SUPPORTING INFORMATION:

- **Note on calculation of the association between adiposity traits and mortality by Mendelian randomization based on the *FTO* SNP as instrumental variable**

- **Table S1: Descriptive information of the 37 study samples included in the meta-analysis sorted alphabetically by study name**

- **Table S2: Main analysis of the association of adiposity phenotypes and *FTO* on all-cause mortality based on all time-at-risk ages, and when using age-restrictions to being older than 60, 65 and 70 years, respectively**

- **Table S3: Main analysis of the association of adiposity phenotypes and *FTO* on all-cause mortality separately for males and females**

Note on calculation of the association between adiposity traits and mortality by Mendelian randomization based on the *FTO* SNP as instrumental variable

Let *M*, *G* and *A* be related to the mortality, genetic (SNP) and adiposity variables, respectively. Further, let $\beta_{M,G}$ and $\beta_{A,G}$ be the calculated regression coefficients related to the *M* vs. *G* and *A* vs. *G* analyses. Here the latter one is based on a standard linear regression, whereas the former one is based on Cox regression and hence the corresponding hazard ratio $HR_{M,G}=exp(\beta_{M,G})$. From this, a crude calculation on the *M* vs. *A*-relation may be calculated through the equation

$$HR_{M,A} = \exp\left[\frac{\log(HR_{M,G})}{\beta_{\mathrm{A,G}}}\right]$$

which is found based on a few basic algebraic steps starting out from

$$\log(HR_{M,A}) \cdot \beta_{\mathrm{A,G}} = \beta_{M,A} \cdot \beta_{\mathrm{A,G}} = \beta_{\mathrm{M,G}} = \log(HR_{M,G})$$

Now, letting *A* correspond to *BMI* and *FMI*, respectively, and the *FTO-SNP* to *G*, one can derive the calculations

$$HR_{M,BMI} = \exp\left[\frac{\log(1.02)}{0.32}\right] = 1.05$$

and

$$HR_{M,FMI} = \exp\left[\frac{\log(1.01)}{0.17}\right] = 1.05$$

(Note that more decimal digits – higher accuracy – have been used for the calculations than are explicitly displayed in rounded form here.)

38 **Table S1: Descriptive information of the 37 study samples included in the meta-analysis sorted alphabetically by study name**

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Study	Country	Sex	N	Deaths	Mean age at entry (years)	Mean follow-up time (years)	Mean BMI (kg/m^2)	*FTO* SNP	MAF
Age, Gene/Environment Susceptibility Study (AGES) (10)	IS	M	1,318	512	76.5	7.4	27.2	rs9939609	0.41
		F	1,769	505	76.2	7.9	27.7	rs9939609	0.40
Australian Twin-Family Study (AUSTWIN) (11)	AUS	M	145	23	59.1	14.6	25.7	rs9939609	0.39
		F	513	61	61.1	14.4	25.2	rs9939609	0.39
British Women's Heart and Health Study (BWHHS)* (12)	UK	F	3,144	521	68.8	9.6	27.8	rs9939609	0.39
The Caerphilly Study (CAERPHILLY) (13)	UK	M	1,152	479	65.7	12.0	27.4	rs9939609	0.38
Cohort Lausanne Study (COLAUS) (14)	CH	M	1,959	98	53.0	5.5	26.7	rs9939609	0.42
		F	2,021	52	54.1	5.6	25.7	rs9939609	0.41
Danish1905 Cohort (DANISH 1905) (15)	DK	M	345	336	93.1	3.2	24.7	rs9939609	0.38
		F	697	677	93.1	4.1	24.1	rs9939609	0.39
Danish diet, cancer & health cohort (DCH)* (16)	DK	M	1,093	46	59.4	6.6	28.4	rs9939609	0.44
		F	1,048	19	59.3	6.7	28.1	rs9939609	0.42
Estonian Genome Center (EGCUT) (17)	EE	M	3,286	651	51.0	4.0	27.1	rs9939609	0.44
		F	3,689	672	54.4	4.3	27.5	rs9939609	0.45

European Prospective Investigation into Cancer and Nutrition Norfolk (EPIC NORFOLK) (18)	UK	M	9,689	1,905	59.7	12.0	26.6	rs1121980	0.43
		F	9,659	1,148	59.4	12.0	26.5	rs1121980	0.43
European Prospective Investigation into Cancer and Nutrition Potsdam (EPIC POTSDAM) (19)	DE	M	1,896	80	52.3	8.5	27.0	rs9939609/ rs9935401	0.42
		F	2,740	44	49.5	8.5	26.2	rs9939609/ rs9935401	0.42
Finnish Cardiovascular Study (FINCAVAS) (20)	FIN	M	1,469	208	57.1	7.0	27.7	rs9939609	0.41
		F	829	82	57.6	7.0	27.8	rs9939609	0.42
Finnish Diabetes prevention Study (FDPS)* (21)	FIN	M	166	21	56.0	14.3	29.8	rs9939609	0.42
		F	341	31	54.0	14.1	31.9	rs9939609	0.43
Finland-United States Investigation of NIDDM (Non-insulin-dependent diabetes mellitus) Genetics (FUSION) (22)	FIN	M	1,422	226	57.9	11.4	28.5	rs9939609	0.39
		F	939	92	61.1	10.8	29.5	rs9939609	0.38
The importance of genes, familiar and common environment for the development of insulin resistance, abdominal adiposity and cardiovascular risk factors (GEMINAKAR)* (23)	DK	M	652	11	38.2	10.5	25.1	*rs9939609*	*0.42*
		F	635	7	37.9	10.6	24.7	rs9939609	0.43
Health, Aging, and Body Composition Study (HEALTH ABC)**	US	M	865	405	73.9	10.5	27.1	rs9939609	0.43
		F	729	240	73.6	11.4	26.7	rs9939609	0.42
Helsinki birth cohort* (HELSINKI) (24)	FIN	M	895	48	61.5	4.9	27.7	rs9939609	0.39
		F	1,019	23	61.6	5.2	28.0	rs9939609	0.41
Heinz Nixdorf Recall Study (HNRS) (25)	DE	M	2,289	288	60.1	8.9	28.2	rs8050136	0.42
		F	2,228	149	60.2	9.1	27.9	rs8050136	0.40

Health Professionals Follow-up Study (HPFS) (26):	US								
Controls		M	3,473	850	62.7	15.9	25.8	rs9939609	0.42
Cases		M	2,952	987	62.5	15.2	27.0	rs9939609	0.44
Carotid Intima Media Thickness (IMT) and IMT Progression as Predictors of Vascular Events in a High Risk European Population (IMPROVE) (27)	SE/NL/FR/IT/FIN	M	1,656	21	64.0	2.9	27.4	rs9939609	0.41
		F	1,725	10	64.3	2.9	27.4	rs9939609	0.41
The Cooperative Health Research in the Region of Augsburg Study (KORA) (28)	DE	M	1,819	117	50.2	8.7	27.6	rs9939609	0.41
		F	1,809	70	50.0	8.7	27.3	rs9939609	0.41
Ludwigshafen Risk and Cardiovascular Health Study (LURIC) (29)	DE	M	2,122	656	61.8	8.8	27.6	rs9939609	0.41
		F	888	235	65.0	9.1	27.5	rs9939609	0.41
The Malmö diet and cancer cohort* (MALMÖ) (30)	SE	M	10,826	2,393	59.2	13.5	26.5	rs9939609	0.41
		F	15,895	1,846	57.4	13.9	25.9	rs9939609	0.42
Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA)* (31)	FR	M	1,680	215	50.9	15.0	26.9	rs9939609	0.44
		F	1,525	100	51.2	15.5	26.5	rs9939609	0.41
Nurses' Health Studies (NHS) (32):	US								
Controls		F	5,852	951	58.4	20.0	25.7	rs9939609	0.40
Cases		F	4,467	1,198	58.3	18.9	27.7	rs9939609	0.41
National Survey of Health and Development (NSHD) (33;34)	UK	M	1,206	83	53.5	12.8	27.5	rs9939609	0.42
		F	1,194	54	53.5	12.9	27.5	rs9939609	0.41

Prevention of Renal and Vascular Endstage Disease study (PREVEND) (35)	NL	M	1,843	201	51.5	9.6	26.5	rs9939609	0.37
		F	1,640	71	49.1	10.0	26.3	rs9939609	0.41
PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) (36)	UK/NL	M	2,460	313	75.0	3.2	26.8	rs9939609	0.37
		F	2,581	202	75.6	3.3	27.5	rs9939609	0.39
The Rotterdam Study (ROTTERDAM) (37)	NL	M	2,381	1,632	68.0	13.1	25.9	rs9939609	0.36
		F	3,484	2,078	69.6	14.4	26.9	rs9939609	0.38
Savitaipale Diabetes Study (SAVITAIPALE) (38)	FIN	M	332	25	51.8	14.9	26.1	rs9939609	0.34
		F	361	11	52.1	15.3	26.3	rs9939609	0.37
Stockholm Heart Epidemiology Program (SHEEP) (39):	SE								
Controls		M	953	84	58.9	8.6	26.0	rs9939609	0.39
		F	438	22	61.9	8.2	25.9	rs9939609	0.41
Cases		M	787	139	58.1	8.2	26.9	rs9939609	0.43
		F	311	45	61.5	7.8	27.6	rs9939609	0.44
Study of Health in Pomerania (SHIP)* (40)	DE	M	1,984	354	51.0	11.0	27.8	rs9939609	0.41
		F	1,946	165	49.4	11.5	27.4	rs9939609	0.41
The Speedwell Study (SPEEDWELL) (13)	UK	M	664	236	71.6	9.2	26.8	rs9939609	0.39
Women's Genome Health Study (WGHS) (41)	US	F	22,099	1,795	54.7	16.5	26.3	rs9939609	0.40
The Whitehall-II Study* (WHITEHALL-II) (42)	UK	M	4,241	214	60.9	8.7	26.7	rs9939609	0.41
		F	1,316	67	61.3	9.0	27.5	rs9939609	0.38

Abbreviations: IS: Iceland; AUS: Australia; UK: United Kingdom; CH: Switzerland; DK: Denmark; EE: Estonia; DE: Germany; FIN: Finland; US: United States of America; SE: Sweden; NL: Netherlands; FR: France; IT: Italy; M: Male; F: Female; N: Number of individuals (combined sample size); BMI: Body mass index; *FTO*: fat mass and obesity-associated gene; SNP: Single nucleotide polymorphism; MAF: Minor allele frequency

* Data was analysed by the Data Hub analyst (LHÄ)

** http://www.grc.nia.nih.gov/branches/leps/healthabc/

Table S2: Analysis of the association of *FTO* and adiposity phenotypes on all-cause mortality based on all time-at-risk ages, and when using age-restrictions to being older than 60, 65 and 70 years, respectively

	HR [95% CI]; p-value		
Analysis	**Age ≥60 years**	**Age ≥65 years**	**Age ≥70 years**
FTO	1.01 [0.99,1.03]; 0.22	1.01 [0.99,1.03]; 0.30	1.01 [0.99,1.03]; 0.51
FTO|BMI	1.01 [0.99,1.02]; 0.48	1.01 [0.99,1.03]; 0.55	1.00 [0.98,1.02]; 0.75
FTO|BMI,WC	1.00 [0.98,1.02]; 0.93	1.00 [0.98,1.02]; 0.89	1.00 [0.97,1.02]; 0.72
FTO|FMI	0.99 [0.96,1.03]; 0.66	0.99 [0.94,1.04]; 0.70	0.99 [0.95,1.03]; 0.66

Abbreviations: HR: estimated hazard ratio of all-cause mortality per unit of the phenotype; *FTO*: fat mass and obesity associated gene; BMI: Body mass index; WC: Waist circumference; FMI: Fat mass index

| means adjusted for; e.g. *FTO*|BMI is *FTO* adjusted for BMI in relation to mortality

Table S3: Analysis of the association of *FTO* and adiposity phenotypes on all-cause mortality separately for males and females

	HR [95% CI]; p-value	
Analysis	**Males**	**Females**
FTO	1.01 [0.98, 1.04]; 0.53	1.02 [1.00, 1.05]; 0.08
FTO|BMI	1.01 [0.98, 1.04]; 0.70	1.02 [0.99, 1.04]; 0.23
FTO|BMI,WC	1.00 [0.96, 1.03]; 0.82	1.01 [0.99, 1.04]; 0.33
FTO|FMI	0.98 [0.92, 1.04]; 0.47	1.02 [0.97, 1.08]; 0.42

Abbreviations: HR: estimated hazard ratio of all-cause mortality per unit of the phenotype; *FTO*: fat mass and obesity associated gene; BMI: Body mass index; WC: Waist circumference; FMI: Fat mass index

| means adjusted for; e.g. *FTO*|BMI is *FTO* adjusted for BMI in relation to mortality