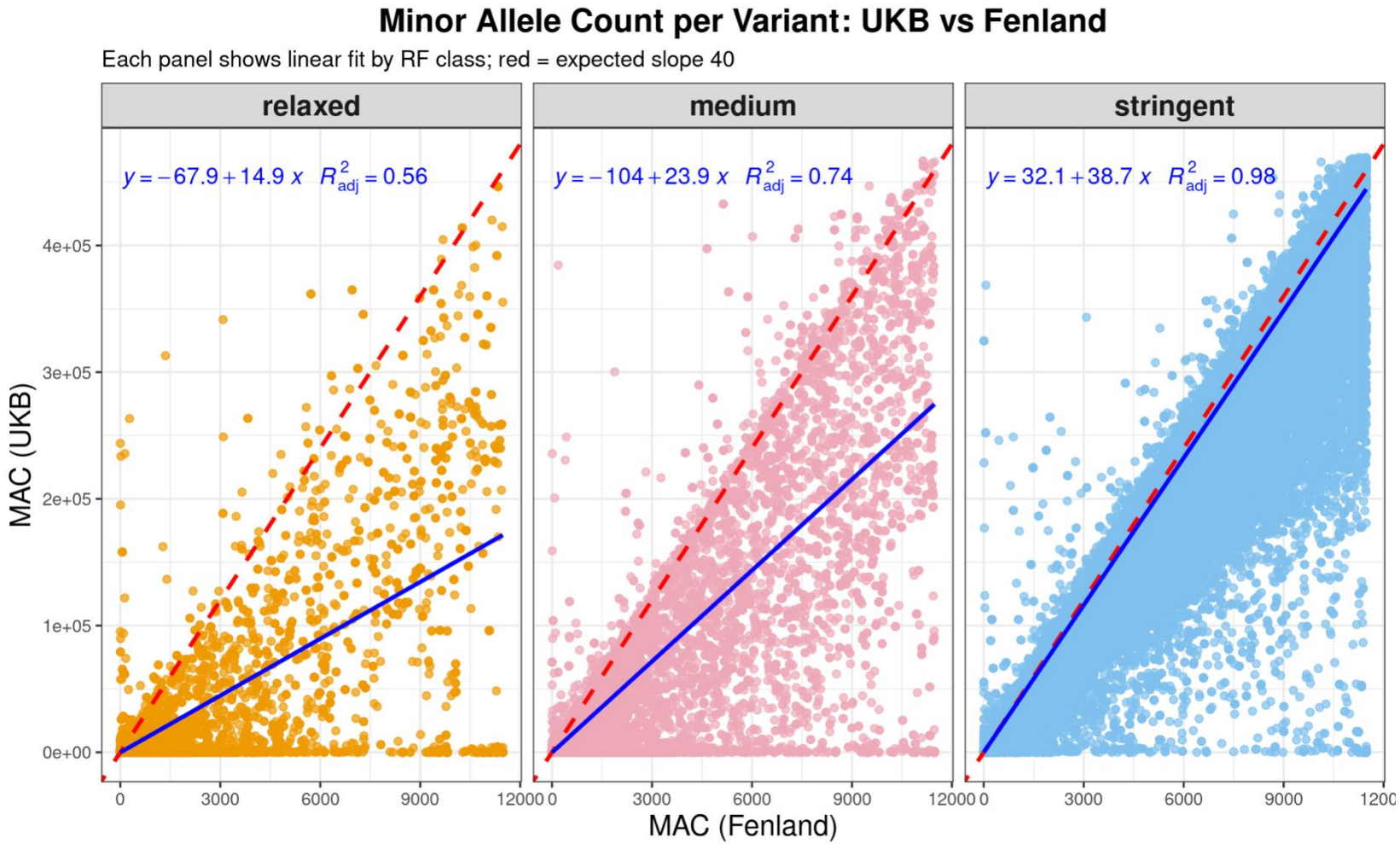
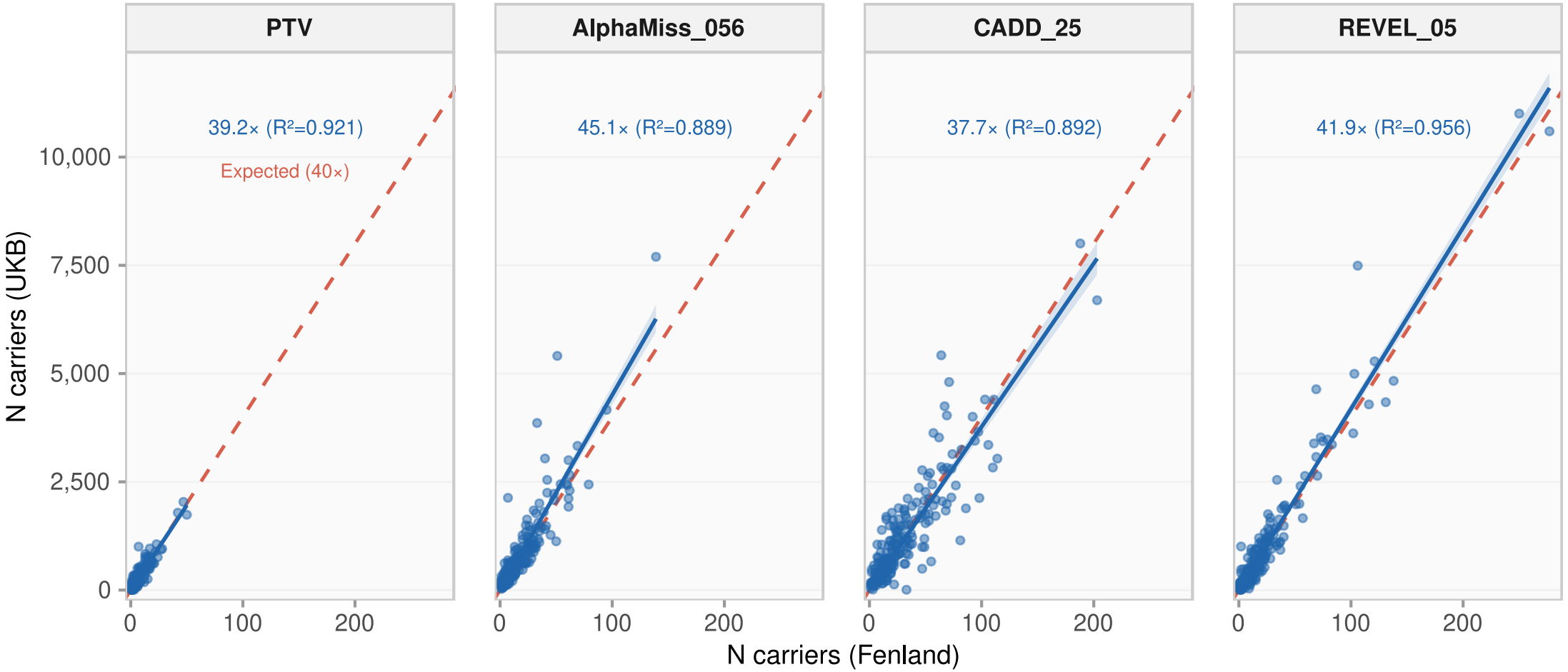
FIGURES

Supplementary Figure 1: Minor Allele Count comparisons for common WES data in Fenland vs the UKB



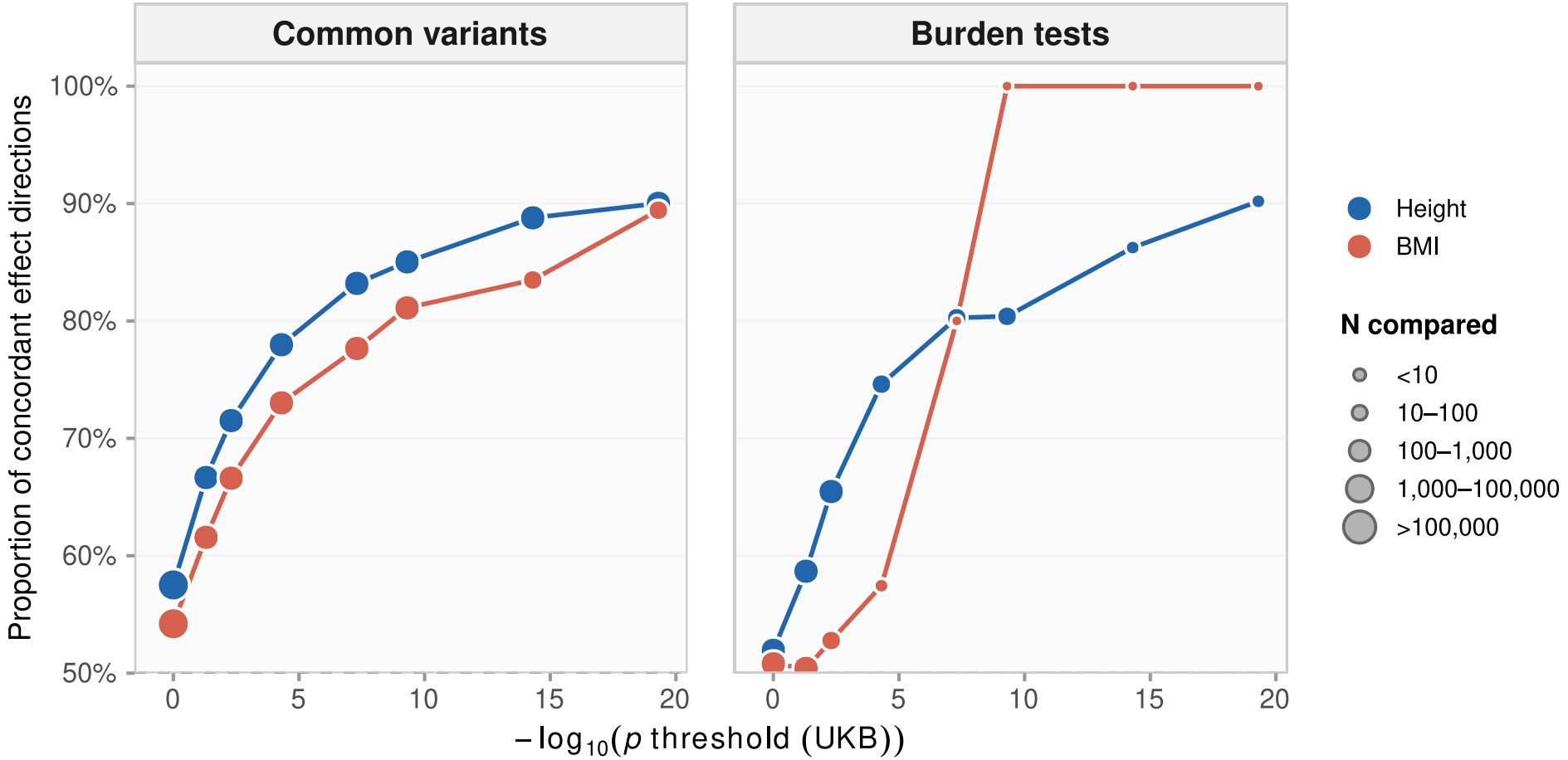
Each point represents a whole-exome sequencing (WES) variant that was matched between the Fenland study and UK Biobank. Minor allele counts (MAC) in Fenland are plotted on the x-axis and corresponding minor allele counts in UK Biobank (UKB) are plotted on the y-axis. Panels show variants passing the relaxed, medium and stringent random-forest (RF) quality-control classifications. The solid blue line represents the fitted linear regression, with the regression equation and adjusted R^2 displayed within each panel. The dashed red line represents the approximately 40-fold increase in allele count expected from the relative sample sizes of the two cohorts.

Supplementary Figure 2: Combined Allele Count comparisons for rare gene burden masks in Fenland vs the UKB



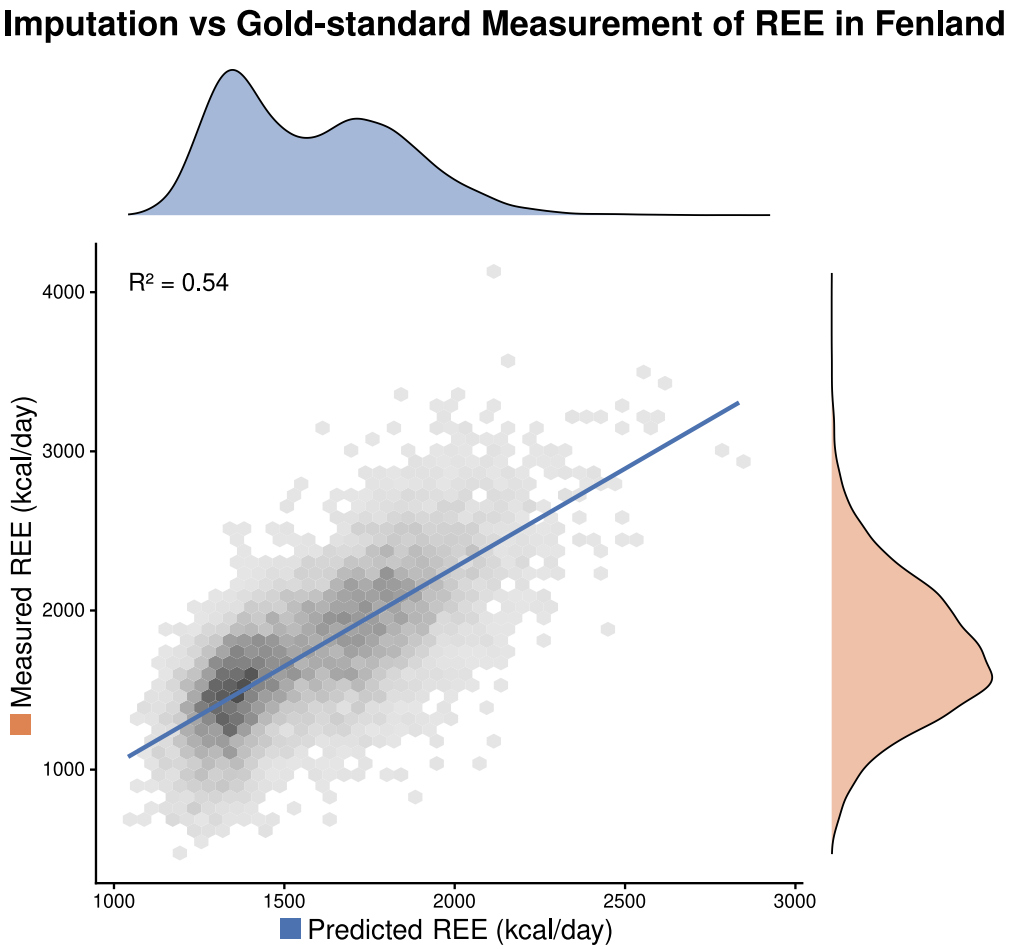
Carrier counts were calculated for a random subset of 200 genes using rare variants with minor allele frequency ≤1%. Each point represents one gene, with the number of carriers in Fenland plotted on the x-axis and the corresponding number in UK Biobank (UKB) plotted on the y-axis. Panels show four gene-burden masks: high-confidence protein-truncating variants (PTV); missense variants with an AlphaMissense pathogenicity score ≥0.564; missense variants with a CADD score ≥25; and missense variants with a REVEL score ≥0.5. Solid blue lines show fitted linear regressions, with the estimated slope and R^2 displayed within each panel. Dashed red lines indicate the approximately 40-fold difference expected from the relative cohort sizes.

Supplementary Figure 3: Variant effect concordance for height and BMI between Fenland and UKB



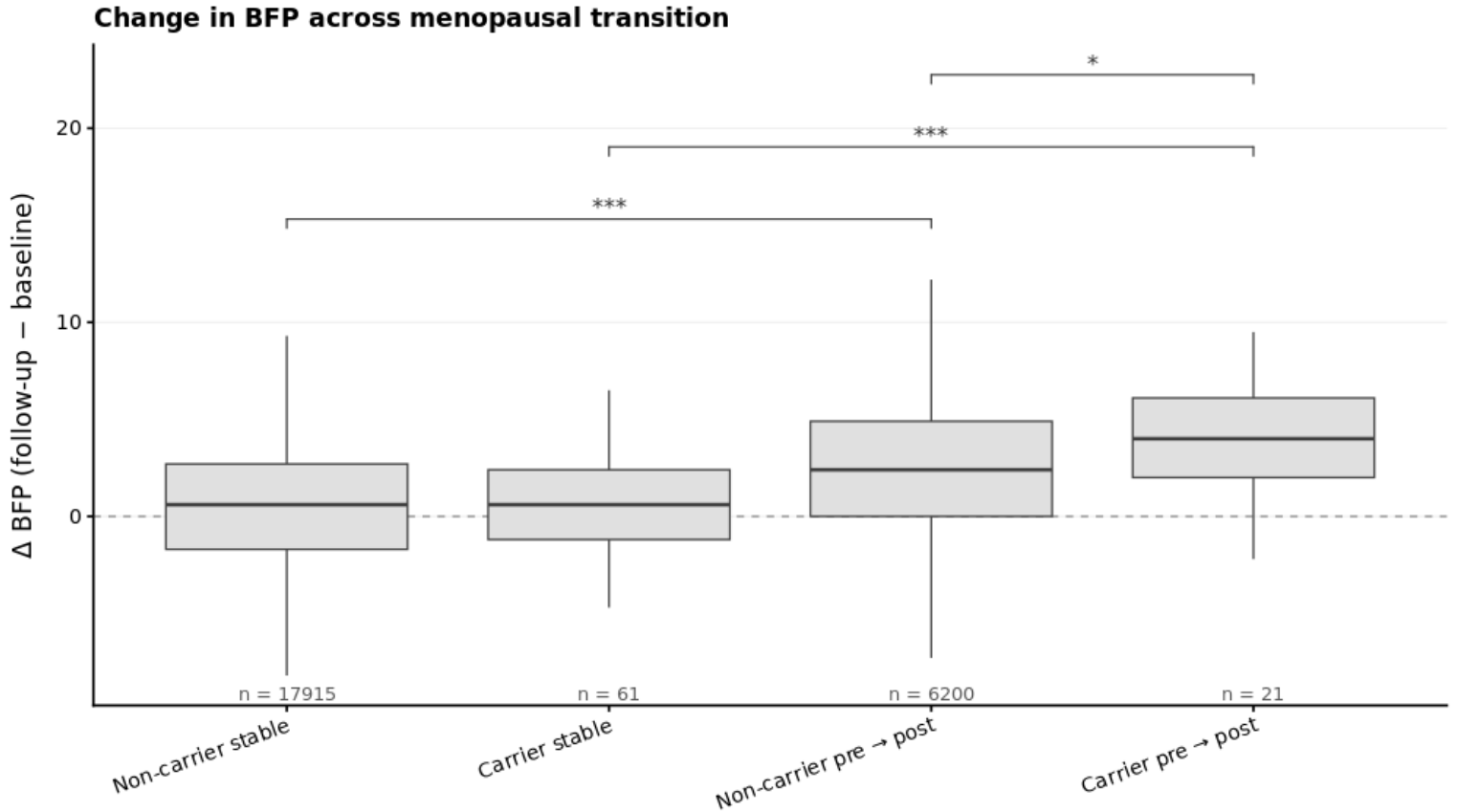
The proportion of associations showing the same direction of effect in Fenland and UK Biobank is plotted across progressively more stringent UK Biobank (UKB) association P-value thresholds. Results are shown separately for common single-variant associations with minor allele frequency >1% and rare-variant gene-burden associations with minor allele frequency ≤1%. Effects were aligned to the same effect allele for single variants and to the same burden definition for gene-based tests. Blue points denote height and orange points denote body mass index. Point size represents the number of variants or gene-burden tests included at each threshold. The dashed horizontal line at 50% indicates the concordance expected by chance.

Supplementary Figure 4: Concordance between imputed and measured Resting Energy Expenditure in Fenland



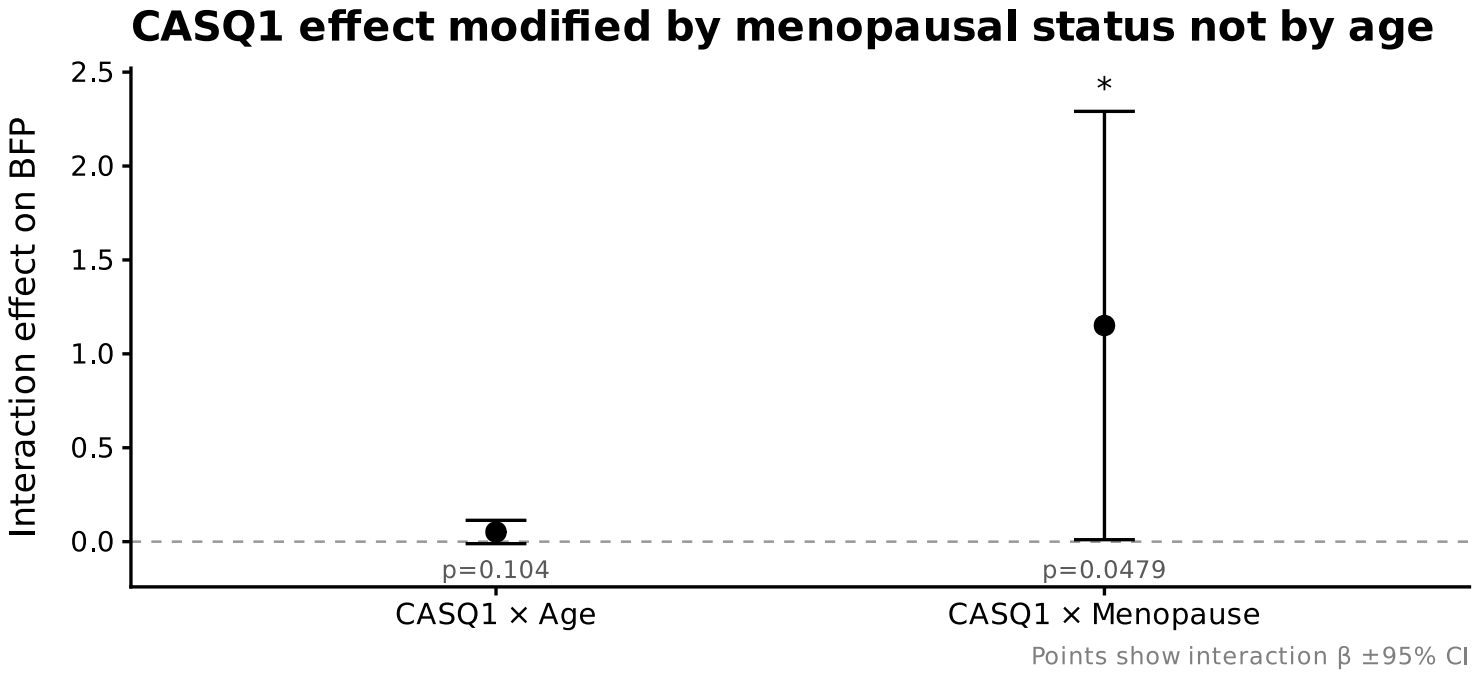
Predicted resting energy expenditure (REE) is plotted against resting energy expenditure measured under standardised resting conditions using indirect calorimetry. Both measures are expressed in kcal/day. Hexagonal bins represent the density of participants with the corresponding predicted and measured values, and the solid blue line shows the fitted linear regression. Marginal density distributions for predicted and measured resting energy expenditure are shown above and to the right of the main panel, respectively. The displayed R^2 indicates the proportion of variance in measured resting energy expenditure explained by the predicted measure.

Supplementary Figure 5: Change in body fat percentage across menopause transition between carriers and non-carriers of rs145486953.



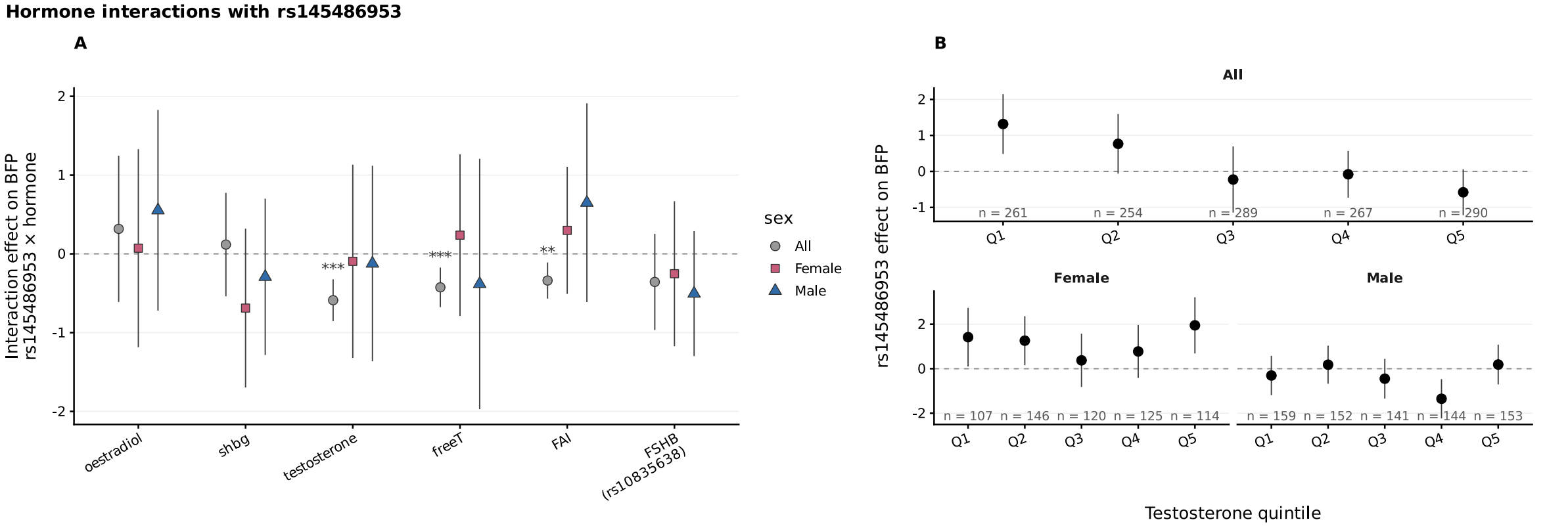
Change in body fat percentage (BF%) was calculated as the follow-up value minus the baseline value in UK Biobank women with repeated body-composition and menopause measurements. Women were divided according to rs145486953 carrier status and whether their menopausal status remained stable or changed from pre-menopausal at baseline to post-menopausal at follow-up. Stable groups include women who were either pre-menopausal at both assessments or post-menopausal at both assessments. The number of women in each group is displayed beneath the corresponding box. Boxes show the median and interquartile range, with whiskers showing the remaining distribution. Brackets show pairwise two-sided t-tests with Benjamini–Hochberg adjustment; only significant comparisons are displayed. *P < 0.05 and ***P < 0.001.

Supplementary Figure 6: Interaction analysis of CASQ1~BFP with age and menopause



Points show the interaction coefficients from models testing whether the association between rs145486953 carrier status and body fat percentage (BFP) differed according to age or menopausal status in UK biobank participants. Vertical bars show 95% confidence intervals and the dashed horizontal line indicates no interaction. The corresponding two-sided interaction P values are displayed beneath each estimate. The star denotes a nominally significant interaction at $P < 0.05$.

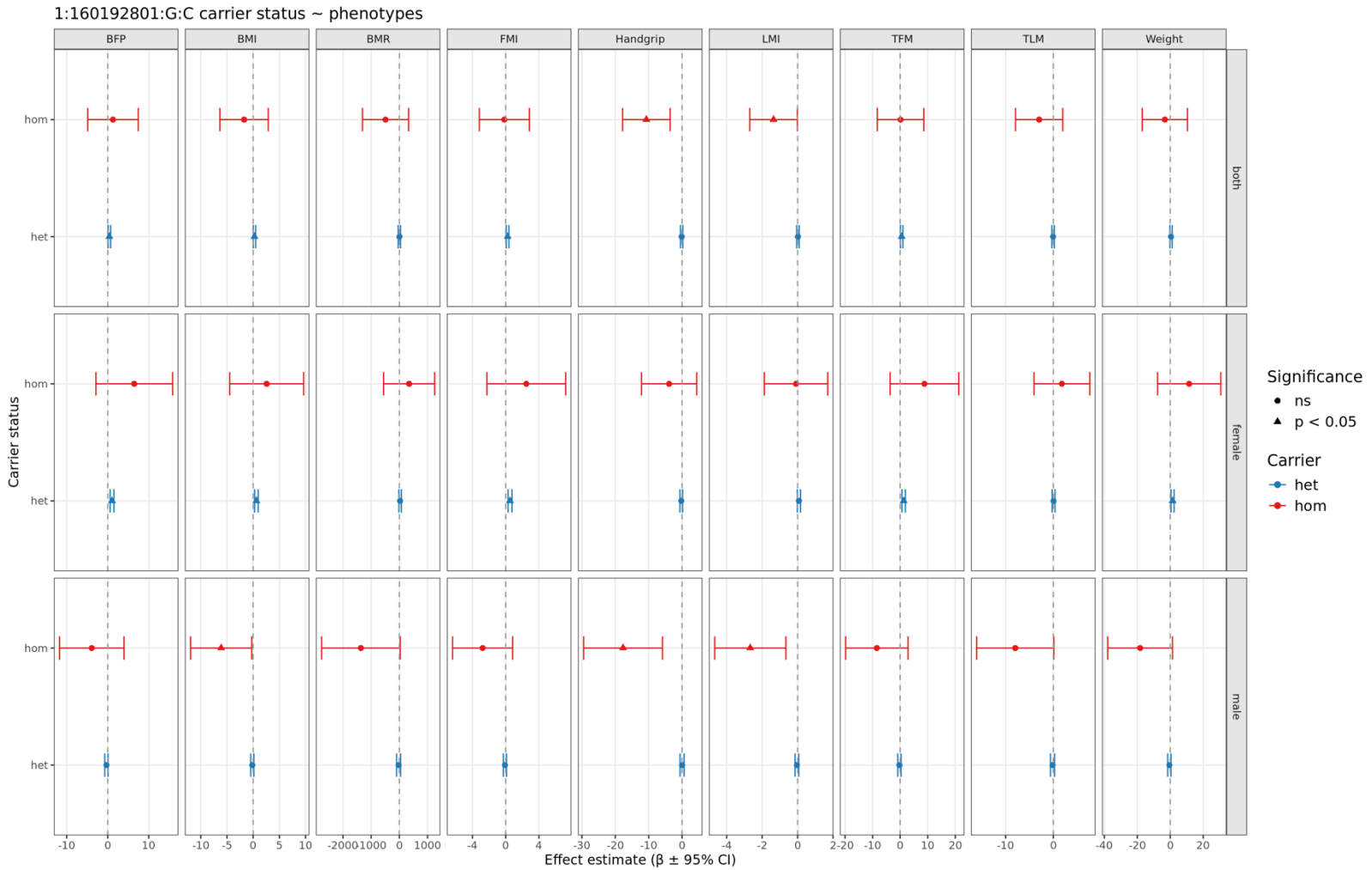
Supplementary Figure 7: Interaction analysis of rs145486953~BFP with hormone levels in the UKB



A: Sex-stratified interaction effects of rs145486953 with circulating hormones on BFP.
B: rs145486953 effect on BFP in testosterone quintiles.
†p<0.1 *p<0.05 **p<0.01 ***p<0.001. Only significant comparisons shown.

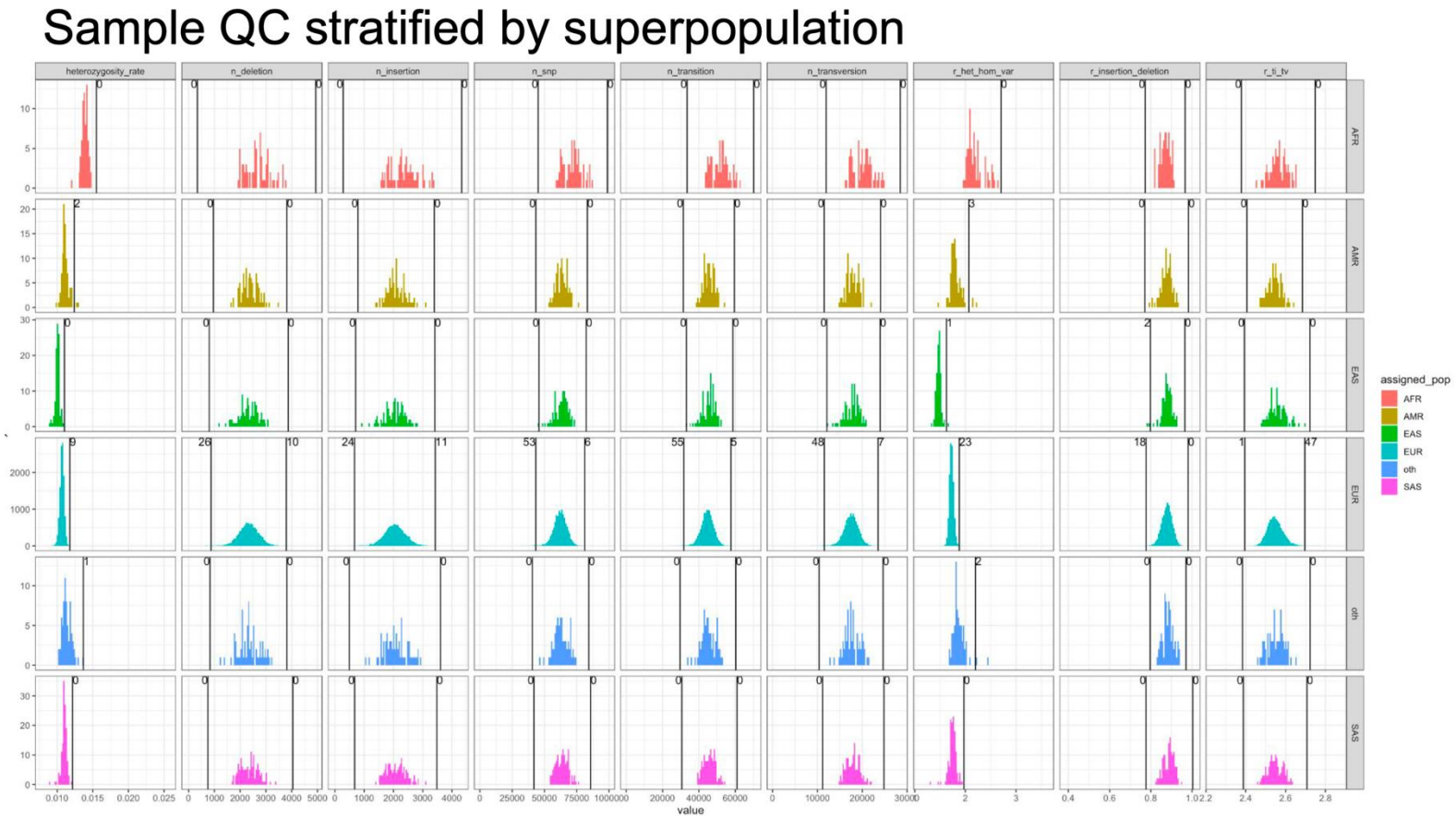
A) Interaction coefficients for rs145486953 carrier status with circulating oestradiol, sex hormone-binding globulin (SHBG), total testosterone, calculated free testosterone (freeT) and free androgen index (FAI), and with genotype at rs10835638 in *FSHB*, used as a genetic proxy for circulating follicle-stimulating hormone. Results are shown for sex-combined analyses, women and men. Points show interaction coefficients and vertical bars show 95% confidence intervals. Significance symbols denote nominal two-sided interaction tests: **P < 0.01 and ***P < 0.001. **B)** Association of rs145486953 carrier status with body fat percentage (BFP) within quintiles of circulating testosterone, shown for all participants and separately for women and men. Quintile 1 represents the lowest testosterone concentrations and quintile 5 the highest. The number of variant carriers or observations contributing to each estimate, as specified by the analysis, is shown below each quintile. The dashed horizontal line indicates no association.

Supplementary Figure 8: Effect of heterozygous vs homozygous rs145486953 carriers across traits in the UKB



Effect estimates for heterozygous carriers and homozygous carriers of the CASQ1 rs145486953 variant are shown relative to non-carriers. Results are presented for the full UK Biobank sample and separately for women and men. Columns show associations with body fat percentage (BFP), body mass index (BMI), predicted basal metabolic rate (BMR), fat mass index (FMI), handgrip strength, lean mass index (LMI), total fat mass (TFM), total lean mass (TLM) and body weight. Points show effect estimates and horizontal bars show 95% confidence intervals; effect scales differ between traits and are presented in their respective measurement units. Blue symbols denote heterozygous carriers and red symbols denote homozygous carriers. Circles denote $P \geq 0.05$ and triangles denote nominal two-sided $P < 0.05$. Homozygous carriers were rare in UK Biobank (n = 4), and their estimates should therefore be interpreted cautiously.

Supplementary Figure 9: Within-ancestry quality control measure distributions



Histograms show sample-level sequencing quality-control measures stratified by assigned genetic ancestry superpopulation. Rows represent African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), other or unassigned (oth), and South Asian (SAS) ancestry groups. Columns show heterozygosity rate, numbers of deletions, insertions, single-nucleotide polymorphisms, transitions and transversions, the heterozygous-to-homozygous variant ratio, insertion-to-deletion ratio and transition-to-transversion ratio. Vertical black lines indicate ancestry-specific outlier thresholds used during sample quality control, defined as values more than six standard deviations from the within-ancestry distribution. Numbers above the thresholds indicate the number of samples falling outside the corresponding lower or upper limit.

TABLES

		Fenland			BiB			MCS			ALSPAC		
		Relaxed	**Medium**	**Stringent**	**Relaxed**	**Medium**	**Stringent**	**Relaxed**	**Medium**	**Stringent**	**Relaxed**	**Medium**	**Stringent**
SNVs	RF bin	92	89	83	92	88	84	86	84	82	42	40	36
	Depth	5	5	5	5	5	5	5	5	5	5	5	5
	Genotype Quality	10	10	10	10	10	15	10	10	15	10	10	20
	Allele Balance	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Missingness	0.5	0.5	0.5	0.5	0.5	0.5	0	0	0	0	0	0
	Precision	0.909	0.917	0.933	0.905	0.912	0.932	0.898	0.918	0.931	0.88	0.885	0.909
	Recall	0.952	0.948	0.933	0.971	0.968	0.951	0.979	0.97	0.953	0.95	0.95	0.928
	True Positives (%)	98.93	98.1	95.95	99.26	98.37	97.05	99.05	98.7	97.87	98.88	98.24	96.85
	False Positives (%)	0.94	0.68	0.51	0.84	0.68	0.462	1.51	0.44	0.27	3.2	0.89	0.15
Indels	RF bin	72	68	56	68	66	58	64	62	58	62	59	56
	Depth	5	5	5	5	5	5	5	5	10	5	5	10
	Genotype Quality	10	10	10	10	15	20	10	15	20	10	10	10
	Allele Balance	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.3	0.3	0.2	0.2	0.3
	Missingness	0.5	0.5	0.5	0.5	0.5	0.5	0	0	0	0	0	0
	Precision	0.666	0.691	0.779	0.677	0.703	0.779	0.665	0.724	0.774	0.666	0.688	0.789
	Recall	0.775	0.77	0.72	0.81	0.787	0.707	0.816	0.779	0.691	0.76	0.757	0.561
	True positives (%)	92.16	91.44	86.97	93.12	91.53	87.78	93.4	92.84	91.18	93.31	92.83	90.46
	False positives (%)	1.52	0.74	0.21	0.8	0.48	0.25	0.73	0.47	0.27	1.5	1.25	0.64

Supplementary Table 1: Quality control thresholds for WES variant binning

Thresholds used to assign single-nucleotide variants and insertions/deletions to relaxed, medium and stringent quality-control sets are shown for Fenland, Born in Bradford (BiB), the Millennium Cohort Study (MCS) and the Avon Longitudinal Study of Parents and Children (ALSPAC). Criteria include the minimum random-forest (RF) classification bin, sequencing depth, genotype quality and alternate-allele balance, and the maximum permitted genotype missingness. Precision, recall and the proportions of benchmark true-positive and false-positive variants retained at each threshold were evaluated using Genome in a Bottle reference samples. Thresholds were calibrated separately for single-nucleotide variants and insertions/deletions.

Group	Phenotype	Sex	Meff-Bonferroni Threshold
REE	REE_adjBMI	both	9.34E-07
Glucose	Glucose0	both	3.78E-07
		men	5.80E-07
		women	5.30E-07
	Glucose120	both	3.78E-07
		men	5.80E-07
		women	5.30E-07
	GlucoseDelta	both	3.78E-07
		men	5.80E-07
		women	5.30E-07
Insulin	Insulin0	both	4.10E-07
		men	6.47E-07
		women	5.77E-07
	Insulin120	both	4.10E-07
		men	6.47E-07
		women	5.77E-07
	InsulinFC	both	4.10E-07
		men	6.47E-07
		women	5.77E-07

Supplementary Table 2: Significance thresholds across tests

Exome-wide significance thresholds are shown for body mass index-adjusted resting energy expenditure (REE_adjBMI) and for fasting, 2-hour post-glucose-challenge and change measures of glucose and insulin. Thresholds are presented for sex-combined and sex-stratified analyses. Bonferroni correction incorporated the number of eligible genes and the effective numbers of independent burden masks and correlated phenotypes (Meff), estimated from the eigenvalues of the corresponding gene-level test-statistic correlation matrices. Sex-specific thresholds differ because the number of gene-mask combinations satisfying the minimum allele-count criterion differed between analyses. Glucose0 and Insulin0 denote fasting measurements; Glucose120 and Insulin120 denote measurements obtained 2 h after oral glucose administration; GlucoseDelta denotes the measurement difference between the two timepoints; and InsulinFC denotes insulin fold change.

Mask Class	Mask Name	VEP_Consequence	Additional Filter
PTV	HCPTV	stop_gained | frameshift | splice_acceptor | splice_donor	LoFTEE=High_Confidence
MISSENSE	MISS_AM034	missense	AlphaMissense Pathogenicity >= 0.34
	MISS_AM056	missense	AlphaMissense Pathogenicity >= 0.564
	MISS_AM07	missense	AlphaMissense Pathogenicity >= 0.7
	MISS_AM09	missense	AlphaMissense Pathogenicity >= 0.9
	MISS_REV05	missense	REVEL Pathogenicity >= 0.5
	MISS_REV07	missense	REVEL Pathogenicity >= 0.7
	MISS_CADD25	missense	CADD Pathogenicity >=25
	MISS_CADD25_REV05	missense	CADD Pathogenicity >=25 & REVEL Pathogenicity >= 0.5
	MISS_CADD25_REV07	missense	CADD Pathogenicity >=25 & REVEL Pathogenicity >= 0.7
Damaging (PTV + MISSENSE)	DMG_AM056		HCPTV | MISS_AM056
	DMG_CADD25		HCPTV | MISS_CADD25
	DMG_REVEL05		HCPTV | MISS_REVEL05
CONTROL	SYN	start_retained_variant | stop_retained_variant | synonymous_variant	

Supplementary Table 3: Rare variant mask definitions

Variants were grouped by their Variant Effect Predictor (VEP) consequence and, for missense variants, by predicted pathogenicity scores from AlphaMissense, REVEL or CADD. The high-confidence protein-truncating variant (HCPTV) mask includes stop-gained, frameshift, splice-acceptor and splice-donor variants classified as high confidence by LOFTEE. Missense masks apply progressively stringent AlphaMissense thresholds or thresholds based on REVEL, CADD, or combinations of CADD and REVEL. Damaging (DMG) masks combine high-confidence protein-truncating variants with the specified missense mask. Synonymous, start-retained and stop-retained variants were grouped into a negative-control mask (SYN).

	BOTH		WOMEN		MEN	
PHENO	**R2**	**PVALUE**	**R2**	**PVALUE**	**R2**	**PVALUE**
weight	0.565	0	0.407	0	0.343	0.00E+00
total_lean_mass	0.538	0	0.374	0	0.299	6.03E-265
BMI	0.508	0	0.331	0	0.265	1.47E-226
total_fat_mass	0.490	0	0.320	0	0.212	1.08E-167
lean_mass_index	0.490	0	0.308	1.4453E-306	0.219	3.00E-175
fat_mass_index	0.458	0	0.271	1.8742E-256	0.170	2.78E-125
body_fat_percent	0.406	1.344E-187	0.180	1.296E-142	0.103	2.32E-60

Supplementary Table 4: Anthropometric correlations with Resting Energy Expenditure in Fenland

Multivariable linear regression models were used to assess the relationships of body weight, total lean mass, body mass index (BMI), total fat mass, lean mass index, fat mass index and body fat percentage with resting energy expenditure measured by indirect calorimetry. Results are presented for the full sample and separately for women and men. Analyses were adjusted for age, sex (where applicable), resting energy expenditure measurement device and room temperature. R^2 represents the variance in resting energy expenditure explained by the complete regression model, and the displayed two-sided P value corresponds to the anthropometric or body-composition term.

			BOTH				MEN				WOMEN				
SYMBOL	MASK	PHENO	AC	BETA	SE	PVALUE	AC	BETA	SE	PVALUE	AC	BETA	SE	PVALUE	Phet
CASQ1	DMG_AM056	**REE_adjBMI**	**70**	**-180.32**	**36.45**	**7.50E-07**	**43**	**-254.16**	**50.78**	**5.60E-07**	**27**	**-46.91**	**53.10**	**3.80E-01**	**4.79E-03**
		REE	70	-161.32	42.22	1.30E-04	43	-255.13	57.99	1.10E-05	27	-5.64	63.22	9.30E-01	3.64E-03
		REE_adjBFP	68	-181.27	40.17	6.40E-06	42	-240.84	55.74	1.60E-05	26	-77.13	59.44	1.90E-01	4.45E-02
		REE_adjFMI	68	-184.28	38.37	1.60E-06	42	-245.15	53.63	4.90E-06	26	-75.73	56.02	1.80E-01	2.89E-02
		REE_adjLMI	68	-168.81	37.20	5.70E-06	42	-246.16	52.00	2.20E-06	26	-30.79	54.55	5.70E-01	4.27E-03
		REE_adjTFM	68	-181.80	37.24	1.10E-06	42	-245.89	52.31	2.60E-06	26	-66.62	54.12	2.20E-01	1.72E-02
		REE_adjTLM	68	-153.22	35.46	1.60E-05	42	-241.72	49.36	9.70E-07	24	2.62	54.15	9.60E-01	8.54E-04
		REE_adjWeight	70	-170.14	34.33	7.20E-07	43	-251.74	48.09	1.70E-07	27	-25.03	49.98	6.20E-01	1.08E-03
COL8A1	MISS_AM034	**REE_adjBMI**	**27**	**-297.09**	**58.57**	**3.90E-07**	**13**	**-346.19**	**92.22**	**1.70E-04**	**14**	**-243.27**	**73.62**	**9.50E-04**	**3.83E-01**
		REE	27	-284.93	67.86	2.70E-05	13	-315.24	105.39	2.80E-03	14	-237.48	87.69	6.80E-03	5.71E-01
		REE_adjBFP	27	-283.40	63.65	8.50E-06	13	-311.14	100.11	1.90E-03	14	-241.98	80.88	2.80E-03	5.91E-01
		REE_adjFMI	27	-286.58	60.80	2.40E-06	13	-322.84	96.29	8.00E-04	14	-240.55	76.22	1.60E-03	5.03E-01
		REE_adjLMI	27	-312.95	58.93	1.10E-07	13	-365.96	93.36	8.90E-05	14	-253.66	74.23	6.30E-04	3.46E-01
		REE_adjTFM	27	-270.07	59.00	4.70E-06	13	-311.85	93.92	9.00E-04	14	-218.41	73.64	3.00E-03	4.34E-01
		REE_adjTLM	27	-247.07	56.17	1.10E-05	13	-311.34	88.61	4.40E-04	13	-165.87	73.47	2.40E-02	2.06E-01
		REE_adjWeight	27	-253.86	55.15	4.20E-06	13	-307.86	87.33	4.20E-04	14	-191.71	69.30	5.70E-03	2.97E-01

Supplementary Table 5: Rare burden test results for COL8A1 and CASQ1 with REE adjusted for other anthropometric traits

Gene-burden results are shown for damaging (DMG) *CASQ1* variants, comprising high-confidence protein-truncating variants and missense variants with AlphaMissense ≥0.564 (AM056), and for *COL8A1* missense variants with AlphaMissense ≥0.34 (AM034). Resting energy expenditure (REE) was analysed without anthropometric adjustment and after separate adjustment for body mass index (BMI), body fat percentage (BFP), fat mass index (FMI), lean mass index (LMI), total fat mass (TFM), total lean mass (TLM) or body weight. Results are shown for sex-combined analyses, men and women. AC is the combined alternate-allele count across qualifying variants; β is the estimated difference in resting energy expenditure in kJ/day per burden allele; SE is its standard error; and Phet is the two-sided test of heterogeneity between male and female effect estimates. Bold values show the primary analysis reported in the paper.

PHENO	VALUE	UNITS	CODE	Male_coeff	Female_coeff
TLM	(Intercept)			2150.509	-2061.581
	Age	Years	21003_i0	-153.101	-83.404
	Arm_imp_sum	Ohms		18.013	
	body_fat_percent	%	23099_i0	140.598	45.547
	Handgrip_max	kg		19.958	22.082
	Height_stand	cm	50_i0	251.413	179.615
	Hip_circum	cm	49_i0		-48.822
	Ht2ImArms	m2/Ohms		3055168.988	753166.302
	Ht2ImBody	m2/Ohms			2462655.433
	Leg_imp_sum	Ohms		-9.590	-8.212
	Physical_Act_mod	Days > 10min	884_i0		22.033
	Physical_Act_vig	Days > 10min	904_i0	190.196	109.309
	Sleep	Hours/Day	1160_i0	-84.599	
	Waist_circum	cm	48_i0	-106.731	
	Weight	kg	23098_i0	181.466	146.305
	Whole_body_imp	Ohms	23106_i0	-29.379	
TFM	(Intercept)			8396.819	13676.469
	Age	Years	21003_i0	-41.512	-155.880
	body_fat_percent	%	23099_i0		296.769
	Handgrip_max	Kg		-29.034	-33.842
	Height_stand	cm	50_i0	-196.088	-165.435
	Hip_circum	cm	49_i0		46.758
	Ht2ImArms	m2/Ohms		-1351380.295	
	Ht2ImBody	m2/Ohms		-1084283.935	-861233.785
	Leg_imp_sum	Ohms		13.397	5.386
	Physical_Act_mod	Days > 10min	884_i0	123.494	
	Physical_Act_vig	Days > 10min	904_i0	-169.718	-101.802
	Smoking	Never/Previous/Current	20116_i0	325.895	
	Waist_circum	cm	48_i0	97.072	-38.811
	Weight	kg	23098_i0	636.584	561.021

Supplementary Table 6: Weights for imputation of total lean mass and total fat mass in Europeans in the UKB

Linear prediction models for total lean mass (TLM) and total fat mass (TFM) were developed separately in men and women using UK-biobank (UKB) participants with whole-body dual-energy X-ray absorptiometry measurements. Candidate predictors included age, anthropometry, bioimpedance, handgrip strength, physical activity, sleep and smoking measures collected at baseline visit. Predictor selection was performed using forward–backward stepwise regression with the Bayesian information criterion; blank cells indicate variables that were not retained in the corresponding sex-specific model. The table reports the model intercepts and regression coefficients, together with measurement units and UKB field codes where applicable. Height-squared impedance indices were calculated using arm or whole-body impedance. Models were developed in 95% of participants with imaging and evaluated in a held-out 5% validation sample, producing R^2 values of approximately 0.93 for TLM and 0.71 TFM before being applied to the wider UKB cohort.

SOURCE	SYMBOL	MASK	PHENO	AC	BETA	SE	PVALUE
FENLAND	CASQ1	DMG_AM056	BMI	91	0.69	0.50	1.70E-01
			BFP	86	0.51	0.69	4.60E-01
			FMI	86	0.33	0.35	3.50E-01
			LMI	86	0.07	0.18	7.20E-01
			TFM	86	0.54	1.00	5.90E-01
			TLM	86	-0.34	0.64	5.90E-01
			Weight	91	0.85	1.52	5.80E-01
	COL8A1	MISS_AM034	BMI	36	0.15	0.79	8.50E-01
			BFP	36	-0.11	1.06	9.20E-01
			FMI	36	0.11	0.54	8.40E-01
			LMI	36	0.16	0.28	5.80E-01
			TFM	36	-0.55	1.54	7.20E-01
			TLM	36	-1.11	0.99	2.60E-01
			Weight	36	-2.10	2.41	3.80E-01
UKB	CASQ1	DMG_AM_056	BMI	1427	-0.06	0.11	1.68E-01
			DXA_FMI	1427	0.16	0.19	5.48E-03
			DXA_TFM	1427	0.44	0.59	2.78E-02
			DXA_LMI	1427	0.06	0.10	6.04E-02
			DXA_TLM	1427	-0.03	0.40	9.06E-01
			PREDICT_TFM	1427	-0.11	0.22	2.09E-01
			PREDICT_FMI	1427	-0.04	0.07	1.92E-01
			PREDICT_TLM	1427	-0.12	0.16	4.58E-01
			PREDICT_LMI	1427	-0.03	0.04	3.24E-01
			BFP	1427	-0.08	0.15	7.06E-02
			Weight	1427	-0.21	0.38	2.83E-01
	COL8A1	MISS_AM_034	BMI	525	-0.20	0.19	3.44E-01
			DXA_FMI	525	-0.14	0.30	7.83E-01
			DXA_TFM	525	-0.50	0.94	7.82E-01
			DXA_LMI	525	-0.16	0.17	4.10E-01
			DXA_TLM	525	-0.71	0.64	4.16E-01
			PREDICT_TFM	525	-0.55	0.37	2.34E-01
			PREDICT_FMI	525	-0.12	0.12	3.87E-01
			PREDICT_TLM	525	-0.52	0.26	9.41E-02
			PREDICT_LMI	525	-0.03	0.06	5.49E-01
			BFP	525	-0.22	0.25	4.42E-01
			Weight	525	-1.26	0.63	1.14E-01

Supplementary Table 7: Gene burden test results for COL8A1 and CASQ1 on anthropometric traits

Associations of the *CASQ1* damaging-variant mask (DMG_AM056) and the *COL8A1* AlphaMissense ≥0.34 missense mask (MISS_AM034) with body mass index (BMI), body fat percentage (BFP), fat and lean mass indices (FMI,LMI), total fat and lean mass (TFM,TLM), and body weight were examined to assess whether their associations with resting energy expenditure could reflect conditioning on correlated body-composition traits. Fenland analyses used measured anthropometric and DXA-derived traits. UK Biobank (UKB) analyses included directly measured DXA traits and total fat and lean mass traits predicted using the models described in Supplementary Table 6. AC is the combined alternate-allele count across qualifying variants; β and SE are shown in the natural measurement units of each phenotype. Displayed P values are two-sided and unadjusted for multiple testing.

		BOTH				MEN				WOMEN				
	test	**AC**	**BETA**	**SE**	**PVALUE**	**AC**	**BETA**	**SE**	**PVALUE**	**AC**	**BETA**	**SE**	**PVALUE**	**Phet**
BFP	DMG_AM_056	3069	0.23	0.106	3.10E-02	1400	-0.1	0.14	4.90E-01	1669	0.51	0.16	1.00E-03	6.71E-03
	MISS_AM_056	1327	0.15	0.161	3.60E-01	586	0.113	0.22	6.10E-01	741	0.19	0.23	4.20E-01	7.61E-01
	HC_PTV	1766	0.33	0.14	2.00E-02	820	-0.25	0.19	1.90E-01	946	0.83	0.21	6.40E-05	3.74E-04
	1:160192801:G:C	1663	0.34	0.146	2.10E-02	1663	-0.28	0.19	1.50E-01	1663	0.87	0.22	6.80E-05	3.08E-04
BMI	DMG_AM_056	3070	0.1	0.079	2.10E-01	1401	-0.11	0.11	2.90E-01	1669	0.28	0.12	1.70E-02	6.71E-03
	MISS_AM_056	1327	0.05	0.12	7.00E-01	586	-0.03	0.16	8.70E-01	741	0.07	0.18	7.00E-01	7.61E-01
	HC_PTV	1767	0.16	0.104	1.20E-01	821	-0.18	0.14	2.00E-01	946	0.48	0.16	2.00E-03	3.74E-04
	1:160192801:G:C	1663	0.13	0.109	2.30E-01	1663	-0.23	0.14	1.10E-01	1663	0.47	0.17	4.80E-03	3.08E-04

Supplementary Table 8: CASQ1 gene-burden and single variant tests in UKB for BFP and bmi

Results are shown for damaging variants (DMG), comprising high-confidence protein-truncating variants (HC_PTV) and missense variants with AlphaMissense ≥0.564 (AM_056); missense variants with AlphaMissense ≥0.564; high-confidence protein-truncating variants alone; and the *CASQ1* protein-truncating variant rs145486953, represented by its GRCh38 coordinate chr1:160192801 G>C. Associations were estimated in the full sample and separately in men and women. AC denotes the alternate-allele count in the corresponding analysis; β is expressed in percentage points for body fat percentage (BFP) and kg m^{-2} for body mass index (BMI); SE is the standard error; and Phet is the two-sided test of heterogeneity between male and female effect estimates. Displayed association P values are two-sided and unadjusted for multiple testing.

				BASELINE				MAGIC_PRS_ADJ			
SYMBOL	**pheno**	**sex**	**MASK**	**AC**	**BETA**	**SE**	**PVALUE**	**AC**	**BETA**	**SE**	**PVALUE**
BRSK2	Glucose0	both	DMG_AlphaMissense0564	16	0.560	0.108	2.30E-07	16	0.545	0.103	1.30E-07
NID2	Glucose120	men	MISS_REVEL05	46	1.047	0.207	4.20E-07	46	0.972	0.205	2.20E-06

Supplementary Table 9: BRSK2 and NID2 associations with glycemic traits after adjusting for MAGIC-derived PRS

Baseline gene-burden results are compared with models additionally adjusted for a polygenic risk score (PRS) constructed using published MAGIC consortium weights for the corresponding glycaemic trait. Results are shown for the association of damaging (DMG) *BRSK2* variants, comprising protein-truncating variants and missense variants with AlphaMissense ≥0.564, with fasting glucose in the sex-combined analysis, and for the association of *NID2* missense variants with REVEL >0.5 with 2-hour post-challenge glucose in men. AC is the combined alternate-allele count across qualifying variants; β is expressed in mmol/L; and displayed P values are two-sided and unadjusted for multiple testing.