The gene-environment interaction in Obesity: EGAT 3/1

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Baseline characteristics

	Men (n=1896)	Women (n=682)	All (n=2578)
Age, yr	41.5 (7.2)	40.6 (6.6)	41.3 (7)
SBP, mmHg	122 (13.8)	112.8 (14.8)	119.4 (14.6)
DBP, mmHg	81.9 (16.7)	76.3 (10.6)	80.3 (15.4)
Glucose, mg/dL	95.5 (26.7)	89 (20.5)	93.8 (25.4)
TG, mg/dL	143.4 (96.3)	90 (53.8)	129.3 (90.2)
HDL-c, mg/dL	48.8 (10.8)	59.5 (12.7)	51.7 (12.3)
LDL-c, mg/dL	151.4 (37.5)	139.8 (34)	148.3 (36.9)

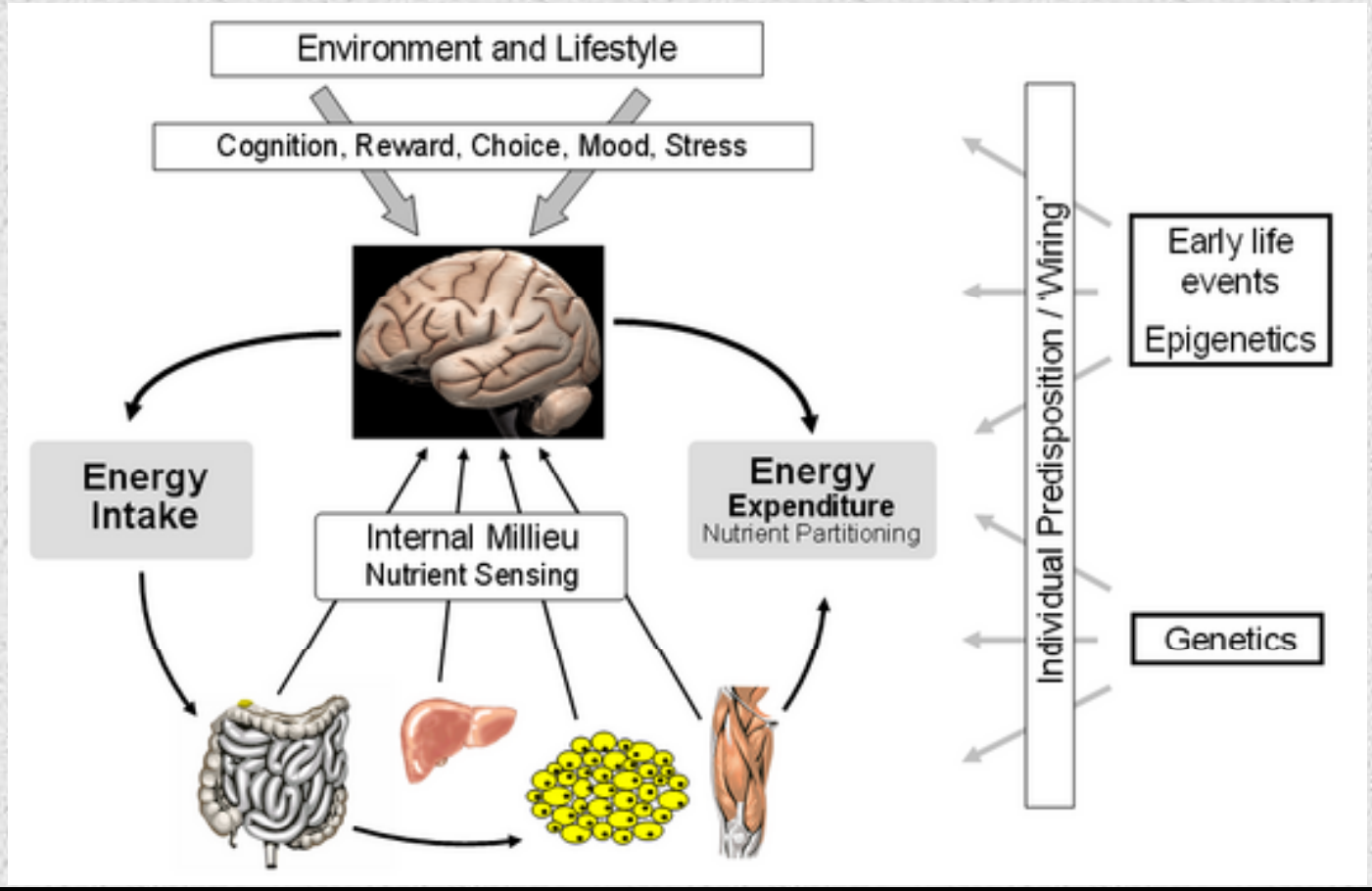
Baseline characteristics

	Men (n=1680)	Women (n=635)	All (n=2315)
BMI, kg/m2	24.6 (3.5)	22.4 (3.9)	24 (3.7)
Waist, cm	89.2 (9.2)	78.9 (9.7)	86.3 (10.4)
Hip, cm	98.7 (6.5)	95.7 (7)	97.8 (6.8)
PBF	24.6 (6.1)	33 (6.9)	26.9 (7.3)
SMM	29.4 (3.7)	19.7 (2.6)	26.7 (5.6)
Visceral fat area	101.2 (34.2)	78.5 (24)	95 (33.3)

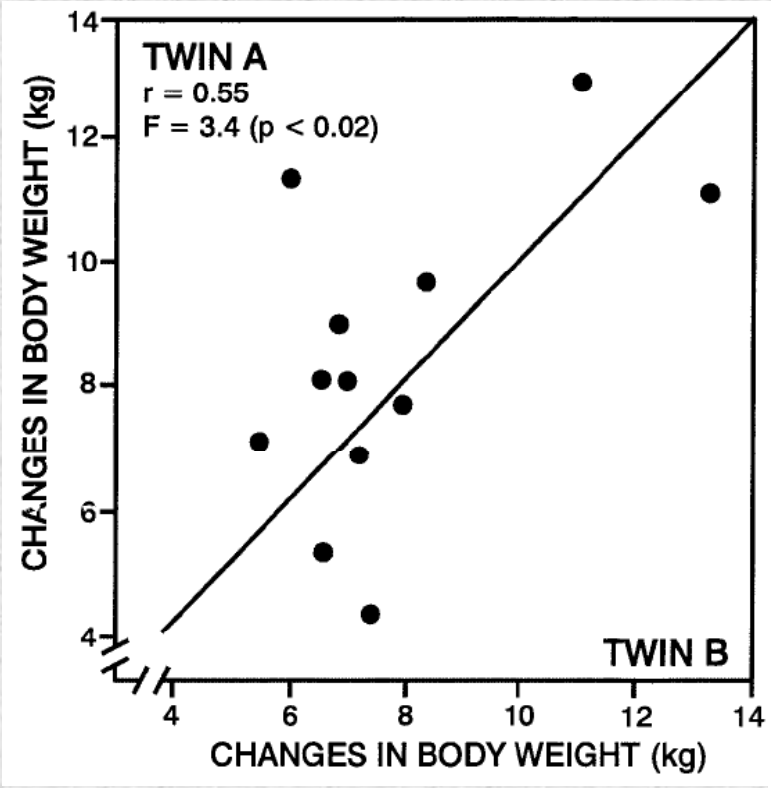
Baseline characteristics

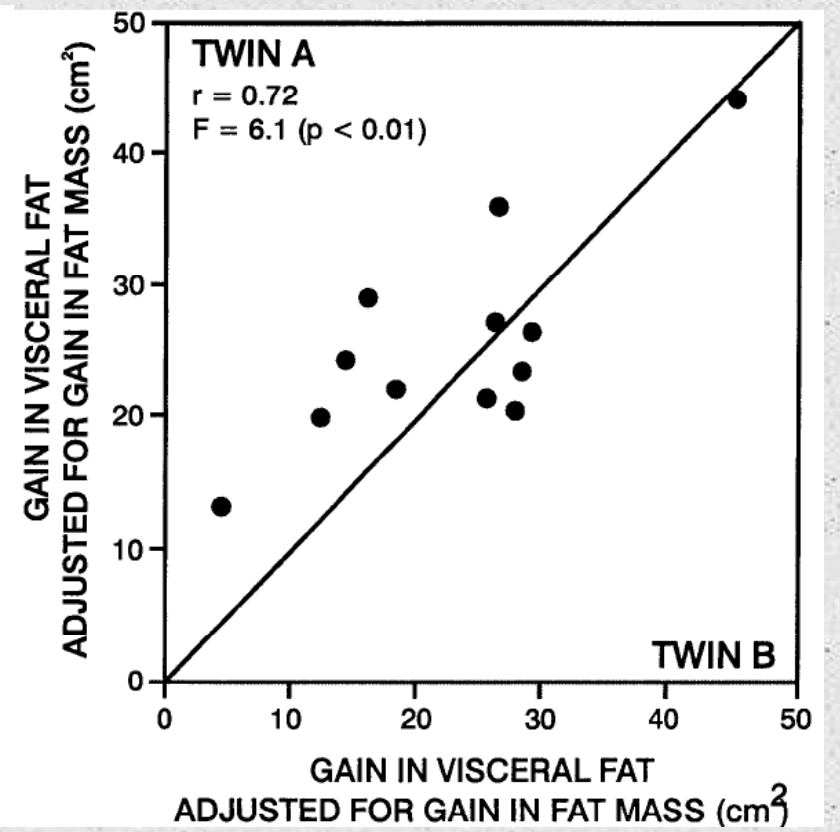
	Men	Women	All
Smoker, n (%)	267 (18.8)	7 (1.2)	274 (13.8)
Drinker, n (%)	1043 (73.6)	177 (31.6)	1220 (61.7)
Overweight, n (%)	1206 (65.4)	237 (35.2)	1443 (57.3)
Obesity, n (%)	727 (39.4)	132 (19.6)	859 (34.1)
Diabetes, n (%)	120 (6.3)	19 (2.8)	139 (5.4)
Hypertension, n (%)	405 (28.7)	88 (15.7)	493 (22.3)
MetS_NCEP, n (%)	362 (25.7)	77 (13.7)	439 (22.3)

Body weight regulation



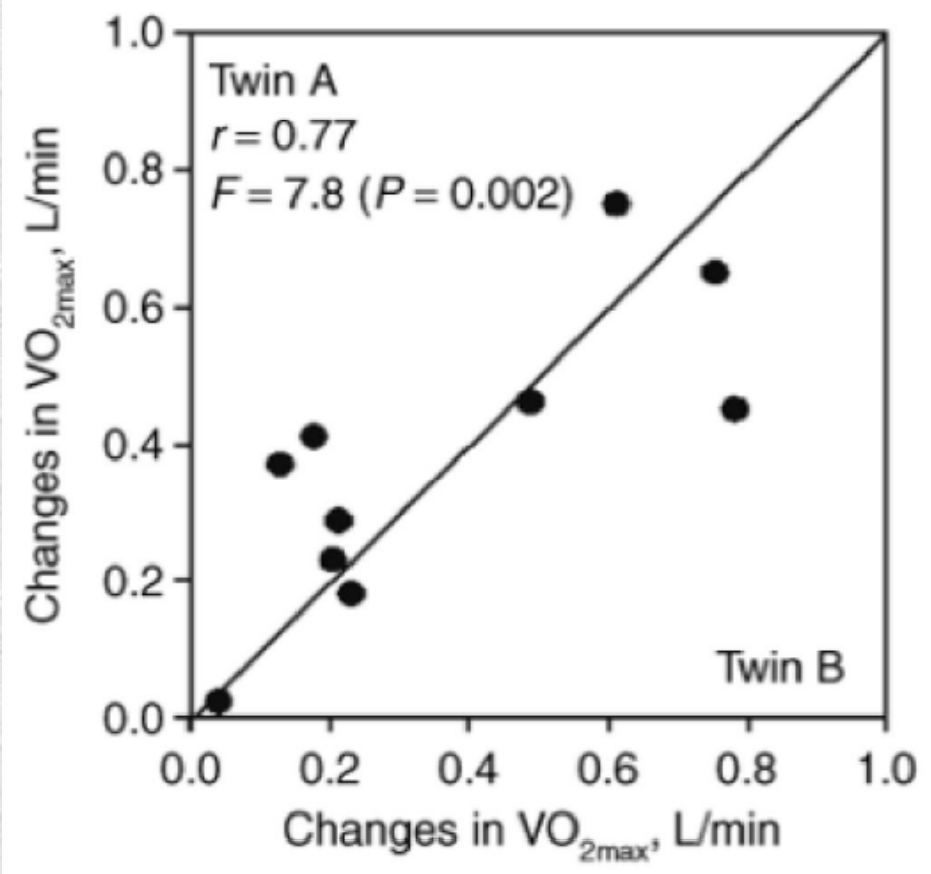
Changes in a 100-d over-feeding in 12 pairs of identical twins.





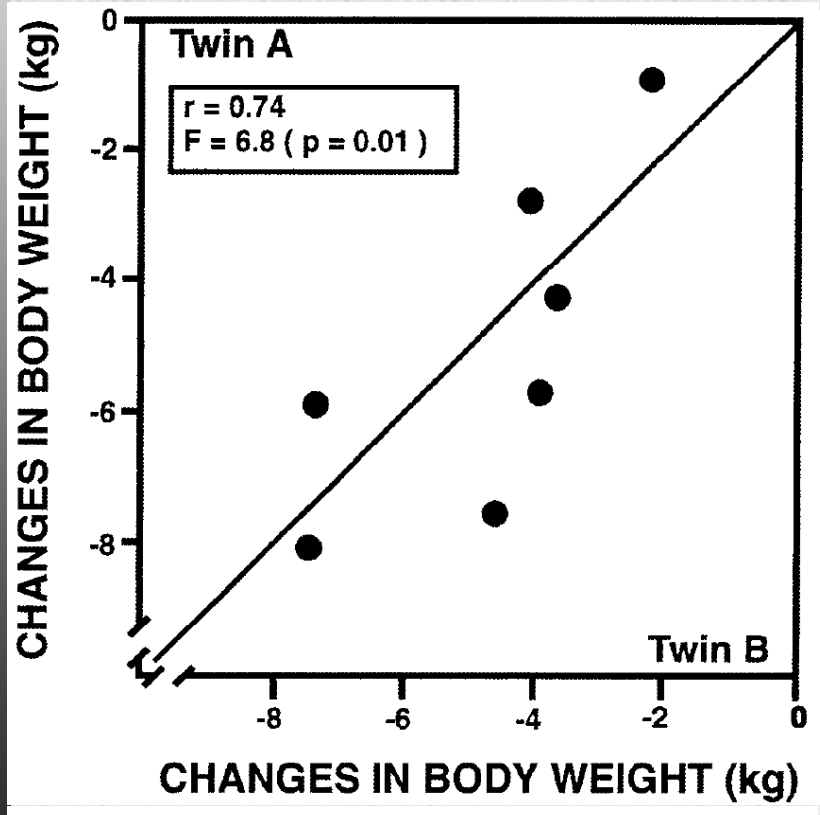
Bouchard C. N Engl J Med 1990; **322**(21): 1477-82.

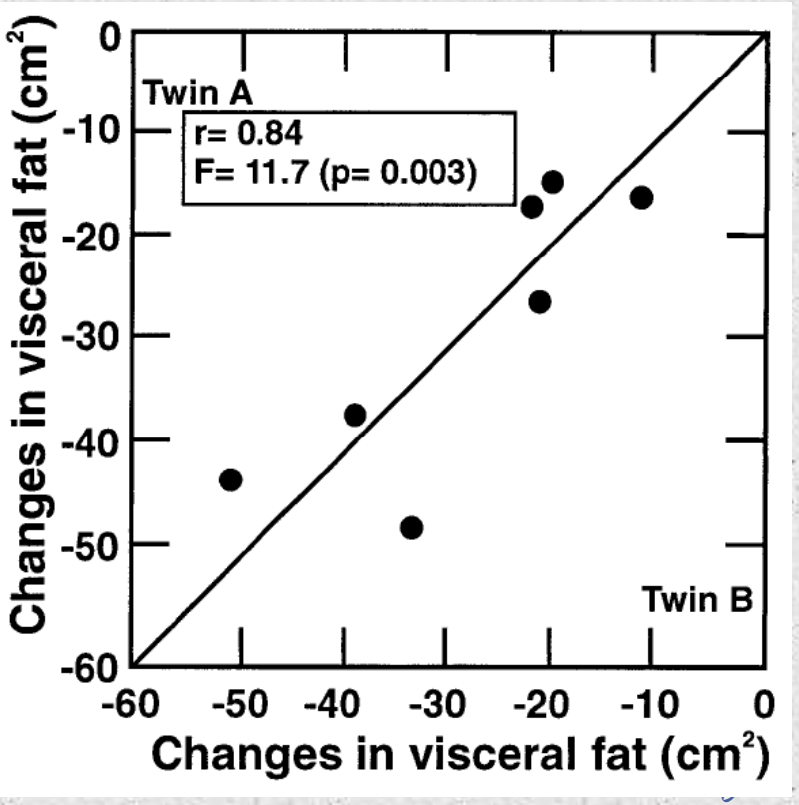
Genetics of aerobic and anaerobic performances



Bouchard C, Dionne FT, Simoneau JA, Boulay MR. Genetics of aerobic and anaerobic performances. Exerc Sport Sci Rev 1992;20:27–58.

Changes in 3-mo.negative energy balance protocol in 7 pairs of identical twins





Bouchard C, Tremblay A, Despres JP, et al. The response to exercise with constant energy intake in identical twins. Obes Res 1994;2:400–410.

Candidates for obesity gene

Variation in *FTO* contributes to childhood obesity and severe adult obesity

nature genetics

2900 affected individuals and 5100 control

Christian Dina[1], David Meyre[1], Sophie Gallina[1],

Sciencexpress Report

A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity

Timothy M. Frayling,[1,2*] Nicholas J. Timpson,[3,4*] Michael N. Weedon,[1,2*] Eleftheria Zeggini,[3,5*] Rachel M. Freathy,[1,2] Cecilia M. Lindgren,[3,5] John R. B. Perry,[1,2] Katherine S. Elliott,[3] Hana Lango,[1,2] Nigel W. Rayner,[3,5] Beverley Shields,[2] Lorna W. Harries,[2] Jeffrey C. Barrett,[3] Sian Ellard,[2,6] Christopher J. Groves,[5] Bridget Knight,[2] Ann-Marie Patch,[2,6] Andrew R. Ness,[7] Shah Ebrahim,[8] Debbie A. Lawlor,[9] Susan M. Ring,[9] Yoav Ben-Shlomo,[9] Marjo-Riitta Jarvelin,[10,11] Ulla Sovio,[10,11] Amanda J. Bennett,[5] David Melzer,[1,12] Luigi Ferrucci,[13] Ruth J. F. Loos,[14] Inês Barroso,[15]

13 cohorts with 38,759 participants

homozygous for the risk allele weighed about 3 kilograms more and had a 1.67-fold increased risk of obesity

10

nature genetics

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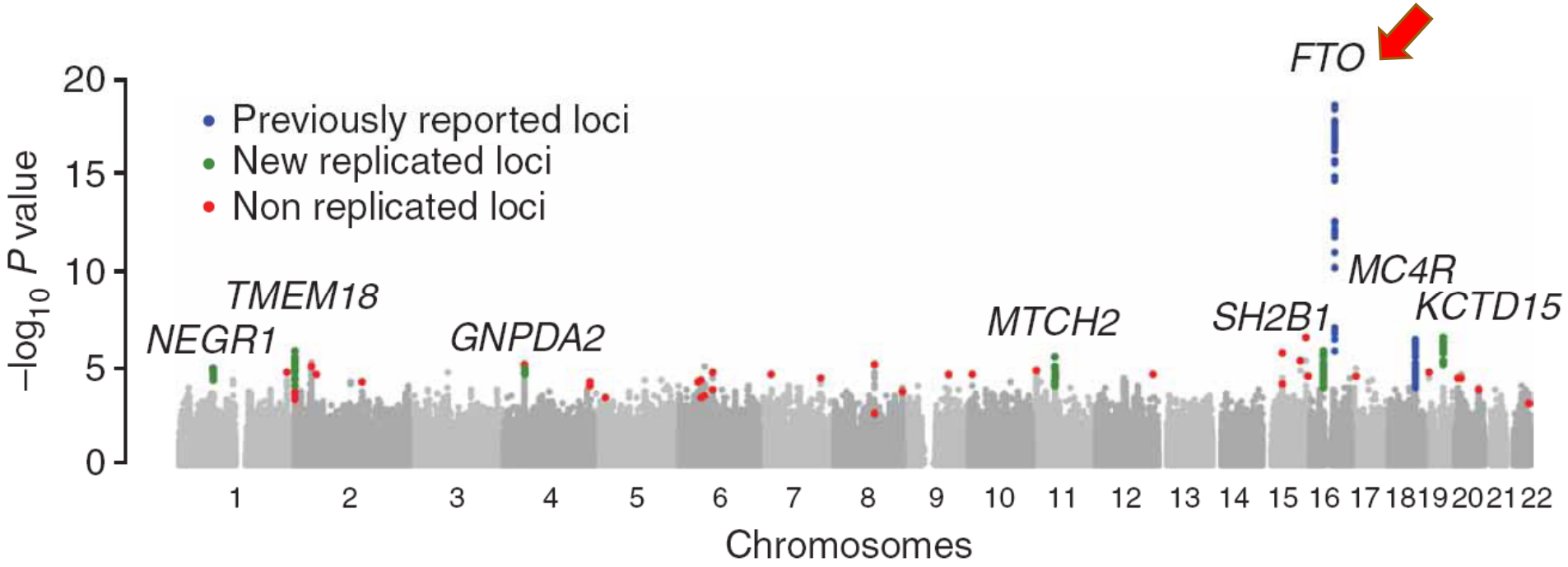
Six new loci associated with body mass index highlight a neuronal influence on body weight regulation

Common variants at only two loci, *FTO* and *MC4R*, have been reproducibly associated with body mass index (BMI) in humans. To identify additional loci, we conducted meta-analysis of 15 genome-wide association studies for BMI ($n > 32{,}000$) and followed up top signals in 14 additional cohorts ($n > 59{,}000$). We strongly confirm *FTO* and *MC4R* and identify six additional loci ($P < 5 \times 10^{-8}$): *TMEM18*, *KCTD15*, *GNPDA2*, *SH2B1*, *MTCH2* and *NEGR1* (where a 45-kb deletion polymorphism is a candidate causal variant). Several of the likely causal genes are highly expressed or known to act in the central nervous system (CNS), emphasizing, as in rare monogenic forms of obesity, the role of the CNS in predisposition to obesity.

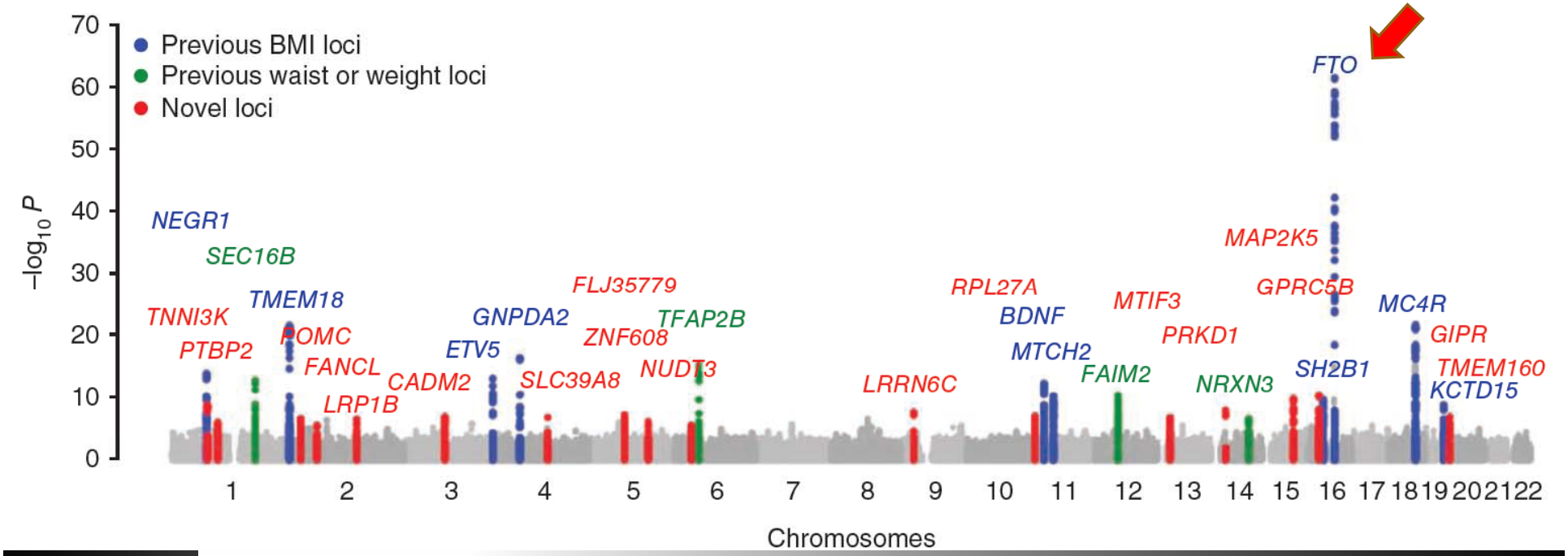


Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index

nature genetics

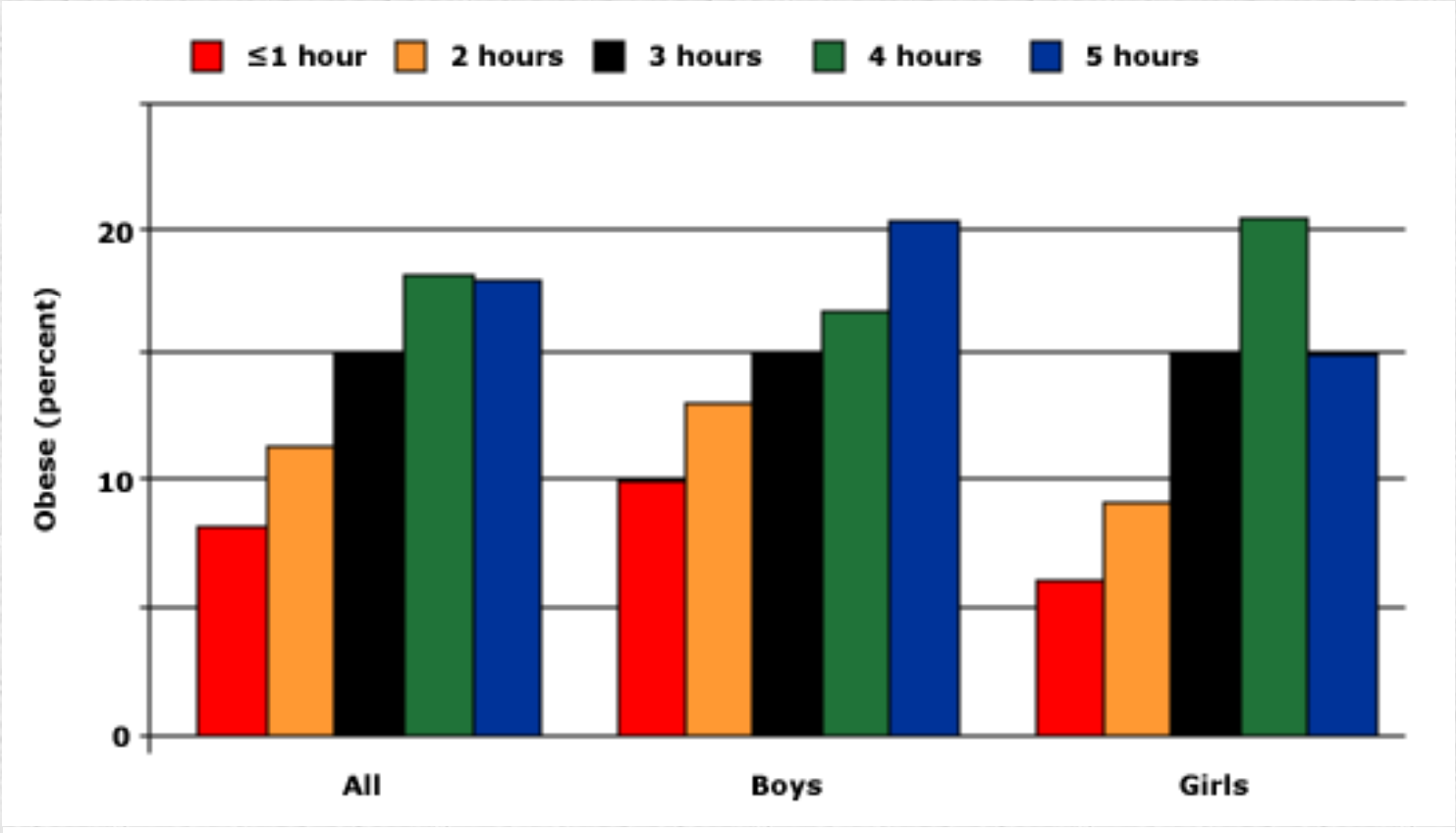
Obesity is globally prevalent and highly heritable, but its underlying genetic factors remain largely elusive. To identify genetic loci for obesity susceptibility, we examined associations between body mass index and ~2.8 million SNPs in up to 123,865 individuals with targeted follow up of 42 SNPs in up to 125,931 additional individuals. We confirmed 14 known obesity susceptibility loci and identified 18 new loci associated with body mass index ($P < 5 \times 10^{-8}$), one of which includes a copy number variant near *GPRC5B*. Some loci (at *MC4R*, *POMC*, *SH2B1* and *BDNF*) map near key hypothalamic regulators of energy balance, and one of these loci is near *GIPR*, an incretin receptor. Furthermore, genes in other newly associated loci may provide new insights into human body weight regulation.

Received 13 May; accepted 15 September; published online 10 October 2010; doi:10.1038/ng.686



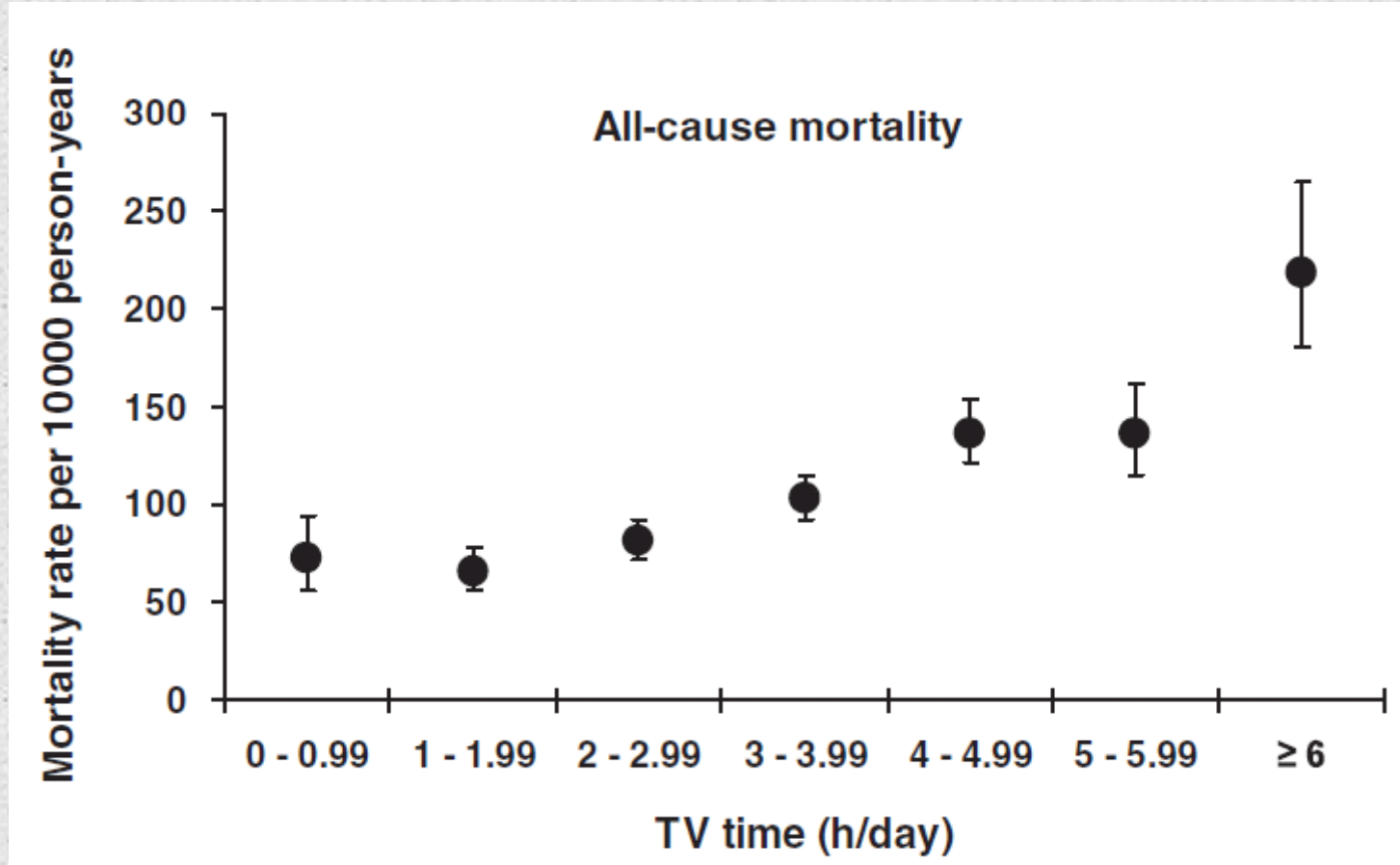
Obesogenic environment

Obesity, Television watching in US children aged 8-16 yrs: NHNES III, 1988 to 1994.



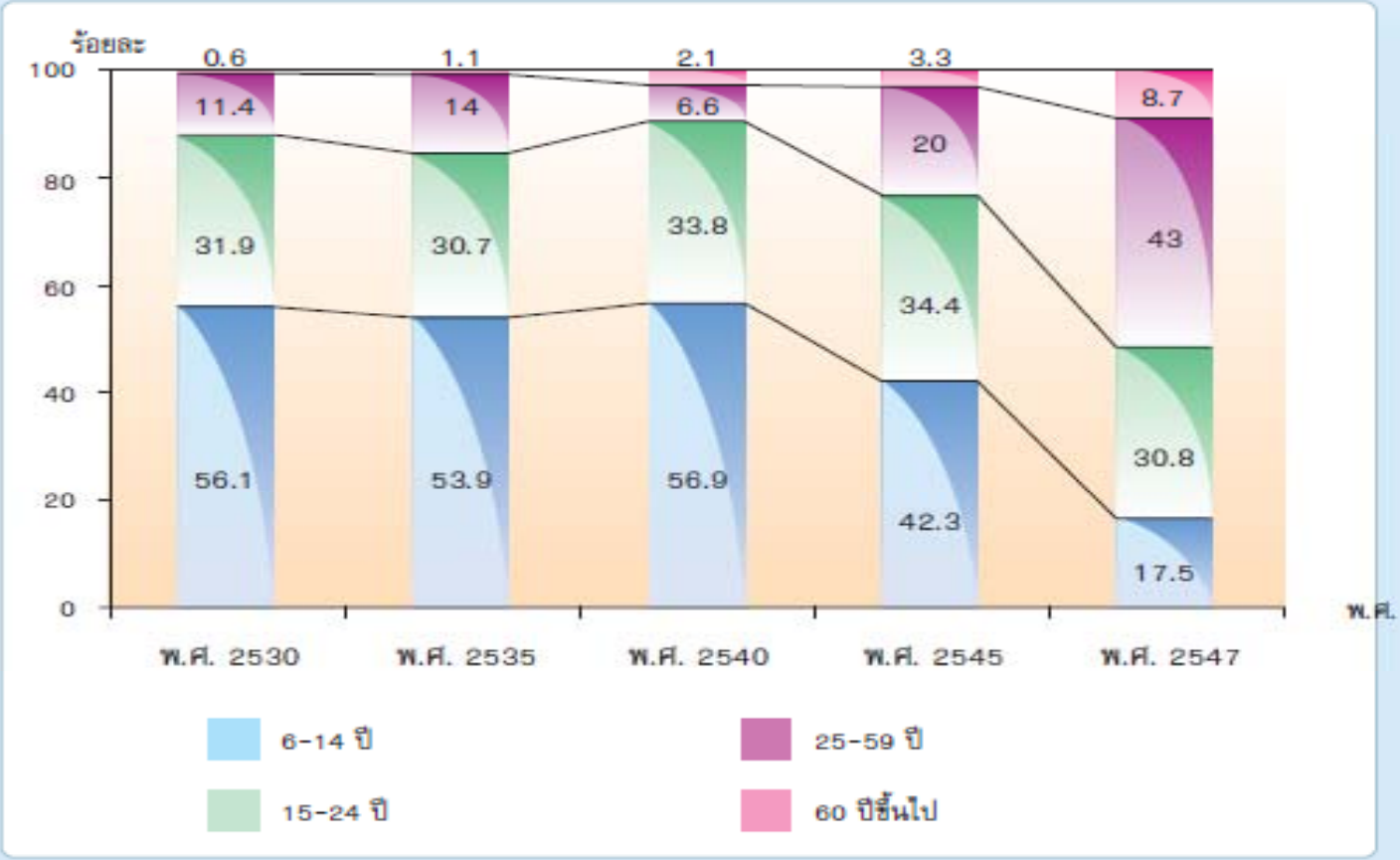
Crespo, CJ. Arch Pediatr Adolesc Med 2001; 155:360.

Television viewing time independently predicts all-cause and cardiovascular mortality: the EPIC Norfolk Study.



Wijndaele, K. Int J Epidemiol 2010 Jun 23. [Epub ahead of print]

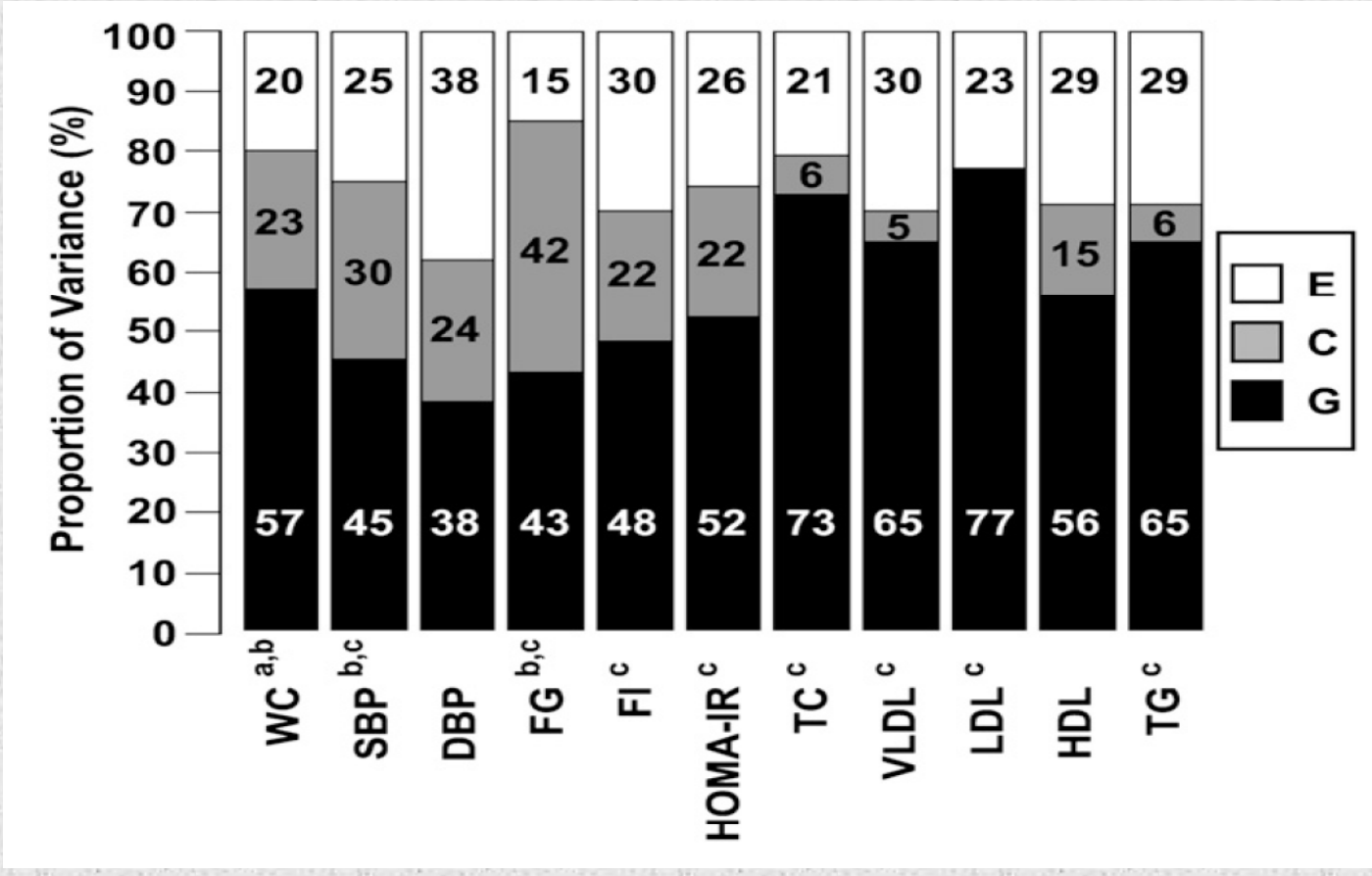
ภาพที่ 4.38 อัตราร้อยละของคนไทยที่ออกกำลังกายเป็นประจำ จำแนกตามอายุ พ.ศ. 2530-พ.ศ. 2547



ที่มา :

1. รายงานการสำรวจพฤติกรรมการเล่นกีฬาและการดูกีฬาของประชากรอายุ 6 ปีขึ้นไป พ.ศ. 2530, พ.ศ. 2535, พ.ศ. 2540 และ พ.ศ. 2545 สำนักงานสถิติแห่งชาติ
2. รายงานการสำรวจพฤติกรรมการออกกำลังกายของประชากรอายุ 11 ปีขึ้นไป พ.ศ. 2547, สำนักงานสถิติแห่งชาติ

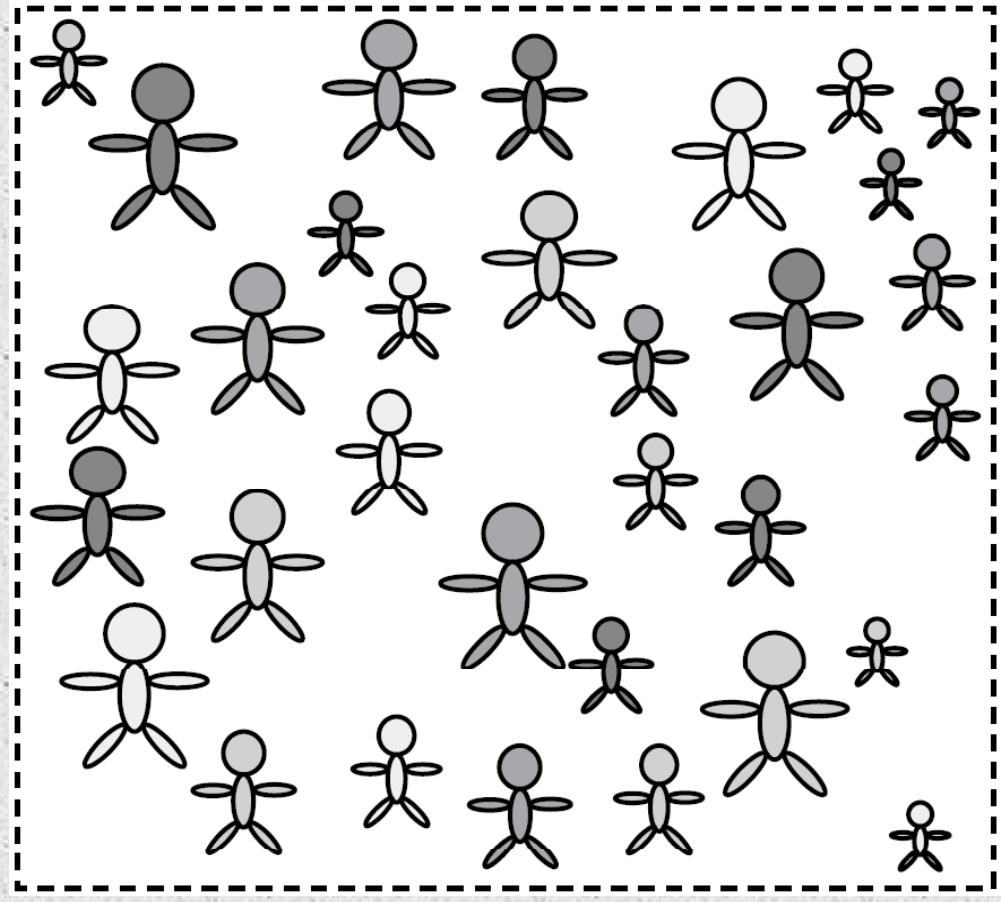
Genetic and environmental influences on CVD risk factors



Elder SJ. J Lipid Res. 2009;50(9):1917-1926.

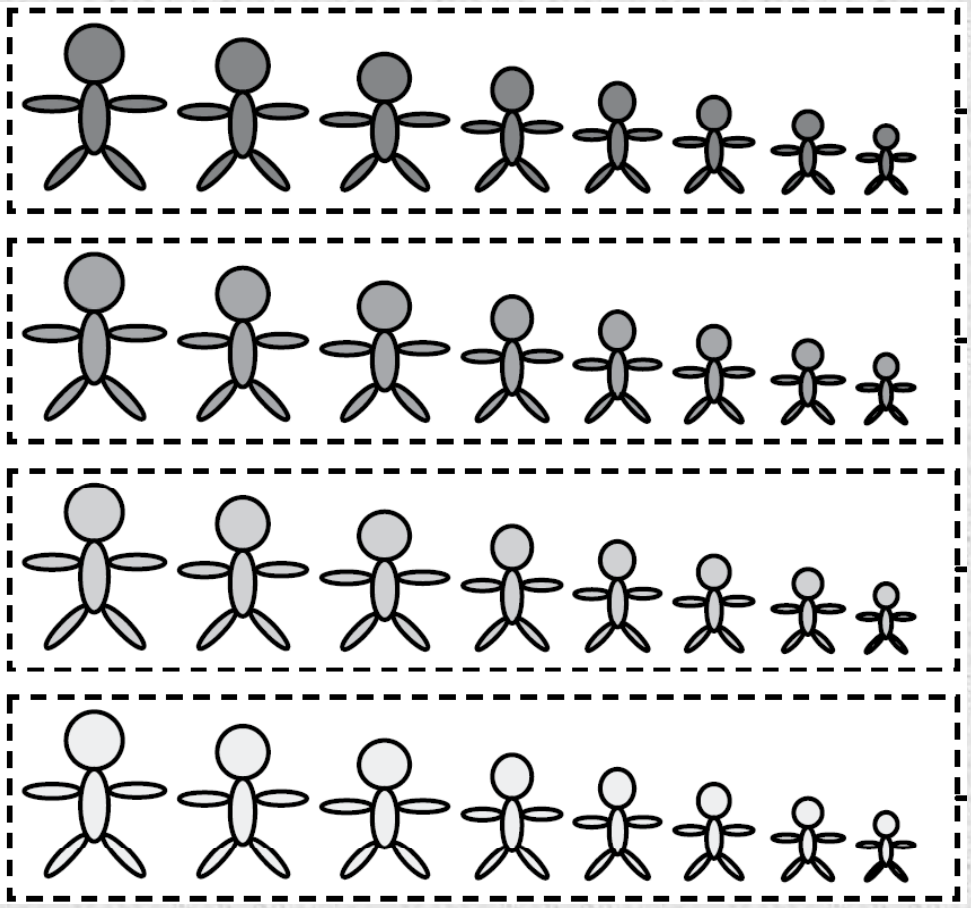
Mixed study population

Low likelihood of detecting GxE

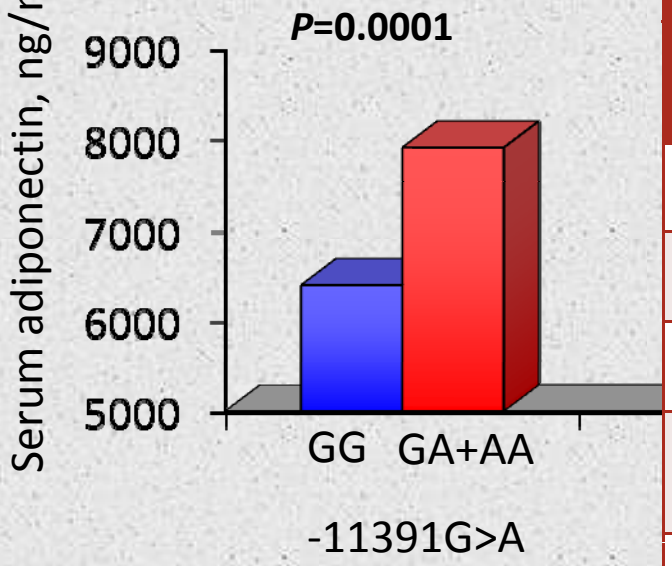


Stratified study population

increased likelihood of detecting GxE

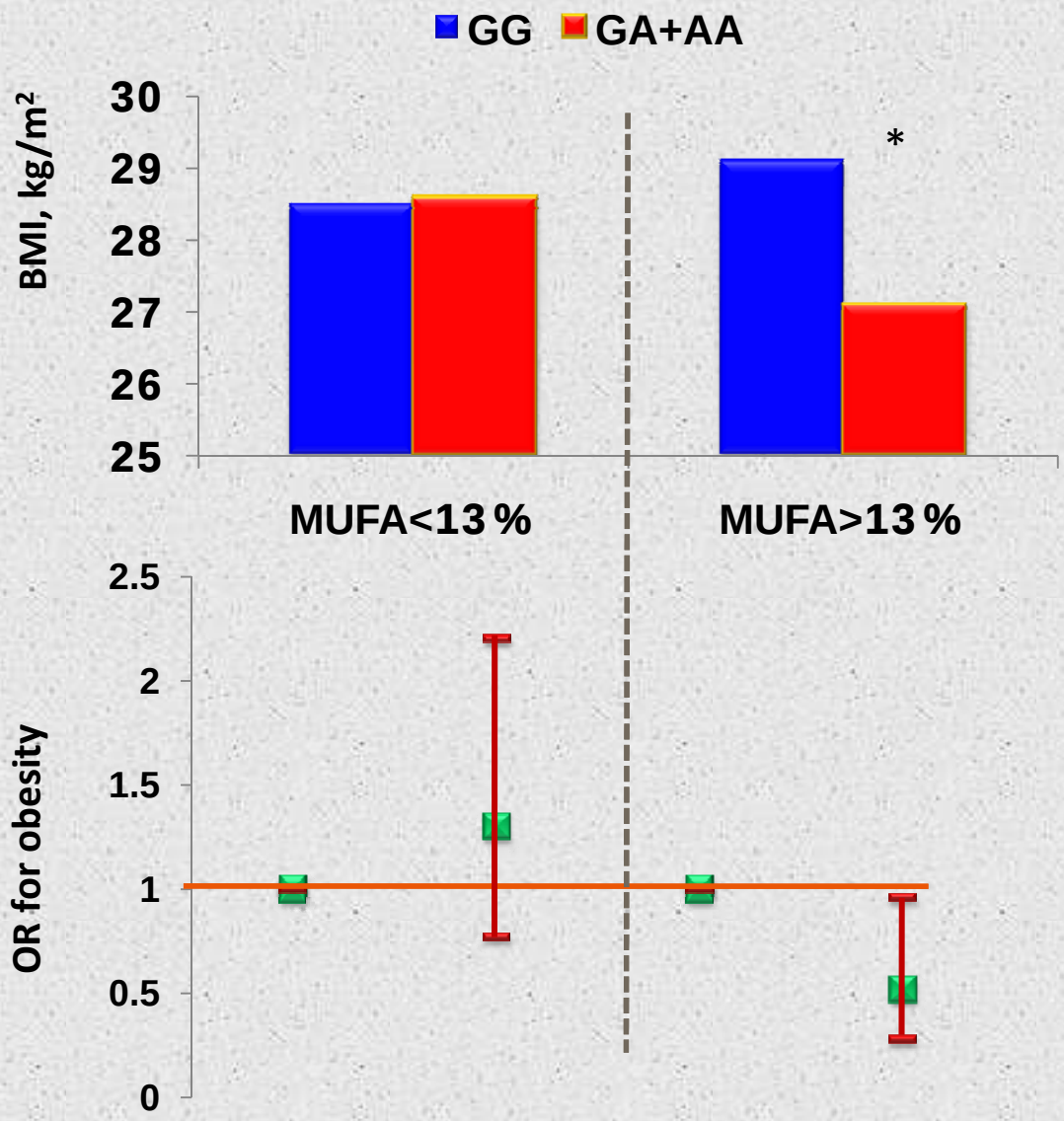


ADIPOQ 111391G>A, adiponectin and adiposity



	ADIPOQ -11391G>A		
	GG (n=930)	GA+AA (n=143)	P
Waist, cm	101 ± 1.1	97 ± 1.3	0.002
Hip, cm	109 ± 0.8	107 ± 1.0	0.004
BMI, kg/m^2	29.6 ± 0.4	28.6 ± 0.5	0.019
Insulin, µU/mL	13.5 (12.6-14.3)	12.0 (11.0-13.2)	0.013
HOMA-R	3.7 (3.5-4.0)	3.3 (3.0-3.6)	0.009

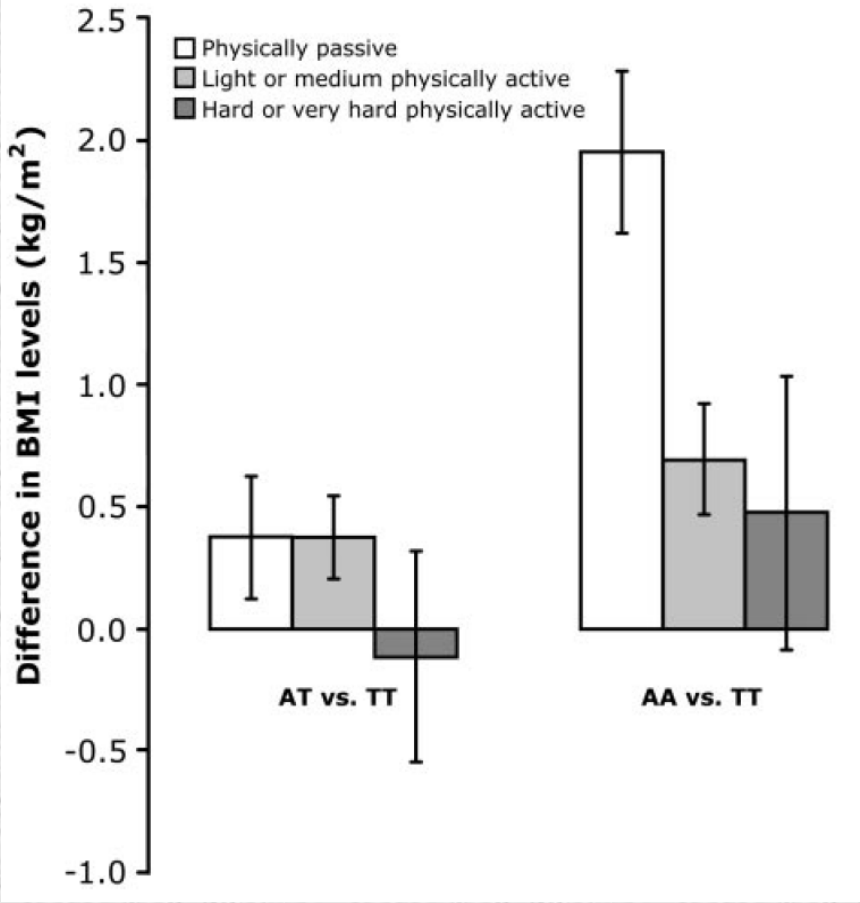
Warodomwichit D. Obesity 2009;17:510-7.



Warodomwichit D. Obesity 2009;17:510-7.

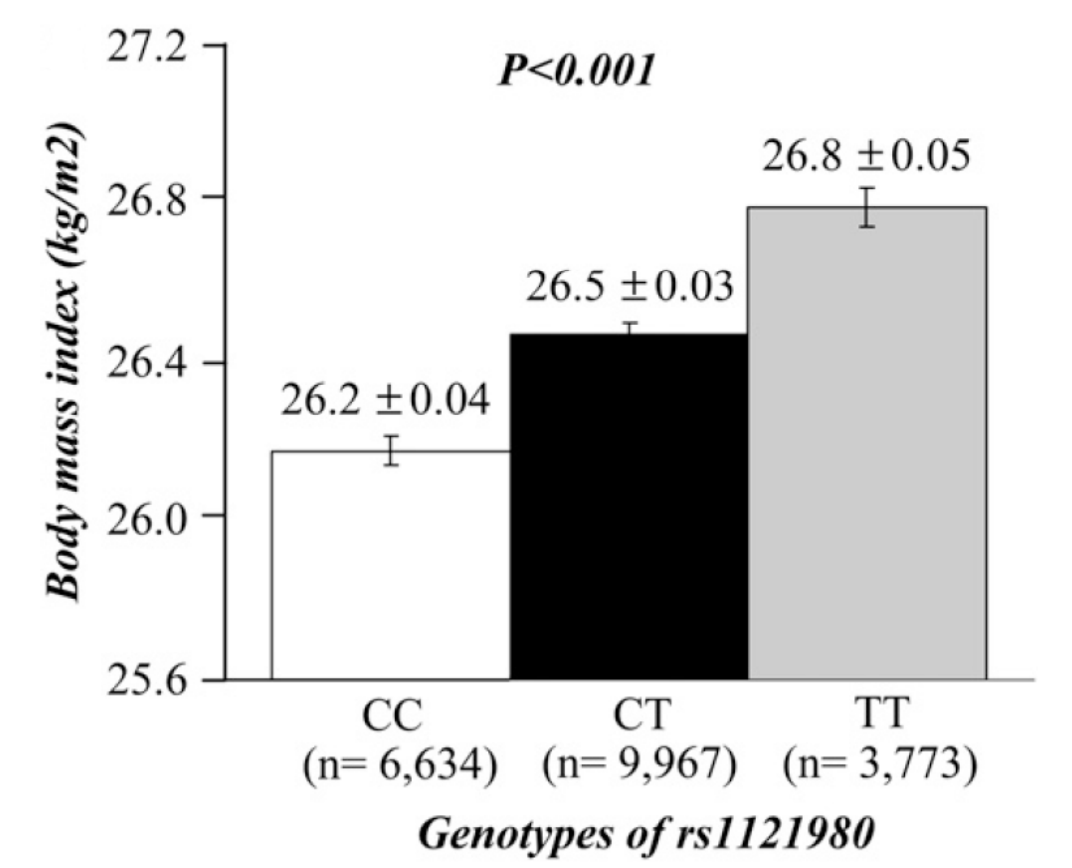
Low Physical Activity Accentuates the Effect of the *FTO* rs9939609 Polymorphism on Body Fat Accumulation

Camilla H. Andreasen,[1] Kirstine L. Stender-Petersen,[1] Mette S. Mogensen,[1] Signe S. Torekov,[1] Lise Wegner,[1] Gitte Andersen,[1] Arne L. Nielsen,[1] Anders Albrechtsen,[2] Knut Borch-Johnsen,[1,3,4] Signe S. Rasmussen,[1] Jesper O. Clausen,[1] Annelli Sandbæk,[5] Torsten Lauritzen,[5] Lars Hansen,[6] Torben Jørgensen,[3] Oluf Pedersen,[1,4] and Torben Hansen[1]



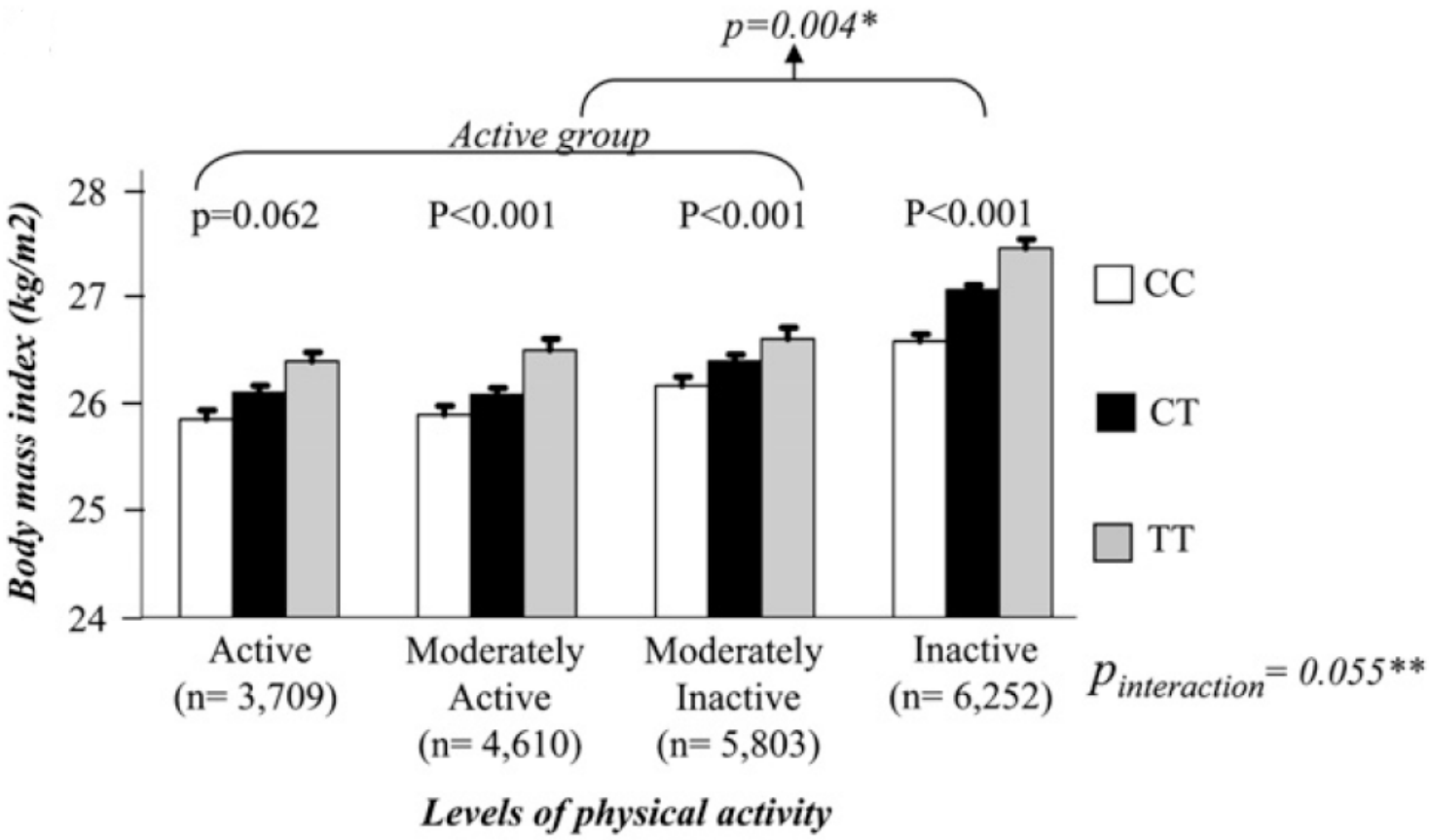
Andreasen CH.*D iabetes. 2008;57(1):95-101.*

FTO genotype, obesity and physical activity



Vimaleswaren KS. AJCN 2009;90:425-8

FTO genotype, obesity and physical activity



Vimaleswaren KS. AJCN 2009;90:425-8

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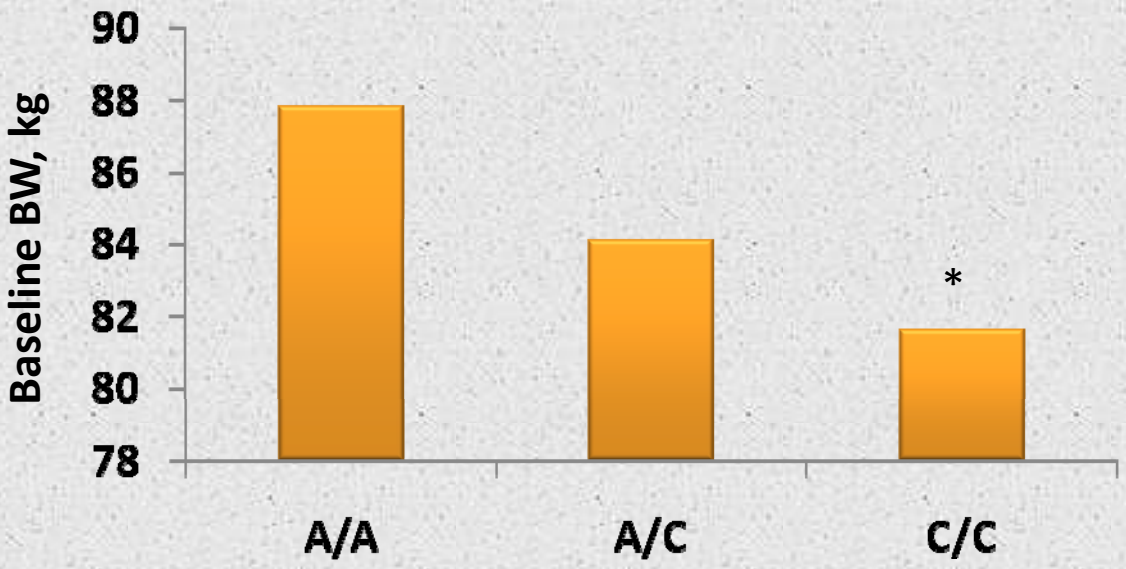
BRIEF REPORTS
GENETIC ANALYSIS

FTO Genotype and the Weight Loss Benefits of Moderate Intensity Exercise

Jonathan A. Mitchell[1], Timothy S. Church[2], Tuomo Rankinen[3], Conrad P. Earnest[2], Xuemei Sui[1] and Steven N. Blair[1,4]



Obesity (2010) **18,** 641–643. doi:10.1038/oby.2009.311

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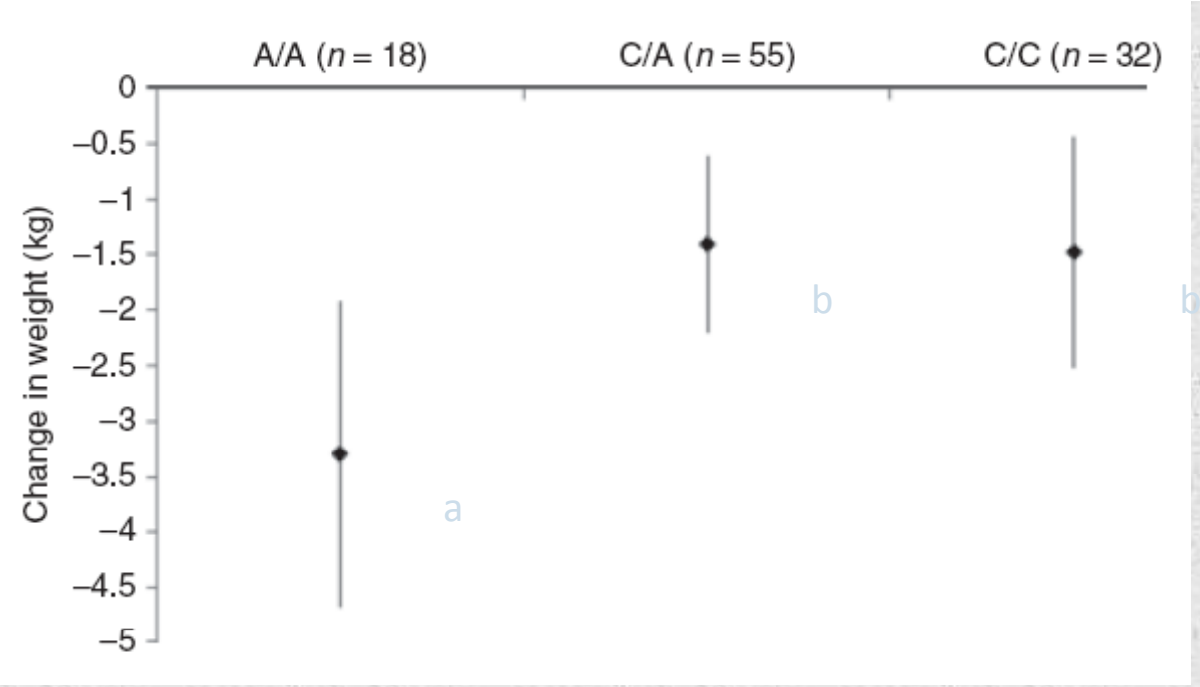

Obesity (2010) **18,** 641–643. doi:10.1038/oby.2009.311

Table 1 **Selected observational studies of gene-lifestyle interactions on obesity.**

Reference	Subjects*	Gene (variants)	Lifestyle factors	Major findings
Meirhaeghe et al. (1999)[68]	1152	ADRB2 (Gln27Glu)	Physical activity	Men carrying Gln27Gln genotype had increased risk of adiposity only with no physical activity. No interaction was observed in women
Luan et al. (2001)[64]	592	*PPARG* (Pro12Ala)	Total fat, P:S ratio	BMI was higher among Ala allele carriers only when the P:S ratio was low, and the opposite was seen when P:S ratio was high (p-interaction = 0.0039)
Corbalan et al. (2002)[69]	252 F	ADRB2 (Gln27Glu)	Physical activity	In women who were more active, Glu-allele carriers had higher BMI than non-carriers.
Marti et al. (2002)[67]	313	*PPARG* (Pro12Ala)	CHO	Pro12Ala was associated with increased risk of obesity only in those with higher CHO intake (p-interaction = 0.02)
Martinez et al. (2003)[66]	313	*ADRB2* (Gln27Glu)	CHO	Women with high CHO intake had greater risk of obesity than those with low CHO intake only in Gln27Glu heterozygotes (p-interaction = 0.058)
Nieters et al. (2002)[62]	306	11 genes (15 SNPs)	n-6 PUFA	Substantial interaction between variants in PPARG2, TNFA, leptin (possibly APM1, HSL) and dietary n-6 FA intake in relation to obesity risk
Robitaille et al. (2003)[65]	313 M/407 F	*PPARG* (Pro12Ala)	Total fat, SFA	In women, Pro12Pro homozygotes were positively associated with total fat and SFA intake in relation to WC and BMI, but not in Ala-allele carriers
Memisoglu et al. (2003)[63]	2142 F	*PPARG* (Pro12Ala)	Total fat, fatty acids, P:S ratio	BMI was positively related to total fat only in Pro12Pro homozygotes (p-interaction = 0.0003); BMI was negatively related to MUFA only in Ala-allele carriers (p-interaction = 0.003)
Robitaille et al. (2004)[61]	632 M	*PPARA* (Leu162Val)	Total fat, SFA	Total fat and saturated fat intake were positively related to WC only in Leu162Leu homozygotes (p-interaction = 0.01 and 0.008, respectively)

Qi L, Cho YA. Gene-environment interaction and obesity. *Nutr Rev. Dec 2008;66(12):684-694.*

Table 1 **Selected observational studies of gene-lifestyle interactions on obesity.**

Reference	Subjects*	Gene (variants)	Lifestyle factors	Major findings
Alonso et al. (2005)[72]	300	UCP3 (-55C > T)	Physical activity	Carrying T-allele was associated with lower risk of obesity only in those with higher physical activity
Berentzen et al. (2005)[73]	1285	UCP2 (ID), UCP3 (-55C > T)	Physical activity	No interaction in relation to 10-year weight change
Miyaki et al. (2005)[59]	295 M	*ADRB3* (Trp64Arg)	Total energy	Arg64-allele carriers were associated with greater obesity risk than Trp64Trp homozygotes, but only in the highest energy intake quartile
Moran et al. (2005)[70]	1016	ACE (I/D)	Physical activity	Carrying D-allele was associated with increased fat thickness; this association was strongest in women with no extra exercise
Ridderstrale et al. (2006)[71]	902 M/899 F	PPARGC1A (GLy482Ser)	Physical activity	Elderly men carrying Ser-allele had increased risk of obesity
Song et al. (2007)[60]	285 M	*IL6R* (Asp358Ala)	Total energy	Energy intake was significantly associated with WC in T-allele carriers, but not in GG homozygotes (p-interaction = 0.03)
Andeasen et al. (2008)[28]	17,162	FTO (rs9939609)	Physical activity	Physically inactive AA homozygotes had an increase in BMI compared with TT homozygotes (p-interaction = 0.007)

Qi L, Cho YA. Gene-environment interaction and obesity. *Nutr Rev. Dec 2008;66(12):684-694.*

Table 2 **Selected intervention studies of gene-lifestyle interactions on weight change.**

Reference	Subjects*	Gene (Variants)	Intervention	Major findings
Yoshida et al. (1995)[75]	88 F	*ADRB3* (Trp64Arg)	LCD + exercise, 3 mo	Arg64-allele carriers lost less weight than Trp64Trp homozygotes ($P < 0.05$)
Fumeron et al. (1996)[81]	163	*UCP1* (*Bcl*I A > G [3826]), *ADRB3* (Trp64Arg)	LCD, 2.5 mo	*UCP1* G-allele carriers lost less weight ($P < 0.05$) than AA homozygotes
Sakane et al. (1997)[76]	61 F	*ADRB3* (Trp64Arg)	LCD + exercise, 3 mo	Arg64-allele carriers had smaller decreases in weight and WHR than Trp64Trp homozygotes
Kogure et al. (1998)[82]	113 F	*UCP1* (-3826 A > G), *ADRB3* (Trp64Arg)	LCD + exercise, 3 mo	*UCP1 GG* homozygotes lost less weight than A-allele carriers ($P < 0.05$); *ADRB3* Arg64-allele carriers lost less weight than Trp64Trp homozygotes; Those carrying both variants had less weight loss than those carrying either genotype alone.
Mammes et al. (1998)[84]	38 M/79 F	*LEP* (8 SNPs)	LCD, 2.5 mo	In women, the SNP -2549C allele was associated with lower BMI loss ($P = 0.05$) after intervention
Mammes et al. (2001)[85]	114 F/65 M	*LEPR* (T343C)	LCD, 2.5 mo	Women carrying C- allele lost more weight than TT homozygotes ($P = 0.006$)
Xinli et al. (2001)[83]	31 M/16 F	*ADRB3* (Trp64Arg)	Low cholesterol and SFA based on NCEPA step1 diet, 3 mo	Increases in weight and BMI were lower in children with Trp64Trp homozygotes than in the Arg64-carriers and the control group ($P < 0.05$)
Rawson et al. (2002)[77]	34 F	*ADRB3* (Trp64Arg)	AHA step2 diet (1200 kcal/d), 13.5 ± 2.6 mo	No interaction in relation to body composition and total daily energy expenditure
Shiwaku et al. (2003)[74]	76 F	*ADRB3* (Trp64Arg)	LCD + exercise, 3 mo	Arg64-allele carriers lost less weight than Trp64Trp homozygotes ($P = 0.035$)

Qi L, Cho YA. Gene-environment interaction and obesity. *Nutr Rev. Dec 2008;66(12):684-694.*

Table 2 **Selected intervention studies of gene-lifestyle interactions on weight change.**

Reference	Subjects*	Gene (Variants)	Intervention	Major findings
Aberle et al. (2005)[86]	606 M	*APOA5* (-1131T > C)	Low fat, 3 mo	C-allele carriers lost more weight than TT homozygotes ($P = 0.002$)
Corella et al. (2005)[87]	9 M/39 F	*PLIN* (11482G > A)	LCD, 1 y	GG homozygotes lost more weight than A-allele carriers ($P = 0.02$)
Shin et al. (2005)[79]	296 F	*UCP1* (A3826G, A1766G, Ala64Thr)	VLCD, 1 mo	The common haplotype [GAG] was associated with less reduction of WHR ($P = 0.006$) and body fat mass ($P = 0.05$) than in non-carriers
Cha et al. (2006)[78]	214 F	*UCP3* (6 SNPs)	VLCD, 1 mo	The common haplotype [CGTACC] was associated with an increased reduction in body weight ($P = 0.016$) and BMI ($P = 0.039$); Int3-47G > A G-carriers lost more weight than AA homozygotes ($P = 0.02$)
De Luis et al. (2006)[88]	14 M/55 F	*FABP2* (Ala54Thr)	LCD + exercise, 3 mo	Thr-allele carriers had greater decrease in fat mass than Ala54Ala homozygotes ($P < 0.05$)
Goyenechea et al. (2006)[89]	22 M/55 F	*IL6* (-174G > C), *PPARG* (Pro12Ala)	LCD, 2.5 mo	*IL6* C-allele carriers had less weight regain after 1-y weight-loss program ($P = 0.049$); carriers of both variants maintained the weight loss better ($P = 0.043$) than non-carriers
Santoro et al. (2007)[90]	107 M/77 F	*MC3R* (C17A, G241A)	LCD + exercise, 2 mo	Wild-type homozygotes lost more weight than rare-allele carriers ($P = 0.03$) after 12 mo
Yoon et al. (2007)[80]	301 F	*UCP2* (4 SNPs), *UCP3* (10 SNPs)	VLCD, 1 mo	UCP2 -866G > A and the major haplotype [GGCdelCGTACC] had a significant reduction in fat mass ($P = 0.002$ and 0.004)

Qi L, Cho YA. Gene-environment interaction and obesity. *Nutr Rev. Dec 2008;66(12):684-694.*

Ongoing project in EGAT 3/1

- Interested outcomes: Obesity, Metabolic syndrome
- Genetic association study: based on candidate SNPs in previous studies (both Thais and GWA)
- Environmental factors:
  - Physical activity: questionnaire
  - Diet: (focus on lipid) serum fatty acid composition
- Replication in intervention study