

Optimizing the Exercise Drug to Oppose Glucose Intolerance/T2D



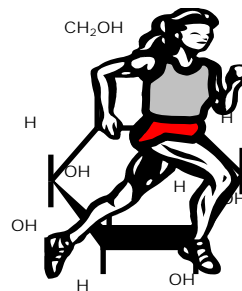
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Lab mission:

Metabolic rehabilitation

Understand how physical activity, diet and pharmacology can be optimally integrated to reverse insulin resistance and prevent T2D





79 million with prediabetes=

everyone in U.S. that is left-handed (30) +
everyone who is Jewish (6) +
all households in U.S. that own dogs (43).

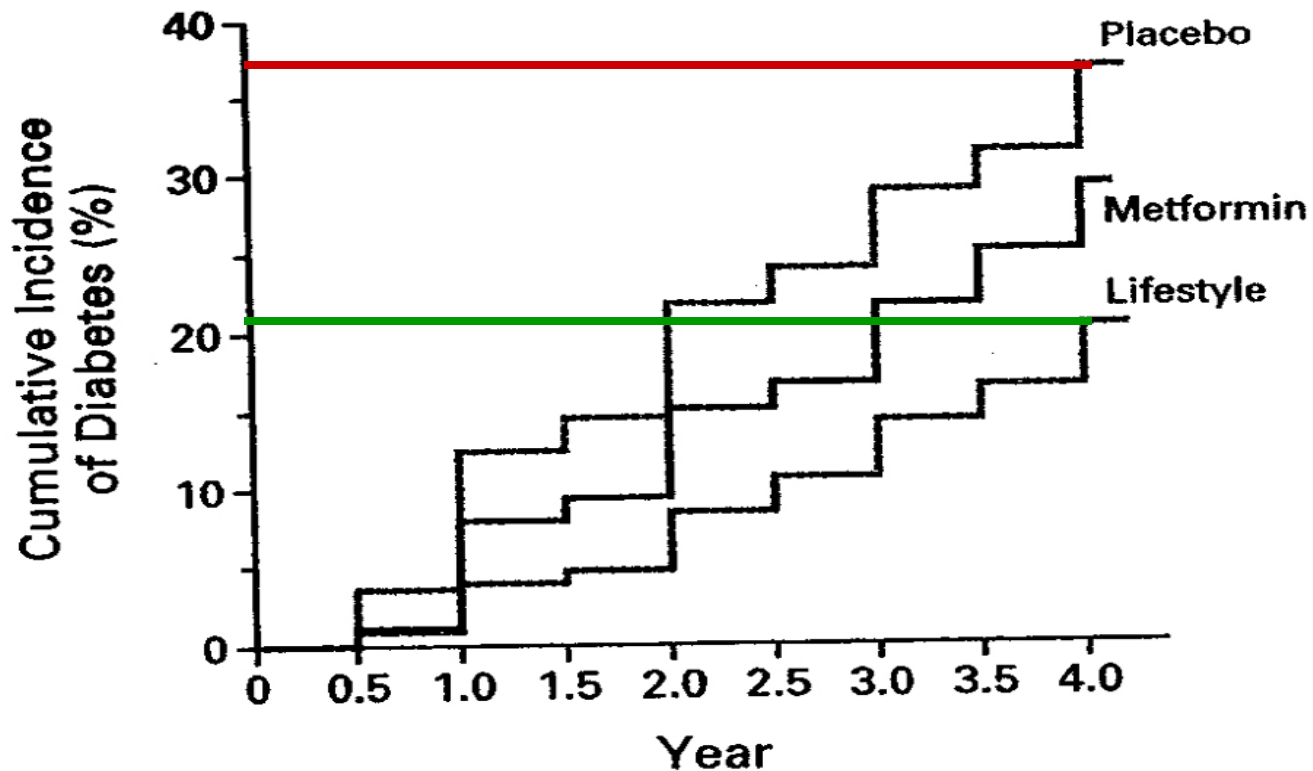
Insulin resistance is an underlying theme for
Type-2 diabetes (as well as CVD)



Energy Metabolism Laboratory



Diabetes Prevention Program, NEJM, 2001



>150' exercise/wk. goal to lose 7% BW.



Lifestyle change



Metformin



Weight loss

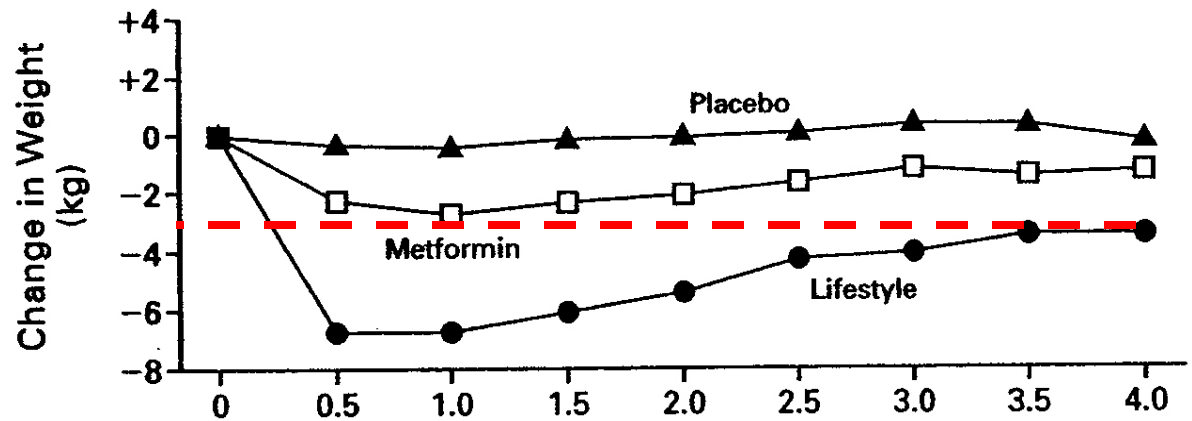
beneficial impact on metabolic health



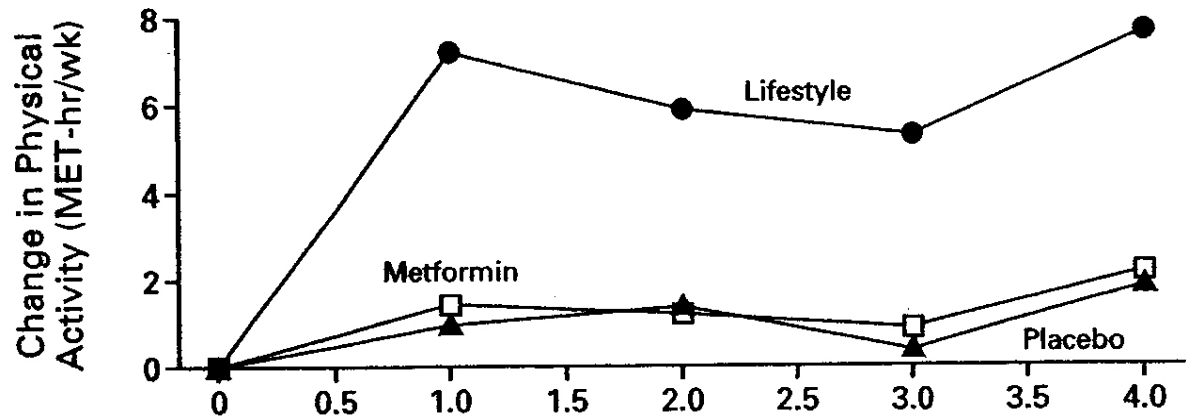
Mean weight
loss: 3.3 kg

Activity
maintained at
about 150'/wk

A



B



C



Lifestyle change

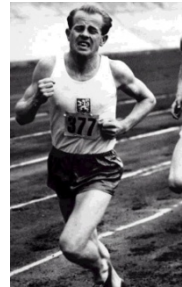


habitual activity

Metformin



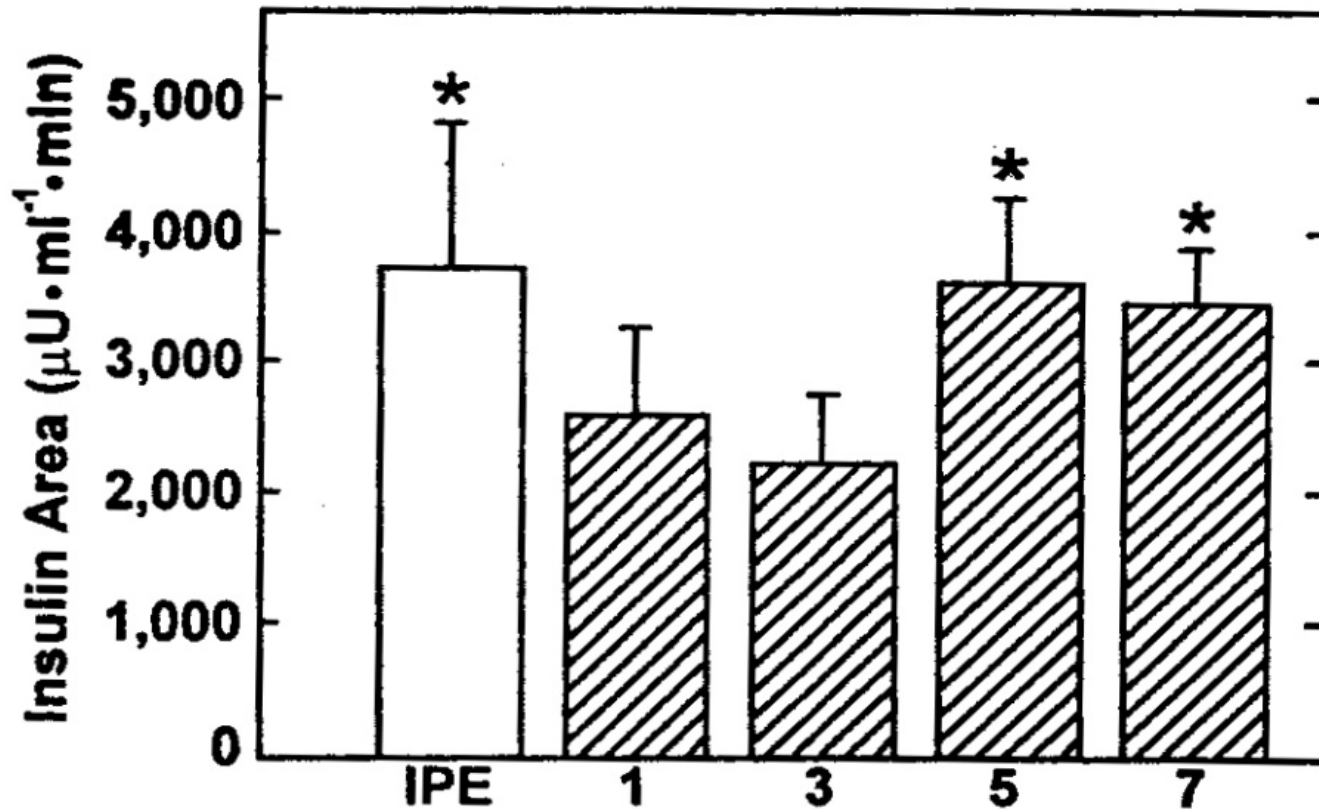
Weight loss



beneficial impact on metabolic health



Single dose



King et al., JAP, 1995



Lifestyle change



Metformin

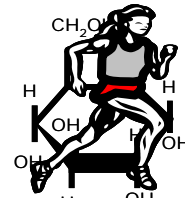


exercise
training

acute exercise



Weight
loss



beneficial impact on metabolic health



Exercise as drug

At sufficient **dose**, exercise improves metabolic function for a period of time but the effect wanes, requiring subsequent doses.

Tailoring dose to achieve maximal effect is likely to result in biggest long-term reward



What do we need to know?

Dose:

Threshold (≈ 150 min/week)

Frequency (3+ d/wk)

Intensity/Duration (HIIT, sedentary time?)

Interactions with diet

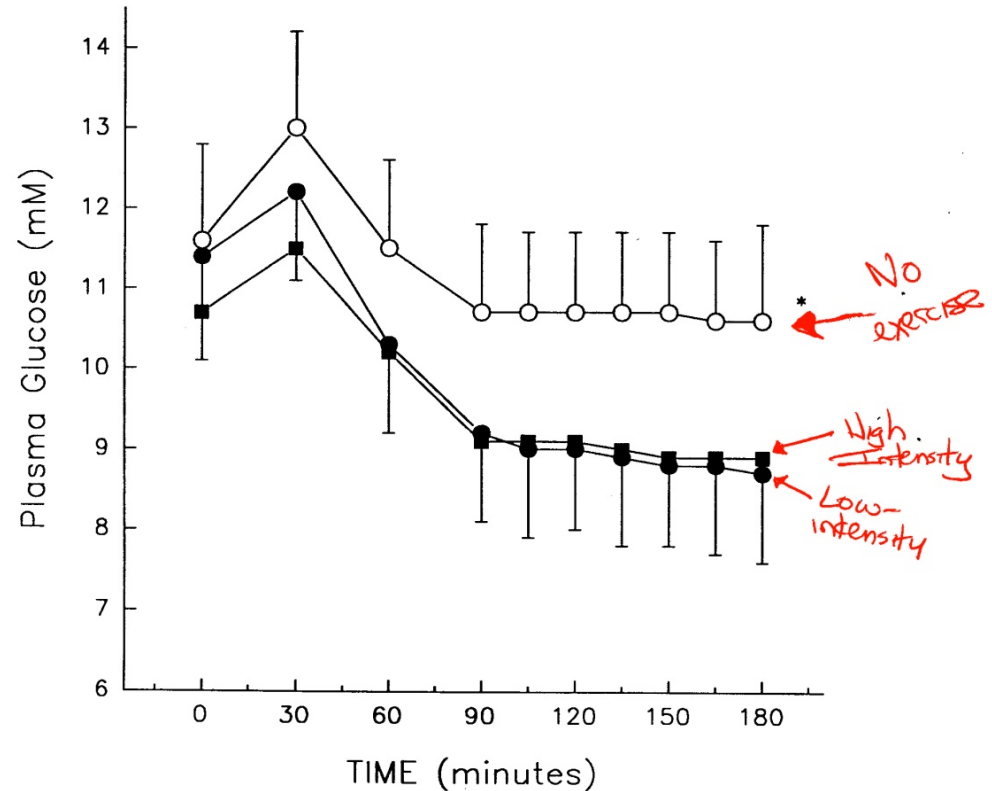
Interactions with other medications



No-Exercise

LO = 3 bouts at 50%
 VO_2max , = 750 kcal

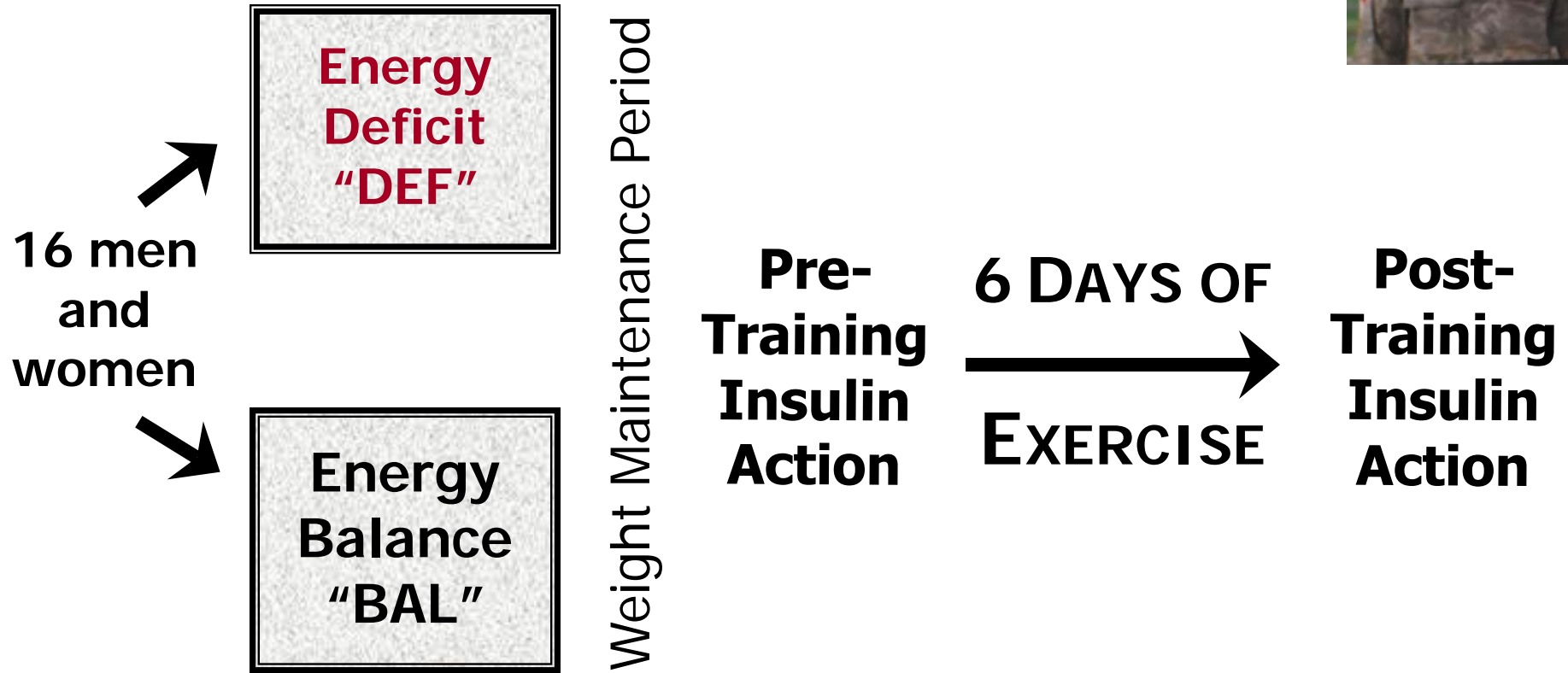
HI = 3 bouts at 75%
 VO_2max , = 750 kcal



Braun et al. J Appl. Physiol. 1995



Interactions with diet: Energy balance?

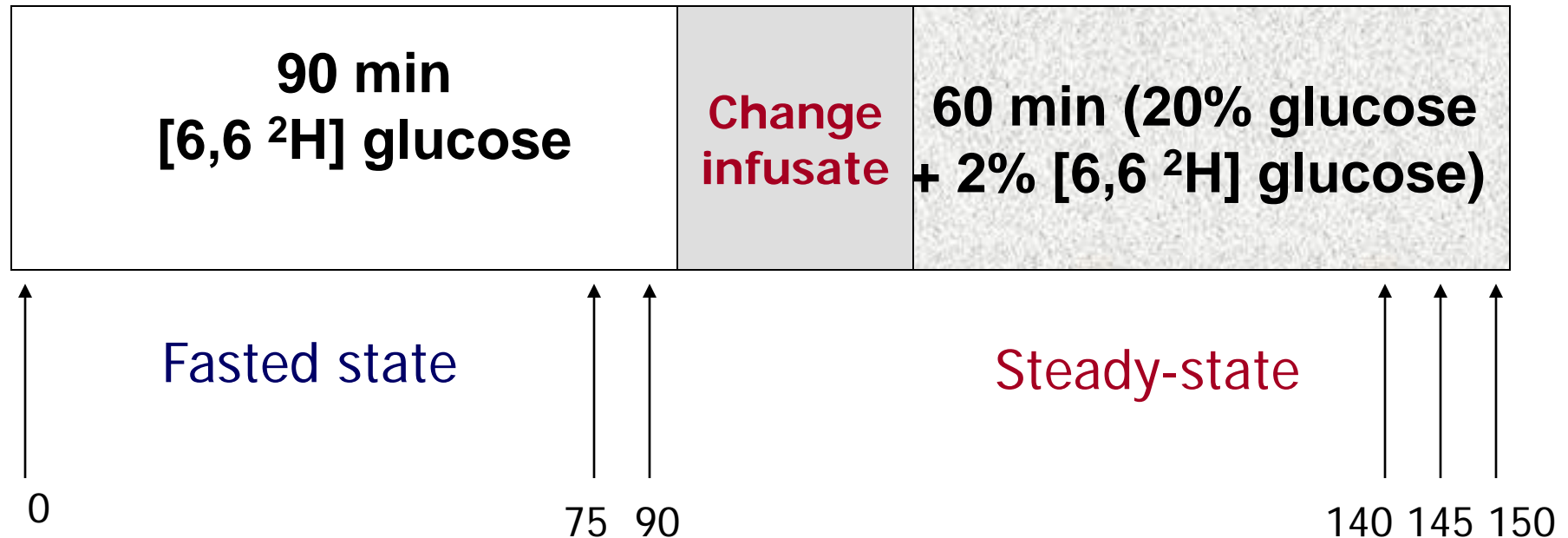


	DEF	BAL
Energy Ingested (kcal)	2246 ± 97	2925 ± 159
Estimated Energy Expenditure (kcal)	2727 ± 182	2917 ± 169
Energy Balance (kcal)	-481 ± 24	+8 ± 20
Weight Change (kg)	-0.62 ± 0.2	+0.03 ± 0.2

All food provided, EE derived from RMR, accelerometers, food, activity records

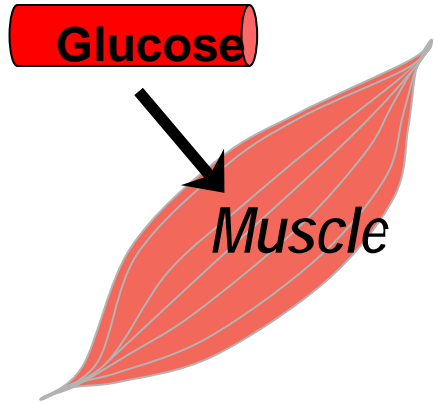


Whole-body and hepatic insulin action (CIG-SIT)

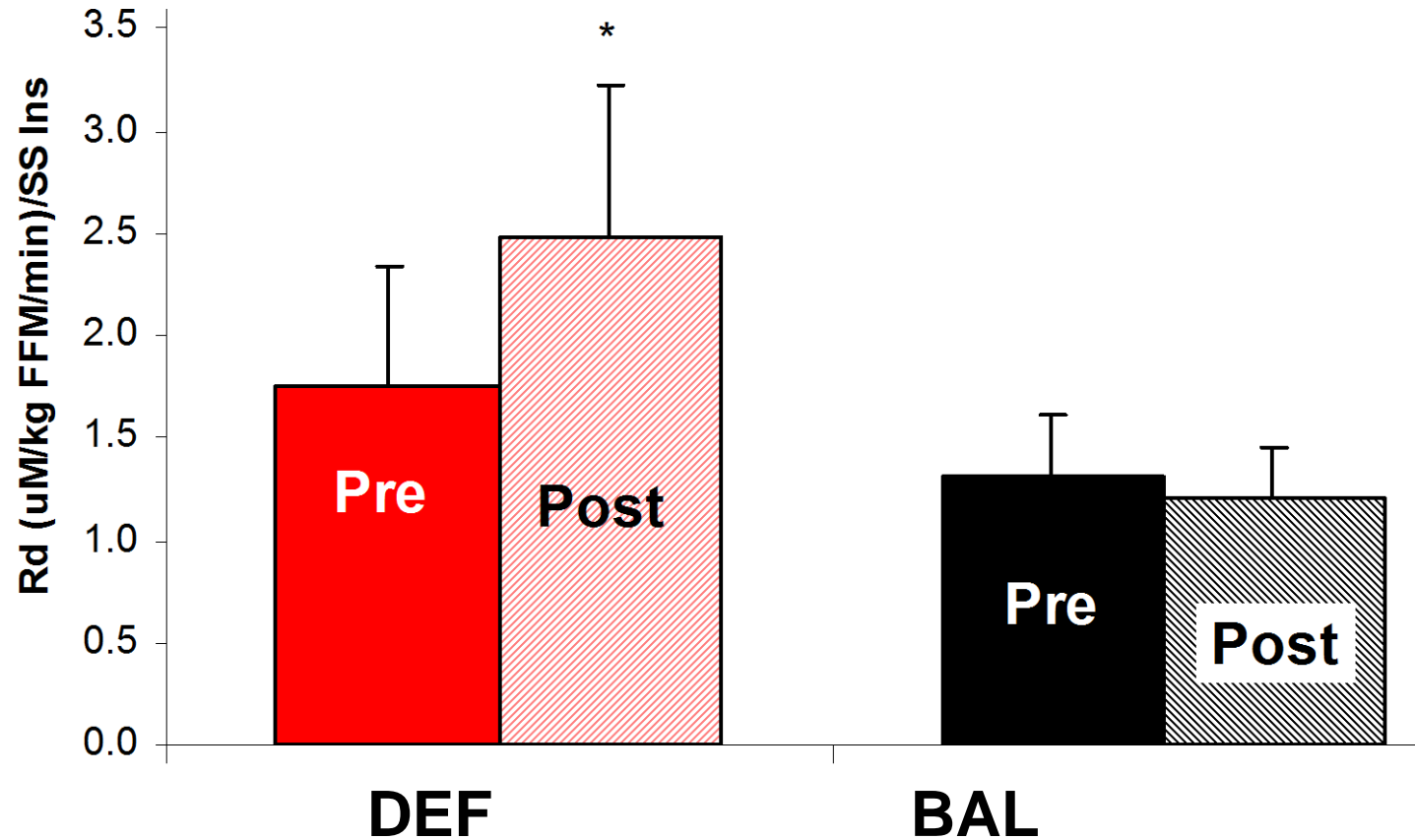


Outcomes: whole-body glucose uptake and suppression of liver glucose output





Black et al. J Appl Physiol, 2005



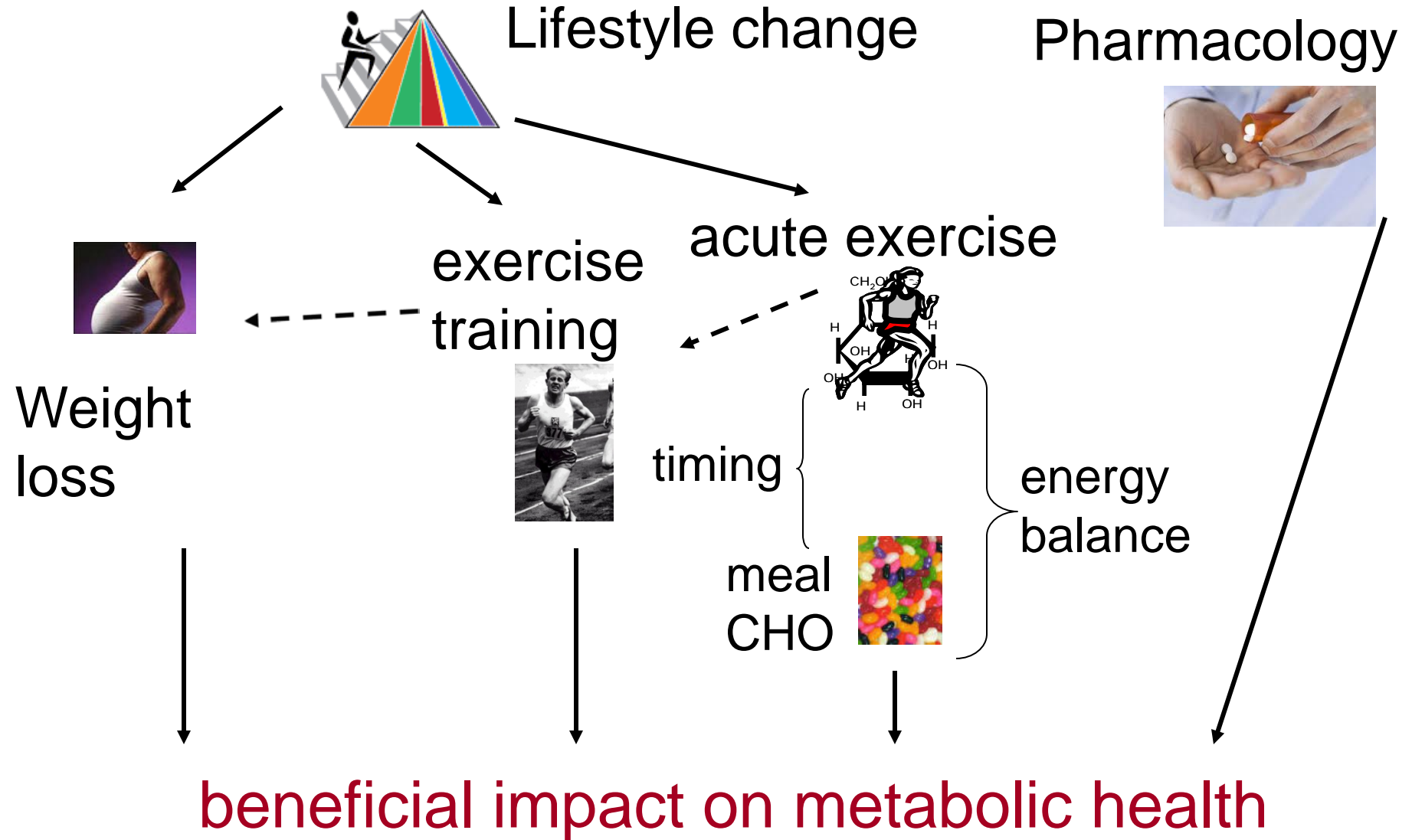
Energy balance the only difference?

CHO content of diets in 2 groups different.

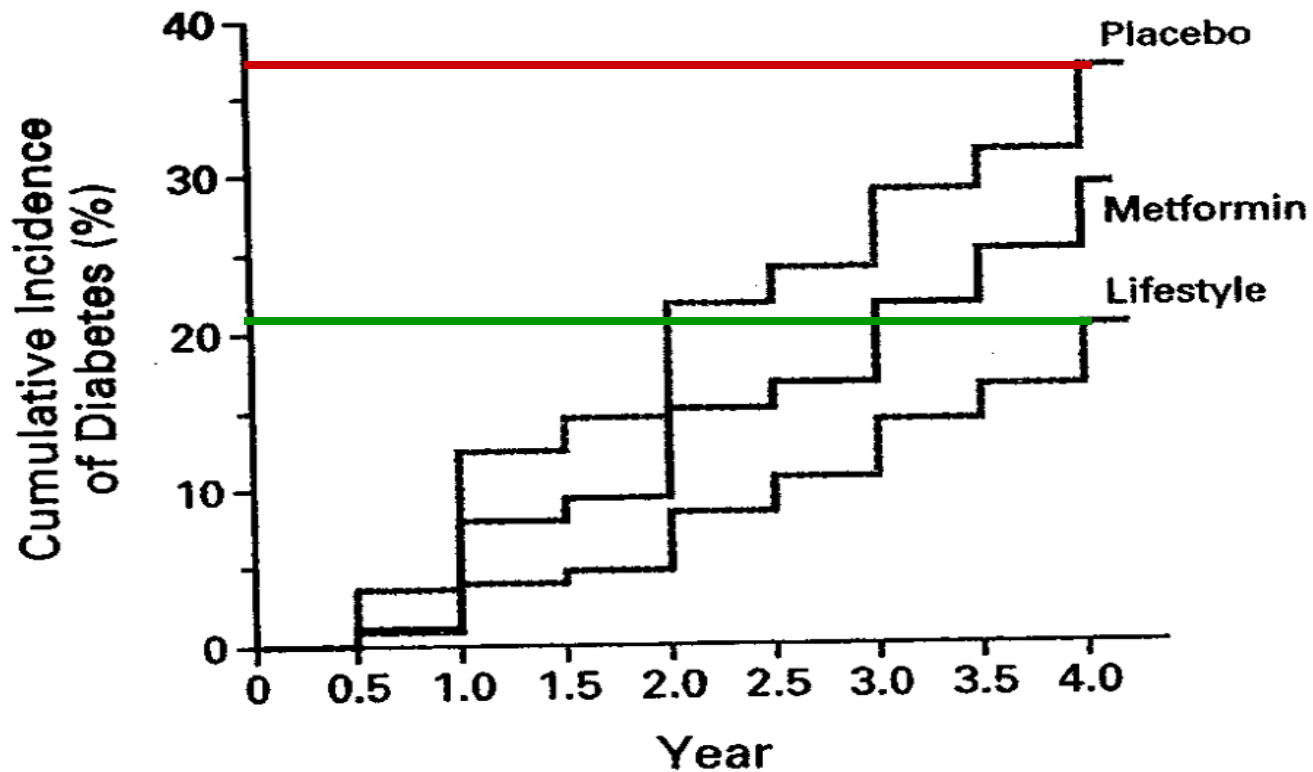
DEF = 330 g CHO/day; BAL = 410g/day.

Meal (60% CHO) **immediately** post-exercise





Diabetes Prevention Program, NEJM, 2001



Lifestyle + metformin = even better?



Exercise and metformin



Purpose: Combined effect of metformin and acute exercise on insulin sensitivity and AMPK $\alpha 2$

Hypothesis: $1 + 1 = 2$



Placebo group: rest, exercise

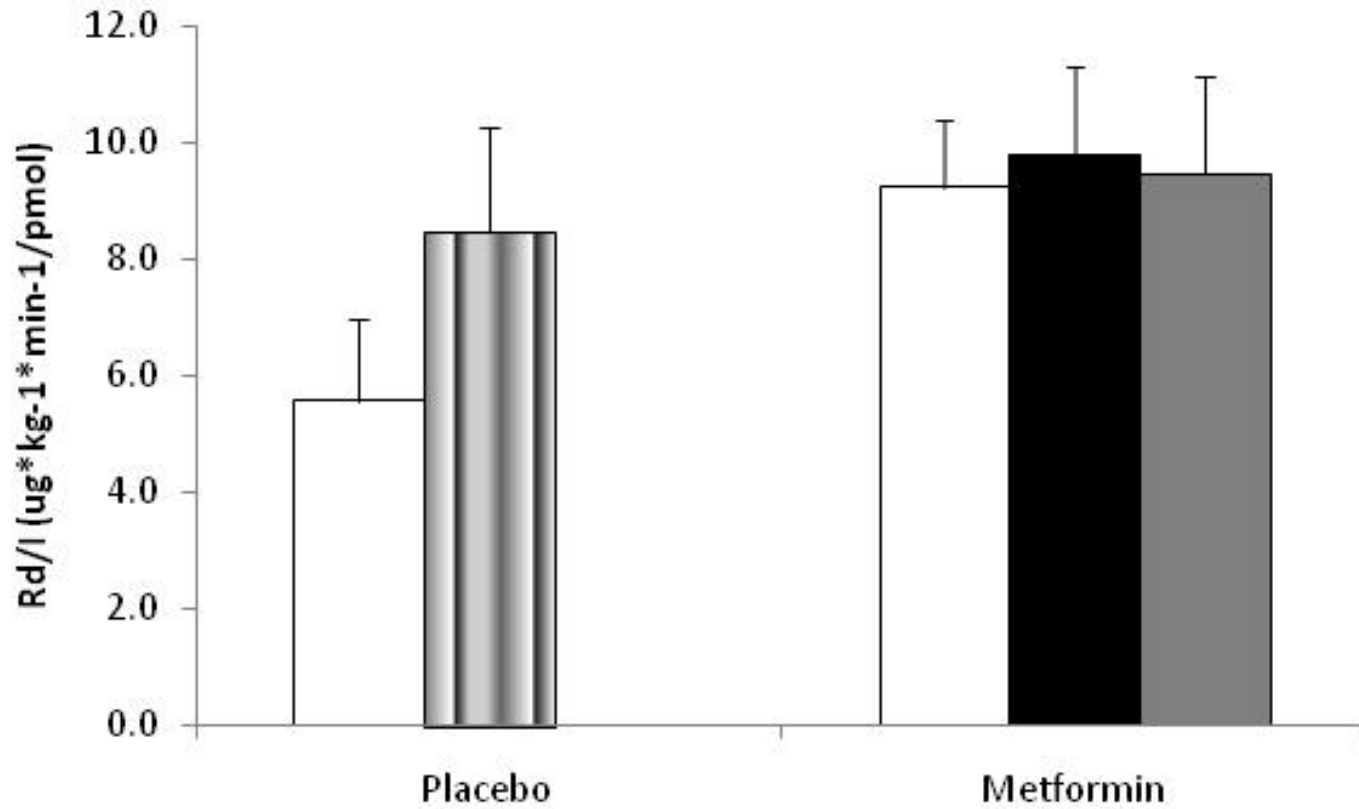


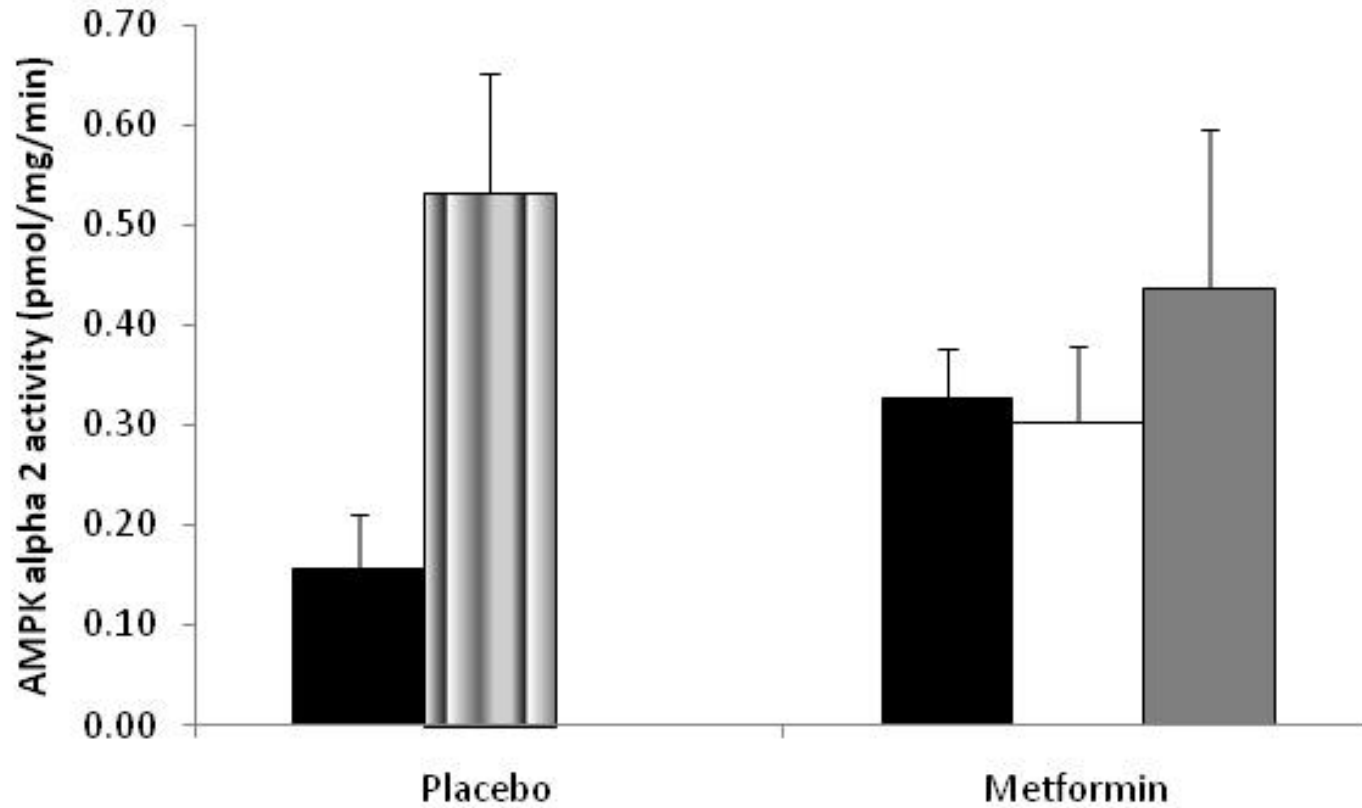
Blood sampling

Goodyear lab for analyses of AMPK activity, glycogen, and western blots.



Sharoff et al., Am J Phys, 2010





Does metformin blunt beneficial effects of training?



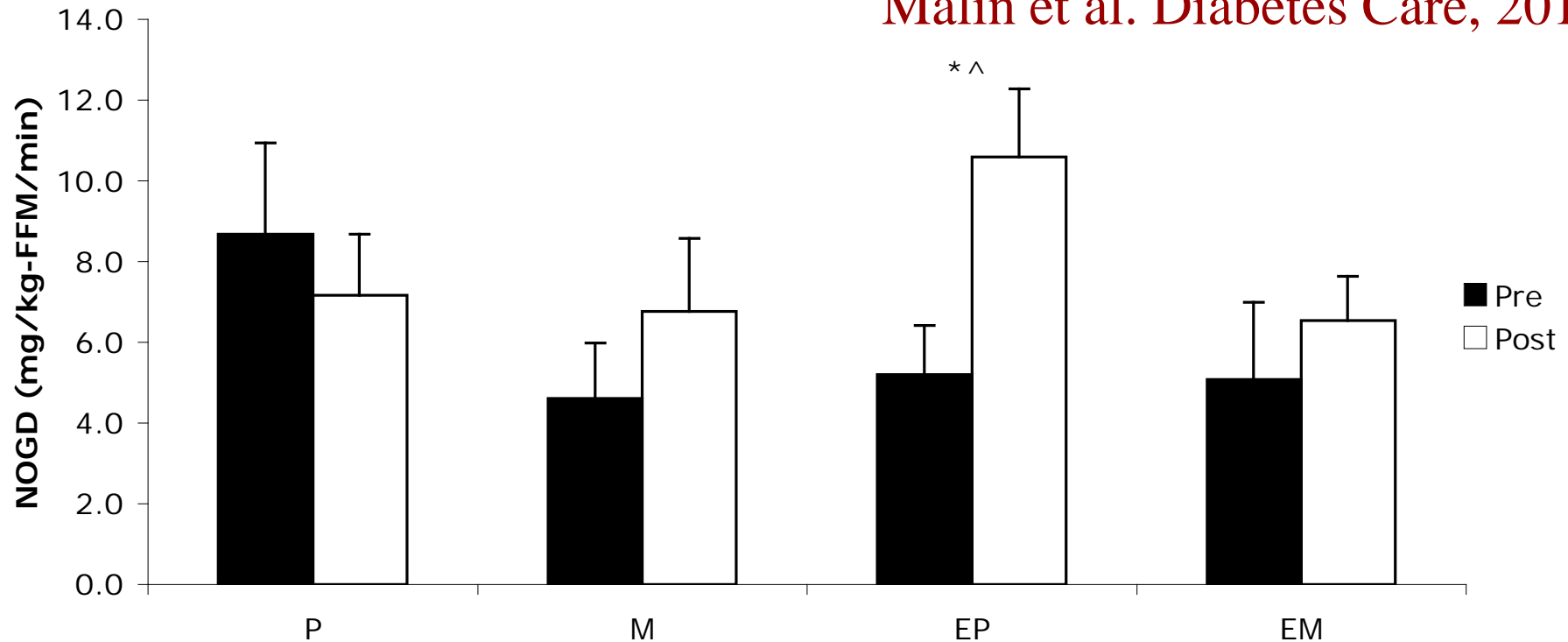
32 men and women with prediabetes

12 wks training with or w/o metformin,
metformin only and control

Insulin sensitivity using clamp and tracers



Malin et al. Diabetes Care, 2011



Insulin sensitivity enhanced more with exercise alone than when combined with metformin



Non glyceimic outcomes

Malin et al. Obesity, 2012

SBP:

C= +6.5%, M= -7.3%, EP= -6.3%, EM= 0.0%

hs-CRP:

C= +6.4%, M= -20.1%, EP= -27.4%, EM=-8.4%

TAG:

C= +3.1% M= -13.8%, EP= -13.5%, EM= -12.0%



Why?

Wt? Only M and E+M lost weight

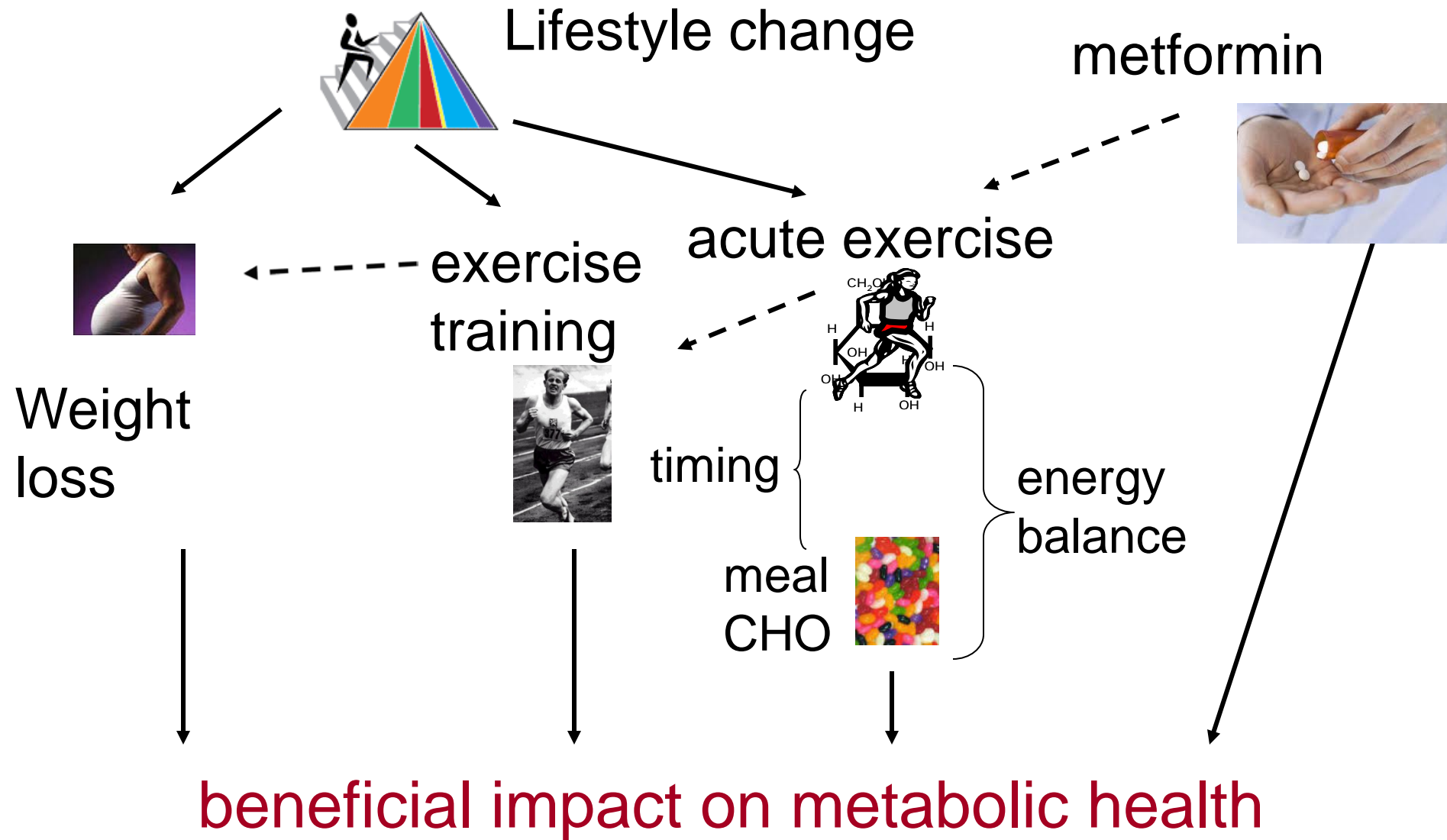
Fat? $M = nc$, E+M and E+P= -2%

Central fat? $M = nc$, E+M and E+P= -1.5%

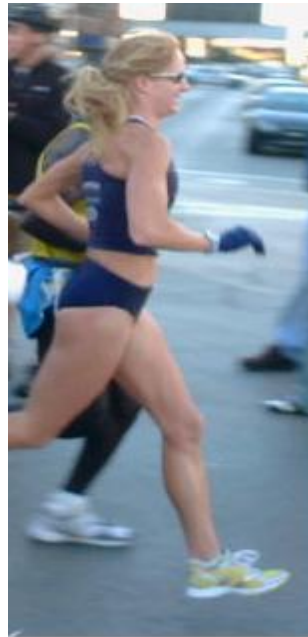
CRF? $M = nc$, $E+M \approx +10\%$, $E+P \approx +20\%$

ΔVO_{2peak} and Δ insulin sensitivity: $r = .70$





Role of “sedentary behavior” in mediating efficacy of the exercise drug??



14 normally active men and women
3 conditions, balanced order



Active, energy bal (no sit 15 hr.)

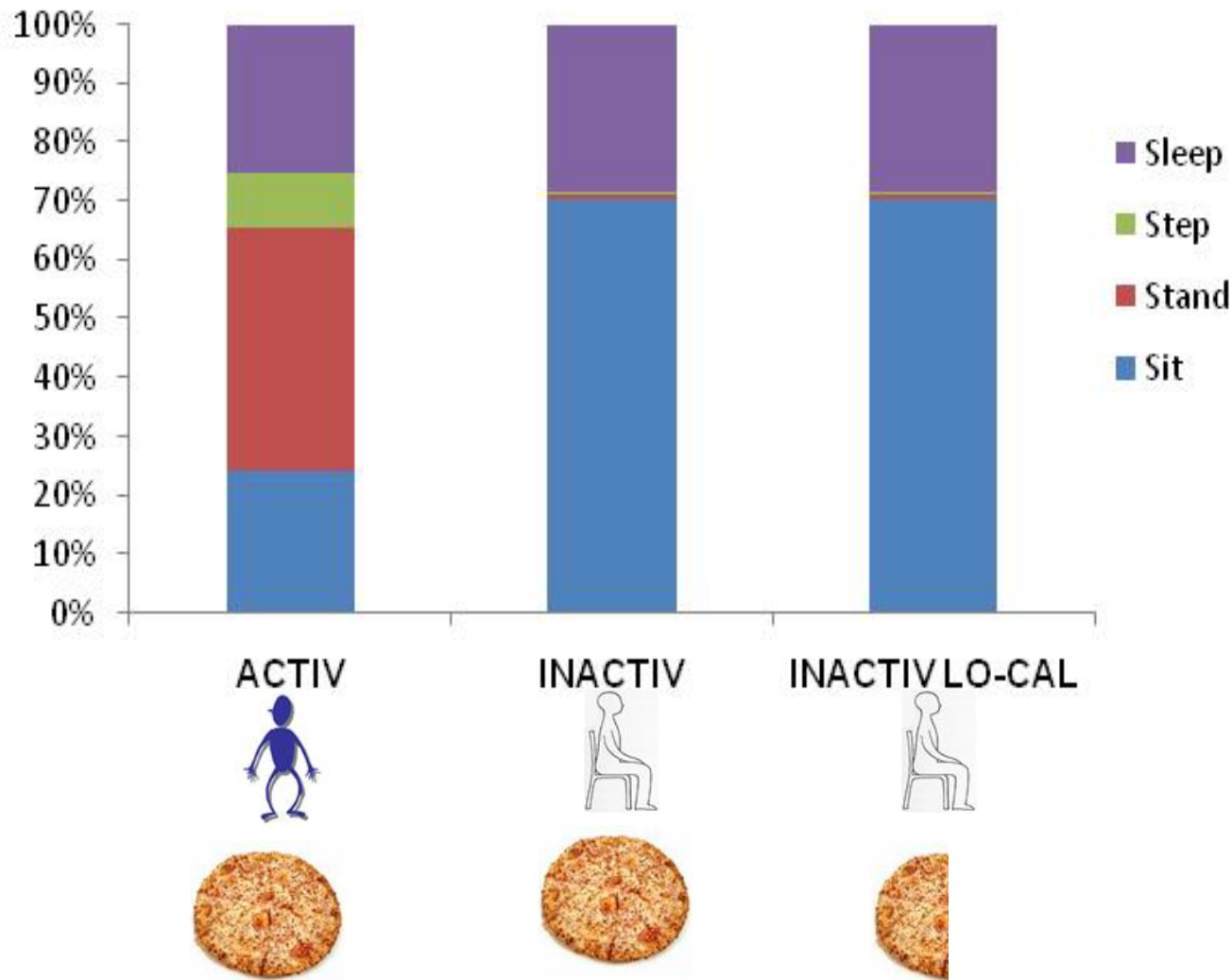


Inactive (sit 15 hr, no diet change)

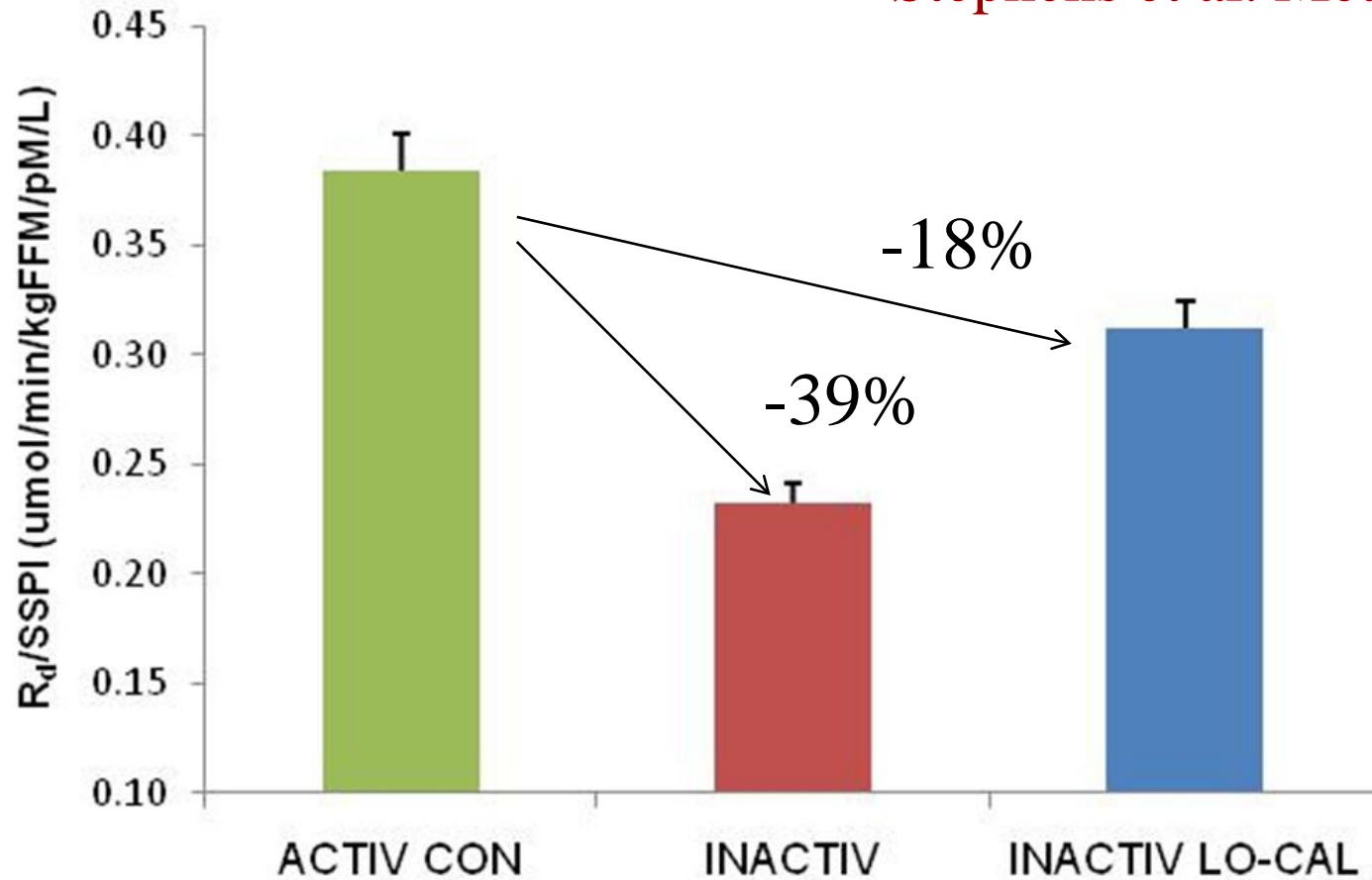


Inactive, (sit 15 hr, cut kcals)





Stephens et al. Metabolism 2010



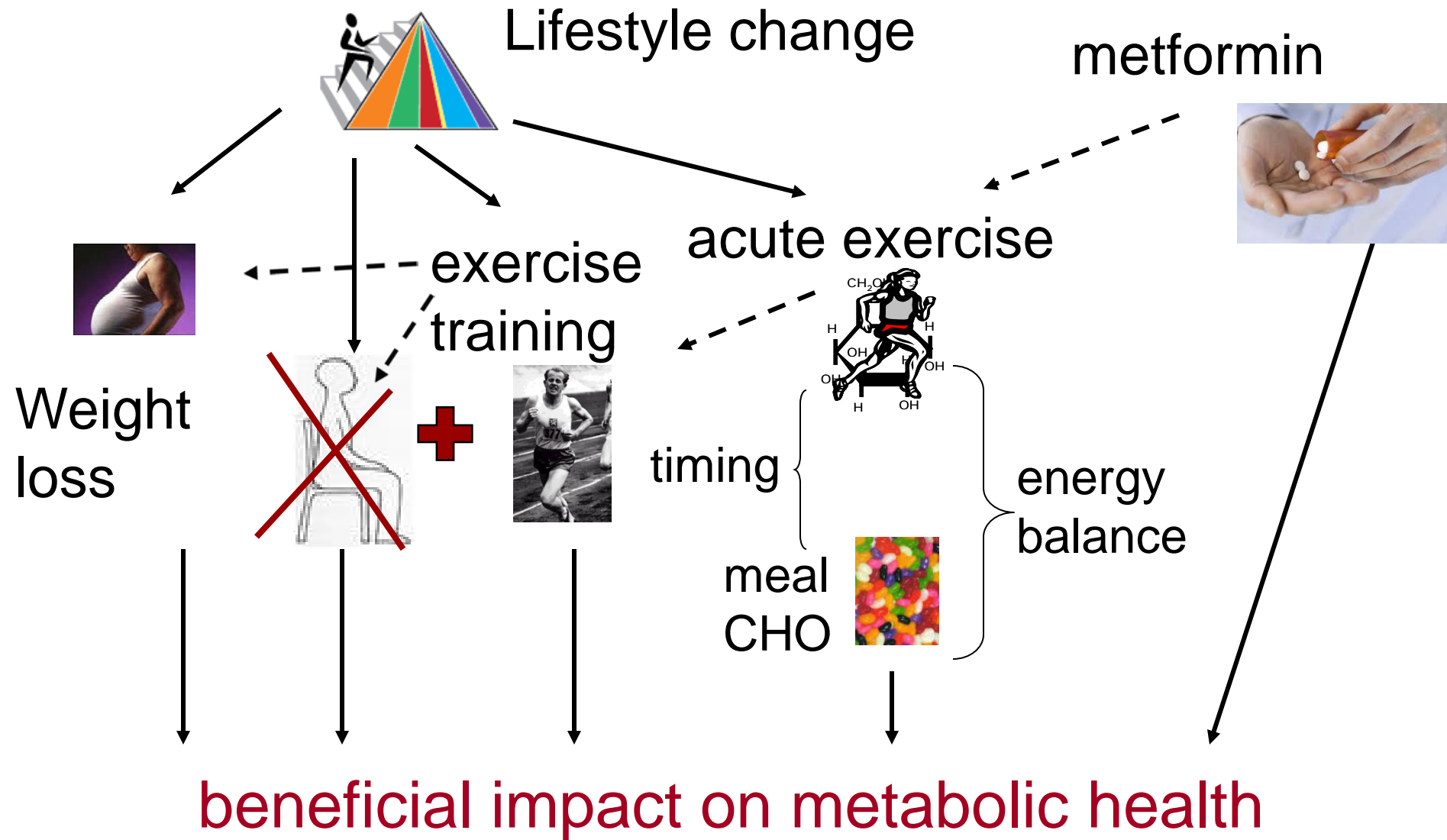
Sedentary subjects

Control, 12 wks training (EX), reduced
sedentary time (rST) OR both (EX+rST).

EX+rST accentuated impact of EX alone
C-ISI up by 24% vs. 17.5% (but TG same)

Little impact of rST alone





Conclusions

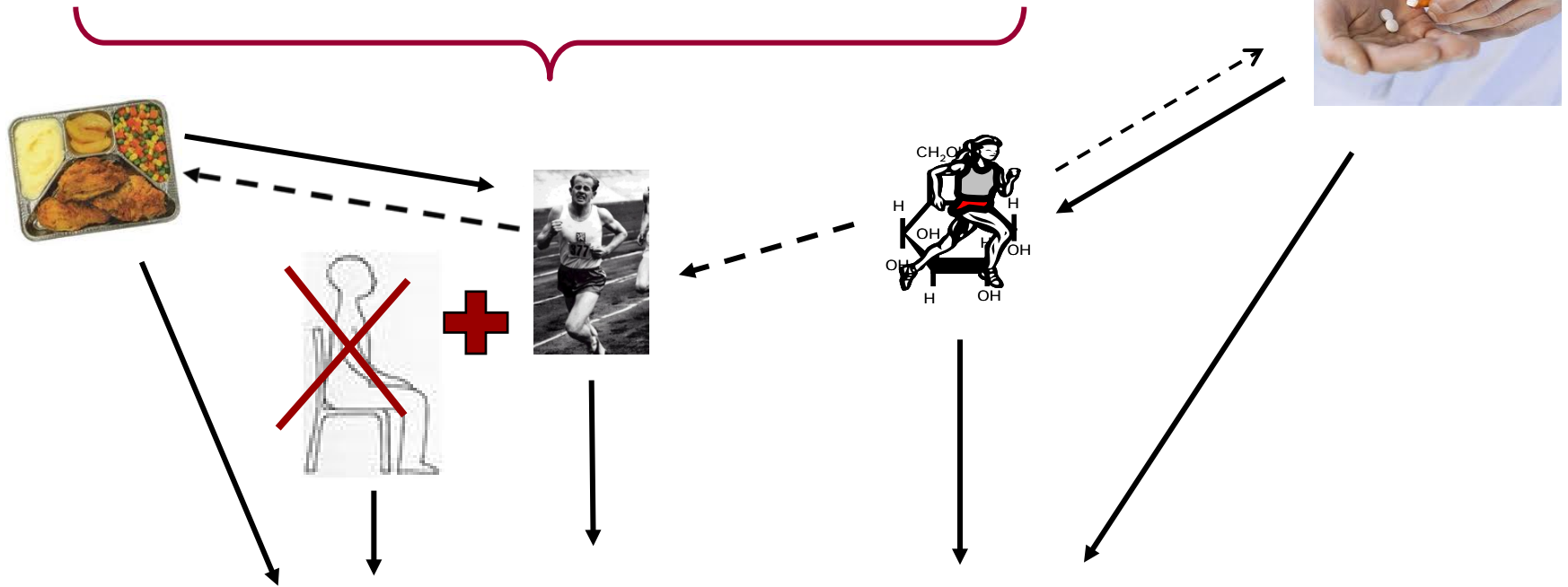
At sufficient dose, exercise/physical activity
potent countermeasure

Less sedentary behavior useful but not sufficient

Interxns between exercise and nutritional context

Interactions with other meds NOT predictable





beneficial impact on metabolic health



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