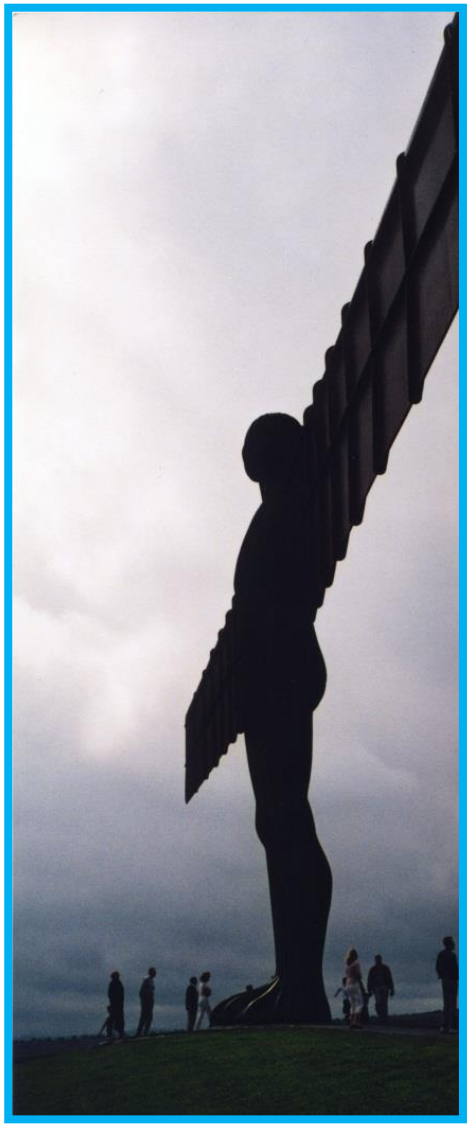
Genetic influences on weight loss – opportunities for personalisation?



John Mathers

Human Nutrition Research Centre

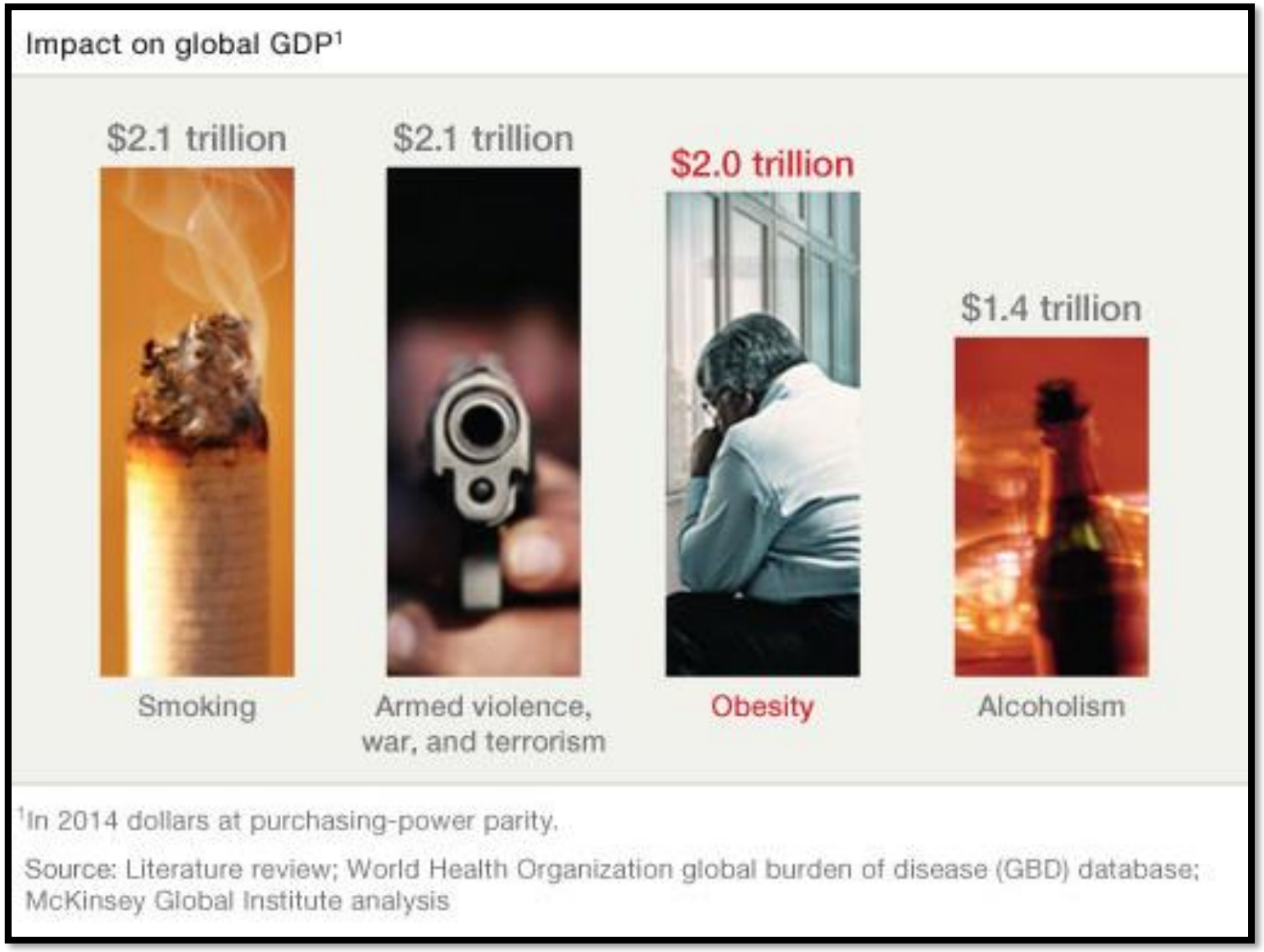
Institute of Cellular Medicine

Newcastle University

Human Nutrition Research Centre

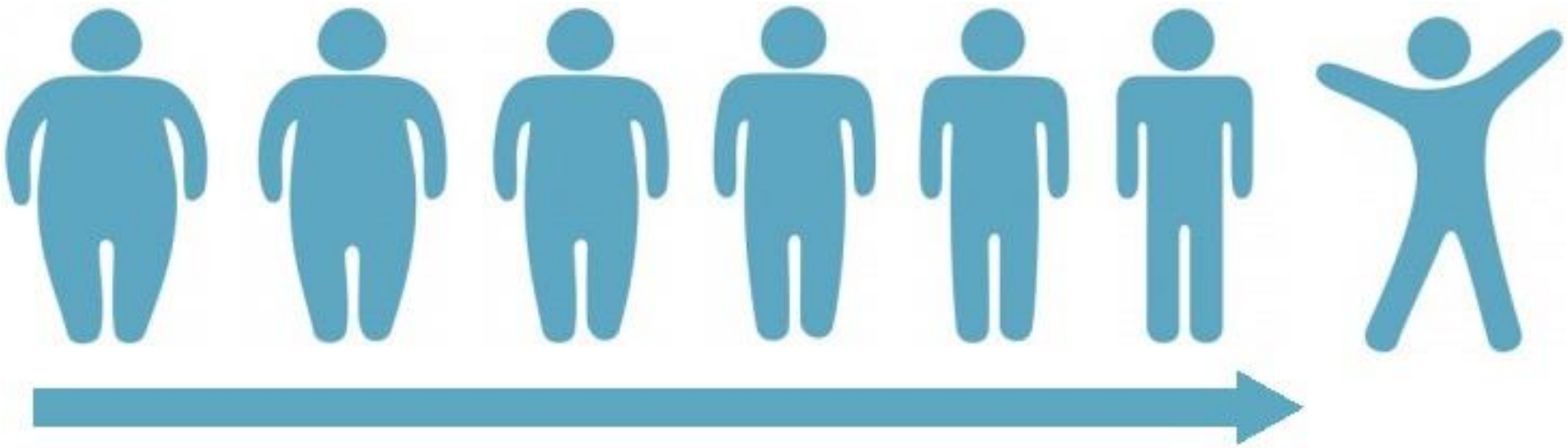
UK

Obesity is 3rd biggest societal burden



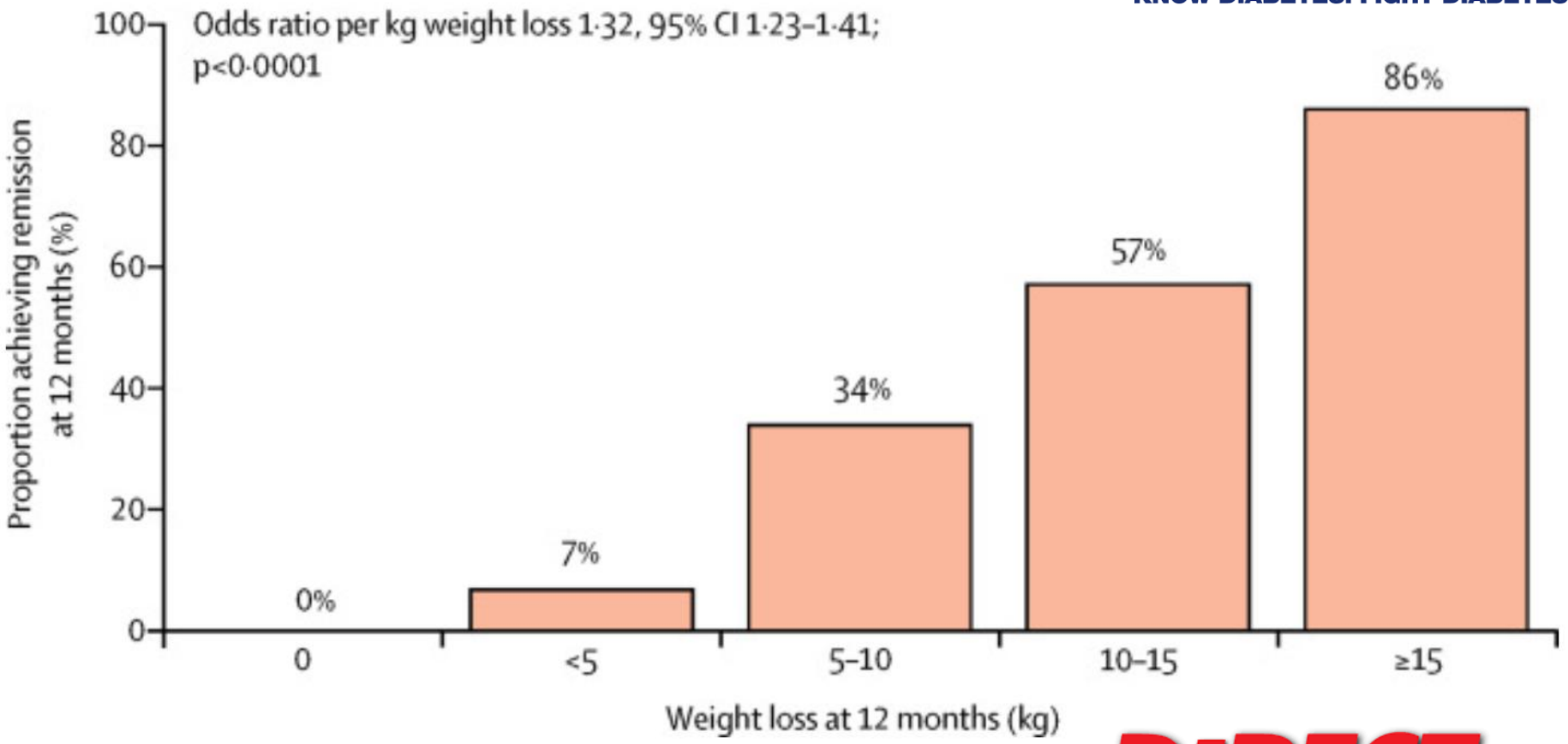
http://www.mckinsey.com/insights/economic_studies/how_the_world_could_better_fight_obesity

Weight loss improves health and wellbeing



Sustained weight loss leads to Type 2 Diabetes remission

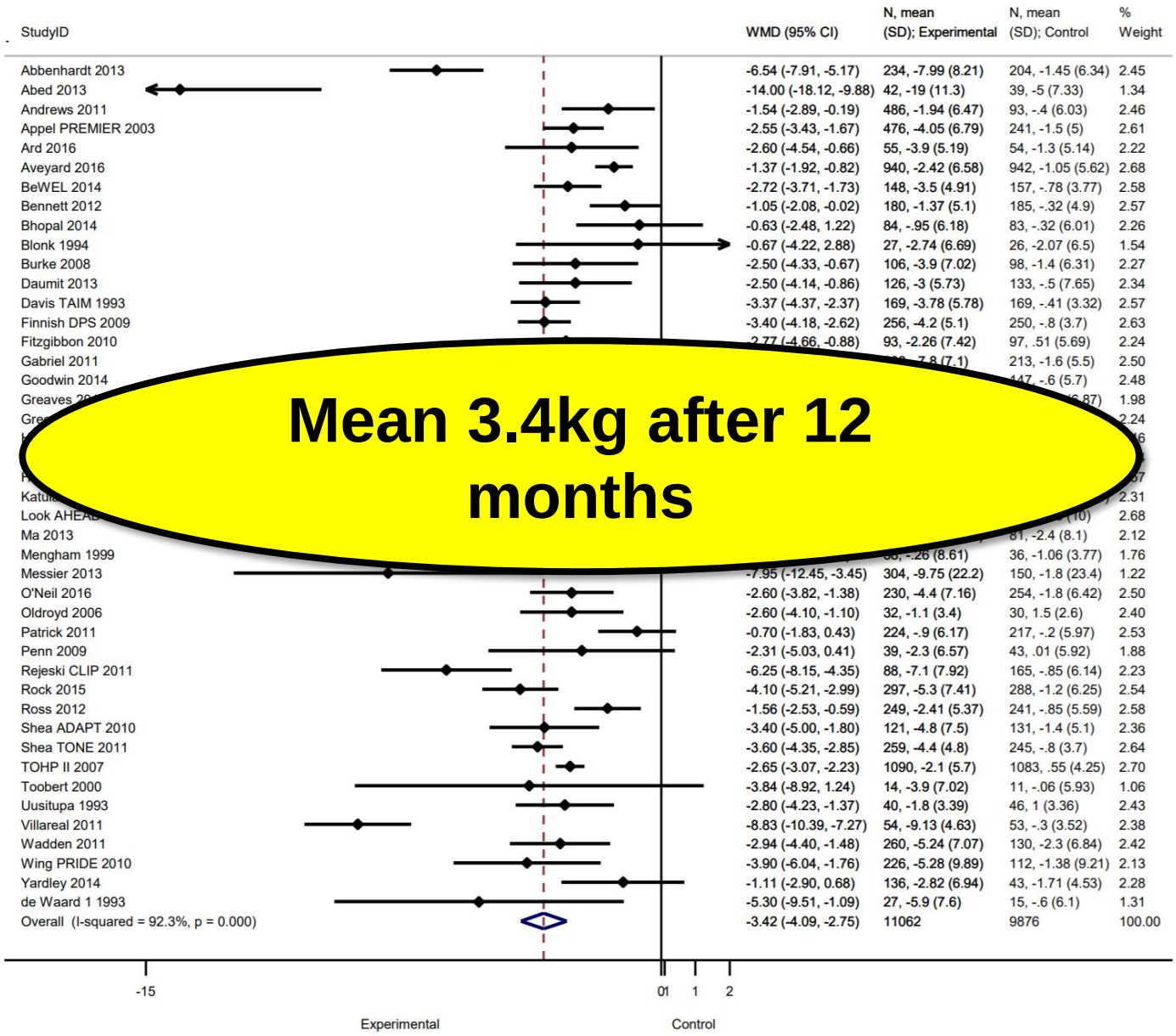
DIABETES UK
KNOW DIABETES. FIGHT DIABETES.



DiRECT
Diabetes Remission Clinical Trial

Lean ME *et al.* (2018) *Lancet* **391:** 541-551

Effect of weight loss interventions

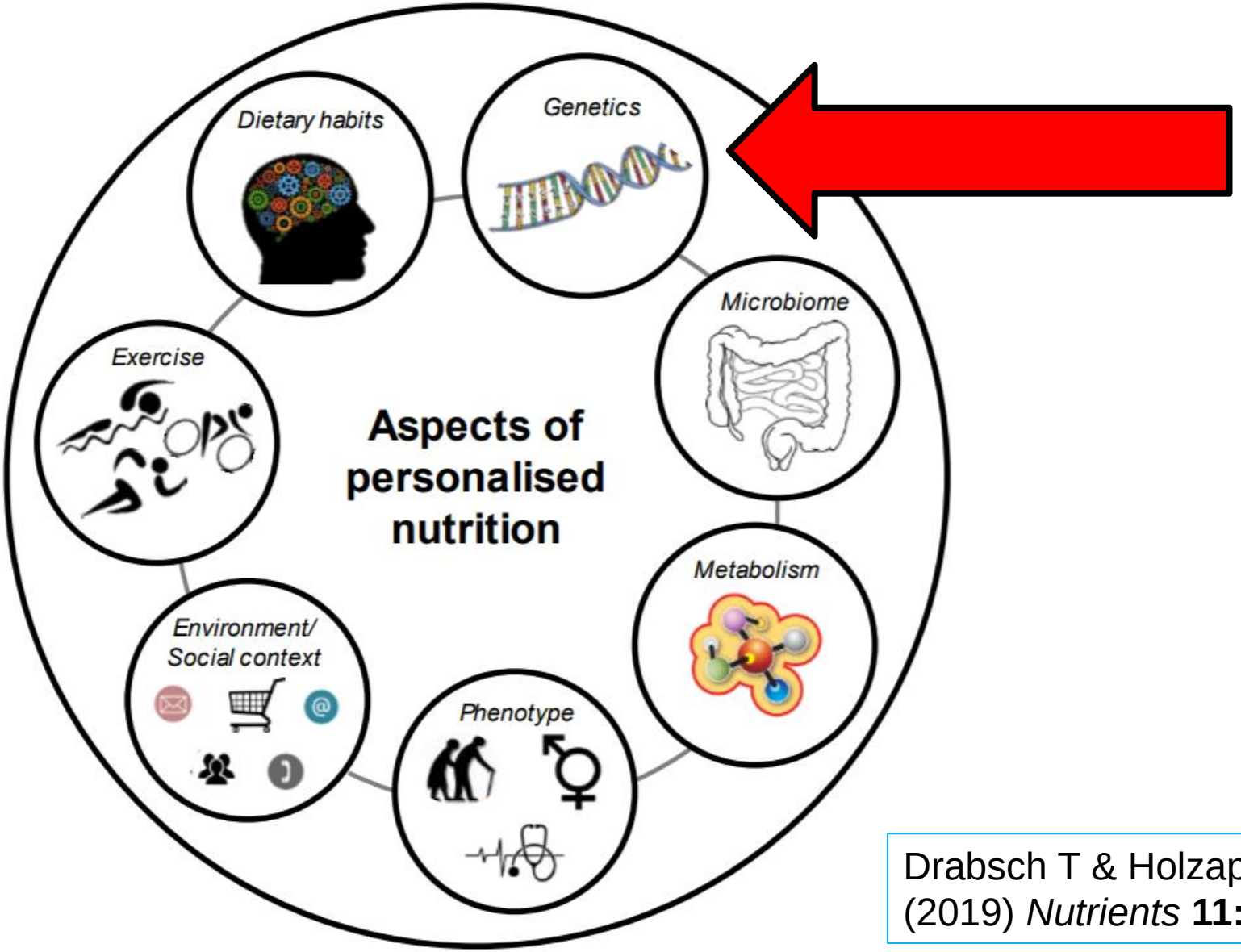


Mean 3.4kg after 12 months

Ma C *et al.* (2017) *BMJ* **359:** j4849


The era of personalised (precision) medicine

Personalised nutrition and weight loss



Drabsch T & Holzapfel C (2019) *Nutrients* **11:** 617

Personalised approaches to lifestyle behaviour change

Rationale for personalised approaches to lifestyle behaviour change .1

Hypothesis: Individualising advice, products, or services will be more effective than more generic approaches.

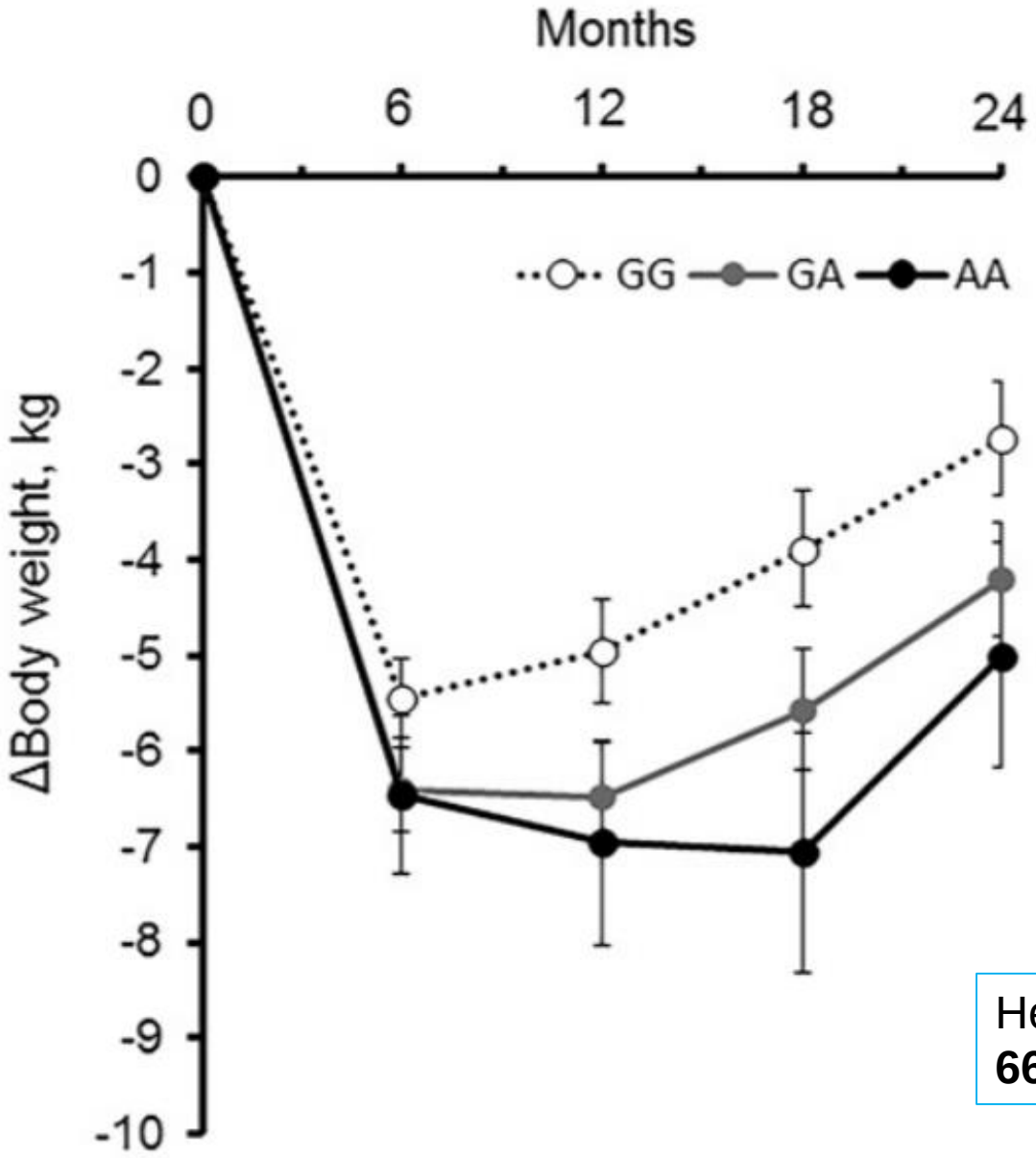
Personalisation can be based on:

1. Biological evidence of differential responses dependent on genotypic or phenotypic characteristics.

2. Analysis of current behaviour, preferences, barriers, and objectives and subsequent delivery of interventions that motivate and enable individuals to make appropriate behavioural changes.

Ordovas JM *et al.* (2018) *BMJ* **361:** k2173

Genotype associated with weight loss



rs11185098 in amylase gene

Mechanism?

Heianza Y *et al.* (2017) *Diabetes* **66:** 2416-2423

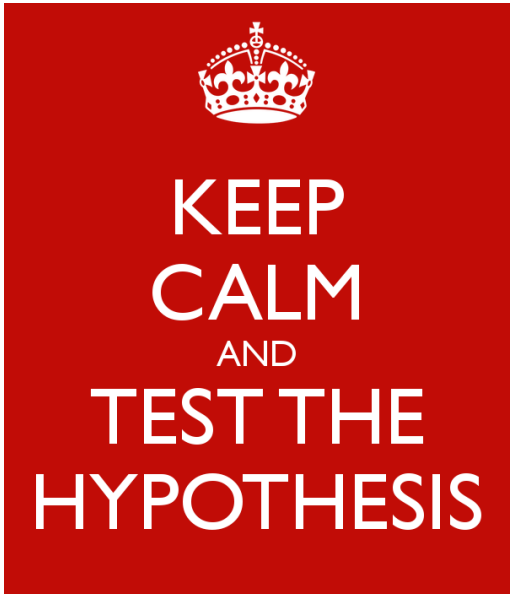
Rationale for personalised approaches to lifestyle behaviour change .2

Personalised approaches **may** be more effective because:

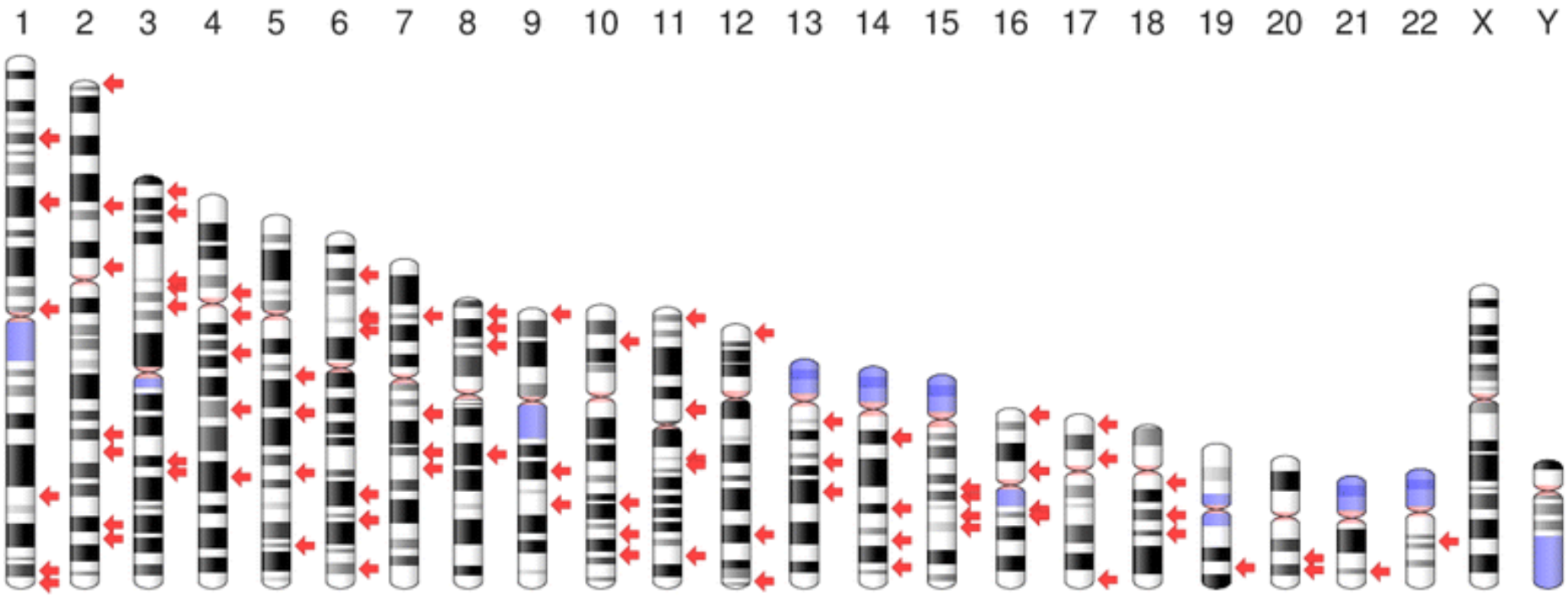
- Such approaches **are** more relevant (biological basis)
- Such approaches **feel** more relevant (improve motivation…)

Hypothesis

Genetic susceptibility that makes it easier to gain weight will make it more difficult to lose weight

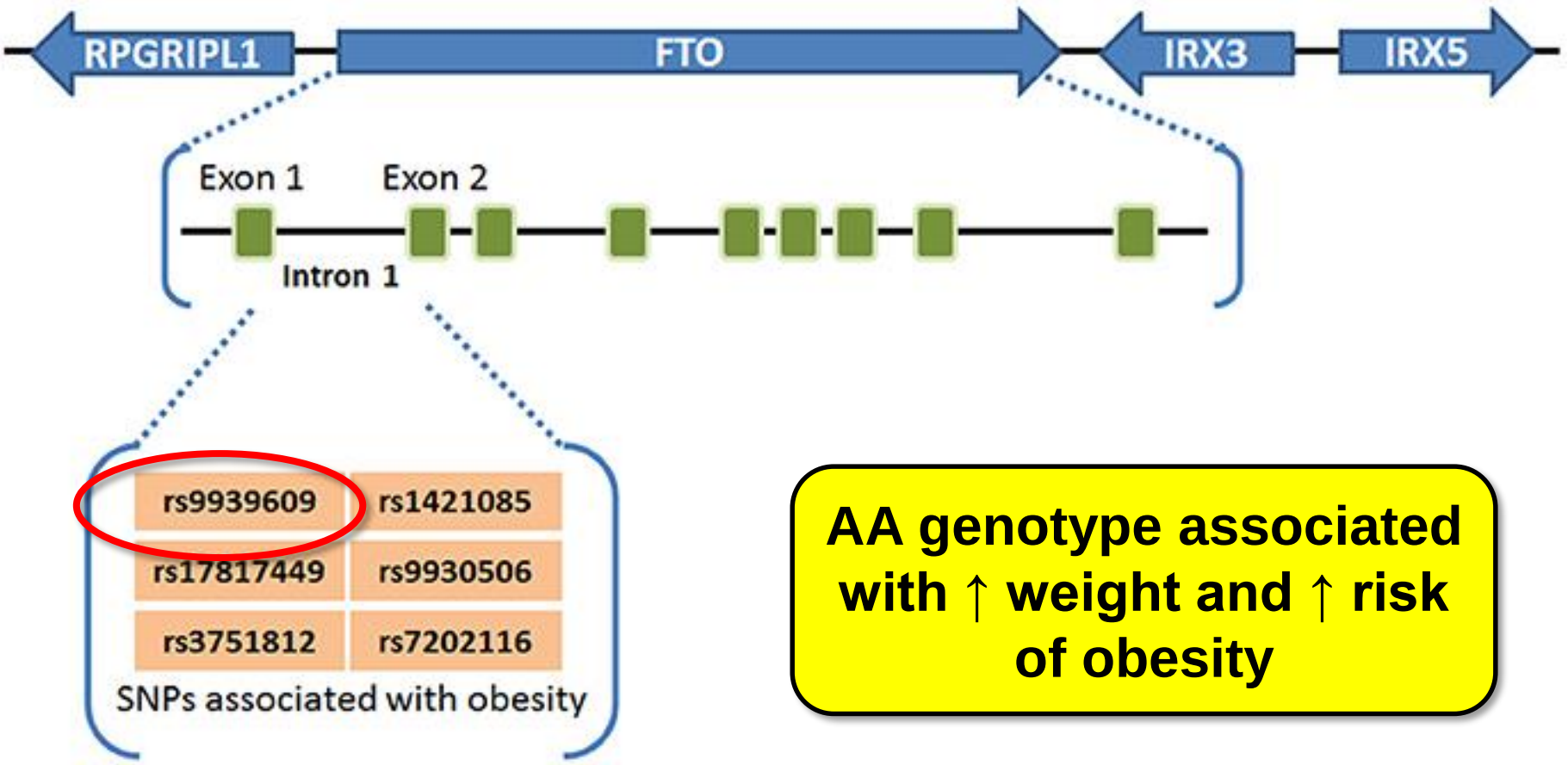


Chromosomal locations of 127 genetic variants associated with obesity



Castillo JJ *et al.* (2017) *Genes & Nutr* **12:** 29

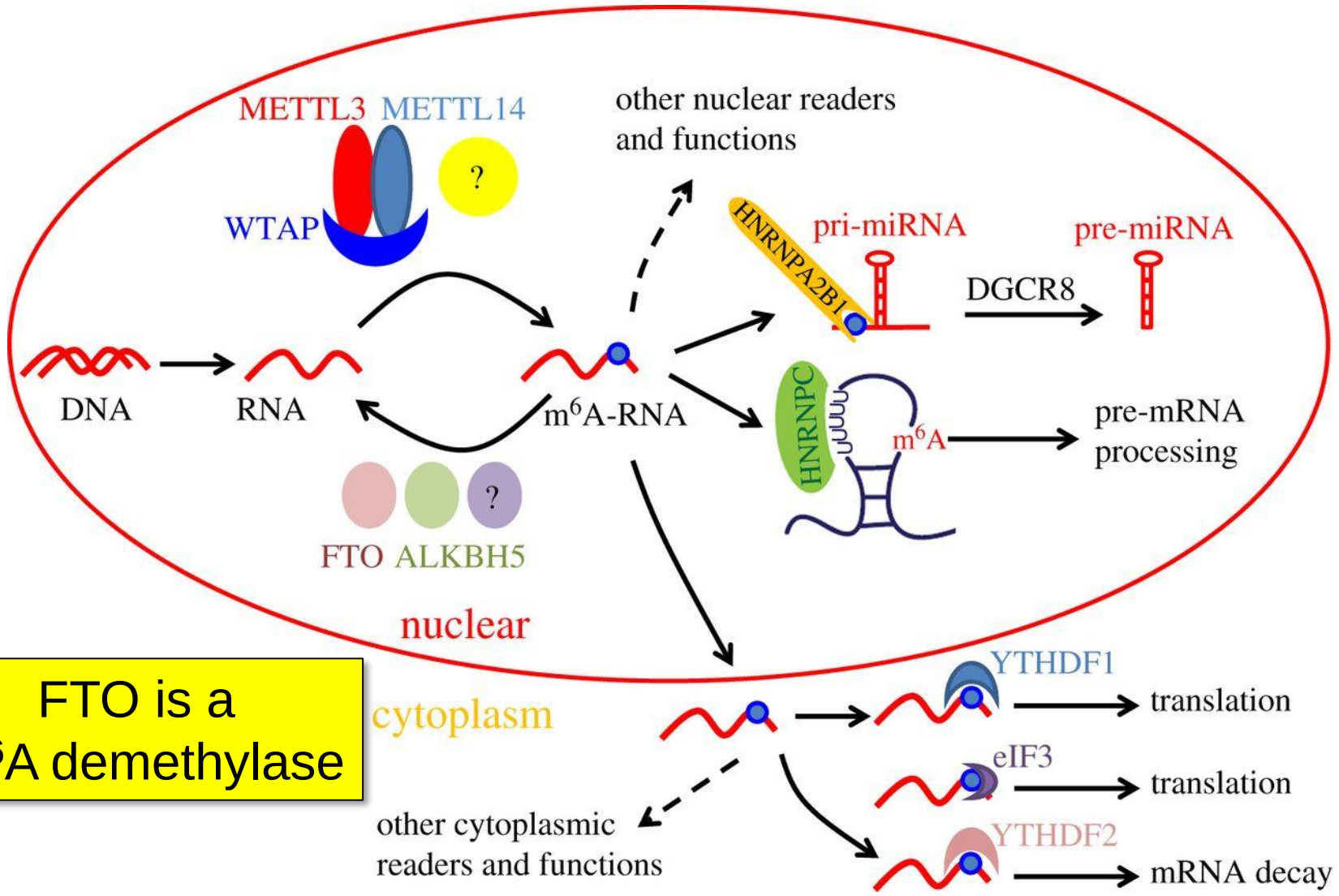
Structure of *FTO* gene on chr 16



AA genotype associated with ↑ weight and ↑ risk of obesity

Deng X *et al.* (2018) *Front. Endocrinol.* **9:** 396

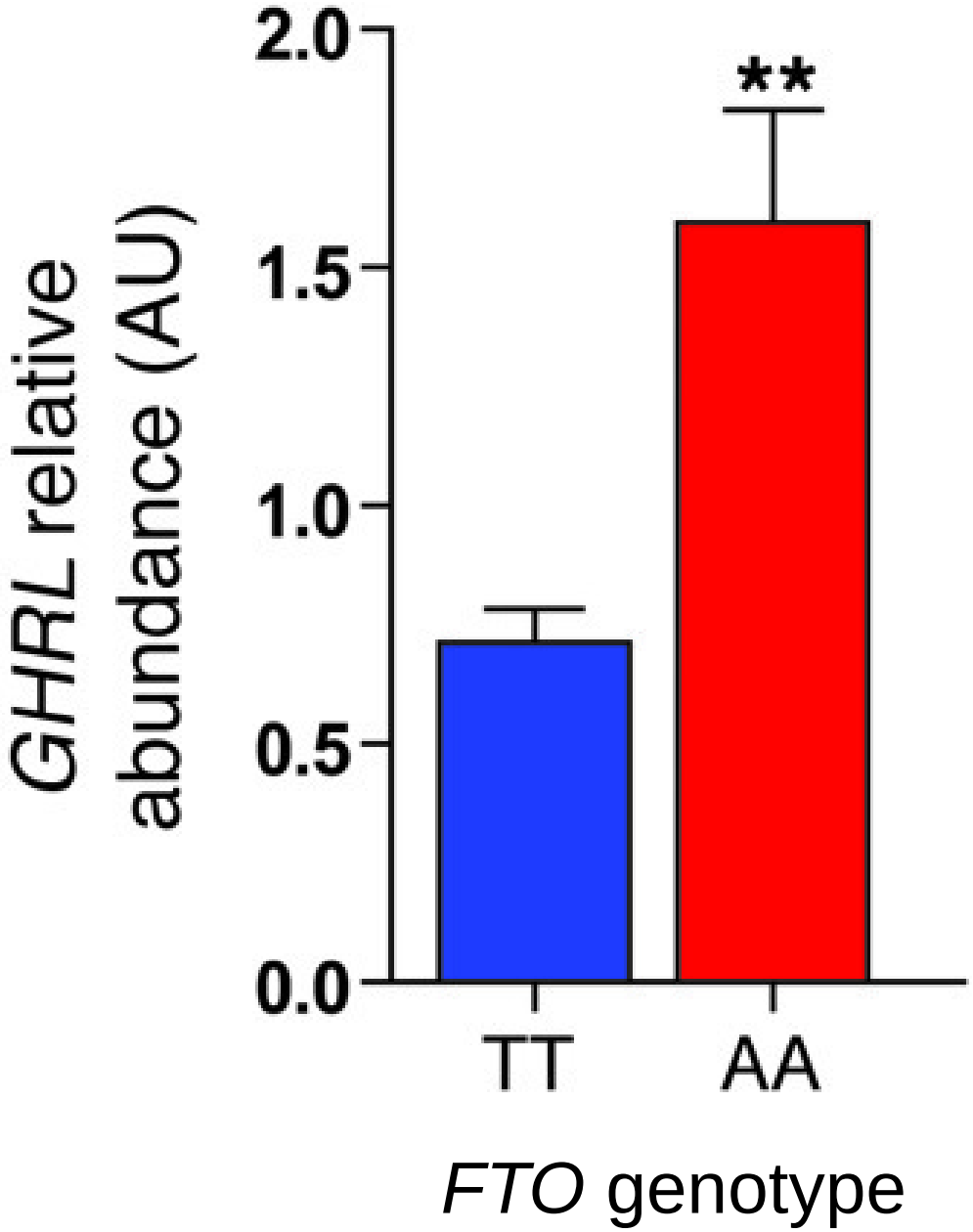
Biological function of FTO protein



FTO is a
m^6A demethylase

Cao G *et al.* (2016) *Open Biol.* **6:** 160003

FTO genotype regulates ghrelin expression



Ghrelin is the "hunger" hormone

Karra E *et al.* (2013) *J. Clin. Invest.* **123:** 3539-3551

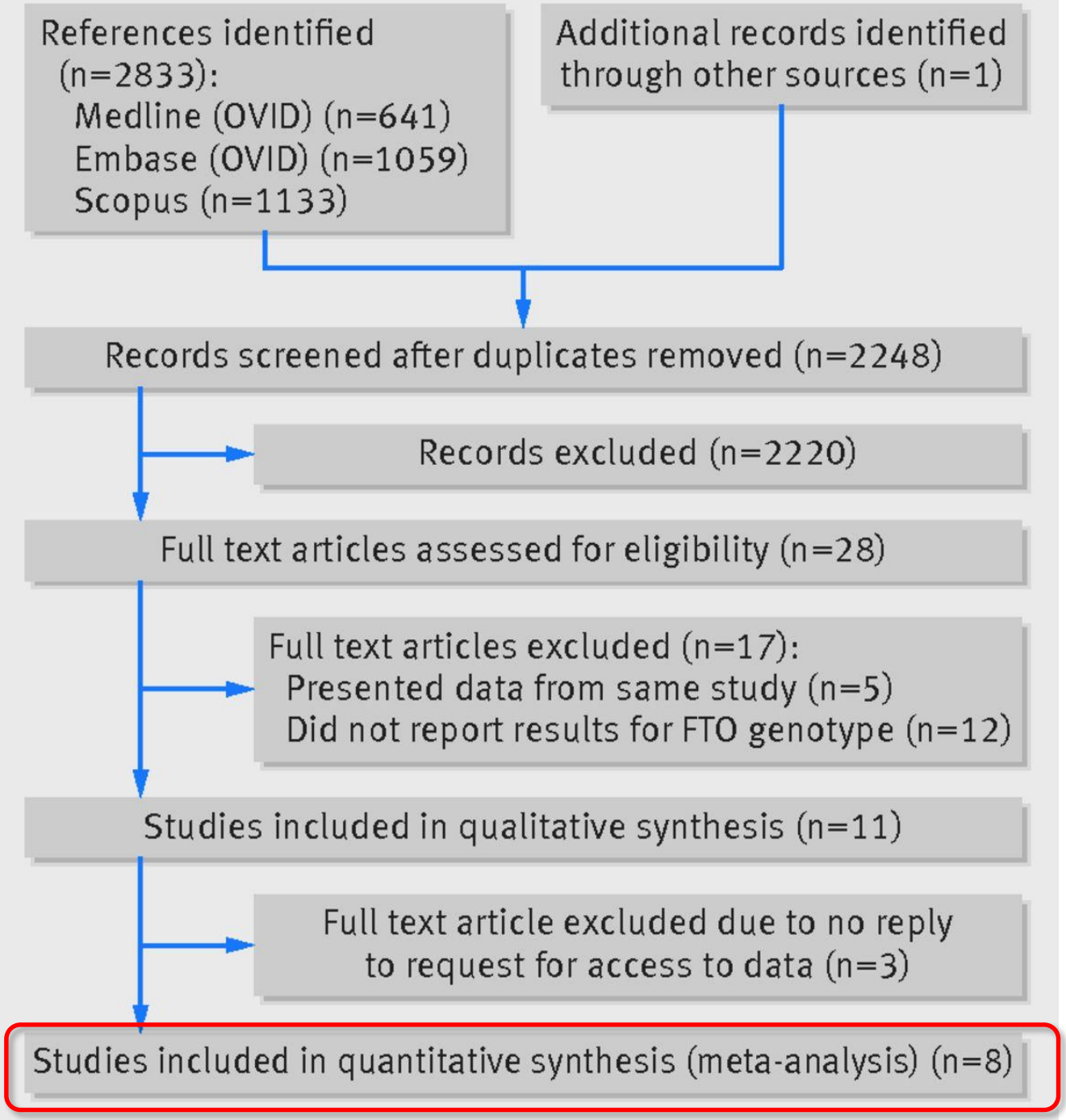
Does *FTO* genotype influence weight loss in intervention studies?

FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials

Katherine M Livingstone,[1,2] Carlos Celis-Morales,[1,3] George D Papandonatos,[4] Bahar Erar,[4] Jose C Florez,[5,6] Kathleen A Jablonski,[7] Cristina Razquin,[8,9] Amelia Marti,[9,10] Yoriko Heianza,[11] Tao Huang,[11,12] Frank M Sacks,[13] Mathilde Svendstrup,[14,15] Xuemei Sui,[16] Timothy S Church,[17] Tiina Jääskeläinen,[18,19] Jaana Lindström,[20] Jaakko Tuomilehto,[21,22] Matti Uusitupa,[18] Tuomo Rankinen,[23] Wim H M Saris,[24] Torben Hansen,[14] Oluf Pedersen,[14] Arne Astrup,[25] Thorkild I A Sørensen,[14,26] Lu Qi,[11,13] George A Bray,[17] Miguel A Martinez-Gonzalez,[9,10] J Alfredo Martinez,[9,10,27] Paul W Franks,[13,28] Jeanne M McCaffery,[29] Jose Lara,[1,30] John C Mathers[1]

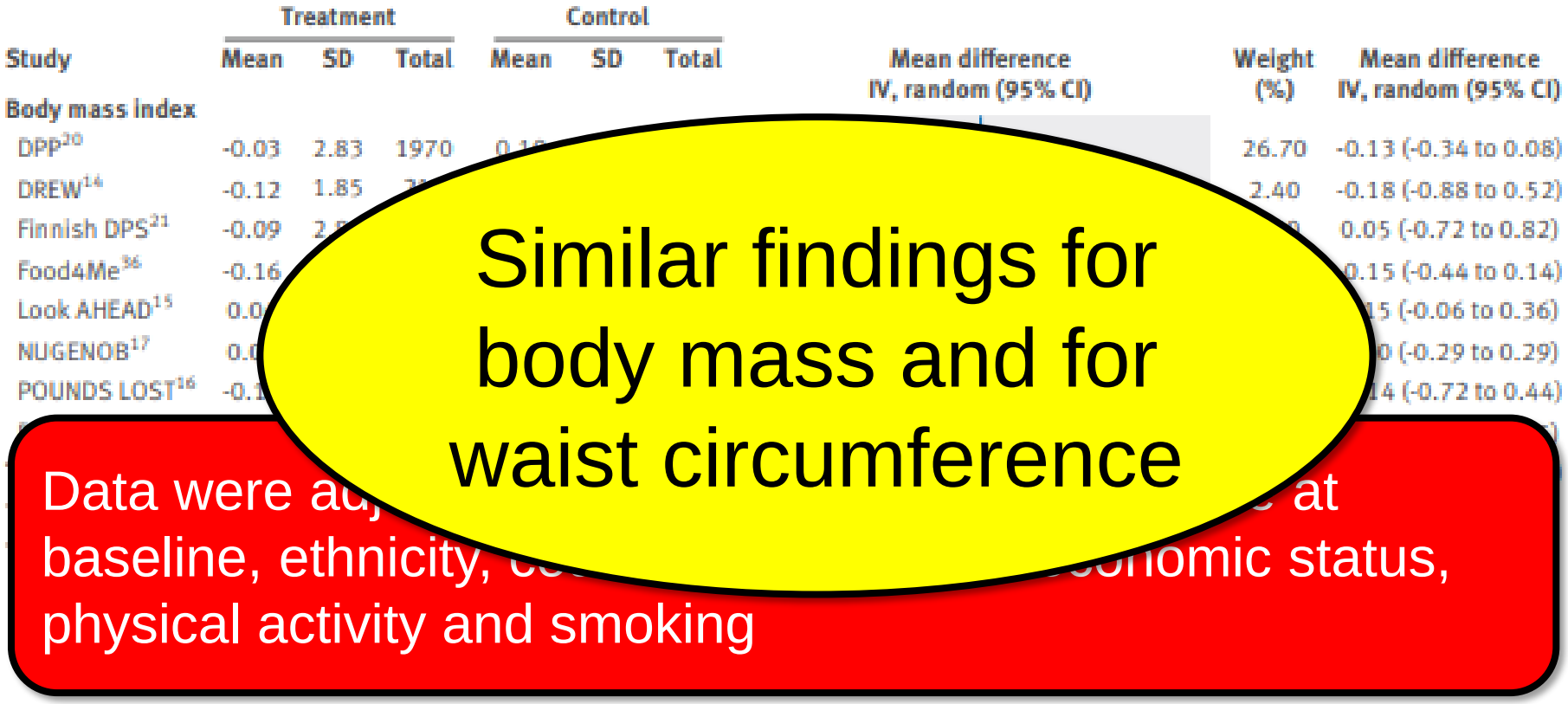
thebmj

Study selection



Livingstone KM *et al.* (2016) *BMJ* **354:** i4707

No effect of *FTO* genotype on BMI response to weight loss intervention



Livingstone KM *et al.* (2016) *BMJ* **354:** i4707

Lack of effect of *FTO* genotype on weight loss is robust

Findings unaffected by:

Intervention characteristics

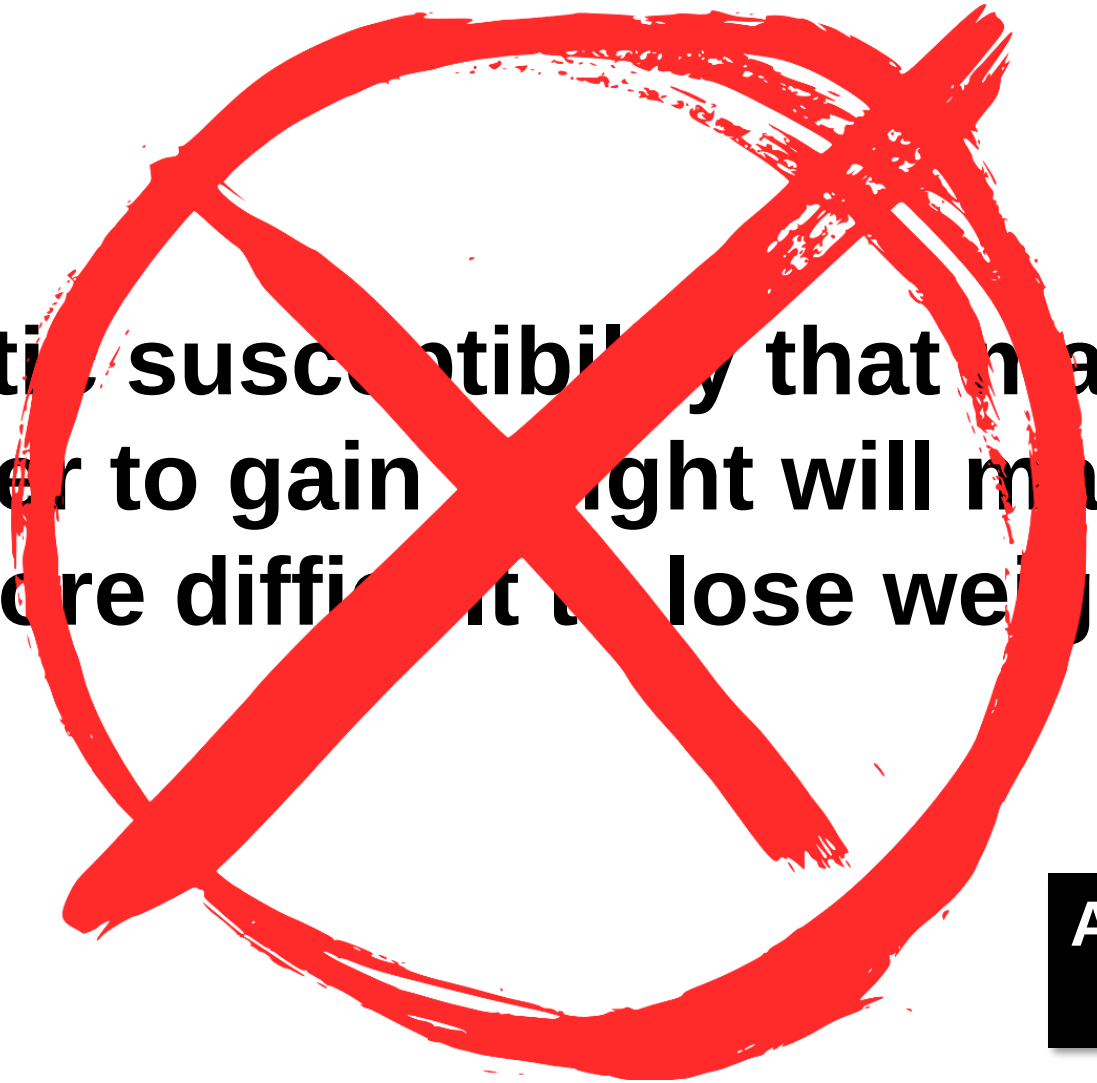
- Modality (diet or diet + exercise)
- Duration

Participant characteristics

- Age
- Sex
- Initial BMI
- Race/ ethnicity

Livingstone KM *et al.* (2016) *BMJ* **354:** i4707

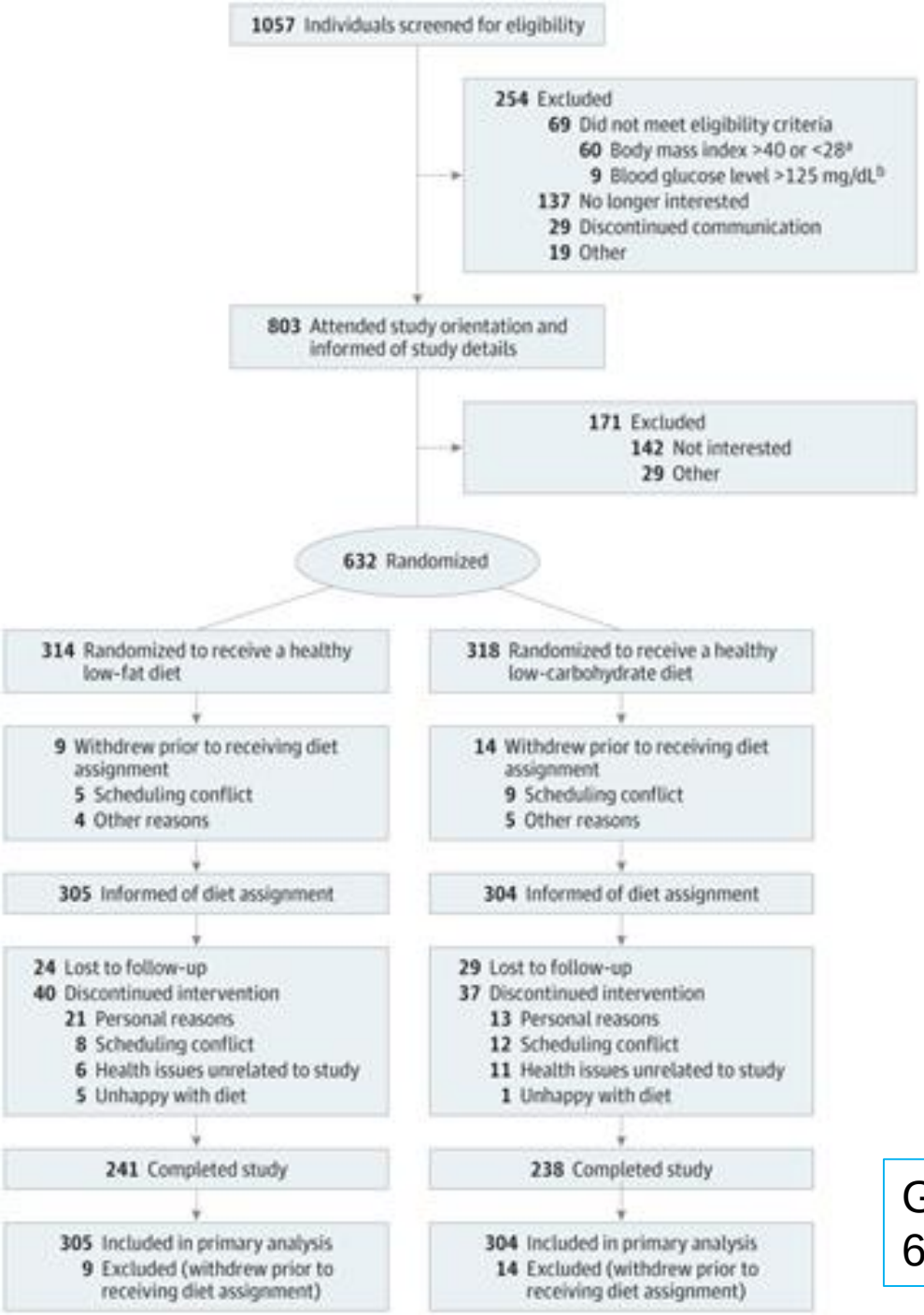
Hypothesis



Genetic susceptibility that makes it easier to gain weight will make it more difficult to lose weight

At least for *FTO* …

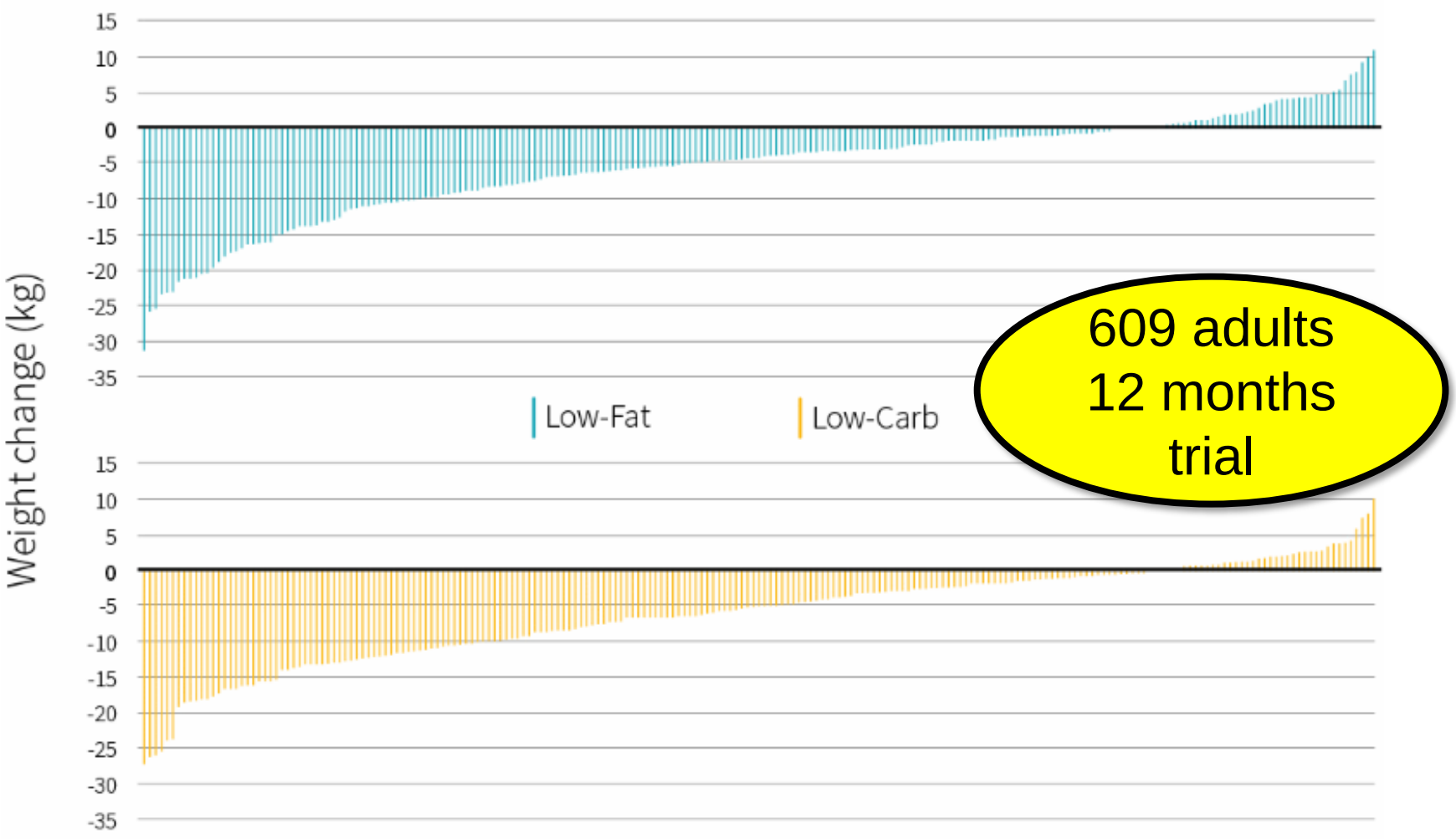
The DIETFITS study



- Compared effects of healthy “low fat” and “low carbohydrate” diets on weight loss over 12 months
- No differences between treatments

Gardner CD *et al.* (2018) *JAMA* **319,** 667-679

Individual variation in weight loss in DIETFITS study



Gardner CD *et al.* (2018) *JAMA* **319,** 667-679

Key questions

- What is the biological (genetic) basis for this inter-individual variation?

- Could knowledge of the (genetic) basis of inter-individual variation in weight loss be used to develop more effective, personalised, weight-loss interventions?

Does genotype influence response to weight loss intervention in DIETFITS study?

Genotypes investigated:

- *PPARG* (rs1801282) – encodes transcription factor for which fatty acids are ligands
- *ADRB2* (rs1042714) – encodes beta-2 adrenergic receptor
- *FABP2* (rs1799883) – encodes fatty acid binding protein

Gardner CD *et al.* (2018) *JAMA* **319,** 667-679

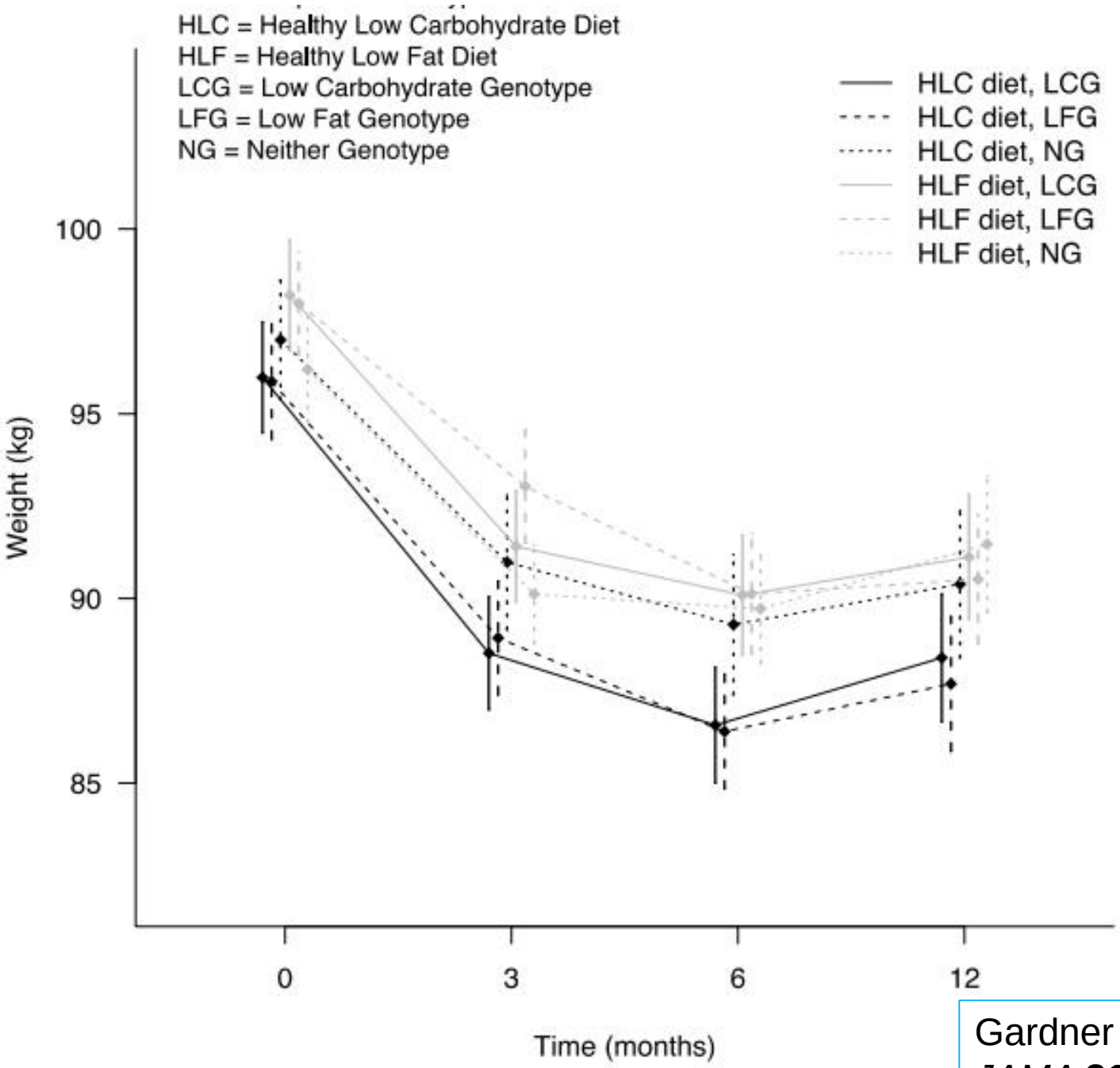
Genotype groups

More sensitive to “Low Fat” diet

More sensitive to “Low Carb” diet

Not sensitive

	Pattern	FABP2 Genotype rs 1799883 G>A[1] (Ala54Thr[2])	PPARG Genotype rs 1801282 C>G (Pro12Ala)	ADRB2 Genotype rs 1042714 C>G (Gln27Glu)	Frequency[3]
LFG	1	G**A**	**CC**	CC	0.140
LFG	2	G**A**	**CC**	CG	0.137
LFG	3	G**A**	**CC**	GG	0.040
LFG	4	**A**A	**CC**	CC	0.037
LFG	5	**A**A	**CC**	CG	0.027
LCG	6	GA	C**G**	C**G**	0.060
LCG	7	GG	C**G**	C**G**	0.050
LCG	8	GG	C**G**	G**G**	0.013
LCG	9	AA	C**G**	C**G**	0.013
LCG	10	GA	C**G**	G**G**	0.010
LCG	11	GG	CC	C**G**	0.190
LCG	12	GG	C**G**	CC	0.043
LCG	13	GA	C**G**	CC	0.027
LCG	14	GG	CC	G**G**	0.027
NG	15	GG	CC	CC	0.167

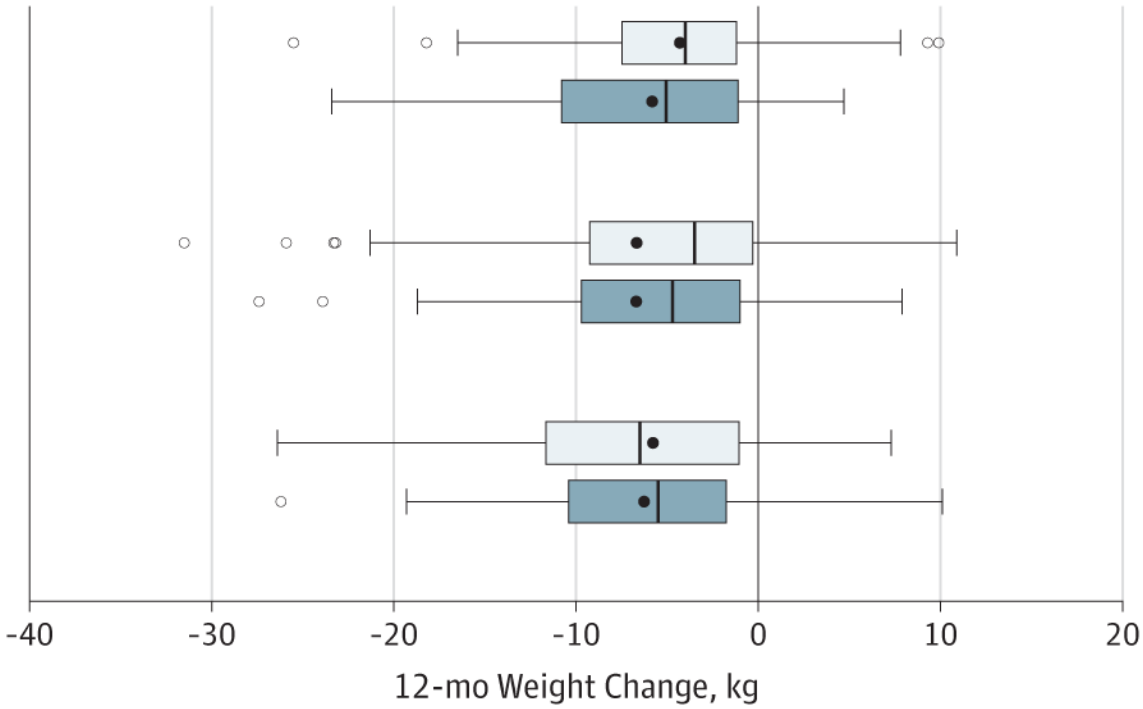


Similar weight trajectories for all treatment groups

Gardner CD *et al.* (2018) *JAMA* **319,** 667-679

No interactions between genotype and dietary intervention on weight loss over 12 months

	No. of Participants
Low-fat genotype	
Healthy low-fat diet	83
Healthy low-carbohydrate diet	70
Low-carbohydrate genotype	
Healthy low-fat diet	63
Healthy low-carbohydrate diet	81
Neither genotype	
Healthy low-fat diet	79
Healthy low-carbohydrate diet	60



Gardner CD *et al.* (2018) *JAMA* **319,** 667-679

Rationale for personalised approaches to lifestyle behaviour change

Rationale: Individualising advice, products, or services will be more effective than more generic approaches.

Personalisation can

1. Biological evidence ses dependent on genotypic or phen

2. Analysis of curren es, barriers, and objectives and su terventions that motivate and enable individuals to make appropriate behavioural changes.

Ordovas JM *et al.* (2018) *BMJ* **361:** k2173

Genetic basis of behaviour change?

Genetic basis for:

- Attention
- Memory
- Reward
- Motivation…

Behavioural genetics

Rationale for personalised approaches to lifestyle behaviour change

Rationale: Individualising advice, products, or services will be more effective than more generic approaches.

Personalisation can be based on:

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Ordovas JM *et al.* (2018) *BMJ* **361:** k2173

Potential for personalised interventions to improve weight loss

Participant characteristics

Barriers & facilitators

Aspirations etc.

Personalised intervention

Self-monitoring

↑ Weight loss

Summary

- Genotype contributes to obesity risk
- Genetic variants that increase susceptibility to obesity are NOT impediments to weight loss
- Lack of knowledge of genetic determinants of behaviour change
- Personalisation of interventions may improve behaviour change

SEVENTH FRAMEWORK PROGRAMME
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Human Nutrition Research Centre

- Understanding Molecular Nutrition
- Tackling Childhood Obesity
- Innovating for Global Nutritional Health

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Human Nutrition Research Centre

Investigating worldwide nutritional issues linked with:

- Obesity
- Ageing

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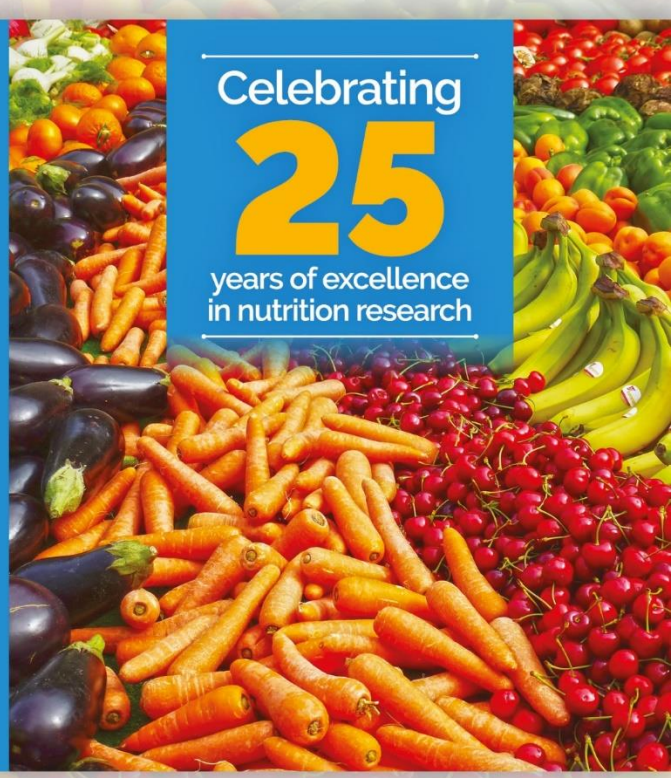

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