

SUPPLEMENTARY RESULTS

Supplementary Table 1: Association of FTO SNPs with body mass index (BMI).

SNP	Position (bp)	N	Str	Alleles 1/2	Allele frequency		Mean BMI			BMI P value			Call Rate
					1	2	11	12	22	ADD	REC	DOM	
rs1861869	52347682	697	-	C/G	0.49	0.51	26.9	26.1	25.5	0.002	0.009	0.02	0.99
rs1861868	52347903	701	-	A/G	0.47	0.53	27.4	26.5	25.9	<0.001	0.002	0.01	0.99
rs9940700	52352910	646	-	C/G	0.8	0.2	26	26	26.4	0.93	1	0.77	0.92
rs9939973	52358069	704	-	C/T	0.49	0.51	25.4	26.2	26.6	0.01	0.02	0.12	1
rs9940128	52358255	703	-	C/T	0.49	0.51	25.4	26.2	26.5	0.01	0.01	0.11	1
rs9922047	52363781	703	-	C/G	0.53	0.47	26.7	26.1	25.5	0.01	0.05	0.05	1
rs16952522	52364999	704	-	C/G	0.04	0.96	26.5	27.4	26	0.07	0.93	0.05	1
rs17817288	52365265	704	+	A/G	0.47	0.53	25.5	26.1	26.7	0.01	0.05	0.04	1
rs1477196	52365759	651	-	C/T	0.65	0.35	26.7	26	24.9	<0.001	0.01	0.005	0.92
rs1121980	52366748	704	-	C/T	0.5	0.5	25.4	26.3	26.5	0.02	0.01	0.18	1
rs7193144	52368187	695	-	A/G	0.52	0.48	25.7	26.2	26.6	0.05	0.06	0.17	0.99
rs8050136	52373776	690	+	A/C	0.48	0.52	26.5	26.3	25.6	0.04	0.20	0.04	0.98
rs9926289	52378004	703	-	C/T	0.52	0.48	25.6	26.2	26.5	0.06	0.06	0.25	1
<u>rs9939609</u>	52378028	703	-	A/T	0.52	0.48	25.6	26.2	26.5	0.06	0.07	0.22	1
<u>rs9930506</u>	52387966	698	-	C/T	0.48	0.52	26.4	26.2	25.6	0.08	0.30	0.08	0.99
rs11075994	52407580	704	-	C/T	0.79	0.21	26.3	25.8	25.3	0.08	0.10	0.32	1
rs1421090	52407671	704	+	A/G	0.76	0.24	26.4	26	24.9	0.03	0.09	0.04	1
rs9972717	52408805	701	+	A/G	0.04	0.96	22.8	24.5	26.2	0.005	0.52	0.006	0.99
rs10852522	52416278	704	-	A/T	0.43	0.57	25.6	26.3	26.1	0.53	0.13	0.75	1
rs10521308	52422627	697	-	C/T	0.96	0.04	26	**	**	**	**	**	0.99
rs17818902	52429307	702	-	A/C	0.58	0.42	25.7	26.5	25.9	0.47	0.09	0.48	1

rs17818920	52429404	672	-	C/T	0.43	0.57	25.9	26.7	25.7	0.40	0.31	0.03	0.95
rs8053367	52432985	661	-	A/C	0.53	0.47	26.2	26.3	25.5	0.23	0.82	0.07	0.94
rs8053740	52433213	703	-	C/G	0.42	0.58	25.6	26.4	26.1	0.38	0.08	0.93	1
rs7203051	52433650	700	-	C/G	0.42	0.58	25.6	26.4	26.2	0.37	0.08	0.93	0.99
rs7205009	52433945	700	+	C/T	0.42	0.58	25.6	26.4	26.1	0.42	0.10	0.90	0.99
rs7205213	52434067	695	+	C/T	0.42	0.58	25.6	26.4	26.1	0.41	0.09	0.90	0.99
rs8061228	52439872	701	+	C/T	0.08	0.92	23.7	25.9	26.1	0.46	0.33	0.57	0.99
rs12448529	52440158	674	+	C/T	0.92	0.08	26	26	23.8	0.77	0.86	0.44	0.96
rs2111114	52440953	704	+	C/T	0.08	0.92	23.7	26	26.1	0.54	0.32	0.66	1
rs12597422	52445239	679	-	C/T	0.06	0.94	22.9	24.9	26.2	0.006	0.53	0.007	0.96
rs8060649	52463600	678	+	A/G	0.39	0.61	25.3	26	26.5	0.02	0.06	0.06	0.96
rs8053707	52466104	701	+	C/T	0.92	0.08	26	26.6	25.4	0.31	0.25	0.70	0.99
rs10521304	52466158	702	-	A/G	0.67	0.33	26.6	25.6	25.5	0.004	0.002	0.29	1
rs10521303	52466686	703	+	C/T	0.60	0.4	26.5	26	25.4	0.02	0.07	0.07	1
rs1362571	52469271	702	-	A/C	0.38	0.62	25.3	26.1	26.4	0.03	0.05	0.11	1
rs2111112	52495133	678	-	A/G	0.22	0.78	26.5	26.3	26	0.34	0.65	0.37	0.96
rs9937234	52495551	704	+	C/T	0.89	0.11	26.1	26.2	26.6	0.68	0.72	0.74	1
rs4784330	52499785	695	+	C/T	0.03	0.97	23.3	24.8	26.2	0.06	0.50	0.07	0.99
rs12935710	52500306	693	-	A/G	0.23	0.77	26.4	26.4	26	0.27	0.70	0.24	0.98
rs12708942	52503705	699	+	A/T	0.03	0.97	23.3	24.8	26.2	0.06	0.50	0.07	0.99
rs16952649	52513553	686	-	A/G	0.11	0.89	25	26.6	25.9	0.27	0.37	0.15	0.97
rs12932428	52518028	695	+	C/T	0.55	0.45	25.8	26.3	25.7	0.92	0.38	0.25	0.99
rs7205426	52531308	702	+	A/C	0.51	0.49	25.8	26.2	26.2	0.50	0.40	0.82	1
rs7203181	52540981	694	+	A/C	0.19	0.81	25.8	26.4	26	0.42	0.75	0.30	0.98
rs12925189	52542774	703	+	A/G	0.79	0.21	26	26.3	25.6	0.55	0.36	0.53	1
rs6499658	52550205	696	-	A/T	0.96	0.04	26.1	**	**	**	**	**	0.99
rs11644943	52553085	703	-	A/T	0.79	0.21	26	26.2	26.2	0.56	0.53	0.90	1
rs17823223	52557139	704	+	C/T	0.72	0.28	26.6	25.8	25	0.001	0.003	0.05	1

rs1111483	52558408	692	-	C/T	0.35	0.65	26.4	26.1	25.9	0.33	0.44	0.42	0.98
rs7194907	52560984	704	+	C/T	0.38	0.62	26.4	26.2	25.8	0.20	0.48	0.22	1
rs8053888	52561306	703	-	A/G	0.62	0.38	25.8	26.2	26.4	0.20	0.21	0.49	1
rs9940629	52562312	688	+	A/G	0.27	0.73	26.7	26.3	25.9	0.09	0.29	0.13	0.98
rs9932411	52562664	697	+	C/T	0.28	0.72	26.7	26.3	25.8	0.05	0.25	0.06	0.99
rs16952725	52571768	681	+	C/G	0.06	0.94	24.8	25.8	26.2	0.38	0.60	0.41	0.97
rs16952728	52572144	702	-	C/G	0.08	0.92	26	26.4	26.1	0.55	0.94	0.53	1
rs13337356	52574811	688	+	C/G	0.75	0.25	26	26.1	26.1	0.90	0.87	1	0.98
rs1125392	52577646	693	-	A/G	0.45	0.55	25.9	26.2	25.9	0.88	0.56	0.47	0.98
rs8049235	52578510	703	-	C/T	0.44	0.56	26.2	26.3	25.6	0.15	0.87	0.05	1
rs4784337	52581767	704	+	A/G	0.14	0.86	25.7	26.3	26	0.70	0.70	0.56	1
rs11864881	52586805	702	-	C/T	0.49	0.51	26.1	26.4	25.5	0.16	0.94	0.02	1
rs41421450	52591295	662	+	C/G	0.91	0.09	25.9	**	**	**	**	**	0.94
rs7205987	52591646	704	-	A/G	0.79	0.21	26.5	25.6	25	0.003	0.004	0.16	1
rs16952770	52592453	704	-	A/G	0.84	0.16	26.1	26.2	26.1	0.87	0.85	1	1
rs13335453	52593744	699	-	A/C	0.79	0.21	26.5	25.5	25.3	0.004	0.003	0.32	0.99
rs7200972	52593853	704	+	A/G	0.73	0.27	25.9	26.2	26.8	0.15	0.28	0.19	1
rs4784338	52595472	679	-	A/C	0.29	0.71	26.8	26.1	25.9	0.19	0.21	0.34	0.96
rs1345390	52602016	704	+	C/T	0.61	0.39	26.6	25.8	25.8	0.03	0.01	0.35	1
rs2111118	52606654	704	+	C/T	0.39	0.61	25.8	25.8	26.6	0.03	0.34	0.01	1
rs17227068	52606706	700	-	C/T	0.94	0.06	26.2	25	26.3	0.02	0.01	0.93	0.99
rs2111116	52606753	704	+	A/G	0.61	0.39	26.6	25.8	25.8	0.03	0.01	0.34	1
rs8043737	52607166	703	-	A/G	0.39	0.61	25.8	25.8	26.6	0.03	0.35	0.01	1
rs1861554	52607268	702	+	A/G	0.39	0.61	25.8	25.8	26.6	0.03	0.35	0.01	1
rs17825567	52615272	695	+	A/C	0.13	0.87	25.7	26.2	26.1	0.89	0.69	0.76	0.99
rs860713	52626966	703	+	A/G	0.61	0.39	26.6	25.8	25.8	0.03	0.01	0.35	1
rs2192872	52632128	697	+	C/T	0.33	0.67	26.1	25.9	26.4	0.36	0.96	0.222	0.99
rs2689249	52639871	704	+	A/G	0.69	0.31	26.4	25.9	25.8	0.20	0.17	0.57	1

rs16952906	52640668	704	+	C/T	0.08	0.92	26.6	25.3	26.2	0.07	0.79	0.05	1
rs2689246	52654678	703	-	A/G	0.91	0.09	26.2	25.2	27.2	0.07	0.03	0.50	1
rs12149010	52665424	681	-	A/G	0.33	0.67	26.1	26.3	25.9	0.45	1	0.33	0.97
rs2540769	52665463	679	-	C/T	0.09	0.91	26.3	25.3	26.2	0.07	0.90	0.04	0.96
rs2665275	52665624	679	+	C/T	0.93	0.07	26.2	25	27.3	0.05	0.02	0.54	0.96
rs12599672	52673577	690	-	A/T	0.9	0.1	26.2	25.5	24.9	0.08	0.09	0.48	0.98
rs3928987	52675012	702	-	C/T	0.65	0.35	26.2	26.2	25.2	0.16	0.53	0.06	1
rs697769	52679248	704	+	A/G	0.58	0.42	26.2	26.2	25.8	0.55	0.83	0.41	1
rs708254	52680890	651	-	C/T	0.45	0.55	25.8	26.1	26.3	0.36	0.41	0.52	0.92
rs708251	52682397	662	+	A/T	0.58	0.42	26.2	26	26.1	0.86	0.74	0.92	0.94
rs2665272	52684118	704	+	C/T	0.44	0.56	26.1	26.1	26.2	0.87	1	0.81	1
rs16953047	52687671	703	-	A/C	0.13	0.87	25.4	26.3	26	0.73	0.53	0.56	1
rs12927155	52691301	704	-	A/G	0.13	0.87	25.4	26.3	26	0.71	0.53	0.54	1
rs12445828	52692303	704	+	C/T	0.87	0.13	26	26.3	25.4	0.71	0.54	0.53	1
rs2540775	52694760	702	-	C/T	0.87	0.13	26	26.3	25.4	0.68	0.52	0.53	1

Underlined SNPs rs9939609 and rs9930506 are the SNPs originally reported to be associated with BMI. SNPs shown in bold are the two SNPs most strongly associated with BMI in the Amish within the *FTO* region ($r^2 = 0.36$).

** Analysis results not shown due to failure of model convergence.

Abbreviations: ADD, additive genetic model; BMI, body mass index; DOM, dominant genetic model; REC, recessive genetic model; STR, strand.

Supplementary Table 2: *Clinical characteristics (mean, SD) of the study population by FTO rs1477196 genotypes.*

	CC	CT	TT	
Characteristics	N=261	N=312	N=78	p^{\dagger}
Women (%)	46	48.4	50.0	0.36
Age (yr)	42.7 ± 14.9	43.9 ± 13.8	46.2 ± 13.8	0.05
BMI (kg/m ²)	26.8 ± 4.7	26.6 ± 4.4	25.5 ± 4.1	0.001
Waist circumference (cm)	87.8 ± 10.6	87.5 ± 11.4	84.9 ± 10.1	0.01
Weight	74.9 ± 12.6	74.6 ± 12.7	71.1 ± 12.3	0.01
Height	167.4 ± 9.3	167.2 ± 9.3	167.3 ± 9.4	0.38
Overweight (25 ≤ BMI < 30) (%)	58.6	61.2	48.7	0.03
Obese (BMI ≥ 30) (%)	23.8	18.3	12.8	0.002
Median total daily accelerometer counts/1000* (25%, 75%)	377 (267, 563)	405 (286, 580)	420 (284, 589)	--
Physical activity**	-0.03 ± 0.45	0.01 ± 0.45	0.06 ± 0.49	0.16
	N=130	N=164	N=44	p^{\dagger}
Total fat mass (kg)	21.6 ± 10.1	20.2 ± 9.2	17.4 ± 8.9	<0.001
Total lean mass (kg)	53.3 ± 9.7	53.6 ± 9.9	51.2 ± 9.8	0.19
Total % fat	28.2 ± 10.8	26.9 ± 9.7	24.9 ± 10.9	0.01

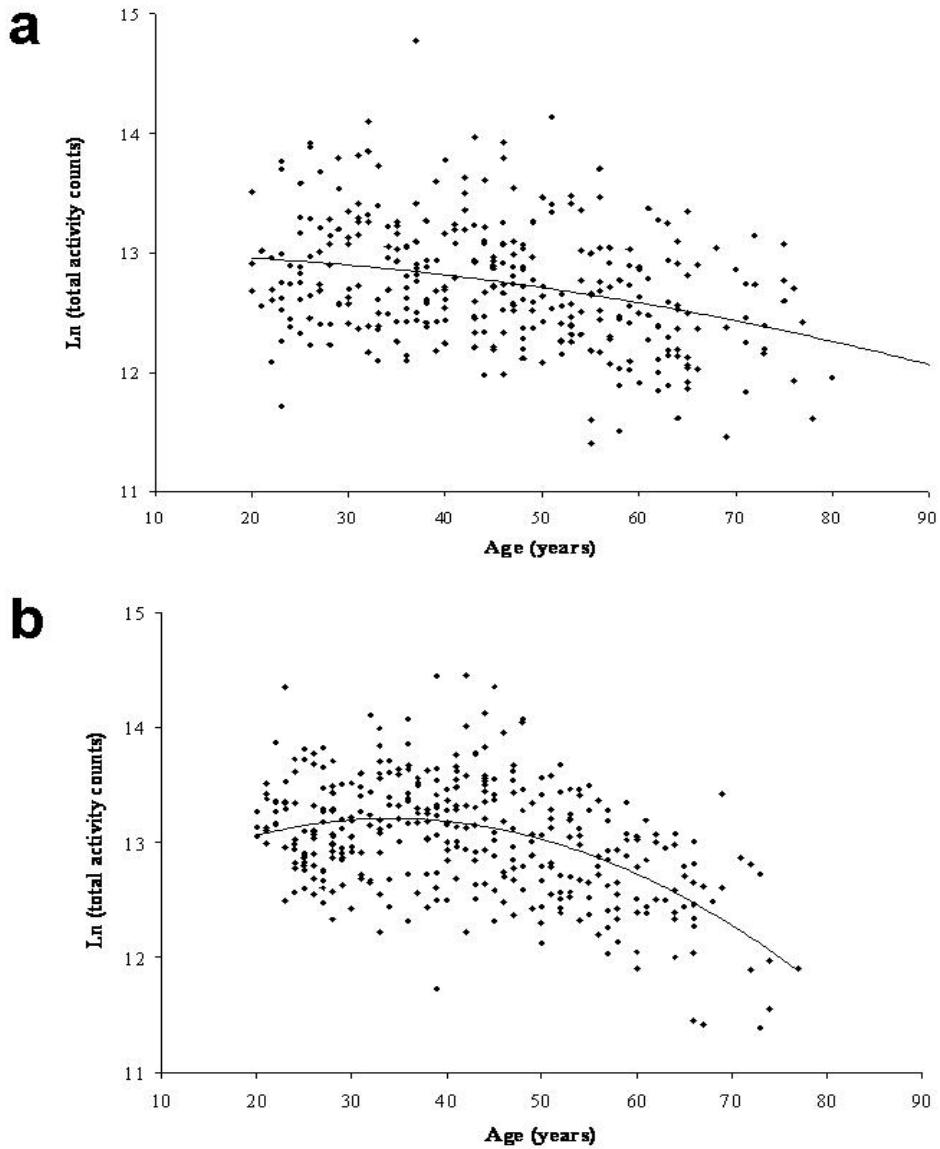
* Total accelerometer counts, a measure of physical activity, were calculated using Actical activity monitors worn for 7 consecutive 24-hour days. ** Physical activity presented as age, age², and sex adjusted mean residuals of ln-transformed total accelerometer counts. † Based on variance components analysis under an additive model. All comparisons were adjusted for sex, age, age², age × sex, and age² × sex, except for women and age variables.

Supplementary Table 3. Haplotypes for FTO SNPs rs1861868, rs1477196, and rs9939609. *P*-value calculated by score test after adjustment for sex, age and age², using HaploStats software. Analysis was restricted to samples completely genotyped at all three SNPs (n= 648).

Haplotype	Frequency	Haplotype score	<i>P</i> value
GTA	0.330	-3.49	<0.001
GCA	0.039	-0.25	0.80
GCT	0.147	-0.13	0.90
ATA	0.030	0.20	0.84
ACT	0.349	1.77	0.08
ACA	0.104	2.73	0.006

Global $p = 0.006$, $df = 5$

Supplementary Figure 1: *Ln-transformed total physical activity as a function of age in women (a) and men (b).* The curve shows the regression line for ln-transformed total physical activity as a function of age and age². Subjects above the regression line (positive residuals) were defined as “high activity” for age and sex, and those below the regression line as “low activity”.



Supplementary Figure 2: Predicted BMI as a function of residualized age- and sex-specific ln-transformed physical activity accelerometer counts according to *FTO* rs1861868 genotypes. On the left side of the plot (low physical activity), BMI levels are strikingly dissimilar between rs1861868 genotypes. In contrast, on the right side of the plot, similar BMI levels can be seen across genotypes, particularly in subjects with very high levels of physical activity.

