



Marmara
Üniversitesi



PKOS yönetiminde birinci basamak tedaviler

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TY

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Fenotipler

Features	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia	+	+	+	+	-	-	+	-	+	-	+	-	-	-	+	-
Hirsutism	+	+	-	-	+	+	+	+	-	-	+	-	-	+	-	-
Oligo-anovulation	+	+	+	+	+	+	-	-	-	+	-	-	+	-	-	-
Polycystic ovaries	+	-	+	-	+	-	+	+	+	+	-	+	-	-	-	-
NIH 1990 criteria	√	√	√	√	√	√	6									
Rotterdam 2003 criteria	√	√	√	√	√	√	√	√	√	√	10					
AE-PCOS 2006 criteria	√	√	√	√	√	√	√	√	√	9						

Belirgin klinik fenotipler

1990 NICHD Guidelines

- 1 Hirsutism, hyperandrogenemia, and oligo-anovulation
- 2 Hirsutism and oligo-anovulation
- 3 Hyperandrogenemia and oligo-anovulation

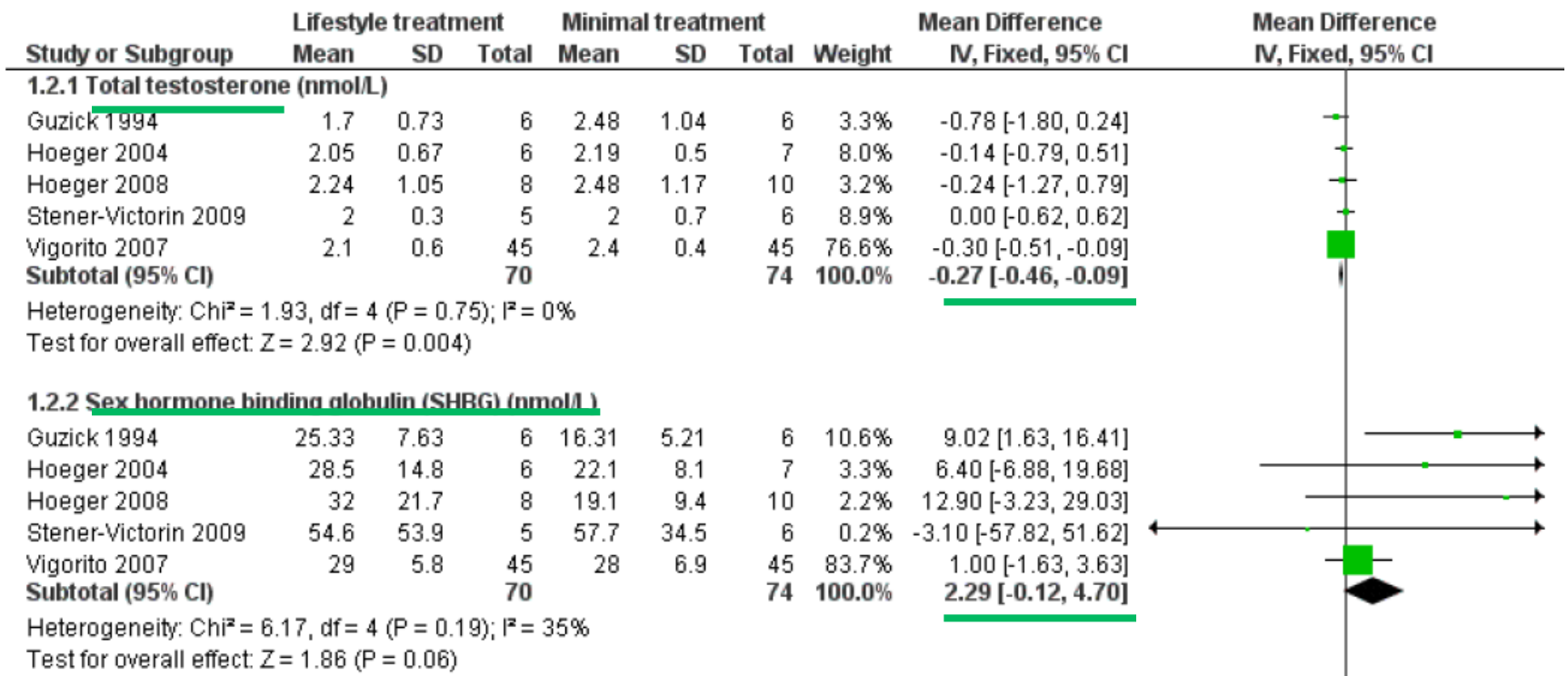
2003 ESHRE/ASRM (Rotterdam) Guidelines

- 1 Oligo-anovulation, hirsutism, and hyperandrogenemia
- 2 Oligo-anovulation, hirsutism, and polycystic ovaries
- 3 Oligo-anovulation, hirsutism, and regular cycles
- 4 Oligo-anovulation, hyperandrogenemia, and polycystic ovaries
- 5 Oligo-anovulation and hyperandrogenemia
- 6 Oligo-anovulation and hyperandrogenemia
- 7 Oligo-anovulation and polycystic ovaries
- 8 Polycystic ovaries, hirsutism, hyperandrogenemia, and regular cycles
- 9 Polycystic ovaries, hirsutism, and regular cycles
- 10 Polycystic ovaries, hyperandrogenemia, and regular cycles

2006 AES Guidelines

- 1 Hirsutism, hyperandrogenemia, oligo-anovulation, and polycystic ovaries
- 2 Hirsutism, hyperandrogenemia, and oligo-anovulation
- 3 Hirsutism, oligo-anovulation, and polycystic ovaries
- 4 Hyperandrogenemia, oligo-anovulation, and polycystic ovaries
- 5 Hirsutism and oligo-anovulation
- 6 Hyperandrogenemia and oligo-anovulation
- 7 Hirsutism, hyperandrogenemia, polycystic ovaries, and regular cycles
- 8 Hirsutism, polycystic ovaries, and regular cycles
- 9 Hyperandrogenemia, polycystic ovaries, and regular cycles

Yaşam tarzı değişiklikleri



Serbest androjen indeksi / FG

1.2.3 Estimated free testosterone measured as free androgen index (FAI)

Hoeger 2004	8.5	3.8	6	10.8	3.8	7	10.6%	-2.30 [-6.23, 1.63]
Hoeger 2008	9.5	5.3	8	16.8	11.2	10	2.6%	-7.30 [-15.15, 0.55]
Stener-Victorin 2009	8.8	3.3	5	5.4	5.2	6	6.4%	3.40 [-1.67, 8.47]
Vigorito 2007	8.7	3.4	45	8.5	3.5	45	80.4%	0.20 [-1.23, 1.63]
Subtotal (95% CI)			64			68	100.0%	-0.06 [-1.34, 1.22]

Heterogeneity: $\text{Chi}^2 = 6.43$, $\text{df} = 3$ ($P = 0.09$); $I^2 = 53\%$

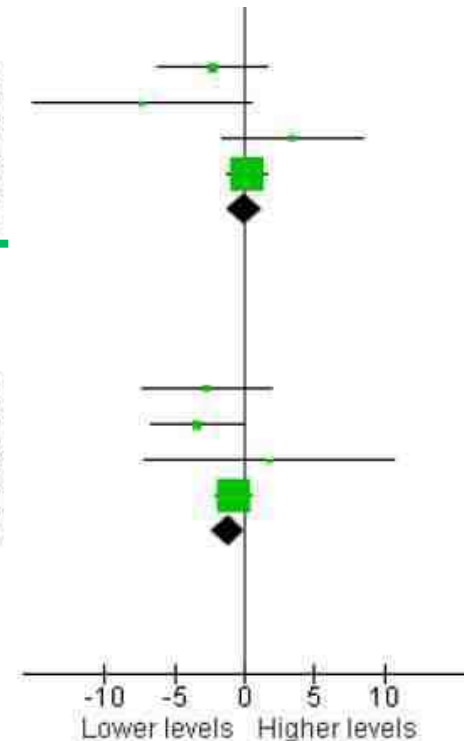
Test for overall effect: $Z = 0.09$ ($P = 0.93$)

1.2.4 Clinical hyperandrogenism (Ferriman-Gallwey score)

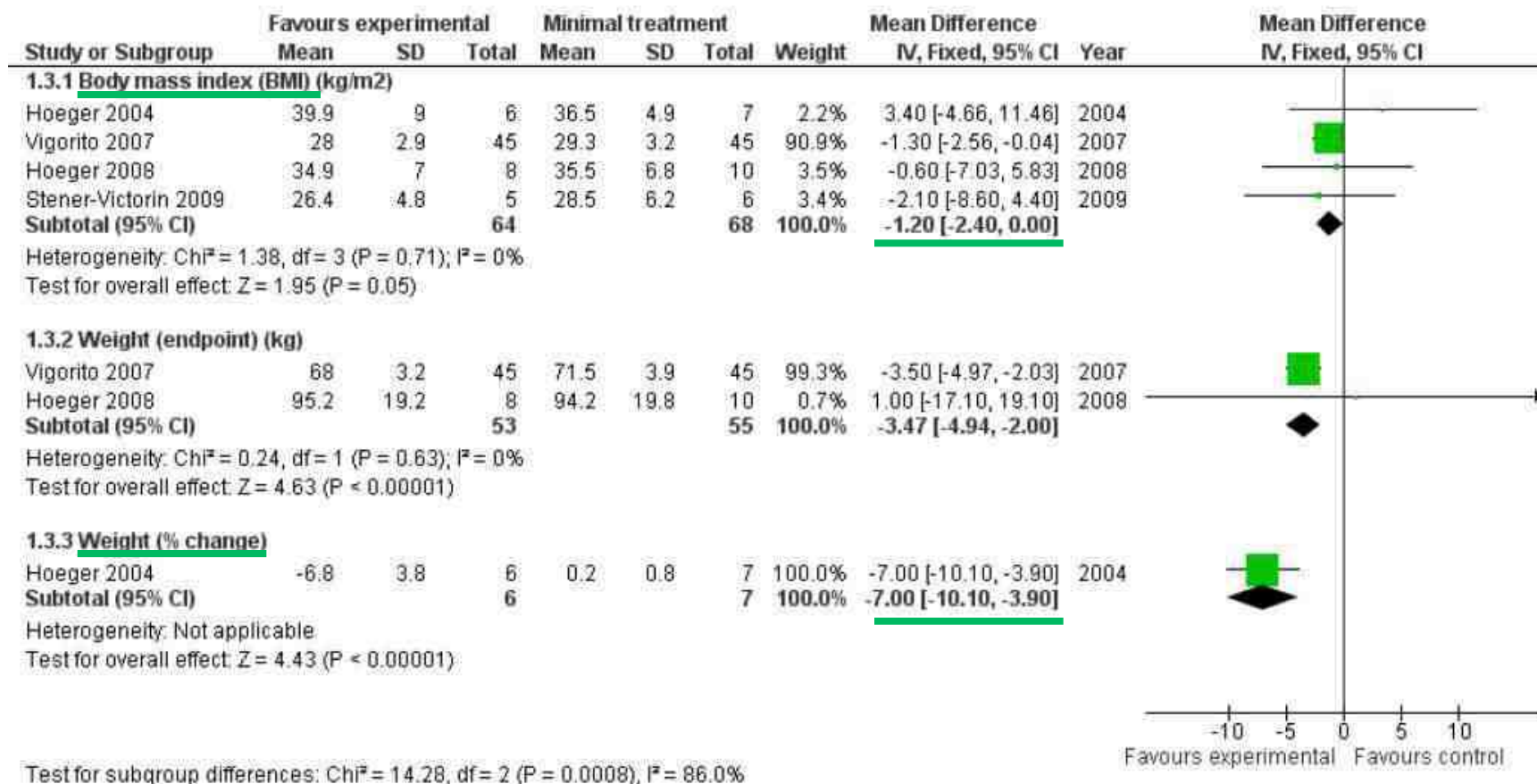
Hoeger 2004	11.7	4	6	14.4	4.5	7	6.3%	-2.70 [-7.32, 1.92]
Hoeger 2008	8.2	2	8	11.6	4.9	10	12.1%	-3.40 [-6.74, -0.06]
Stener-Victorin 2009	12.6	9.1	5	10.8	5	6	1.7%	1.80 [-7.12, 10.72]
Vigorito 2007	11.5	3.1	45	12.3	3.2	45	79.8%	-0.80 [-2.10, 0.50]
Subtotal (95% CI)			64			68	100.0%	-1.19 [-2.35, -0.03]

Heterogeneity: $\text{Chi}^2 = 2.87$, $\text{df} = 3$ ($P = 0.41$); $I^2 = 0\%$

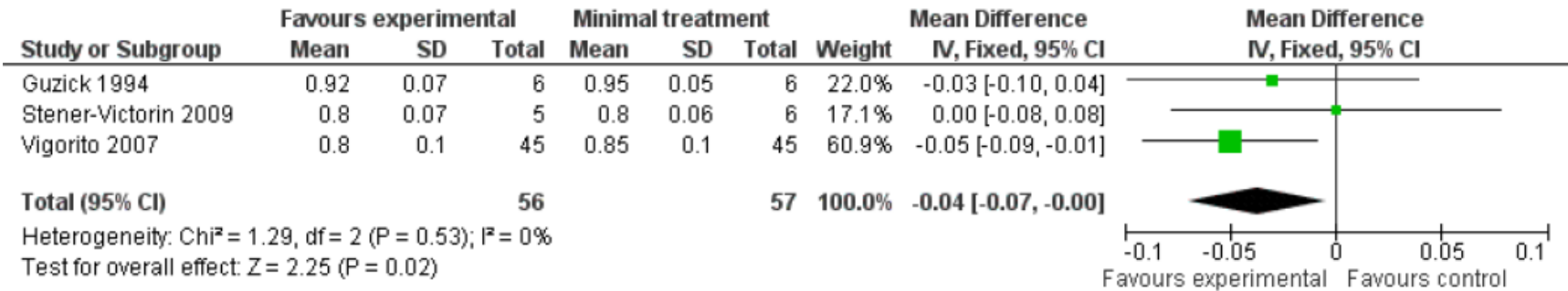
Test for overall effect: $Z = 2.01$ ($P = 0.04$)



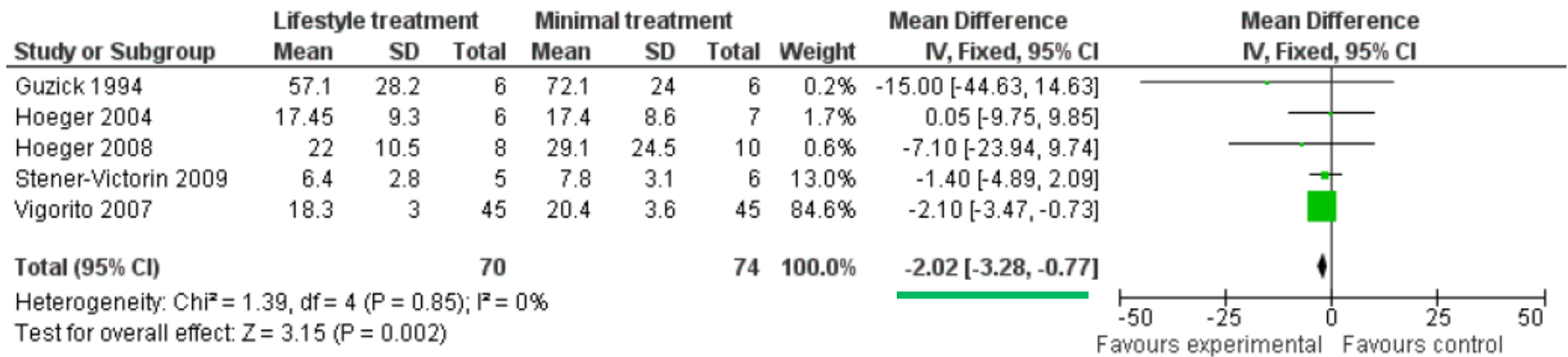
VKI / Kilo



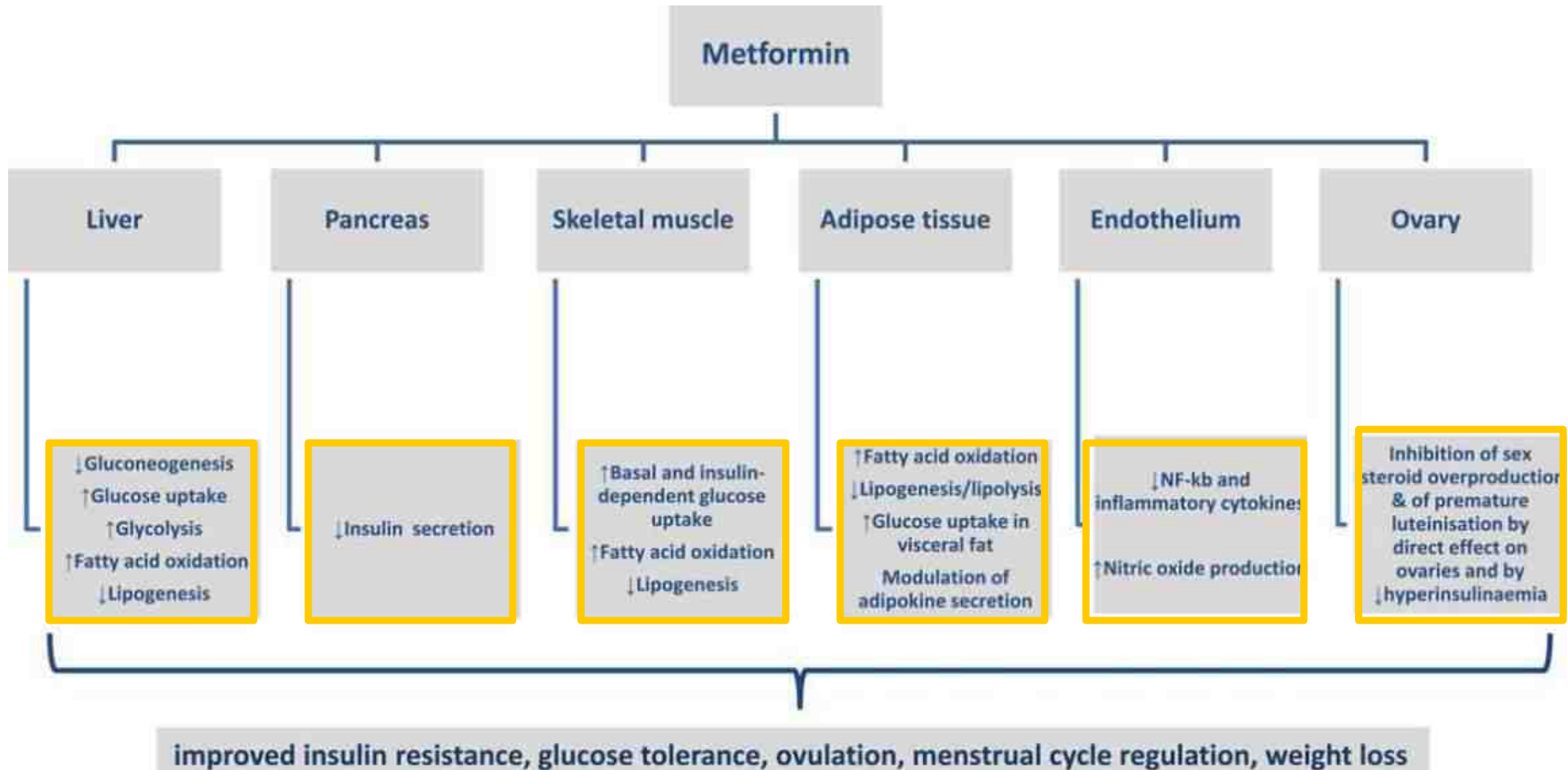
Yağ dağılımı



Açlık kan şekeri



Metforminin potansiyel mekanizmaları



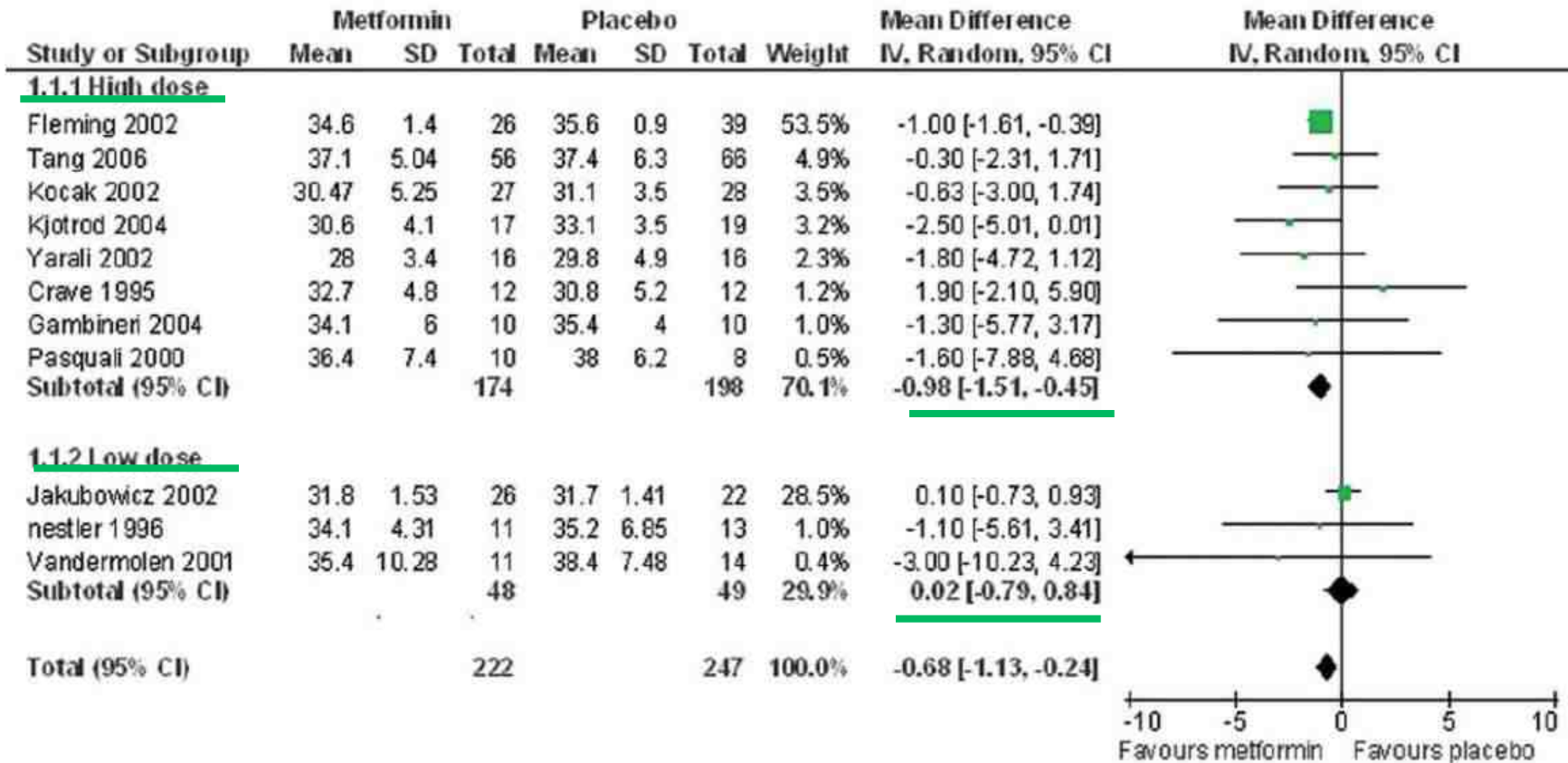
Insulin hassaslaştırıcılar –obez& kilolu

Trial	Methods	Number randomized inclusion criteria	Main intervention
Crave et al. (1995)	Method of randomization: not stated Blinding: double blind Intention to treat analysis: no	24 BMI > 25 kg/m ² , hirsutism	High dose metformin (n = 12), placebo (n = 12) Duration: 4 months
Ferring et al. (2002)	Method of randomization: computer generation by pharmacy in blocks of four Blinding: double blind Intention to treat analysis: yes	94 Oligomenorrhea, PCO* detected by ultrasound	High-dose metformin (n = 26), placebo (n = 39) Duration: 14 weeks
Gambineri et al. (2004)	Method of randomization: randomly placed Blinding: single-blind Intention to treat analysis: no	20 (only the data of the metformin and placebo arms were used) BMI > 28 kg/m ² and waist:hip ratio > 0.8; PCOS; oligomenorrhea or amenorrhea, hyperandrogenism, PCO detected by ultrasound	High dose metformin (n = 10), placebo (n = 10) Duration: 6 months
Jakubowicz et al. (2001)	Method of randomization: sequentially numbered, identical containers of identical drugs** Blinding: double blind Intention to treat analysis: no	56 Oligomenorrhea, PCO detected by ultrasound, elevated free testosterone, ovulation with clomiphene citrate 150 mg	Low-dose metformin (n = 28), placebo (n = 28) Duration: 7–8 weeks
Kilicdag et al. (2005)	Method of randomization: random number tables and assigned through consecutively numbered opaque, sealed envelopes Blinding: double blind Intention to treat analysis: no	30 Oligomenorrhea, hyperandrogenism and/or an elevated serum testosterone level, PCO detected by ultrasound	High dose metformin (n = 15), rosiglitazone (n = 15) Duration: 3 months
Kjorod et al. (2004)	Method of randomization: randomization was performed by the hospital pharmacist, performed in blocks of four Blinding: double blind Intention to treat analysis: yes	40 Criteria for overweight: BMI > 28 kg/m ² , PCO detected by ultrasound, oligomenorrhea or amenorrhea and 1 out of the next 5: high level of testosterone, low SHBG level, high LH/FSH ratio, high level of fasting insulin C, hirsutism NOTE: the baseline vals	High-dose metformin (BMI > 28, n = 19), placebo (BMI > 28, n = 21) Duration: 16 weeks
Kocak et al. (2002)	Method of randomization: sequential by order of admission Blinding: double blind Intention to treat analysis: no	56 Oligomenorrhea with hirsutism, hyperandrogenaemia, or ultrasound findings of PCO	High-dose metformin (n = 28), placebo (n = 28) Duration: 3 cycles
Mitkov et al. (2006)	Method of randomization: not stated Blinding: not stated Intention to treat analysis: no	30 Oligomenorrhea, PCO detected by ultrasound, hyperandrogenaemia	High dose metformin (n = 15), rosiglitazone, 4 mg/day (n = 15) Duration: 3 months
Nestler et al. (1996)	Method of randomization: centralized randomization process Blinding: single blind-patient blinded Intention to treat analysis: no	25 Oligomenorrhea, hyperandrogenism, PCO detected by ultrasound	Low-dose metformin (n = 12), placebo (n = 13) Duration: 4–8 weeks
Ortega-Gonzalez et al. (2005)	Method of randomization: random number tables Blinding: double blind Intention to treat analysis: no	52 Oligomenorrhea, PCO detected by ultrasound, hyperandrogenism, acanthosis nigricans, fasting hyperinsulinemia and fasting glucose/insulin	High-dose metformin (n = 27), pioglitazone, 30 mg/day (n = 25) Duration: 6 months
Pisuquill et al. (2000)	Method of randomization: generated in blocks of four Blinding: double-blind Single centre intention to treat analysis: no	20 (only the data of the PCOS women were used) Obese women with PCOS diagnosed by: oligomenorrhea, hyperandrogenism, PCO detected by ultrasound	High-dose metformin (n = 12), placebo (n = 8) Duration: 6 months
Tang et al. (2006)	Method of randomization: by means of block-of-four randomization using random tables Blinding: double blind Intention to treat analysis: no	143 Desire to conceive, PCOS diagnosed by: oligomenorrhea or amenorrhea, PCO detected by ultrasound. All patients had normal serum prolactin levels and normal thyroid, liver- and renal function tests.	High dose metformin (n = 69), placebo (n = 74) Duration: 6 months
Vandermolen et al. (2001)	Method of randomization: computer-generated in blocks of six Blinding: double blind Intention to treat analysis: yes	27 Oligo-ovulation, hyperandrogenism NOTE: all patients received CC (50 mg/d) for ovulation induction as co-intervention after the initial 7 weeks treatment period	Low-dose metformin (n = 12), placebo (n = 15) Duration: 7 weeks
Yarali et al. (2002)	Method of randomization: computer-generated numbers. Centralized randomization process** Blinding: double blind Intention to treat analysis: no	32 Oligo-ovulation, hyperandrogenism, PCO on ultrasound	High dose metformin (n = 16), placebo (n = 16) Duration: 6 weeks

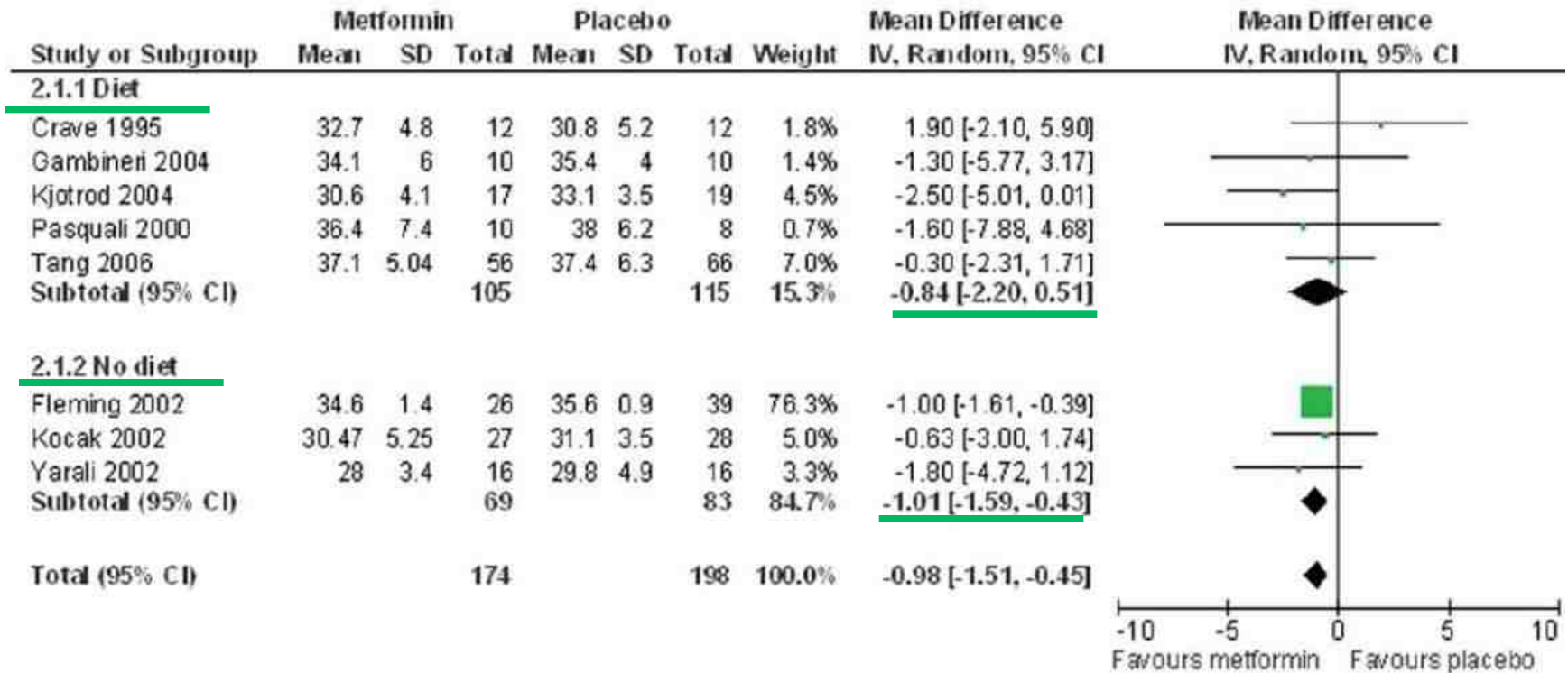
14 RKÇ

<1500 mg v >1500 mg

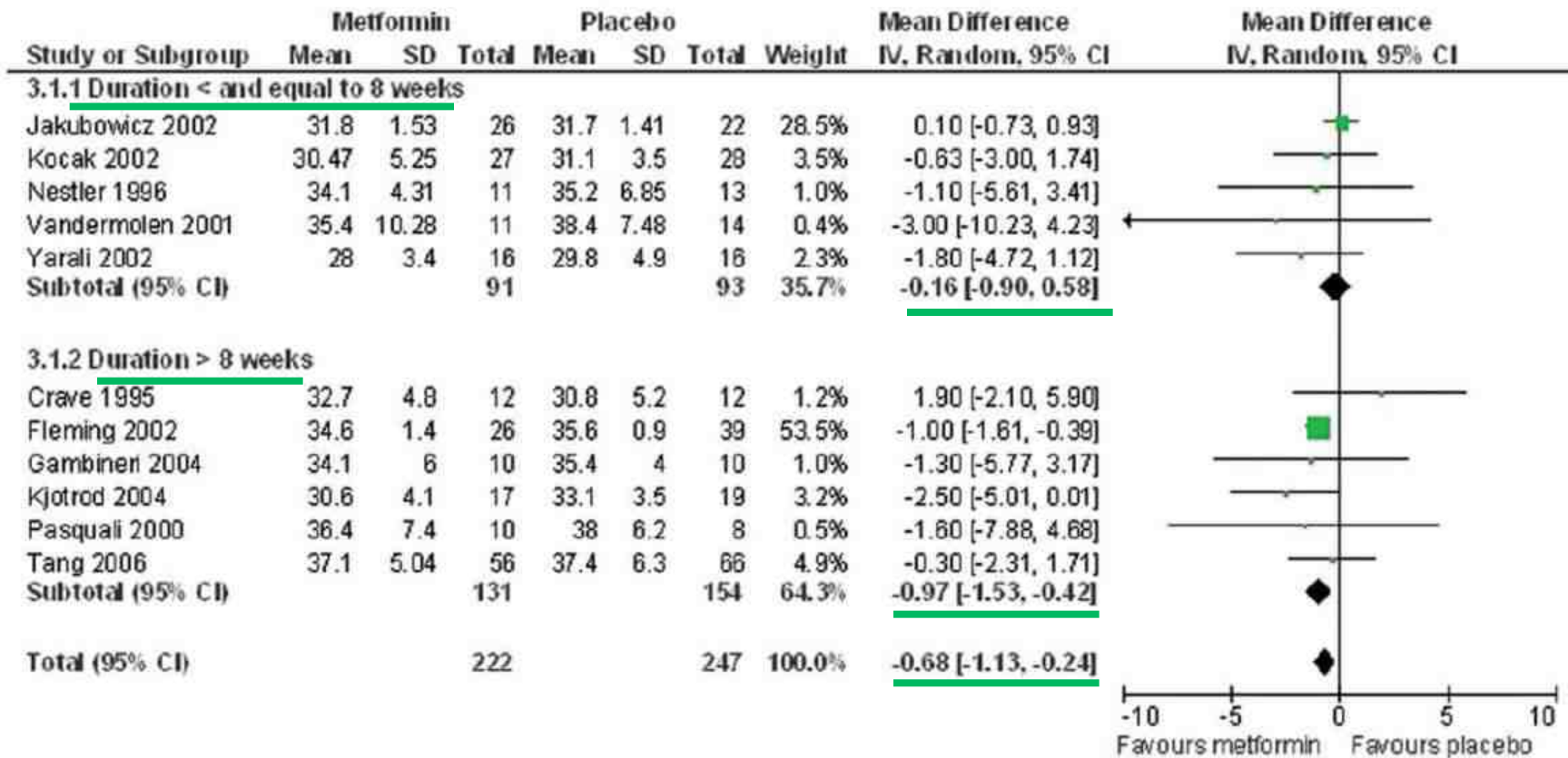
VKI - yüksek doz v düşük doz IH



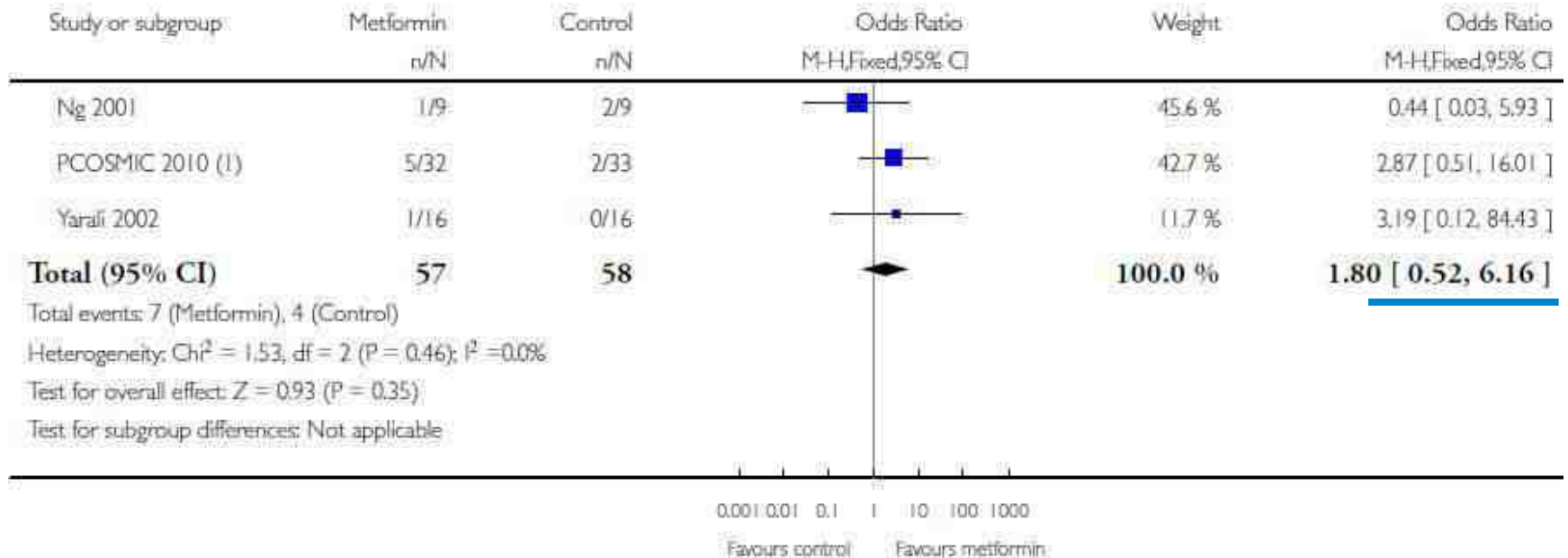
Yüksek doz IH - diyet v diyet yok



VKI – 8 hfdan az v 8 hfdan uzun

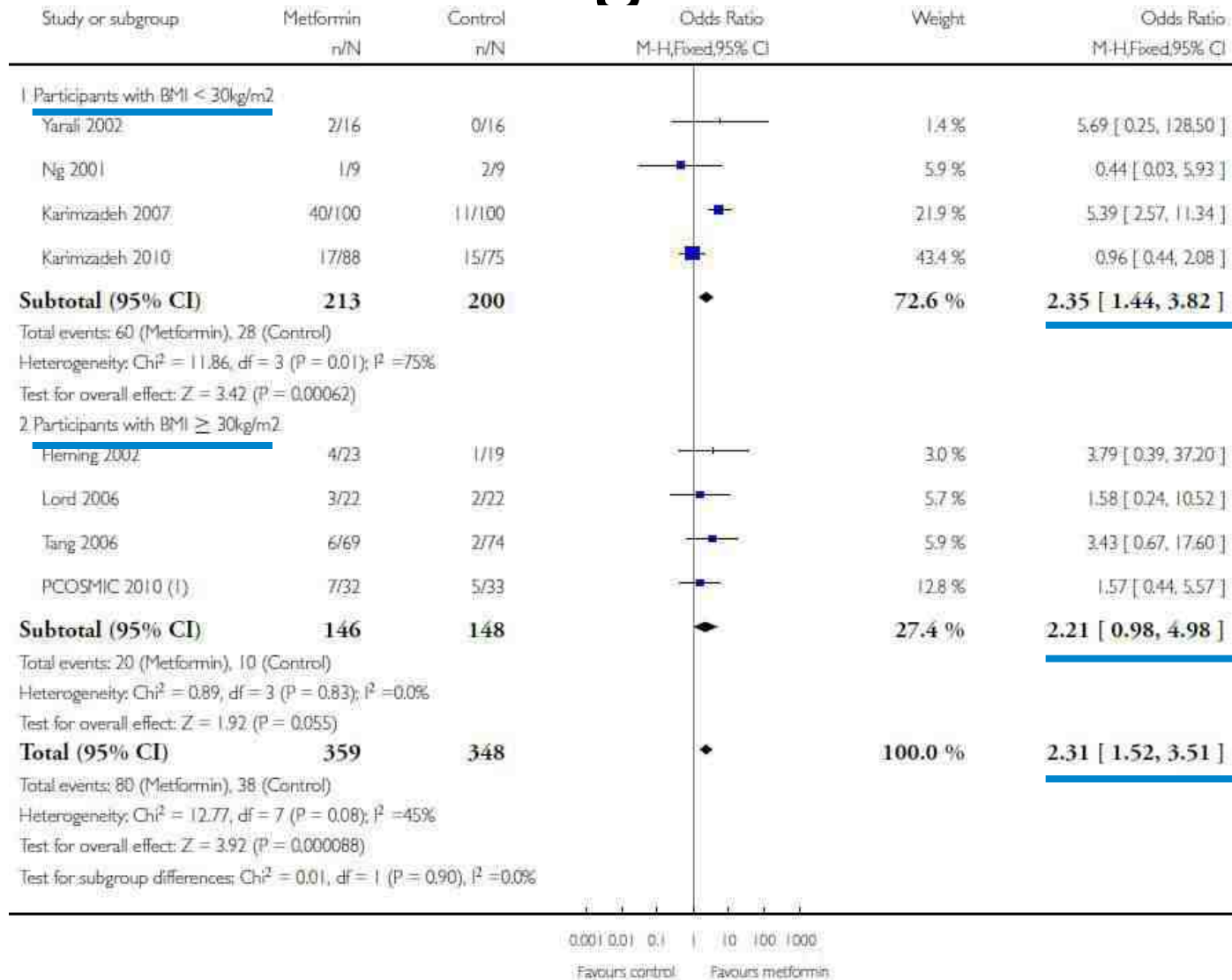


Canlı doğum



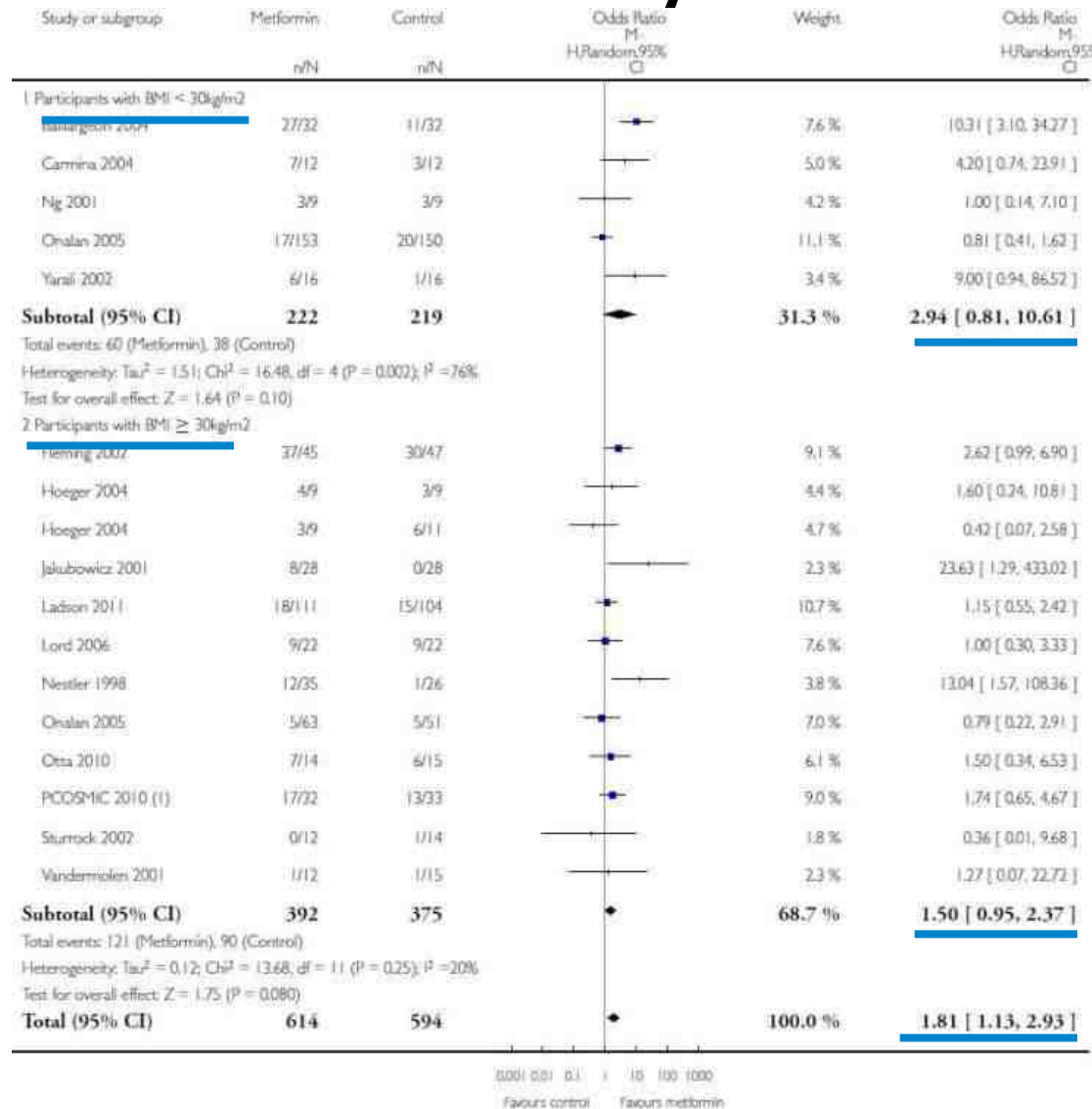
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Klinik gebelik



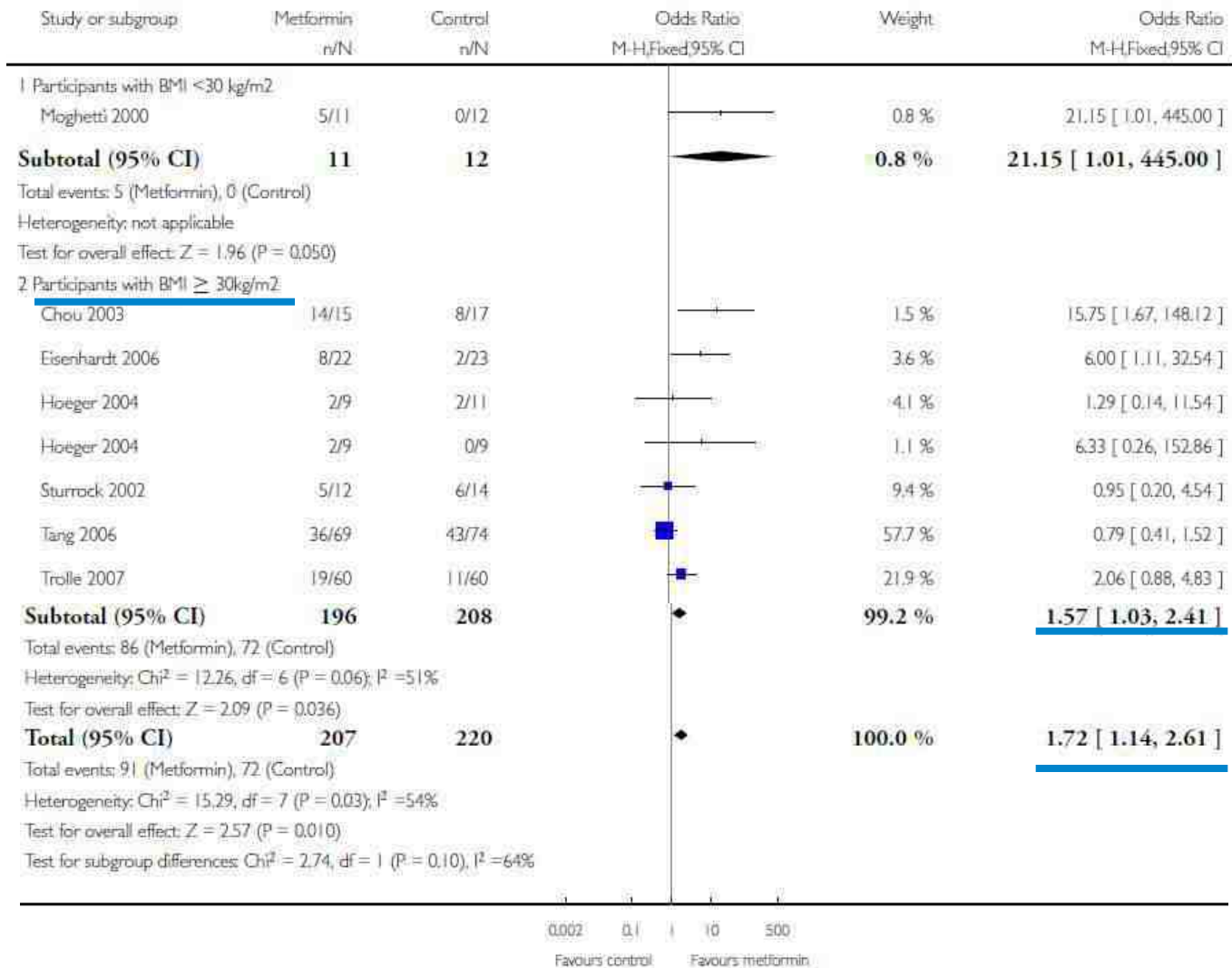
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Ovulasyon



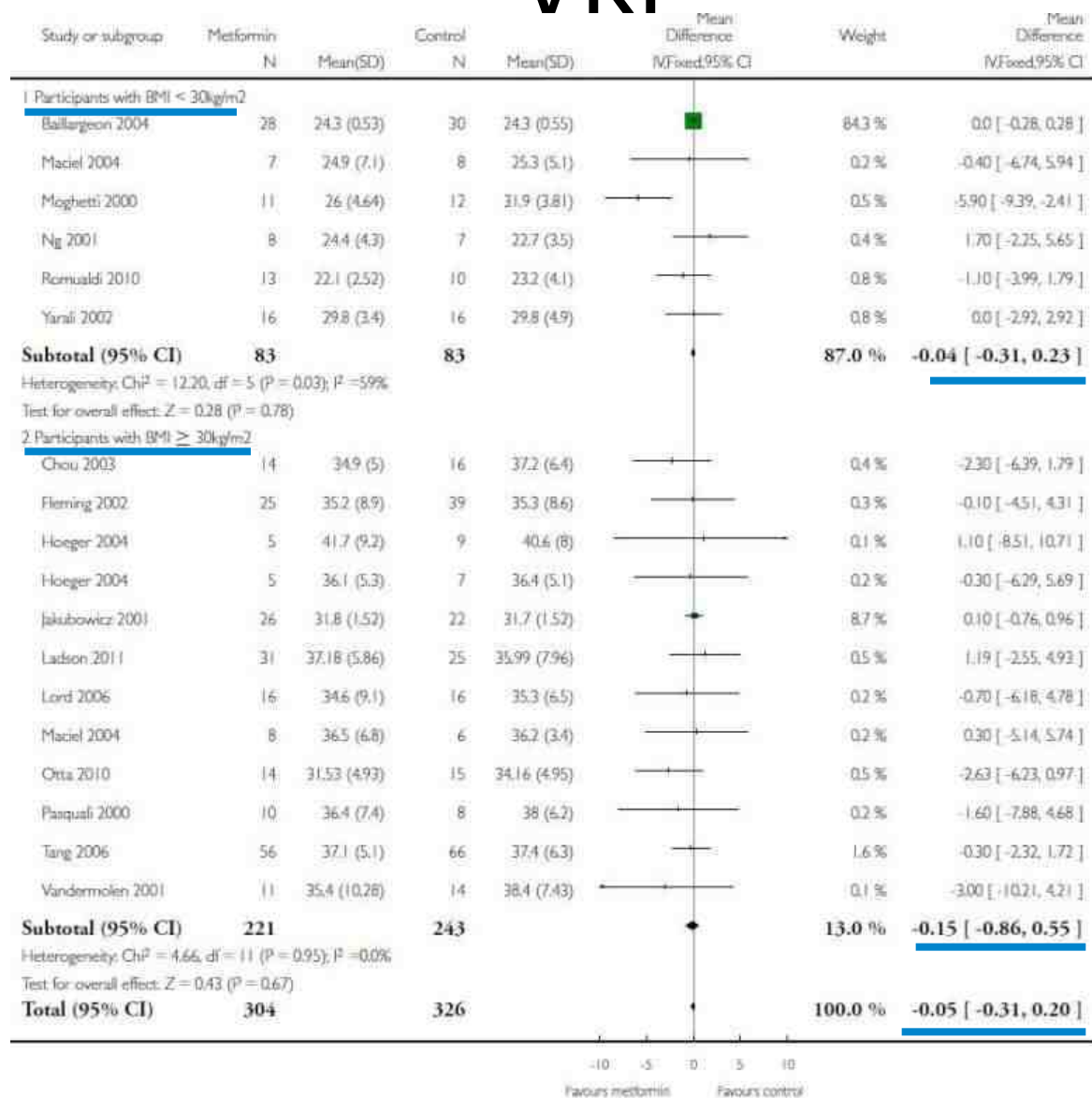
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Menstruel siklus



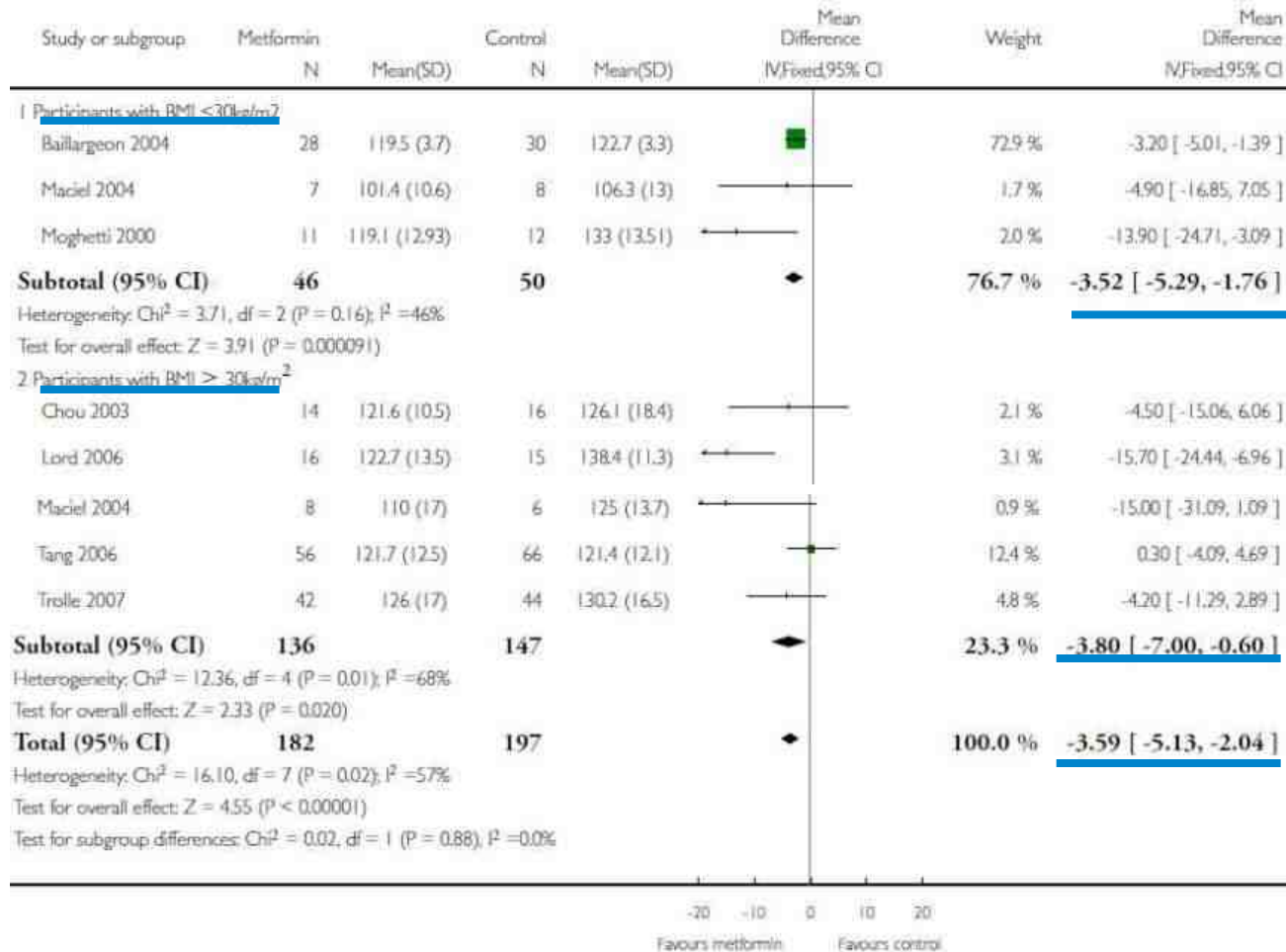
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VKI



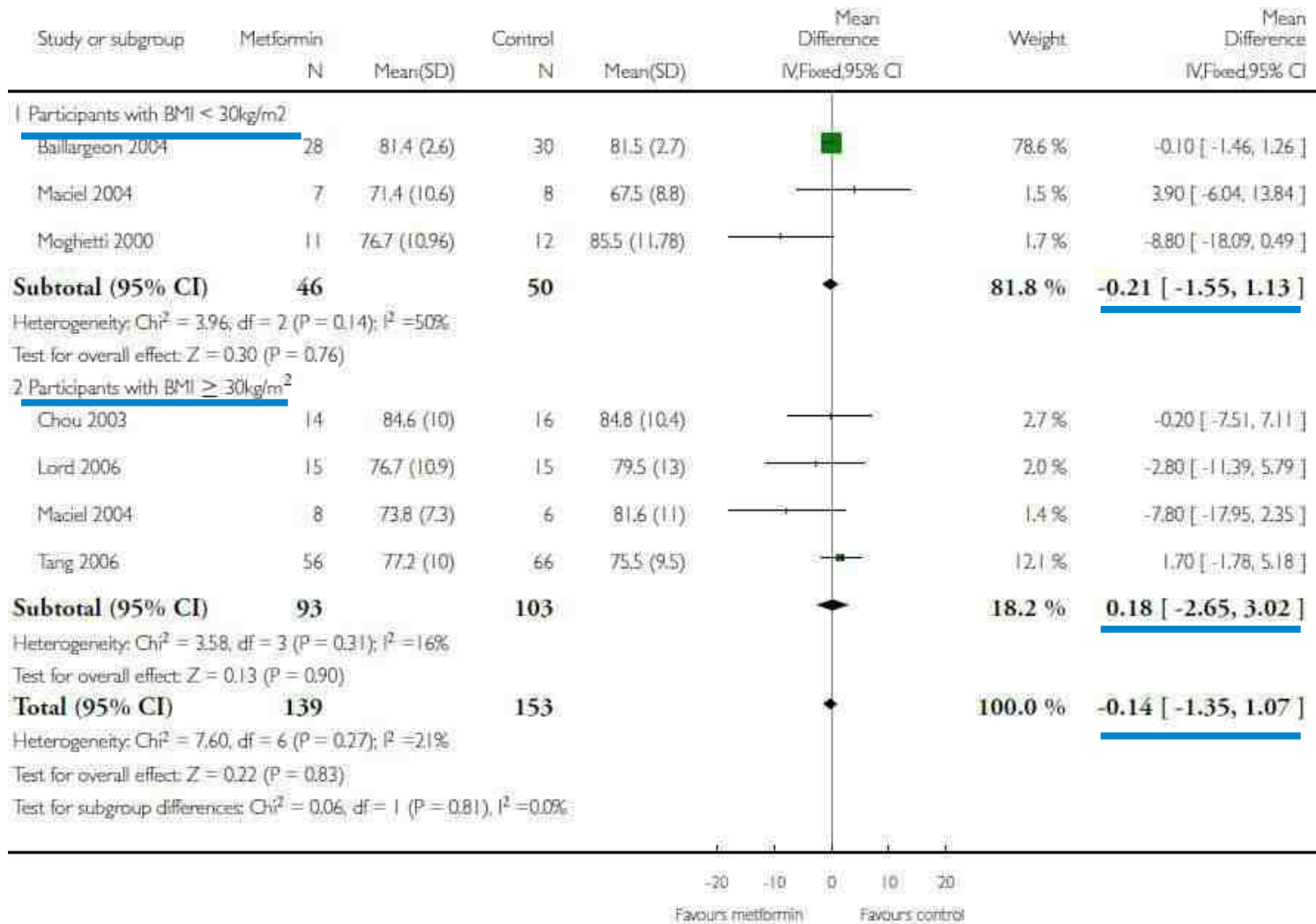
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Sistolik kan basıncı



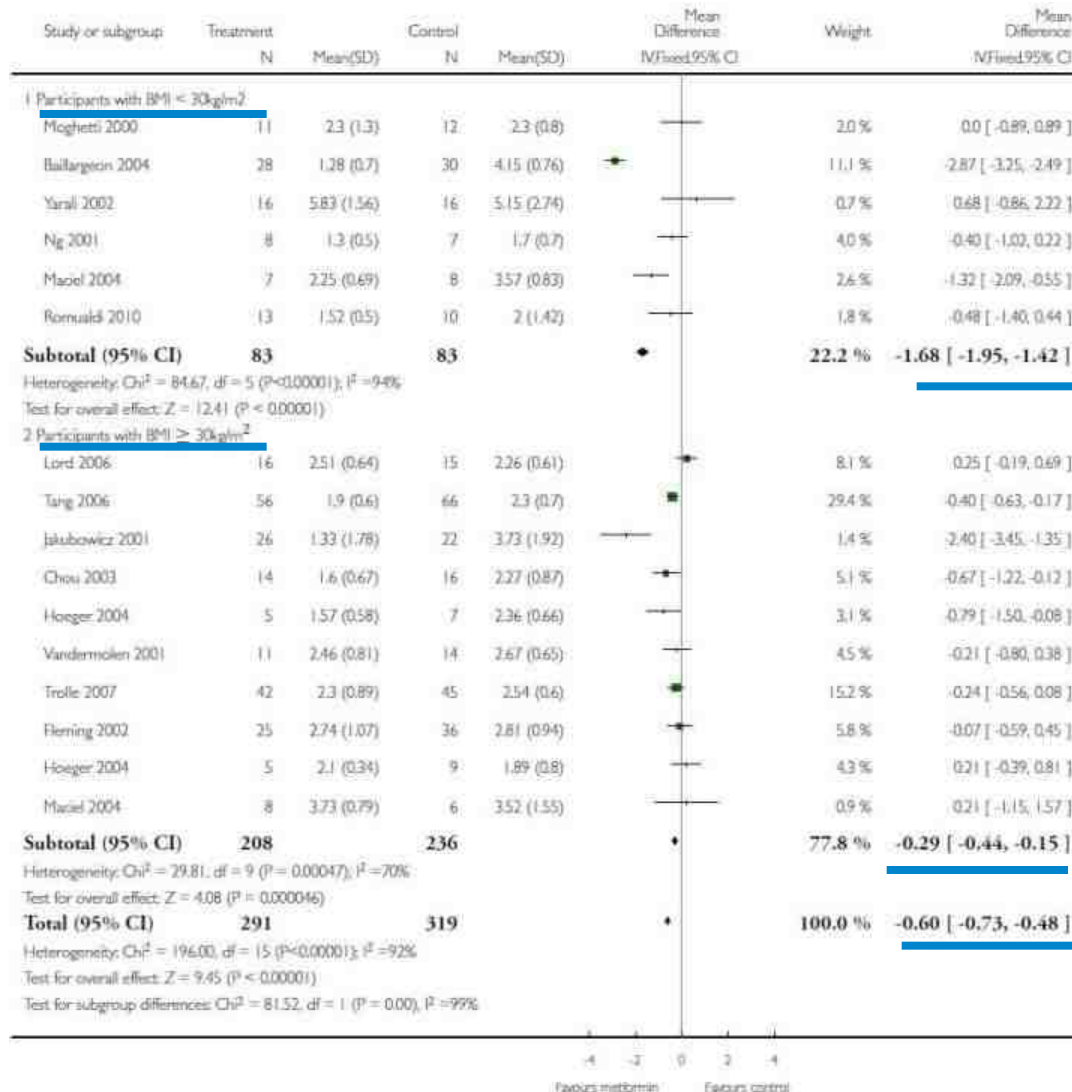
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Diastolik kan basinci



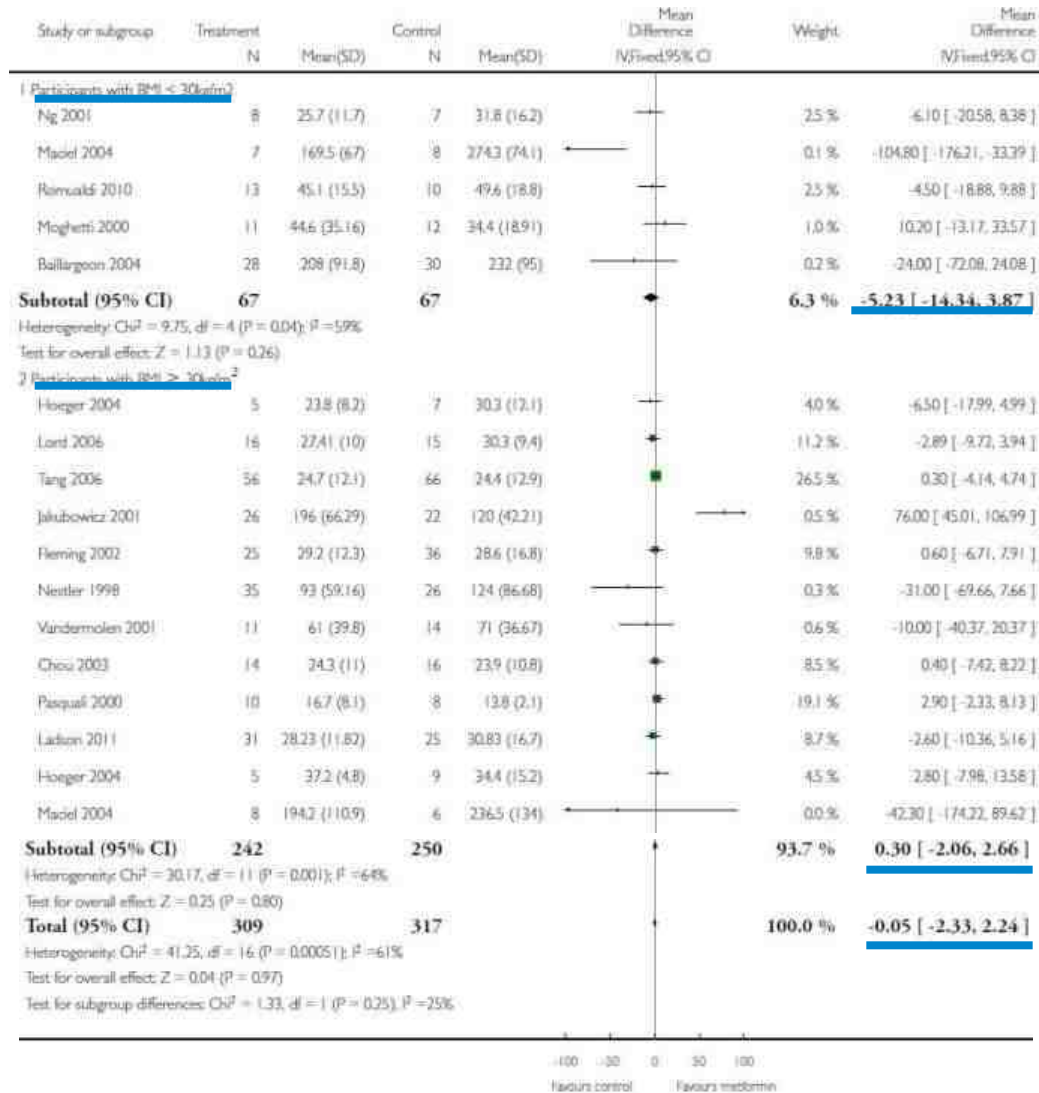
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Testosterone



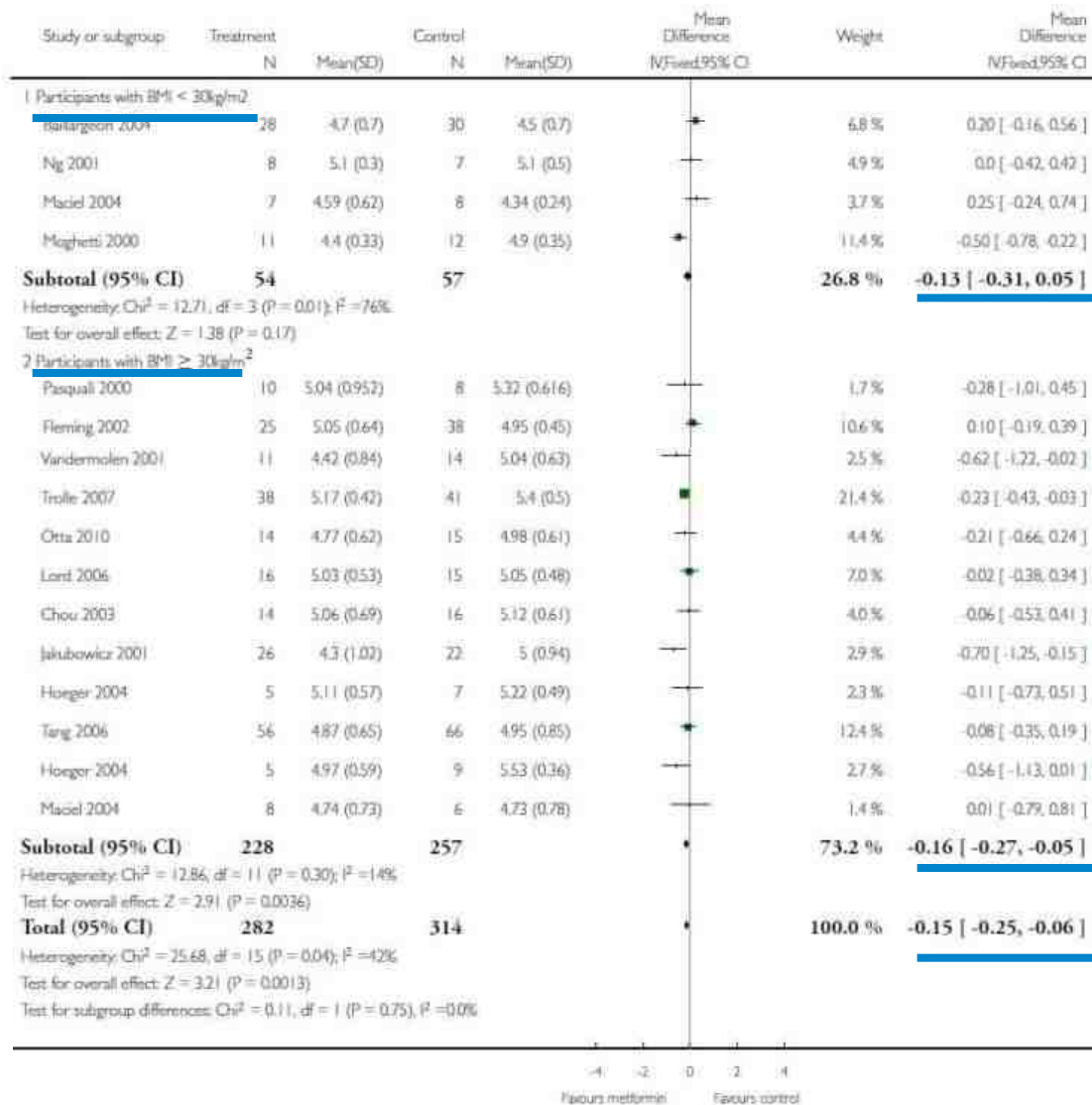
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

SHBG



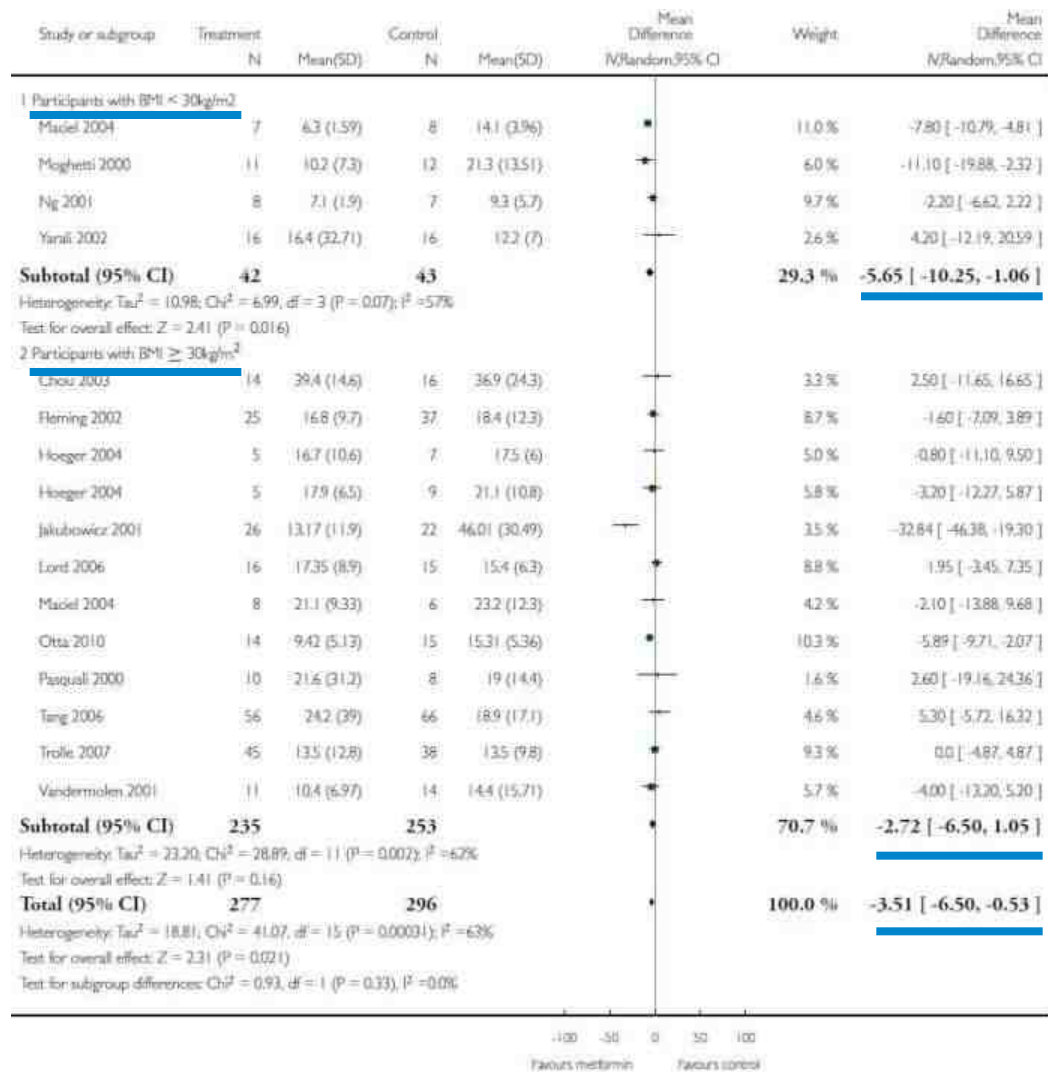
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Açlık kan şekeri



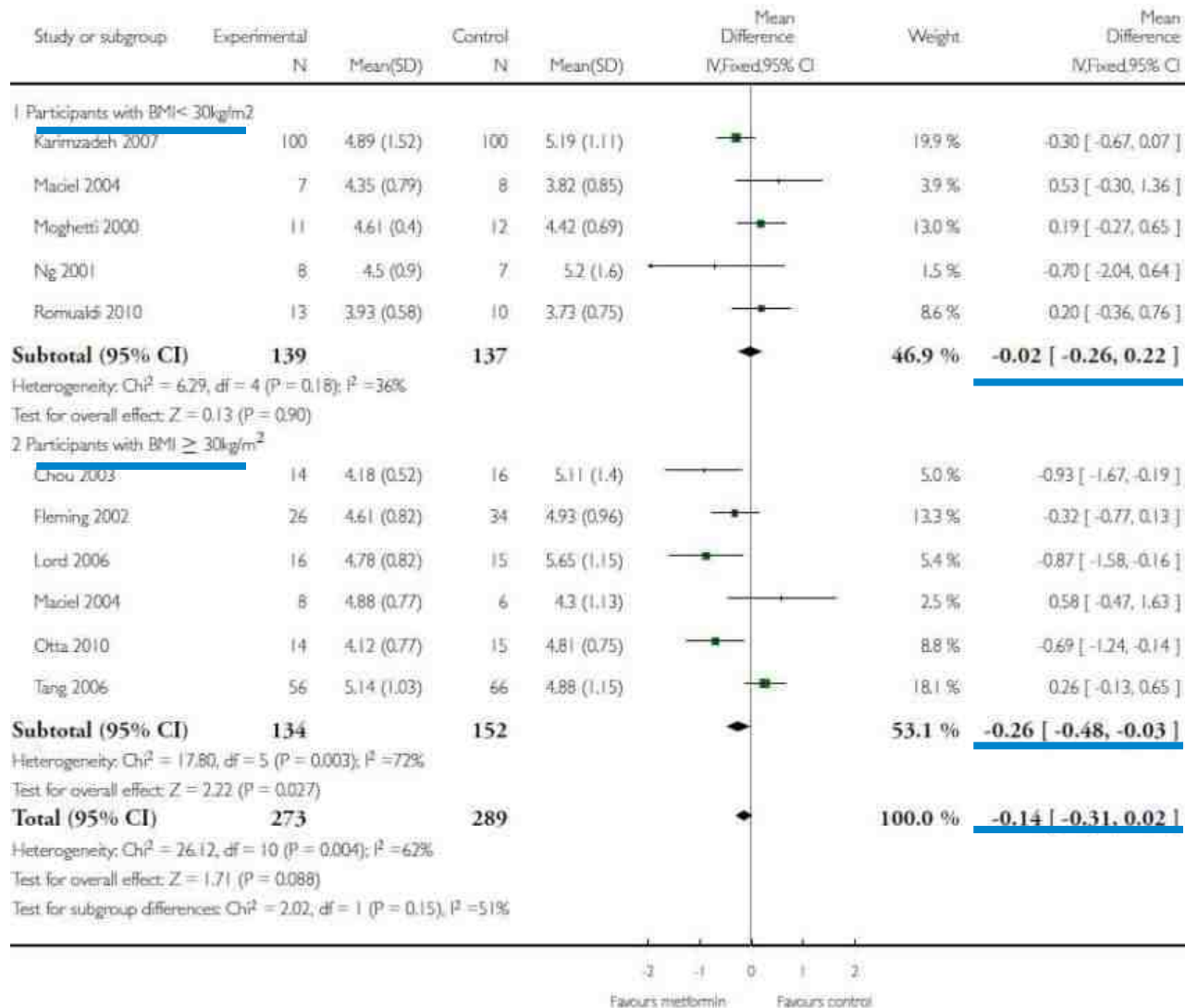
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Açlık insulin



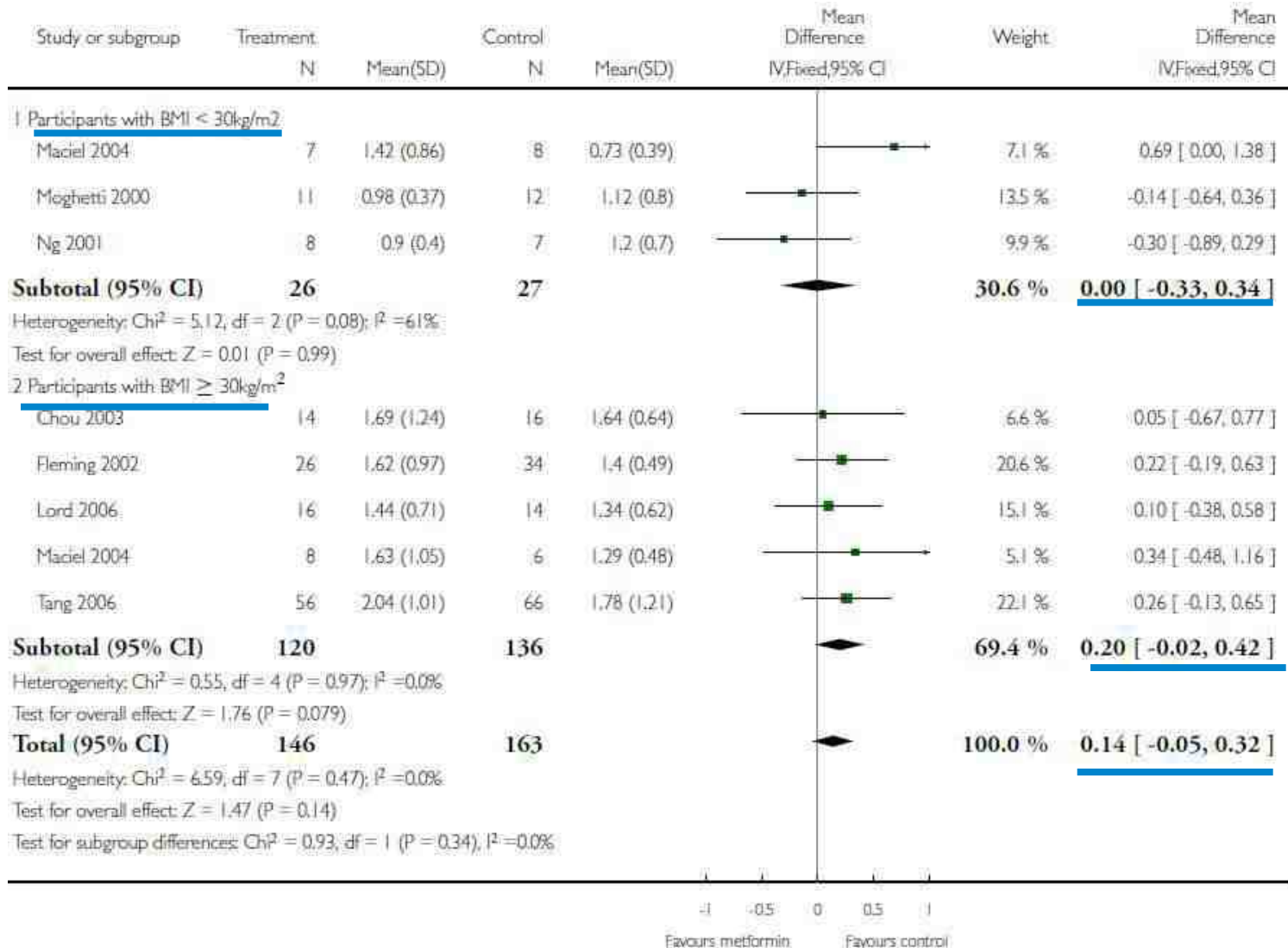
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Total kolesterol



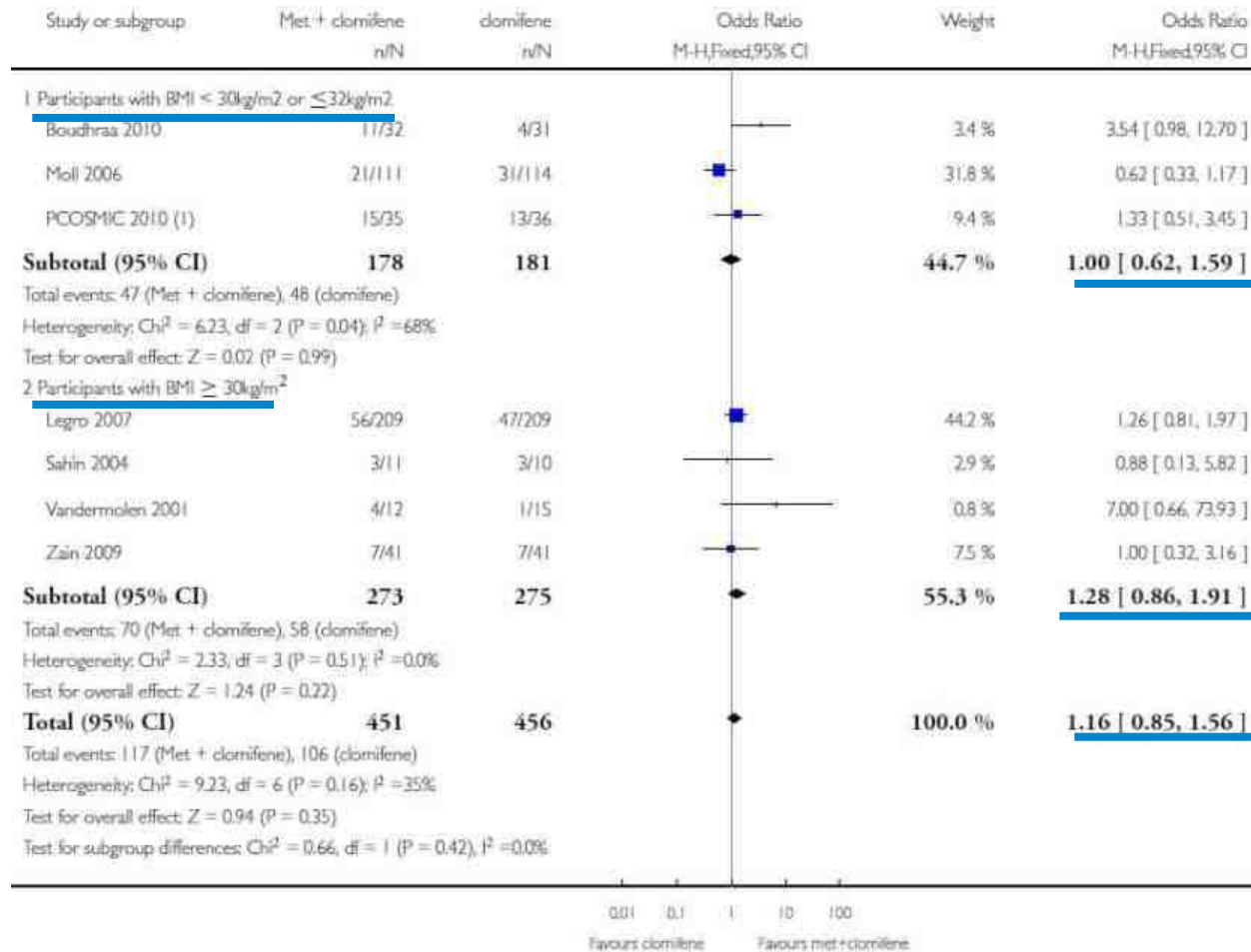
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Triglycerid



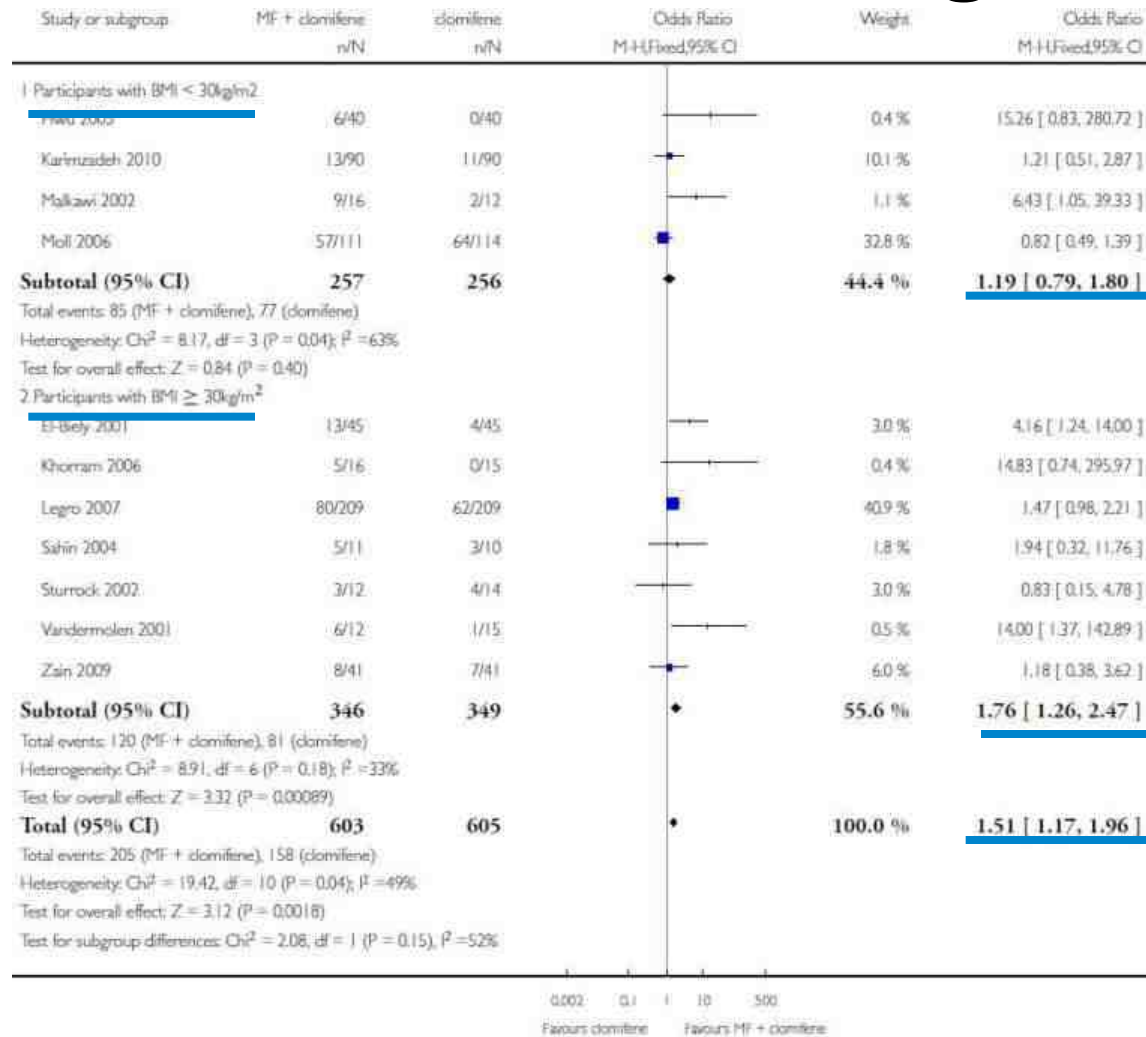
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

KS v Met+KS – canlı doğum



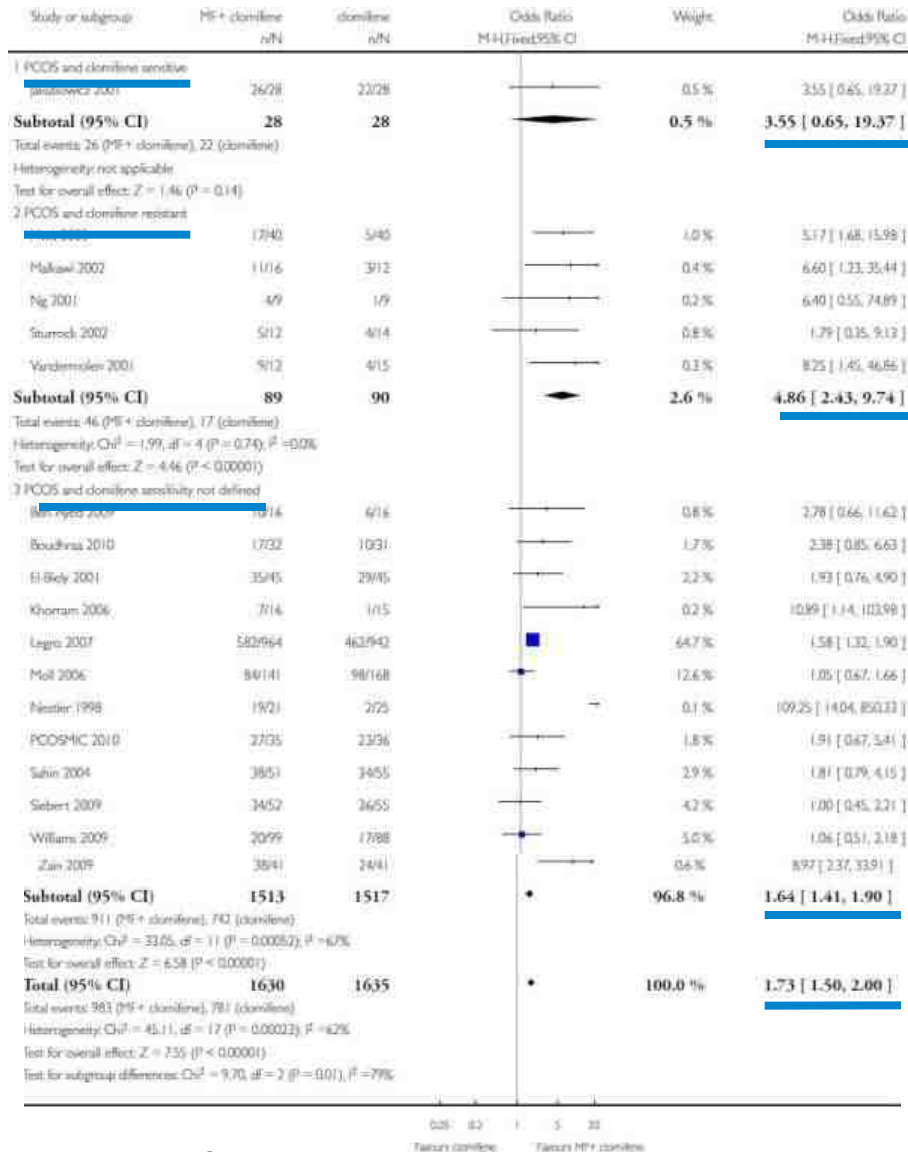
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

KS v Met+KS – klinik gebelik



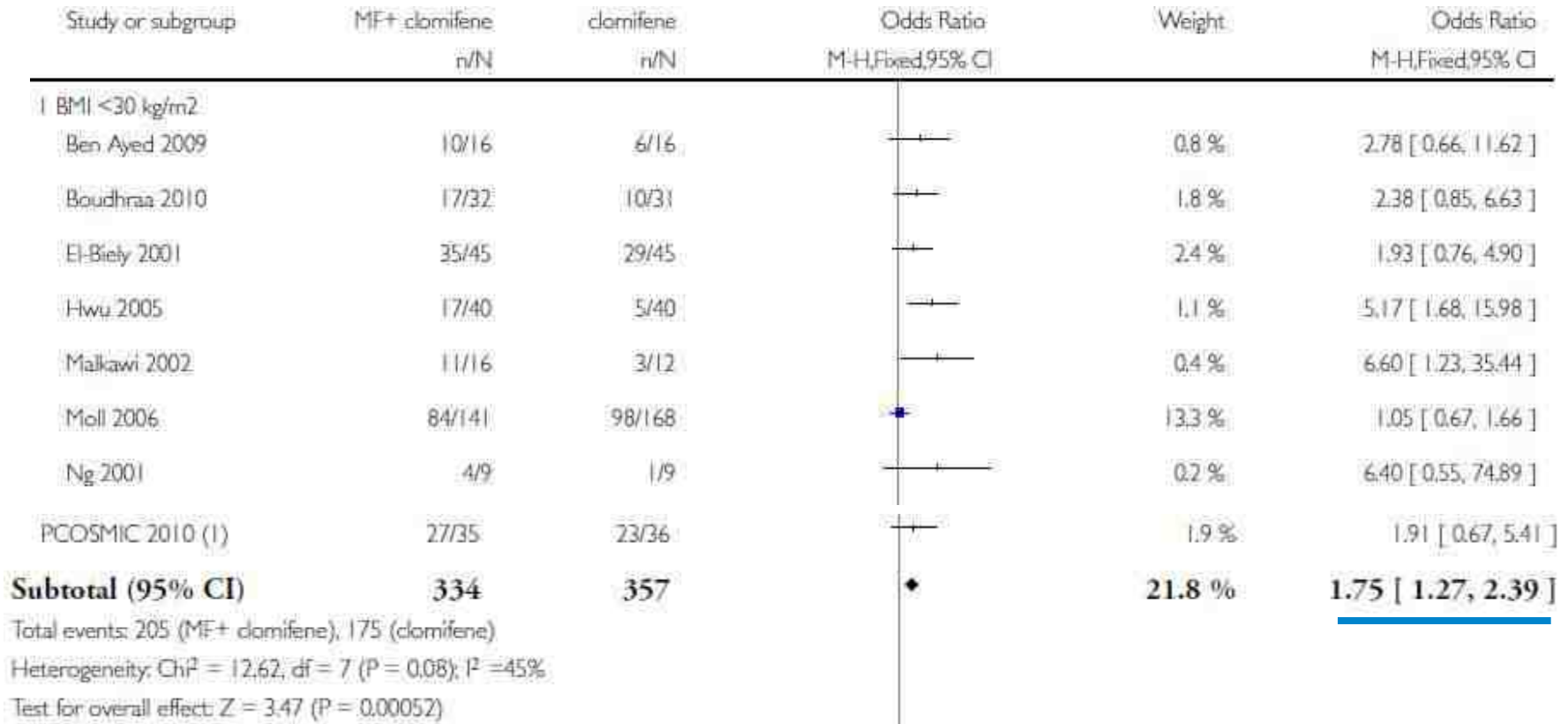
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

Ovulasyon hızı

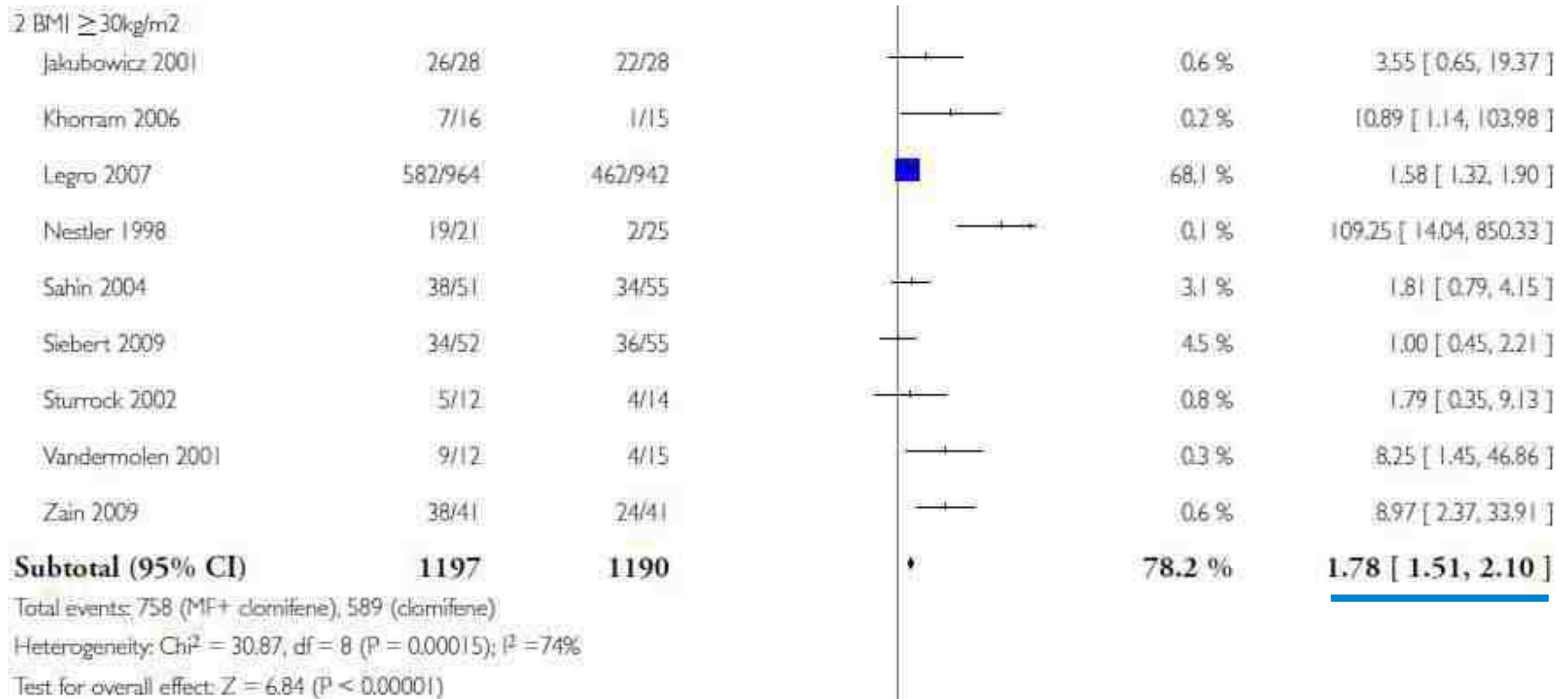


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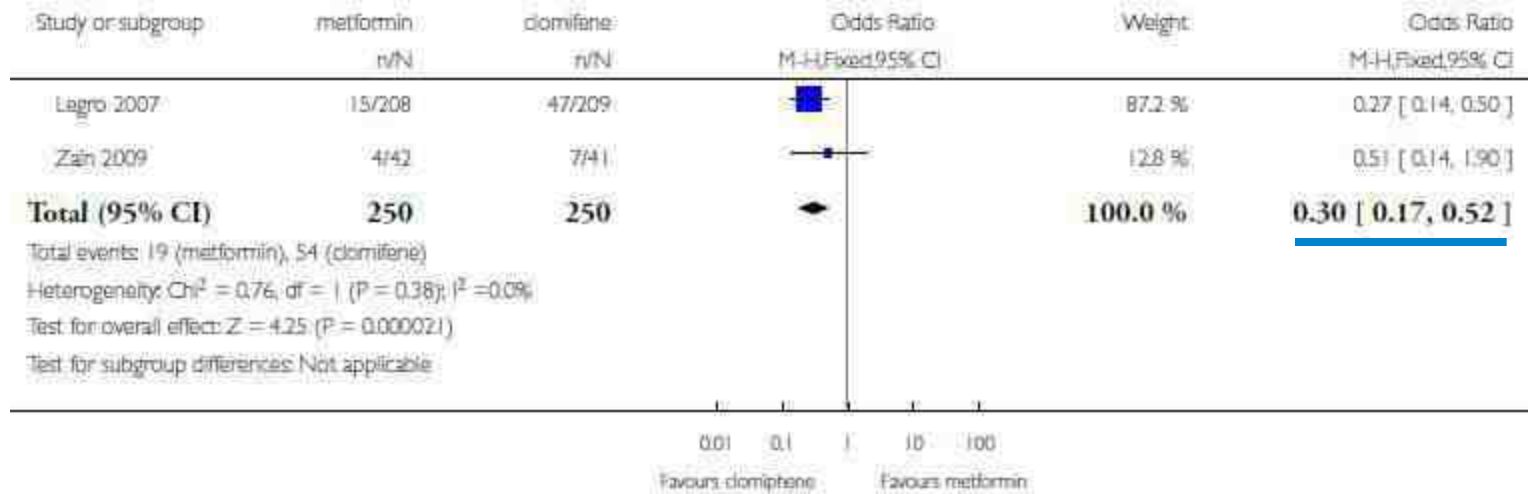
Ovulasyon VKI < 30



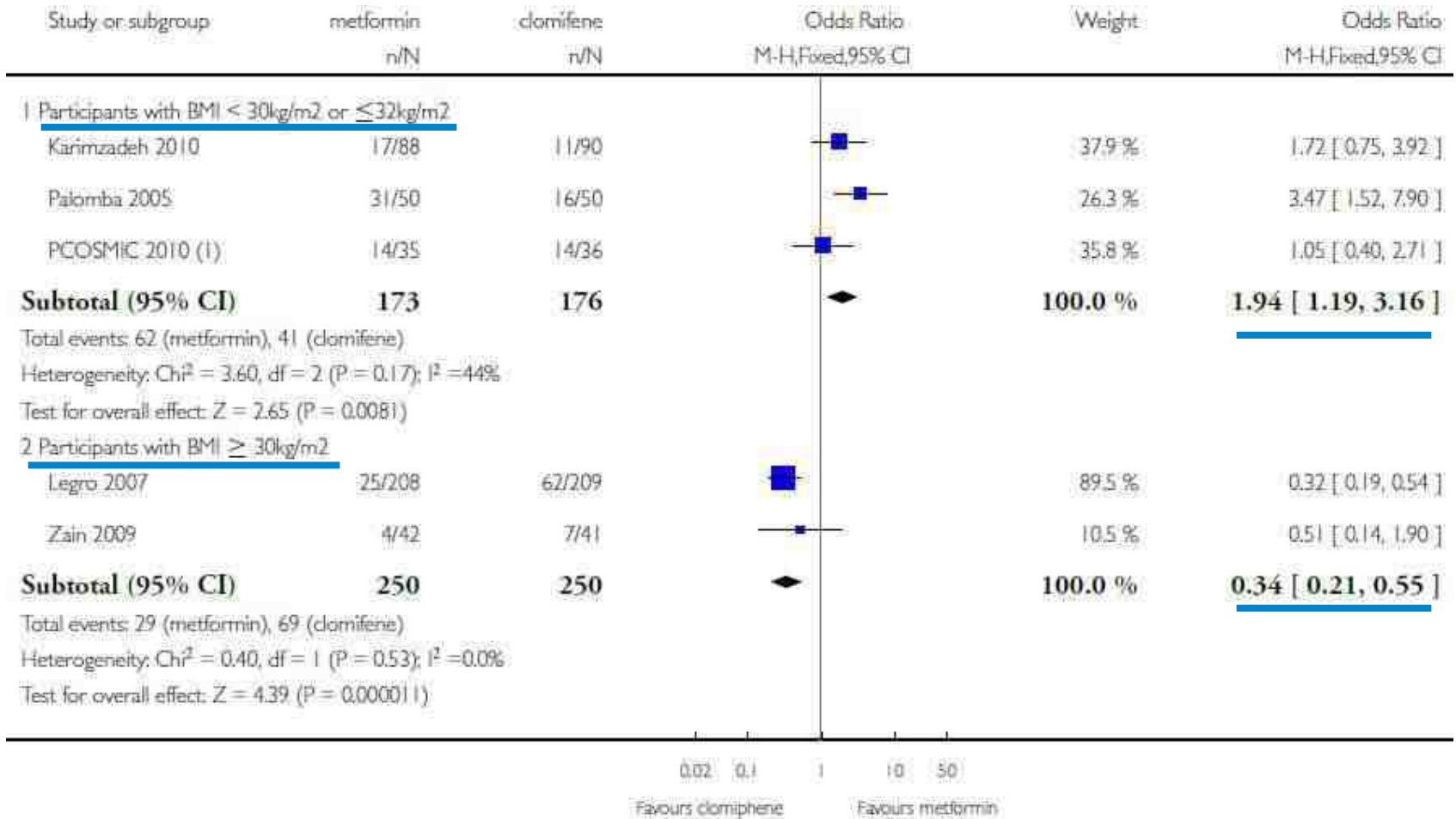
Ovulasyon VKI ≥ 30



KS v Met - Canlı doğum VKI ≥ 30

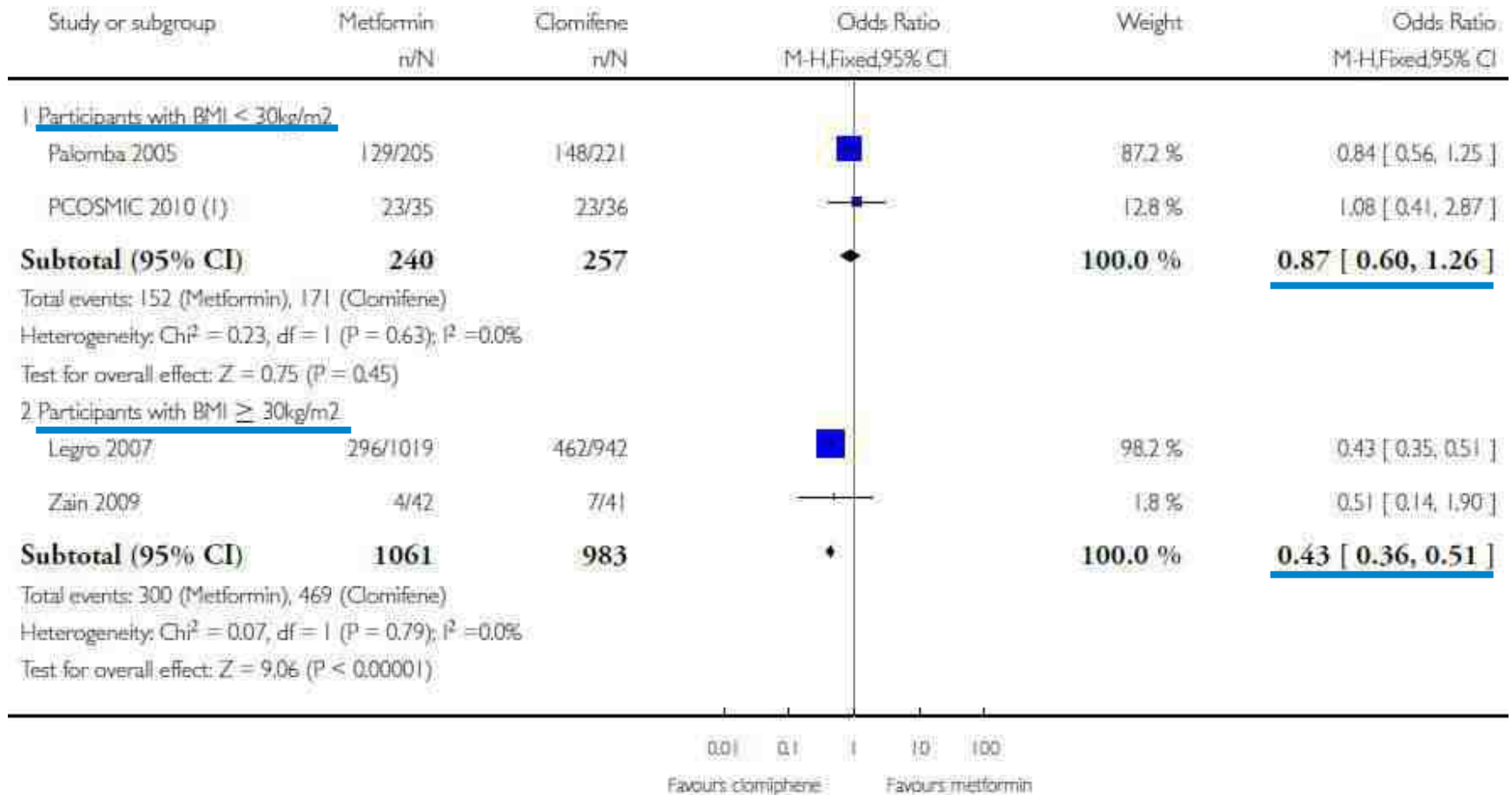


KS v Met - Klinik gebelik



Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

KS v Met - Ovulasyon



Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review) 2012 The Cochrane Collaboration

PKOS, KS dirençli

	5 mg x 5 g	2.5 mg x 10 g		<i>P</i> value
	Short letrozole group (n = 110)	Long letrozole group (n = 108)	t	
Number of ovulating patients	68 (61.8%)	71 (65.7%)	23.2	.11
Total number of follicles	3.9 ± 0.4	6.7 ± 0.3	8.0	.01*
Number of follicles >14 mm	2.1 ± 0.4	3.7 ± 0.3	9.2	.03*
Number of follicles >18 mm	1.8 ± 0.1	3.0 ± 0.4	6.3	.03*
Pretreatment endometrial thickness (mm)	4.8 ± 0.4	4.5 ± 0.6	0.64	.12
Endometrial thickness at hCG (mm)	10.4 ± 0.6	11.2 ± 0.6	0.90	.11
Serum E2 (pg/mL)	315.5 ± 60.2	338 ± 70.3	2.0	.08
Serum progesterone (ng/mL)	9.0 ± 0.8	10.3 ± 1.0	1.5	.08
<u>Pregnancy/cycle</u>	28/225 (12.4%)	38/219 (17.4%)	X ² = 4.37	.03*
Miscarriage/patient	5/28 (17.9%)	7/38 (18.4%)	X ² = 0.12	.64

KS dirençli PKOS – AI vs Met+KS

	2.5 mg	1500 mg 2 ay ve sonra 150 mg			
	Group A (letrozole group) (n = 123)	Group B (combined metformin-CC group) (n = 127)	t	χ^2	P value
Total no. of follicles	4.4 ± 0.4	6.8 ± 0.3	4.3		.042 ^a
No. of follicles >14 mm	2.1 ± 0.3	3.7 ± 0.5	6.13		.008 ^a
No. of follicles >18 mm	2.3 ± 0.1	3.1 ± 0.8	5.03		.003 ^a
Pretreatment endometrial thickness	5.5 ± 0.5	5.3 ± 0.6	1.31		.22
Endometrial thickness at hCG (mm)	9.5 ± 0.2	9.1 ± 0.1	1.44		.53
Serum E ₂ (pg/mL)	258 ± 62.2	386 ± 88.3	4.12		.022 ^a
Serum P (ng/mL)	7.3 ± 0.9	11.4 ± 1.2	6.33		.024 ^a
Duration of stimulation (d)	12.2 ± 1.3	8.1 ± 2.8	4.91		.036 ^a
Ovulation/cycle	185/285 (64.9%)	207/297 (69.6%)		1.63	.62
<u>Pregnancy/cycle</u>	42/285 (14.7%)	43/297 (14.4%)		1.32	.53
Miscarriage/patient	4 (10.2%)	4 (9.5%)		1.73	.43

PKOS- KS vs AI

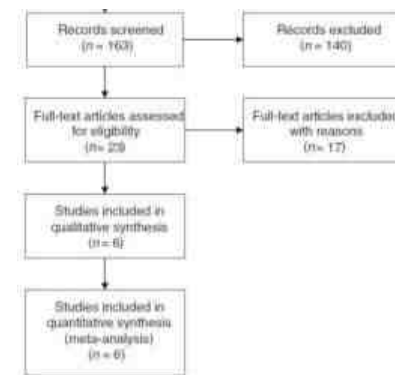
Parameters	Letrozole (n = 32)		CC (n = 32)		P value
	Mean ± SD	Range	Mean ± SD	Range	
Follicular development by day 16 (mm)	18.84 ± 3.17	14–23	16.19 ± 3.47	12–22	<.001
Serum E ₂ on day of hCG (pg/mL)	444.03 ± 85.42	310–650	817.75 ± 286.70	55–1,232	<.001
Endometrial development by day 16 (mm)	10.37 ± 1.2	8–12	9.03 ± 0.89	7–14	<.001
Serum P on day 21 (ng/mL)	19.09 ± 10.47	3–37	13.90 ± 12	2–35	<.05

7.5 mg 150 mg

Letrozole CC
(n = 32) (n = 32)

Parameters	No.	%	No.	%	P value
Ovulation	20/32	62.50	12/32	37.50	<.05 ^a
Pregnancy	13/32	40.62	6/32	18.75	>.05 ^b
Pregnancy among ovulatory patients	13/20	65	6/12	50	>.05 ^c

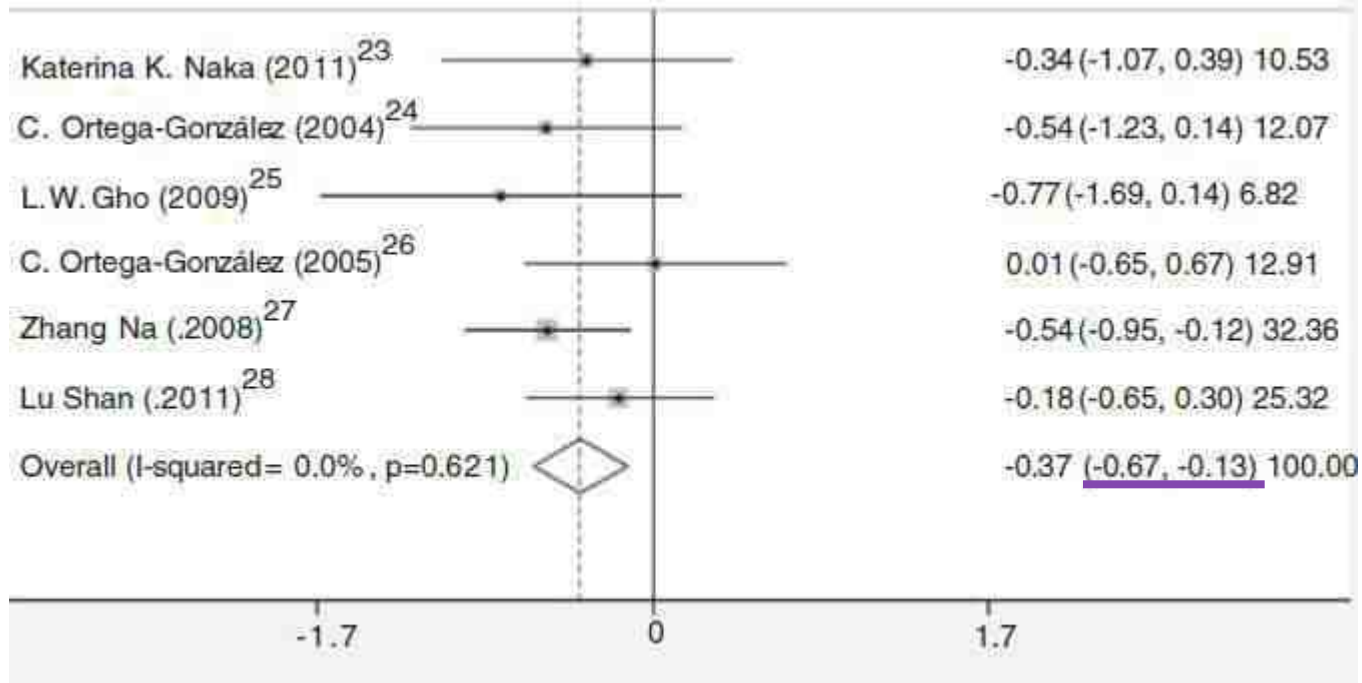
Pioglitazon v Metformin



Study ^a	Methodological quality				Participants				Intervention	
	Randomization	Blinding	Concealment	ITT	Country	Baseline comparable	Withdrawal	Age experiment/control group	Duration (month)	Pioglitazone/metformin
Naka, 2011 ²³	Yes	Not used	NR	NR	Greece	Yes	2	23.6 ± 5.1/22.2 ± 3.6	6	30 mg daily/850 mg 2 times daily
Ortega-González, 2004 ²⁴	Yes	Yes	Yes	NR	Mexico	Yes	23	25.2 ± 4.8/22.9 ± 4.5	6	30 mg daily/850 mg 3 times daily
Cho, 2009 ²⁵	Yes	Not used	NR	NR	England	Yes	0	26.4 ± 1.5	3	45 mg daily/500 mg 3 times daily
Ortega-González, 2005 ²⁶	Yes	Yes	Yes	NR	Mexico	Yes	17	28.8 ± 0.9/29.0 ± 0.8	6	30 mg daily/850 mg 3 times daily
Zhang, 2008 ²⁷	Yes	Yes	Yes	NR	China	Yes	0	27.43 ± 3.01	3	15 mg daily/500 mg 3 times daily
Lu, 2011 ²⁸	Yes	Yes	Yes	NR	China	Yes	0	29 ± 3.1/30 ± 2.8	3	30 mg daily/850 mg 3 times daily

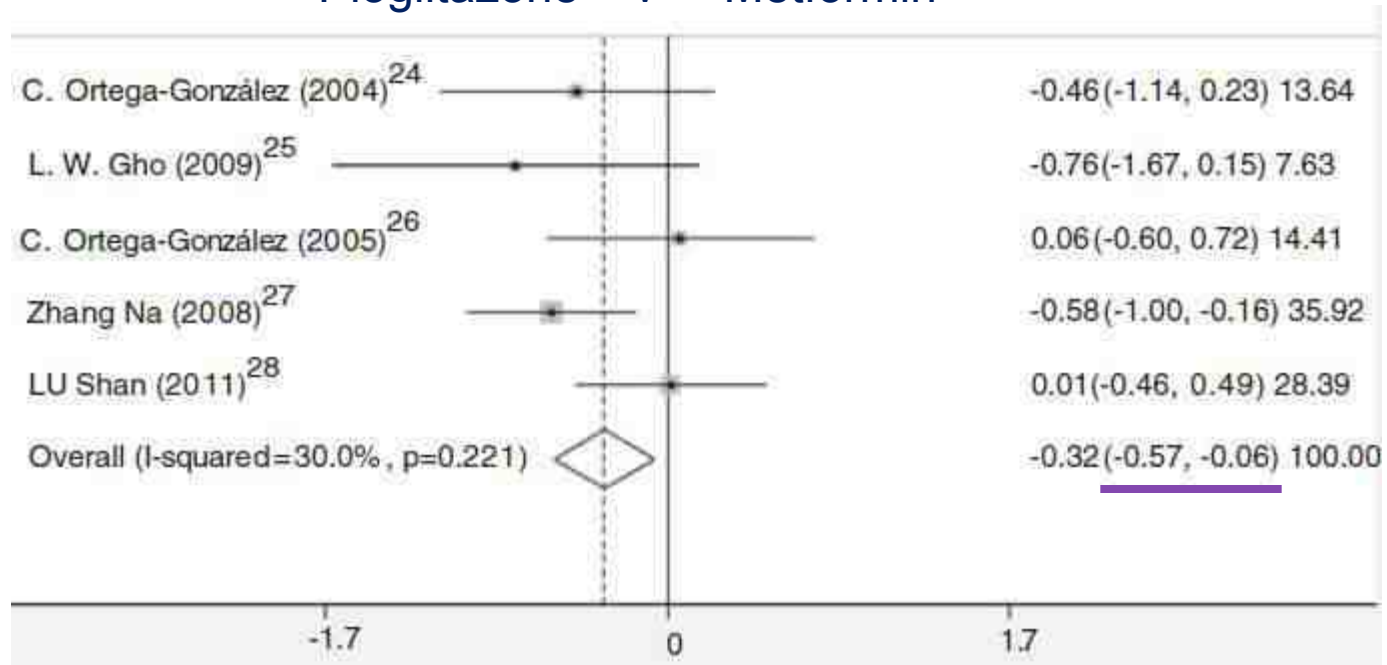
Hiperinsulinemi

Pioglitazone v Metformin



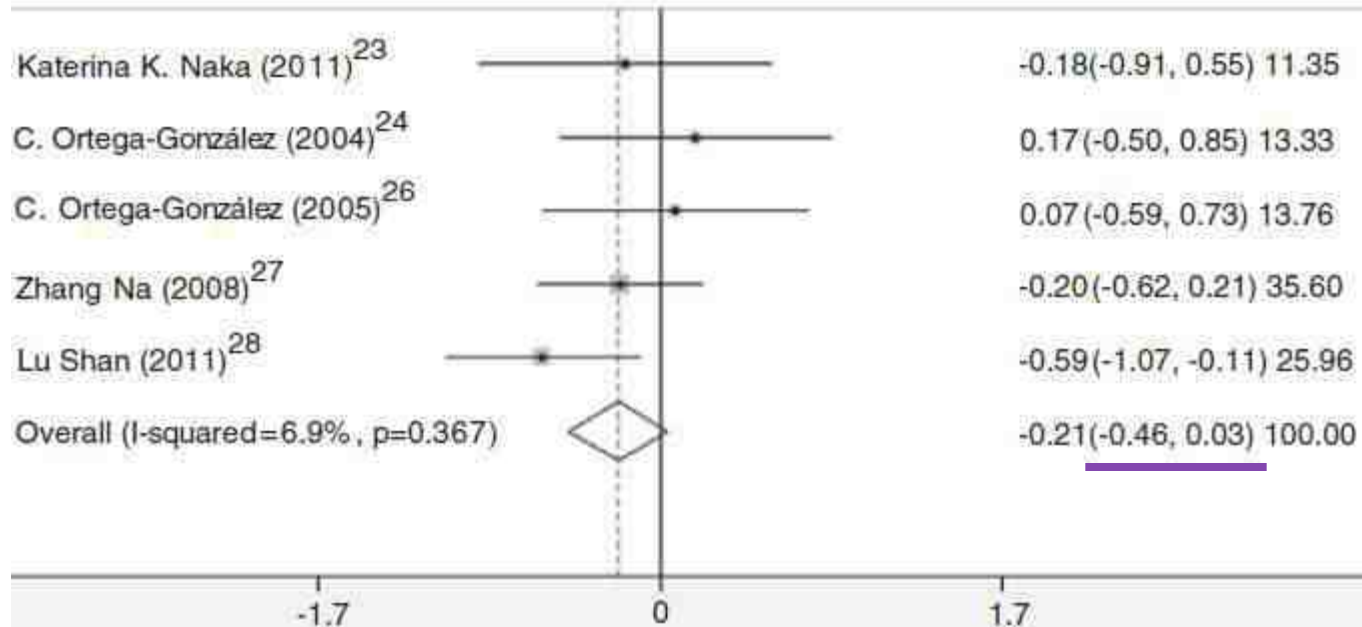
insulin direncinde iyileşme

Pioglitazone v Metformin



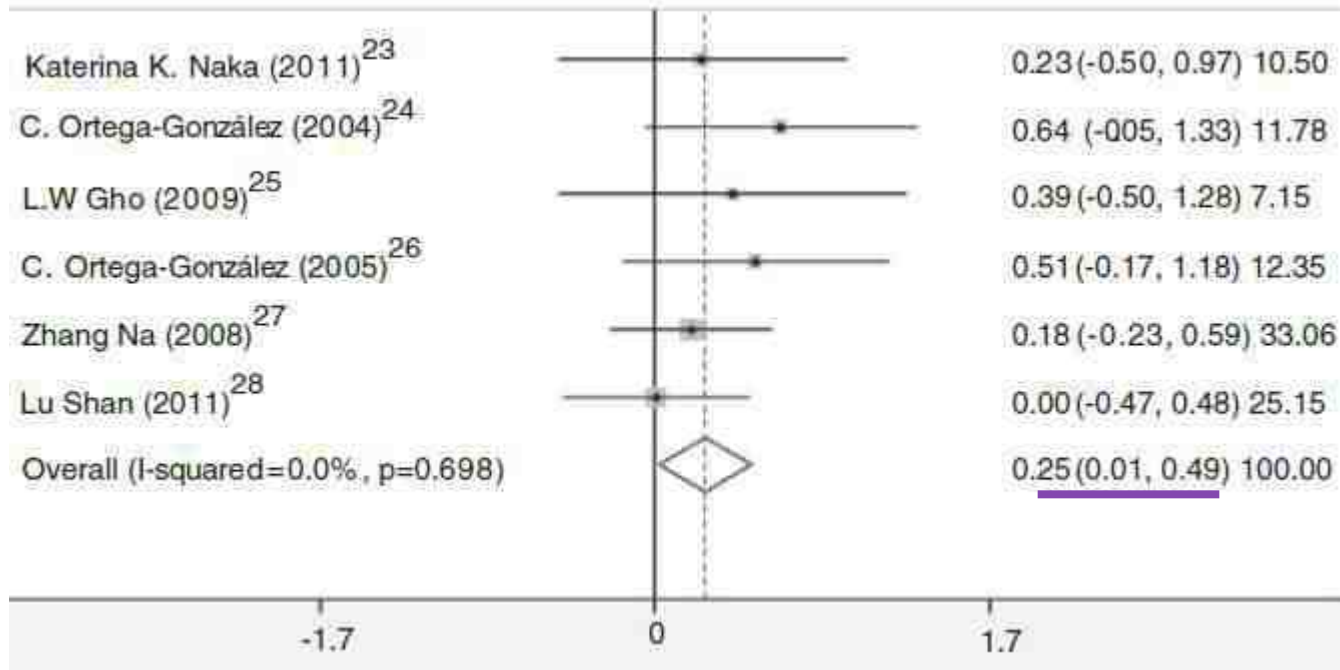
açlık kan şekerinde düşme

Pioglitazone v Metformin

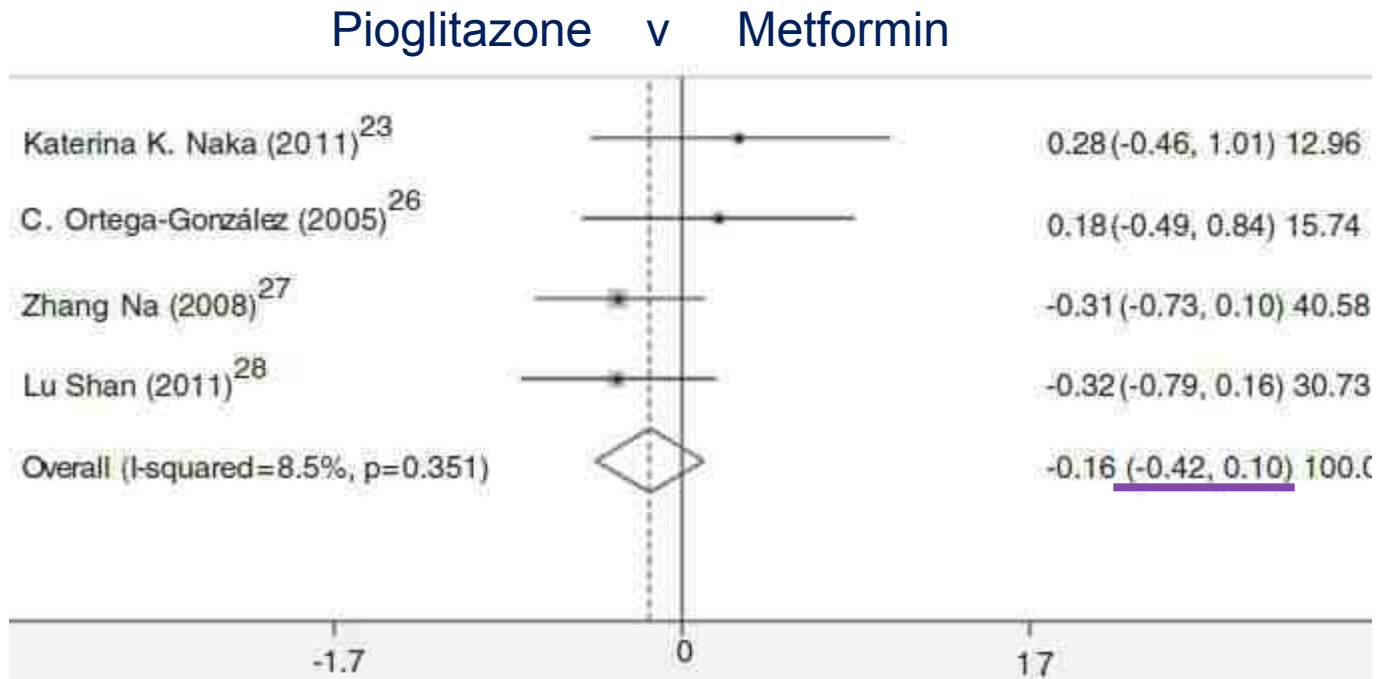


VKI

Pioglitazone v Metformin

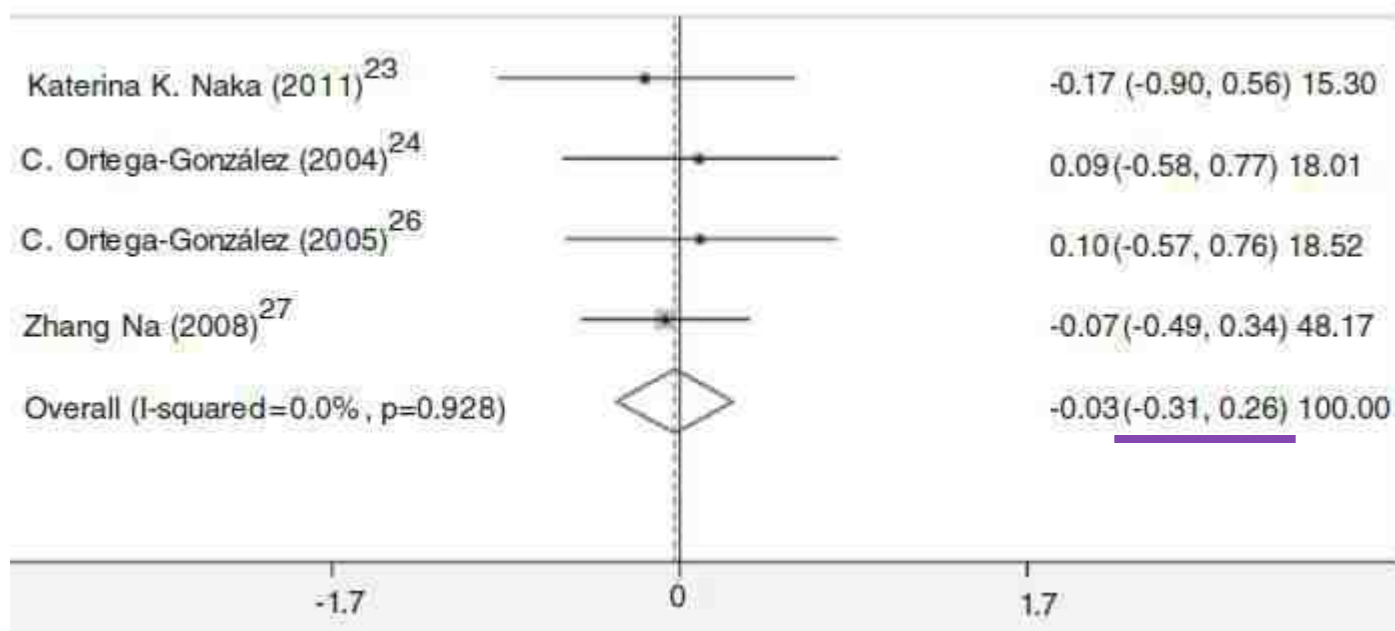


testosteron seviyesinde düşme

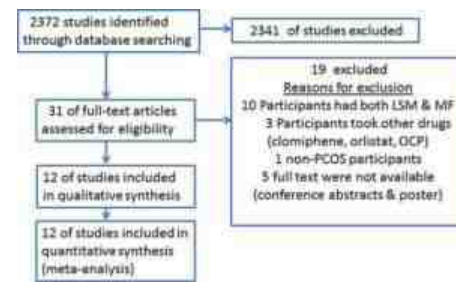


Ferriman Gallwey skorunda azalma

Pioglitazone v Metformin

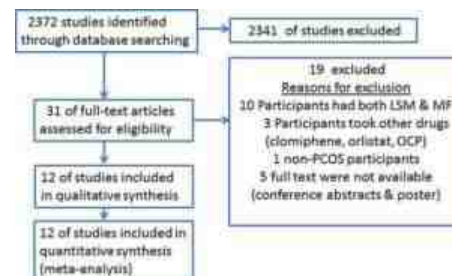


Met + yaşam değişiklikleri



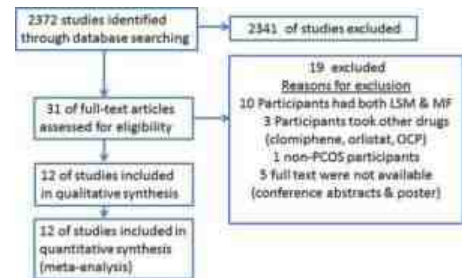
Study	Setting	Sample size	PCOS diagnostic criteria	Inclusion criteria	Exclusion criteria	Primary outcomes	Mean age (years)	Mean BMI (baseline)	Lifestyle modification	Metformin dose	Duration
Pasquali, 2000 (Pasquali et al., 2000)	Outpatient clinic (endocrine and gastroenterology)	LS + MF: 10. LS + P: 8	Rotterdam criteria	BMI > 28 kg/m ² and waist to hip ratio > 0.8	DM2, cardiovascular, renal or liver dysfunction, diet or medication 3 months prior to study	Body composition, fat distribution, androgens, insulin, glucose	LS + MF: 30.8 (7.4). LS + P: 32.3 (5.0)	LS + MF: 39.8 (7.9). LS + P: 39.6 (6.9)	1200–1400 kcal/day, 50% CHO, 20% protein, 30% fat.	850 mg bd	6 months
Vanky, 2004 (Vanky et al., 2004)	Outpatient clinic (gynaecology and infertility)	LS + MF: 17 LS + P: 21	Rotterdam criteria	Diagnosis of PCOS before pregnancy, age 18–40, gestation 5–12 weeks, singleton fetus by US	Known liver disease, or > 130 mmol/l, known alcohol abuse, DM, FBGL > 5.6, on oral glucocorticoids or any drug known to interfere with MF	Androgens	LS + MF: 28.9 (4.8). LS + P: 28.3 (3.7)	LS + MF: 32.0 (6.3). LS + P: 29.4 (8.2)	Verbal and written diet and lifestyle counselling at inclusion and after GDM diagnosis	850 mg/day for first week followed by 850 mg bd	from week 5–12 of pregnancy till post-partum
Gambineri, 2006 (Gambineri et al., 2006)	University medical centre, endocrine division	LS + MF: 20 LS + P: 19	Rotterdam criteria	Reproductive age (18–45), BMI ≥ 28 kg/m ² , waist circumference ≥ 88 cm	Use of any medications, significant modification in weight within previous 3 m, dieting	Androgens	LS + MF: 28 (8). LS + P: 26 (5)	LS + MF: 35 (4). LS + P: 37 (5)	500 kcal deficit, final composition ranged 1200–1400 kcal/day	850 mg bd	12 months
Tang, 2006 (Tang et al., 2006)	Infertility clinic	LS + MF: 56 LS + P: 66	Rotterdam criteria	BMI > 30 kg/m ² , 18–39 years old and a desire to conceive. Presence of at least one patent Fallopian tube, normal semen analysis, normal PRL, thyroid, renal and liver function, haematological indices including Bl2, negative Bhcg	Concurrent hormone therapy within the previous 6 weeks, any chronic dis that could interfere with absorption, distribution, metabolism or excretion of metformin, renal or liver dis. Sig systemic dis or DM2, irregular menses due to pathology of genital tract	Menstrual cycle, anthropometric measurements, endocrine parameters, insulin sensitivity, lipids	LS + MF: 29.7 (3.7). LS + P: 29.8 (3.8)	LS + MF: 38.1 (5.08). LS + P: 37.9 (6.5)	Verbal and written advice, 500 kcal/day deficit, 50% CHO, 10% fat, encouraged to adhere to regime at monthly visits. Encouraged to increase daily exercise by 15 min but not formally assessed.	850 mg bd	6 months

Met + yaşam değişiklikleri



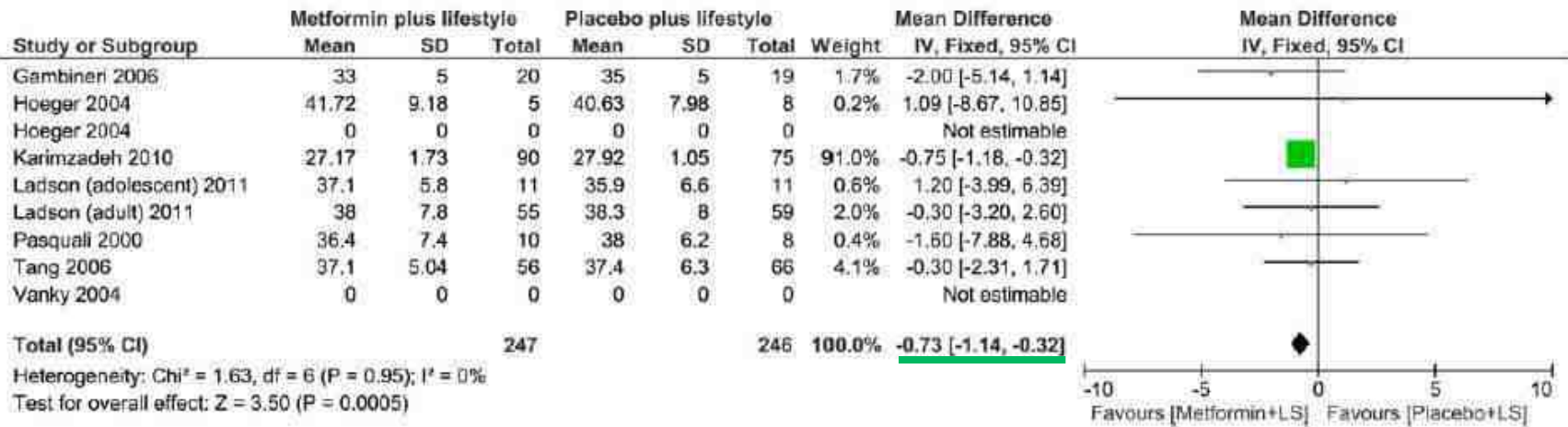
Study	Setting	Sample size	PCOS diagnostic criteria	Inclusion criteria	Exclusion criteria	Primary outcomes	Mean age (years)	Mean BMI (baseline)	Lifestyle modification	Metformin dose	Duration
Hoeger, 2008 (Hoeger et al., 2008)	Community or local physician referral	MF: 6 LS: 8	NIH criteria	Age 12–18, BMI > 95th percentile, post-menarchal	Any hormonal therapy or insulin sensitizers in previous 2 months	Androgens, lipids	MF: 16 (1.7), LS: 15.4 (1.2)	MF: 35.0 (8.2), LS: 36.0 (6.2)	500 kcal/day deficit, 30 min/day of mod to intense activity. Closed group format with 5–6 subjects per group (16-session core curriculum) hands-on kitchen training, behavioural support including peer support, electronic communications + structured group exercise weekly	850 mg bd (started with 425 mg and was increased gradually)	6 months
Hoeger, 2004 (Hoeger et al., 2004)	Direct advertisement, referral from physicians, reproductive endocrinology clinic	LS + MF: 9 LS + P: 11 MF: 9	NIH criteria	BMI > 25 kg/m ² , normal TSH, PRL, FSH and metabolic profile, DHEAS, 17 OH progesterone and 24 h UFC, negative Bhcg	Any hormonal medication within the last 2 months before entry, not desing at the time of entry	Ovulation, recruitment, dropout and compliance with a long-term, lifestyle intervention in PCOS	LS + MF: 30.4 (5.4), LS: 27.1 (4.3), MF: 29.5 (6.4)	LS + MF: 41.7 (6.2), LS: 40 (7.4), MF: 37.1 (4.9)	Modified from Diabetes Prevention Trial, aim for 7–10% weight loss, 500–1000 kcal/day deficit, 50% CHO, 25% protein, 25% fat, weekly interactive group education and monitoring (2 groups of 10 individuals) and 24 weeks maintenance (biweekly progress monitoring and group support meetings)	850 mg bd	48 weeks
Karimzadeh, 2010 (Karimzadeh and Javedani, 2010)	Infertility clinic	LS + MF: 90 LS: 75	Rotterdam criteria	Age 19–35, BMI 25–29.9 kg/m ² with primary infertility, normal thyroid, liver and kidney function, PRL, negative hCG, spouse with sperm concentration ≥ 20 million/ml, motility > 50%, morphology > 30%	taking MF in previous 8 weeks	menstrual cycle, waist circumference, lipids, endocrine parameters	LS + MF: 27.33 (2.34), LS: 27.84 (2.69)	LS + MF: 27.17 (1.73), LS: 27.92 (1.05)	500 kcal/day deficit, 50–60% CHO, 15–20% protein, 25–30% fat and 3–5 times a week exercise of 20–60 min both aerobic and strength training	500 mg/day gradually increased to 1.5 g/day	6 months
Ladson, 2011 (adolescents) (Ladson et al., 2011a)		LS + MF: 11 LS + P: 11	NIH criteria	age 13–18, BMI > 27 kg/m ² , otherwise healthy	Use of any confounding medications (hormonal contraceptives, diabetic medications)	Androgens	LS + MF: 16.1 (1.5), LS + P: 15.4 (1.2)	LS + MF: 37.1 (5.8), LS + P: 35.9 (6.6)	3d food log, 500 kcal/day deficit, 55% CHO, 15% protein, 30% fat, goal of ≥ 7% weight loss, monthly review by a dietitian and a personal trainer, 150 min/week aerobic exercise including an opportunity to attend ≥ 2 sessions per week a fitness facility	500 mg/day gradually increased to 2 g/day every 5 days	6 months

Met + yaşam değişiklikleri

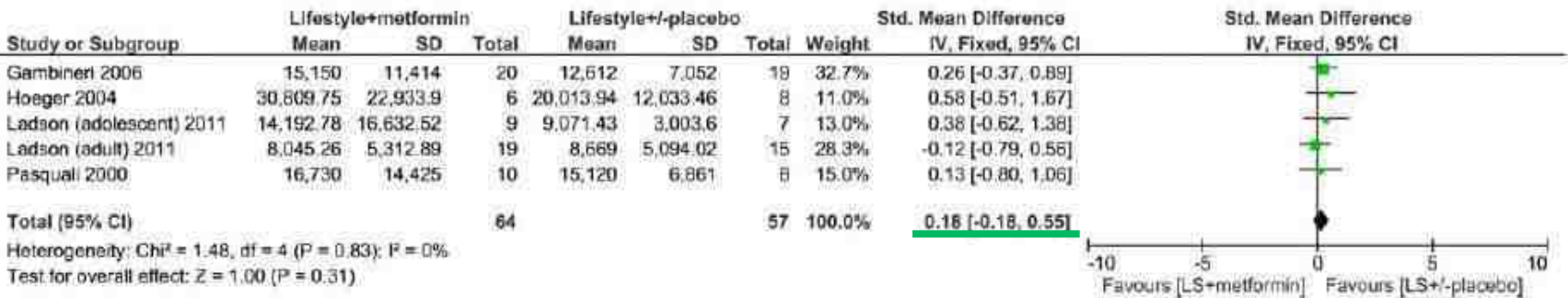


Ladson, 2011 (adults) (Ladson et al., 2011b)	Two academic medical centres	LS + MF: 22 LS + P: 16	NIH criteria	Age 21–39, otherwise healthy, any BMI	Use of any confounding meds (hormonal contraceptives, diabetic medications)	Ovulation, androgens	LS + MF: 29 (4.5), LS + P: 28.8 (4.6)	LS + MF: 38.0 (7.8), LS + P: 38.3 (8.0)	500 kcal/day deficit, goal of ≥7% weight loss, 150 min/week aerobic exercise with an opportunity to attend ≥2 sessions per week a fitness facility, a daily physical activity log once per month and monthly test of aerobic capacity	500 mg/day gradually increased to 2 g/day every 5 days	6 months
Esfahanian, 2012 (Esfahanian et al., 2013)	Endocrine clinic	MF: 17 LS: 13	Rotterdam criteria	Age 20–30, BMI ≥ 27 kg/m ²	DM2, smoking, alcohol use, taking sex steroids or drugs known to affect lipids and weight during the preceding 3m	CRP, insulin resistance	MF: 21.9 (9.3), LS (diet): 20 (4.6)	MF: 31.1 (3.3), LS: 34.1 (5.4)	Dietitian review for 5–10% weight loss, frequent contacts (phone, email and visit) to support diet programme	500 mg bd, gradually built to 1 g bd	12 weeks
Otta, 2010 (Otta et al., 2010)	Endocrine clinic	LS + MF: 14 LS + P: 15	NIH criteria	Age 20–34, negative Bhcg, any BMI kg/m ²	Cushing, thyroid, late CAH, DM, high PRL, androgen-secreting tumours, Hepatic or renal dysfunction, severe infections, CVD, no meds for at least 3 m prior to study	Endocrine and metabolic parameters	LS + MF: 25.47 (4.82), LS + P: 24.7 (3.46)	LS + MF: 32.4 (6.7), LS + P: 35.6 (4.98)	1500 kcal/day diet, 50% CHO, 20% protein, 30% fat, minimum of 40 min daily brisk walk, 4 times/week, monthly visits	500 mg/day week 1, increased to 500 mg bd at week 2 and 750 mg bd week 3	4 months
Curi, 2012 (Curi et al., 2012)	Obstetrics and gynaecology clinic (presentation for hirsutism or menstrual disturbances)	MF: 15 LS: 12	Rotterdam criteria	Age 18–34, BMI > 25 kg/m ² , sedentary lifestyle	Cushing, thyroid, late CAH, DM, high PRL, androgen-secreting tumours, HTN, GI, hepatic or renal dysfunction, hormonal or other medications interfering with weight in the preceding 6 months before study	Menstrual pattern	MF: 24.6 (1.3), LS: 26.3 (1.4)	MF: 31.4 (1.4), LS: 31.8 (1.6)	500 kcal deficit, 50% CHO, 20% protein, 30% fat, 30 min walk and 3 self-weight resistance exercise (total 40 min), record of food intake and physical activity on a daily card, monthly review by dietitian	850 mg bd	6 months

VKI



Insulin AUC



Açlık kan şekeri



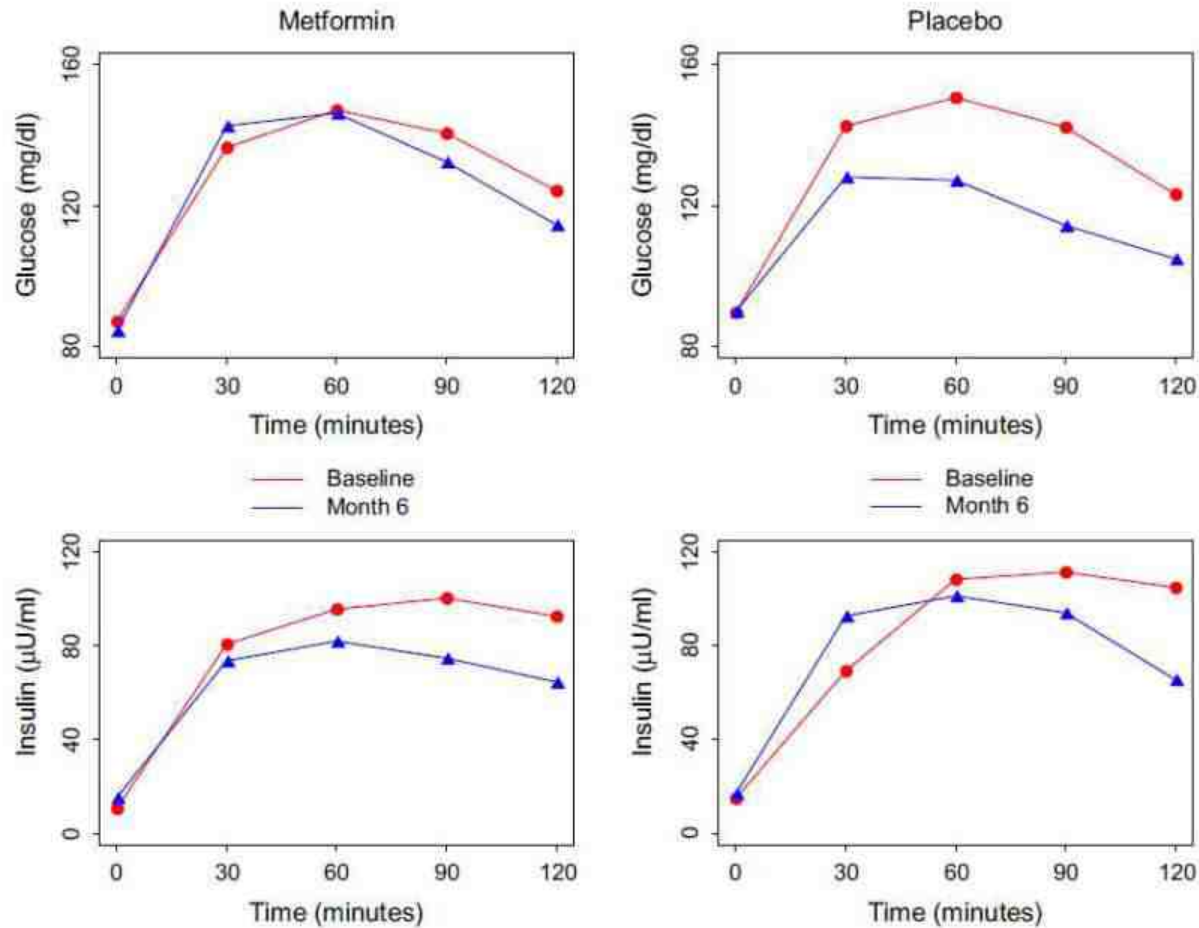
Subkutan yağ dokusu



Mensturasyon

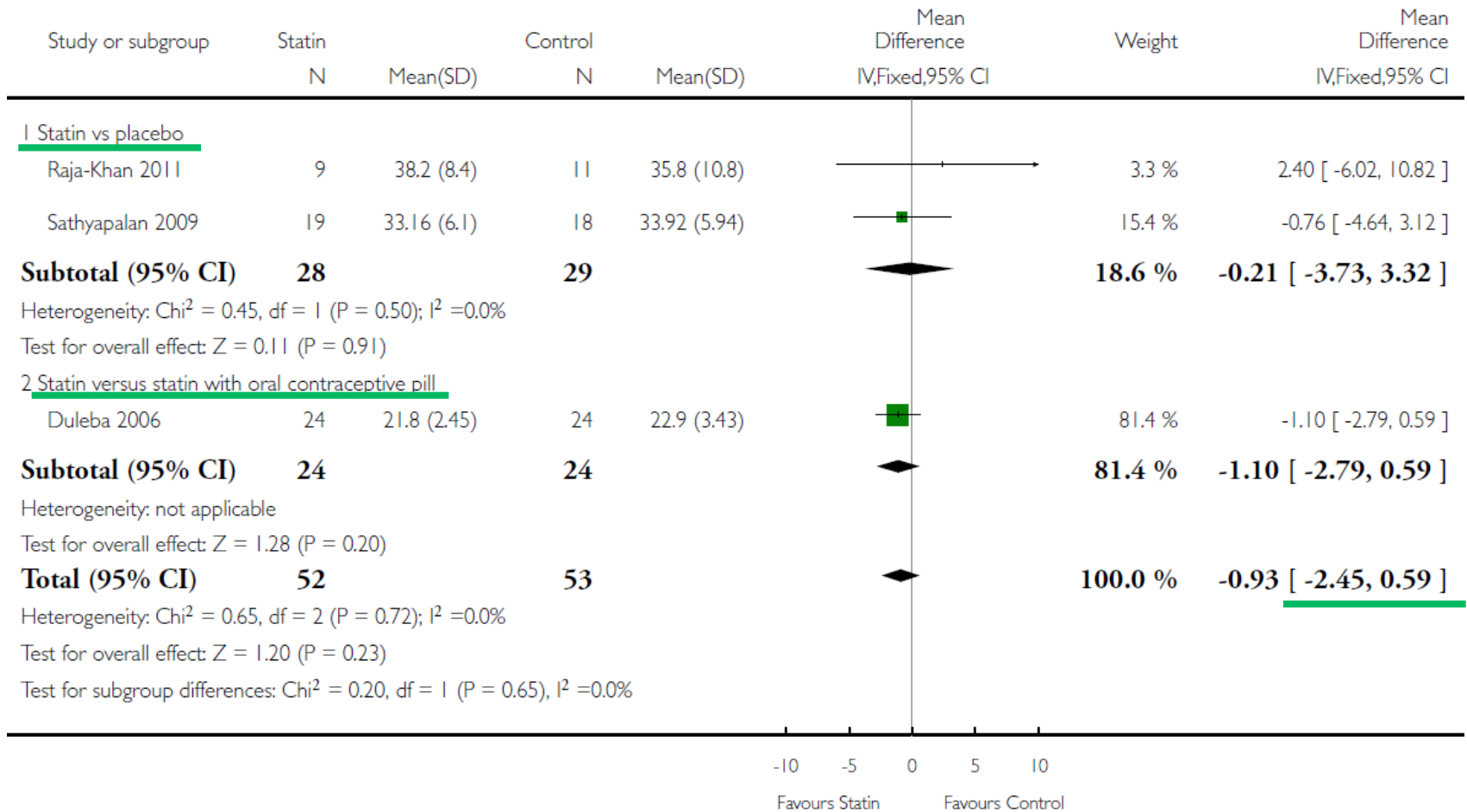


Metformin v Plasebo + fiziksel aktivite

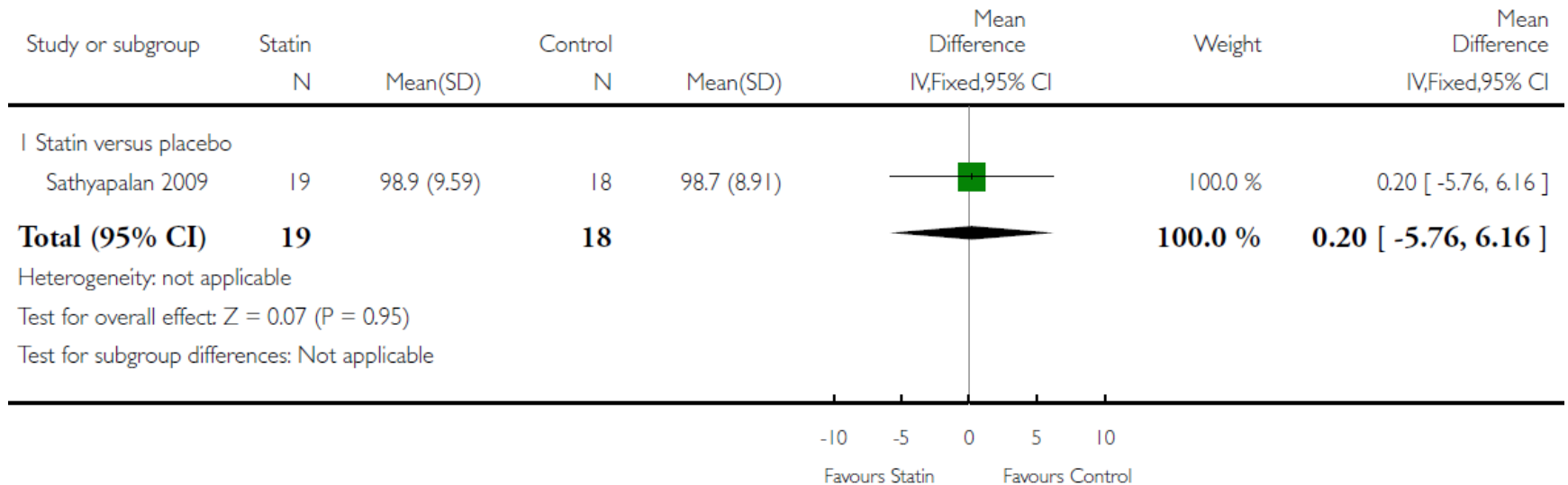


Anlamlı değil

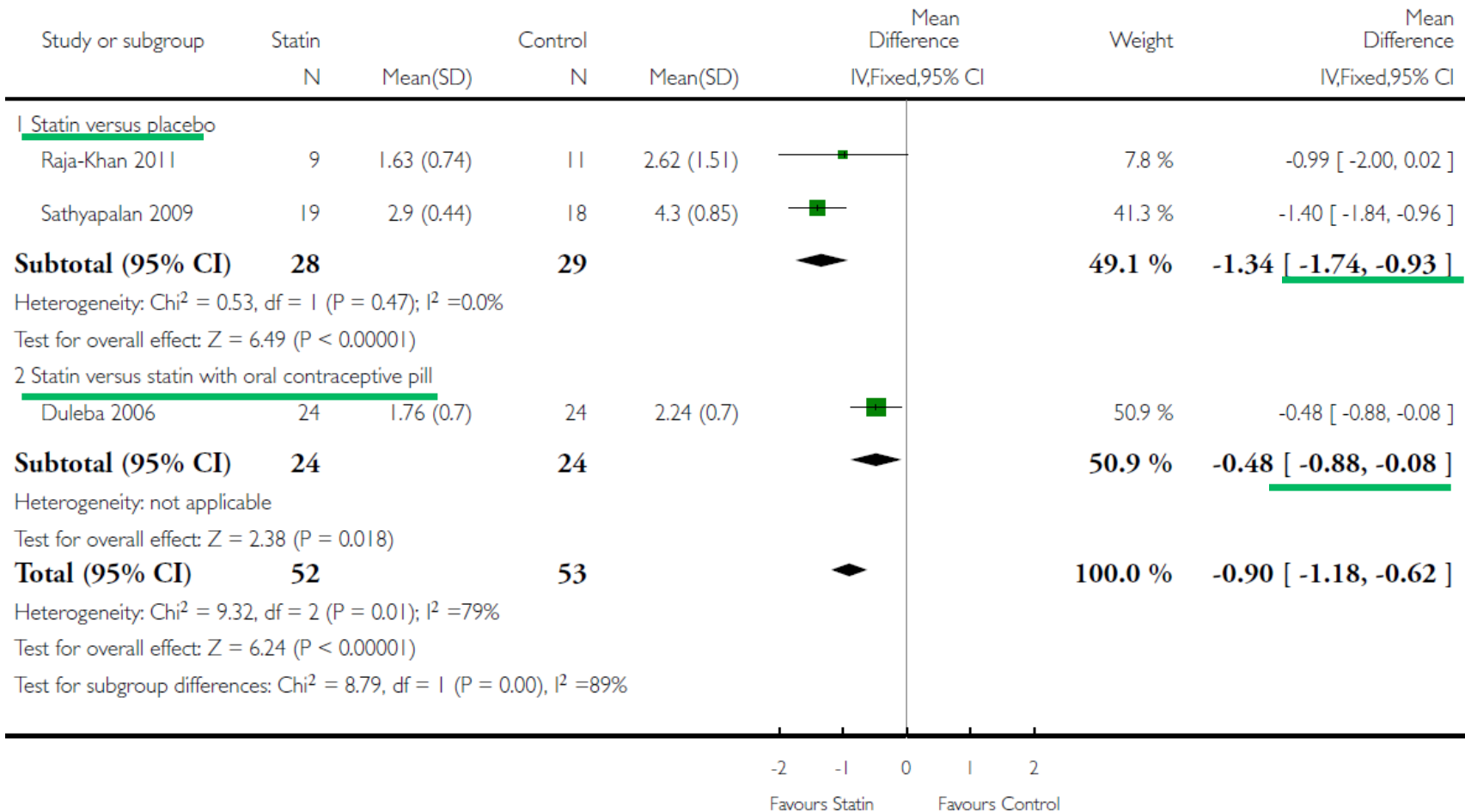
Statinler- VKI



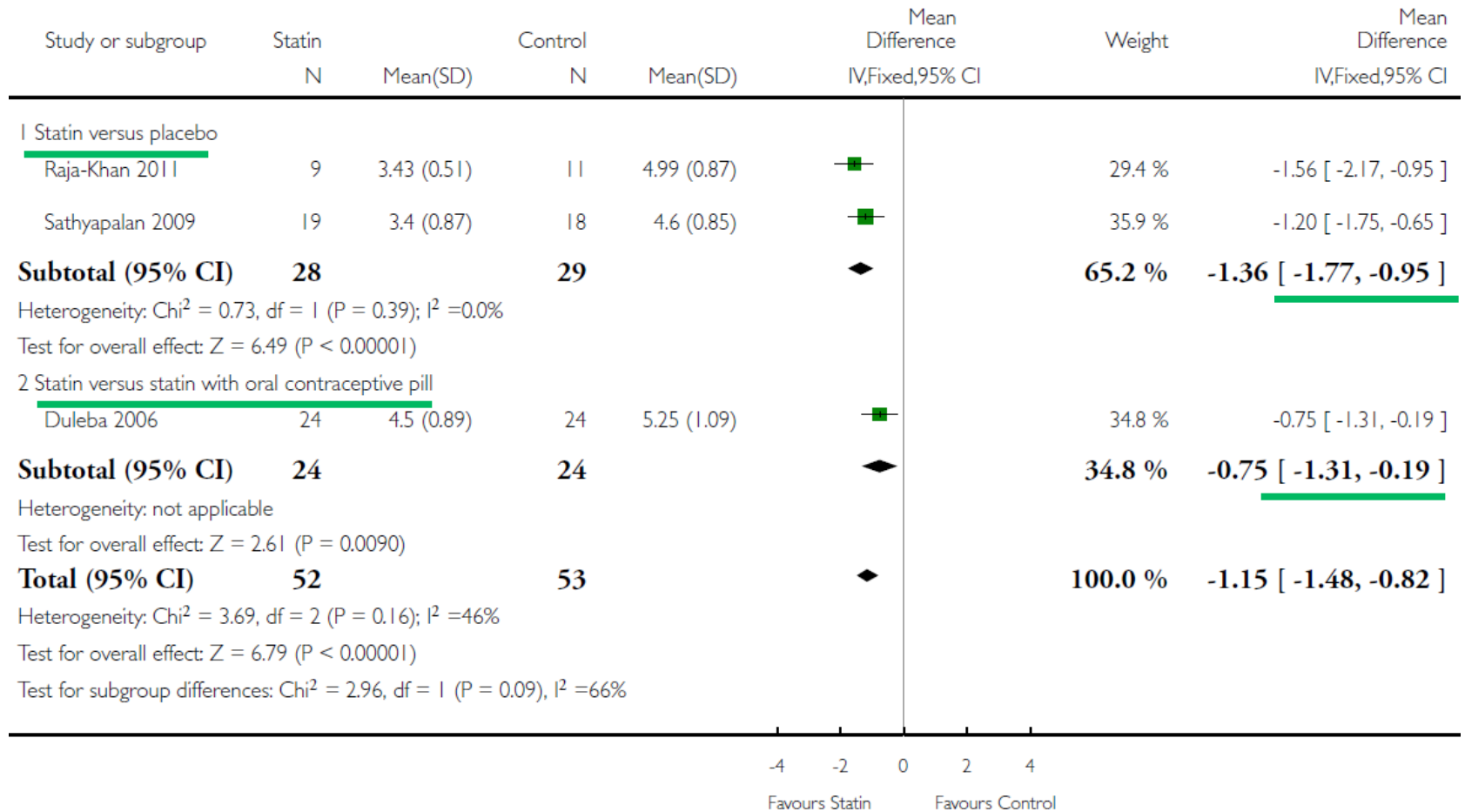
Bel çevresi



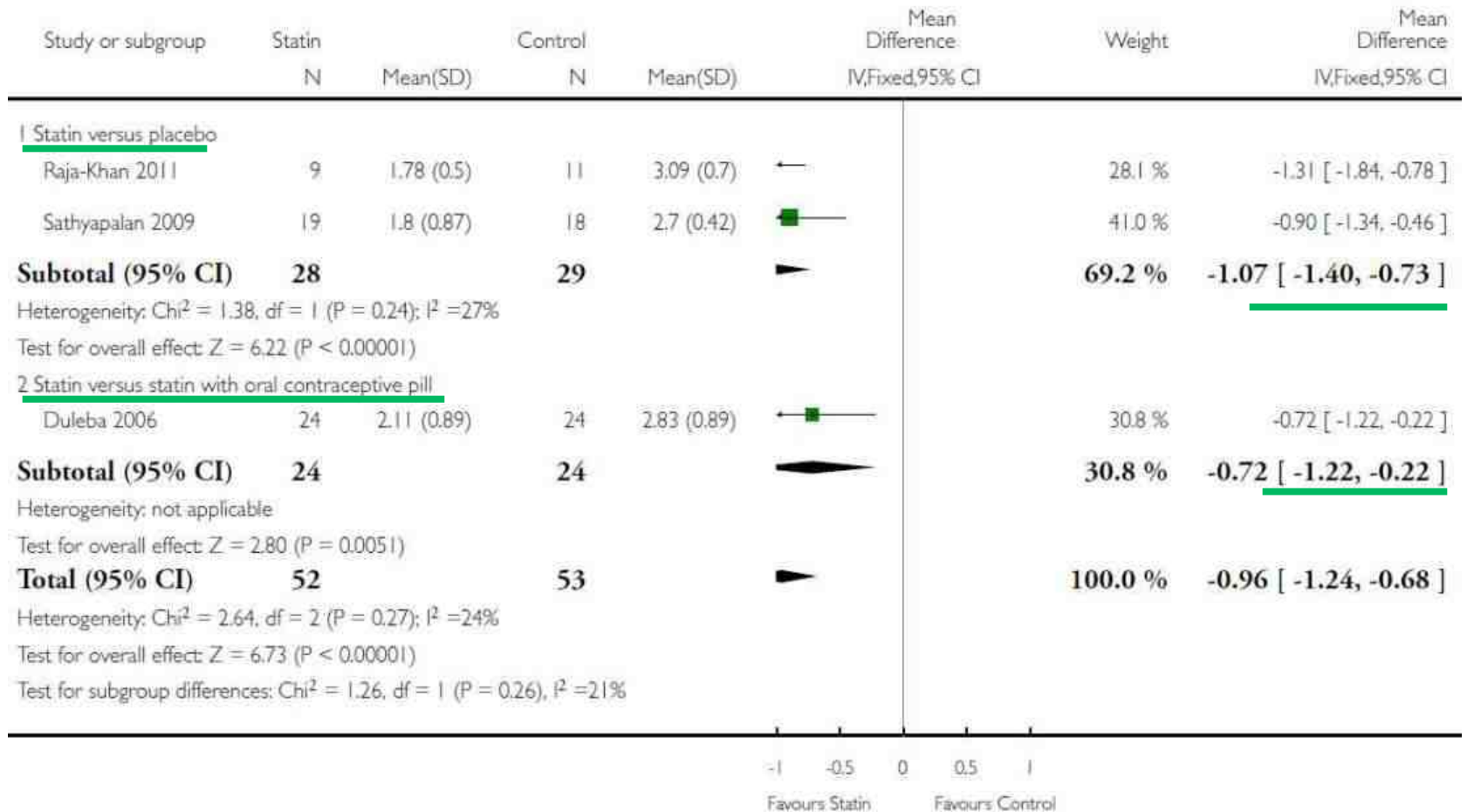
Testosterone



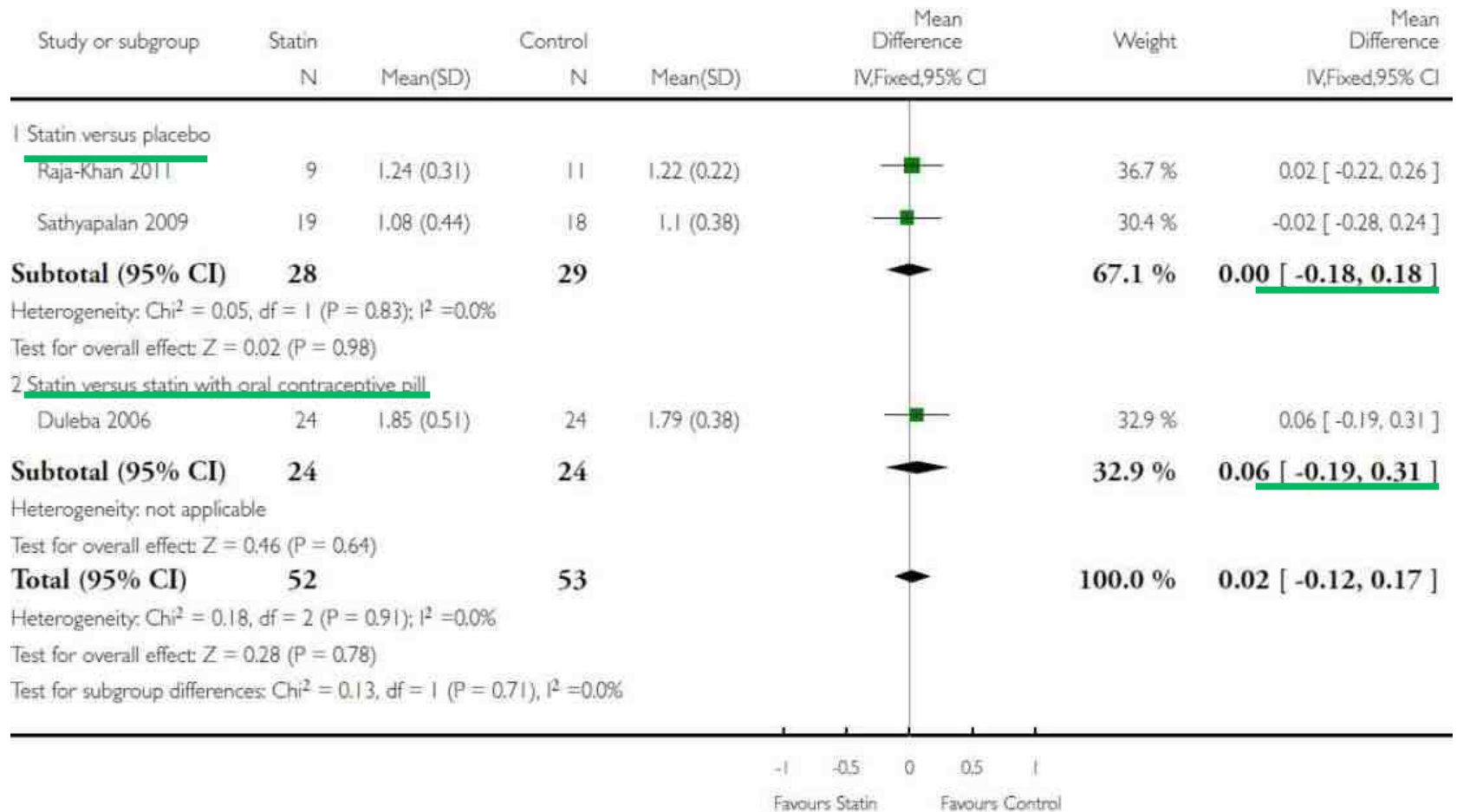
Total kolesterol



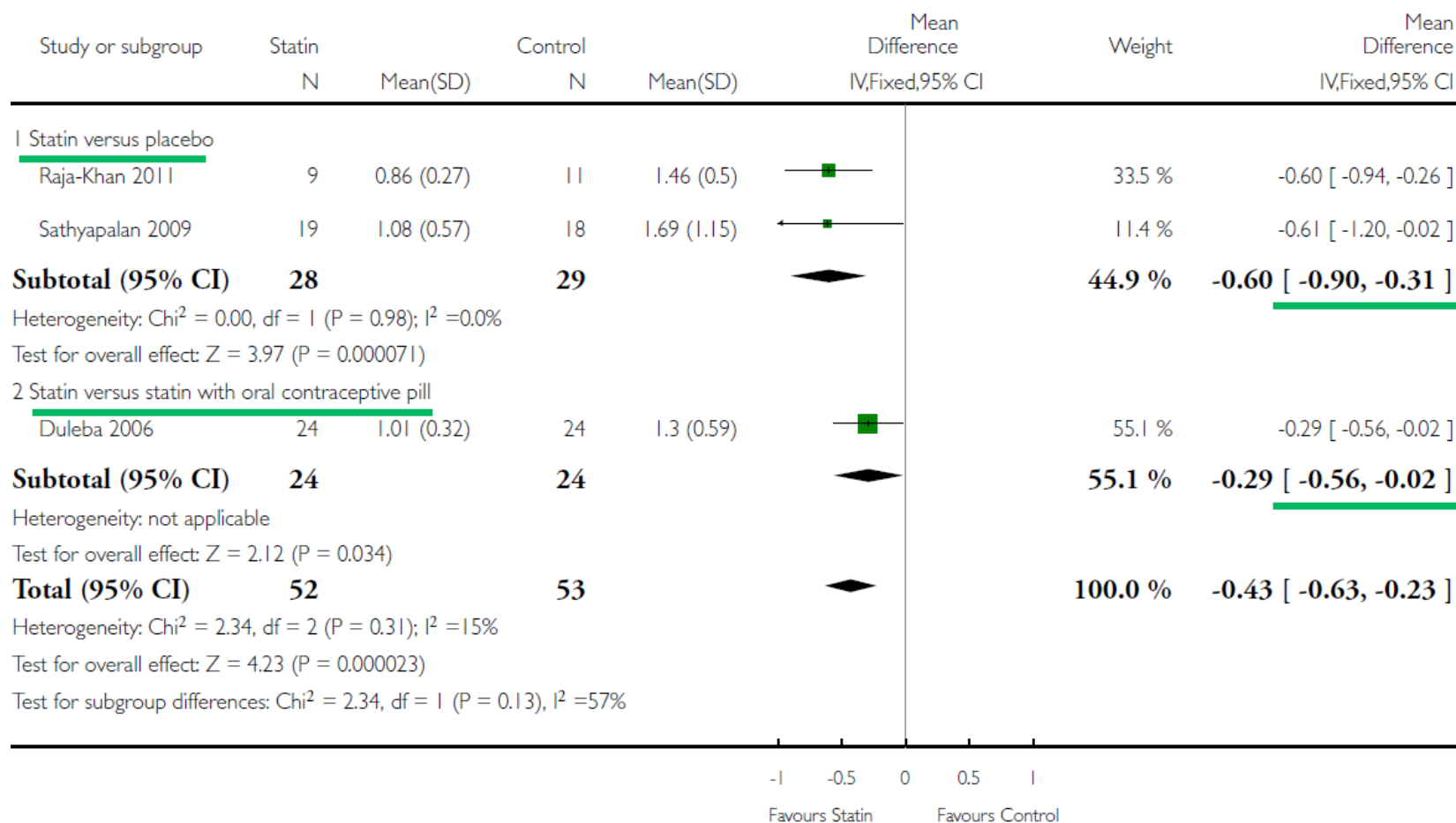
LDL Kolesterol



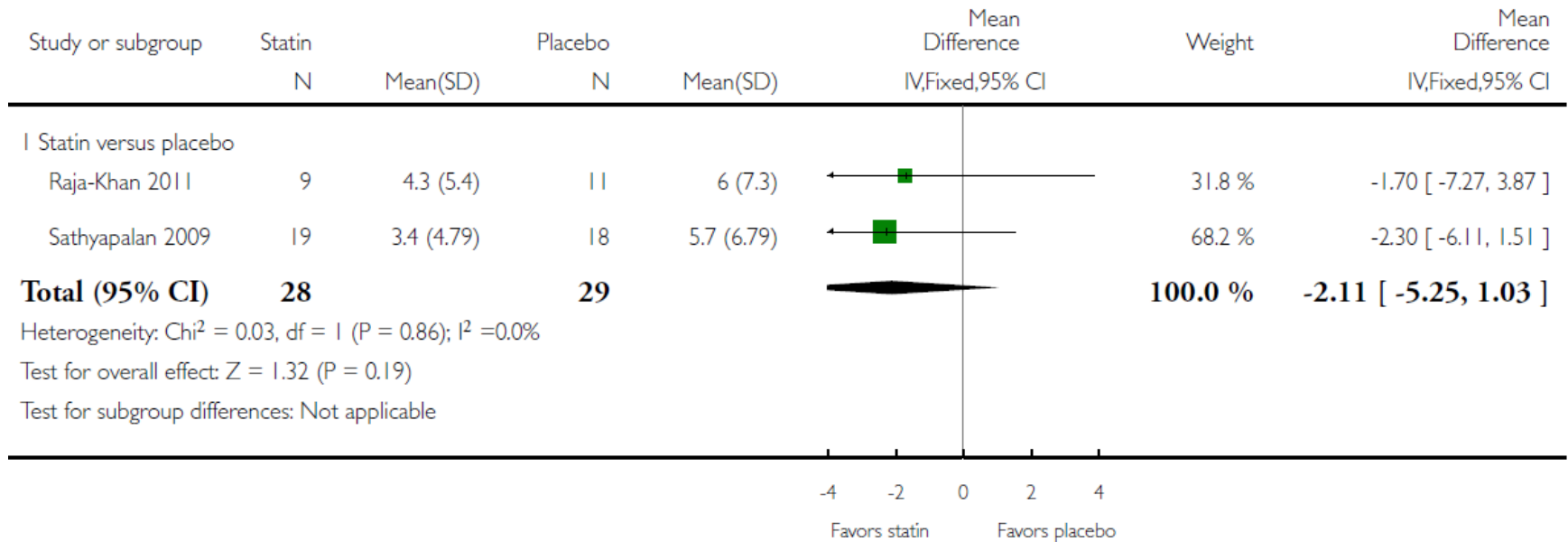
HDL Kolesterol



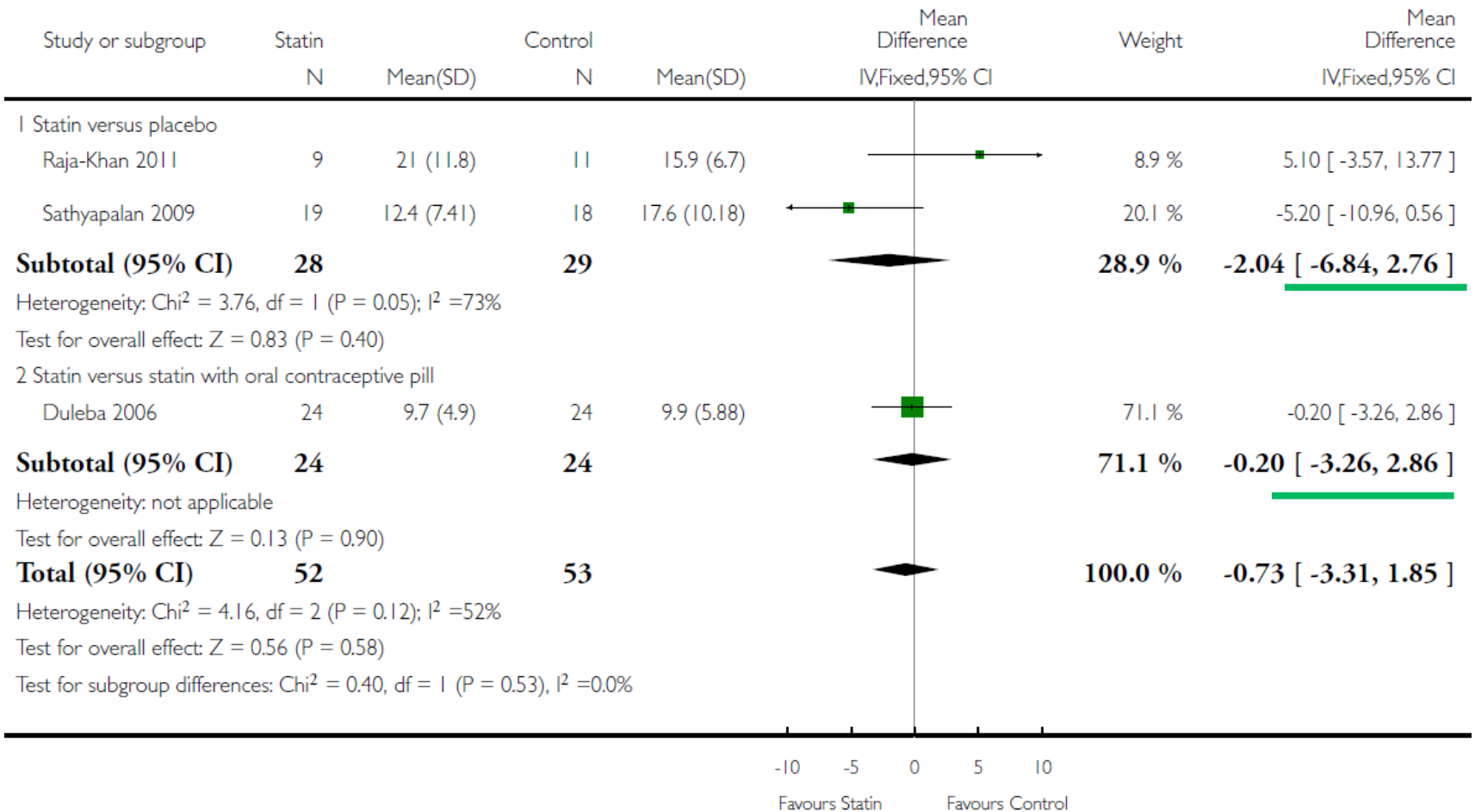
Triglycerid



HS CRP



Açlık insülin



PKOS'DA YAYGIN OLARAK GÖRÜLEN PSİKOLOJİK SORUNLAR

- Duygusal bozuklukların PKOS olmayan kadınlara göre PKOS'lu kadınlarda daha sık olduğu gösterilmiştir. PKOS'lu kadınlardaki depresyon prevalansı, **%40** kadar yüksek bulunmuştur.
- PKOS'lu kadınların **%23.9 ve %25.2**'sinde, *Beck Depresyon Ölçeği*nde (BDÖ) klinik olarak anlamlı sırasıyla **hafif ile orta** ağırlıkta skorlar elde edilmiştir.
- PKOS'lu kadınlarda PKOS olmayan kadınlara göre, sosyal olarak içine kapanma, yeme bozuklukları ve anksiyete bozuklukları görülme olasılığı daha yüksektir.

- PKOS'lu obez kadınların, PKOS olmayan obez kontrollere göre depresif bozukluklar geliştirme açısından daha büyük risk altında olduğu bulunmuştur. (**%44 v %7**)
- Bu durum yine obezite varlığından bağımsız olarak PKOS'lu kadınların PKOS olmayan kadınlara göre depresyon için daha fazla risk altında olabileceğini düşündürmektedir.

- Depresyon ve kronik stres gibi duygusal bozukluklar, bađışıklık sistemi aktivitesinde ve proinflamatuvar belirteçlerde artış olması gibi çeşitli fizyolojik deđişikliklerle ilişkilidir.
- Bu bozukluklar; sonuç olarak kardiyovasküler hastalıklar, diyabet ve kanser gibi hastalıkların riskini artırmaktadır.
- Muhtemelen inflamatuvar belirteçlerin kronik olarak yükselmesi sebebiyle, PKOS'lu kadınlarda yorgunluk, depresif duygudurum, sosyal geri çekilme ve uyku bozuklukları dahil olmak üzere bazı hastalık davranışı belirtileri görölmektedir.

- Proinflamatuvar sitokinler ve diđer inflamatuvar belirteçlerdeki artış, PKOS olmayan kadınlar ile karşılaştırıldığında, PKOS'lu kadınlarda yorgunluk artışı ve daha fazla sayıda ve çeşitlilikte uyku bozuklukları dahil olmak üzere çok çeşitli hastalık davranışı belirtilerinin bildirilmesinin sebebini açıklamaktadır.
- Kontrol grubu ile kıyaslandığında, PKOS'lu kadınlarda, uykuda nefes bozukluğu, daha fazla gündüz uyku hali ve yorgunluk ve uykuya dalmada daha fazla zorluk olması çok daha muhtemeldir.

- PKOS'lu kadınlarda uyku bozukluklarının hafifletmek sadece uyku kalitesini artırmaz, aynı zamanda gündüz yorgunluğunu ve depresif duygudurumunu hafifletir, bu sayede de genel sađlık durumunu etkiler.
- İnflamatuvar belirteçlerdeki artış ile ilişkili olmasının yanı sıra, depresyonun anormal (genellikle artmış) kortisol sekresyonu ile ilişkili olduđu bildirilmiştir.
- PKOS'lu kadınlarda, duygudurumundan bağımsız olarak genellikle kortisol sekresyonu anormallikleri görülür.

- Kortizol, tüm bireylerde stresli uyarılara yanıt olarak salgılanmakta ve viseral yağ ve inflamasyondaki artışına katkıda bulunmaktadır.
- Normal kadınlara göre PKOS'lu kadınlarda daha fazla viseral yağ ve inflamatuvar belirteçler olduğu için ve kortisol sekresyonu hiperandrojenizme katkıda bulunduğu için, bu mekanizma bu kadınlarda özellikle problemlili olabilir.
- Yüksek VKİne sahip zayıf kadınlarda, düşük VKİ olan zayıf kadınlara göre, yeni ve bilinen bilişsel laboratuvar stresörleri uygulanmasından sonra daha fazla kortisol sekresyonu olduğu bildirilmiştir.

- Metformin tedavisi stres reaktivitesini etkilemeyebileceđi için, *stres azaltma giriřimleri*, PKOS'lu kadınların tedavisi sırasında önemli adjuvan yaklaşımlar olabilmektedir.
- PKOS'lu kadınların çođunluđunda T düzeylerinin artmış olması sebebiyle, PKOS'lu kadınların öfkenin yanı sıra inflamasyonu řiddetlendirebilen diđer negatif duygulanımlara abartılı bir SSS yanıtı vermesi olasıdır.
- PKOS'lu kadınlarda psikolojik stresten kaynaklanabilecek olumsuz fizyolojik deđişiklikleri azaltacak olan *stres yönetimi* girişimlerinin önemi vurgulanmaktadır

Egzersiz

- Psikolojik parametrelerle ilgili olarak, düzenli egzersizin kilo kaybından bağımsız olarak *vücut imajını* iyileştirdiği görünmektedir.
- Yapılan bir çalışmada, daha önceden egzersiz yapmayan PKOS'lu kadınlarda, başlangıçtaki vücut dismorfik semptomatolojileri ile karşılaştırıldığında, kendilerinin bildirdiği 6 aylık düzenli (örn, haftada 3 gün) ve orta yoğunluktaki bir egzersiz program sonrasında anlamlı olarak daha az miktarda vücut dismorfik semptomu görüldüğü teyit edilmiştir.

- Çocukluk döneminde egzersize yönelme, PKOS'un semptomlarının ortaya çıkma ihtimalini azaltmada özellikle önemli ve etkili olabilmektedir.
- PKOS'lu kadınların çocukluk dönemlerinde, PKOS olmayan kadınlarla karşılaştırıldığında, erkeksi davranışlara (örn, daha erkeksi oyuncaklar ve oyunların tercih edilmesi, diğer kızlardan daha yüksek aktivite düzeyine sahip olunması) ilgi duyma ve katılma oranlarının anlamlı miktarda daha fazla olduğu teyit edilmiştir .

Diyet Deęişiklikleri

- 16 hafta boyunca düşük karbonhidratlı, yüksek proteinli bir diyete uymak üzere rastgele atanan PKOS'lu kadınlarda, *depresyon ve benlik saygısı* açısından anlamlı düzelmeler görülmüştür.
- Yüksek karbonhidrat içerikli bir yemek sonrasında PKOS olmayan kadınlara göre PKOS'lu kadınlarda proinflamatuvar belirteç sekresyonunun daha fazla olabileceęi gösterilmiştir.
- Kontrol grubu ile karşılaştırıldığında PKOS'lu kadınlarda hipergliseminin , inflamasyon açısından dezavantajlı olduęu gösterilmiştir.

- Diyetin potansiyel olarak inflamasyon aracılığıyla *duygudurumunu* etkileyebileceği ortaya konulmaktadır.
- Yaşam tarzı değişiklikleri *duygudurumunda* pozitif bir katkı sağlayabilir.
- Yaşam tarzı değişiklikleri ve psikolojik sağlığın, bu bireylerde çift yönlü bir ilişkiye sahip olduğu görünmektedir.

Stres ve Duygudurumu Yönetimi

- Duygudurumunu iyileştirmesi ve stresi azaltmasının yanı sıra, *stres yönetimi* müdahalelerinin dahil olduğu *bilişsel davranışsal yaklaşımlarının*, HPA eksenini regülasyonunu normalize etme ve aynı zamanda SSS aktivitesini düşürme yeteneğine sahip olduğu görülmektedir.
- Stresle daha iyi bir şekilde başa çıkmaya yönelik *gevşeme ve bilişsel davranışsal terapi* gibi teknikler, PKOS'lu kadınlarda sıklıkla görülen kortisol sekresyonu anormalliklerini gidermek amacıyla kullanılabilir.

Stres ve Duygudurumu Yönetimi

- PKOS'lu kadınlarda *bilişsel kognitif davranışsal terapi* (BDT) ya da diğer psikolojik müdahalelerin kullanıldığı az sayıda araştırma bulunmaktadır.
- PKOS'lu adölesanların dahil edildiği bir pilot çalışmada, 8 haftalık bir BDT müdahalesi ile, kilo ve depresif belirtilerde anlamlı azalmalar ve adet düzeni ve uyku ile ilişkili solunumda anlamlı düzelmeler elde edilmiştir.
- Genel popülasyonda, BDT müdahaleleri; VKİ, yağ yüzdesi, bel çevresi, lipitler ve kalori alımının azaltılması gibi değişikliklerin elde edilmesinde birevlere yardımcı olmuştur.

Dikkatiniz için teŖekkür ederim.

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