SUPPLEMENTARY MATERIALS

Supplemental tables

Table S1. Population characteristics of studies included in DietGen by cohort.

Study		Female (%)	Age (y)	BMI (kg/m2)	Total Energy Intake (kcal)	% kcals from Carbohydrates	% kcals from Protein	% kcals from Fat
HPFS								
T2D Cohort	Cases	0	55.0 (8.5)	27.6 (4.0)	2057.1 (627.4)	45.7 (15.5)	18.5 (6.5)	34.5 (12.4)
N=2315	Controls	0	55.0 (8.4)	25.0 (2.7)	2038.0 (611.7)	47.8 (16.3)	18.4 (5.7)	32.6 (11.5)
CHD Cohort	Cases	0	56.4 (8.7)	25.7 (3.0)	2063.1 (655.0)	48.7 (16.6)	18.9 (5.7)	33.2 (10.5)
N=1212	Controls	0	56.2 (8.6)	25.2 (3.1)	2020.9 (613.8)	48.2 (16.8)	19.0 (6.8)	32.9 (12.4)
KS Cohort	Cases	0	49.4 (7.9)	25.3 (2.8)	1961.5 (589.3)	48.7 (16.3)	19.0 (6.9)	34.2 (13.9)
N=549	Controls	0	48.7 (6.8)	25.5 (2.8)	2040.4 (584.5)	46.8 (15.6)	18.2 (5.5)	33.0 (11.0)
NHS								
T2D Cohort	Cases	100	53.6 (6.7)	27.8 (7.8)	1803.4 (541.1)	48.3 (7.5)	19.3 (3.4)	33.1 (5.7)
N=3218	Controls	100	53.2 (6.7)	24.0 (6.2)	1780.0 (514.9)	48.2 (7.8)	18.7 (3.2)	32.9 (5.6)
CHD Cohort	Cases	100	56.1 (6.3)	26.4 (5.2)	1820.1 (543.9)	48.1 (7.7)	18.8 (3.4)	32.9 (5.8)
N=1013	Controls	100	56.0 (6.3)	24.9 (4.3)	1765.7 (520.3)	47.8 (8.0)	18.7 (3.3)	32.7 (5.8)
KS Cohort	Cases	100	52.2 (4.4)	25.1 (5.4)	1815.1 (564.1)	47.9 (7.4)	18.5 (3.3)	34.0 (6.1)
N=490	Controls	100	52.0 (3.7)	23.3 (4.5)	1770.5 (502.4)	48.4 (7.5)	18.5 (2.8)	33.2 (5.6)
BC Cohort	Cases	100	54.4 (6.4)	25.2 (4.7)	1769.7 (512.6)	47.9 (7.9)	18.8 (3.2)	32.4 (5.7)
N=2043	Controls	100	54.5 (6.4)	25.0 (4.5)	1781.3 (502.1)	48.7 (7.8)	18.7 (3.3)	32.4 (5.8)
WGHS N=22691	Cohort	100	54.7 (7.1)	25.9 (5.0)	1732.4 (524.9)	51.0 (8.0)	18.9 (3.3)	30.0 (6.1)

Abbreviations: HPFS, Health Professionals' Follow-up Study; NHS, Nurses' Health Study; WGHS, Women's Genome Health Study; T2D, type 2 diabetes; CHD, coronary heart disease; KS, kidney stone; BC, breast cancer; BMI, body mass index; MET, metabolic equivalent of task; HRT, hormone replacement therapy

Table S1. cont.

Study			Current Smoking (%, n)	Alcohol Use (g/day)	Exercise (METs/wk)	Menopause (%,n)	HRT user (%,n)
HPFS							
	T2D Cohort	Cases	11.8 (139)	11.3 (16.3)	14.6 (18.7)	NA	NA
	N=2315	Controls	7.2 (94)	12.0 (15.2)	21.1 (25.2)	NA	NA
	CHD Cohort	Cases	10.8 (47)	11.2 (15.9)	18.3 (23.1)	NA	NA
	N=1212	Controls	10.3 (90)	13.3 (16.4)	20.0 (27.0)	NA	NA
	KS Cohort	Cases	2.3 (23)	8.8 (13.0)	22.3 (41.2)	NA	NA
	N=549	Controls	3.4 (24)	14.0 (18.2)	24.4 (41.3)	NA	NA
NHS							
	T2D Cohort	Cases	17.5 (268)	4.0 (9.5)	11.9 (15.4)	84.8 (1297)	8.5 (130)
	N=3218	Controls	10.3 (90)	6.4 (10.4)	14.2 (18.6)	81.7 (1428)	6.5 (114)
	CHD Cohort	Cases	30.6 (154)	5.7 (10.0)	14.4 (21.3)	91.2 (453)	0 (0)
	N=1013	Controls	28.5 (290)	7.5 (12.2)	14.3 (19.2)	89.6 (917)	0 (0)
	KS Cohort	Cases	6.7 (66)	4.3 (7.6)	14.8 (19.4)	76.7 (302)	0 (0)
	N=490	Controls	5.6(39)	5.3 (8.7)	12.5 (13.9)	72.4 (165)	0 (0)
	BC Cohort	Cases	17.7 (203)	7.8 (12.4)	14.5 (18.2)	87.0 (996)	0 (0)
	N=2043	Controls	13.0 (148)	6.5 (10.3)	16.0 (26.2)	87.2 (996)	0 (0)
WGHS	N=22691	Cohort	11.0 (2710)	4.3 (8.4)	14.7 (18.4)	54.3 (12660)	43.8 (10197)

Table S2. Genome-wide and sub-genome-wide association results from discovery (DietGen) meta-analysis, and replication (CHARGE), and combined joint meta-analysis for percentage of total caloric intake from macronutrients (carbohydrates, protein, and fat), sorted by P-value (P(2GC)) and regression model for association in the discovery cohort.

								DietGen			
Model	**SNPID**	**Nearest Gene**	**Chr**	**BP**	**EA**	**non EA**	**EAF**	**β (%)**	**SE**	**P(2GC)**	**I^2**
Carbohydrates											
Model 1*	rs10163409	*FTO*	16	52696381	a	t	0.69	0.441	0.075	7.4E-09	8.7
	rs6558687	*CSMD1*	8	2591594	t	g	0.07	0.653	0.131	9.1E-07	30.9
	rs197273	*TANK*	2	161602909	a	g	0.48	0.309	0.064	2.4E-06	0.0
	rs133055	*MKL1*	22	39380817	a	g	0.35	0.317	0.067	2.9E-06	0.0
	rs703058	*CUBN*	10	16916058	t	g	0.14	-0.481	0.102	3.2E-06	0.0
	rs7689746	*PDLIM5*	4	95793146	a	g	0.24	-0.357	0.076	3.5E-06	0.0
	rs2970933	*DPP4*	2	162562522	t	c	0.39	-0.316	0.067	4.0E-06	0.0
	rs13065635	*ARGFX*	3	122785100	t	g	0.13	-0.493	0.108	6.5E-06	11.4
	rs1512130	*GABRA4*	4	46647228	a	g	0.33	0.304	0.068	9.5E-06	16.0
Model 2†	rs10163409	*FTO*	16	52696381	a	t	0.69	0.420	0.075	3.4E-08	19.9
	rs197273	*TANK*	2	161602909	a	g	0.48	0.310	0.064	2.0E-06	0.0
	rs2014821	*ITGA8*	10	15588753	a	g	0.11	0.493	0.106	4.2E-06	0.0
	rs13065635	*ARGFX*	3	122785100	t	g	0.13	-0.501	0.108	4.6E-06	26.4
	rs2970933	*DPP4*	2	162562522	t	c	0.39	-0.312	0.067	5.0E-06	0.0
	rs6558687	*CSMD1*	8	2591594	t	g	0.07	0.605	0.131	5.2E-06	40.2
	rs139920	*TNRC6B*	22	39056695	t	c	0.51	-0.299	0.065	5.4E-06	0.0
	rs2896655	*KCNQ3*	8	133354156	a	g	0.11	-0.454	0.099	6.5E-06	0.0
	rs7689746	*PDLIM5*	4	95793146	a	g	0.24	-0.345	0.076	7.3E-06	0.0
	rs589064	*KATNAL1*	13	29589808	c	g	0.39	0.306	0.068	8.3E-06	0.0
Protein											
Model 1*	rs7958151	*GPR133*	12	130183588	a	c	0.38	0.138	0.025	9.6E-08	7.9
	rs17158276	*PRR15*	7	29614602	t	c	0.86	-0.172	0.036	2.4E-06	0.0
	rs1039755	*BUD13*	11	115889336	t	c	0.70	0.136	0.029	3.6E-06	9.5
	rs1440620	*PROX1*	1	212327973	t	c	0.65	-0.158	0.035	7.6E-06	0.0
	rs152621	*FAM105A*	5	14636006	a	g	0.18	0.145	0.032	8.4E-06	0.0
	rs1457974	*IMPG1*	6	77481181	a	g	0.34	-0.114	0.025	9.1E-06	0.0
Model 2†	rs7958151	*GPR133*	12	130183588	a	c	0.38	0.131	0.025	3.8E-07	5.2
	rs1039755	*BUD13*	11	115889336	t	c	0.70	0.145	0.029	7.7E-07	15.1
	rs838133	*FGF21*	19	53951341	a	g	0.45	-0.124	0.026	2.3E-06	29.2
	rs17810895	*PRR15*	7	29581016	c	g	0.07	0.220	0.046	2.5E-06	0.0
	rs152621	*FAM105A*	5	14636006	a	g	0.18	0.148	0.032	5.0E-06	0.0
	rs1440620	*PROX1*	1	212327973	t	c	0.65	-0.159	0.035	7.0E-06	0.0
Fat											
Model 1*	rs6598192	*EP400*	12	131095602	t	c	0.92	-0.480	0.104	5.2E-06	0.0
	rs10789371	*EDN2*	1	41711015	a	g	0.30	0.248	0.054	6.2E-06	19.1
Model 2†	rs10789371	*EDN2*	1	41711015	a	g	0.30	0.251	0.054	4.9E-06	18.7
	rs6598192	*EP400*	12	131095602	t	c	0.92	-0.465	0.104	9.9E-06	0.0

Table S2. cont.

		CHARGE					Joint analysis			
Model	**SNPID**	**β (%)**	**SE**	**P(2GC)**	**1sidedP**	**I^2**	**β (%)**	**SE**	**P**	**N**
Carbohydrates										
Model 1*	rs10163409	-0.029	0.069	6.9E-01	3.5E-02	34.8	0.188	0.051	2.2E-04	71885
	rs6558687	0.016	0.117	8.9E-01	5.9E-02	23.9	0.300	0.087	6.0E-04	71802
	rs197273	0.141	0.058	1.8E-02	2.9E-02	0.0	0.217	0.043	5.4E-07	71887
	rs133055	0.066	0.060	2.8E-01	3.0E-02	45.5	0.178	0.045	6.4E-05	71773
	rs703058	0.065	0.085	4.6E-01	4.3E-02	6.8	-0.161	0.065	1.4E-02	71888
	rs7689746	0.165	0.072	2.5E-02	3.6E-02	16.9	-0.084	0.052	1.1E-01	69585
	rs2970933	0.040	0.061	5.2E-01	3.0E-02	0.8	-0.120	0.045	7.9E-03	71888
	rs13065635	0.094	0.091	3.1E-01	4.6E-02	0.0	-0.151	0.070	3.0E-02	71883
	rs1512130	-0.033	0.060	5.9E-01	3.0E-02	24.7	0.116	0.045	1.0E-02	71879
Model 2†	rs10163409	-0.052	0.070	4.6E-01	3.5E-02	32.3	0.166	0.051	1.1E-03	71326
	rs197273	0.165	0.058	5.7E-03	2.9E-02	0.0	0.231	0.043	9.6E-08	71328
	rs2014821	-0.055	0.096	5.8E-01	4.8E-02	0.0	0.194	0.071	6.4E-03	71329
	rs13065635	0.054	0.091	5.7E-01	4.6E-02	0.0	-0.178	0.070	1.1E-02	71324
	rs2970933	0.006	0.061	9.2E-01	3.0E-02	15.9	-0.137	0.045	2.5E-03	71329
	rs6558687	-0.020	0.117	8.7E-01	5.9E-02	37.6	0.259	0.087	3.0E-03	71243
	rs139920	-0.086	0.063	1.8E-01	3.1E-02	1.0	-0.189	0.045	2.7E-05	69024
	rs2896655	-0.082	0.090	3.8E-01	4.5E-02	0.0	-0.250	0.067	1.7E-04	71279
	rs7689746	0.184	0.072	1.3E-02	3.6E-02	9.7	-0.069	0.052	1.9E-01	69026
	rs589064	0.059	0.059	3.2E-01	2.9E-02	0.0	0.165	0.044	1.9E-04	71327
Protein										
Model 1*	rs7958151	0.016	0.026	5.4E-01	1.3E-02	0.0	0.079	0.018	1.4E-05	71764
	rs17158276	0.073	0.036	5.1E-02	1.8E-02	0.0	-0.052	0.026	4.4E-02	71889
	rs1039755	-0.044	0.036	2.4E-01	1.8E-02	0.0	0.066	0.023	3.2E-03	62060
	rs1440620	-0.067	0.034	5.6E-02	1.7E-02	0.0	-0.112	0.024	4.3E-06	68633
	rs152621	-0.011	0.034	7.7E-01	1.7E-02	1.1	0.073	0.023	1.9E-03	69538
	rs1457974	-0.021	0.026	4.4E-01	1.3E-02	41.2	-0.069	0.018	1.5E-04	71890
Model 2†	rs7958151	0.007	0.026	8.0E-01	1.3E-02	0.0	0.071	0.018	9.2E-05	71151
	rs1039755	-0.037	0.038	3.4E-01	1.9E-02	0.0	0.078	0.023	6.3E-04	68028
	rs838133	-0.098	0.030	1.5E-03	1.5E-02	48.7	-0.113	0.020	7.9E-09	68968
	rs17810895	-0.076	0.047	1.2E-01	2.4E-02	0.0	0.077	0.033	2.0E-02	71263
	rs152621	-0.008	0.034	8.1E-01	1.7E-02	0.0	0.075	0.023	1.2E-03	68925
	rs1440620	-0.078	0.032	1.8E-02	1.6E-02	0.0	-0.116	0.024	1.0E-06	61460
Fat										
Model 1*	rs6598192	-0.026	0.128	8.4E-01	6.4E-02	0.0	-0.299	0.081	2.1E-04	59982
	rs10789371	-0.010	0.052	8.5E-01	2.6E-02	0.0	0.113	0.037	2.5E-03	71880
Model 2†	rs10789371	-0.014	0.052	8.0E-01	2.6E-02	0.0	0.112	0.037	2.7E-03	71267
	rs6598192	-0.041	0.128	7.6E-01	6.4E-02	0.0	-0.297	0.081	2.3E-04	59390

* Model 1 adjusts for age, sex (if applicable), location and sub-population stratification

† Model 2 adjusts for model 1 covariates in addition to BMI (kg/m^2)

Abbreviations: CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair position – build 36; EA, effect allele; nonEA, non-effect allele; EAF, effect allele frequency; β, beta-coefficient; SE, standard error; P(2GC), p-value doubly corrected for genomic control; 1sidedP, one-sided p-value; P, p-value; N, sample size

Table S3. Secondary macronutrient intake associations in DietGen (HPFS/NHS/WGHS) for SNPs with genome-wide associations for macronutrient intake from discovery or joint meta-analysis.

				Carbohydrates			Protein			Fat		
SNP	**Model**	**Gene**	**Chr**	**β%**	**SE**	**P**	**β%**	**SE**	**P**	**β%**	**SE**	**P**
rs197273		*TANK*	2									
	Model 1*			0.31	0.06	2.4E-06	-0.05	0.02	6.8E-02	-0.16	0.05	1.4E-03
	Model 2†			0.31	0.06	2.0E-06	-0.04	0.02	8.6E-02	-0.17	0.05	7.8E-04
rs10163409		*FTO*	16									
	Model 1*			0.44	0.08	7.4E-09	-0.05	0.03	6.1E-02	-0.23	0.06	6.1E-05
	Model 2†			0.42	0.07	3.4E-08	-0.05	0.03	8.0E-02	-0.22	0.06	1.6E-04
rs838133		*FGF21*	19									
	Model 1*			0.22	0.07	1.3E-03	-0.12	0.03	1.1E-05	-0.22	0.05	3.5E-05
	Model 2†			0.23	0.07	5.9E-04	-0.12	0.03	2.3E-06	-0.21	0.05	7.1E-05

* Model 1 adjusts for age, sex, location and sub-population stratification

† Model 2 adjusts for model 1 covariates in addition to BMI (kg/m^2)

Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; β, beta-coefficient; SE, standard error; P, p-value; N, sample size

Table S4. Estimates of variance in percentage of caloric intake from carbohydrates, protein and fat explained by 339,596 genotyped SNPs with MAF>1% (top panel) and 326,504 genotyped SNPs with MAF>5% (bottom panel) from the WGHS.

MAF>0.01	**Univariate**			**Model 1***			**Model 2†**		
	h^2	**SE**	**P**	h^2	**SE**	**P**	h^2	**SE**	**P**
Carbohydrates	0.066	0.021	9.1E-05	0.066	0.021	1.2E-04	0.061	0.021	2.9E-04
Protein	0.081	0.022	2.7E-05	0.081	0.022	1.5E-05	0.081	0.022	2.6E-05
Fats	0.073	0.022	3.8E-05	0.067	0.022	2.3E-04	0.061	0.022	8.1E-04

MAF>0.05	**Univariate**			**Model 1***			**Model 2†**		
	h^2	**SE**	**P**	h^2	**SE**	**P**	h^2	**SE**	**P**
Carbohydrates	0.062	0.021	1.4E-04	0.062	0.021	2.1E-04	0.057	0.021	5.5E-04
Protein	0.080	0.022	2.4E-05	0.080	0.022	1.4E-05	0.079	0.022	2.4E-05
Fats	0.070	0.021	5.1E-05	0.064	0.021	3.2E-04	0.057	0.021	1.3E-03

* Model 1 adjusts for age, sex, location and sub-population stratification

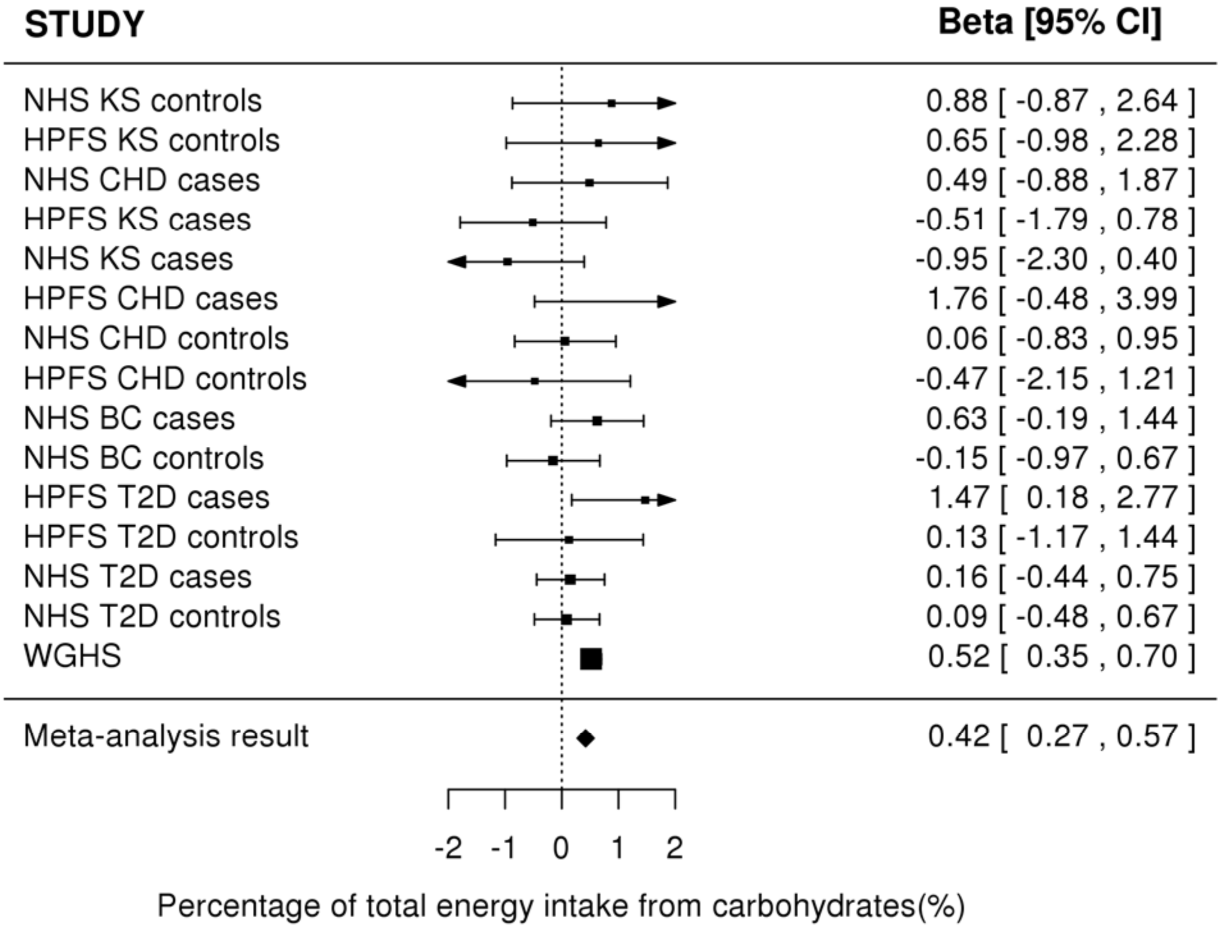
† Model 2 adjusts for model 1 covariates in addition to BMI (kg/m^2)

Abbreviations: h^2, proportion of variance explained or heritability; SE, standard error; P, p value

Supplemental figures

Figure S1. Forest plot of the effect of rs10163409 in *FTO* on percentage of total energy intake from carbohydrates in a fixed-effects meta-analysis of 33,388 men and women of European ancestry in models with (a) and without adjustment for BMI (b). Studies are listed in ascending order by sample size starting with the smallest study (NHS kidney stone controls) to the largest (WGHS). The beta represents the percentage of total energy intake from carbohydrates per “A” allele of rs10163409.

a.



b.

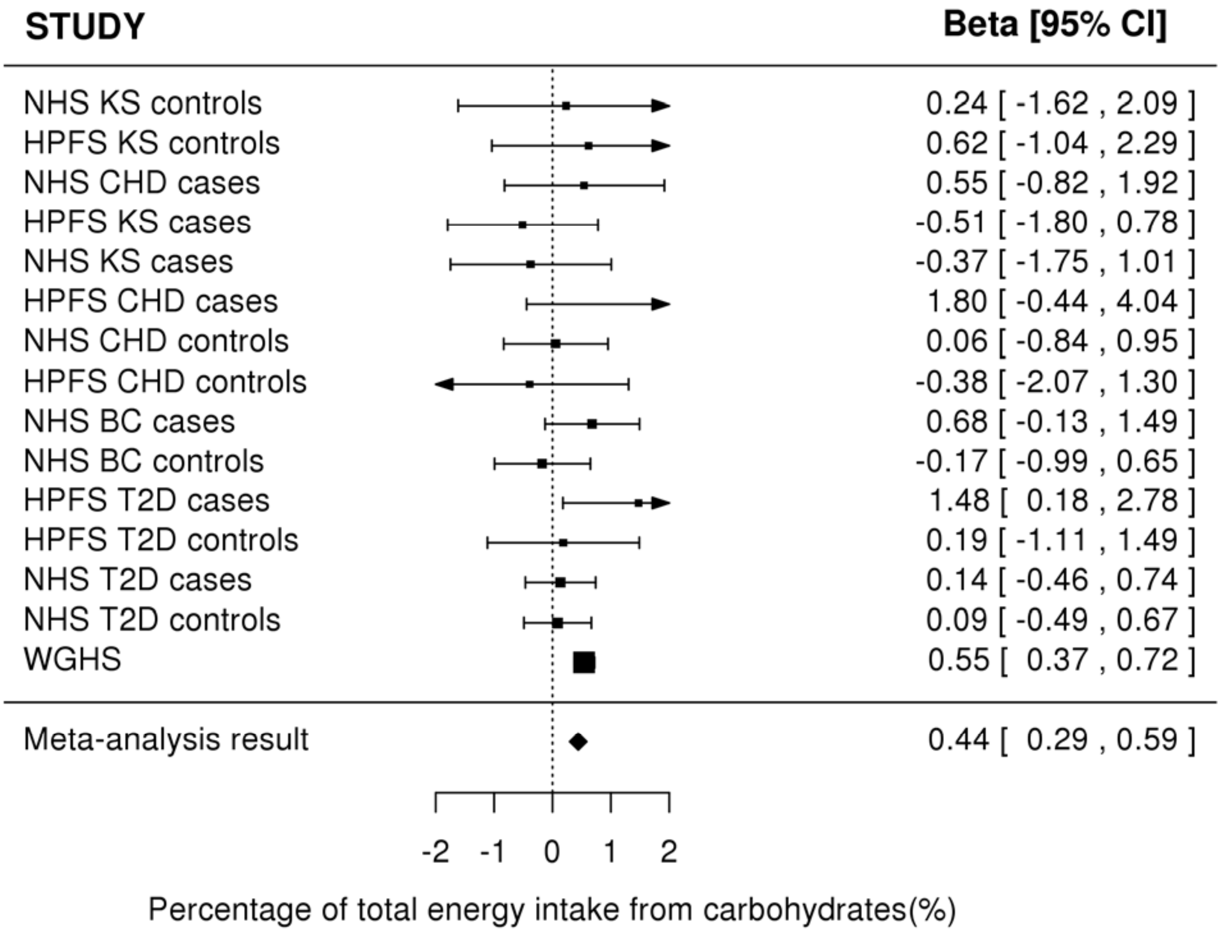
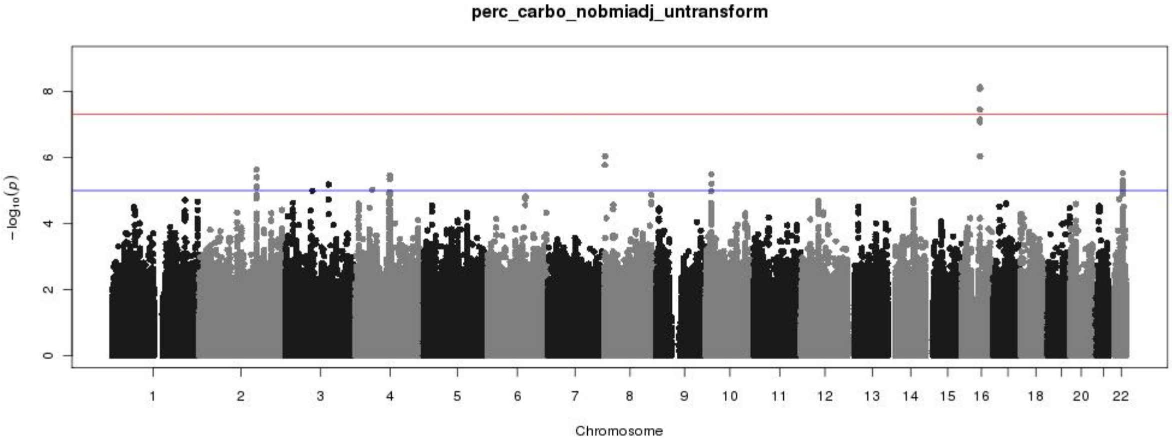
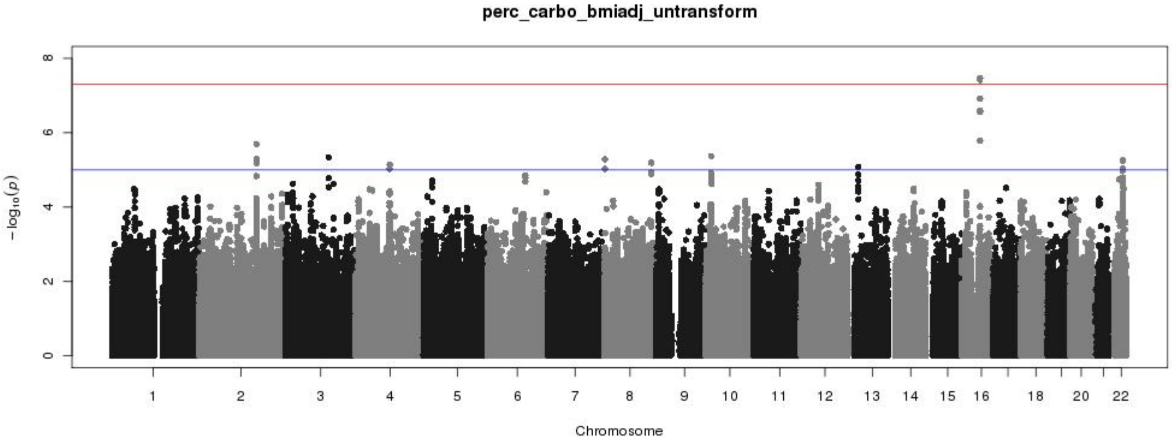

STUDY
Beta [95% CI]
NHS KS controls 0.24 [-1.62 , 2.09]
HPFS KS controls 0.62 [-1.04 , 2.29]
NHS CHD cases 0.55 [-0.82 , 1.92]
HPFS KS cases -0.51 [-1.80 , 0.78]
NHS KS cases -0.37 [-1.75 , 1.01]
HPFS CHD cases 1.80 [-0.44 , 4.04]
NHS CHD controls 0.06 [-0.84 , 0.95]
HPFS CHD controls -0.38 [-2.07 , 1.30]
NHS BC cases 0.68 [-0.13 , 1.49]
NHS BC controls -0.17 [-0.99 , 0.65]
HPFS T2D cases 1.48 [0.18 , 2.78]
HPFS T2D controls 0.19 [-1.11 , 1.49]
NHS T2D cases 0.14 [-0.46 , 0.74]
NHS T2D controls 0.09 [-0.49 , 0.67]
WGHS 0.55 [0.37 , 0.72]
Meta-analysis result 0.44 [0.29 , 0.59]
-2
-1
0
1
2
Percentage of total energy intake from carbohydrates(%)

Figure S2. Manhattan plots of –log10 *P* values from genome-wide association by meta-analysis for percentage of caloric intake from carbohydrates (a, b), protein (c, d), and fat (e, f). All regression models included basic adjustment for age, location and sub-population stratification measures (a-f). Additional adjustment for BMI was included for regression results shown in b, d and f. The threshold for genome-wide significance ($P<5x10^{-8}$) is indicated by the red horizontal line in the Manhattan plot, and the threshold for sub-genome-wide significance is indicated by the blue horizontal line.

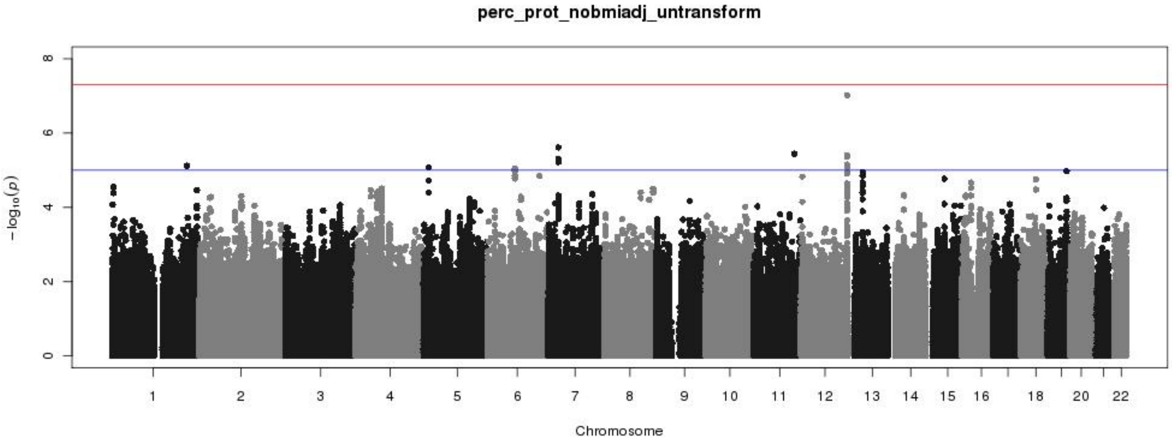
a.



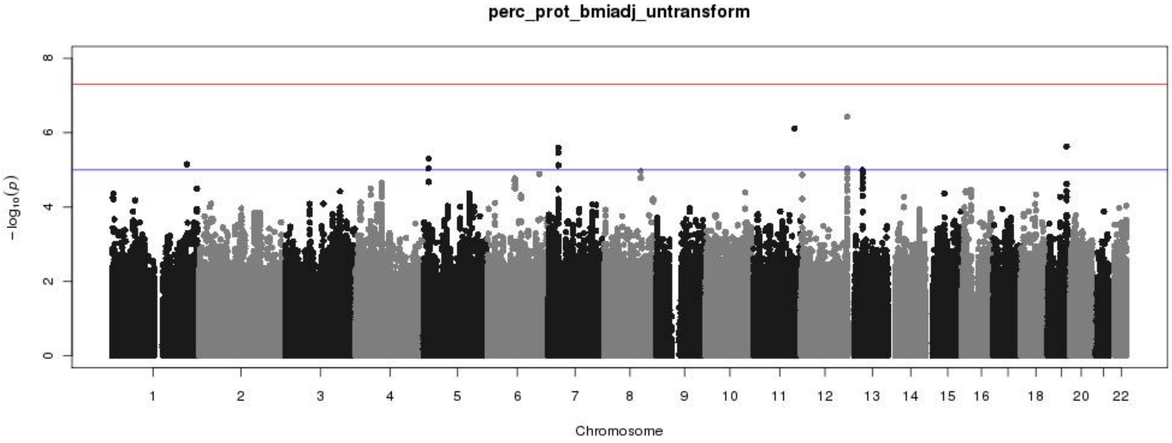
b.



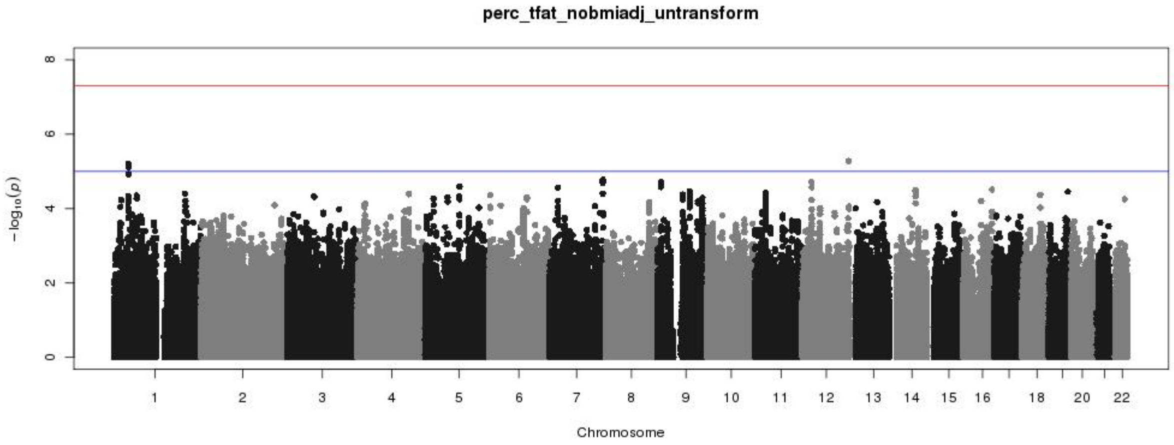
c.


perc_prot_nobmiadj_untransform
$-\log_{10}(p)$
0
2
4
6
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
18
20
22
Chromosome

d


perc_prot_bmiadj_untransform
$-\log_{10}(p)$
0
2
4
6
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
18
20
22
Chromosome

e.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f.

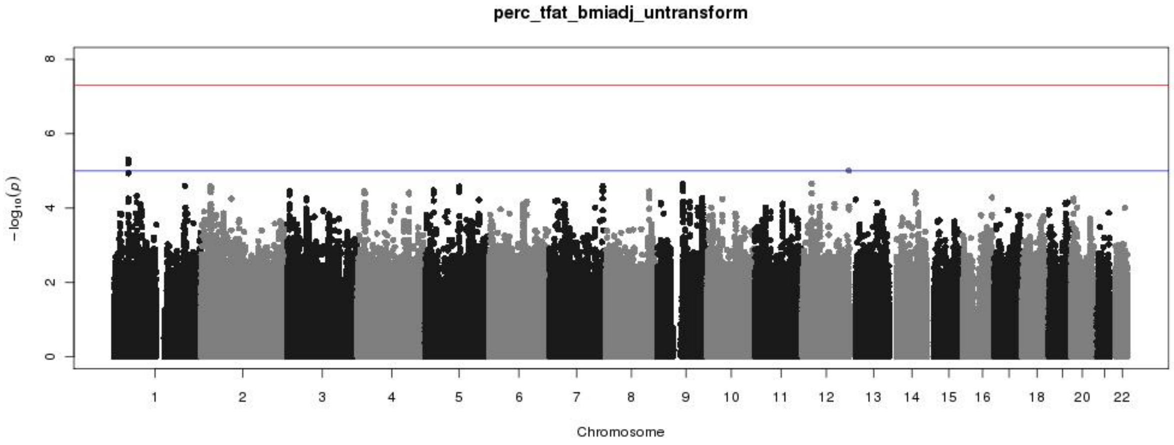
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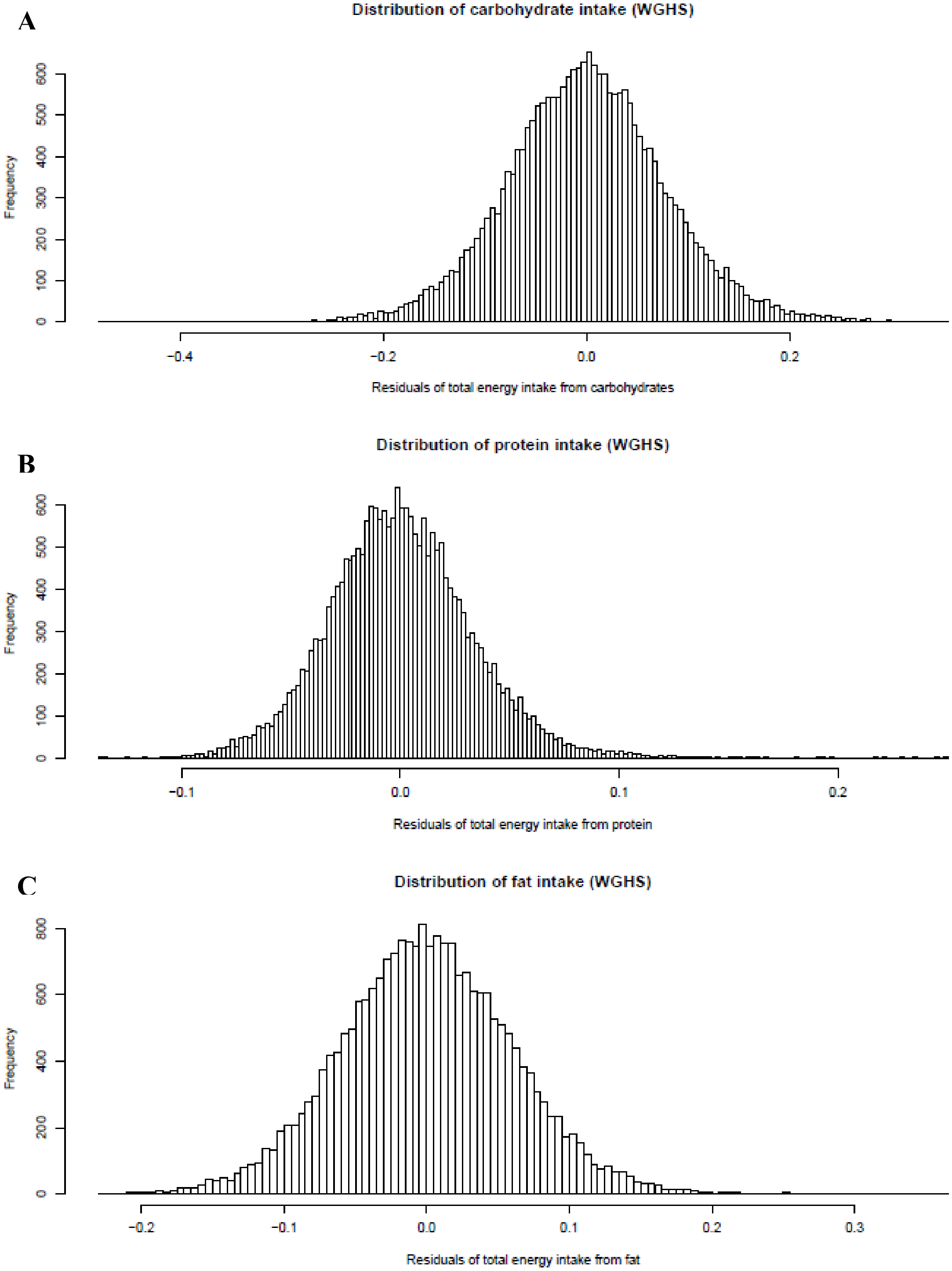
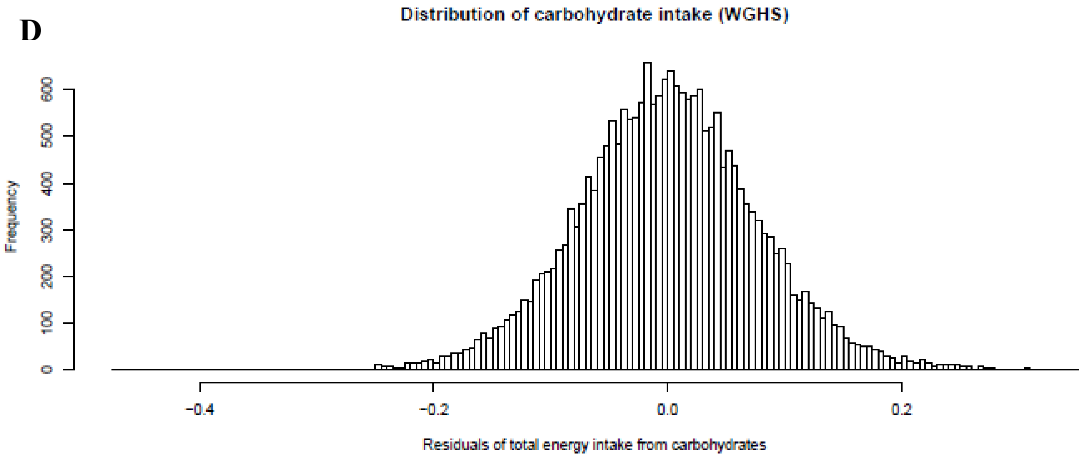
Figure S3. Distributions of macronutrient intake in the Women's Genome Health Study (WGHS). Residuals from percentage of total energy intake from A+D) carbohydrates, B+E) proteins, and C+F) fats adjusted for age, location, measures of population stratification, with (D-F) and without (A-C) adjustment for BMI.

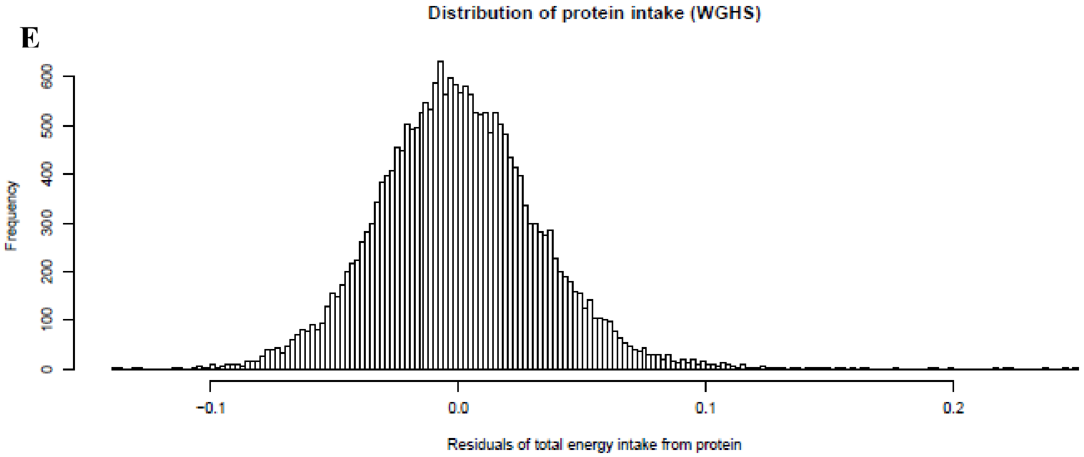


D



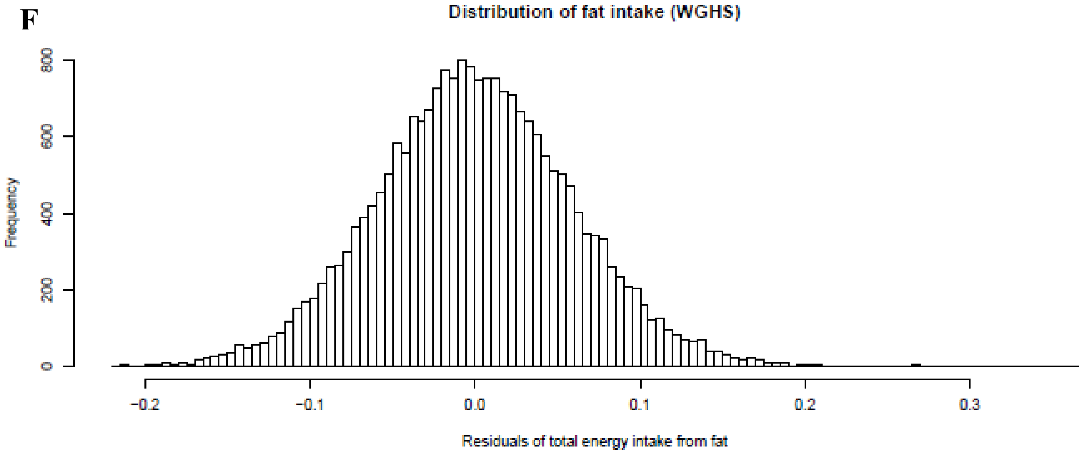
Distribution of carbohydrate intake (WGHS)

E



Distribution of protein intake (WGHS)

F



Distribution of fat intake (WGHS)