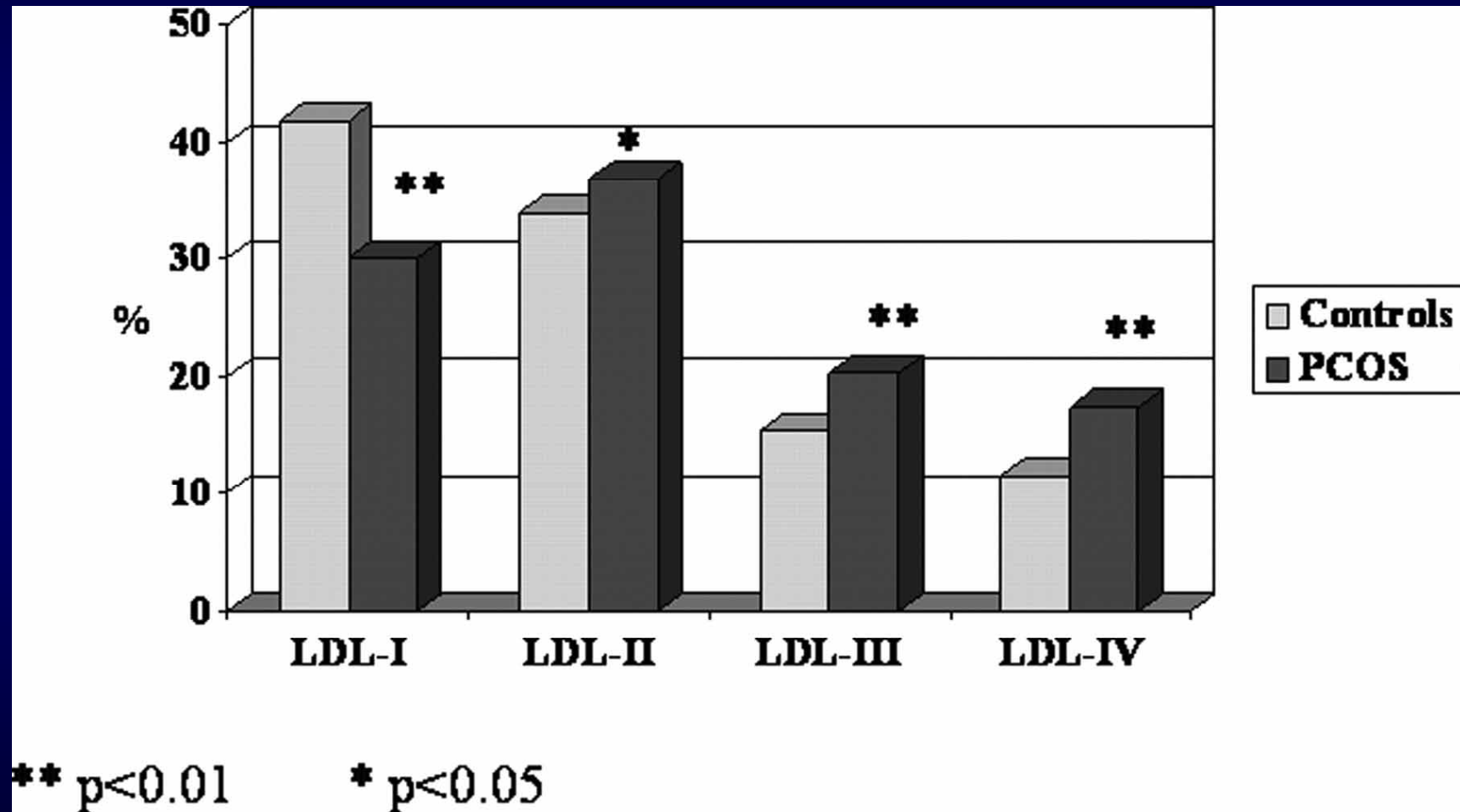
Non PCOS (n=14)

- BMI= 31.2
- Age = 31.2 yrs
- Waist = 82.9 cm
- FAI = 3.8
- *Triglycerides (mmol/L)=0.9
- HDL Cholesterol = 1.31

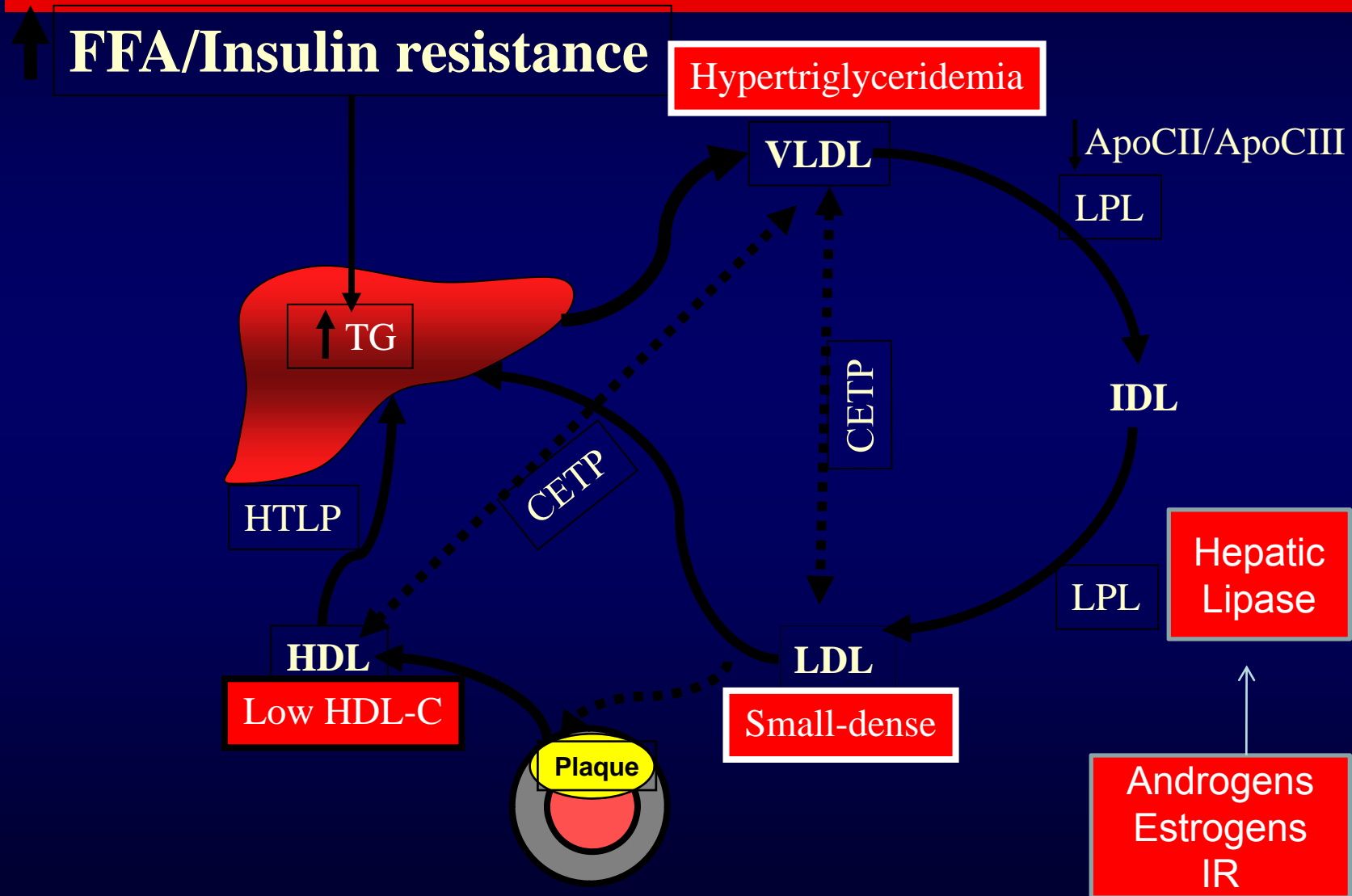
- **Hepatic lipase (mmol FA/ml/h) = 10.2**

- **LDL III (mg/dL) = 25**

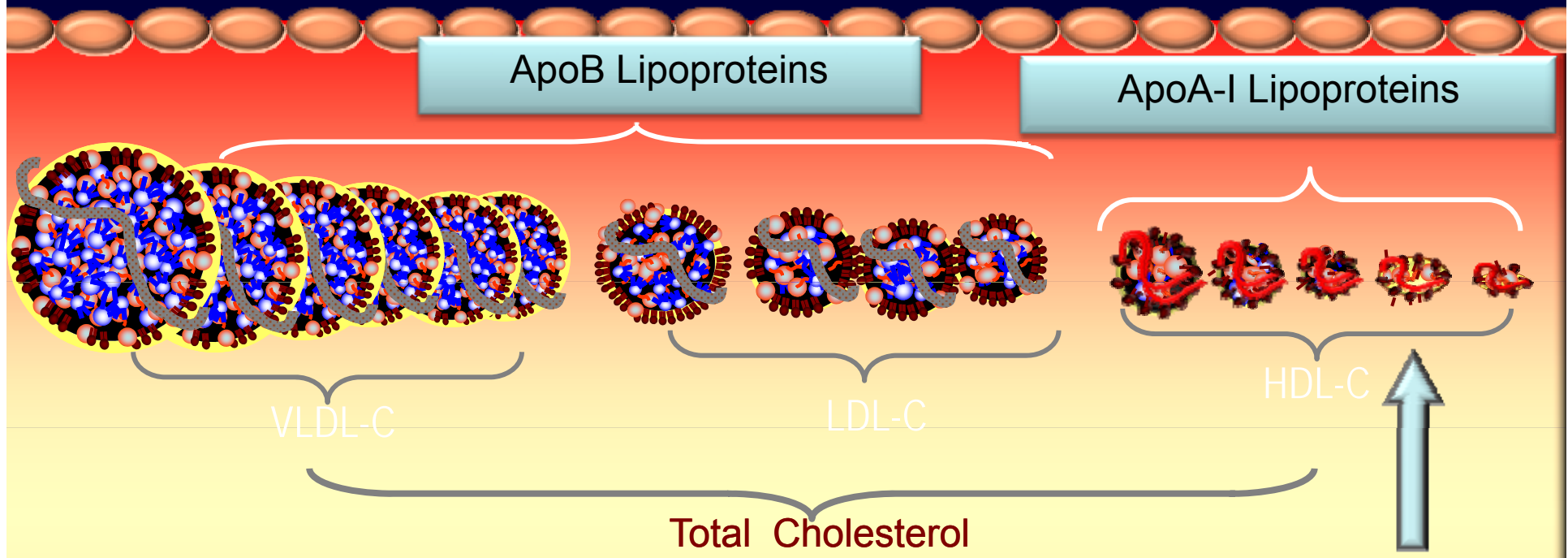
LDL classes in 30 PCOS patients and 24 weight-matched controls



Dyslipidemia of PCOS



Apolipoprotein B & A-I Surrogates

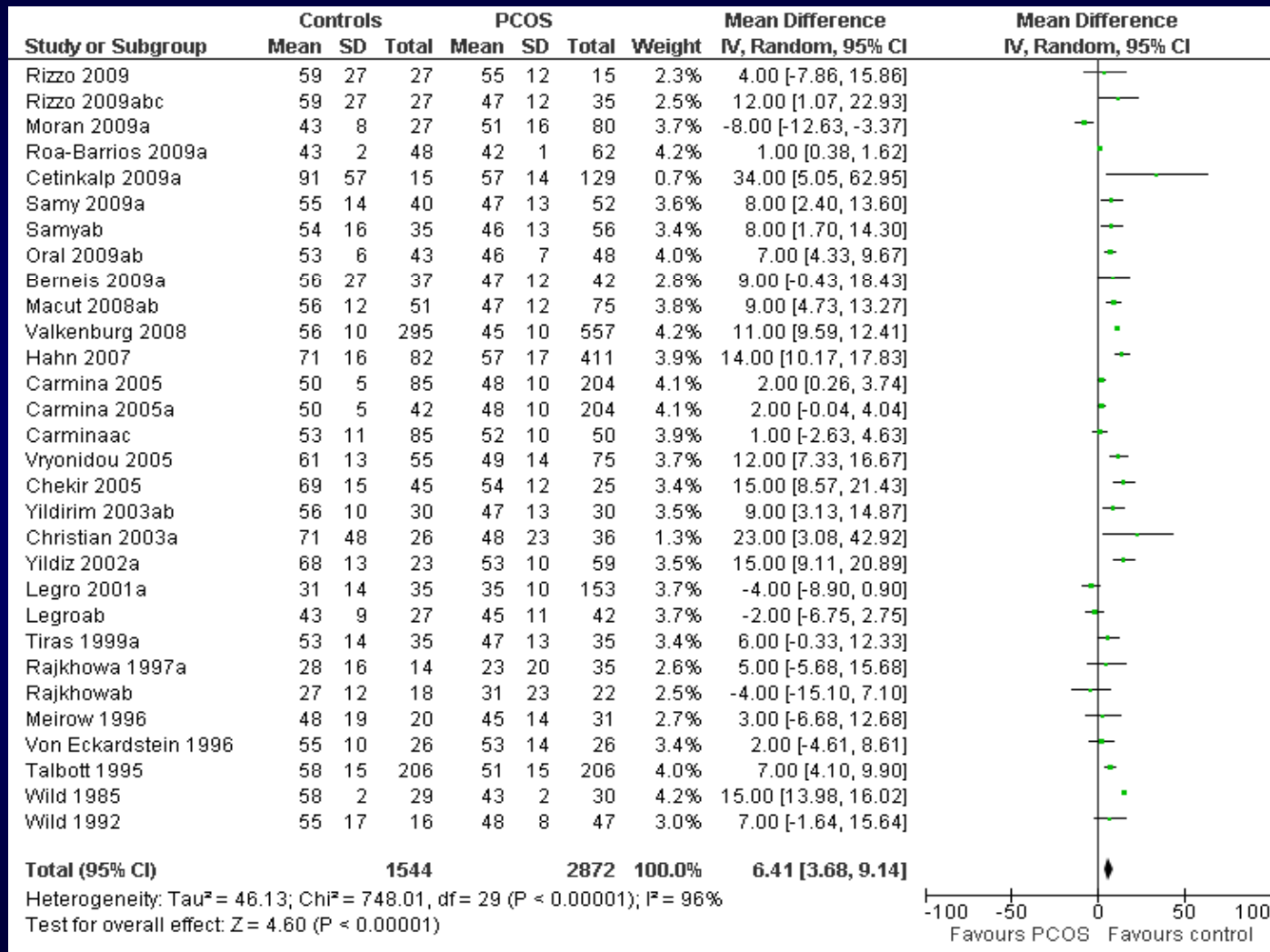


TC is an apoB surrogate

HDL-C is the lipid surrogate of apoA-I

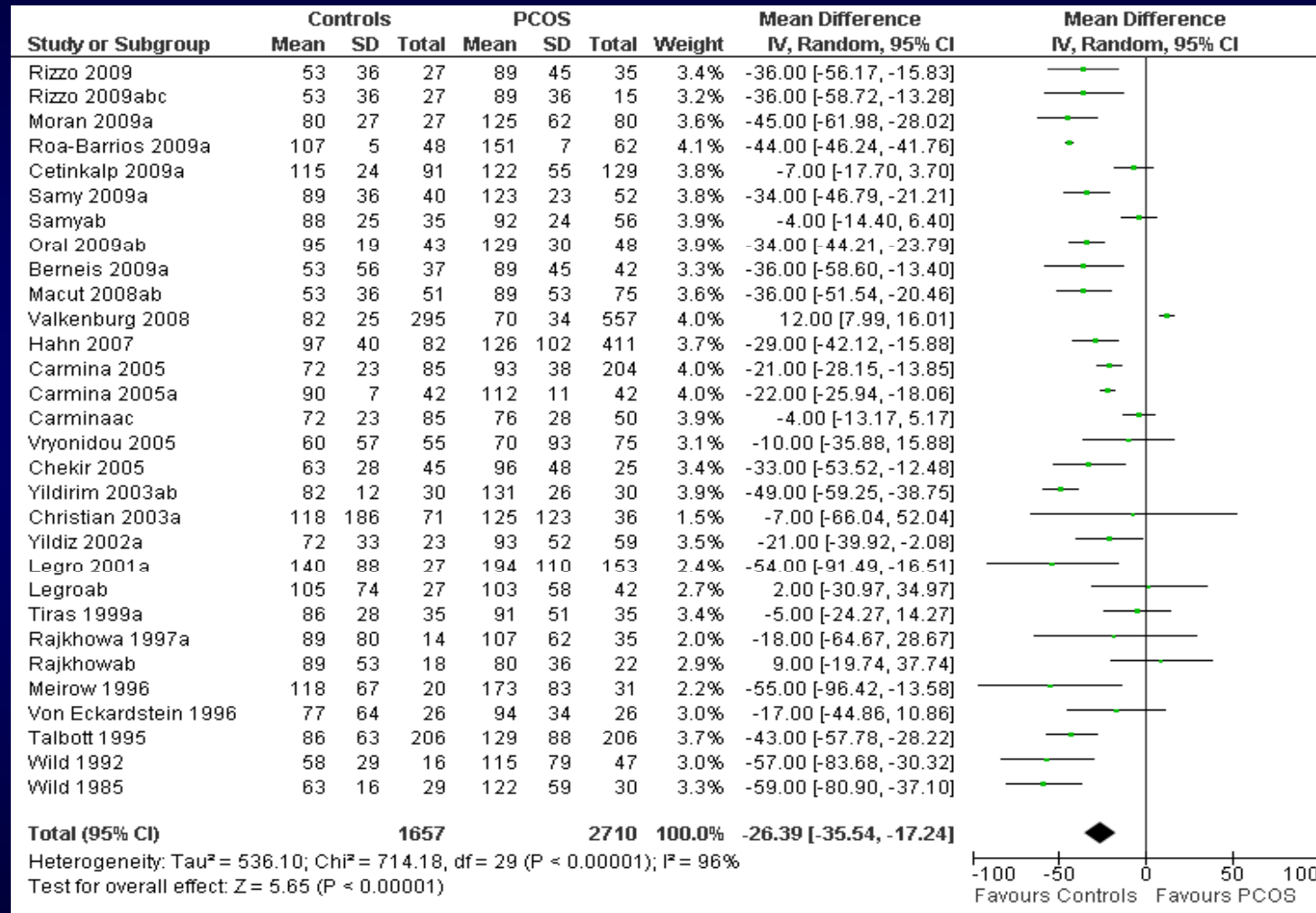
TC/HDL-C or LDL-C/HDL-C ratios
are apoB/A-I surrogates

HDL-C PCOS vs. Controls (mg/dL)



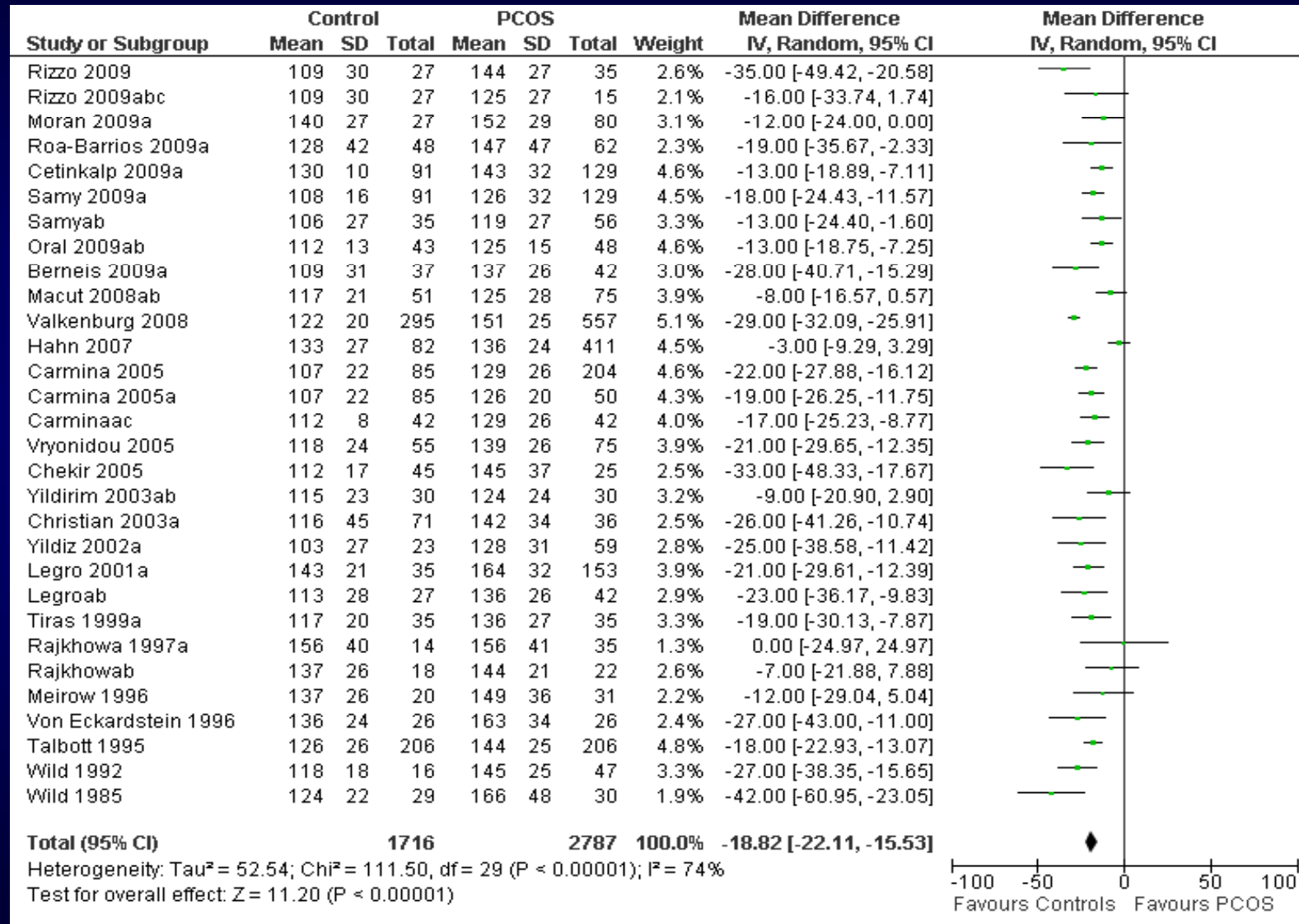
Wild et al 2010

PCOS vs. Controls Triglycerides (mg/dL)

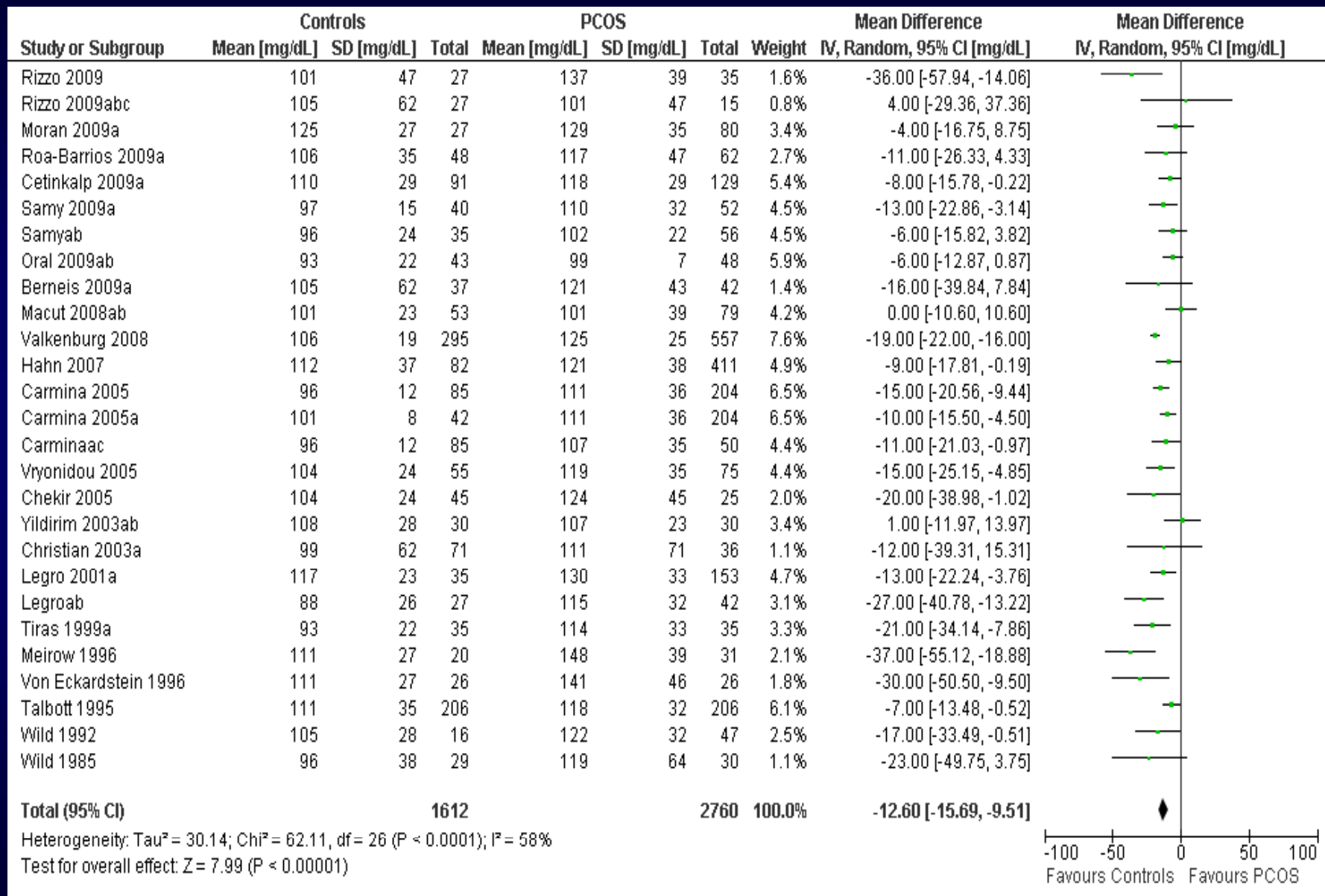


Wild et al 2010

Non-HDL-C PCOS vs. Controls (mg/dL)



LDL -C in PCOS vs. controls (mg/dL)

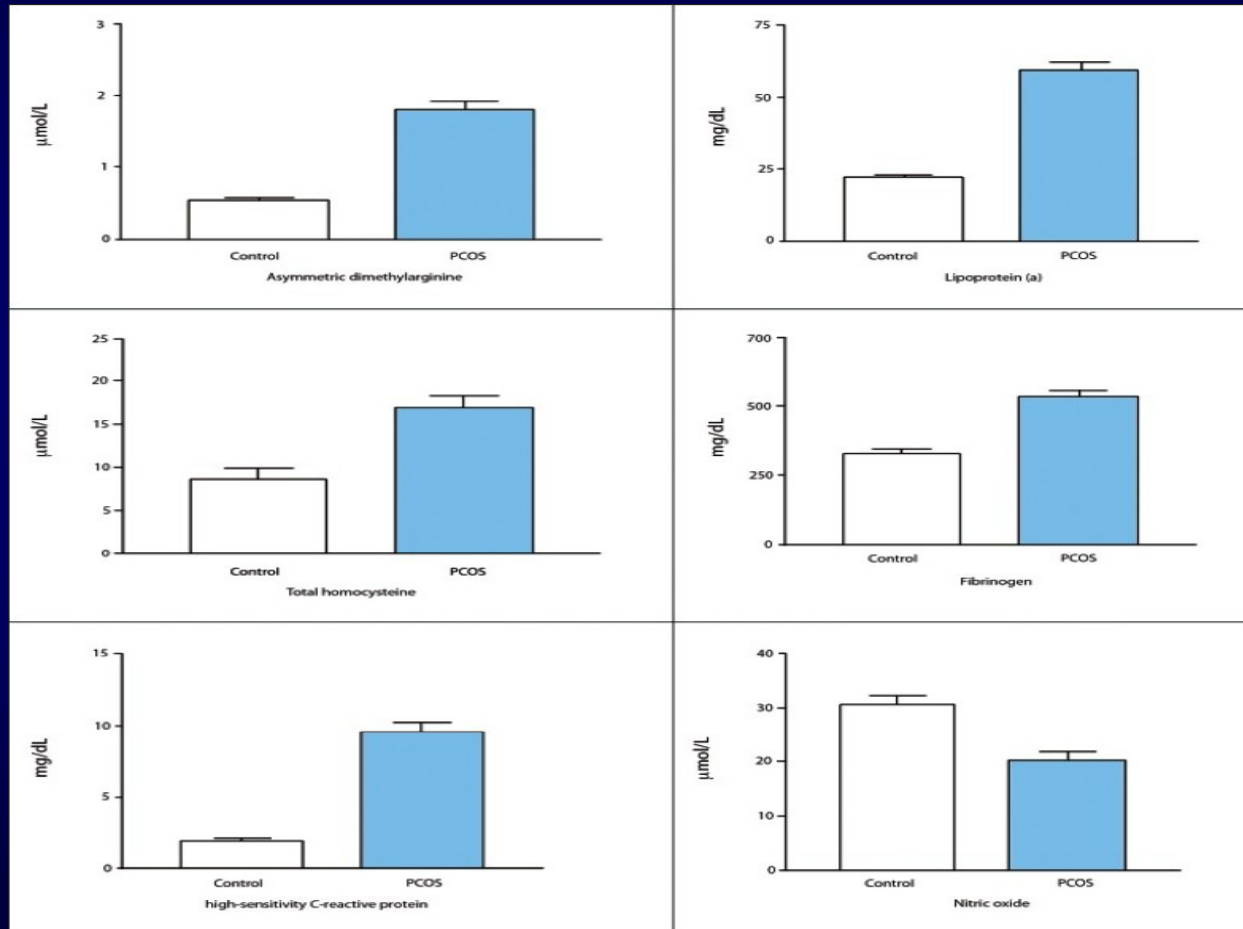


Inflammatory Markers in PCOS

n=108 PCOS vs. n=75 normal

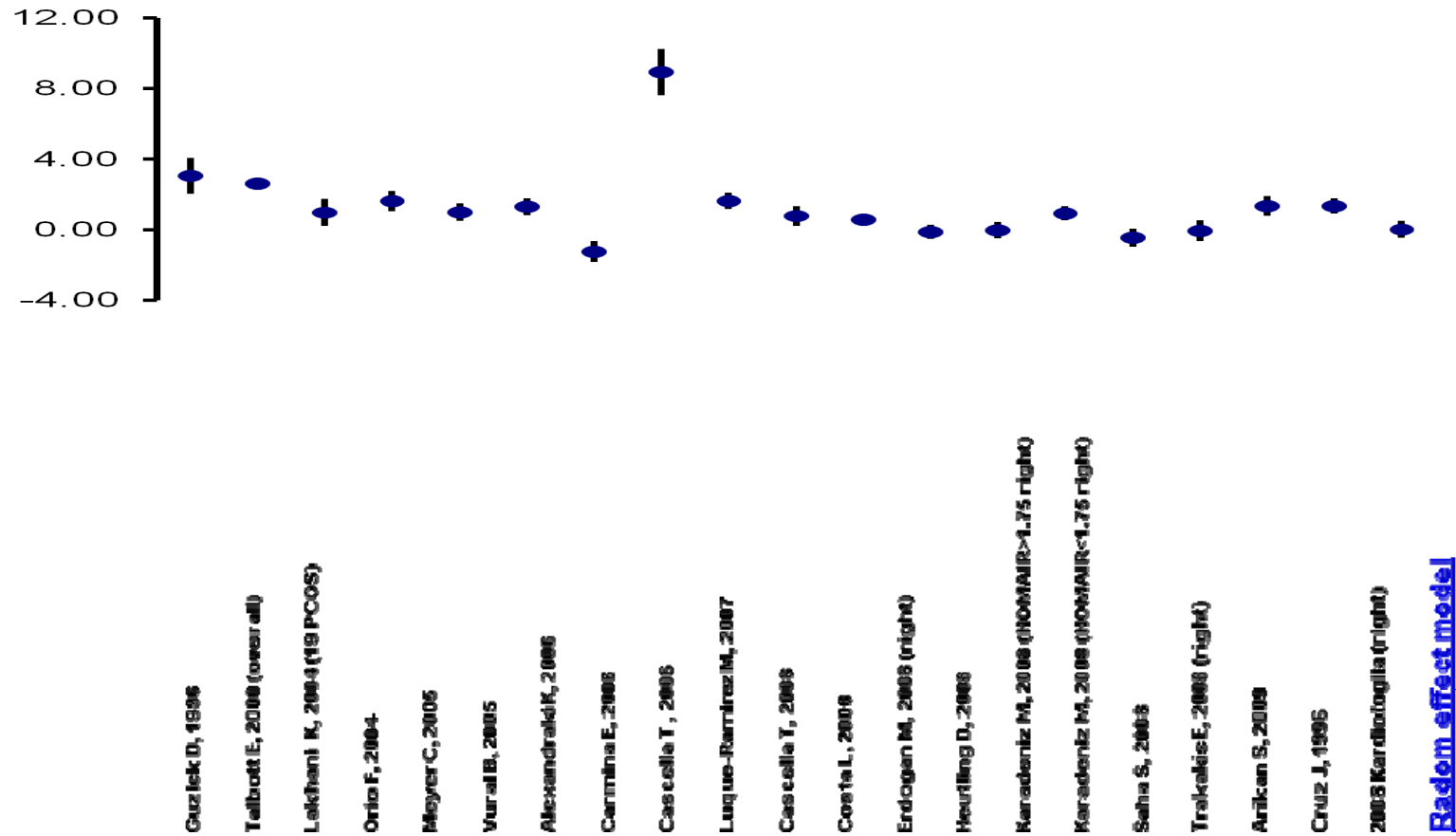
	BMI < 27 Kg/m ²	BMI < 27 Kg/m ²	BMI ≥ 27 Kg/m ²	BMI ≥ 27 Kg/m ²
	Controls (n=35)	PCOS (n=56)	Controls (n=40)	PCOS (n=52)
hs-CRP(mg/L)	104 _± 0.25	1.67 _± 0.23*	1.15 _± 0.22	3.45 _± 0.35**
IL-6(pg/mg/L)	1.25 _± 0.31	1.52 _± 0.34*	1.34 _± 0.35	6.45 _± 2.27**
TNF-a	3.66 _± 1.02	3.72 _± 1.26	3.76 _± 1.04*	6.87 _± 1.12**

Inflammatory Markers in PCOS



PCOS
&
CVD

Carotid Intimal Thickness in PCOS



PCOS & Coronary Artery Calcium

Author, Year	Study Size	Study Population/ Study Design	Control for Age and BMI		Outcome Measure/ Results
			Design	Analysis	
Shroff, 2007	24 cases 24 controls	Obese, premenopausal, clinic population [cross-sectional]	Frequency match for age & BMI	None	Prevalence of CAC (>0) OR=5.5 (95% CI=1.03, 29.45) p<0.03
Christian, 2003	36 cases 71 controls	Premenopausal, age 30-45 [cross-sectional]	Frequency match for age & BMI	Age & BMI adjusted	Prevalence of CAC (>0) OR=1.99 (95% CI=0.68,5.82) p=0.21 (NS)
Talbott, 2004	61 cases 85 controls	White women, BMI < 35 [prospective]	BMI restricted (<35)	Age & BMI adjusted	Prevalence of CAC (>0) OR=2.31 (95% CI=1.00, 5.33) p=0.049
Talbott, 2008	149 cases 166 controls	All races All BMI [cross-sectional]		Age & BMI adjusted	Prevalence of CAC >10 OR=1.90 (95% CI=1.04, 3.48) p=0.037

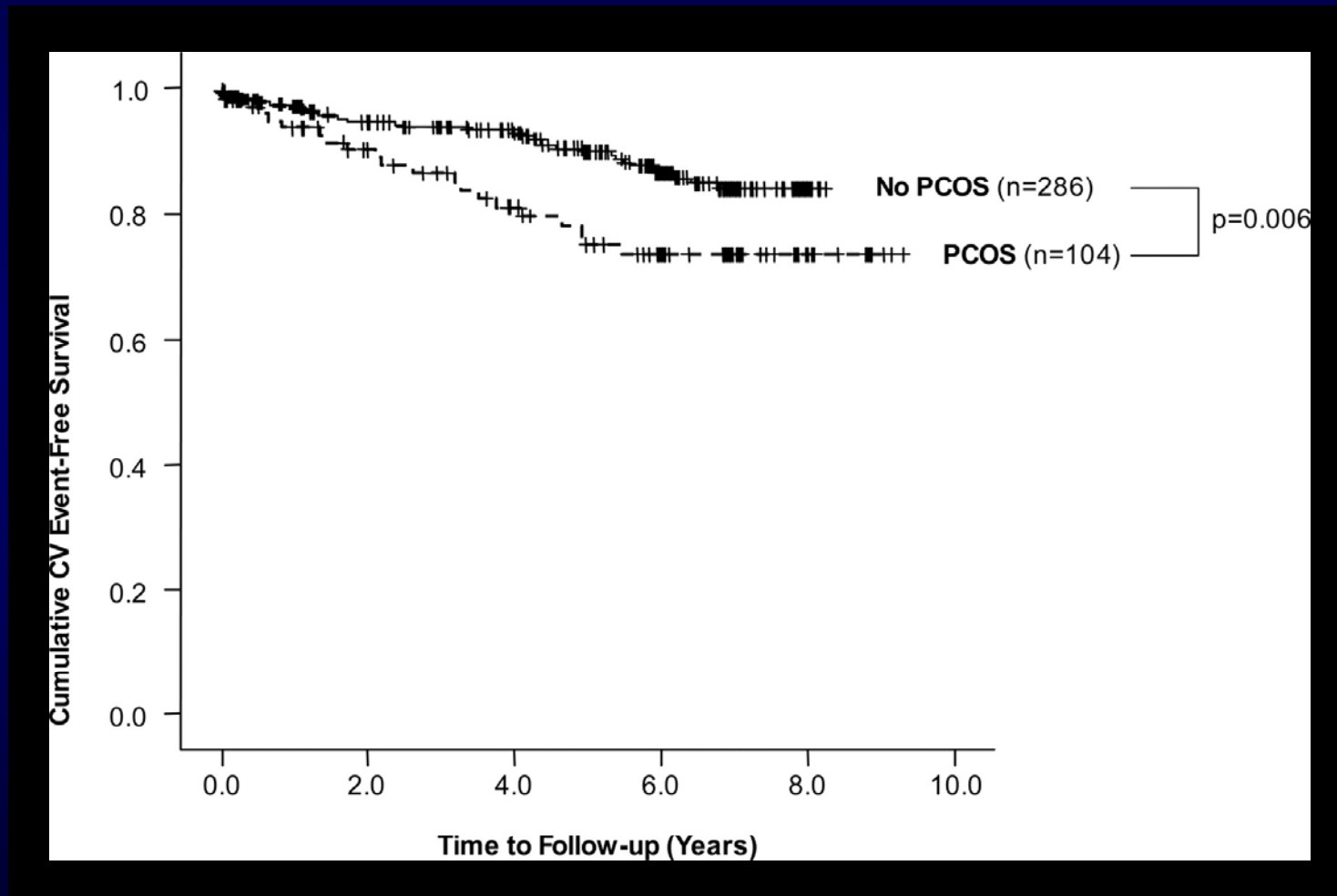
NICHD Criteria was used to diagnose PCOS cases in all studies.

PCOS in Postmenopausal Women

N=601 , non-diabetic non-oophorectomized women

	Exp (B)	95% confidence interval	p
Cardiovascular disease			
Age	1.056	1.021–1.093	<0.01
PCOS	1.362	1.052–1.762	0.02
Coronary heart disease			
Age	1.050	1.012–1.090	<0.01
PCOS	1.360	1.030–1.796	0.03

Cumulative Unadjusted CV Death or MI Free Survival in Postmenopausal Women \pm Clinical Features of PCOS



Shaw et al 2008

Shaw et al 2008

First Author	Date	Journal	N	(S.D.) Age range	Endpoints	Criteria for PCOS	P value	Odds ratio C.I.
1. Pierpoint	1998	J Clin Epid	786 women diagnosed between 1930-1979	20-74	Follow-up 1955-1997 Ischemic (CHD) Heart Disease, Diabetes Mortality	NIH	n.s.	Ischemic heart disease SMR= 1.40 (.75-2.40) ;Diabetes: 3.5 (1.5-8.4)
2. Cibula	2000	Human Reproduc.	28 cases 752 controls	51.9 (4.64) (45 – 59)	6/28 (21%) cases with CHD compared to 38/752 or (5%)controls	NIH	P<.001	4.2
3. Wild	2000	J. Clinical Endocrin.	390 PCOS and 1060 age matched controls	56.7 (38-98)	CHD and cerebrovascular disease endpoints	Rotterdam	n.s. for CHD	4.7% CHD cases and 4.0% controls p=.6 CVD: 3.1% in cases versus 1.2%
4. Elting	2001	Human Repro	346 cases control rates from general population	38.7 (30.3 – 55.7)	CHD endpoints in 0.9% PCOS women	NIH	n.s	CHD Prevalence rates: .9 (.2-2.6) in cases .7 (.5-.9) in controls
5. Talbott	2004	Minerva Ginecol	127 PCOS white cases; 142 white controls seen in 1997 CHARM II f-up	Mean age: 42.8(6.3) cases and 43.4 (6.25) (30-62)	CHD endpoints: MI, CA bypass surgery, angina pectoris))	NIH	P<.05	1 MI, 1 CA bypass, 3 angina pectoris among cases OR=5.86
6. Shaw ²	2008	JCEM	390 women : cohort study	62.5 ± 10	CHD death or on fatal Myocardial Infarction	Premenopausal hx of irregular Menses & current biochemical evidence of hyperandrogenemia.	P <.001	Hazard ratio: 1.61 (1.22-2.12)
7. Solomon ¹	2002	JCEM	82,439 women	Range:47.3-48.6 at f-up	Fatal and non fatal (NF) CHD	History of premenopausal menstrual irregularity	P< .05	1.25(1.07-1.47 NF 1.67 (1.35-2.06 fatal

¹ Solomon: menstrual cycle irregularity at age 20-35 baseline & free of CHD at baseline

² Shaw: top quartile of hyperandrogenemia and menstrual cycle irregularity

AE-PCOS STATEMENT

Prevention of CVD in PCOS

2010 Consensus Statement (AE-PCOS Society)

- At risk
 - obesity (especially abdominal), smoking, hypertension
 - dyslipidemia (increased LDL-C and/or non-HDL-C)
 - subclinical vascular disease,
 - IGT
 - FH of premature CVD (<55 yrs, male relative; <65 yrs, female relative)
- At high risk
 - MBS
 - T2DM, overt vascular or renal disease

Prevention of CVD in PCOS

2010 Consensus Statement (AE-PCOS Society)

- BP, BMI and waist circumference
 - Every visit
- Lipid profile
 - Repeat every 2 yrs, or sooner if weight gain occurs
- 2-h post 75-g oral glucose challenge
 - Obese women
 - Any woman with >40 yr, PMH of gestational DM or FH of T2DM
 - Repeat every 2 yrs, or sooner if additional risk factors, or IGT.

Wild et al 2010

Wild et al 2010

Prevention of CVD in PCOS

Lifestyle Modification

- Positive Multiple factor approach simultaneously is recommended coupled with understanding stages of change
 - Pre-contemplation, contemplation, preparation, action, maintenance, relapse
- Hypocaloric diet (i.e., 500 Kcal/day deficit) with reduced glycemic load to decrease weight by 5%-10%
- Exercise with orthopedic and cardiovascular limitations
 - Individualized exercise program for optimal compliance
 - Walking (10,000 steps = 30 minutes daily exercise; 15,000 steps usually needed for weight loss)
- Smoking cessation
- Medication as needed to reach targets

CONCLUSION

INTERHEART study: case-control study
9 risk factors accounted for
94% of the Population Attributable Risk
for myocardial infarction

PCOS at RISK or HIGH RISK

Risk	Odds	Protective Odds
✓ Smoking	2·86 (2·36–3·48)✓	Fruits/Vegs 0·58 (0·48–·71)
✓ Diabetes	4·26 (3·51–5·18)✓	Alcohol 0·41 (0·32–·53)
✓ Hypertension	2·95 (2·57–3·39)✓	Exercise 0·48 (0·39–·59)
✓ Abdominal obesity	2·26 (1·90–2·68)	
✓ Psycho/Social	3·49 (2·41–5·04)	
✓ ApoB/ApoA1	4·42 (3·43–5·70)	