

**METFORMIN IN PREVENTIA
CRESTERII IN GREUTATE INDUSE
DE TRATAMENTUL ANTIPSIHOTIC:
O REVIZUIRE SISTEMATICA SI
META-ANALIZA**

BMC Psychiatry

de Silva et al. BMC Psychiatry (2016) 16:341

DOI 10.1186/s12888-016-1049-5



INTRODUCERE

- majoritatea antipsihoticelor sunt asociate cu creșterea în greutate și alte complicații metabolice;
- prevalența ↑ a sindromului metabolic la pacienții tratați cu antipsihotice
- rata de creștere în greutate - mai mare în primele șase luni;
- clozapină și olanzapină - risc de creștere în greutate



- metformin - antidiabetic din clasa biguanidelor
- modalitatea de actiune nu este explicata in totalitate
- produce efecte metabolice diferite in functie de celule, tesuturi, organe
- la persoanele sanatoase mecanismele de contrareglare mascheaza efectele hipoglicemizante – glicemia nu este modificata



- determina scadere moderata in greutate – efectul ar fi explicat printr-un mecanism central de a reduce ingestia calorica/ cresterea pierderilor de energie
- **metformin → bariera hemotoencefalica → hipotalamus → ↓ AMPK → ↓neuropeptid Y- blocare receptori Y1 si Y5; ↓AgRP**
- metformin ↑ acțiunea insulinei în ficat → scade rata producției de glucoză hepatică
- metformin ↑ utilizarea periferică a glucozei și suprimă apetitul



METODA

- trialuri - perioada ian. 2000 – dec. 2015 din Registrul Central Cochrane, MEDLINE si EMBASE
- studii controlate placebo randomizate dublu-orb
- pacienti - ambele sexe
 - - toate grupele de varsta
 - - diagnosticati cu schizofrenie/tulburare schizoafectiva conform DSM-IV, DSM-5 si ICD-10
 - in tratament cu antipsihotice
- obiective - modificarea medie în greutate, modificarea IMC, indicele de rezistenta la insulina, glicemie a jeun



Table 1 Study Characteristics

Study	Methods	Participants	Country	Numbers	Intervention
1. Armen 2008	Parallel group RCT Duration 12 weeks	Age < 20 years On risperidone 2–6 mg	Saudi Arabia	Metformin N = 16 Placebo N = 16	Metformin 500 mg twice daily or placebo
2. Baptista 2006	Parallel group RCT Duration 14 weeks	Age ≥ 18 years Olanzapine monotherapy > 4 months	Venezuela	Metformin N = 19 Placebo N = 18	Metformin 850–1750 mg Balanced diet of 2500–300Kcal
3. Baptista 2007	Parallel group RCT Duration 12 weeks	Age ≥ 18 years Olanzapine monotherapy > 4 months	Venezuela	Metformin N = 36 Placebo N = 36	Metformin 850–2550 mg or placebo Diet and exercise counseling at start of study
4. Carrizo 2009	Parallel group RCT Duration 14 weeks	clozapine treatment > 3 months	Venezuela	Metformin N = 31 Placebo N = 30	Extended release metformin 500–1000 mg/day or placebo
5. Chen	Parallel group RCT Duration 24 weeks	clozapine treatment > 3 months BMI ≥ 24 or one metabolic syndrome criteria	Taiwan	Metformin N = 28 Placebo N = 27	Metformin 1500 mg/day
6. De Silva 2015	Parallel group RCT Duration 24 weeks	Age ≥ 18 years Weight gain > 10 % of body weight Females 78.8 %	Sri Lanka	Metformin N = 34 Placebo N = 32	Metformin or placebo 500 mg twice daily Diet and exercise counseling given at start of study
7. Jarskog 2013	Parallel group RCT Duration 16 weeks	Age 18–65 years BMI ≥ 27 Duration of illness ≥ 1 year Females 30.8 %	United States	Metformin N = 75 Placebo N = 71	Metformin 500 mg twice daily increased upto maximum of 2000 mg/day or placebo Weekly diet and exercise counseling
8. Klein	Parallel group RCT Duration 16 weeks	Age 10–17 years Gained > 10 % body weight	United States	Metformin N = 34 Placebo N = 32	Metformin 850 mg twice daily or placebo nutritional counseling
9. Wang 2012	Parallel group RCT Duration 12 weeks	Age 18–60 years Gained > 7 % of body weight	China	Metformin N = 32 Placebo N = 34	Metformin 500 mg twice daily or placebo
10. Wu 2012	Parallel group RCT Duration 24 weeks	Age 18–40 years First episode Female patients only	China	Metformin N = 42 Placebo N = 42	Metformin 1000 mg/day or placebo
11. Wu 2008a JAMA	Parallel group RCT Duration 12 weeks	Age 18–45 years First episode patient who gained > 10 % of bodyweight	China	Metformin N = 32 Placebo N = 32	Metformin 750 mg or placebo (also metformin + lifestyle and lifestyle + placebo groups)
12. Wu 2008b AM J	Parallel group RCT Duration 12 weeks	Age 18–50 years First episode patients on olanzapine	China	Metformin N = 18 Placebo N = 19	Metformin 250 mg thrice daily or placebo No special diet or exercise program

SINTEZA REZULTATELOR

○ Greutate corporala

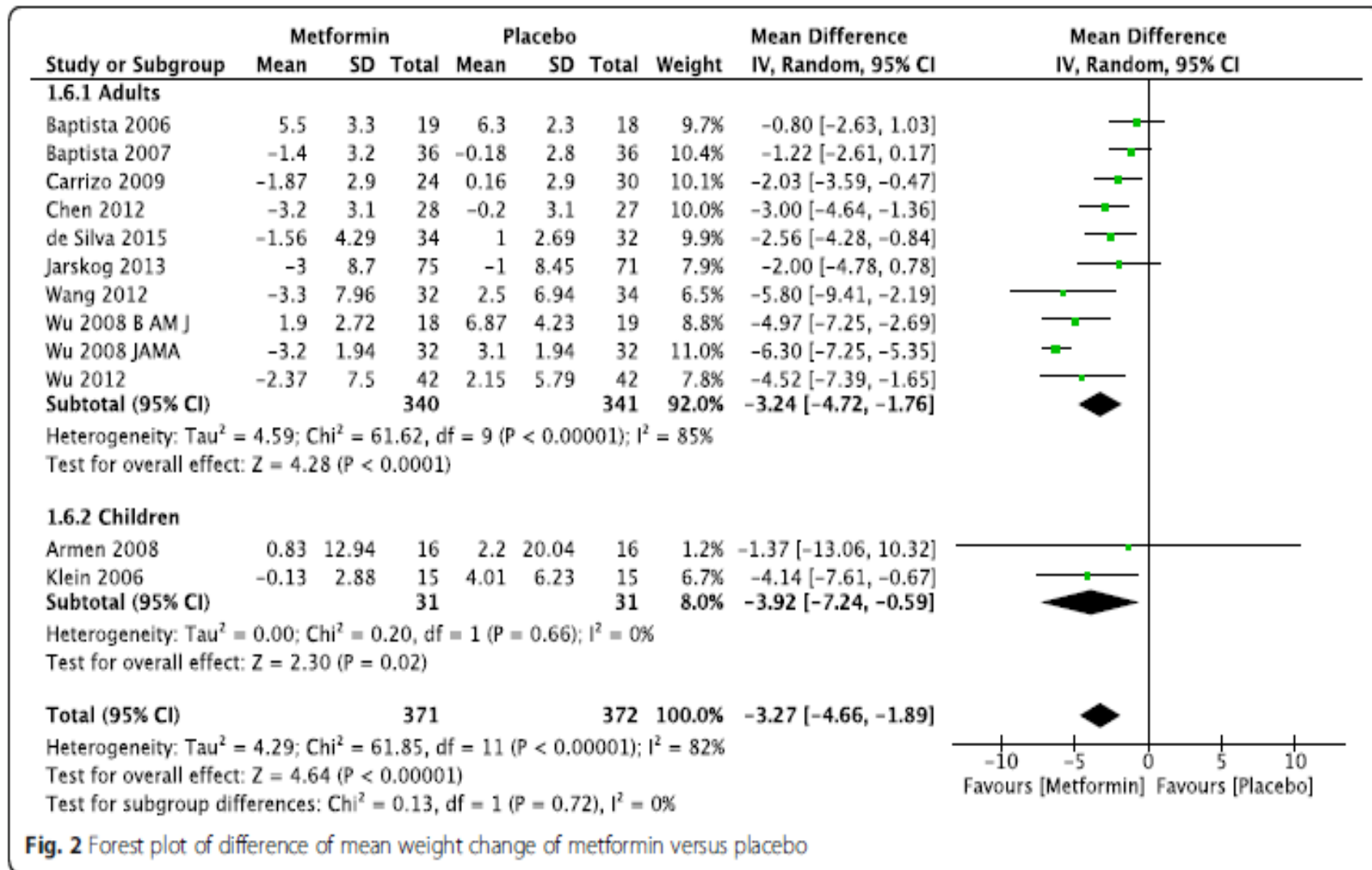
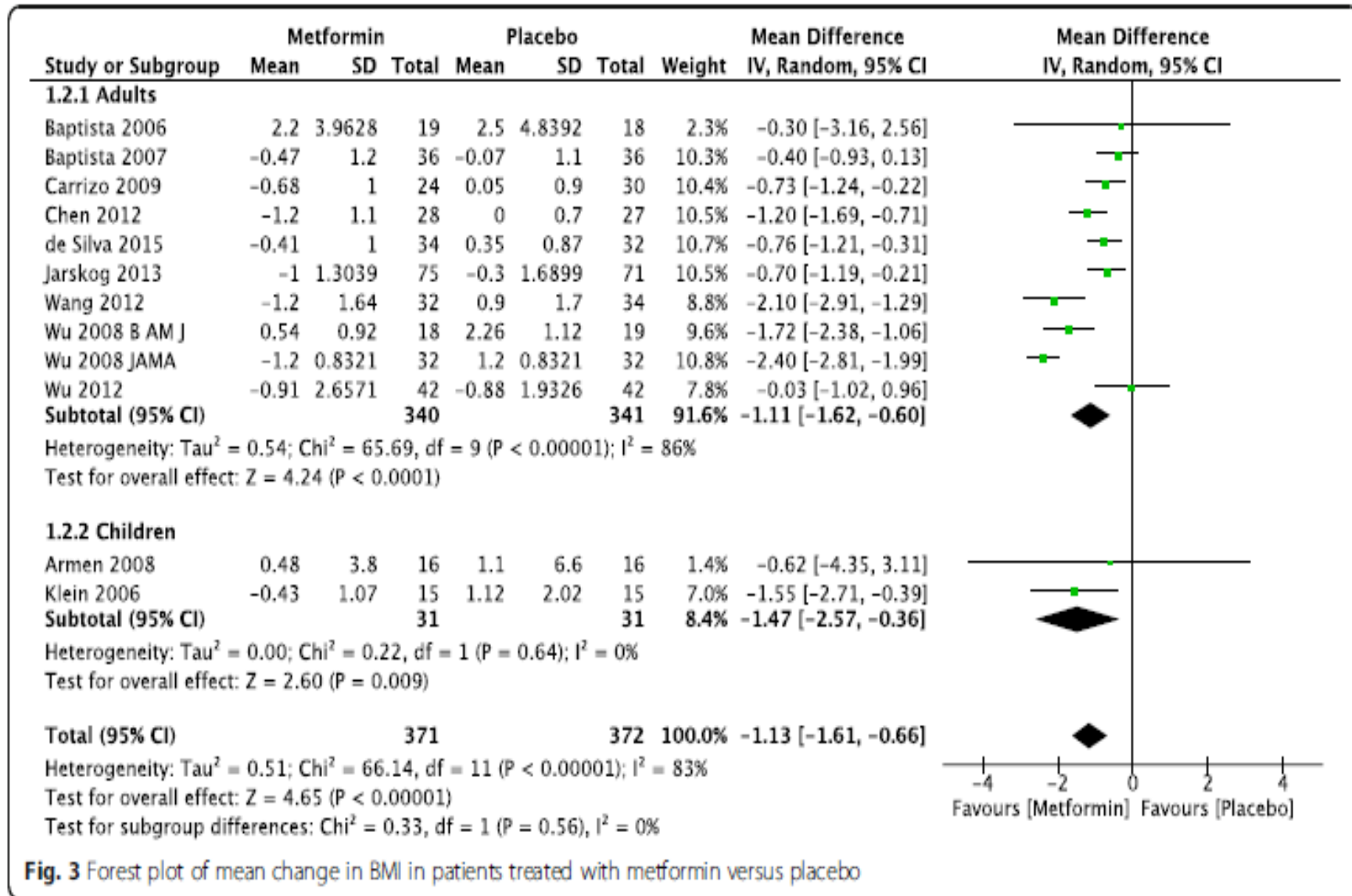


Fig. 2 Forest plot of difference of mean weight change of metformin versus placebo

○ Indicele de masa corporala



- Glicemie a jeun

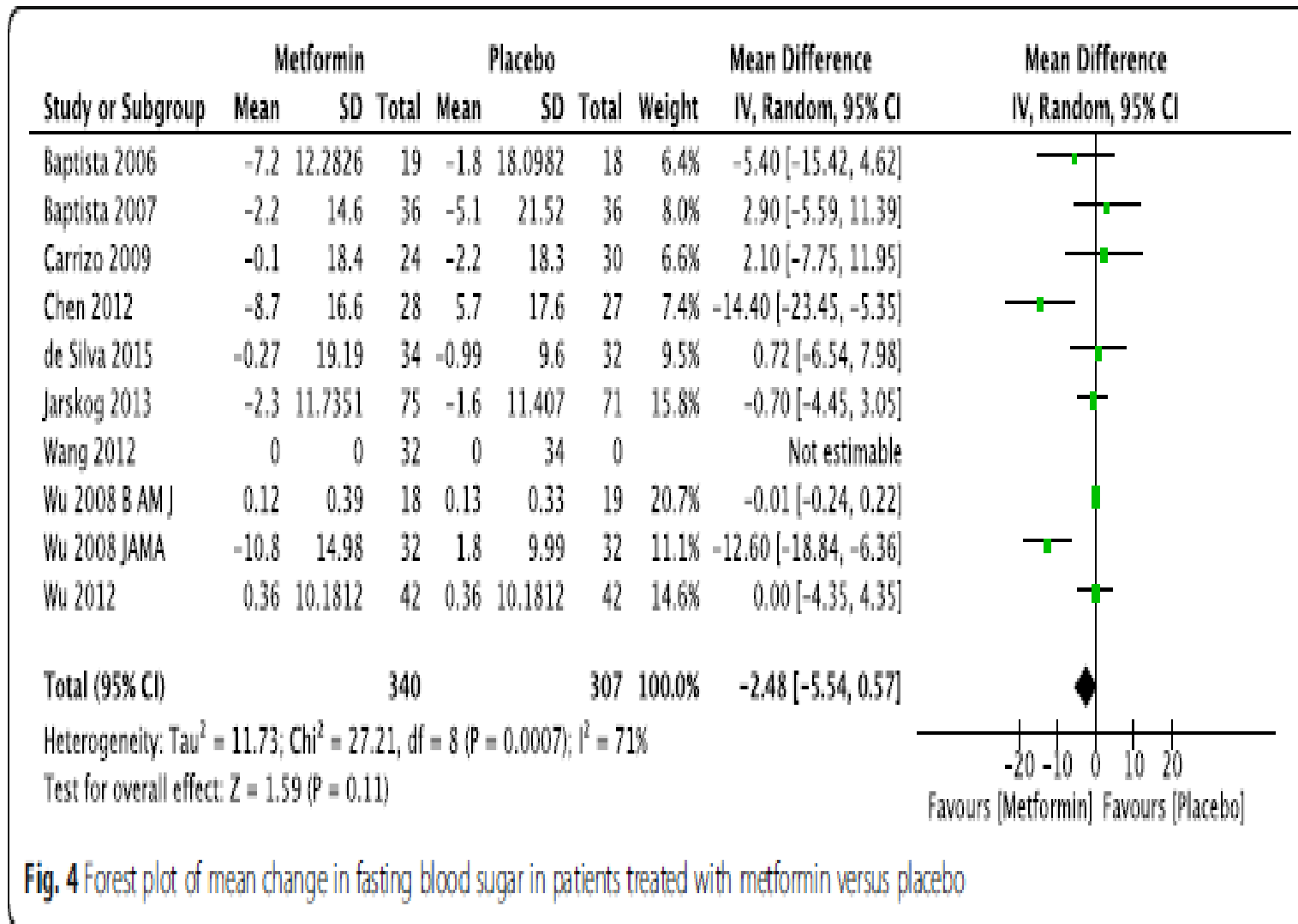


Fig. 4 Forest plot of mean change in fasting blood sugar in patients treated with metformin versus placebo

- Indicele de rezistenta la insulina

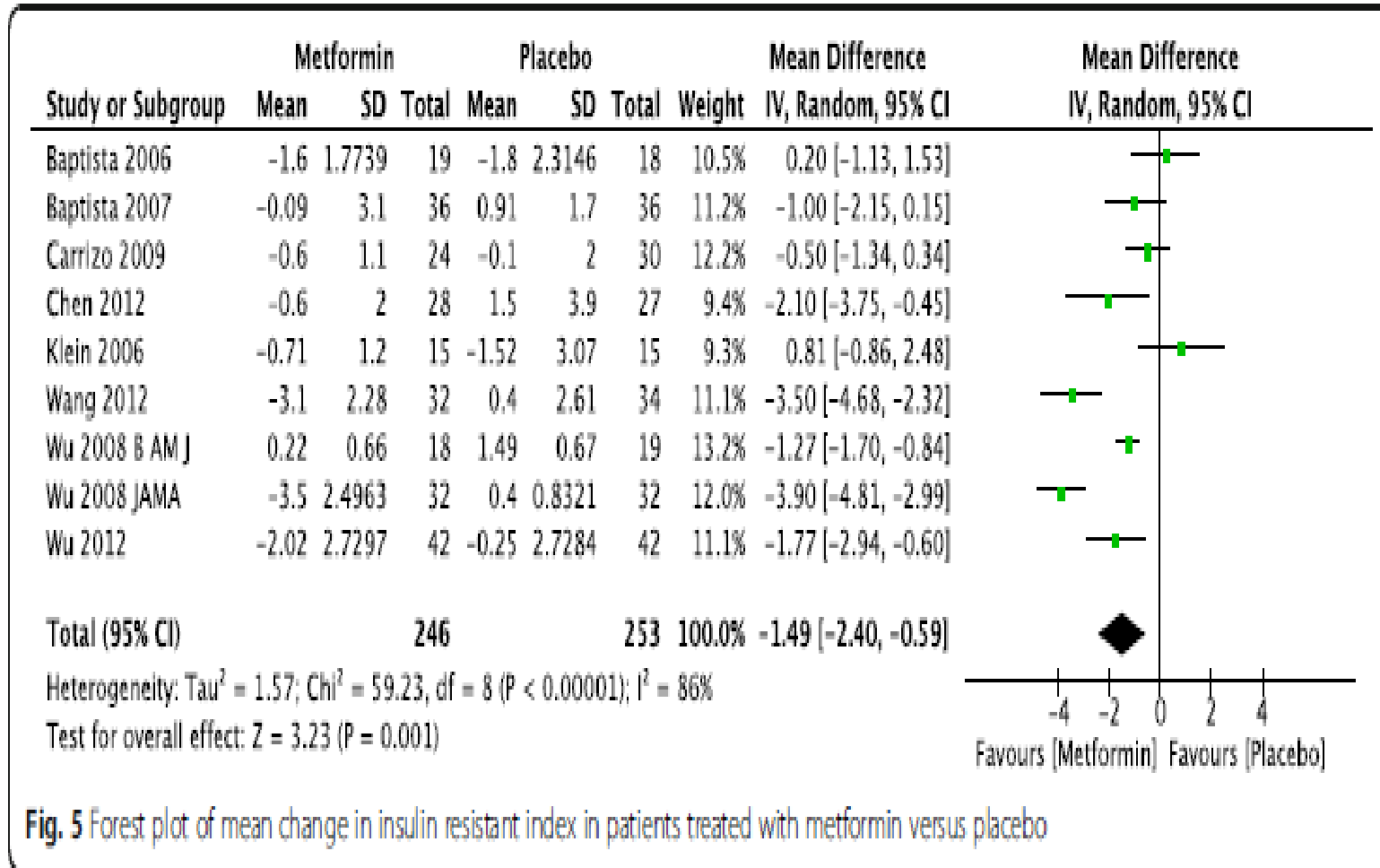


Fig. 5 Forest plot of mean change in insulin resistant index in patients treated with metformin versus placebo



SUBGRUP DE ANALIZA ADULTI VERSUS COPII

- diferenta medie semnificativa in greutate favorizand metformin – adulti -3,24 kg
– copii -3,29 kg
- diferenta semnificativa in modificarea IMC
– adulti -1.11
– copii – 1,47



PRIMUL EPISOD VERSUS CRONICI

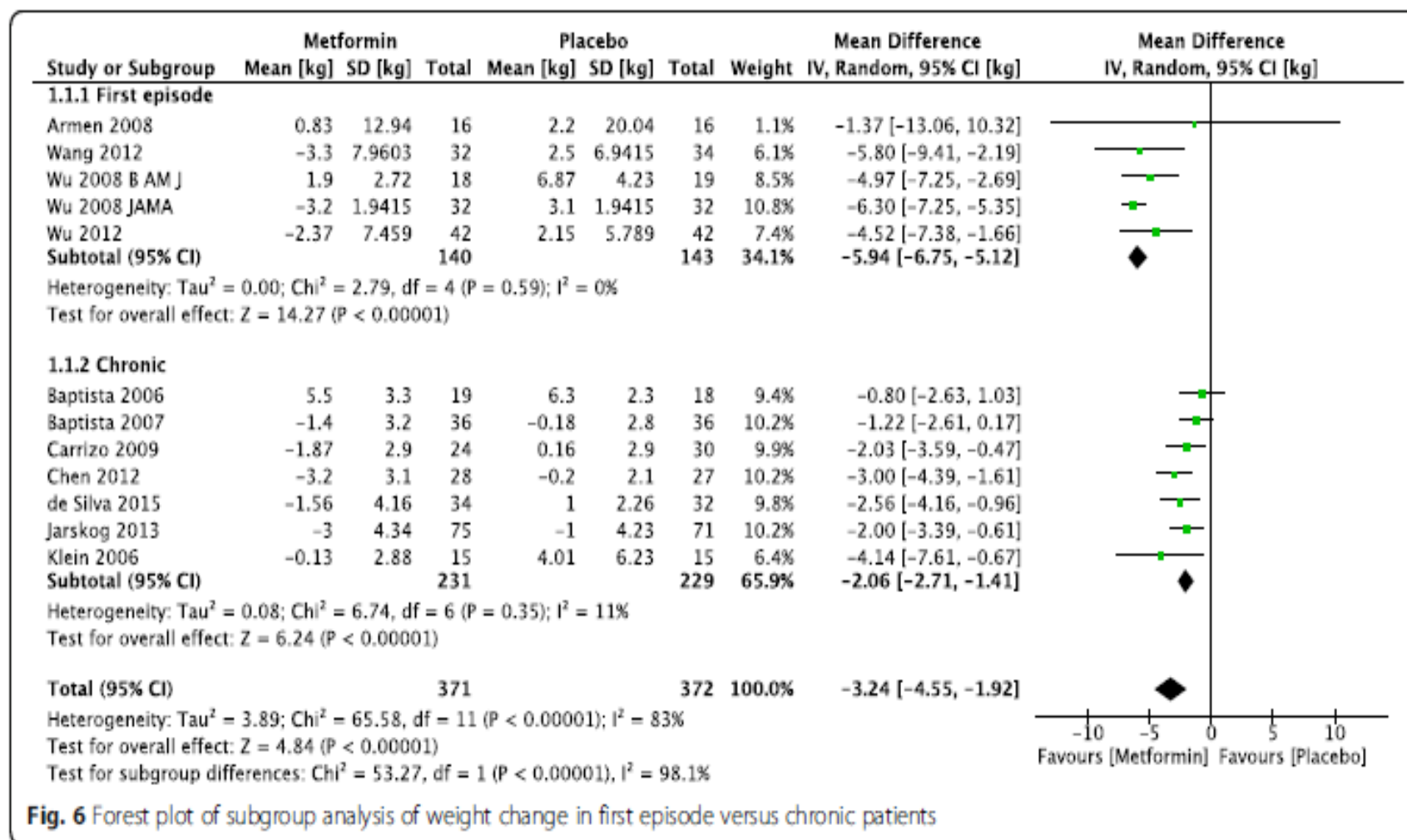


Fig. 6 Forest plot of subgroup analysis of weight change in first episode versus chronic patients

ANALIZA DE SENSIBILITATE

- Deoarece cea mai mare diferenta de greutate corporala a fost în populatia de etnie chineza s-au exclus aceste studii
- metformin a fost semnificativ mai eficace decât placebo

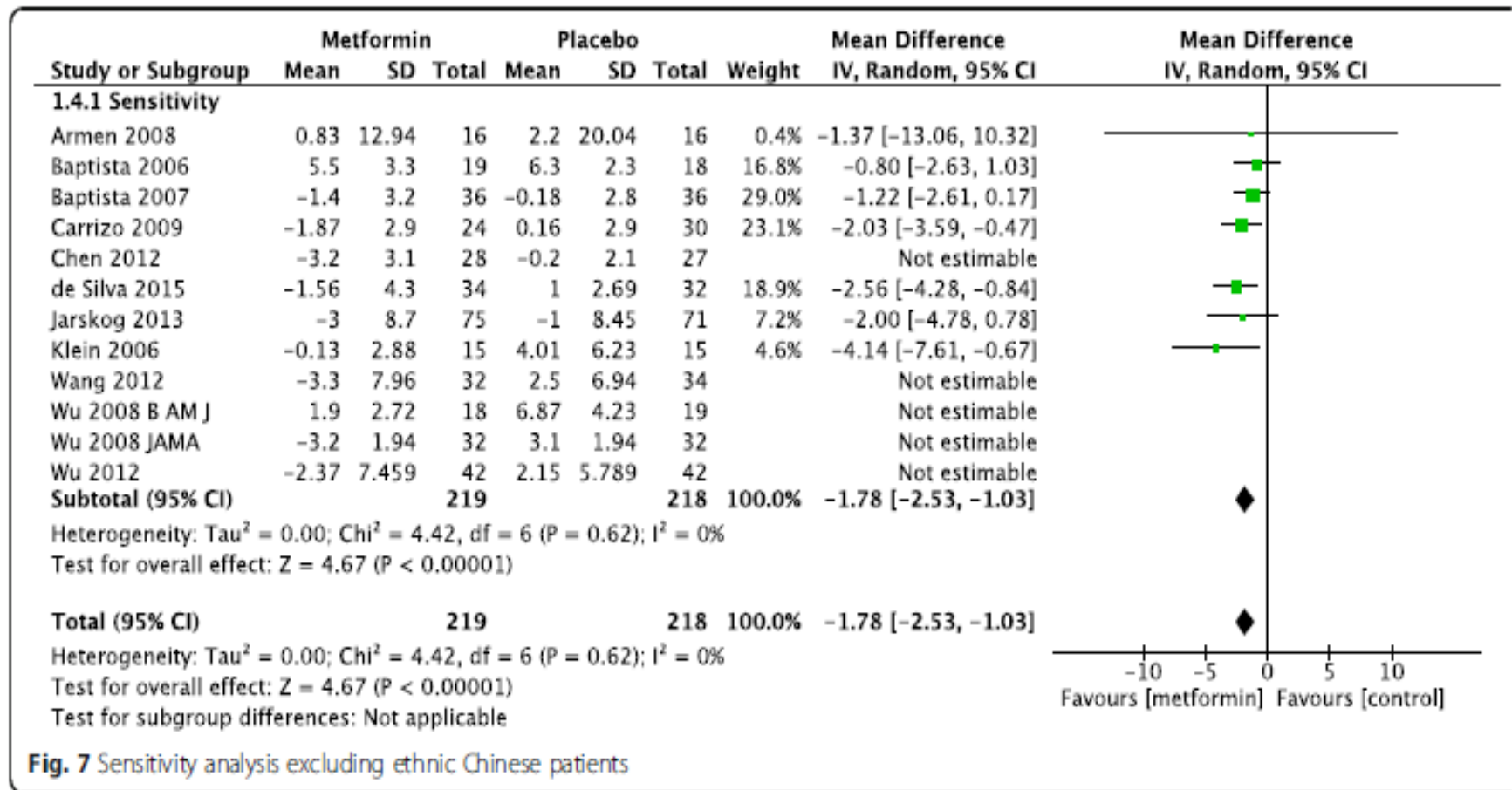


Fig. 7 Sensitivity analysis excluding ethnic Chinese patients

CONCLUZII

- meta-analiza a 12 studii publicate – 743 pacienti a contatat parametri antropometrici si metabolici semnificativ mai buni decat placebo la pacientii in tratament cu metformin;
- diferenta medie în greutate a fost de -3.27 kg;
- reducerea semnificativă a IMC -1.13 kg / m²;
- metformin pare a fi mai eficace la pacientii aflatii la primul episod decat la pacientii cronici



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