CETP and IRS1 Genetic Variation Modulates Effects of Weight-loss Diets on Lipid Profile in Two Independent 2-Year Diet Intervention Studies: The Pounds Lost and DIRECT Trails

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- No conflict of interests to declare.

Background

- Clear association between overweight and risk for IHD and diabetes
- Weight reduction diets improve glucose and lipid profiles

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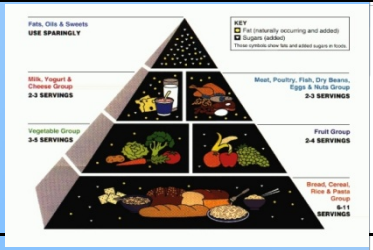
Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet

Iris Shai, R.D., Ph.D., Dan Schwarzfuchs, M.D., Yaakov Henkin, M.D., Danit R. Shahar, R.D., Ph.D., Shula Witkow, R.D., M.P.H., Ilana Greenberg, R.D., M.P.H., Rachel Golan, R.D., M.P.H., Drora Fraser, Ph.D., Arkady Bolotin, Ph.D., Hilel Vardi, M.Sc., Osnat Tangi-Rozental, B.A., Rachel Zuk-Ramot, R.N., Benjamin Sarusi, M.Sc., Dov Brickner, M.D., Ziva Schwartz, M.D., Einat Sheiner, M.D., Rachel Marko, M.Sc., Esther Katorza, M.Sc., Joachim Thiery, M.D., Georg Martin Fiedler, M.D., Matthias Blüher, M.D., Michael Stumvoll, M.D., and Meir J. Stampfer, M.D., Dr.P.H., for the Dietary Intervention Randomized Controlled Trial (DIRECT) Group

- **Moderately obese; BMI=31kg/m^2**
- **Age=52 yrs**
- **n=322; 86% men**
- **One phase**
- **Equal intensity**
- **Spouse support program**

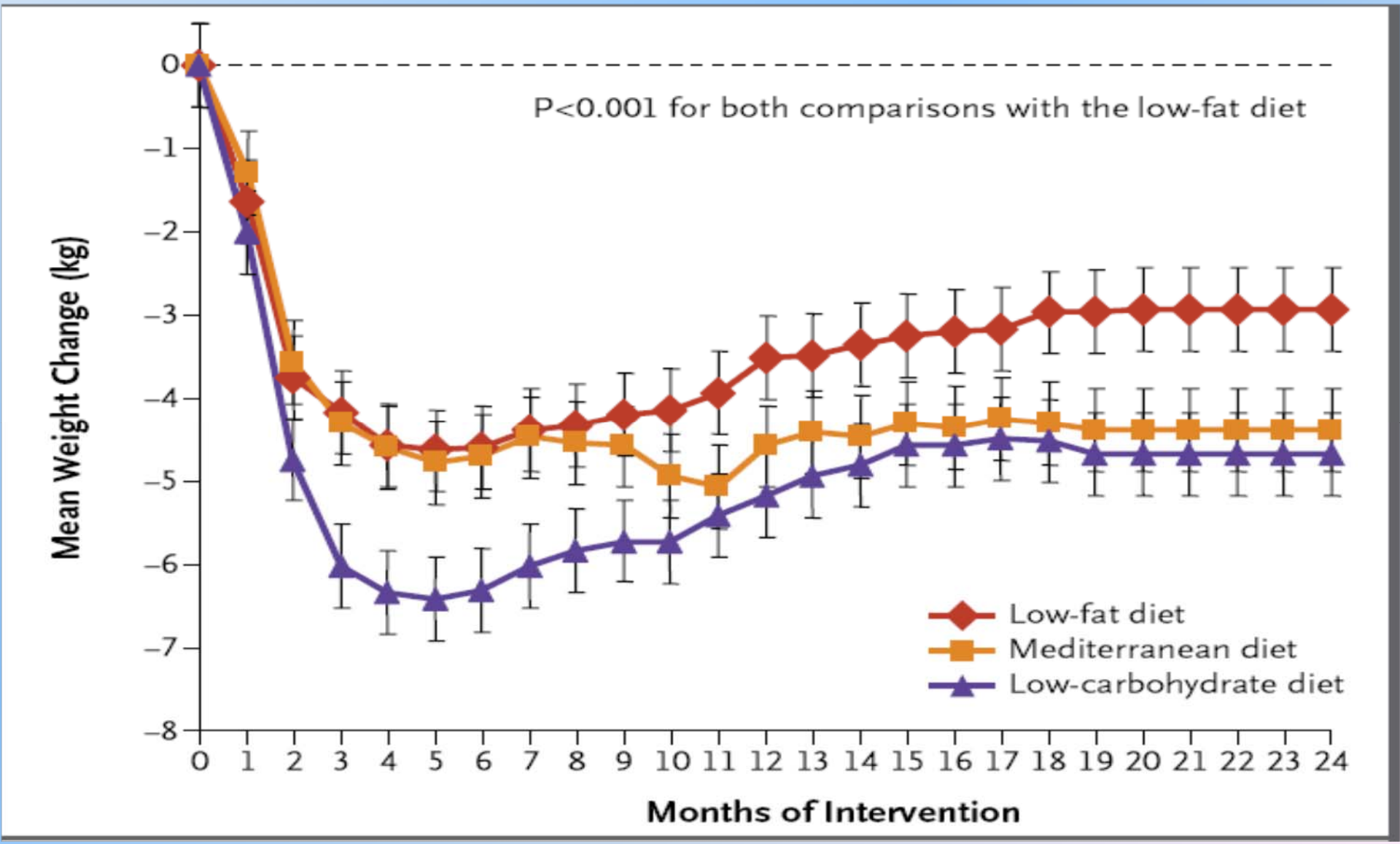
  (Public Health Nutrition 2009)
- **Adherence : 95% after 1 yr; 85% after 2 yrs**
- **Significant actual differences between the dietary strategies during 2 years**

Dietary intervention protocol

	Low-fat	MED	Low-carb
Energy	restricted	restricted	liberal
Total fat	≤ 30%	≤ 35%	liberal
Saturated fat	≤ 10%	≤ 10%	not recommended (also for *trans*)
Dietary cholesterol	≤ 300 mg	≤ 300 mg	liberal
Carbohydrates			Restricted ≤ 20gr in induction phases Gradually added to maintain achieved weight loss
Specific foods added		30-45gr virgin olive oil/day, 3-7 nuts/day, 2 fish /wk	

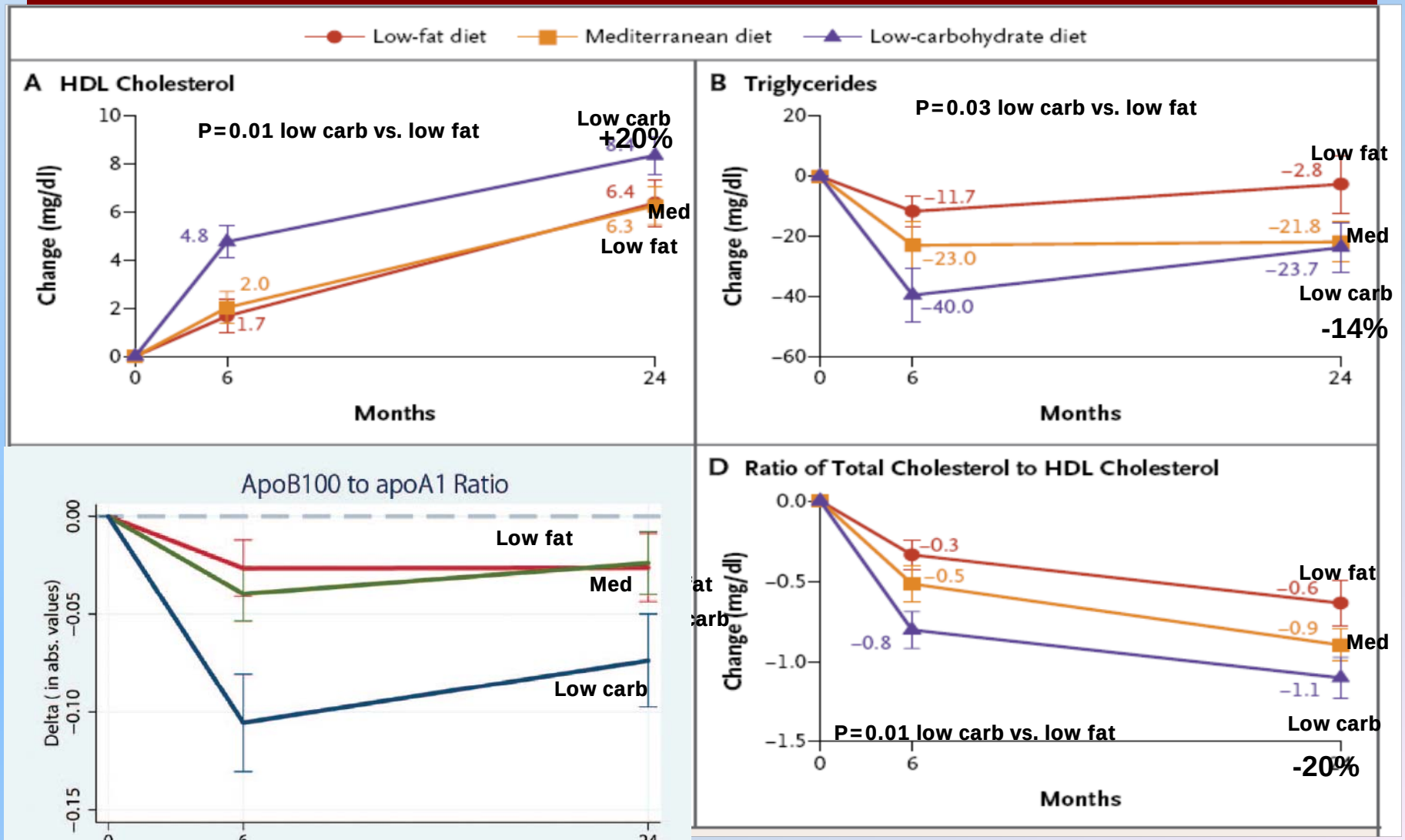
- No specific recommendations for alcohol and vitamin supplements
- Standard protocol messages (e.g physical activity) and Power-Point slides program

The Dietary Intervention Randomized Controlled Trial- DIRECT



New Eng J Med 2008

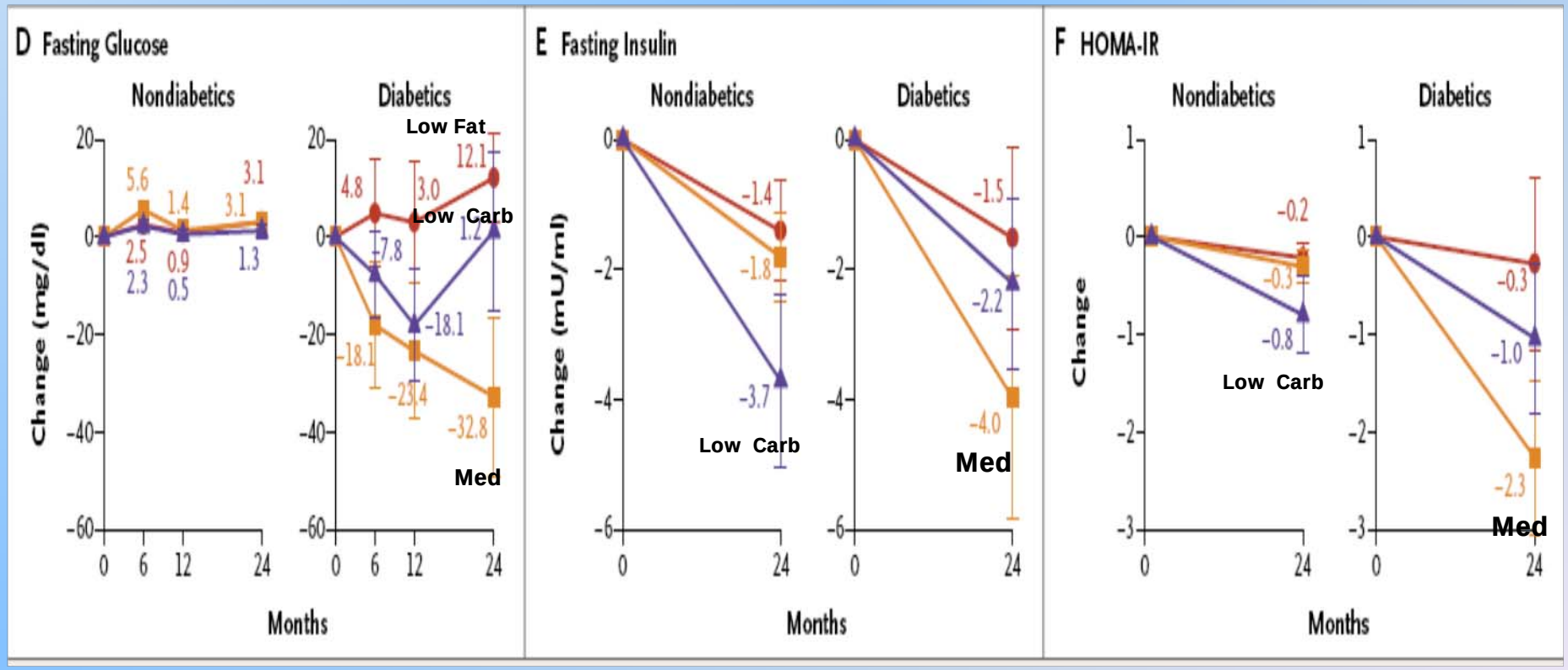
Low carb and Med diets → favorable in lipid profile



Shai I, et al. Circulation 2010

Shai I, et al. New Eng J Med 2008

favorable glycemic control in type 2 diabetes in non low fat diets



Shai I, et al. New Eng J Med 2008

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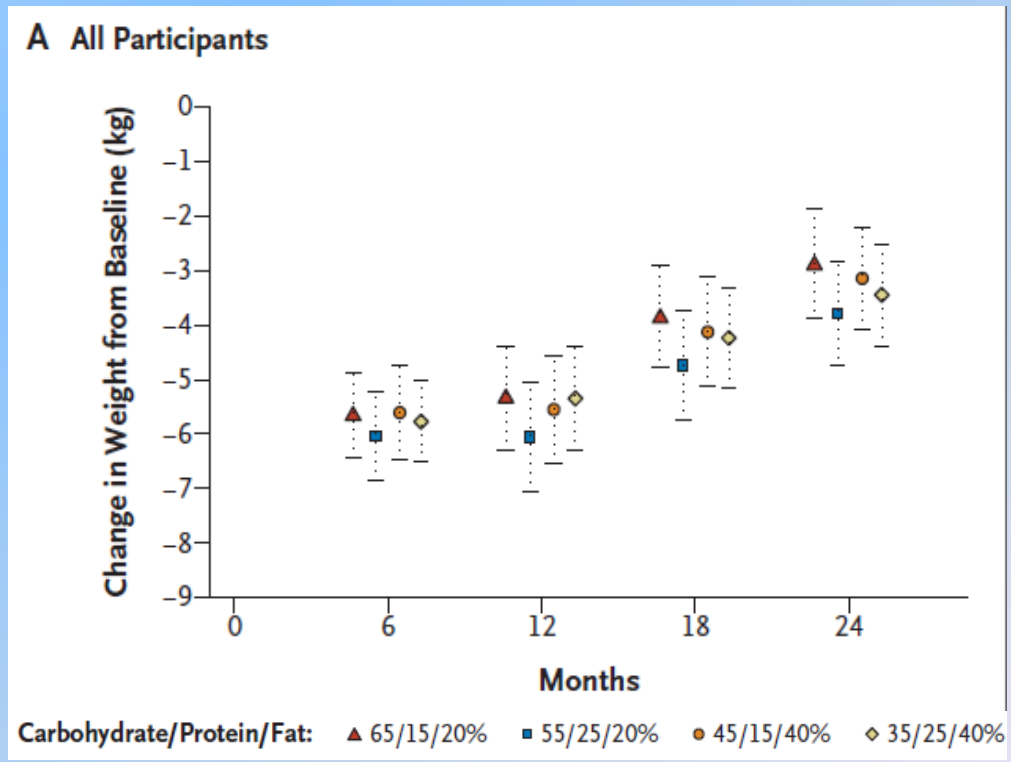
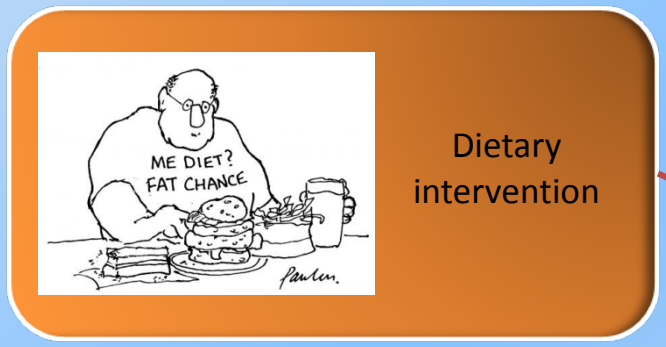
Ponds lost study

- A two year randomized clinical trial
- 811 overweight adults
- Four diets varying in macronutrients



Is there gene environment interaction?



Dietary intervention

Interaction

response to diet

Genetic Background

Objective

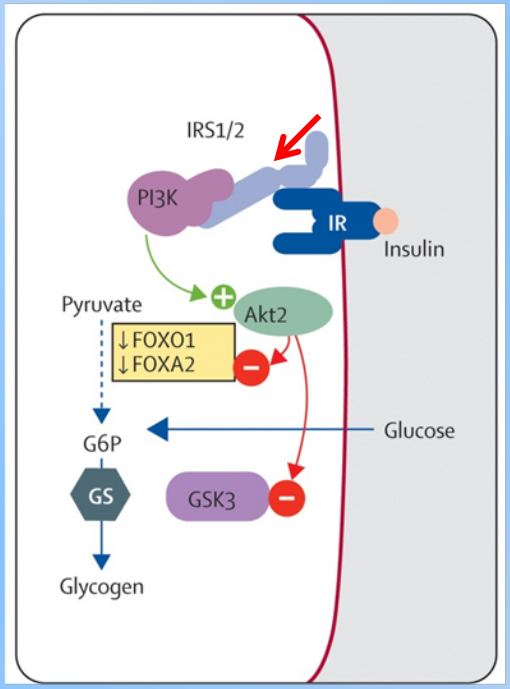
To examine whether:

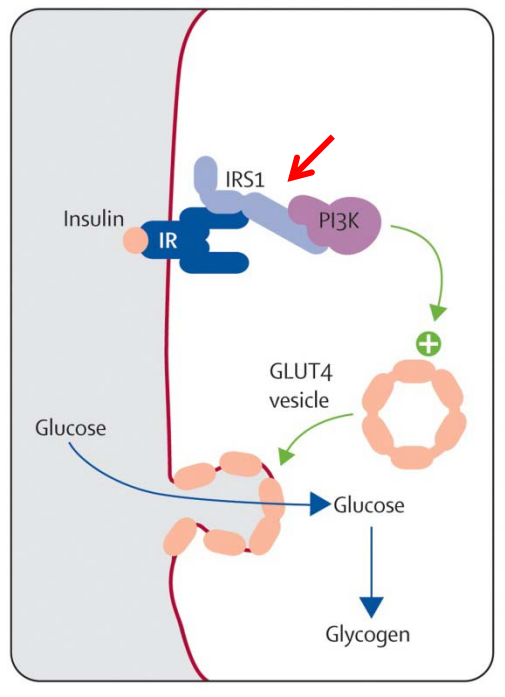
- rs2943641 of *IRS1* changes in insulin resistance and body weight loss
- Rs3764261 of CETP changes lipid profile

in response to a 2 year randomized trial (the DIRECT trial).

Insulin Receptor Substrate 1 Gene

Key player in insulin signal transduction





Genetic variant near *IRS1* is associated with type 2 diabetes, insulin resistance and hyperinsulinemia

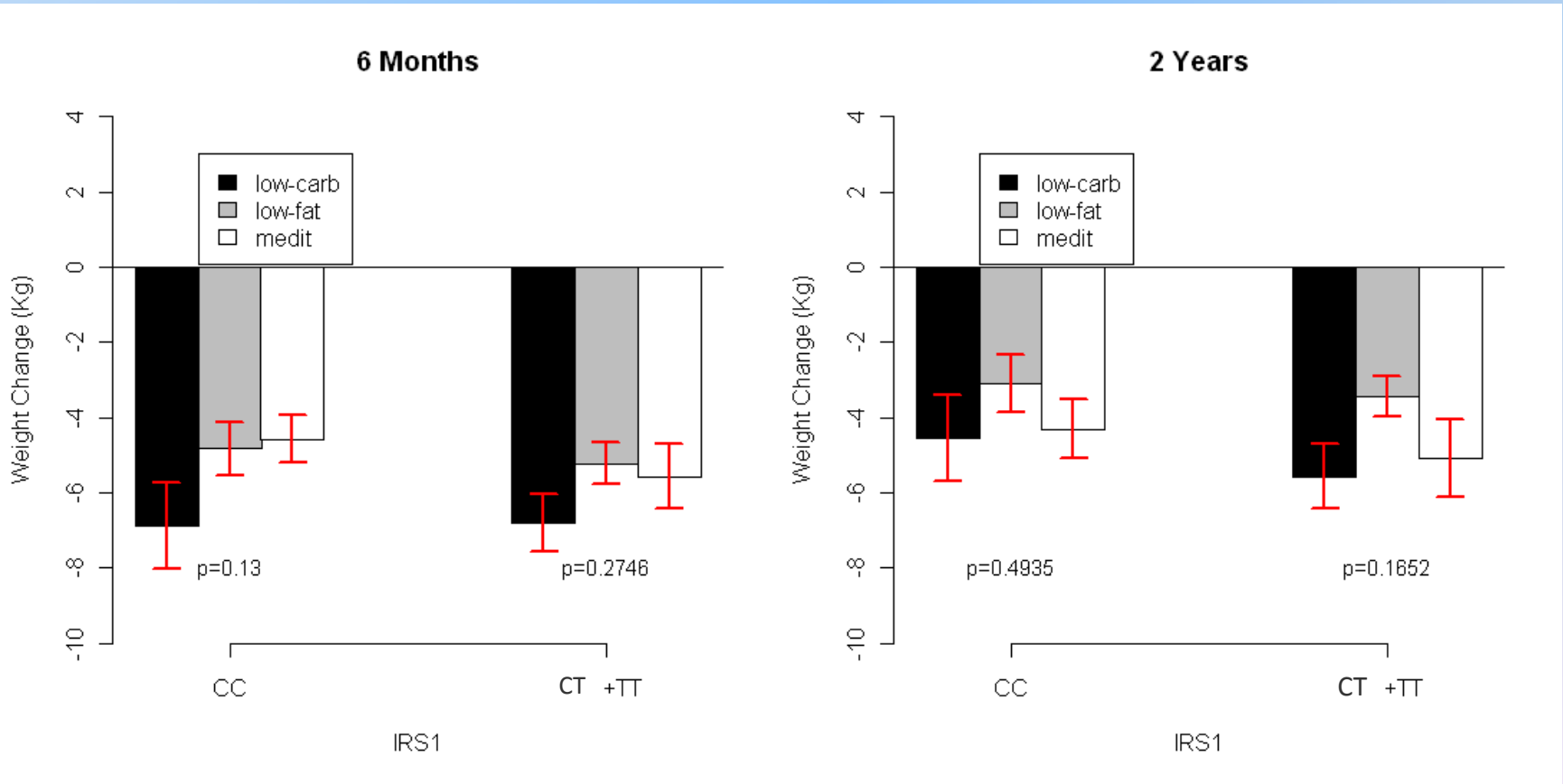
nature genetics

The insulin sensitivity response is determined by the interaction between the G972R polymorphism of the insulin receptor substrate 1 gene and dietary fat

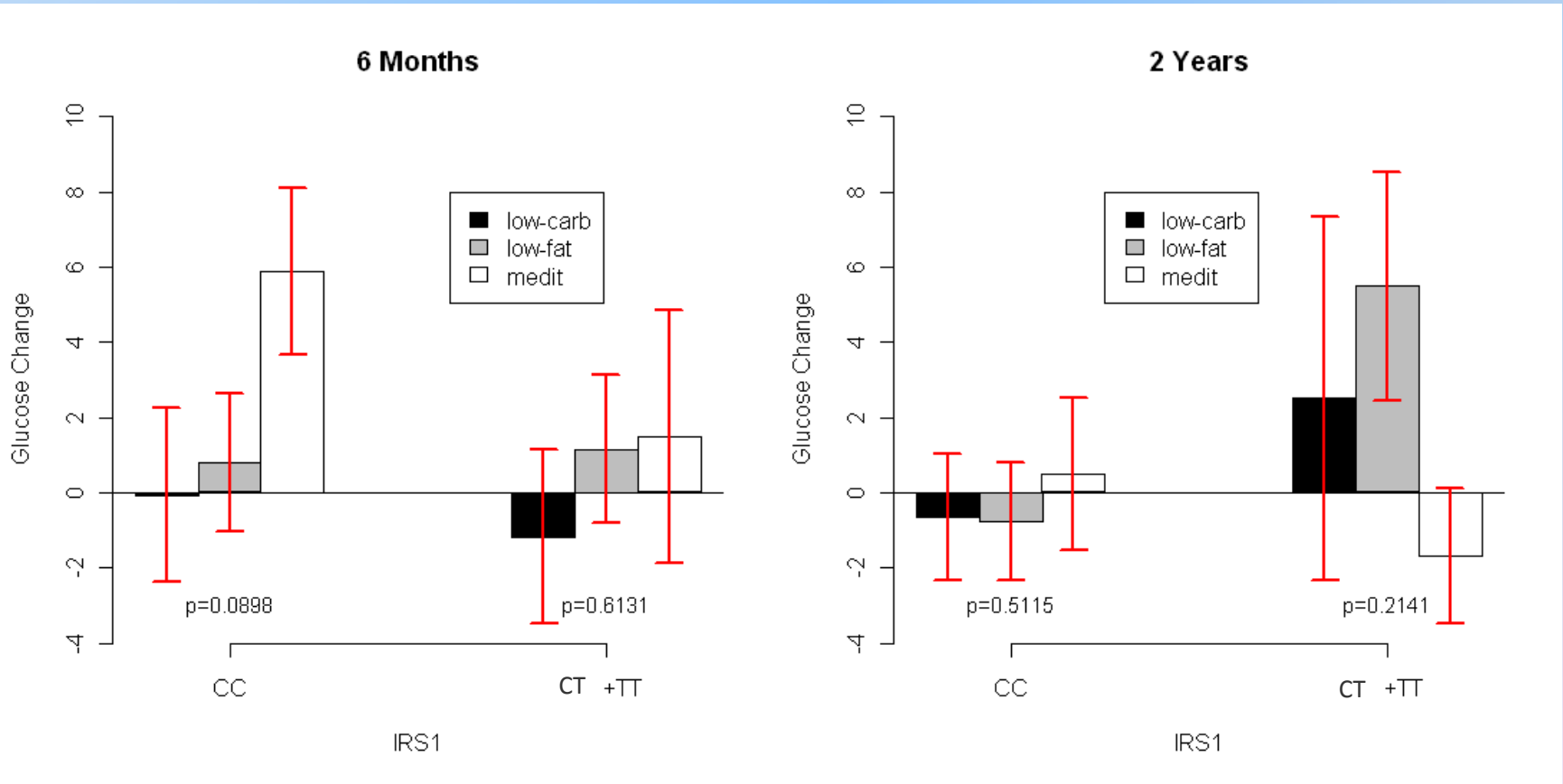
Molecular Nutrition & Food Research

Samuel et al. Lancet 2010

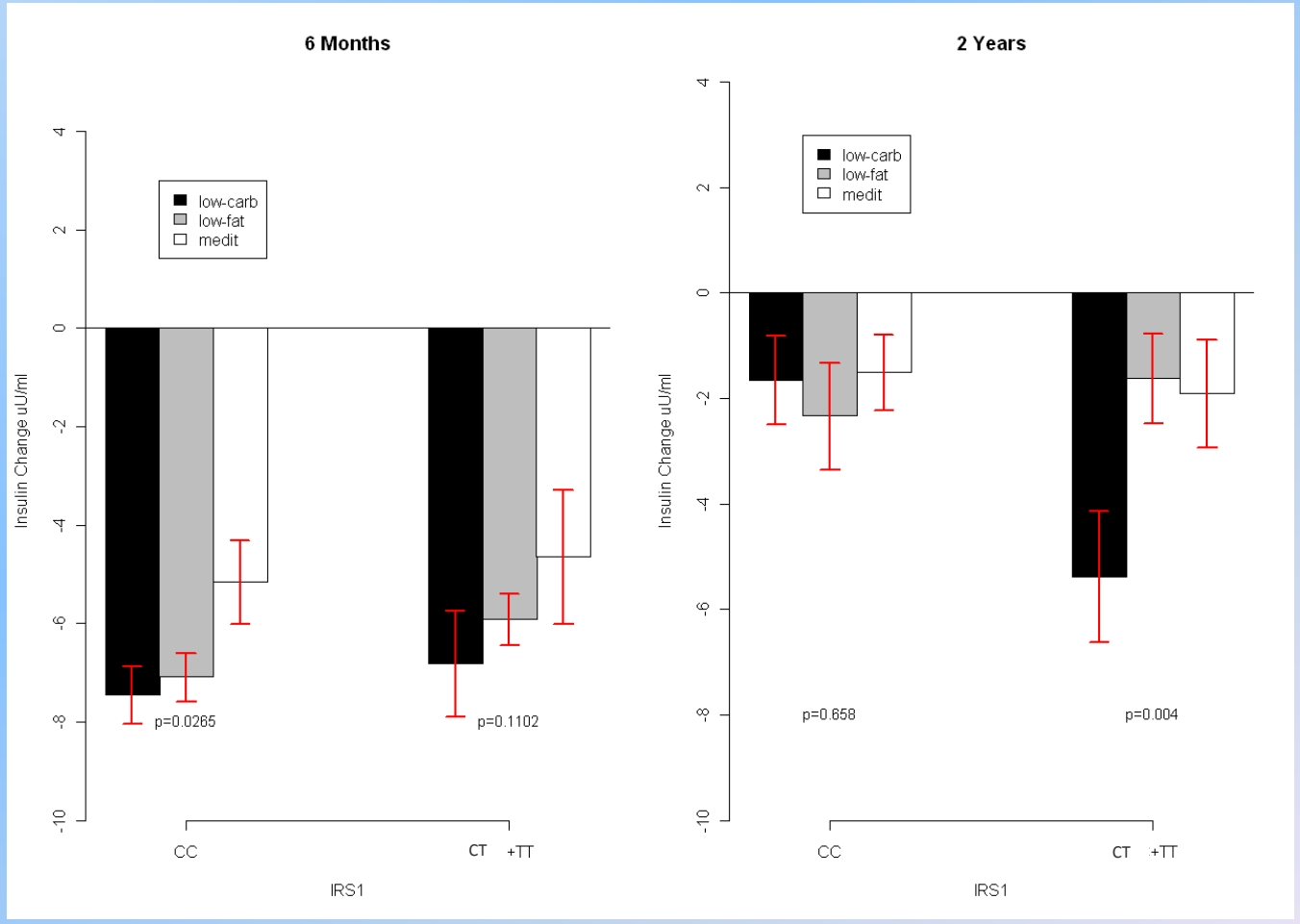
Diet group and genotype **did not** effect **Weight** change



Diet group and genotype **did not** change Glucose level

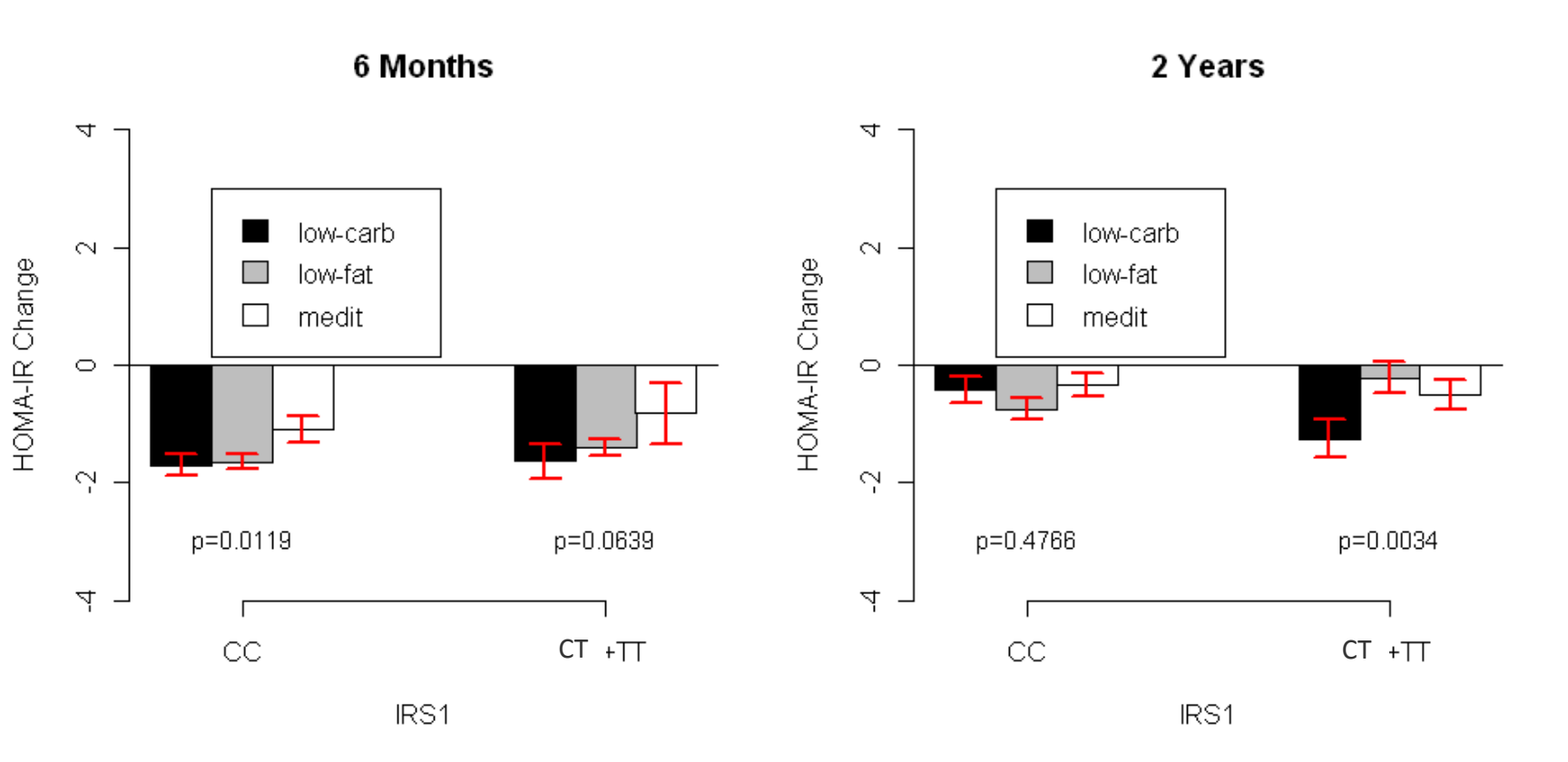


Positive interaction between diet group and genotype **on Insulin** level



P=0.004

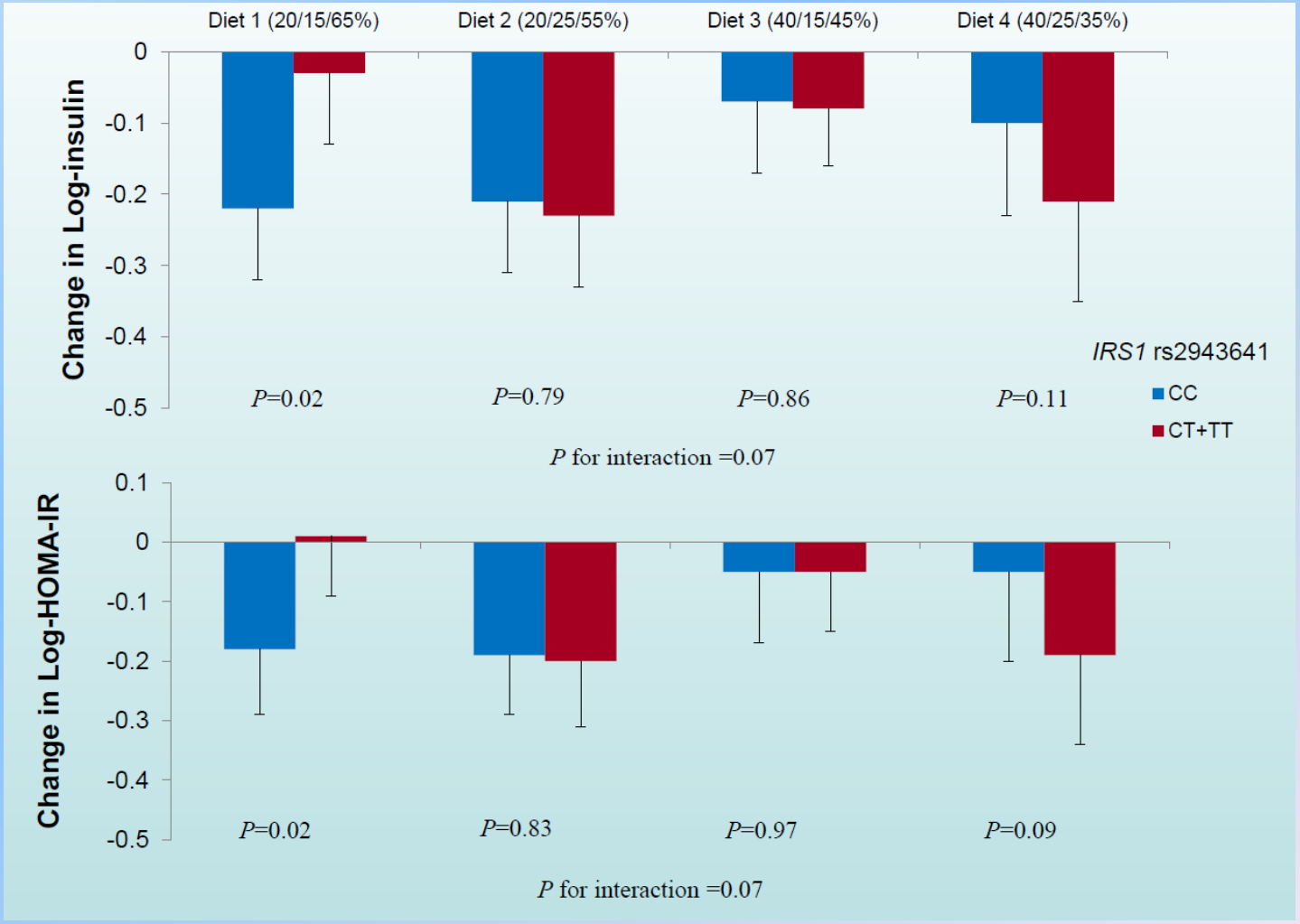
HOMA-IR change by diet group and genotype



P=0.0013

Insulin and **HOMA-IR** @ 2 years pound loss cohort

Low fat diet ⟶ **Low carb diet**

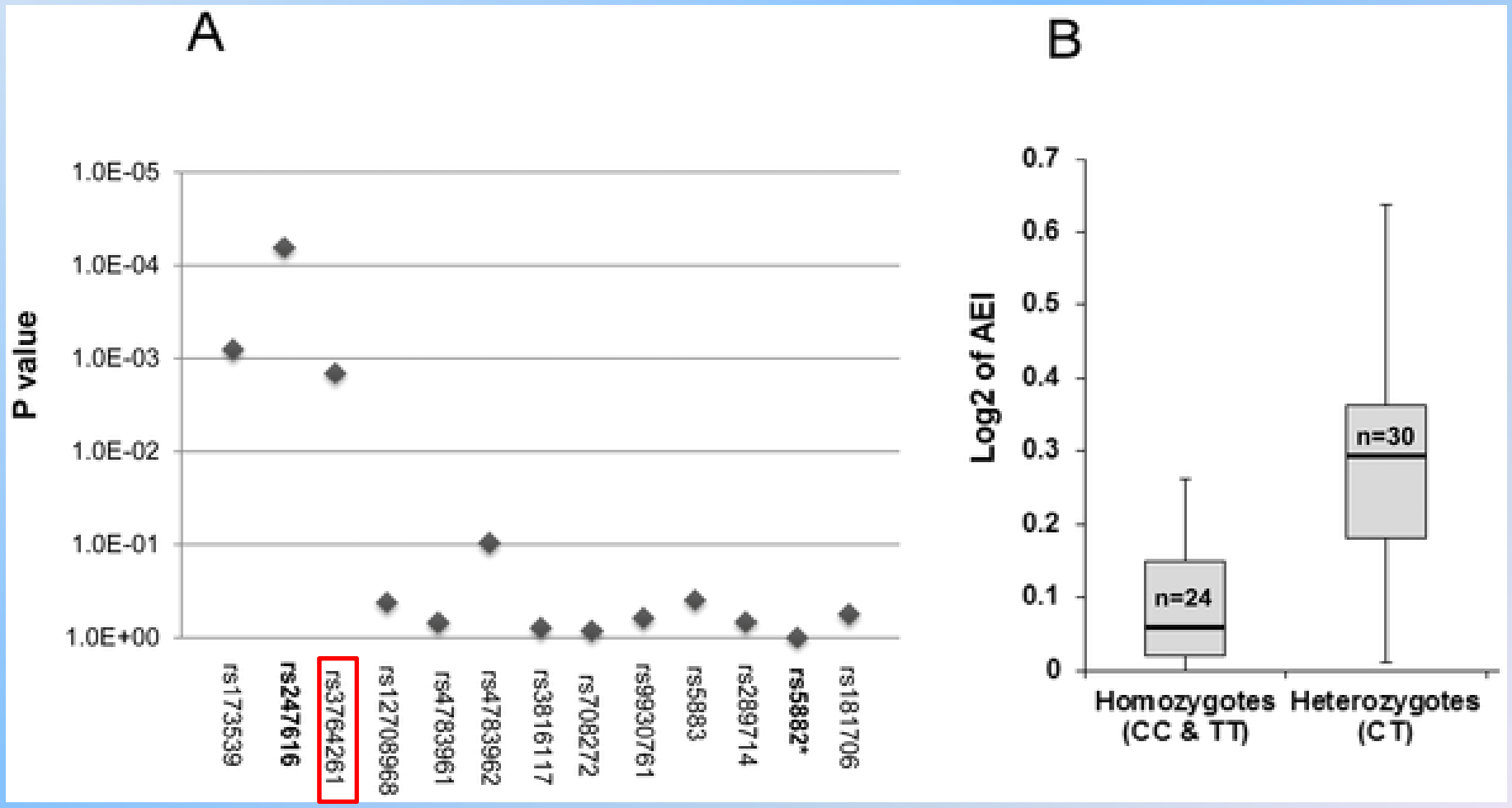


Rs3764261 SNP is most associated with HDLc level

SNP	Chr	Pos(Mb)	Alleles (+/-)	Freq (+)	Effect (mg/dl)	Combined (two-sided)	Nearby genes
rs3764261	**16**	**55.6**	**A/C**	**0.69**	**3.47**	**10^{-57} 2.3**	***CETP***
rs1864163	16	55.6	G/A	0.80	4.12	10^{-39} 6.9	*CETP*
rs9989419	16	55.5	G/A	0.65	1.72	10^{-31} 3.2	*CETP*
rs12596776	16	55.5	G/C	0.13	1.26	10^{-8} 2.8	*CETP*
rs1566439	16	55.6	C/T	0.45	0.96	10^{-8} 3.3	*CETP*
rs4775041	15	56.5	C/G	0.67	1.38	10^{-20} 3.2	*LIPC*

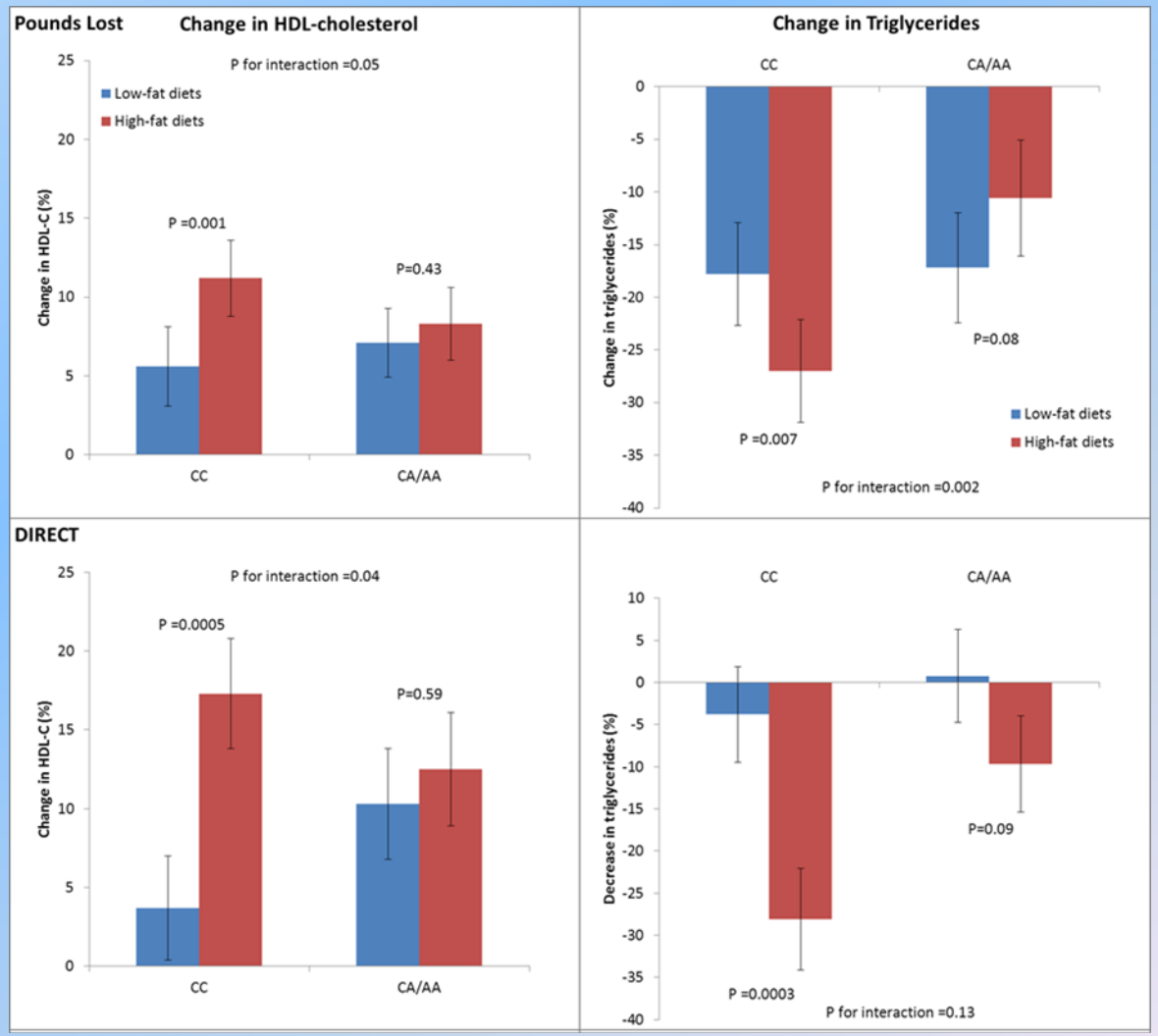
Willer et al. Nature genet. 2008

Figure 1. Association of CETP SNPs with Allelic Expression Ratios.



Papp AC, Pinsonneault JK, Wang D, Newman LC, et al. (2012) Cholesteryl Ester Transfer Protein (CETP) Polymorphisms Affect mRNA Splicing, HDL Levels, and Sex-Dependent Cardiovascular Risk. PLoS ONE 7(3): e31930. doi:10.1371/journal.pone.0031930
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0031930

Percent changes in HDL and triglycerides by diet and *CETP* rs376426 genotype - Pounds Lost and DIRECT trials



Significance and limitations

- The study demonstrated gene-diet interaction on improved insulin resistance in a long term interventional trial
- Replicates previous similar trial (Pounds lost)
- Provides information that may help tailor effective dietary interventions based on genetic background.

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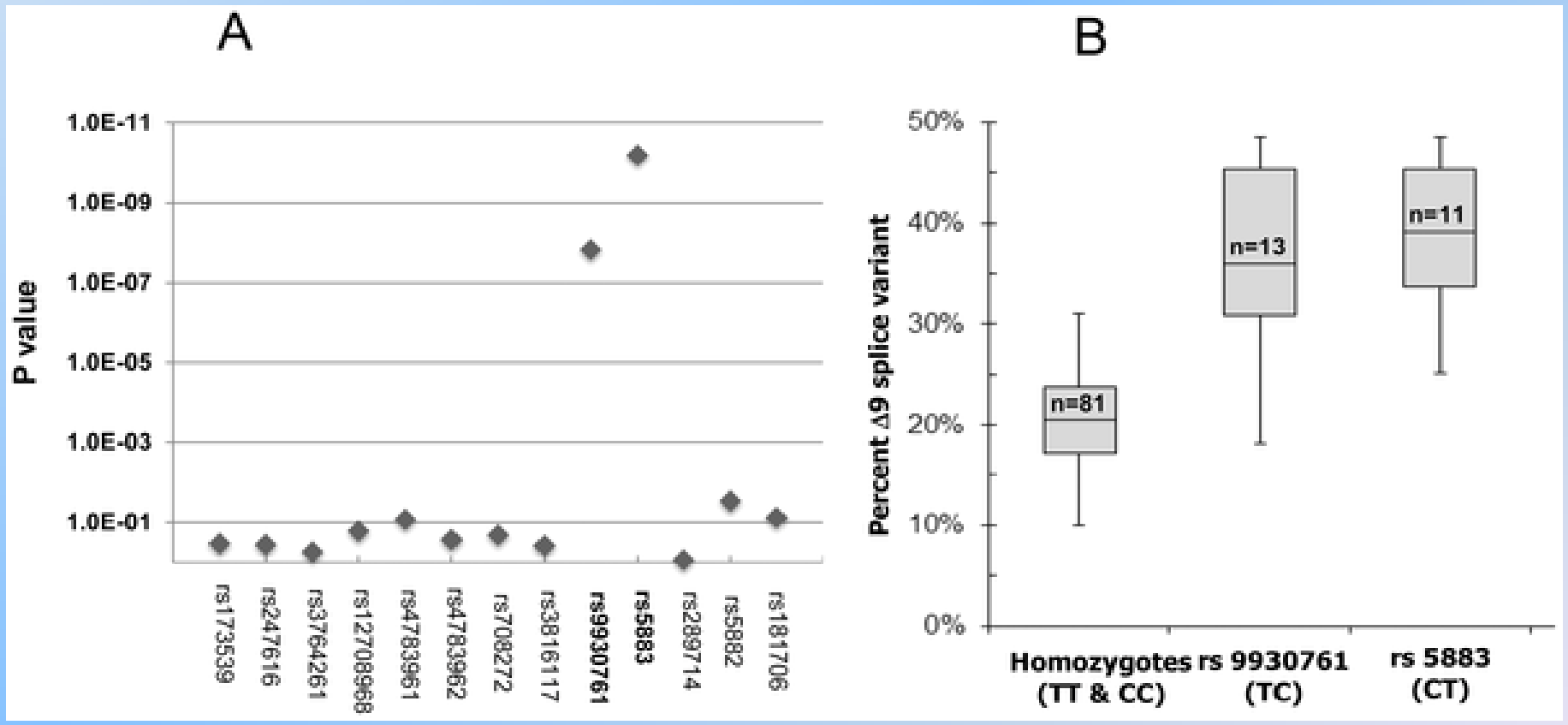
Association of CETP SNPs with the Δsplice variant.



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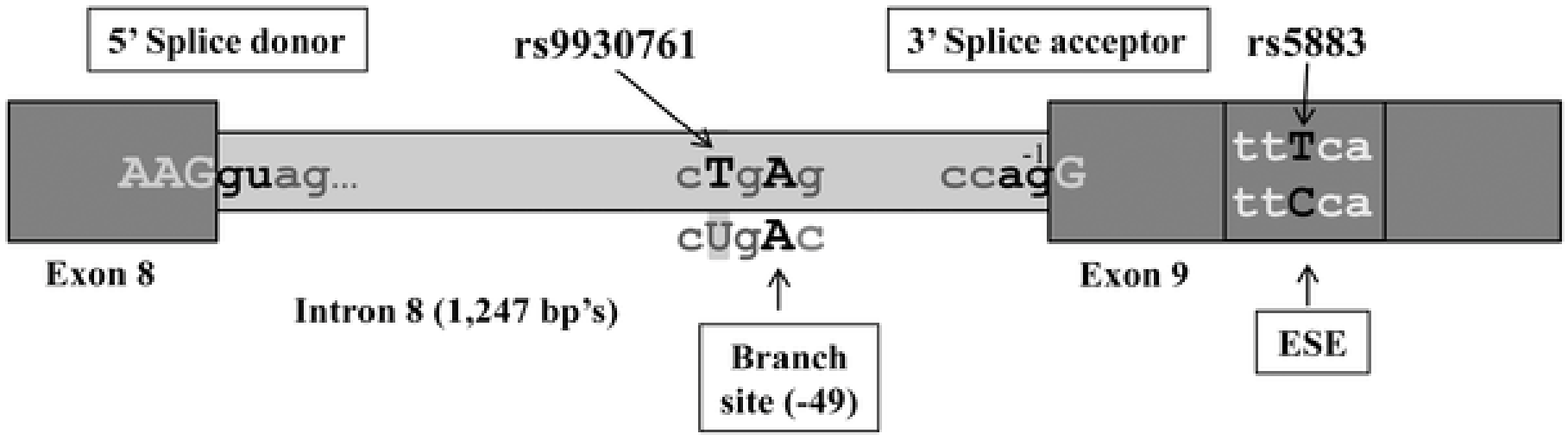
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0031930

Intron 8 splice site is associated with reduced plasma CETP



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http://www.plosone.org/article/info:doi/10.1371/journal.pone.0031930