HAROKOPIO UNIVERSITY

Genes-Physical activity interactions on glycemic traits

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Professor of Human Biology

Μέθοδοι μέτρησης φυσικής δραστηριότητας (ΦΔ)

- Ερωτηματολόγια
- Βηματομετρητές
- Επιταχυνσιόμετρα

Ερωτηματολόγια

Pediatric Exercise Science, 1998, **10**, 176-188
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Physical Activity of 6-Year-Old Children: Validation of Two Proxy Reports

Yannis Manios, Anthony Kafatos, and George Markakis

Heart rate monitoring was used to evaluate the validity and reliability of 2 proxy report measures in assessing moderate to vigorous physical activity (MVPA) in 39 six-year-old children. Significant positive correlations were found between the proxy measures and corresponding heart rate data for school hours and leisure time, respectively (teacher reports, $r = .58$, $p < .001$; parent reports, $r = .71$ to $.81$, $p < .001$), but these decreased when each proxy measure was compared with heart rate data collated over a 3-day period (teacher reports, $r = .40$, $p = .01$; parent reports, $r = .68$, $p < .001$). Repeating the measurements gave a positive test-retest reliability coefficient of $r = .84$ ($p < .001$) and $r = .64$ ($p < .001$) for teacher and parent reports, respectively. The results indicate that both proxy reports can be useful tools in assessing MVPA in young children but that leisure-time activity reports provide a better basis for extrapolation in assessing weekly MVPA.

Ερωτηματολόγια

Παράδειγμα συμπλήρωσης πίνακα

Ώρες ημέρας	**Δραστηριότητες**	**Κατηγορία έντασης**	**Διάρκεια Δραστηριότητας (λεπτά)**
1-2 μ.μ.	Τηλεόραση	Α	-
2-3 μ.μ.	Φαγητό	Α	-
3-4 μ.μ.	Διάβασμα	Α	-
4-5 μ.μ.	Σχοινάκι	Γ	20 λεπτά
5-6 μ.μ.	Επιτραπέζια παιχνίδια	Α	-

Πίνακας 1. Δραστηριότητες μιας καθημερινής ημέρας της περιόδου .....

Ώρες ημέρας	**Δραστηριότητες**	**Κατηγορία έντασης**	**Διάρκεια δραστηριότητας (λεπτά)**
7-8 π.μ.			
8-9 π.μ.			
9-10 π.μ.			
10-11 π.μ.			
11-12 π.μ.			
12-1 π.μ.			
1-2 μ.μ.			
2-3 μ.μ.			
3-4 μ.μ.			
4-5 μ.μ.			
5-6 μ.μ.			
6-7 μ.μ.			
7-8 μ.μ.			
8-9 μ.μ.			
9-10 μ.μ.			
10-11 μ.μ.			

MET

- Το MET το πηλίκο της καταναλισκόμενης ενέργειας (δηλ. της ενεργειακής δαπάνης) (σε kj ή kcal) προς την ενέργεια μεταβολισμού ηρεμίας (σε kj ή kcal) και τα δυο υπολογισμένα με βάση το μέγεθος σώματος.

MET

- Συνεπώς, το MET μας δείχνει πόσες φορές πάνω από το μεταβολισμό ηρεμίας ανεβαίνει η ενεργειακή δαπάνη (ΕΔ) κατά την χρονική περίοδο που εκτελείται μια δραστηριότητα.

- Η κάθε δραστηριότητα μπορεί να ανεβάσει την ΕΔ από 1 έως και 14 φορές πάνω από το μεταβολισμό ηρεμίας και ταξινομείται βάσει του επόμενου πίνακα.

Ερωτηματολόγια

ΕΝΤΑΣΗ ΔΡΑΣΤΗΡΙΟΤΗΤΑΣ		ΤΥΠΟΣ ΔΡΑΣΤΗΡΙΟΤΗΤΑΣ
Πολύ Χαμηλή <4 METs	Οικιακές	Πλύσιμο πιάτων, ξεσκόνισμα, σφουγγάρισμα. Κάθισμα, ορθοστασία.
	Εκτός σπιτιού Αθλήματα	Μπιλιάρδο, μποουλινγκ, σκάκι, ψάρεμα, σκοποβολή.
Χαμηλή 4-7 METs	Οικιακές	Ήπια κηπουρική εργασία, τίναγμα χαλιών, βάψιμο, τρίψιμο πατωμάτων, μηχανολογικές και ξυλουργικές εργασίες.
	Εκτός σπιτιού Αθλήματα	Ποδηλασία, έντονο περπάτημα, κωπηλασία Μπαλέτο, χορός, επιτραπέζια αντισφαίριση, βόλεϊ, βάρη, ενόργανη γυμναστική, ορειβασία.
Μέτρια προς έντονη 7-10 METs	Οικιακές	Ανέβασμα σκάλας. Βαριές αγροτικές εργασίες, χαλαρό τρέξιμο.
	Εκτός σπιτιού Αθλήματα	Χαλαρό μπάσκετ, χαλαρό ποδόσφαιρο, χαλαρή κολύμβηση, ξιφασκία, ρακέτες.
Έντονη ≥10 METs	Οικιακές	-
	Εκτός σπιτιού Αθλήματα	Έντονο τρέξιμο, Αγώνες μπάσκετ, ποδοσφαίρου, πόλο, πάλης, τένις, πολεμικές τέχνες.

TABLE I.—*Gender differences in physical activity out of school.*

Physical activity intensity groups	Boys n=305		Girls n=264		ANCOVA (p value)
	Mean (hours)	SD	Mean (hours)	SD	
"Sedentary"	64.0	5.1	65.2	4.2	p<0.005
"Light"	4.8	3.3	4.3	3.7	N.S.
"Moderate-Vigorous"	1.2	2.1	0.5	1.2	p<0.0005

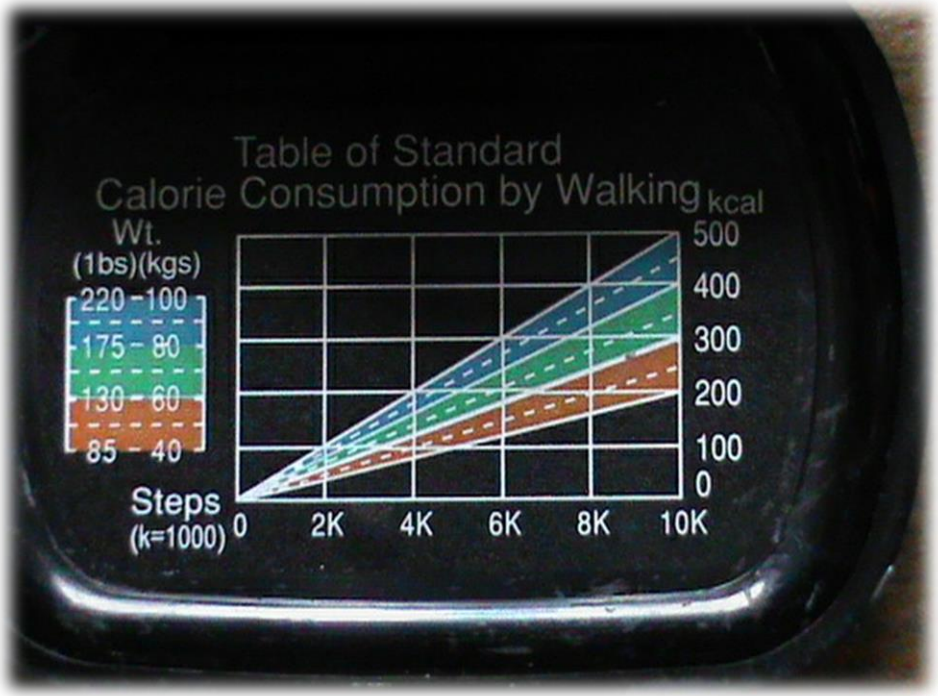
ANCOVA with covariates residence and social group.

Manios et al. 1999 J Sports Med Phys Fit

Βηματομετρητές

Πχ. άτομο 70Kg κάνοντας 6.000 βήματα
→ καταναλώνει 350kcal

Προσδιορισμός Ενεργειακής Δαπάνης από τον Αριθμό των Βημάτων

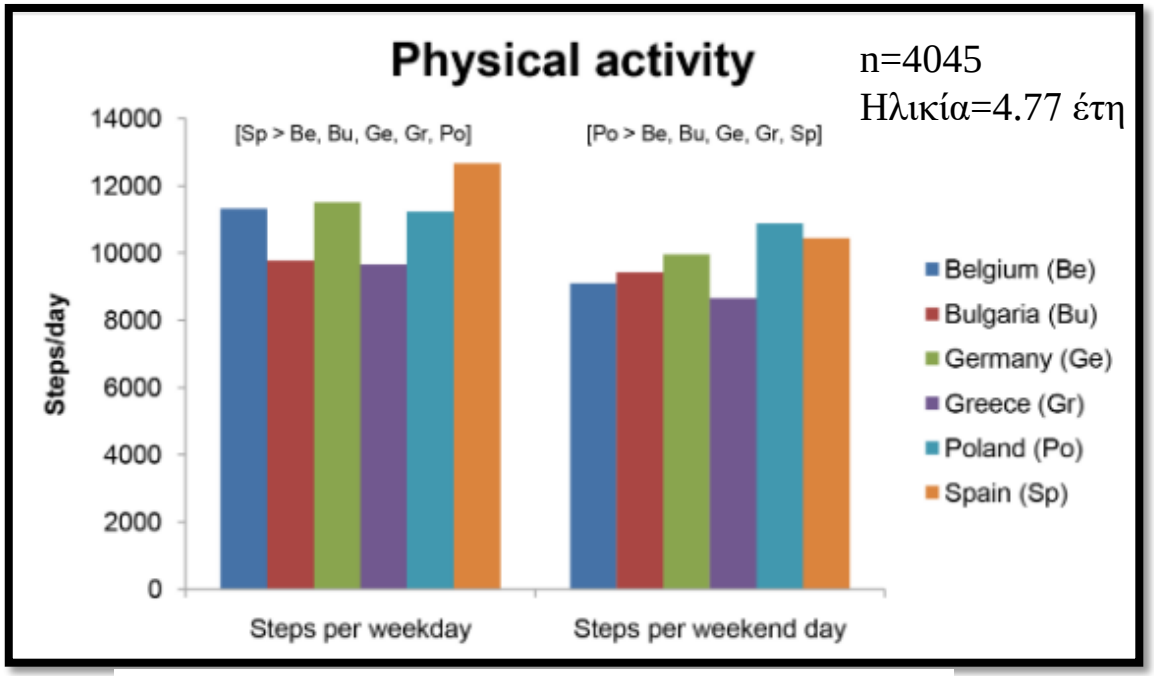


Βηματομετρητές

Σε νεότερα μοντέλα υπάρχουν οι ενδείξεις:

- ✓διανυόμενης απόστασης
- ✓των θερμίδων

ToyBox-study



Differences in preschoolers' physical activity across countries.

De Craemer et al. 2015 PLOS ONE

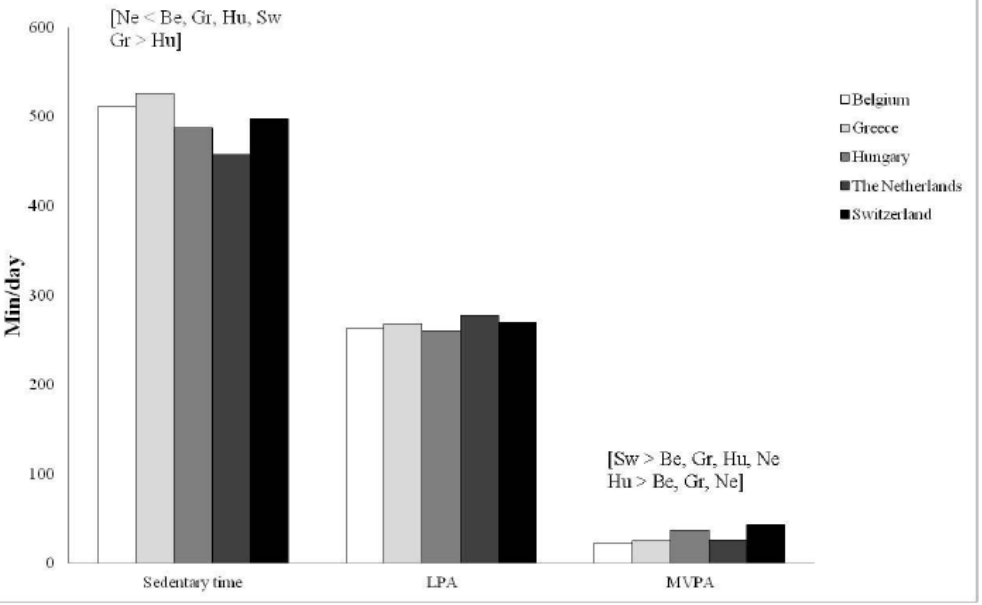
Επιταχυνσιόμετρα

- Επιταχυνσιόμετρα (Accelerometers)
  - Καταγραφή επιτάχυνσης (g) σε 3 άξονες
    - Axis 1: vertical
    - Axis 2: horizontal
    - Axis 3: perpendicular

Επιταχυνσιόμετρα

- Επιταχυνσιόμετρα (Accelerometers)
  - Δίνουν πληροφορίες για
    - ✓ συχνότητα, ένταση & διάρκεια άσκησης
    - ✓ βήματα
    - ✓ ενεργειακή δαπάνη
    - ✓ καθιστικό χρόνο

ENERGY project



Be = Belgium; Gr = Greece; Hu = Hungary; Ne = The Netherlands; Sw = Switzerland

Figure 1 Mean levels of sedentary time, LPA and MVPA among girls.

Verloigne et al. 2012 ISBNPA

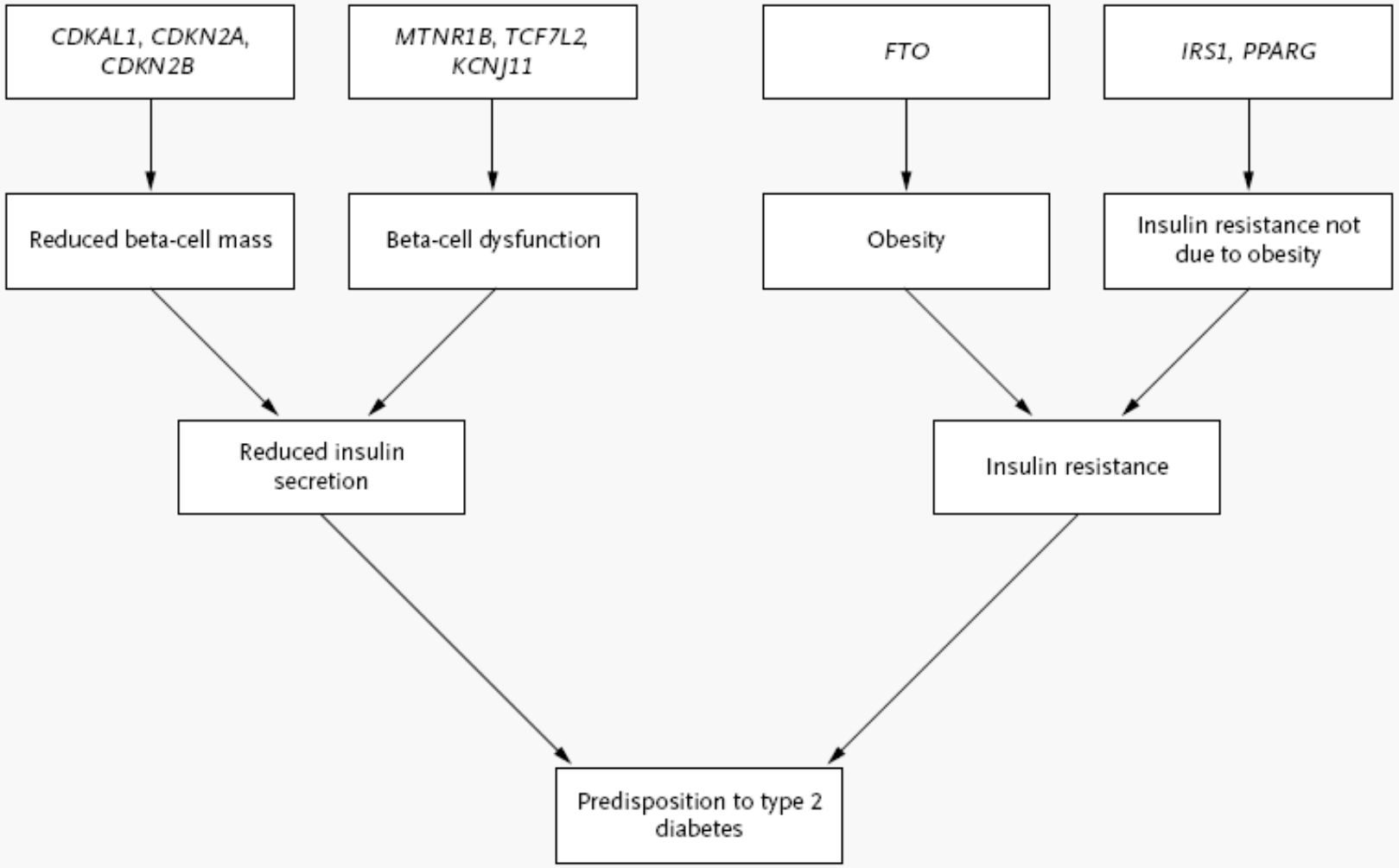
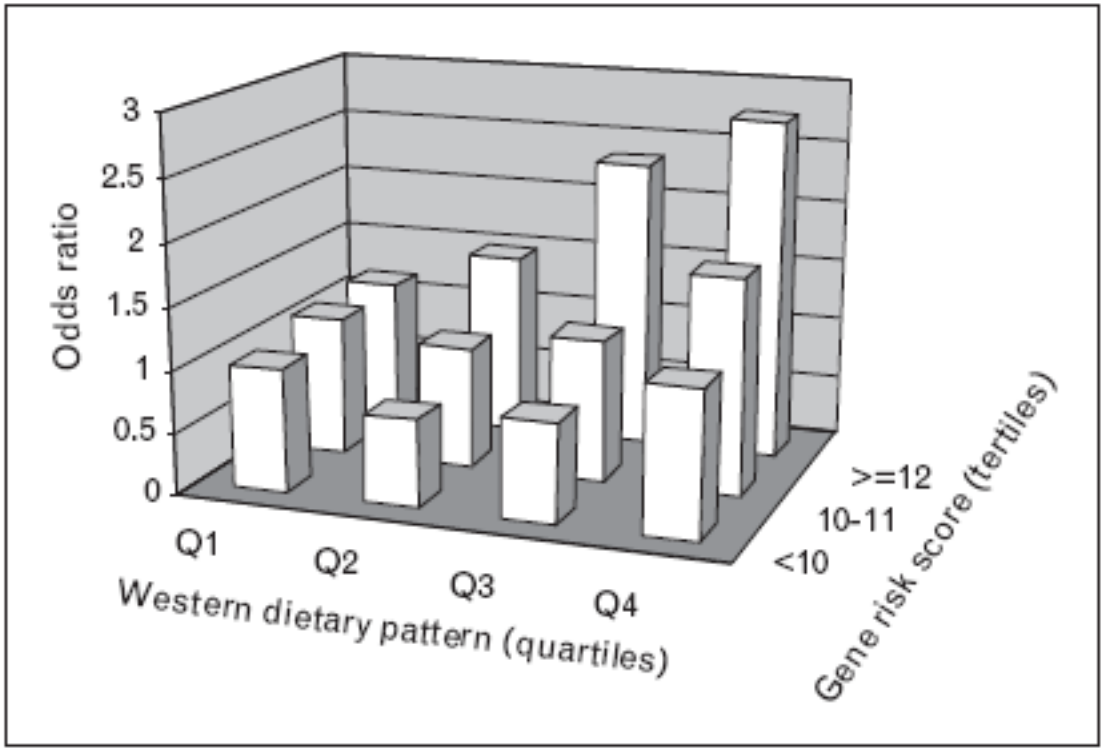


Figure 3. Pathways to Type 2 Diabetes Implicated by Identified Common Variant Associations.

Type 2 diabetes results when pancreatic beta cells are unable to secrete sufficient insulin to maintain normoglycemia, typically in the context of increasing peripheral insulin resistance. The beta-cell abnormalities fundamental to type 2 diabetes are thought to include both reduced beta-cell mass and disruptions of beta-cell function. Insulin resistance can be the consequence of obesity or of obesity-independent abnormalities in the responses of muscle, fat, or liver to insulin. Examples of susceptibility variants that, given current evidence, are likely to influence predisposition to type 2 diabetes by means of each of these mechanisms are shown.

McCarthy 2010

Figure 1 Odds ratios of diabetes risk according to joint classifications of Western dietary pattern score (in quartiles) and genetic risk score (GRS, <10, 10–11, and ≥12)



The analyses were adjusted for age, BMI, smoking, alcohol consumption, physical activity, family history of diabetes, and total energy intakes. Modified with permission [41••].

Interactions of Dietary Whole-Grain Intake With Fasting Glucose– and Insulin-Related Genetic Loci in Individuals of European Descent

A meta-analysis of 14 cohort studies

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Stavroula Kanoni, phd[3]
Rozenn N. Lemaitre, phd[4]
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Julius Ngwa, ms[6]
Frank J.A. van Rooij, dsc[7]
Emily Sonestedt, phd[8]
Mary K. Wojczynski, phd[9]
Zheng Ye, phd[10]
Tosh Tanaka, phd[11]
the CHARGE Whole Grain Foods Study Group*

Table 3—*Meta-analyzed interactions between daily whole-grain intake and genotype for select SNPs for fasting glucose and fasting insulin in 14 cohorts**

SNP	Nearest gene	Glucose- or insulin-raising allele/other allele	Number of cohorts	*n*	Regression coefficient for interaction between daily servings of whole grains × SNP for fasting glucose (mmol/l) β	SE	*P*	I^2 (95% uncertainty interval) (%)
Glucose-related SNP								
rs340874	*PROX1*	C/T	13	43,527	−0.0011	0.0030	0.71	0 (0–57)
rs780094	*GCKR*	C/T	14	48,303	0.0040	0.0027	0.13	0 (0–55)
rs560887	*G6PC2*	C/T	13	43,488	−0.0001	0.0032	0.98	0 (0–57)
rs11708067	*ADCY5*	A/G	13	43,555	0.0039	0.0036	0.28	24 (0–61)
rs11920090	*SLC2A2*	T/A	13	43,451	0.0006	0.0043	0.89	0 (0–57)
rs2191349	*DGKB/TMEM195*	T/G	13	43,561	−0.0044	0.0029	0.13	0 (0–57)
rs4607517	*GCK*	A/G	14	48,323	0.0002	0.0035	0.95	0 (0–55)
rs11558471	*SLC30A8*	A/G	10	40,776	−0.0007	0.0034	0.84	0 (0–62)
rs7034200	*GLIS3*	A/C	13	43,362	0.0015	0.0029	0.60	0 (0–57)
rs10885122	*ADRA2A*	G/T	13	43,391	0.0082	0.0044	0.06	0 (0–57)
rs4506565	*TCF7L2*	T/A	12	45,911	0.0004	0.0030	0.88	51 (6–75)
rs11605924	*CRY2*	A/C	13	43,567	−0.0016	0.0029	0.58	0 (0–57)
rs7944584	*MADD*	A/T	13	43,361	0.0049	0.0033	0.14	0 (0–57)
rs174550	*FADS1*	T/C	14	48,162	−0.0027	0.0028	0.34	32 (0–64)
rs10830963	*MTNR1B*	G/C	13	43,433	0.0028	0.0035	0.42	32 (0–65)
rs11071657	*C2CD4B*	A/G	13	42,500	0.0035	0.0031	0.26	0 (0–57)
Insulin-related SNP					Regression coefficient for interaction between daily servings of whole grains × SNP for fasting insulin [(ln)pmol/l]			
rs780094	*GCKR*	C/T	14	33,784	0.0091	0.003	0.006	1 (0–36)
rs35767	*IGF1*	G/A	13	29,078	0.0022	0.005	0.69	0 (0–57)

*Regression coefficient for interaction between daily servings of whole grains × SNP for fasting glucose (mmol/l) and fasting insulin [(ln)pmol/l], adjusted for age, sex, energy intake (not in the Age, Gene/Environment Susceptibility-Reykjavik Study), and field center (Health, Aging, and Body Composition Study; the Cardiovascular Health Study; the Atherosclerosis Risk in Communities Study; and the Invecchiare in Chianti [Aging in the Chianti Area] Study) and population structure by principal components in the Framingham Heart Study and the Family Heart Study.

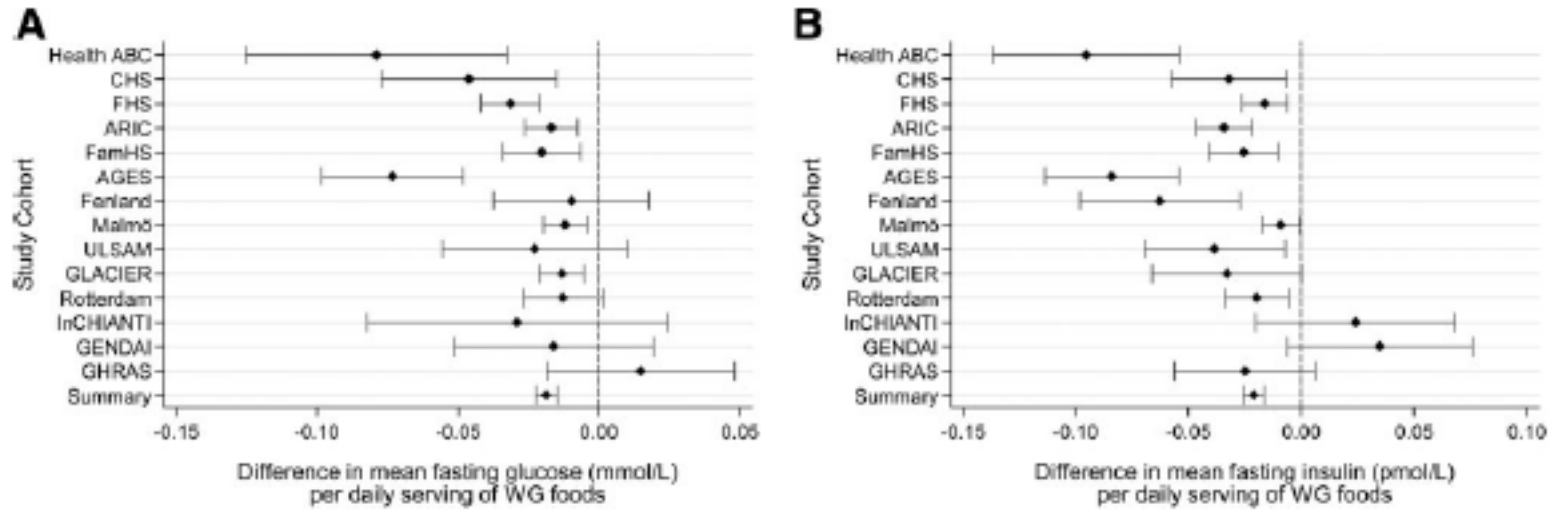


Figure 1—*Associations between daily whole-grain intake (A) and fasting glucose (B) and fasting insulin in 14 cohorts. A: Regression coefficient (β [95% CI]) representing expected change in fasting glucose (mmol/l) per one-daily-serving–greater whole-grain intake. B: Regression coefficient (β [95% CI]) representing expected change in fasting insulin [(ln)pmol/l] per one-daily-serving–greater whole-grain intake. Data are adjusted for model one covariates: age, sex, energy intake, field center, or population structure (Note: energy intake was not estimated in the AGES cohort; field center was included as a covariate in Health ABC, CHS, ARIC, FamHS, and InCHIANTI; population structure by principal components in FHS and FamHS).*

Conclusions

- Understanding how a potentially modifiable dietary characteristic like whole-grain food intake influences genetic effects on metabolic homeostasis may help elucidate the therapeutic potential of personalized medicine.
- This is, to our knowledge, the largest and most comprehensive study of gene x lifestyle interactions conducted to date.
- The polymorphic locus rs780094 lies near a splice site in intron 18 of the GCKR gene whose product is a regulatory protein that inhibits glucokinase, a key regulatory step in glucose metabolism that is influenced by dietary composition
- The locus was originally identified in the Diabetes Genetics Initiative GWAS for triglyceride levels
- Later, the triglyceride-raising T allele was associated with lower fasting glucose and insulin concentrations
- The mechanism by which whole-grain food intake improves insulin resistance may involve glucokinase, and our results suggest that allelic variation at GCKR could diminish the beneficial effects of whole-grain foods on insulin homeostasis, possibly via the strong effect of GCKR variant on both triglyceride and glucose levels.
- Furthermore, because it is unknown whether the SNPs studied here are the causal variants, it is possible that stronger effects attributable to rarer SNPs could underlie some of the examined loci.
- Studies will require more precisely measured exposures (such as nutritional biomarkers of wholegrain intake)

The rs1800629 Polymorphism in the TNF Gene Interacts with Physical Activity on the Changes in C-reactive Protein Levels in the Finnish Diabetes Prevention Study

T. O. Kilpeläinen[1], D. E. Laaksonen[1,2], T. A. Lakka[1,3], C. Herder[4], W. Koenig[5], J. Lindström[6], J. G. Eriksson[6,7,8,9], M. Uusitupa[10], H. Kolb[4], M. Laakso[2], J. Tuomilehto[6,7,11] for the Finnish Diabetes Prevention Study Group

They assessed whether rs1800629 and rs1800795 modified the effect of moderate-to-vigorous physical activity on changes in serum levels of high-sensitivity CRP and IL-6 in the Finnish Diabetes Prevention Study (DPS).

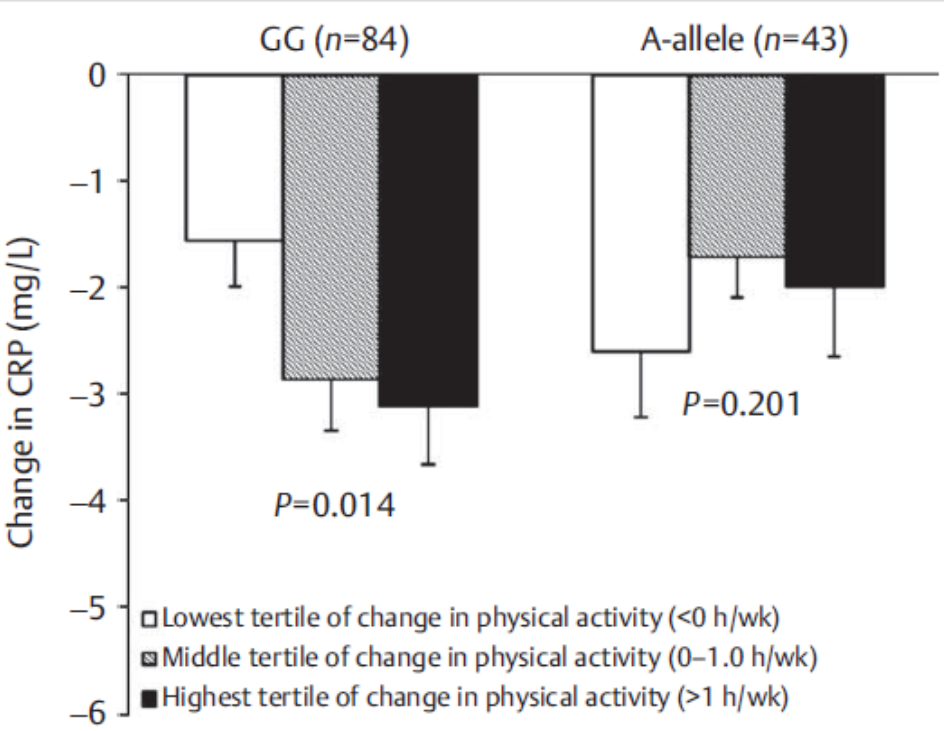
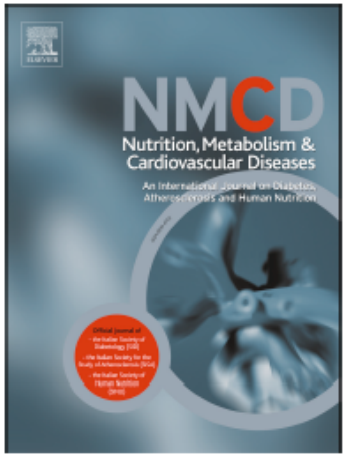


Fig. 1 Changes of serum CRP among genotypes of rs1800629 in *TNF* according to tertiles of change in moderate-to-vigorous physical activity during the first year of the Finnish Diabetes Prevention Study. Only the individuals with high (≥3 mg/L) baseline levels of CRP are included (n=127). Bars indicate adjusted mean of 1-year change in serum CRP in each tertile of 1-year change in moderate-to-vigorous physical activity.

In summary, the rs1800629 SNP in the *TNF* gene modified the effect of moderate-to-vigorous physical activity on serum CRP in subjects participating in the Finnish DPS. It is possible that the anti-inflammatory effect of physical activity may partly depend on genetic variation.

Accepted Manuscript



Lifestyle may modify the glucose-raising effect of genetic loci. A study in the Greek population

E. Marouli, S. Kanoni, M. Dimitriou, G. Kolovou, P. Deloukas, G. Dedoussis, PhD

The lifestyle parameters used for the score included three with glucose-lowering association (**hours in movement during work per day, vegetable consumption** (servings per day)and **fruits and fresh juice**; servings/day) and one with glucose-raising association (**consumption of soft drinks and beverages with sugar**; servings per day).

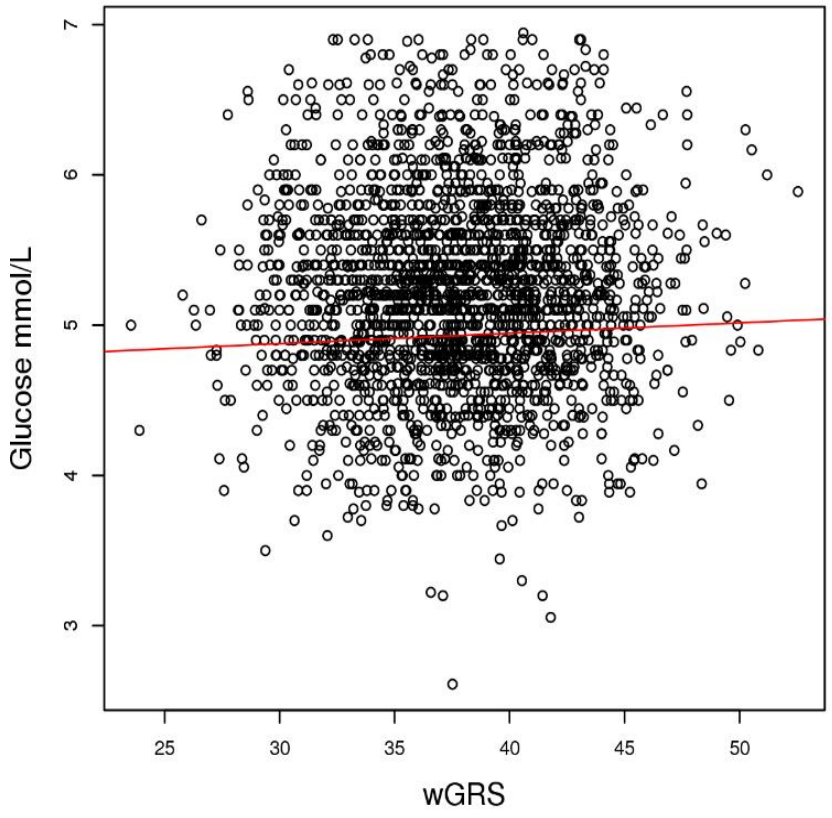
Table 1 Associations of glucose preventive score with glycaemic traits.

	Beta[a]	SE[a]	*P*	*N*[b]
Glycaemic traits				
Glucose (mmol/L)	−0.083	0.021	1.6×10^{-04}	552
Insulin (ln-pmol/L)	0.031	0.029	0.298	243
HOMA.IR	−0.006	0.084	0.938	240

Regression models for the association of the GPS with glycaemic traits, adjusted for age, sex, BMI and total energy intake.

[a] Beta coefficient and standard error for the estimated difference in glycaemic traits per 1-unit increase in GPS.

[b] N indicates the sample size.



Supplemental Figure S2: Scatterplot of the positive correlation between the unweighted genetic risk score (wGRS) and glucose levels (mmol/L) in the total sample, after controlling for age, sex and BMI.

Table 2 Associations[a] of the genetic risk scores with glycaemic traits.

A. Associations[a] of the weighted genetic risk score with glycaemic traits.

	Beta[b]	SE[b]	P	N[c]
Glycaemic traits				
Glucose (mmol/L)	0.020	0.007	8.4×10^{-03}	1132
Insulin (ln-pmol/L)	−0.003	0.009	0.7	586
HOMA.IR	−0.003	0.024	0.9	582

B. Associations[a] of the unweighted genetic risk score with glycaemic traits

	Beta[b]	SE[b]	*P*	*N*[c]
Glycaemic Traits				
Glucose (mmol/L)	0.018	0.007	0.011	1132
Insulin (ln-pmol/L)	−0.006	0.008	0.439	586
HOMA.IR	−0.011	0.022	0.588	582

[a] Adjusted for age, sex and BMI.
[b] Beta coefficient and standard error for the estimated difference in glucose (mmol/L), fasting insulin (ln-pmol/L) concentration or HOMA.IR values per 1-unit increase in the weighted genetic risk score (wGRS).
[c] *N* indicates the sample size.

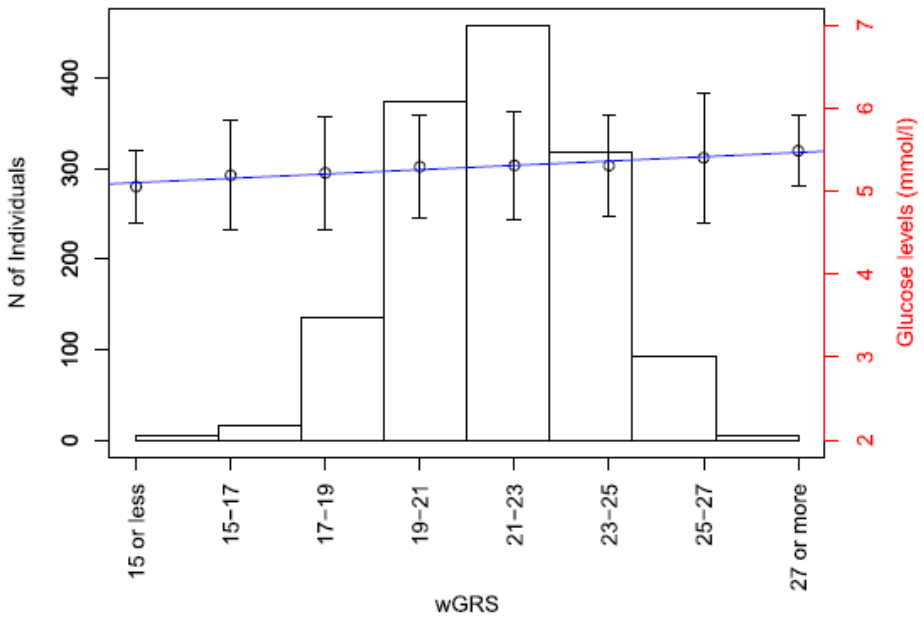


Figure 1 Glucose level increment by increasing the number of known glucose-increasing loci, weighted by the published effect size. The bar plots show the average and standard error of glucose in mmol/L for each genotype score group (right Y-axis). The histogram denotes the distribution of individuals in every genotype score group (left Y-axis).

Table 3 Interaction analysis of the genetic risk scores and GPS on glucose levels.

A. Interaction analysis of the weighted genetic risk score and GPS on glucose levels

	Beta[a]	SE	*P*	*N*[b]
Glycaemic trait				
Glucose (mmol/L)	−0.019	0.007	0.014	533

B. Interaction analysis of the unweighted genetic risk score and GPS on glucose levels

	Beta[a]	SE	*P*	*N*[b]
Glycaemic trait				
Glucose (mmol/L)	−0.015	0.007	0.036	533

Abbreviations: wGRS: weighted genetic risk score, GPS: glucose preventive score.

Regression model for interaction analysis of the GPS and wGRS on the glucose levels. Beta coefficient and standard error for the estimated difference in glucose (mmol/L), per 1-unit increase in the wGRS, assuming the additive genetic model, interacting with a 1-point increase in the lifestyle score.

[a] Results adjusted for age, sex, BMI and total energy intake.

[b] *N* indicates the sample size.

Table 4 Stratified associations of the weighted genetic risk score with glycaemic traits per GPS tertile.

Glycaemic trait	GPS tertile											
	<3 points				3–5 points				>5 points			
	Beta[a]	SE[a]	*P*	*N*[b]	Beta[a]	SE[a]	*P*	*N*[b]	Beta[a]	SE[a]	P	N[b]
Glucose (mmol/L)	0.035	0.019	0.068	104	0.007	0.014	0.602	287	−0.043	0.021	0.043	142

Regression models for the association of the wGRS with glucose levels, adjusted for age and sex.

[a] Beta coefficient and standard error for the estimated difference in glucose (mmol/L) per 1-unit increase in the weighted genetic risk score (wGRS) for each GPS tertile.

[b] *N* indicates the sample size.

In summary, screening of predisposing genetic variants, reliably associated with glycaemic traits that demonstrate an attenuated impact under the influence of protective lifestyle behaviour, could contribute to better recommendations for glucose homeostasis control. Further research in this direction could contribute to a better comprehension of how dietary intake and physical activity recommendations could be customised to the individual's genetic background. A combination of these tools would be useful to evaluate the gene–environment interaction, elucidate our understanding in terms of the biological pathways involved and help in prognosis, prevention and monitoring of glucose homeostasis.

No Interactions Between Previously Associated 2-Hour Glucose Gene Variants and Physical Activity or BMI on 2-Hour Glucose Levels

Robert A. Scott,[1] Audrey Y. Chu,[2,3] Niels Grarup,[4,5] Alisa K. Manning,[6] Marie-France Hivert,[7]

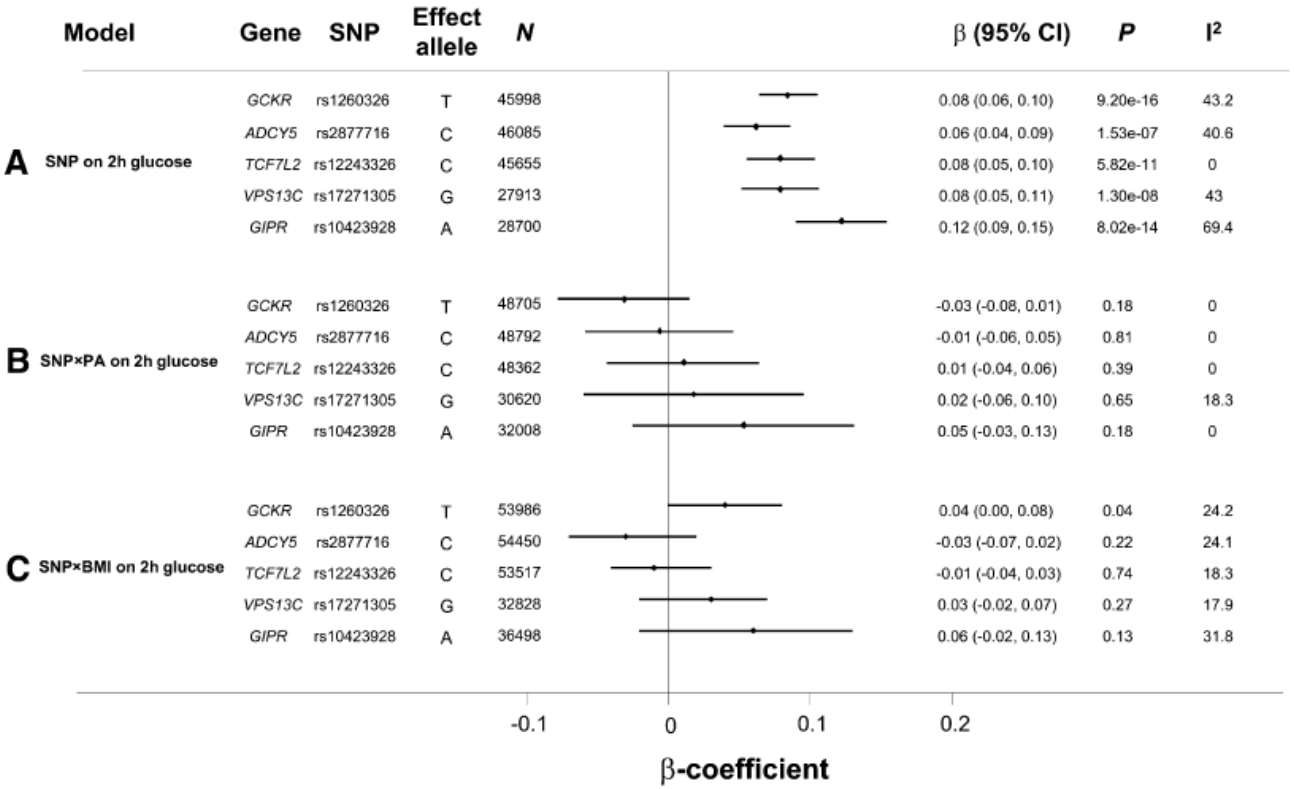


FIG. 1. *A*: Effect of SNP is shown on 2-h glucose. The β-coefficient is the magnitude of the observed association. *B*: Shows the SNP×PA interaction effect in which the β-coefficient is the difference in SNP association effect between inactive and active individuals. Inactive individuals were coded as 0 and active individuals a 1; therefore, a value of 0 for the interaction coefficient reflects equivalent SNP effect in inactive and active strata, whereas a positive value reflects a larger SNP effect in active individuals. *C*: The SNP×BMI interaction is shown. Here, the β-coefficient is the difference in SNP effect per 10 kg/m^2 difference in BMI. A positive value reflects a larger SNP effect in those with higher BMI. The 2-h glucose–raising allele in *A* is always the effect allele.

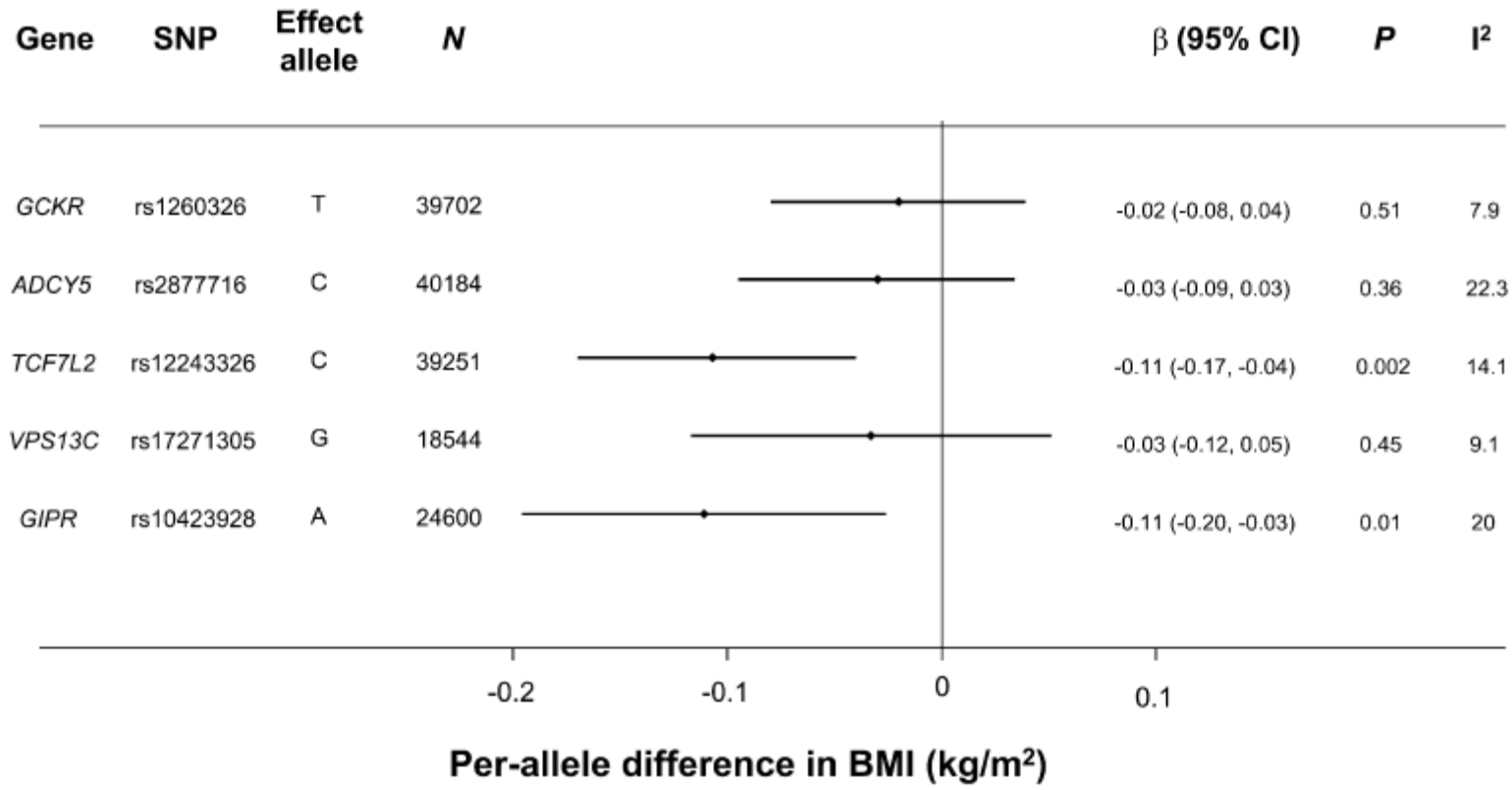


FIG. 2. The SNP association with BMI is shown. The 2-h glucose–raising allele from Fig. 1*A* is shown as the effect allele.

In conclusion, in our study of up to 54,884 individuals from 22 studies, we found no evidence of gene–lifestyle interaction among the variants studied. This was despite the clear association of 2-h glucose with PA, BMI, and genetic exposures. Although the descriptive epidemiology of diabetes suggests an influence of gene–lifestyle interaction in its etiology, our study finds no evidence to that effect for SNPs known to be associated with 2-h glucose. Further, our study supports the use of large-scale analyses to robustly investigate gene–lifestyle interaction. In future, hypothesis-generating approaches may offer a valuable opportunity to detect gene–lifestyle interactions in type 2 diabetes and related traits.

Interaction between rs10830963 polymorphism in *MTNR1B* and lifestyle intervention on occurrence of gestational diabetes

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Aims/hypothesis The aim of this study was to assess the interaction between melatonin receptor 1B gene (MTNR1B) rs10830963 polymorphism and lifestyle intervention during pregnancy on occurrence of gestational diabetes mellitus (GDM) in high-risk women.

MTNR1B is one of the seven transmembrane G-protein coupled melatonin receptors expressed in the central nervous system and in the peripheral tissues including the pancreatic beta cells

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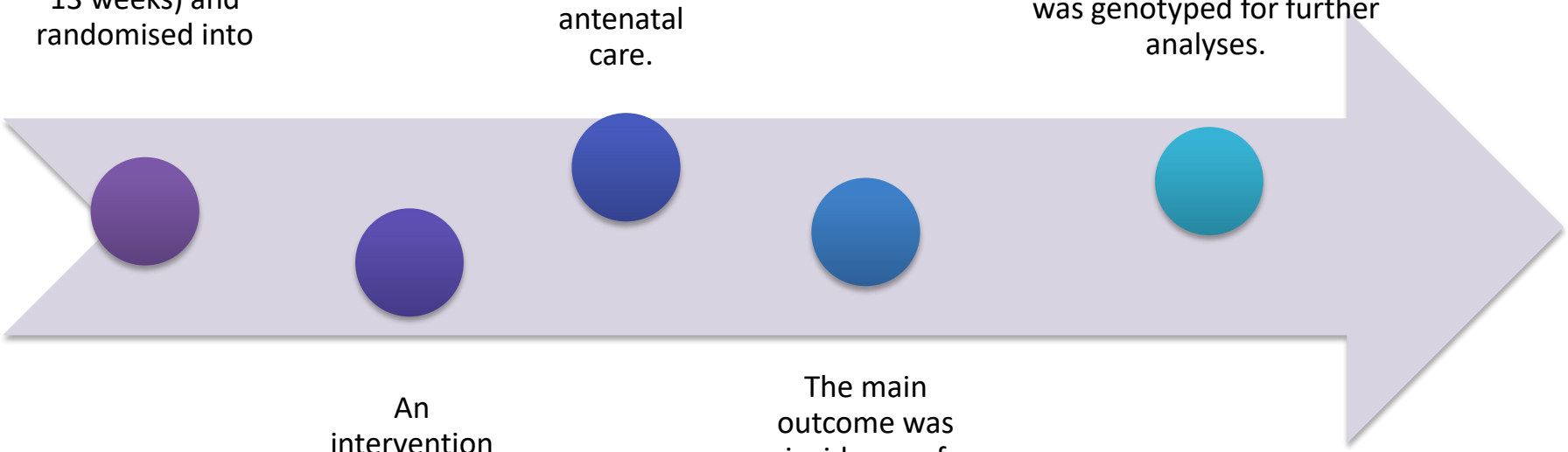
A total of **226 women** with a history of **GDM** and/or a pre-pregnancy **BMI≥ 30** kg/m2 were enrolled at <20 weeks of gestation (mean 13 weeks) and randomised into

A control group receiving standard antenatal care.

The MTNR1B rs10830963 was genotyped for further analyses.



An intervention group receiving counseling on diet, physical activity and weight control

The main outcome was incidence of GDM, defined as one or more pathological glucose values in a standard 75 g 2-h OGTT.

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Table 1 Genotype frequencies of *MTNR1B* polymorphism rs10830963. Clinical characteristics at baseline according to genotype in 226 participants from the RADIEL trial

	Total, $n=226$	CC $n=103$	CG $n=94$	GG $n=29$	p value[a]	p value for CC/CG	p value for CC/GG	p value for CG/GG
Genotype frequency (%)		46	42	13				
Intervention group, I/C[b] n, (%)		55 (46) / 48 (45)	47 (39) / 47 (44)	18 (15) / 11 (10)	0.52			
Age (years)	32.5 (4.6)	32.1 (4.5)	32.4 (4.7)	34.0 (4.7)	0.15	1.00	0.16	0.35
Gestational weeks	23.0 (1.4)	23.1 (1.3)	22.9 (1.5)	22.8 (1.3)	0.48	1.0	0.81	1.00
Pre-pregnancy BMI (kg/m^2)	31.7 (5.8)	32.8 (5.3)	30.9 (6.0)	30.4 (6.0)	0.03	0.06	0.16	1.00
Weight (kg)	89.4 (17.0)	91.5 (15.0)	87.5 (18.5)	87.7 (18.4)	0.22	0.31	0.92	1.00
Systolic BP (mmHg)	121.5 (13.3)	122.8 (13.3)	120.5 (12.1)	120.2 (16.4)	0.44	0.68	1.00	1.00
Diastolic BP (mmHg)	77.4 (8.9)	77.0 (8.7)	77.6 (8.5)	78.3 (10.5)	0.75	1.00	1.00	1.00
Fasting plasma glucose (mmol/l)	4.9 (0.2)	4.9 (0.2)	4.9 (0.2)	4.9 (0.3)	0.85	1.00	1.00	1.00
HbA_{1c} (%)	5.2 (0.27)	5.2 (0.26)	5.2 (0.31)	5.2 (0.22)				
HbA_{1c} (mmol/mol)	33.5 (3.0)	33.5 (2.8)	33.7 (3.4)	32.8 (2.4)	0.33	1.00	0.56	0.47
Insulin (pmol/l)	51.5 (39.8)	55.9 (25.9)	46.0 (26.8)	54.3 (89.0)	0.04	0.04	1.00	1.00
HOMA-IR	1.1 (0.5)	1.2 (0.5)	1.0 (0.6)	0.9 (0.4)	<0.005	0.13	<0.005	0.24
Total cholesterol (mmol/l)	4.9 (0.9)	5.0 (1.0)	4.7 (0.8)	5.0 (0.7)	0.02	0.02	1.00	0.21
HDL-cholesterol (mmol/l)	1.7 (0.3)	1.7 (0.3)	1.8 (0.4)	1.8 (0.2)	<0.005	0.10	<0.005	0.61
LDL-cholesterol (mmol/l)	2.8 (0.7)	3.0 (0.8)	2.6 (0.6)	2.7 (0.6)	<0.01	<0.005	0.29	1.00
Total triacyglycerol (mmol/l)	1.3 (0.7)	1.4 (0.6)	1.3 (0.7)	1.3 (0.6)	0.45	0.63	1.00	1.00

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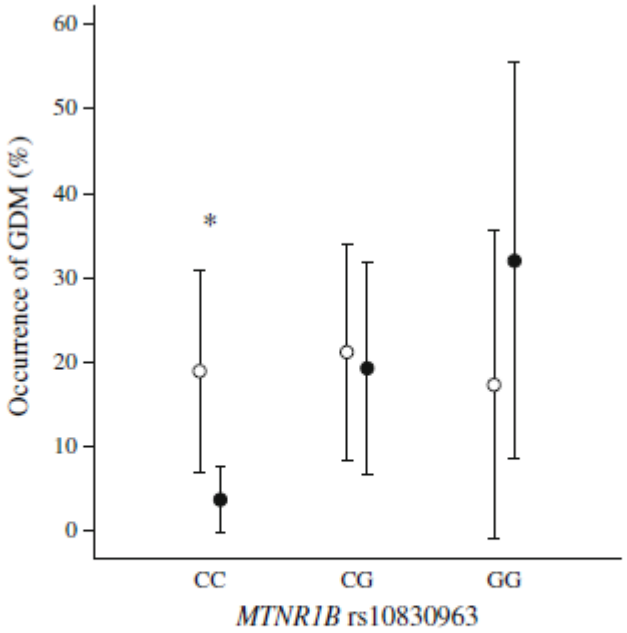

Fig. 1 Association between *MTNR1B* rs10890363 polymorphism and age-adjusted occurrence of GDM in the control group (white circles, p for linearity = 0.991) and in the lifestyle intervention group (black circles, p for linearity = 0.003) (p for interaction = 0.038) in 226 women participating in the RADIEL trial. Error bars indicate 95% CIs

Among women at high risk for GDM, only those **not carrying the rs10830963 risk allele** G seem to benefit from the RADIEL lifestyle intervention. Our results suggest that the risk for GDM associated with one or two copies of the rs10830963 risk allele G is not modifiable by the otherwise successful lifestyle intervention in the RADIEL study.

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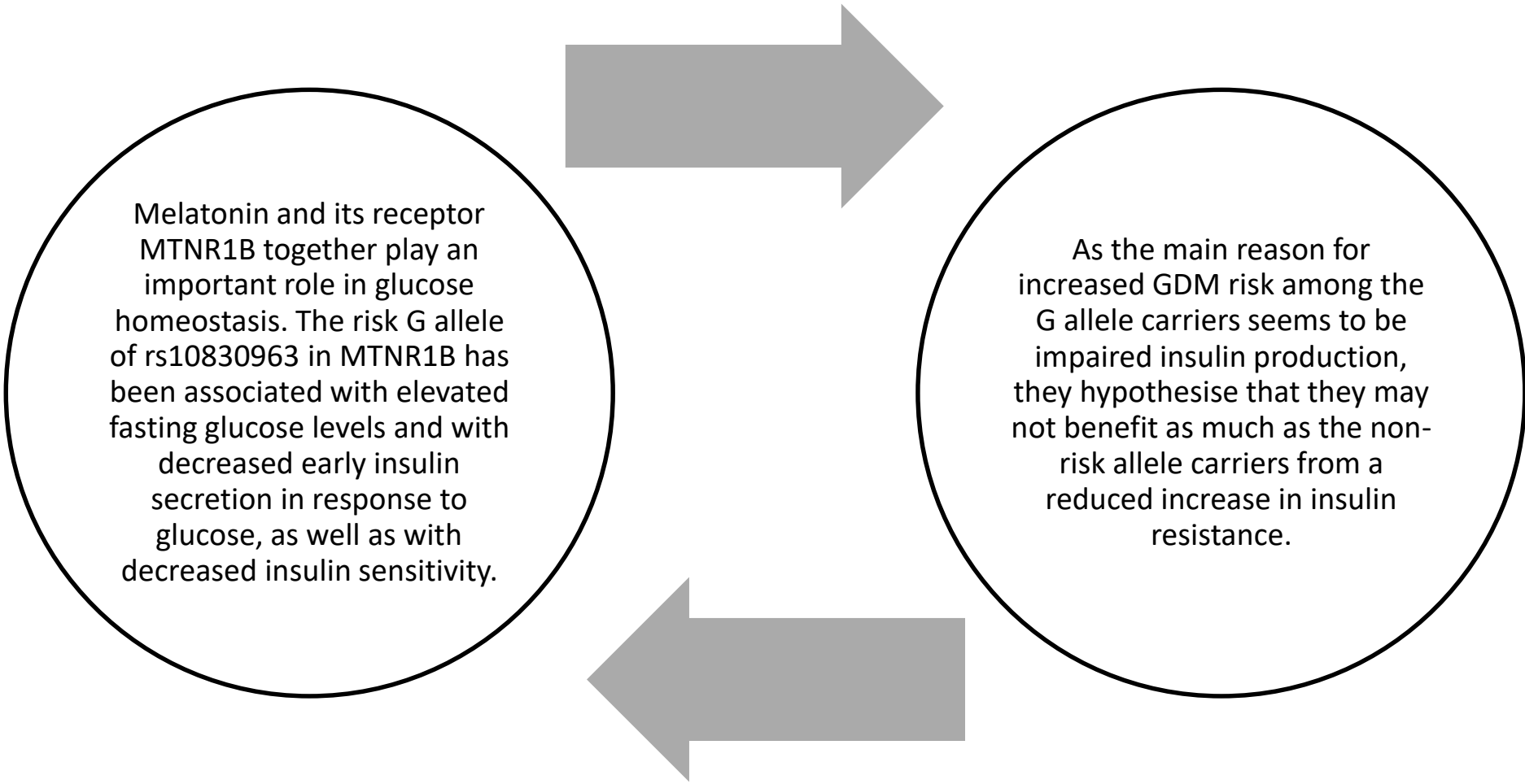

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Obesity and associated lifestyles modify the effect of glucose metabolism-related genetic variants on impaired glucose homeostasis among postmenopausal women

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With data from **1,027 postmenopausal** participants of the Genomics and Randomized Trials Network study and 15 single-nucleotide polymorphisms (SNPs) associated with glucose homeostasis, they assessed whether obesity, physical activity, and high dietary fat intake with the SNP–glucose variations.

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TABLE 3 Results from linear regression for 15 glucose metabolism–relevant SNPs predicting glucose, insulin, and HOMA-IR levels, stratified by obesity (measured by BMI) among 1,027 participants in the Genomics and Randomized Trials Network Study of the Women's Health Initiative

	Nonobese group (BMI < 30.0) (n = 633)						Obese group (BMI ≥ 30.0) (n = 394)					
	Glucose		Insulin[b]		HOMA-IR[b]		Glucose		Insulin[b]		HOMA-IR[b]	
SNP name	Effect size[c](95% CI)		Effect size[c](95% CI)		Effect size[c](95% CI)		Effect size[c](95% CI)		Effect size[c] (95% CI)		Effect size[c] (95% CI)	
rs340874	−1.05	(−2.98–0.89)	−0.02	(−0.07–0.02)	−0.03	(−0.08–0.02)	2.60	(−0.35–5.55)	0.04	(−0.20–0.10)	0.06	(−0.01 - 0.13)
rs780094	0.87	(−1.01–2.76)	0.03	(−0.02–0.08)	0.04	(−0.02–0.09)	0.66	(−2.61–3.94)	0.04	(−0.02 - 0.11)	0.05	(−0.03 - 0.13)
rs560887	**3.71**	**(1.49–5.93)** [a]	−0.01	(−0.07–0.04)	0.02	(−0.04–0.08)	1.12	(−2.59–4.83)	0.06	(−0.02–0.13)	0.07	(−0.02 - 0.16)
rs11920090	0.08	(−2.52–2.68)	−0.03	(−0.09–0.03)	−0.04	(−0.11–0.03)	−1.67	(−6.18–2.84)	−0.02	(−0.11–0.07)	−0.03	(−0.14 - 0.08)
rs2191349	−0.34	(−2.25–1.58)	**−0.05**	**(−0.09–−0.001)**	−0.05	(−0.10–0.002)	0.88	(−2.35–4.10)	0.01	(−0.06–0.07)	0.01	(−0.07 - 0.09)
rs4607517	0.38	(−2.32–3.09)	−0.02	(−0.08–0.05)	−0.01	(−0.09–0.06)	3.50	(−0.81–7.80)	−0.02	(−0.11–0.06)	−0.001	(−0.10 - 0.10)
rs11558471	**−2.50**	**(−4.55–−0.45)**	−0.03	(−0.08–0.02)	−0.05	(−0.10–0.01)	1.58	(−2.00–5.15)	**0.08**	**(0.01–0.15)**	**0.09**	**(0.01 - 0.17)**
rs7034200	0.99	(−0.94–2.92)	0.01	(−0.03–0.06)	0.02	(−0.03–0.08)	2.06	(−1.11–5.22)	−0.002	(−0.07–0.06)	0.02	(−0.06 - 0.09)
rs10885122	0.24	(−2.34–2.83)	0.0001	(−0.06–0.06)	0.003	(−0.07–0.07)	2.84	(−1.39–7.07)	0.01	(−0.07–0.10)	0.04	(−0.06 - 0.14)
rs4506565	0.52	(−1.49–2.53)	−0.04	(−0.09–0.01)	−0.03	(−0.09–0.02)	**3.28**	**(0.03–6.52)**	0.02	(−0.05–0.08)	0.04	(−0.04 - 0.11)
rs11605924	0.52	(−1.46–2.51)	−0.03	(−0.08–0.02)	−0.03	(−0.08–0.02)	2.14	(−0.89–5.18)	0.02	(−0.04–0.08)	0.03	(−0.04 - 0.11)
rs174550	1.95	(−0.11–4.00)	0.03	(−0.02–0.08)	0.05	(−0.01–0.10)	2.09	(−1.08–5.27)	0.06	(0.00006–0.13)	**0.08**	**(0.005 - 0.16)**
rs10830963	1.44	(−0.72–3.60)	−0.03	(−0.09–0.02)	−0.02	(−0.08–0.04)	1.57	(−2.03–5.17)	0.02	(−0.05–0.10)	0.04	(−0.05 - 0.13)
rs11071657	−0.99	(−3.01–1.03)	**−0.07**	**(−0.12–−0.02)**	**−0.08**	**(−0.13—0.02)**	−0.52	(−3.79–2.75)	−0.01	(−0.07–0.06)	−0.01	(−0.09 - 0.07)
rs35767	−0.41	(−3.00–2.17)	−0.03	(−0.09–0.04)	−0.03	(−0.10–0.04)	0.46	(−3.49–4.41)	−0.05	(−0.13–0.03)	−0.05	(−0.15 - 0.04)

BMI, body mass index; CI, confidence interval; HOMA-IR, homeostatic model assessment–insulin resistance; SNP, single-nucleotide polymorphism

Numbers in **bold** face are statistically significant ($P < 0.05$).

[a] Bonferroni correction for multiple testing was applied and statistically significant effect-size is indicated.

[b] Number of participants in analysis with insulin or HOMA-IR levels as an outcome of interest was 1,012 (621, nonobese group; 391, obese group).

[c] Effect sizes were estimated from an additive model of linear regression (i.e. regressed against effect allele) adjusting for age, race, education, marital status, family history of diabetes, cancer ever, cardiovascular disease ever, diabetes ever, hypertension ever, high cholesterol requiring pills ever, oral contraceptive use, exogenous estrogen use, pregnancy history, history of hysterectomy or oophorectomy, age at menarche, age at menopause, physical activity, depression, waist/hip ratio, and selected diet-related variables (total calories, % calories from protein, % calories from monounsaturated fatty acids, % calories from polyunsaturated fatty acids, and dietary total sugars).

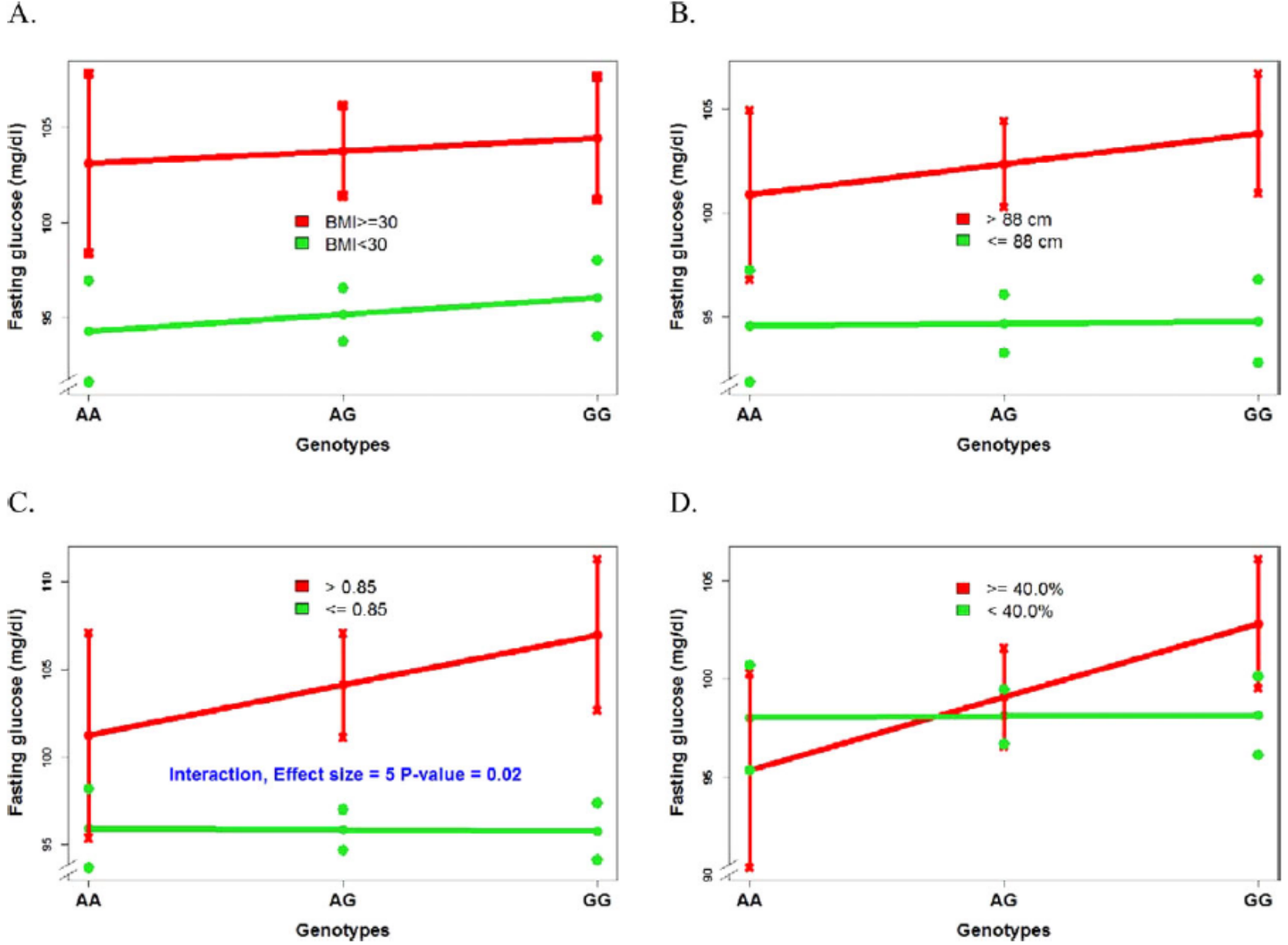

FIGURE 1 Graphs present distributions of adjusted mean levels of fasting glucose by genotypes of rs780094 in GCKR in 1,027 participants in the Genomics and Randomized Trials Network Study of the Women's Health Initiative, stratified by ***A*** body mass index, ***B*** waist circumference, ***C*** waist/hip ratio, and ***D*** high fat diet intake

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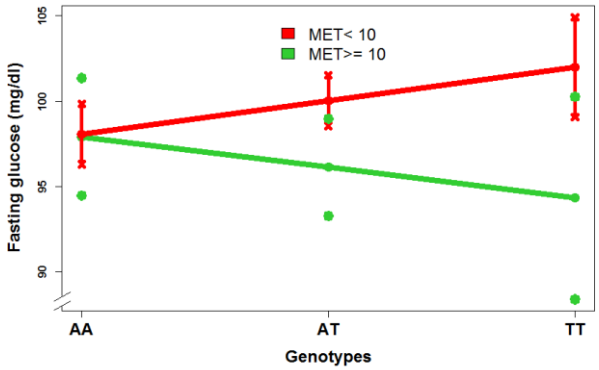
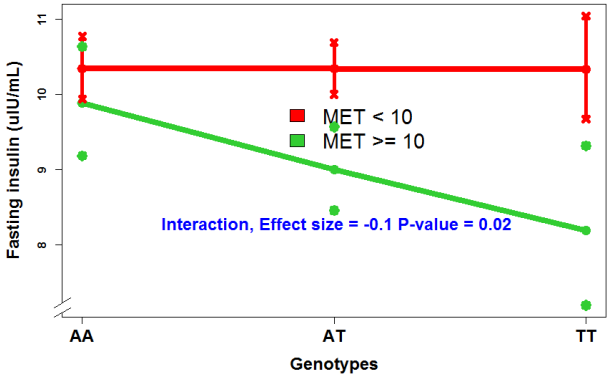
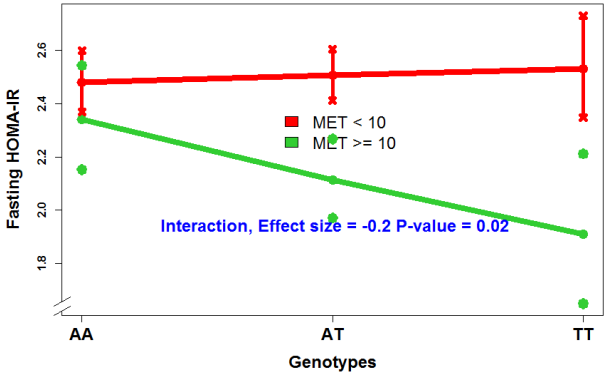
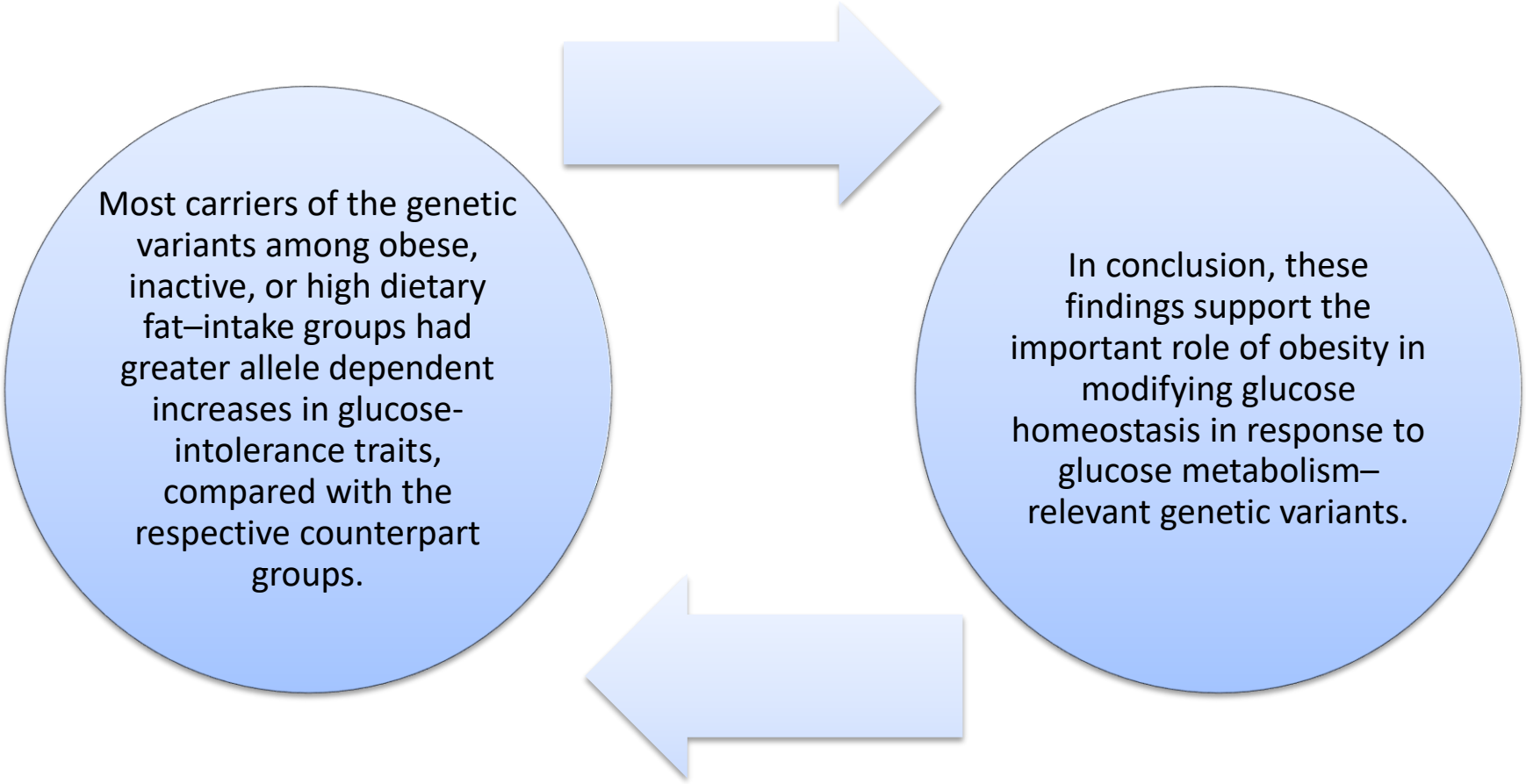

MET< 10
MET>= 10
Fasting glucose (mg/dl)
105
100
95
90
AA
AT
TT
Genotypes


MET < 10
MET >= 10
Interaction, Effect size = -0.1 P-value = 0.02
Fasting insulin (uIU/mL)
11
10
9
8
AA
AT
TT
Genotypes


MET < 10
MET >= 10
Interaction, Effect size = -0.2 P-value = 0.02
Fasting HOMA-IR
2.6
2.4
2.2
2.0
1.8
AA
AT
TT
Genotypes



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Gene-Physical Activity Interactions and Their Impact on Diabetes

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Med Sport Sci. Basel, Karger, 2014, vol 60, pp 94–103 (DOI: 10.1159/000357339)

Association of physical activity with lower type 2 diabetes incidence is weaker among individuals at high genetic risk

Yann C. Klimentidis · Zhao Chen · Amit Arora · Chiu-Hsieh Hsu

Physical activity and dietary intake Each individual's level of physical activity was assessed using the Baecke Physical Activity questionnaire

Genetic markers and risk scores They selected 65 SNPs confidently associated with type 2 diabetes and their respective risk alleles and effect sizes as listed in Morris et al.

GRSs were calculated as the weighted sum of risk alleles, with weights corresponding to the respective SNP effect size as estimated in the respective meta-analysis mentioned above.

Diabetologia (2014) 57:2530–2534

Table 1 Baseline and incidence characteristics in the overall sample and in each tertile of type 2 diabetes GRS

	Overall (n=8,101)	Low type 2 diabetes GRS	Intermediate type 2 diabetes GRS	High type 2 diabetes GRS
Age (years)	54.2±5.7	54.2±5.7	54.2±5.6	54.0±5.6
Women (%)	53.6	54.5	52.8	53.5
BMI (kg/m^2)	26.7±4.6	26.7±4.6	26.7±4.6	26.6±4.6
Smoking (cigarette years)	331±428	330±427	336±438	327±421
Dietary fibre intake (g/day)	17.6±8.1	17.5±8.1	17.5±8.0	17.7±8.1
Dietary carbohydrate intake (g/day)	199.0±83.0	198.1±81.2	198.3±82.8	200.7±84.8
Physical activity (sport) index	2.6±0.8	2.5±0.8	2.6±0.8	2.6±0.8
Incident cases (n)[a]	821	180	296	345

The incidence among physically active individuals was lower than the incidence among physically inactive individuals across all three strata of type 2 diabetes GRS. However, the decrease in incidence among active vs inactive individuals was steepest among the low GRS individuals.

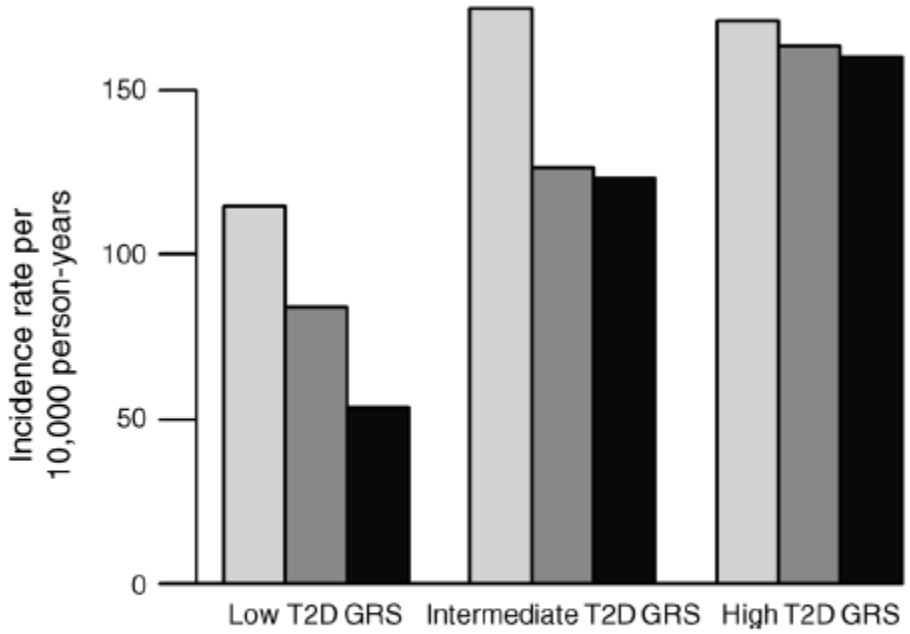

Fig. 1 Incidence rates of type 2 diabetes per 10,000 person-years across strata of type 2 diabetes (T2D) GRS and physical activity tertile. Light grey bar, low levels of physical activity; medium grey bar, intermediate levels of physical activity; black bar, high levels of physical activity

They found a significant interaction of the type 2 diabetes GRS with physical activity on type 2 diabetes incidence

As shown in Fig. 2, they found that the association of physical activity with type 2 diabetes incidence was strongest in the low GRS group and weakest in the high GRS group

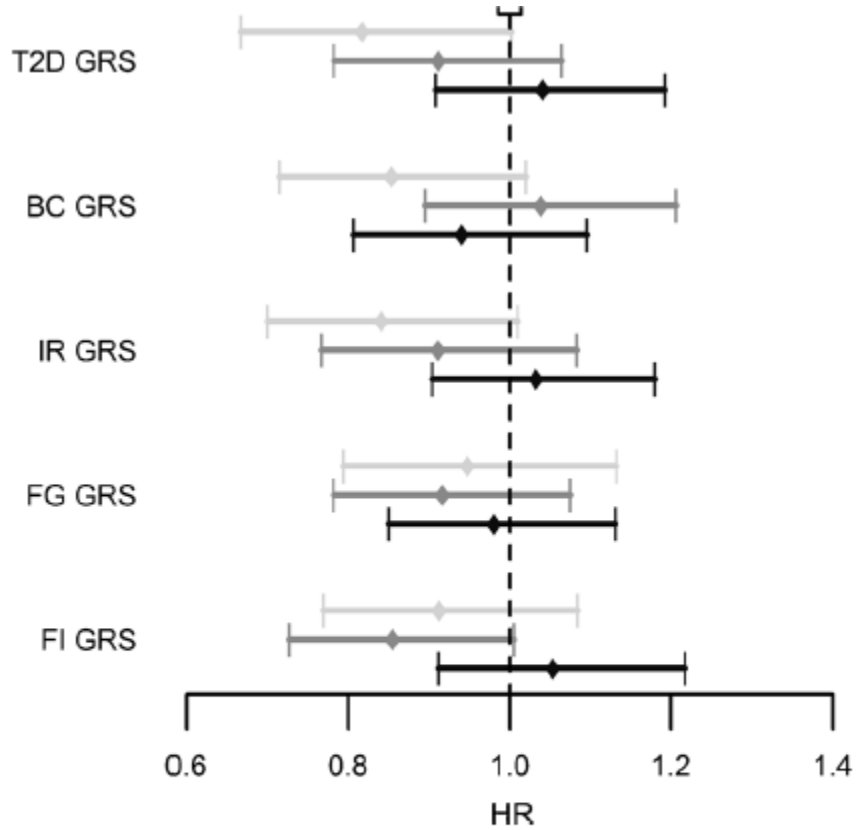

Fig. 2 HRs and 95% CIs for type 2 diabetes per 1 unit increase in physical activity in three strata of type 2 diabetes (T2D), beta cell (BC), IR, FG and FI GRS. Physical activity is measured as an index between 1 and 5. Light grey lines, low GRS; medium grey lines, intermediate GRS; black lines, high GRS

Although physical activity generally protects against type 2 diabetes, their findings suggest that the level of protection conferred by physical activity is lower in individuals (especially women) with a higher genetic risk for type 2 diabetes or IR.