Plasma proteomes of obesity and allometric body shapes in the EPIC cohort

Running head: Proteomes of obesity and body shape in EPIC

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Supplementary Tables

Supplementary Table S1 SomaScan aptamers 3
Supplementary Table S2 Characteristics of study participants by country, study centre and sex 3
Supplementary Table S3 Proteomic associations of allometric indices and height 4
Supplementary Table S4 Gene sets for allometric indices and height 5
Supplementary Table S5 Protein-coding genes for allometric indices and height by gene set 6
Supplementary Table S6 Alternative aptamers for associations with allometric indices and height 7
Supplementary Table S7 Proteomic summary statistics for anthropometric indices 8

Supplementary Figures

Supplementary Figure S1A Phenotypic correlations between anthropometric indices 9
Supplementary Figure S1B Anthropometric characteristics by sex and study centre 9
Supplementary Figure S2A Mapping of study centres on proteomic PC1-PC2 scores 11
Supplementary Figure S2B Mapping of covariates on proteomic PC1-PC2 scores 11
Supplementary Figure S2C Mapping of aptamers on proteomic PC1-PC2 loadings 12
Supplementary Figure S3A Proteomic comparisons of body shape indices and BMI 13
Supplementary Figure S3B Proteomic comparisons of allometric and traditional obesity indices 13
Supplementary Figure S3C Proteomic standard errors for obesity indices and height 14
Supplementary Figure S3D Proteomic comparisons of allometric and traditional indices with height 14
Supplementary Figure S4 Pairwise correlations of top proteins for allometric indices and height 16
Supplementary Figure S5A Top-ranked proteins for BMI, WC and HC 17
Supplementary Figure S5B Associations of LEP and GRH related proteins 17
Supplementary Figure S5C Top-ranked proteins for WHR and WHI 18

Supplementary Figure S5D Top-ranked proteins for height 18
Supplementary Figure S6A Associations with cortisol-related proteins 20
Supplementary Figure S6B Correlations of cortisol-related proteins with top ranked proteins..... 20
Supplementary Figure S7 Gene ontology gene set mapping for allometric indices and height 22
Supplementary Figure S8A Gene expression in GTEx for top-ranked and cortisol proteins..... 23
Supplementary Figure S8B Gene expression in BrainSpan for top-ranked and cortisol proteins 23
Supplementary Figure S8C Gene expression in SC-WAT for top-ranked and cortisol proteins..... 24
Supplementary Figure S8D Gene expression in WATLAS for top-ranked and cortisol proteins 25
Supplementary Figure S9A Sex differences for BMI at Bonferroni significance level 27
Supplementary Figure S9B Sex differences − top ten proteins for BMI by sex..... 27
Supplementary Figure S9C Sex differences − top ten proteins for ABSI by sex..... 28
Supplementary Figure S9D Sex differences − top ten proteins for WHI by sex..... 28
Supplementary Figure S9E Sex differences − top ten proteins for HI by sex 29
Supplementary Figure S9F Sex differences − top ten proteins for height by sex 29
Supplementary Figure S9G Sex differences − cortisol related proteins by sex 30
Supplementary Figure S10A Comparison of minimally and fully adjusted models − overall..... 32
Supplementary Figure S10B Comparison of minimally and fully adjusted models − women 32
Supplementary Figure S10C Comparison of minimally and fully adjusted models − men 33
Supplementary Figure S10D Comparison of minimally and fully adjusted models – sex differences..... 33
Supplementary Figure S10E Comparison of energy adjusted and fully adjusted models – overall 33
Supplementary Figure S11A Alternative aptamers for associations with allometric indices & height 35
Supplementary Figure S11B Discordant alternative aptamers for top ranked proteins 35
Supplementary Figure S12A Proteomic comparisons of SomaScan in EPIC vs Icelanders 36
Supplementary Figure S12B Proteomic comparisons of SomaScan (EPIC) vs Olink (UKB) 36
Supplementary Figure S12C Proteomic comparisons of body shape vs BMI for Olink (UKB) 37
Supplementary Figure S12D BMI associations for top allometric set in EPIC vs Icelanders & UKB 37
Supplementary Figure S12E Top ten proteins for BMI in Icelanders & UKB vs EPIC..... 38
Supplementary Figure S12F Top ten proteins for height in EPIC vs Icelanders & UKB 38
Supplementary Figure S12G Top ten proteins for height in Icelanders & UK Biobank vs EPIC 39
Supplementary Figure S12H Cortisol-related proteins in EPIC vs Icelanders & UK Biobank..... 39
Supplementary Figure S13A SMP vs NoSMP normalisation − EPIC (full adjustment) 42
Supplementary Figure S13B SMP vs NoSMP normalisation − Icelanders (minimal adjustment) ... 42
Supplementary Figure S13C SMP vs NoSMP normalisation − top ten proteins for BMI..... 43
Supplementary Figure S13D SMP vs NoSMP normalisation − top ten proteins for height..... 43
Supplementary Figure S13E SMP vs NoSMP normalisation − top ten proteins for body shape..... 44
References……..46

Supplementary Table S1 SomaScan aptamers

See Supplementary Tables Excel file (sheet **ST1_SomaScan**)

n − aptamer number (alphabetical order of aptamer sequence ID)
seq − aptamer sequence ID
target − protein nick name
target_full_name – protein full name (could be a specific section of a protein or a protein complex)
gene – gene symbol used in association tables
gene_soma – gene symbol provided by Somalogic
entrez_soma – entrez ID provided by Somalogic
ensg – Ensembl ID provided by Somalogic
ensg_soma – Ensembl IDs including protein complexes
protein – UniProt ID
dilution – sample dilution sets according to expected protein levels − 20% low level proteins; 0.5% medium level proteins; 0.005% high level proteins.
ensg_fuma – Ensembl ID used by FUMA v1.5.2 (Functional Mapping and Annotation) [24]
entrez_fuma – Entrez ID used by FUMA
gene_fuma – gene symbol used by FUMA
asig – aptamer associated with allometric indices or height at Bonferroni significance level $p<(0.05/7289)\approx7*10^{-6}$ (0 no; 1 yes) (summary statistics shown in **Supplementary Table S3)**
soma_5k – available in SomaScan v4.0 (5k) (0 no; 1 yes)

Supplementary Table S2 Characteristics of study participants by country, study centre and sex

See Supplementary Tables Excel file (sheet **ST2_Demo**)

ABSI – allometric body shape index; **BMI** – body mass index; **HI** – hip index; **HRT** – hormone replacement therapy; **MP** – menopause; **WHI** – waist-to-hip index; **WHR** – waist-to-hip ratio.

For variables on a continuous scale, differences by country (**p-country**) or study centre (**p-centre**) were examined with Kruskal-Wallis test and differences by sex (**p-sex**) were examined with Wilcoxon-Mann-Whitney test. For categorical variables, differences by country, centre or sex were examined with chi-squared test.

Supplementary Table S3 Proteomic associations of allometric indices and height

See Supplementary Tables Excel file (sheet **ST3_AsigAlloHt**)

ABSI – allometric body shape index; **BMI** – body mass index; **HI** – hip index; **Hip** – hip circumference; **Waist** – waist circumference; **WHI** – waist-to-hip index; **WHR** – waist-to-hip ratio.

seq − aptamer sequence ID
gene – gene symbol
target_full_name – protein full name (could be a specific section of a protein or a protein complex)
entrez_soma – entrez ID provided by Somalogic
ensg – Ensembl ID provided by Somalogic
gene_fuma – gene symbol used by FUMA v1.5.2 (Functional Mapping and Annotation) [24]
ensg_fuma – Ensembl ID used by FUMA
entrez_fuma – Entrez ID used by FUMA
protein – UniProt ID
dilution – sample dilution sets according to expected protein levels − 20% low level proteins; 0.5% medium level proteins; 0.005% high level proteins
beta_index – proteomic regression coefficient
se_index – standard error of the proteomic regression coefficient
pval_index – Wald test p-value for the anthropometric index term
rank_index – aptamer rank order (lowest p-value first), defined for Bonferroni significance level $p<(0.05/7289)\approx7*10^{-6}$; NA not ranked.
top_allo – highest ranked aptamer for proteins in the top ten for any allometric index
top_height – highest ranked aptamer for proteins in the top ten for height
soma_5k – available in SomaScan v4.0 (5k) (0 no; 1 yes)

Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer individually as outcome variable.

Fully adjusted regression models were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre. All regression models for BMI were additionally adjusted for height. All regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.

Aptamer levels in men vs women were compared with variable **sex** (women reference) in fully adjusted models using the SMP-normalised dataset (participants overall) and omitting the adjustment for menopausal statis and hormone replacement therapy use.

The table includes aptamers associated at Bonferroni significance level with any allometric index (BMI, ABSI, WHI, HI) or height and summary statistics for all anthropometric indices.

Supplementary Table S4 Gene sets for allometric indices and height

See Supplementary Tables Excel file (sheet **ST4_GeneSets**)

Index – ABSI – allometric body shape index; BMI – body mass index; HI – hip index; WHI – waist-to-hip index.

Set – Hallmark pathways MsigDB h v7.0 [27]; GO – gene ontology gene sets [71, 72]; GTEx – genotype-tissue expression gene sets v8.0 [25]; BrainSpan – brain developmental gene sets [26]

Category – GO_bp – GO biological process GOBP; GO_cc – GO cellular component GOCC; GO_mf – GO molecular function GOMF; DEG.twoside – differentially expressed gene (DEG) set; DEG.up – upregulated DEG set; DEG.down – downregulated DEG set

GeneSet – gene set (Hallmark, GO) or tissue (GTEx) or developmental stage (BrainSpan) name

N_genes – number of genes in the gene set available in SomaScan

N_overlap – number of genes overlapping between the gene set and the protein-coding genes associated with the corresponding anthropometric index

N_index – number of protein-coding genes associated with the corresponding anthropometric index

Pvalue– p-value from a hypergeometric test performed in FUMA v1.5.2 (Functional Mapping and Annotation) [24]. Background genes have average expression above one in at least one of the labels and are available in SomaScan (6334 for GTEx and BrainSpan with unique identified Ensembl ID; 6302 for Hallmark and GO with unique identified Entrez ID).

Padj – Bonferroni corrected p-value, adjusted for 5 anthropometric indices (BMI, ABSI, WHI, HI, height) and either 50 pathways for Hallmark; 7751 gene sets for GOBP; 1009 gene sets for GOCC; 1772 gene sets for GOMF; 54 tissues and 3 DEGs (upregulated, downregulated, twosided) for GTEx; 11 developmental stages and 3 DEGs for BrainSpan.

GenesOverlap – overlap of genes associated with the corresponding anthropometric index with the corresponding gene set – gene name (Hallmark, GO) corresponding to gene_fuma; Ensembl ID (GTEx, BrainSpan) corresponding to ensg_fuma in **Supplementary Table S1**.

The table includes only gene sets with Bonferroni significance level (Padj<0.05).

Supplementary Table S5 Protein-coding genes for allometric indices and height by gene set

See Supplementary Tables Excel file (sheet **ST5_GeneByGS**)

ABSI – allometric body shape index; **BMI** – body mass index; **HI** – hip index; **GO** – gene ontology (BP biological process; CC cellular component; MF molecular function); **WHI** – waist-to-hip index.

ensg_fuma – Ensembl ID used by FUMA v1.5.2 (Functional Mapping and Annotation) [24]

entrez_fuma – Entrez ID used by FUMA

gene_fuma – gene symbol used by FUMA

INDEX – associations with the corresponding anthropometric index at Bonferroni significance level $p<(0.05/7289)\approx7*10^{-6}$ – **0** no association; **1** positively associated; **2** negatively associated; **3** alternative aptamers showing directionally discordant associations (positive and negative).

Cortisol – cortisol related proteins (*a priori* selected group) – **0** not included in the group; **1** cortisol related and associated with BMI; **2** cortisol related but not associated with allometric indices or height.

GeneSet – GTEx – genotype-tissue expression gene sets v8.0 [25]; BrainSpan – brain developmental gene sets [26]; HALLMARK – Hallmark pathways MsigDB h v7.0 [27]; GO – gene ontology gene sets (GOBP biological process; GOCC cellular component; GOMF molecular function) [71, 72]

GTEx & BrainSpan – included in a differentially expressed gene set (**1** upregulated; **2** downregulated) for the corresponding tissue or brain developmental stage

HALLMARK & GO – included in the corresponding gene set (**0** no; **1** yes) with Bonferroni significance level.

The table includes all protein-coding genes associated with any allometric index (BMI, ABSI, WHI, HI) or height at Bonferroni significance level $p<(0.05/7289)\approx7*10^{-6}$ and seven additional cortisol-related proteins not associated with allometric indices or height (the latter can be filtered out with option 2 in column Cortisol).

Supplementary Table S6 Alternative aptamers for associations with allometric indices and height

See Supplementary Tables Excel file (sheet **ST6_AlterApta**)

absi – allometric body shape index; **bmi** – body mass index; **hi** – hip index; **whi** – waist-to-hip index.

n − aptamer number (alphabetical order of aptamer sequence ID)
index – anthropometric index
seq − aptamer sequence ID
beta – regression coefficient
se – standard error
t – statistic
pval – Wald test p-value for the anthropometric index term
rank – aptamer rank order (lowest p-value first), defined for p<0.05 (nominal significance level)
gene – Entrez gene symbol (corresponds to column Gene in **Supplementary Table S1**)
lowest – lowest regression coefficient per gene per anthropometric index
highest – highest regression coefficient per gene per anthropometric index
largest – largest absolute value regression coefficient per gene per anthropometric index (sign-free)
set – 0 if *beta* between *lowest* & *highest*; 1 if *beta*=*lowest*, 2 if *beta*=*highest*
class – 1 strongest aptamer (aptamer with absolute value *beta*=*largest*), 2 alternative aptamer
colour – 1 *pval*<(0.05/7289)≈7*10^{-6} (Bonferroni), 2 *pval*<0.05 (nominal); 3 *pval*≥0.05 (colour in plot)
top – 1 if gene in top ten proteins for any allometric index or height; 2 if not in top ten
discord – 1 if *lowest***highest*<0 discordant signs of lowest & highest per gene; 2 otherwise (note that this value applies to the gene and is the same for all aptamers per gene per anthropometric index)
group – 1 if *colour*=1 (Bonferroni) & *discord*=2 (lowest & highest per gene have the same sign), 2 if *colour*=2 (nominal) & *discord*=2 (lowest & highest per gene have the same sign), 3 if *colour*=3 (non-significant), 4 if *colour*=2 (nominal) & *discord*=1 (lowest & highest per gene have opposite signs), 5 if *colour*=1 (Bonferroni) & *discord*=1 (lowest & highest per gene have opposite signs)
cor – partial Pearson correlation coefficient between each aptamer and the strongest aptamer per gene per anthropometric index (1 for the strongest aptamer)
protein – UniProt ID
name – protein name (corresponds to column *target_full_name* in **Supplementary Table S1**)

Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable.

All regression models and partial Pearson correlations were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre (regression) or country (partial correlation). Regression models for BMI were additionally adjusted for height. Regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.

The strongest aptamer for each protein (*cor*=1) was associated at Bonferroni significance level with the corresponding anthropometric index.

Supplementary Table S7 Proteomic summary statistics for anthropometric indices

See Supplementary Table S7 file at https://doi.org/10.1038/s41598-026-64282-5

A separate file will be provided after review containing regression coefficients for all aptamers for:

- all anthropometric indices (allometric (BMI, ABSI, WHI, HI), traditional (weight, waist and hip circumferences, WHR) and height) and sex in fully adjusted and minimally adjusted models (participants overall) using the SMP-normalised and NoSMP datasets (**overall**)
- allometric indices (BMI, ABSI, WHI, HI) and height in fully adjusted and minimally adjusted models (separately women and men) using the SMP-normalised dataset (**women**, **men**)
- interaction terms with sex for allometric indices and height in fully adjusted and minimally adjusted models (participants overall) using the SMP-normalised dataset (**i.sex**)

absi – allometric body shape index; **bmi** – body mass index; **hi** – hip index; **hip** – hip circumference; **waist** – waist circumference; **whi** – waist-to-hip index; **whr** – waist-to-hip ratio**.**

n − aptamer sequence number (alphabetical order)

index – anthropometric index (see above)

seq − aptamer sequence ID

beta – regression coefficient

se – standard error

t – t-statistic

pval – Wald test p-value for the anthropometric index term

rank – aptamer rank order (lowest p-value first), defined for $p<(0.05/7289)\approx7*10^{-6}$ (Bonferroni significance level)

norm – **smp** – sample-normalised (SMP) dataset Somalogic; **nosmp** – dataset provided by Somalogic without sample normalisation (NoSMP)

covar – **adj** – fully adjusted model, **min** – minimally adjusted model (see below)

group – participants overall or separately women and men or interaction term with sex (**i.sex**)

gene – gene symbol (corresponds to column *gene* in **Supplementary Table S1**)

Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer individually as outcome variable.

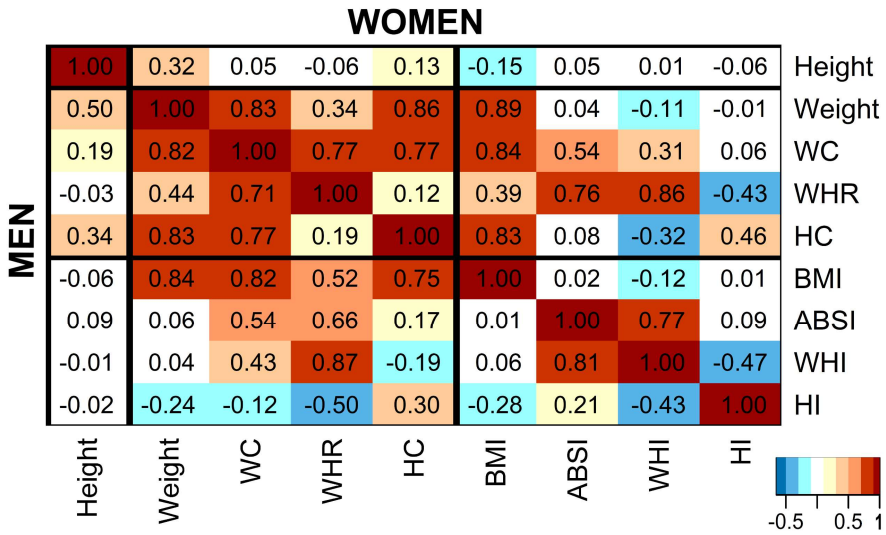
Minimally adjusted regression models (**min**) were adjusted for sex, age and study centre.

Fully adjusted regression models (**adj**) were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre.

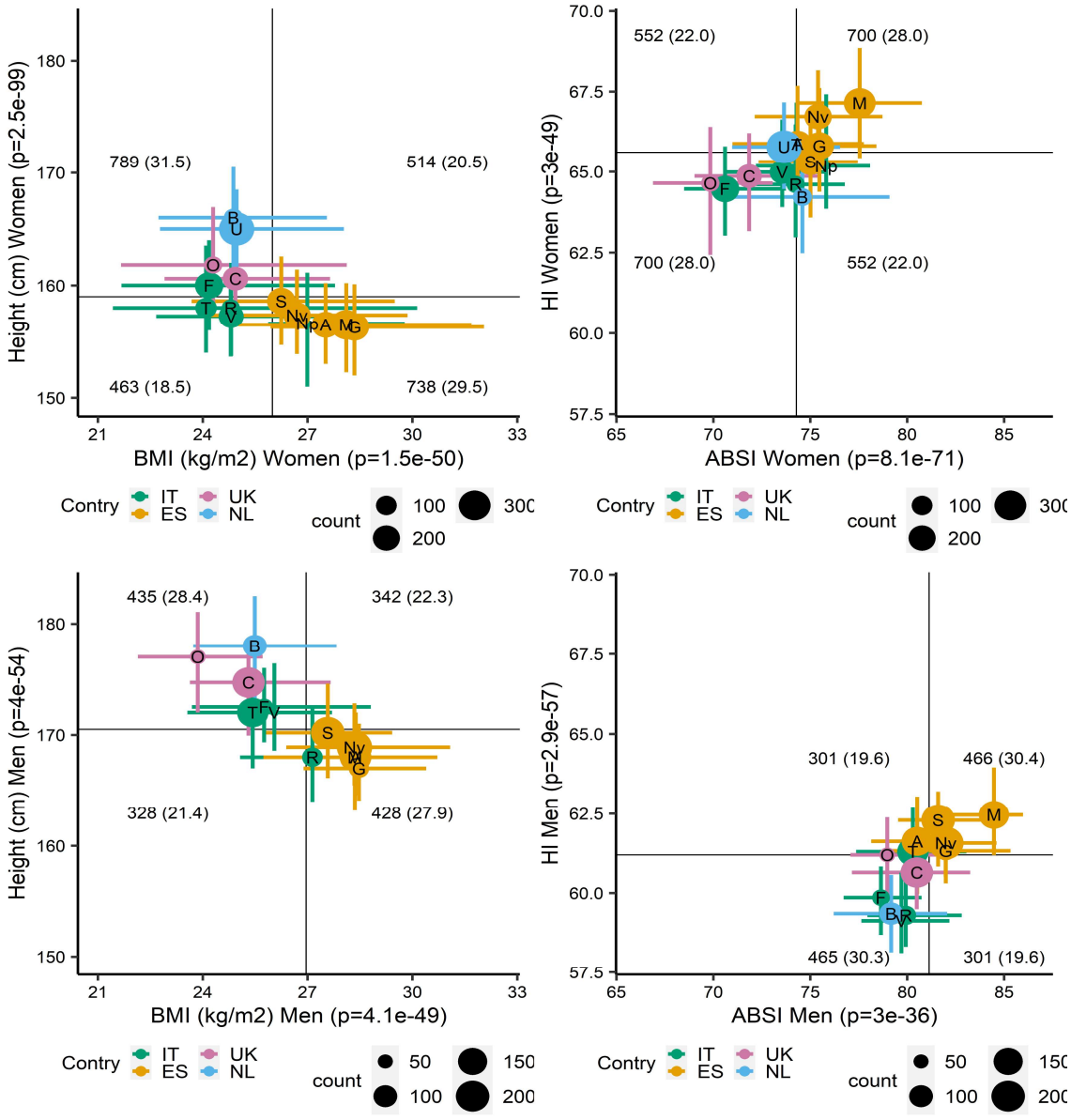
All regression models for BMI (minimally and fully adjusted) were additionally adjusted for height. All regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.

Sex differences were tested for each anthropometric index with the interaction term with sex (**i.sex**) in models additionally including interaction terms with sex for all covariates (participants overall).

Aptamer levels in men vs women were compared with variable **sex** (women reference), omitting the adjustment for menopausal status and hormone replacement therapy use (participants overall).



Supplementary Figure S1A Phenotypic correlations between anthropometric indices



Supplementary Figure S1B Anthropometric characteristics by sex and study centre

Supplementary Figure S1 Anthropometric characteristics *(legend)*

ABSI – a body shape index; **BMI** – body mass index; **HC** – hip circumference; **HI** – hip index; **WC** – waist circumference; **WHI** – waist-to-hip index; **WHR** – waist-to-hip ratio.

Heatmap: sex-specific partial Pearson correlation coefficients, with adjustment for age, smoking status, alcohol intake, physical activity, education, and country and in women also menopausal status and hormone replacement therapy use.

Country: **ES** – Spain (women=1199, men=838); **IT** – Italy (w=592, m=352); **NL** – Netherlands (w=472, m=101); **UK** – United Kingdom (w=241, m=242).

Centre: **A** – Asturias (w=219, m=173); **B** – Bilthoven (w=81,m=101); **C** – Cambridge (w=170; m=189); **F** – Florence (w=223, m=61); **G** – Granada (w=246, m=75); **M** – Murcia (w=301, m=162); **Np** – Naples (w=22); **Nv** – Navarra (w=206, m=225); **O** – Oxford (w=71, m=53); **R** – Ragusa (w=73, m=77); **S** – San Sebastian (w=227, m=203); **T** – Turin (w=110,m=175); **V** – Varese (w=164, m=39); **U** – Utrecht (w=391).

Circle (whiskers) – median (25^{th} to 75^{th} centile) per centre; Lines – median per sex.

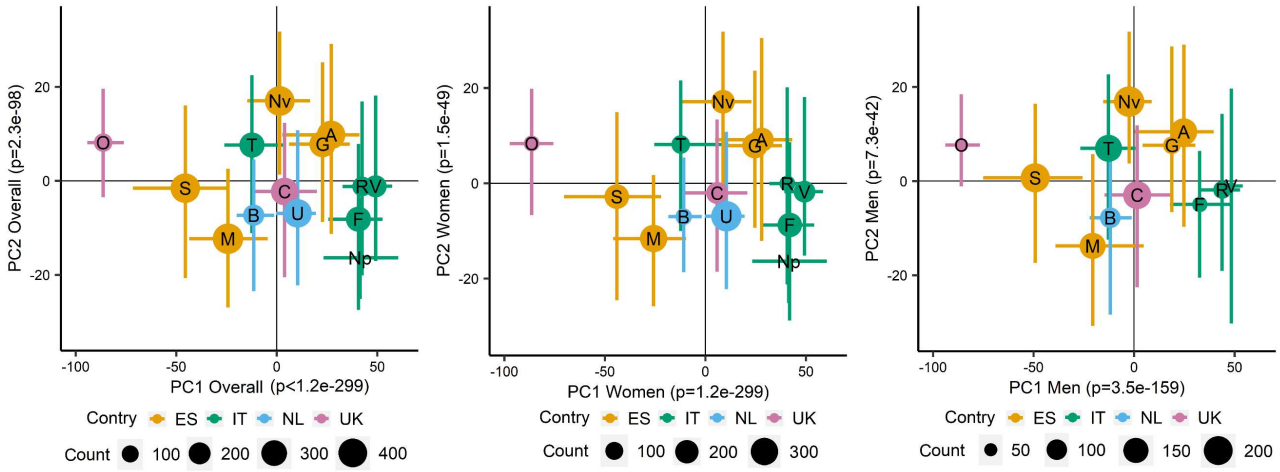
Axes (p-value) – Kruskal-Wallis test for the difference between study centres in the axis variable.

Corners – number (%) – total counts per cross-classification group (% from total per sex).

Summary by sex:

	Women					**Men**					p-value
	2.5^{th} centile	25^{th} centile	Median	75^{th} centile	97.5^{th} centile	2.5^{th} centile	25^{th} centile	Median	75^{th} centile	97.5^{th} centile	
Height (cm)	147.1	154.8	159.0	164.0	173.0	157.5	166.1	170.5	175.3	185.6	$<1*10^{-300}$
BMI (kg/m^2)	19.7	23.3	26.0	29.5	37.5	20.9	24.8	27.0	29.5	35.0	$1*10^{-10}$
ABSI	65.5	71.0	74.3	77.4	84.9	72.9	78.5	81.1	84.0	89.1	$<1*10^{-300}$
WHI	3.10	3.40	3.55	3.71	4.11	3.69	3.96	4.10	4.24	4.53	$<1*10^{-300}$
HI	60.5	64.0	65.6	67.3	70.8	56.7	59.8	61.2	62.6	66.2	$<1*10^{-300}$
Weight (kg)	49.9	59.8	66.0	74.4	94.5	61.0	72.0	78.6	85.8	104.1	$3*10^{-200}$
WC (cm)	66.0	75.0	82.3	91.0	109.0	77.0	89.0	95.5	102.0	118.0	$2*10^{-209}$
WHR	0.69	0.76	0.81	0.85	0.95	0.81	0.90	0.94	0.97	1.06	$<1*10^{-300}$
HC (cm)	88.0	97.0	102.5	109.0	125.5	90.0	97.8	102.0	106.5	117.4	0.002

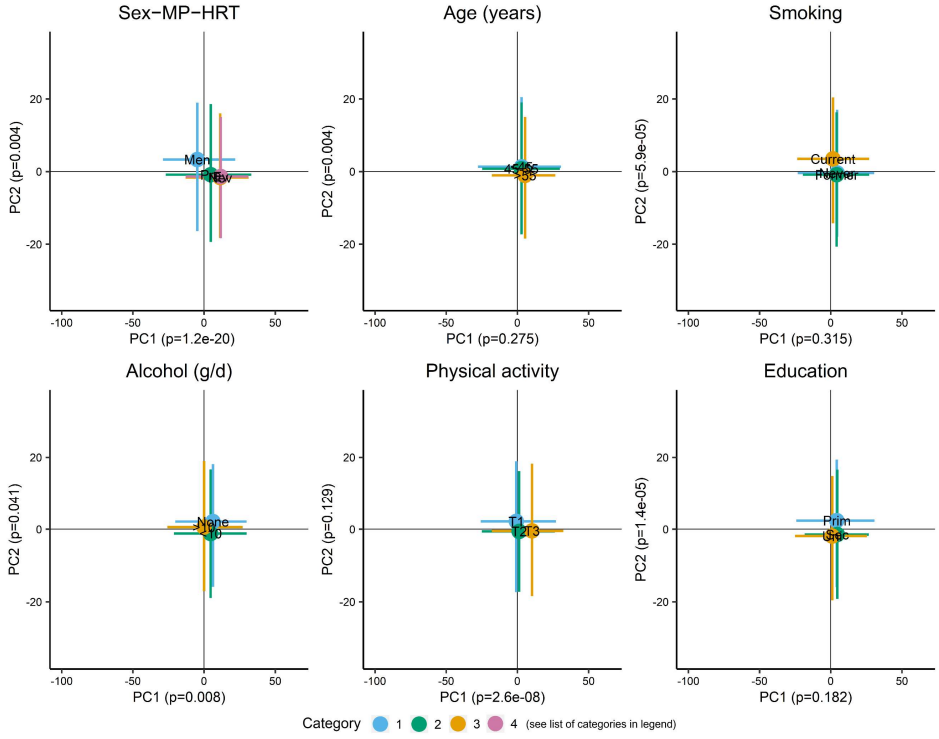
p-value – Kruskal-Wallis test for the difference between sexes.



Supplementary Figure S2A Mapping of study centres on proteomic PC1-PC2 scores

Country: **ES** – Spain, **IT** – Italy, **NL** – Netherlands, **UK** – United Kingdom

Centre: **A** – Asturias, **B** – Bilthoven, **C** – Cambridge, **F** – Florence, **G** – Granada, **M** – Murcia, **Np** – Naples, **Nv** – Navarra, **O** – Oxford, **R** – Ragusa, **S** – San Sebastian, **T** – Turin, **V** – Varese, **U** – Utrecht

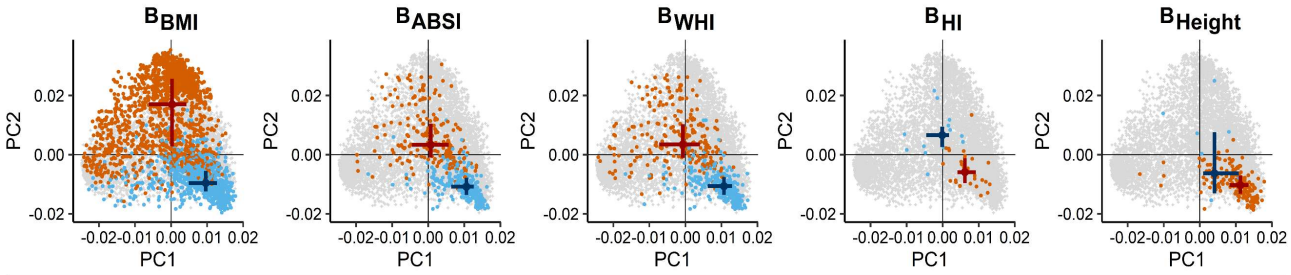


Supplementary Figure S2B Mapping of covariates on proteomic PC1-PC2 scores

Sex-MP-HRT – classification by sex, menopausal status and hormone replacement therapy (HRT) use – 1) men, 2) pre-menopausal women, 3) post/unknown menopause never HRT, 4) post/unknown menopause ever HRT); **Age** – 1) <45 years, 2) 45 to <55 years, 3) ≥55 years; **Smoking** – 1) never, 2) former, 3) current smoker; **Alcohol intake** – 1) None, 2) <10 g/day, 3) ≥10 g/day; **Physical activity** – tertiles of Cambridge physical activity index (tertile boundaries: 64.3 Mets and 121.5 Mets); **Education** – 1) primary, 2) secondary/vocational, 3) university degree.

Circle (whiskers) – median (25^{th} to 75^{th} centile) of PC1 and PC2.

p-value – difference between centres (A) or covariate categories (B) from Kruskal-Wallis test.



PC1–PC2 region	Regional (%)	ALLO–Height (%)	BMI (%) (neg–pos)	ABSI (%) (neg–pos)	WHI (%) (neg–pos)	HI (%) (neg–pos)	Height (%) (neg–pos)
pos–pos	1878 (25.8)	696 (27.1)	685 (27.7) (40–645)	78 (17.0) (6–72)	84 (15.7) (10–74)	11 (25.0) (6–5)	6 (3.1) (3–3)
pos–neg	2457 (33.7)	947 (38.5)	921 (37.2) (767–154)	277 (60.3) (231–46)	305 (57.0) (264–41)	23 (52.3) (0–23)	178 (92.7) (6–172)
neg–neg	1606 (22.0)	234 (9.1)	226 (9.1) (98–128)	27 (5.9) (10–17)	48 (9.0) (14–34)	1 (2.3) (1–0)	6 (3.1) (0–6)
neg–pos	1348 (18.5)	651 (25.3)	644 (26.0) (13–631)	77 (16.8) (1–76)	98 (18.3) (0–98)	9 (20.5) (9–0)	2 (1.0) (2–0)
total	7289	2576	2476 (918–1558)	459 (248–211)	535 (288–247)	44 (16–28)	192 (11–181)

Supplementary Figure S2C Mapping of aptamers on proteomic PC1-PC2 loadings

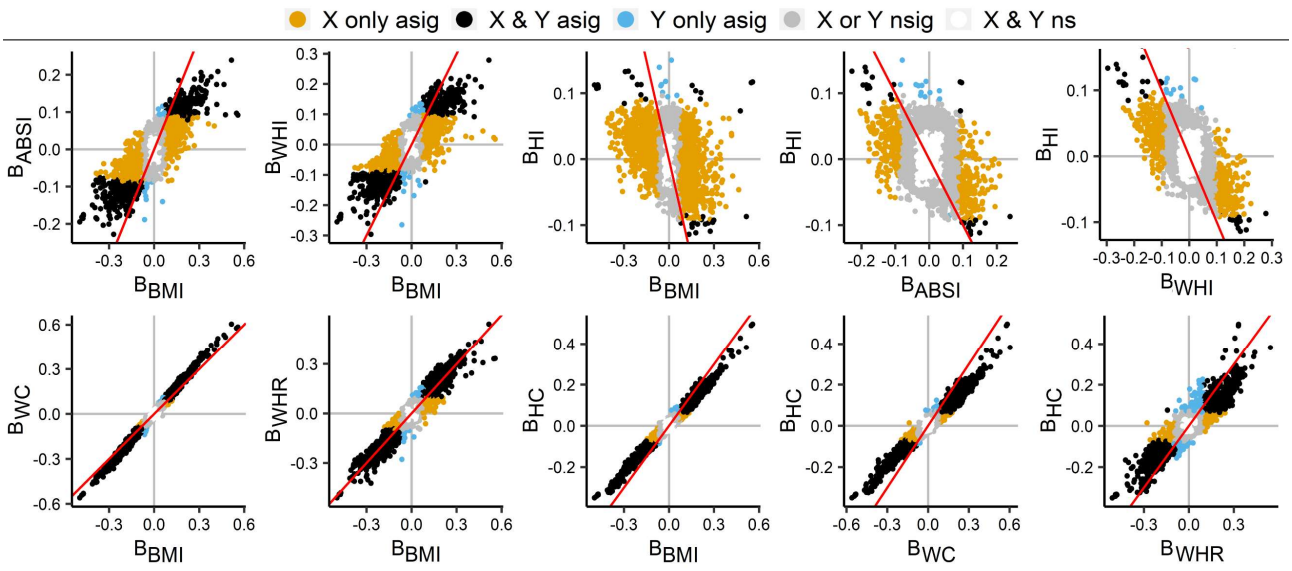
ABSI – a body shape index, **BMI** – body mass index, **HI** – hip index; **WHI** – waist-to-hip index; **B_{INDEX}** – proteomic regression coefficient; **PC** – principal component scores (A, B) or loadings (C); **neg–pos** – number of aptamers with a negative or positive B_{INDEX} (Bonferroni significance level); **PC1-PC2 region** – negative (neg) or positive (pos) sign of PC1 and PC2.

Principal Component (PC) scores (A, B) and loadings (C) were obtained from principal component analysis of unadjusted protein measurements from the sample-normalised (SMP) dataset (PC1 explained 20.9% of total proteomic variability; PC2 explained 8.6%).

Regression coefficient estimates determining whether a given aptamer is associated with allometric indices and height (C) were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable. All models were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre. Models for BMI were additionally adjusted for height. Models for ABSI and HI were additionally adjusted for BMI and height. Aptamers are coloured according to their association with allometric indices and height (orange – positive; blue – negative; grey – not associated at Bonferroni significance level).

Note for proteomic PC-loadings plot (C):

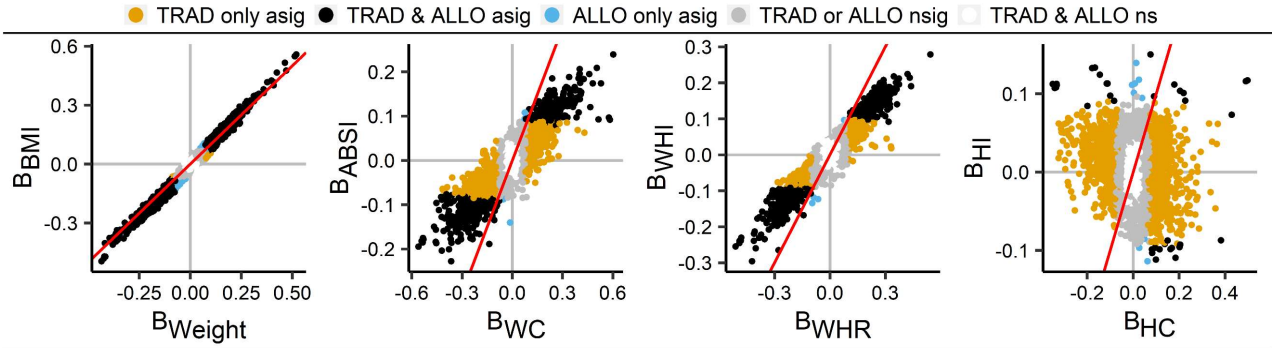
- a set of aptamers grouped in region PC1-positive-PC2-negative were associated negatively with general obesity (BMI) and allometric abdominal obesity (ABSI, WHI) and positively with HI and height;
- a set of aptamers grouped towards PC2-positive were positively associated with general obesity;
- a set of aptamers grouped in region PC1-negative-PC2-negative were mostly unrelated to obesity indices or height.



X index	Y index	X total asig (neg−pos)	Y total asig (neg−pos)	X only asig (neg−pos)	X & Y asig (nn−pp−pn−np)	Y only asig (neg−pos)	r_{beta}	r_{pheno}
BMI	**ABSI**	2476 (918−1558)	459 (248−211)	2039 (684−1355)	437 (234−203−0−0)	22 (14−8)	0.79	0.02
BMI	**WHI**	2476 (918−1558)	535 (288−247)	1981 (653−1328)	495 (265−229−1−0)	40 (22−18)	0.73	−0.07
BMI	**HI**	2476 (918−1558)	44 (16−28)	2440 (905−1535)	36 (0−7−16−13)	8 (0−8)	−0.17	−0.07
ABSI	**HI**	459 (248−211)	44 (16−28)	428 (235−193)	31 (0−3−15−13)	13 (1−12)	−0.17	0.13
WHI	**HI**	535 (288−247)	44 (16−28)	502 (271−231)	33 (0−0−16−17)	11 (0−11)	−0.53	−0.46
WHI	**ABSI**	535 (288−247)	459 (248−211)	134 (68−66)	401 (220−181−0−0)	58 (28−30)	0.91	0.80
BMI	**WC**	2476 (918−1558)	2447 (890−1557)	157 (73−84)	2319 (845−1474−0−0)	128 (45−83)	0.99	0.83
BMI	**WHR**	2476 (918−1558)	1704 (690−1014)	901 (273−628)	1575 (645−930−0−0)	129 (45−84)	0.93	0.43
BMI	**HC**	2476 (918−1558)	1832 (632−1200)	680 (289−391)	1796 (629−1167−0−0)	36 (3−33)	0.97	0.81
WC	**HC**	2447 (890−1557)	1832 (632−1200)	667 (270−397)	1780 (620−1160−0−0)	52 (12−40)	0.96	0.77
WHR	**HC**	1704 (690−1014)	1832 (632−1200)	449 (176−273)	1255 (513−741−0−1)	577 (119−458)	0.86	0.14
WHR	**WC**	1704 (690−1014)	2447 (890−1557)	67 (24−43)	1637 (666−971−0−0)	810 (224−586)	0.96	0.73

asig − p<(0.05/7289) (Bonferroni) nsig − p<0.05 (nominal) ns − p≥0.05 (non-significant) equivalence line

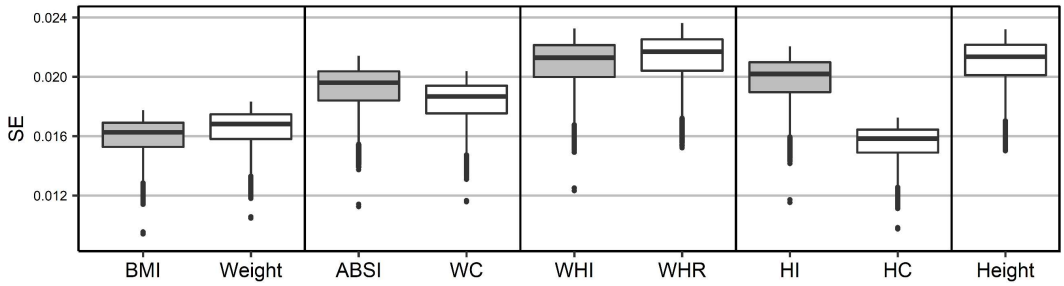
Supplementary Figure S3A Proteomic comparisons of body shape indices and BMI



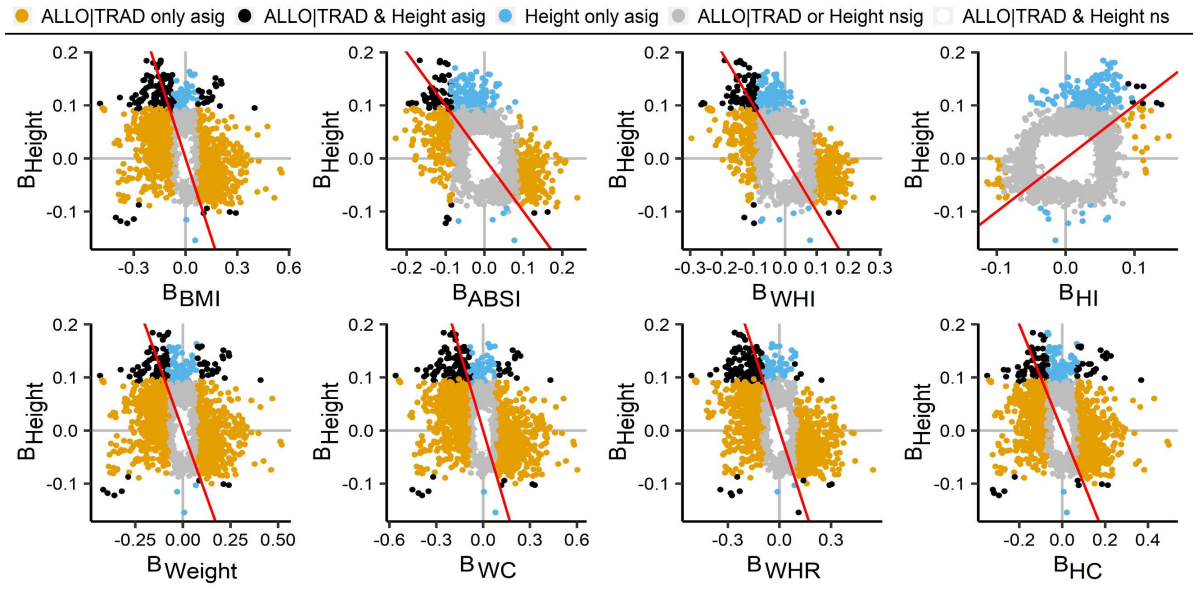
ALLO	TRAD	ALLO total asig (neg−pos)	ALLO total nsig (neg−pos)	TRAD total asig (neg−pos)	TRAD total nsig (neg−pos)	TRAD only asig (neg−pos)	TRAD & ALLO asig (nn−pp−pn−np)	ALLO only asig (neg−pos)	r_{beta}	r_{pheno}
BMI	**Weight**	2476 (918−1558)	4708 (2021−2687)	1964 (707−1257)	4193 (1744−2449)	23 (6−17)	1941 (701−1240−0−0)	535 (217−318)	0.99	0.87
ABSI	**WC**	459 (248−211)	2459 (929−1530)	2447 (890−1557)	4673 (1961−2712)	1993 (645−1348)	454 (245−209−0−0)	5 (3−2)	0.85	0.54
WHI	**WHR**	535 (288−247)	2536 (1056−1480)	1704 (690−1014)	4256 (1685−2571)	1173 (405−768)	531 (285−246−0−0)	4 (3−1)	0.92	0.87
HI	**HC**	44 (16−28)	1344 (621−723)	1832 (632−1200)	4072 (1727−2345)	1797 (619−1178)	35 (0−9−13−13)	9 (3−6)	0.01	0.42

asig − p<(0.05/7289) (Bonferroni) nsig − p<0.05 (nominal) ns − p≥0.05 (non-significant) equivalence line

Supplementary Figure S3B Proteomic comparisons of allometric and traditional obesity indices



Supplementary Figure S3C Proteomic standard errors for obesity indices and height



X-index	Y-index	ALLO|TRAD total asig (neg−pos)	Height total asig (neg−pos) *	ALLO|TRAD only asig (neg−pos)	ALLO|TRAD & Height asig (nn−pp−pn−np)	Height only asig (neg−pos)	r_{beta}	r_{pheno}
BMI	**Height**	2476 (918−1558)	192 (11−181)	2336 (801−1535)	140 (5−19−4−112)	52 (2−50)	−0.59	−0.12
ABSI	**Height**	459 (248−211)	192 (11−181)	395 (186−209)	64 (4−0−2−58)	128 (5−123)	−0.55	0.06
WHI	**Height**	535 (288−247)	192 (11−181)	455 (210−245)	80 (3−0−2−75)	112 (6−106)	−0.58	0.01
HI	**Height**	44 (16−28)	192 (11−181)	37 (16−21)	7 (0−7−0−0)	185 (11−174)	0.24	−0.04
Weight	**Height**	1964 (707−1257)	192 (11−181)	1850 (622−1228)	114 (5−26−3−80)	78 (3−75)	−0.48	0.37
WC	**Height**	2447 (890−1557)	192 (11−181)	2313 (776−1537)	134 (5−16−4−109)	58 (2−56)	−0.58	0.10
WHR	**Height**	1704 (690−1014)	192 (11−181)	1579 (573−1006)	125 (5−4−4−112)	67 (2−65)	−0.64	−0.05
HC	**Height**	1832 (632−1200)	192 (11−181)	1723 (551−1172)	109 (5−24−4−76)	83 (2−81)	−0.48	0.19

asig − p<(0.05/7289) (Bonferroni) nsig − p<0.05 (nominal) ns − p≥0.05 (non-significant) equivalence line

Supplementary Figure S3D Proteomic comparisons of allometric and traditional indices with height

ABSI – a body shape index; **B_{INDEX}** – proteomic regression coefficient; **BMI** – body mass index; **HC** – hip circumference; **HI** – hip index; **SE** – standard error (the lowest outliers belong to leptin); **WC** – waist circumference; **WHI** – waist-to-hip index; **WHR** – waist-to-hip ratio.

***** – total aptamer count at nominal significance level for height was 2056 (1023−1033).

ALLO | TRAD – allometric (BMI, ABSI, WHI, HI) or traditional (weight, WC, WHR, HC) obesity indices.

neg−pos – total number of aptamers with negative or positive associations at Bonferroni significance level p<(0.05/7289)≈$7*10^{-6}$ (asig) or nominal significance level p<0.05 (nsig).

Supplementary Figure S3 Proteomic comparisons of obesity indices and height *(legend)*

Overlaps at Bonferroni significance level:

nn – number of aptamers with negative associations for both X-index and Y-index (A), or bothTRAD and ALLO (B) or both ALLO or TRAD and height (D)

pp – number of aptamers with positive associations for both X-index and Y-index (A), both TRAD and ALLO (B) or both ALLO or TRAD and height (D)

pn – number of aptamers with positive associations for X-index and negative for Y-index (A), or positive association for TRAD and negative for ALLO (B) or positive associations for ALLO or TRAD and negative for height (D)

np – number of aptamers with negative associations for X-index and positive for Y-index (A), or negative association for TRAD and positive for ALLO (B) or negative association for ALLO or TRAD and positive for height (D)

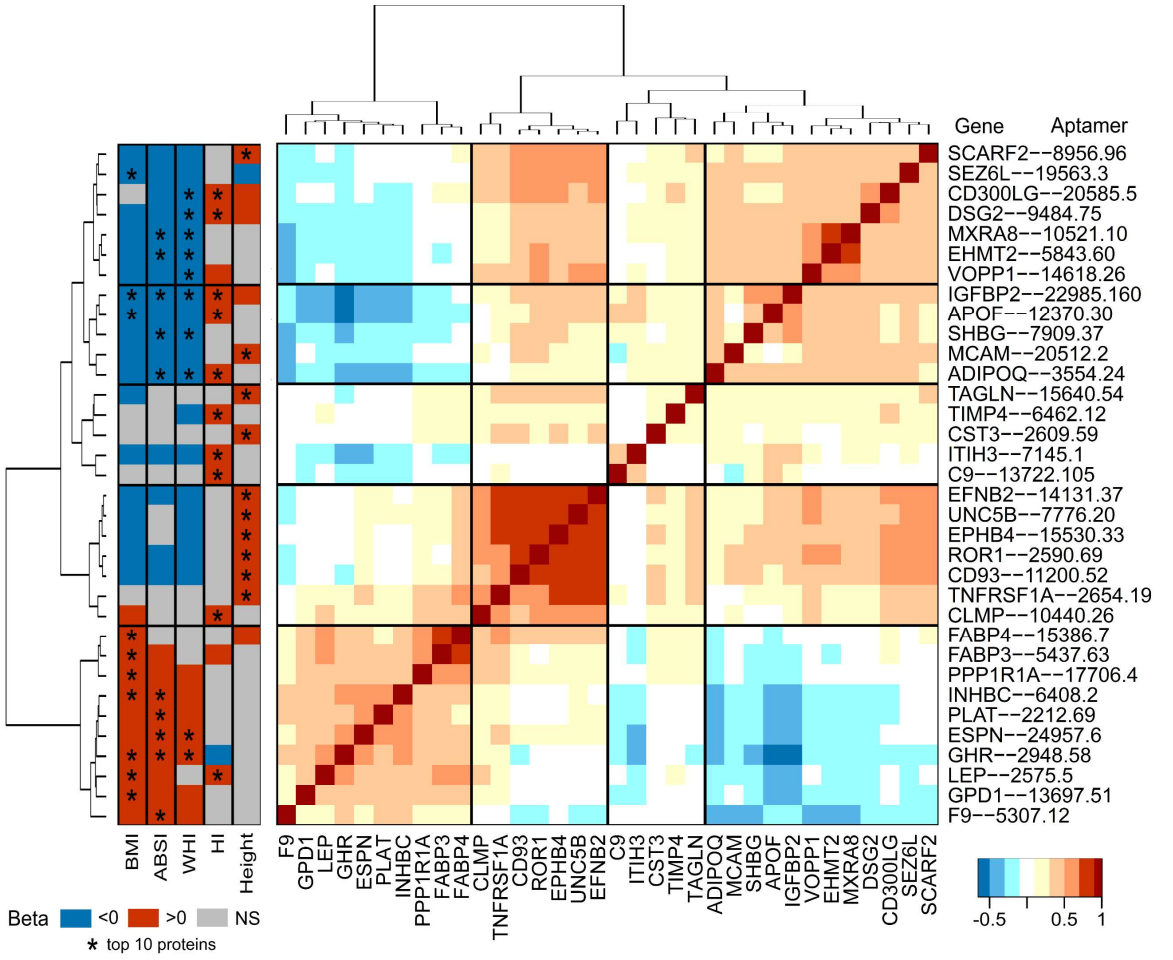
Correlations for X-index−Y-index pairs (A), or TRAD–ALLO index pairs (B)
or ALLO|TRAD−height pairs (D):

$\mathbf{r_{beta}}$ – Spearman rank correlation coefficient between proteomic regression coefficients

$\mathbf{r_{pheno}}$ – partial Pearson correlation coefficient between phenotypic traits

Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable. Correlation coefficients (r_{beta}, r_{pheno}) were significant at $p<1*10^{-9}$ for absolute values >0.1 and at $p<1*10^{-300}$ for absolute values >0.5.

All regression models and phenotypic partial Pearson correlations were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre (regression) or country (correlation). Regression models for BMI were additionally adjusted for height. Regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.



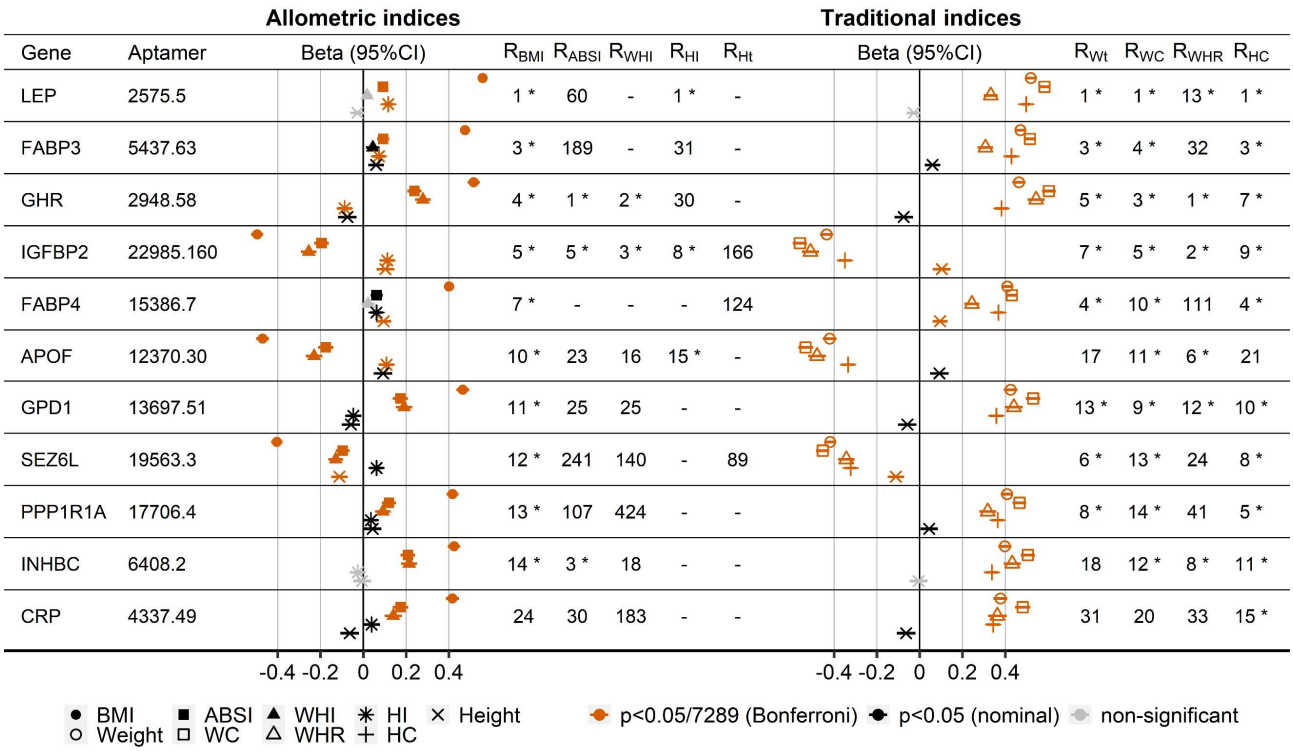
Supplementary Figure S4 Pairwise correlations of top proteins for allometric indices and height

ABSI – a body shape index; **BMI** – body mass index; **HI** – hip index; **WHI** – waist-to-hip index.

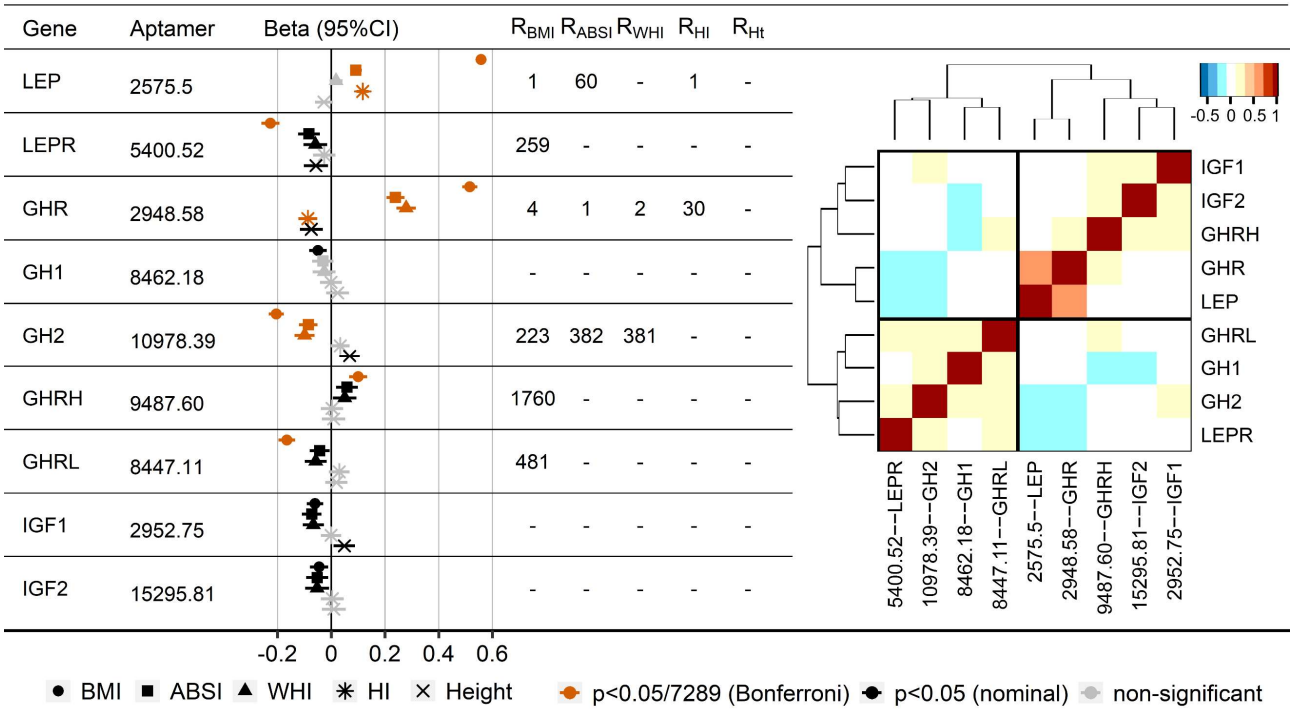
Beta – proteomic regression coefficient; **Strip** – colour coded by the direction of the association; **NS** – non-significant at Bonferroni significance level $p \geq (0.05/7289) \approx 7*10^{-6}$.

ADIPOQ − Adiponectin; **APOF** − Apolipoprotein F; **C9** − Complement component C9; **CD300LG** − CMRF35-like molecule 9; **CD93** − Complement component C1q receptor; **CLMP** − CXADR-like membrane protein:Extracellular domain; **CST3** − Cystatin-C; **DSG2** − Desmoglein-2; **EFNB2** − Ephrin-B2:Extracellular domain; **EHMT2** − Histone-lysine N-methyltransferase EHMT2; **EPHB4** − Ephrin type-B receptor 4; **ESPN** − Espin; F9 − Coagulation factor IXab; **FABP3** − Fatty acid-binding protein, heart; **FABP4** − Fatty acid-binding protein, adipocyte; **GHR** − Growth hormone receptor; **GPD1** − Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic; **IGFBP2** − Insulin-like growth factor-binding protein 2; **INHBC** − Inhibin beta C chain; **ITIH3** − Inter-alpha-trypsin inhibitor heavy chain H3; **LEP** − Leptin; **MCAM** − Melanoma-associated antigen MUC18; **MXRA8** − Matrix-remodeling-associated protein 8:Extracellular domain; **PLAT** − Tissue-type plasminogen activator; **PPP1R1A** − Protein phosphatase 1 regulatory subunit 1A; **ROR1** − Inactive tyrosine-protein kinase transmembrane receptor ROR1; **SCARF2** − Scavenger receptor class F member 2:Extracellular domain; **SEZ6L** − Seizure 6-like protein; **SHBG** − Sex hormone-binding globulin; **TAGLN** − Transgelin; **TIMP4** − Metalloproteinase inhibitor 4; **TNFRSF1A** − Tumor necrosis factor receptor superfamily member 1A; **UNC5B** − Netrin receptor UNC5B; **VOPP1** − Vesicular, overexpressed in cancer, prosurvival protein 1.

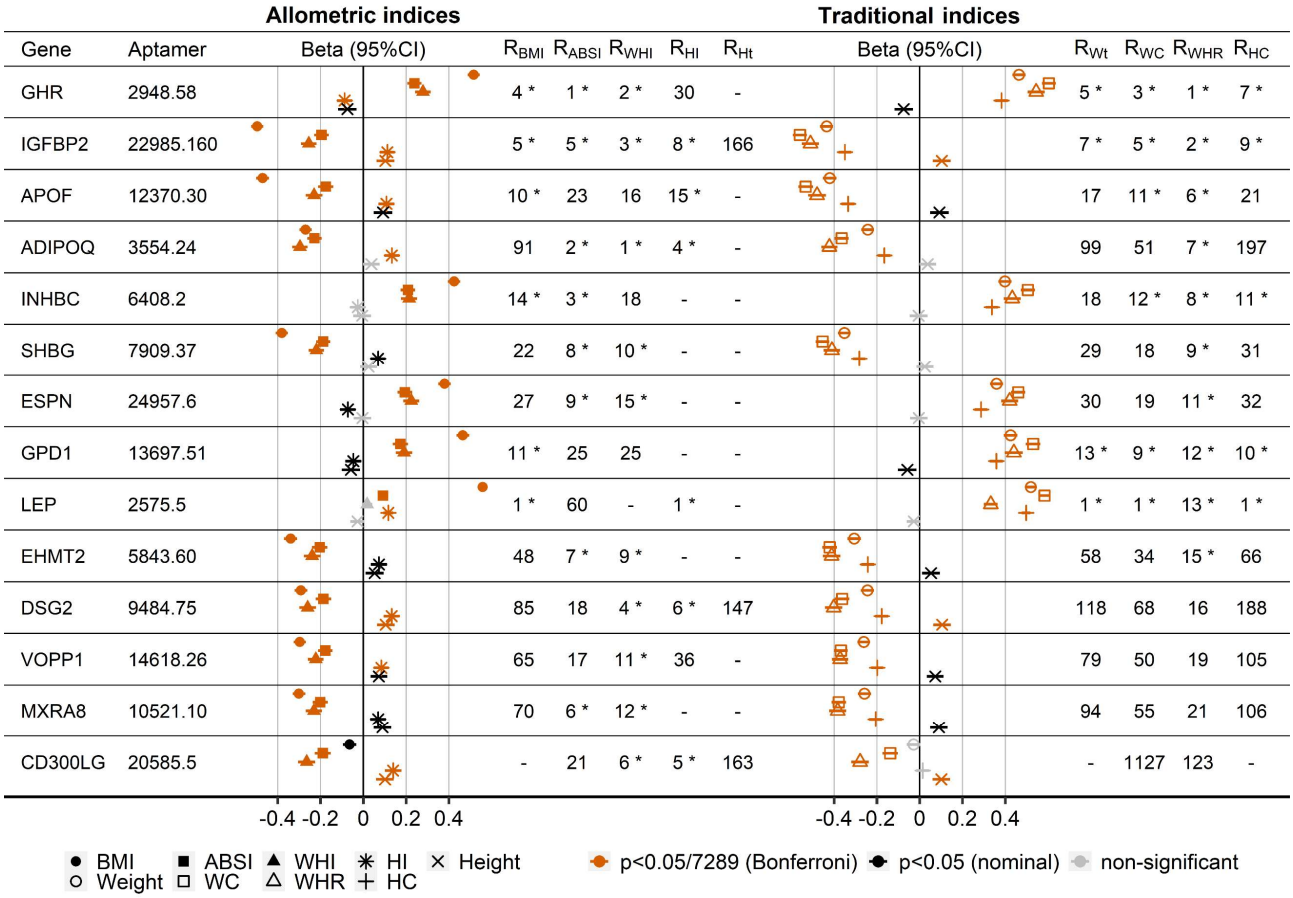
Pairwise partial Pearson correlation coefficients between aptamers corresponding to proteins ranked within the top ten for at least one allometric index (BMI, ABSI, WHI or HI), adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and country.



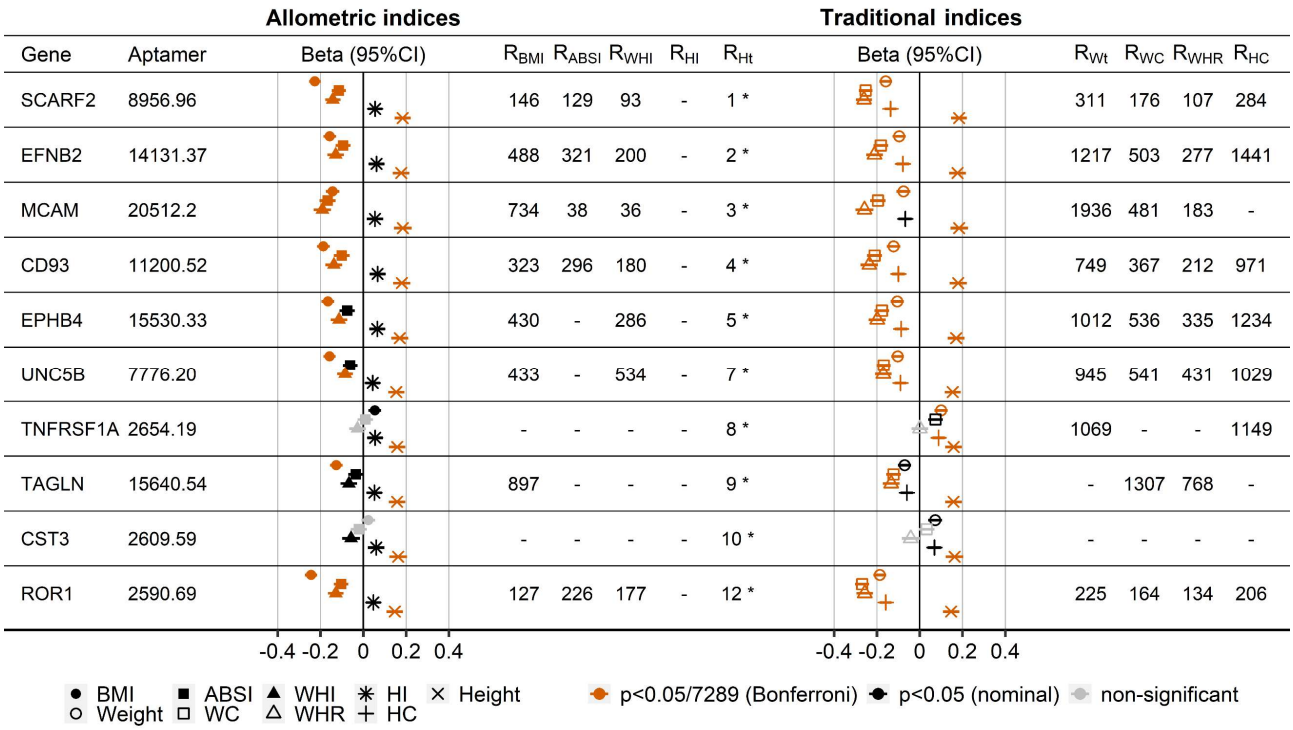
Supplementary Figure S5A Top-ranked proteins for BMI, WC and HC



Supplementary Figure S5B Associations of LEP and GRH related proteins



Supplementary Figure S5C Top-ranked proteins for WHR and WHI



Supplementary Figure S5D Top-ranked proteins for height

Supplementary Figure S5 Top-ranked proteins for BMI, traditional indices and height *(legend)*

ABSI – a body shape index; **Aptamer** – aptamer sequence number; **Beta** – proteomic regression coefficient; **BMI** – body mass index; **CI** – confidence interval; **HC** – hip circumference; **HI** – hip index; **Ht** – height; $\mathbf{R_{INDEX}}$ – aptamer rank order (lowest p-value first), defined for $p<(0.05/7289)\approx7*10^{-6}$ (Bonferroni significance level); **WC** – waist circumference; **WHI** – waist-to-hip index; **WHR** – waist-to-hip ratio; **Wt** – weight.

ADIPOQ − Adiponectin; **APOF** − Apolipoprotein F; **CD300LG** − CMRF35-like molecule 9; **CD93** − Complement component C1q receptor; **CRP** − C-reactive protein; **CST3** − Cystatin-C; **DSG2** − Desmoglein-2; **EFNB2** − Ephrin-B2:Extracellular domain; **EHMT2** − Histone-lysine N-methyltransferase EHMT2; **EPHB4** − Ephrin type-B receptor 4; **ESPN** − Espin; **GHR** − Growth hormone receptor; **FABP3** − Fatty acid-binding protein, heart; **FABP4** − Fatty acid-binding protein, adipocyte; **GH1** − Somatotropin; **GH2** – Growth hormone variant; **GHR** – Growth hormone receptor; **GHRH** − Somatoliberin; **GHRL** − Appetite-regulating hormone; **GPD1** − Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic; **IGF1** − Insulin-like growth factor I; **IGF2** − Insulin-like growth factor II:Mature; **IGFBP2** − Insulin-like growth factor-binding protein 2; **INHBC** − Inhibin beta C chain; **LEP** − Leptin; **LEPR** − Leptin receptor, soluble; **MCAM** − Melanoma-associated antigen MUC18; **MXRA8** − Matrix-remodeling-associated protein 8:Extracellular domain; **PPP1R1A** − Protein phosphatase 1 regulatory subunit 1A; **ROR1** − Inactive tyrosine-protein kinase transmembrane receptor ROR1; **SCARF2** − Scavenger receptor class F member 2:Extracellular domain; **SEZ6L** − Seizure 6-like protein; **SHBG** − Sex hormone-binding globulin; **TAGLN** − Transgelin; **TNFRSF1A** − Tumor necrosis factor receptor superfamily member 1A; **UNC5B** − Netrin receptor UNC5B; **VOPP1** − Vesicular, overexpressed in cancer, prosurvival protein 1.

Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable. The heatmap (S5B) includes partial Pearson correlation coefficients between the corresponding pairs of aptamers.

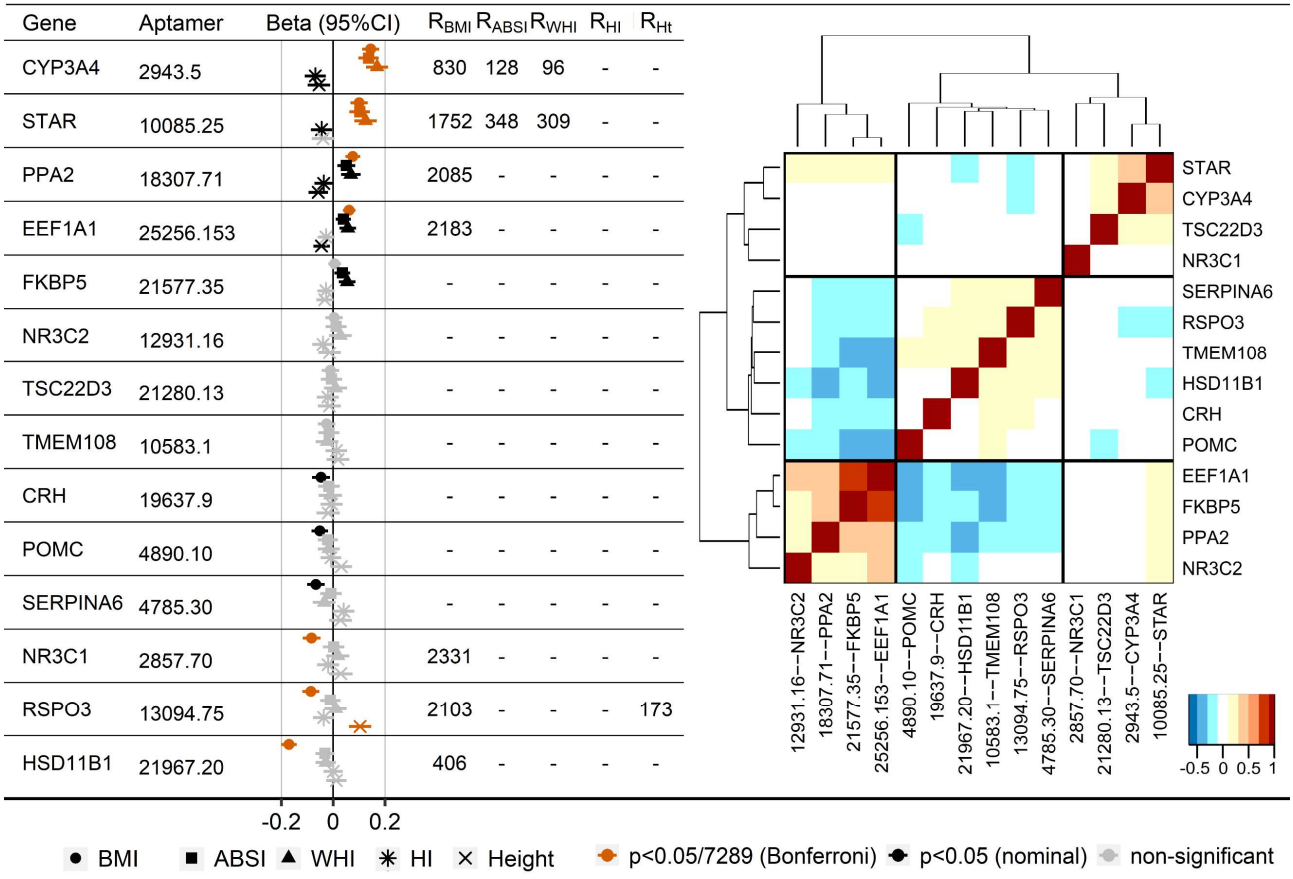
All models and partial correlation coefficients were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre (regression) or country (correlation). Regression models for BMI were additionally adjusted for height. Regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.

Aptamers are ordered according to the p-value of their association with BMI (S5A), WHR (S5C) or height (S5D) or in alphabetical order, separately for LEP and GHR related proteins (S5B).

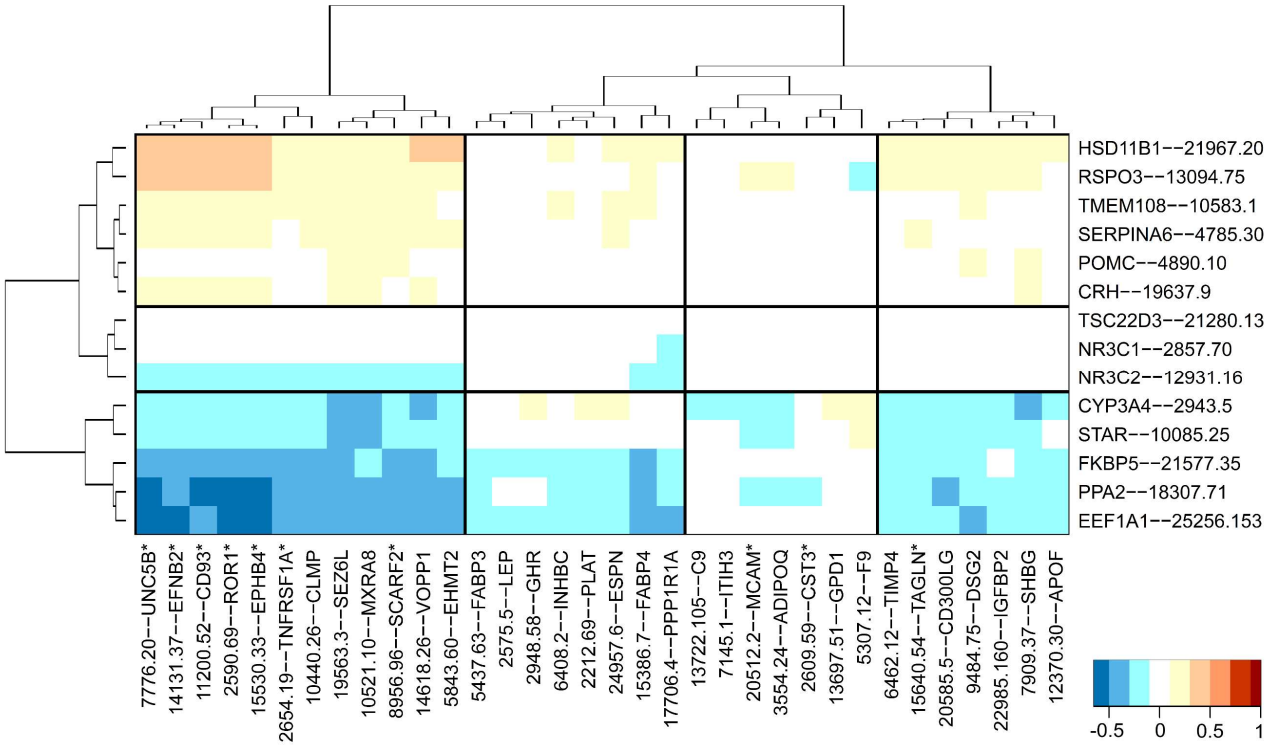
Discussion notes

S5B: In our study, LEP receptor (LEPR) was negatively associated with BMI, which may relate to leptin resistance. LEP was also substantially negatively associated with GHR, although LEP does not directly affect growth hormone (GH) secretion [57]. Also in our study, GHR was positively associated with general and abdominal obesity (BMI, ABSI, WHI) and negatively associated with large hip size (HI) but mainly GH variant GH2 and not somatotropin GH1 mirrored the proteomic association pattern of GHR. Our findings partly agree with higher GHR and lower GH expression in mature adipocytes from morbidly obese individuals compared to non-obese individuals [42], a negative association of circulating GH with BMI and insulin resistance in adipose tissue of obese individuals [73], and a suppression of GHR levels by exogenous GH administration [45]. Our study, however, found little evidence for association of BMI with IGF1, which is induced by exogenous GH administration [45] and would thus be expected to be lower when GH is lower in obesity. Further in our study, GH releasing hormone (GHRH) was higher for higher BMI, but measurement of the corresponding receptor GHRH-R was not available. This partial information agrees with higher expression of GHRH but lower expression of GHRH-R in mature adipocytes from morbidly obese individuals compared to non-obese individuals [42]. GHRH induces the differentiation of human mesenchymal stem cells to adipocytes and downregulates GHRH-R expression [42].

S5D: Genetic defects in SCARF2 have been reported in Ende-Gupta syndrome of congenital heart and skeletal malformations [74]. SCARF2 encodes a scavenger receptor expressed in endothelial cells protein (SREC-II) but has no known scavenging function, although its ectodomain can bind LDL-related scavenger ligands and complement factor 1q [75]. CD93 and ROR1, positively correlated and with similar associations patterns, together with CST3, which has different association pattern, increase after exogenous growth hormone administration [45].



Supplementary Figure S6A Associations with cortisol-related proteins



Supplementary Figure S6B Correlations of cortisol-related proteins with top ranked proteins

ABSI – a body shape index; **Beta** – proteomic regression coefficient; **BMI** – body mass index; **CI** – confidence interval; **HI** – hip index; **Ht** – height; **R_{INDEX}** – aptamer rank order (lowest p-value first), defined for p<(0.05/7289)≈7*10^{-6} (Bonferroni significance level); **WHI** – waist-to-hip index.

Supplementary Figure S6 Associations with cortisol-related proteins (*legend continued*)

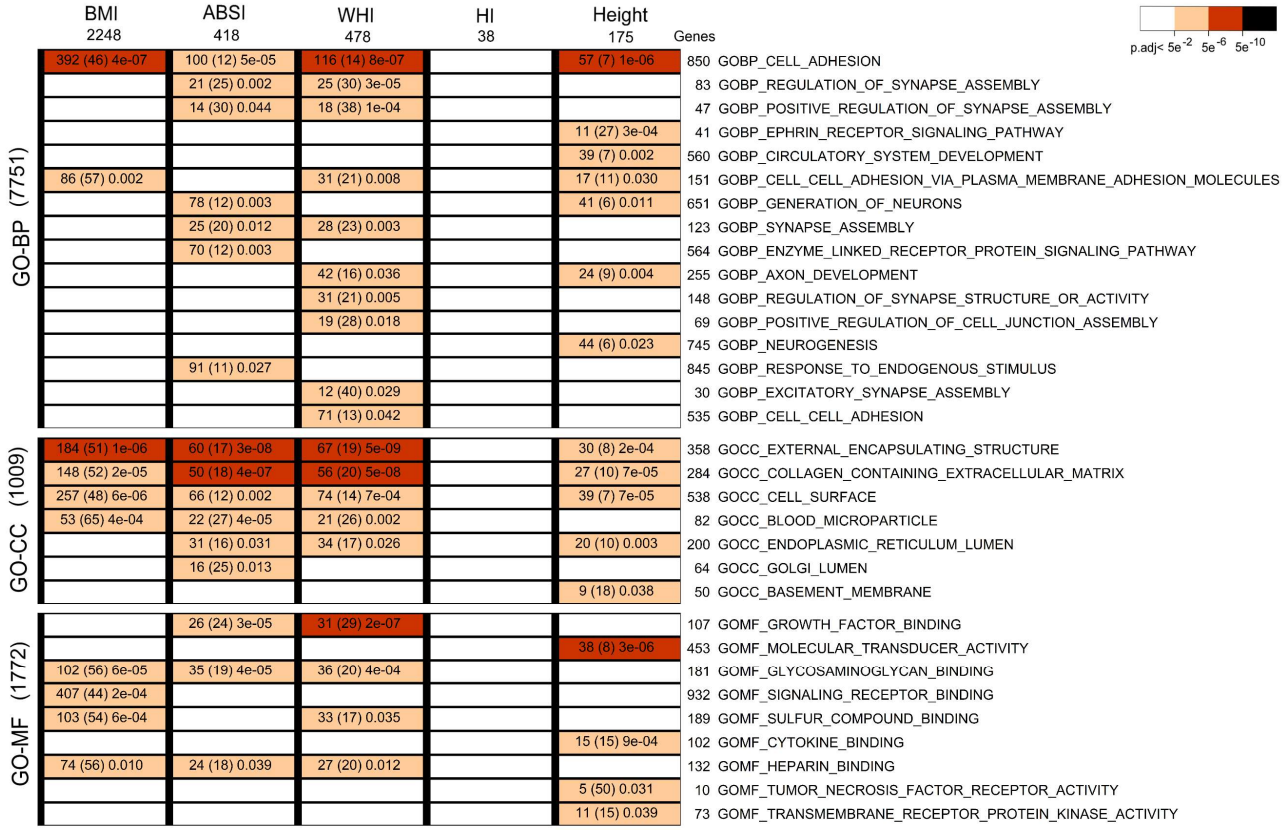
Cortisol-related: **CRH** – Corticoliberin (hypothalamus, part of the hypothalamus-pituitary-adrenal (HPA) axis); **CYP3A4** − Cytochrome P450 3A4 (cortisol 6β hydroxylation); **EEF1A1** − Elongation factor 1-alpha 1 (genetic association with morning plasma cortisol [23]); **FKBP5** − FK506-binding protein 5 (glucocorticoid responsive gene, part of the heat shock protein complex related to the glucocorticoid receptor) − cortisol-responsive gene; **HSD11B1** − Corticosteroid 11-beta-dehydrogenase isozyme 1 (cortisol activation) [76]; **NR3C1** − Glucocorticoid receptor (anti-inflammatory); **NR3C2** − Mineralocorticoid receptor (pro-inflammatory); **POMC** – Corticotropin (adrenocorticotropic hormone ACTH) (pituitary, part of the HPA axis); **PPA2** − Inorganic pyrophosphatase 2, mitochondrial (genetic association with morning plasma cortisol [23]); **RSPO3** − R-spondin-3 (highest ranked genetic polymorphisms associated with allometric body shape indices [30]); **SERPINA6** – serpin family A member 6 gene (corticosteroid-binding globulin); **STAR** − Steroidogenic acute regulatory protein, mitochondrial (regulates cholesterol supply to mitochondria for cortisol synthesis); **TMEM108** − Transmembrane protein 108 (genetic association with morning plasma cortisol [23]); **TSC22D3** − TSC22 domain family protein 3 (glucocorticoid induces glycine zipper (GILZ), anti-inflammatory protein).

Top ranked: **ADIPOQ** − Adiponectin; **APOF** − Apolipoprotein F; **C9** − Complement component C9; **CD300LG** − CMRF35-like molecule 9; **CD93** − Complement component C1q receptor (*); **CLMP** − CXADR-like membrane protein:Extracellular domain; **CST3** − Cystatin-C (*); **DSG2** − Desmoglein-2; **EFNB2** − Ephrin-B2:Extracellular domain (*); **EHMT2** − Histone-lysine N-methyltransferase EHMT2; **EPHB4** − Ephrin type-B receptor 4 (*); **ESPN** − Espin; **F9** − Coagulation factor IXab; **FABP3** − Fatty acid-binding protein, heart; **FABP4** − Fatty acid-binding protein, adipocyte; **GHR** − Growth hormone receptor; **GPD1** − Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic; **IGFBP2** − Insulin-like growth factor-binding protein 2; **INHBC** − Inhibin beta C chain; **ITIH3** − Inter-alpha-trypsin inhibitor heavy chain H3; **LEP** − Leptin; **MCAM** − Melanoma-associated antigen MUC18 (*); **MXRA8** − Matrix-remodeling-associated protein 8:Extracellular domain; **PLAT** − Tissue-type plasminogen activator; **PPP1R1A** − Protein phosphatase 1 regulatory subunit 1A; **ROR1** − Inactive tyrosine-protein kinase transmembrane receptor ROR1 (*); **SCARF2** − Scavenger receptor class F member 2:Extracellular domain (*); **SEZ6L** − Seizure 6-like protein; **SHBG** − Sex hormone-binding globulin; **TAGLN** – Transgelin (*); **TIMP4** − Metalloproteinase inhibitor 4; **TNFRSF1A** − Tumor necrosis factor receptor superfamily member 1A (*); **UNC5B** − Netrin receptor UNC5B (*); **VOPP1** − Vesicular, overexpressed in cancer, prosurvival protein 1.

***** top ranked proteins for height.

Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable. Heatmaps include partial Pearson correlation coefficients between the corresponding pairs of aptamers.

All models and partial correlation coefficients were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre (regression) or country (correlation). Regression models for BMI were additionally adjusted for height. Regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.

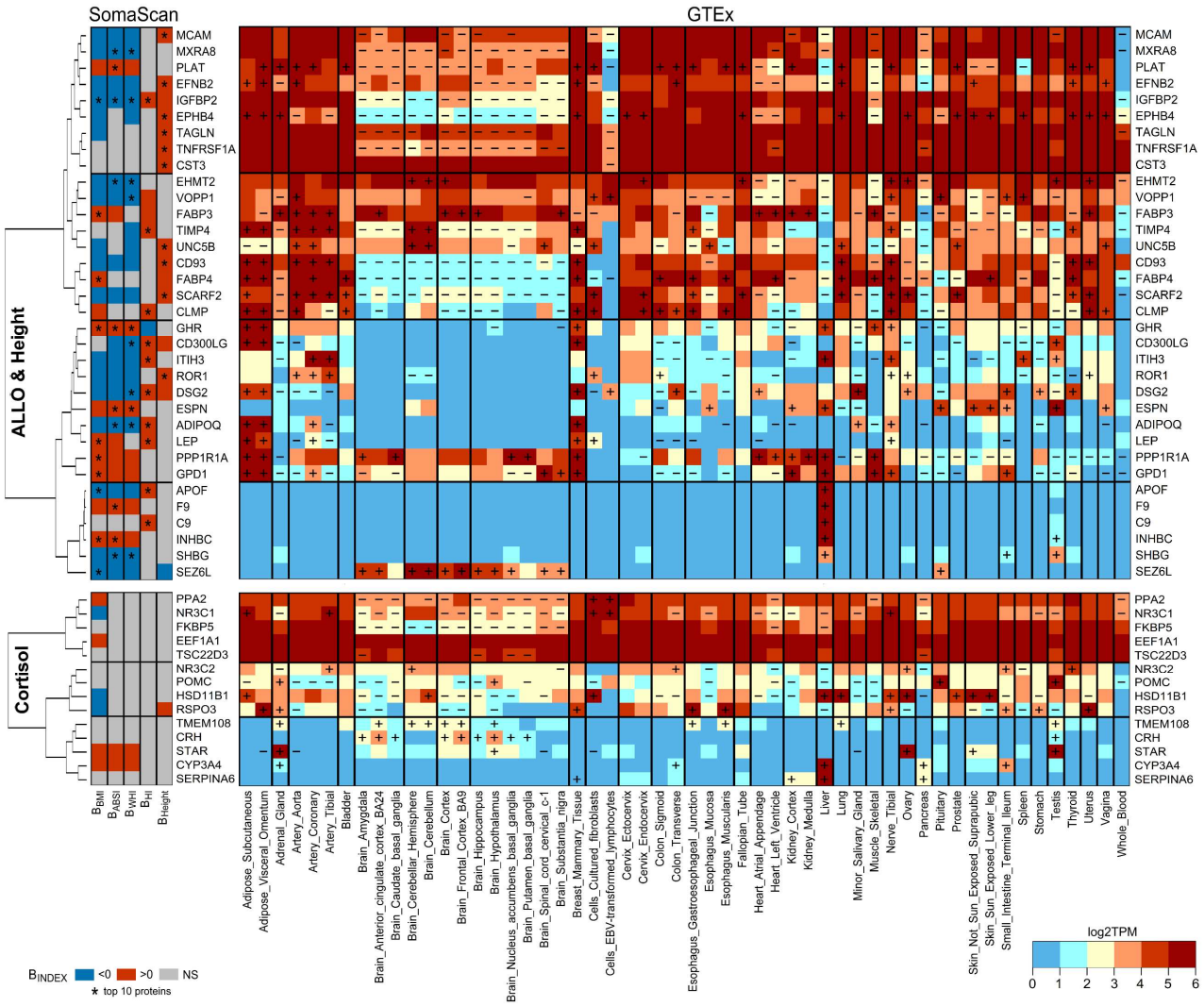


Supplementary Figure S7 Gene ontology gene set mapping for allometric indices and height

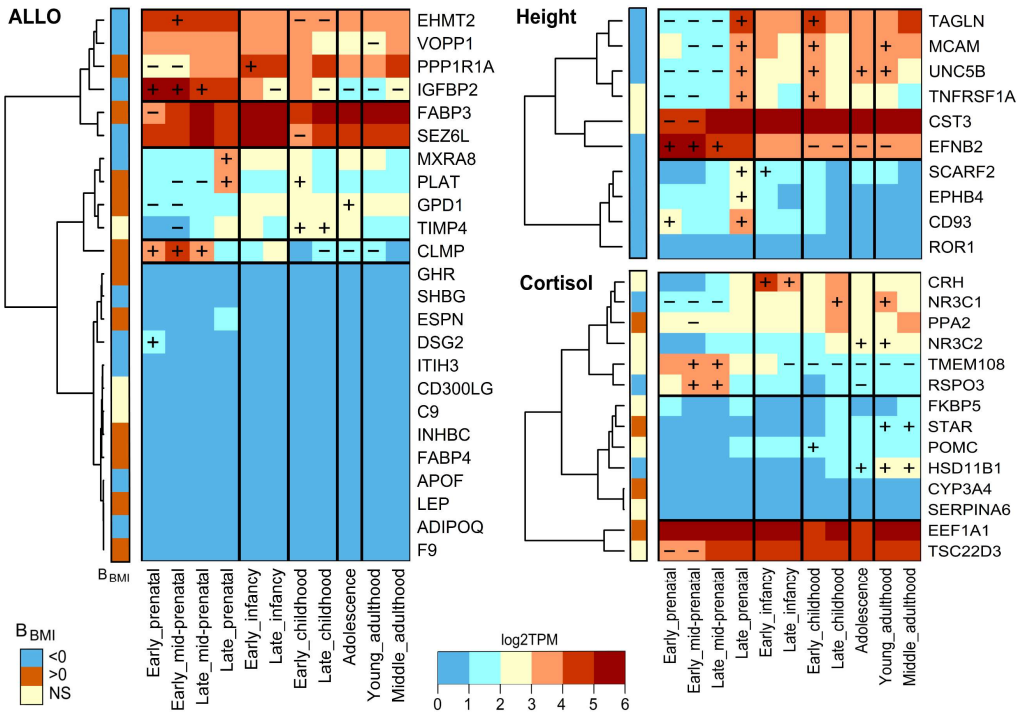
ABSI – a body shape index; **BMI** – body mass index; **HI** – hip index; **WHI** – waist-to-hip index.

p_{adj} – colour-coded Bonferroni adjusted p-value for associations with gene ontology (GO) gene sets [71, 72] – adjustment for 5 anthropometric index groups (BMI, ABSI, WHI, HI, height) and either 7751 gene sets for GO biological processes (GOBP); 1009 gene sets for GO cellular components (GOCC), or 1772 gene sets for GO molecular function (GOMF). Mapping was performed in FUMA v1.5.2 (https://fuma.ctglab.nl/). Background genes included genes for proteins targeted by SomaScan v4.1 (7k) (6302 unique available Entrez IDs, 6334 unique Ensembl IDs).

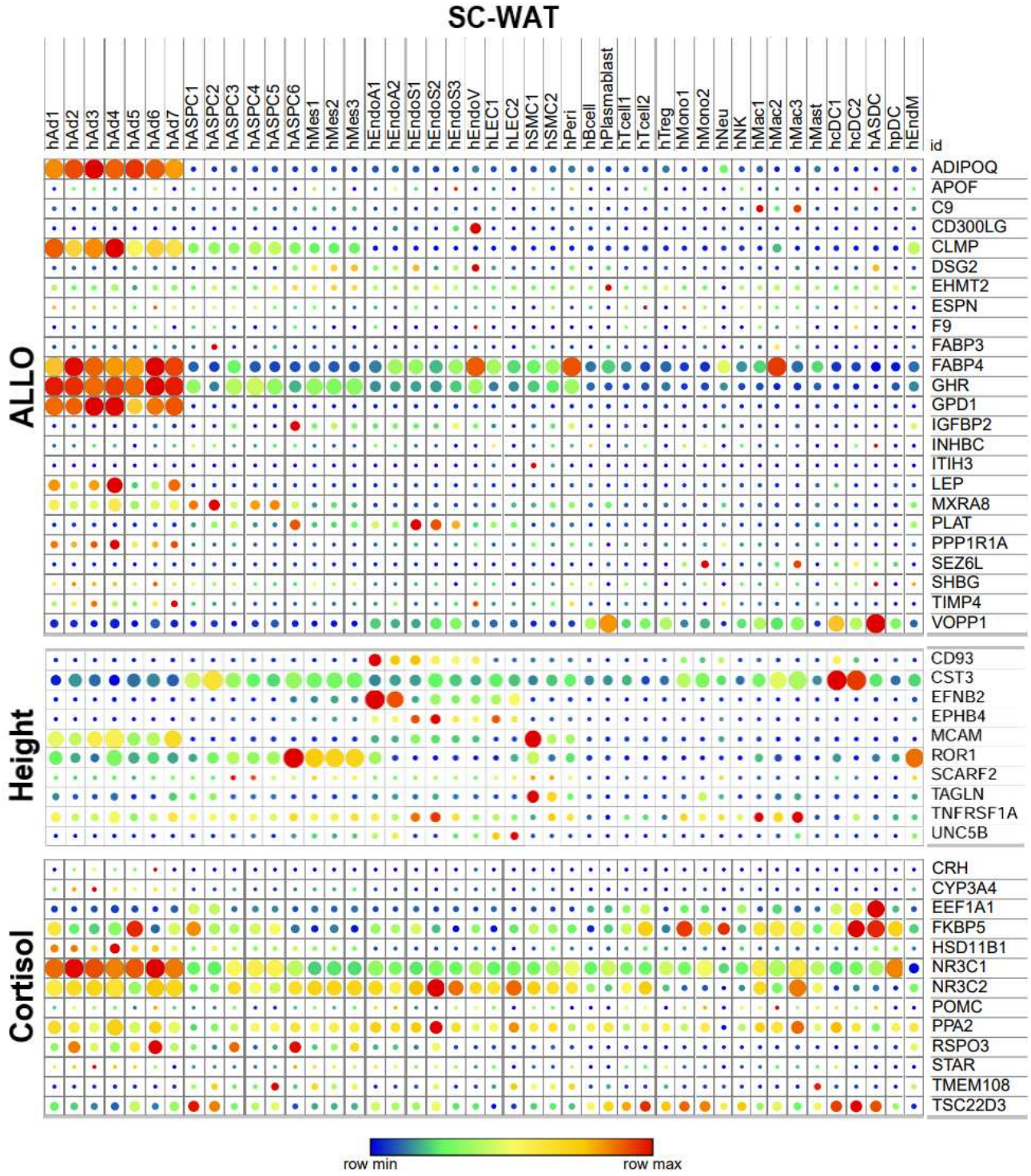
Prioritised protein-coding genes corresponded to aptamers associated with anthropometric indices at Bonferroni significance level $p<(0.05/7289)\approx7*10^{-6}$. Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable. All models were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre. Models for BMI were additionally adjusted for height. Models for ABSI, WHI and HI were additionally adjusted for BMI and height.



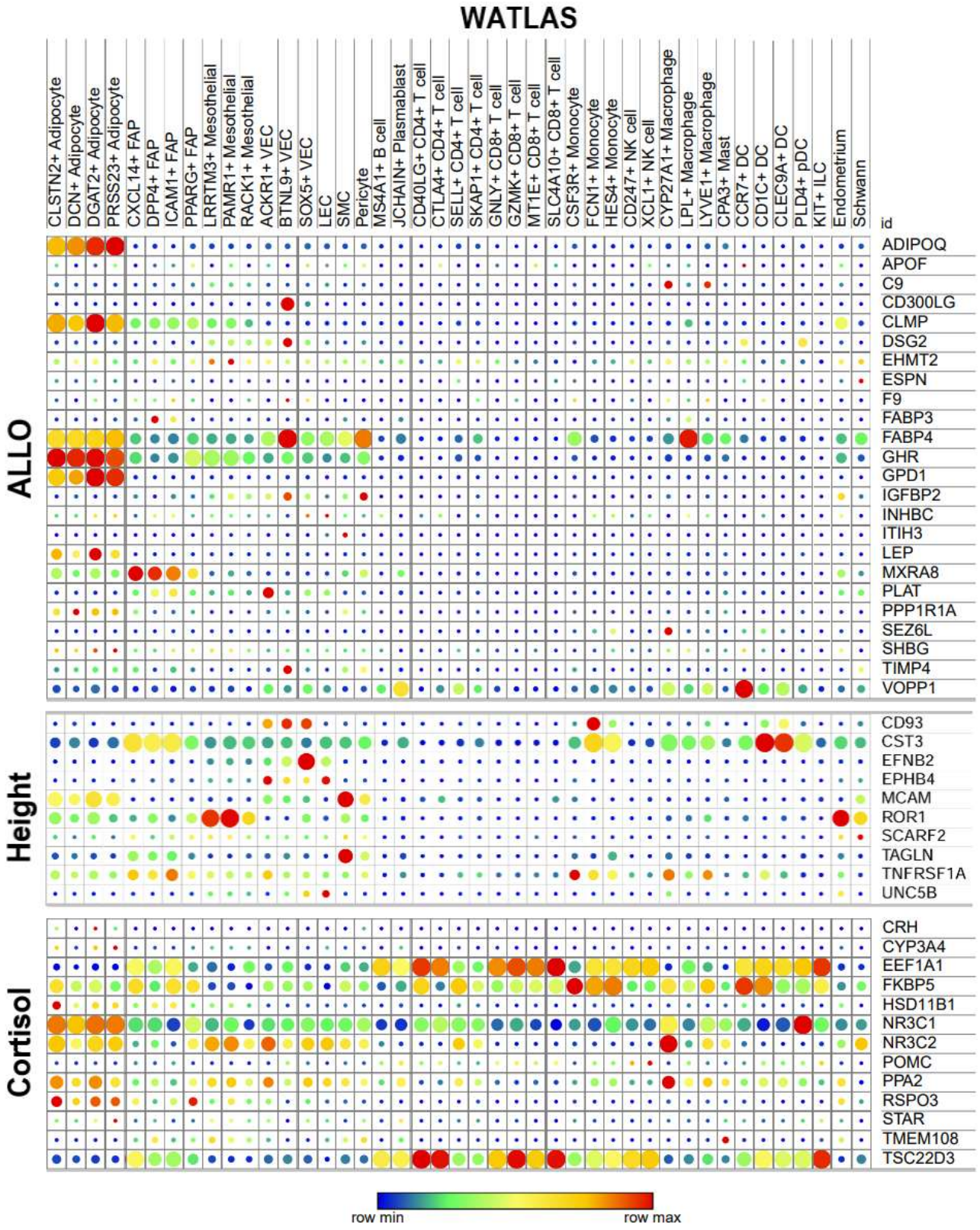
Supplementary Figure S8A Gene expression in GTEx for top-ranked and cortisol proteins



Supplementary Figure S8B Gene expression in BrainSpan for top-ranked and cortisol proteins



Supplementary Figure S8C Gene expression in SC-WAT for top-ranked and cortisol proteins



Supplementary Figure S8D Gene expression in WATLAS for top-ranked and cortisol proteins

Supplementary Figure S8 Gene expression mapping in tissues for top-ranked and cortisol related proteins *(legend)*

ABSI – a body shape index; **ALLO** – protein-coding genes ranked within the top ten for at least one allometric index (BMI, ABSI, WHI, HI); **B_{INDEX}** – proteomic regression coefficients; **BMI** – body mass index; **Height** – genes for top ten ranked proteins for height; **HI** – hip index; **Cortisol** – selected cortisol-related genes with protein measurements available in SomaScan v.4.1 (7k); **WAT** – white adipose tissue; **WHI** – waist-to-hip index.

A – tissue gene expression (TPM – Transcripts Per Million) according to GTEx v8.0 used in FUMA v1.5.2 (https://fuma.ctglab.nl/), with genes marked according to inclusion in upregulated (+) or downregulated (-) gene sets.

B – developmental brain stage gene expression (RPKM – Reads per Kilobase per Million mapped reads) according to BrainSpan used in FUMA v1.5.2., with genes marked according to inclusion in upregulated (+) or downregulated (-) gene sets.

C – single-cell RNA expression in SC-WAT plotted at https://singlecell.broadinstitute.org/single_cell/study/SCP1376/a-single-cell-atlas-of-human-and-mouse-white-adipose-tissue [28]

D – single-cell RNA expression in WATLAS plotted at https://singlecell.broadinstitute.org/single_cell/study/SCP2289/an-integrated-single-cell-and-single-nucleus-rna-seq-white-adipose-tissue-atlas-watlas [29]

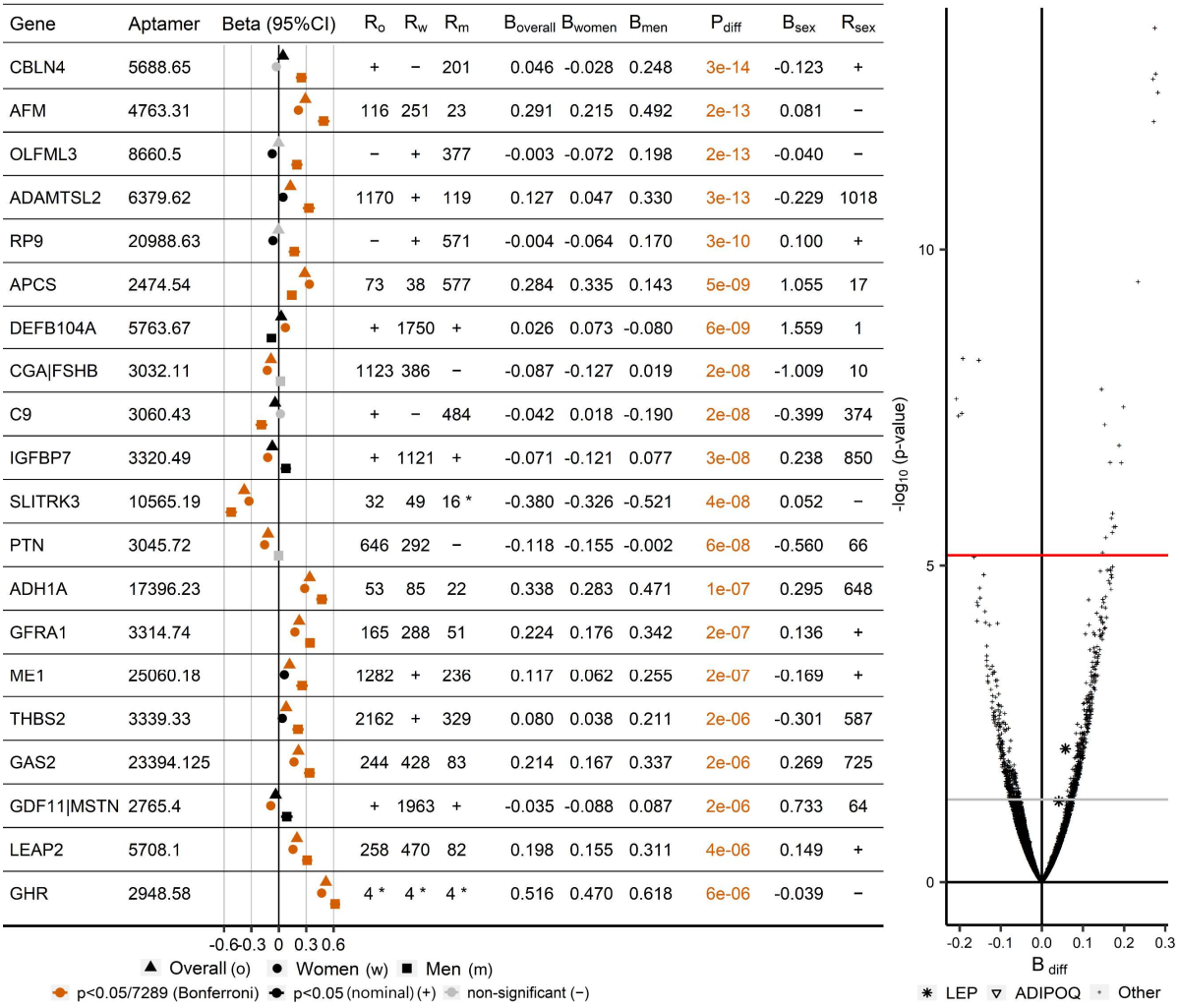
Dot size (C, D) – percent cells in subcluster expressing the gene (max≥75%); **Dot colour** (C, D) – relative gene expression (min–max per gene).

SC-WAT Clusters: **Adipocyte** (hAd1–7); **ASPC** (adipose stem and progenitor cells hASPC1–6); **Mesothelium** (hMes1–3); **Vascular cells: Endothelial cells** (hEndoA1–2 Arteriolar, hEndoS1–3 Stalk, hEndoV Venular), **Lymphatic endothelial cells** (hLEC1–2), **Pericyte** (hPeri), **Smooth muscle cells** (hSMC1–2); **Immune cells: Dendritic cells** (hASDC (AXL+SIGLEC6+ dendritic cells), hcDC1–2 (conventional dendritic cells – cDC1 primarily activate CD8+ T-cells, cDC2 primarily activate CD4+ T-cells), hpDC (plasmacytoid dendritic cells – produce large amounts of type I interferon INF-I)), **B-cell** (hBcell, hPlasmablast), **Mast cell** (hMast), **Macrophage** (hMac1–3), **Monocyte** (hMono1–2), **Neutrophil** (hNeu), **NK cell** (hNK), **T cell** (hTcell1–2, hTreg), **Endometrium** (hEndM).

WATLAS Clusters: **Adipocyte** (CLSTN2+, PRSS23+, DGAT2+, DCN+); **Endothelial** (Vascular endothelial cells (VEC): BTNL9+ Capillary, SOX5+ Arterial, ACKR1+ Venous; **Lymphatic**: LYVE1+); **FAP** – fibro-adipogenic progenitors (CXCL14+, PPARG+, DPP4+, ICAM1+); **Mural** (MYH11+ SMC (smooth muscle cell), STEAP4+ Pericyte); **Nervous** (XKR4+ Schwann); **Mesothelial** (LRRTM3+, RACK1+, PAMR1+); **Immune**: **T-lymphocytes** (**CD4+** (CD40LG+ TH1, SKAP1+, CTLA4+ Treg, SELL+ Tcm); **CD8+** (GZMK+ Tem, GNLY+ NKT, SLC4A10+ MAIT, MT1E+); **NK cells** (CD247+ CD16+, XCL1+ CD16-); **ILC** (KIT+); **B-lymphocytes** (MS2A1+ B-cell, JCHAIN+ Plasmablast); **Myeloid**: **Monocytes** (HES4+ non-classical; CSF3R+ neutrophil-like, FCN1+ classical); **Dendritic cells** (CLEC9A+ cDC1, CD1C+ cDC2, CCR7+ migDC, PLD4+ pDC); **Macrophages** (LPL+ LAM, CYP27A1+ Foam-like, LYVE1 ATM); **Mast cells** (CPA3+).

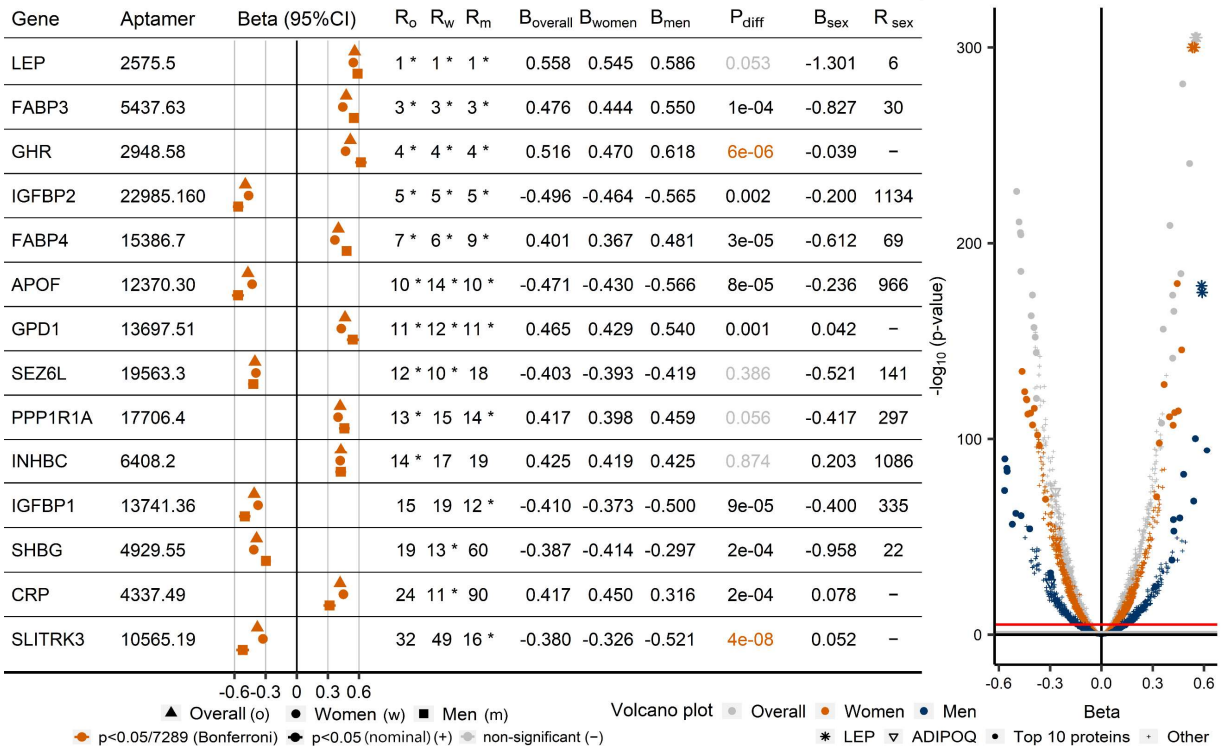
Genes: **ADIPOQ** − Adiponectin; **APOF** − Apolipoprotein F; **C9** − Complement component C9; **CD300LG** − CMRF35-like molecule 9; **CD93** − Complement component C1q receptor; **CLMP** − CXADR-like membrane protein:Extracellular domain; **CRH** – Corticoliberin; **CST3** − Cystatin-C; **CYP3A4** − Cytochrome P450 3A4; **DSG2** − Desmoglein-2; **EEF1A1** − Elongation factor 1-alpha 1; **EFNB2** − Ephrin-B2:Extracellular domain; **EHMT2** − Histone-lysine N-methyltransferase EHMT2; **EPHB4** − Ephrin type-B receptor 4; **ESPN** − Espin; **F9** − Coagulation factor IXab; **FABP3** − Fatty acid-binding protein, heart; **FABP4** − Fatty acid-binding protein, adipocyte; **FKBP5** − FK506-binding protein 5; **GHR** − Growth hormone receptor; **GPD1** − Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic; **HSD11B1** − Corticosteroid 11-beta-dehydrogenase isozyme 1; **IGFBP2** − Insulin-like growth factor-binding protein 2; **INHBC** − Inhibin beta C chain; **ITIH3** − Inter-alpha-trypsin inhibitor heavy chain H3; **LEP** − Leptin; **MCAM** − Melanoma-associated antigen MUC18; **MXRA8** − Matrix-remodeling-associated protein 8:Extracellular domain; **PLAT** − Tissue-type plasminogen activator; **NR3C1** − Glucocorticoid receptor; **NR3C2** − Mineralocorticoid receptor; **POMC** – Corticotropin (adrenocorticotropic hormone ACTH); **PPA2** − Inorganic pyrophosphatase 2, mitochondrial; **PPP1R1A** − Protein phosphatase 1 regulatory subunit 1A; **ROR1** − Inactive tyrosine-protein kinase transmembrane receptor ROR1; **RSPO3** − R-spondin-3; **SCARF2** − Scavenger receptor class F member 2:Extracellular domain; **SERPINA6** – serpin family A member 6 gene (corticosteroid-binding globulin); **SEZ6L** − Seizure 6-like protein; **SHBG** − Sex hormone-binding globulin; **STAR** − Steroidogenic acute regulatory protein, mitochondrial; **TAGLN** – Transgelin; **TIMP4** − Metalloproteinase inhibitor 4; **TMEM108** − Transmembrane protein 108; **TNFRSF1A** − Tumor necrosis factor receptor superfamily member 1A; **TSC22D3** − TSC22 domain family protein 3 (glucocorticoid induces glycine zipper, GILZ); **UNC5B** − Netrin receptor UNC5B; **VOPP1** − Vesicular, overexpressed in cancer, prosurvival protein 1.

Gene	Aptamer	Beta (95%CI)	R_o	R_w	R_m	$B_{overall}$	B_{women}	B_{men}	P_{diff}	B_{sex}	R_{sex}
CBLN4	5688.65		+	−	201	0.046	-0.028	0.248	3e-14	-0.123	+
AFM	4763.31		116	251	23	0.291	0.215	0.492	2e-13	0.081	−
OLFML3	8660.5		−	+	377	-0.003	-0.072	0.198	2e-13	-0.040	−
ADAMTSL2	6379.62		1170	+	119	0.127	0.047	0.330	3e-13	-0.229	1018
RP9	20988.63		−	+	571	-0.004	-0.064	0.170	3e-10	0.100	+
APCS	2474.54		73	38	577	0.284	0.335	0.143	5e-09	1.055	17
DEFB104A	5763.67		+	1750	+	0.026	0.073	-0.080	6e-09	1.559	1
CGA|FSHB	3032.11		1123	386	−	-0.087	-0.127	0.019	2e-08	-1.009	10
C9	3060.43		+	−	484	-0.042	0.018	-0.190	2e-08	-0.399	374
IGFBP7	3320.49		+	1121	+	-0.071	-0.121	0.077	3e-08	0.238	850
SLITRK3	10565.19		32	49	16 *	-0.380	-0.326	-0.521	4e-08	0.052	−
PTN	3045.72		646	292	−	-0.118	-0.155	-0.002	6e-08	-0.560	66
ADH1A	17396.23		53	85	22	0.338	0.283	0.471	1e-07	0.295	648
GFRA1	3314.74		165	288	51	0.224	0.176	0.342	2e-07	0.136	+
ME1	25060.18		1282	+	236	0.117	0.062	0.255	2e-07	-0.169	+
THBS2	3339.33		2162	+	329	0.080	0.038	0.211	2e-06	-0.301	587
GAS2	23394.125		244	428	83	0.214	0.167	0.337	2e-06	0.269	725
GDF11|MSTN	2765.4		+	1963	+	-0.035	-0.088	0.087	2e-06	0.733	64
LEAP2	5708.1		258	470	82	0.198	0.155	0.311	4e-06	0.149	+
GHR	2948.58		4 *	4 *	4 *	0.516	0.470	0.618	6e-06	-0.039	−



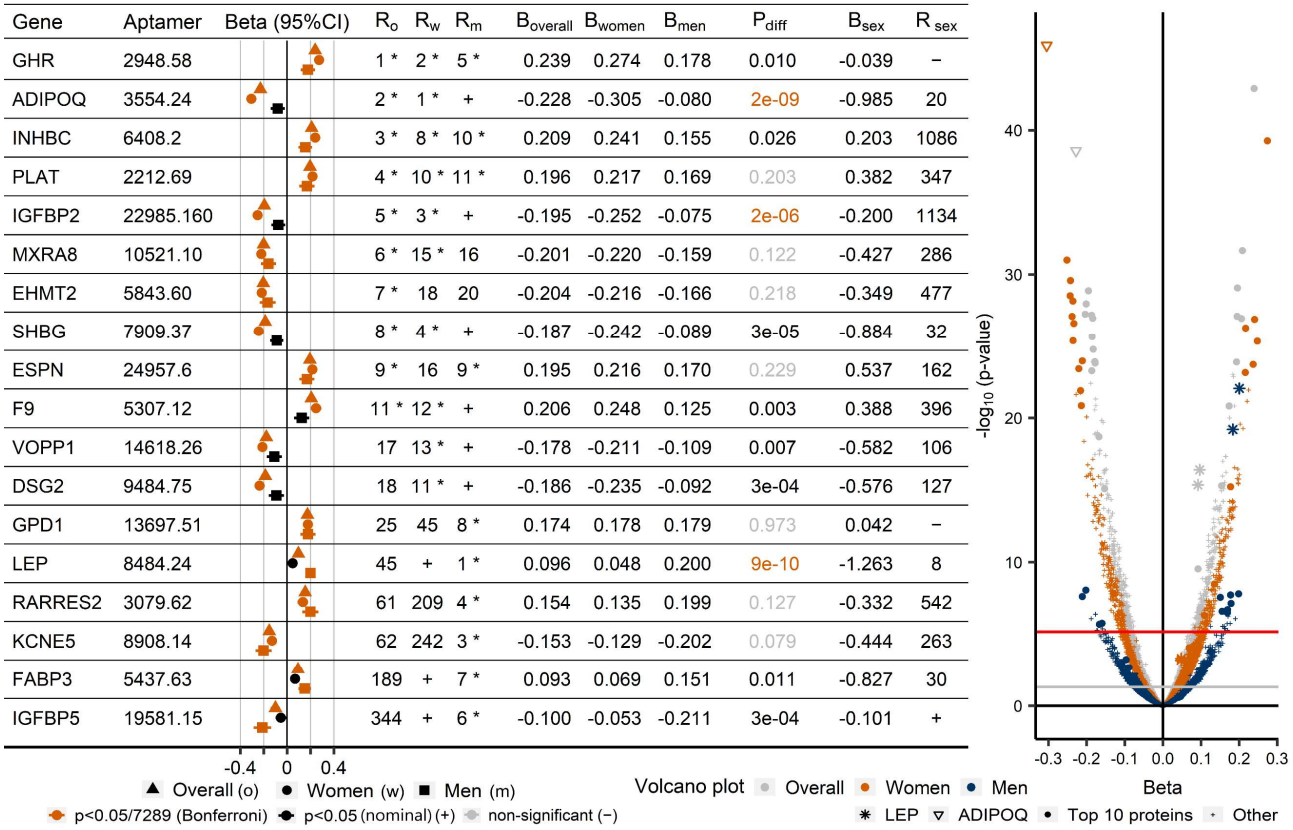
Supplementary Figure S9A Sex differences for BMI at Bonferroni significance level

Gene	Aptamer	Beta (95%CI)	R_o	R_w	R_m	$B_{overall}$	B_{women}	B_{men}	P_{diff}	B_{sex}	R_{sex}
LEP	2575.5		1 *	1 *	1 *	0.558	0.545	0.586	0.053	-1.301	6
FABP3	5437.63		3 *	3 *	3 *	0.476	0.444	0.550	1e-04	-0.827	30
GHR	2948.58		4 *	4 *	4 *	0.516	0.470	0.618	6e-06	-0.039	−
IGFBP2	22985.160		5 *	5 *	5 *	-0.496	-0.464	-0.565	0.002	-0.200	1134
FABP4	15386.7		7 *	6 *	9 *	0.401	0.367	0.481	3e-05	-0.612	69
APOF	12370.30		10 *	14 *	10 *	-0.471	-0.430	-0.566	8e-05	-0.236	966
GPD1	13697.51		11 *	12 *	11 *	0.465	0.429	0.540	0.001	0.042	−
SEZ6L	19563.3		12 *	10 *	18	-0.403	-0.393	-0.419	0.386	-0.521	141
PPP1R1A	17706.4		13 *	15	14 *	0.417	0.398	0.459	0.056	-0.417	297
INHBC	6408.2		14 *	17	19	0.425	0.419	0.425	0.874	0.203	1086
IGFBP1	13741.36		15	19	12 *	-0.410	-0.373	-0.500	9e-05	-0.400	335
SHBG	4929.55		19	13 *	60	-0.387	-0.414	-0.297	2e-04	-0.958	22
CRP	4337.49		24	11 *	90	0.417	0.450	0.316	2e-04	0.078	−
SLITRK3	10565.19		32	49	16 *	-0.380	-0.326	-0.521	4e-08	0.052	−



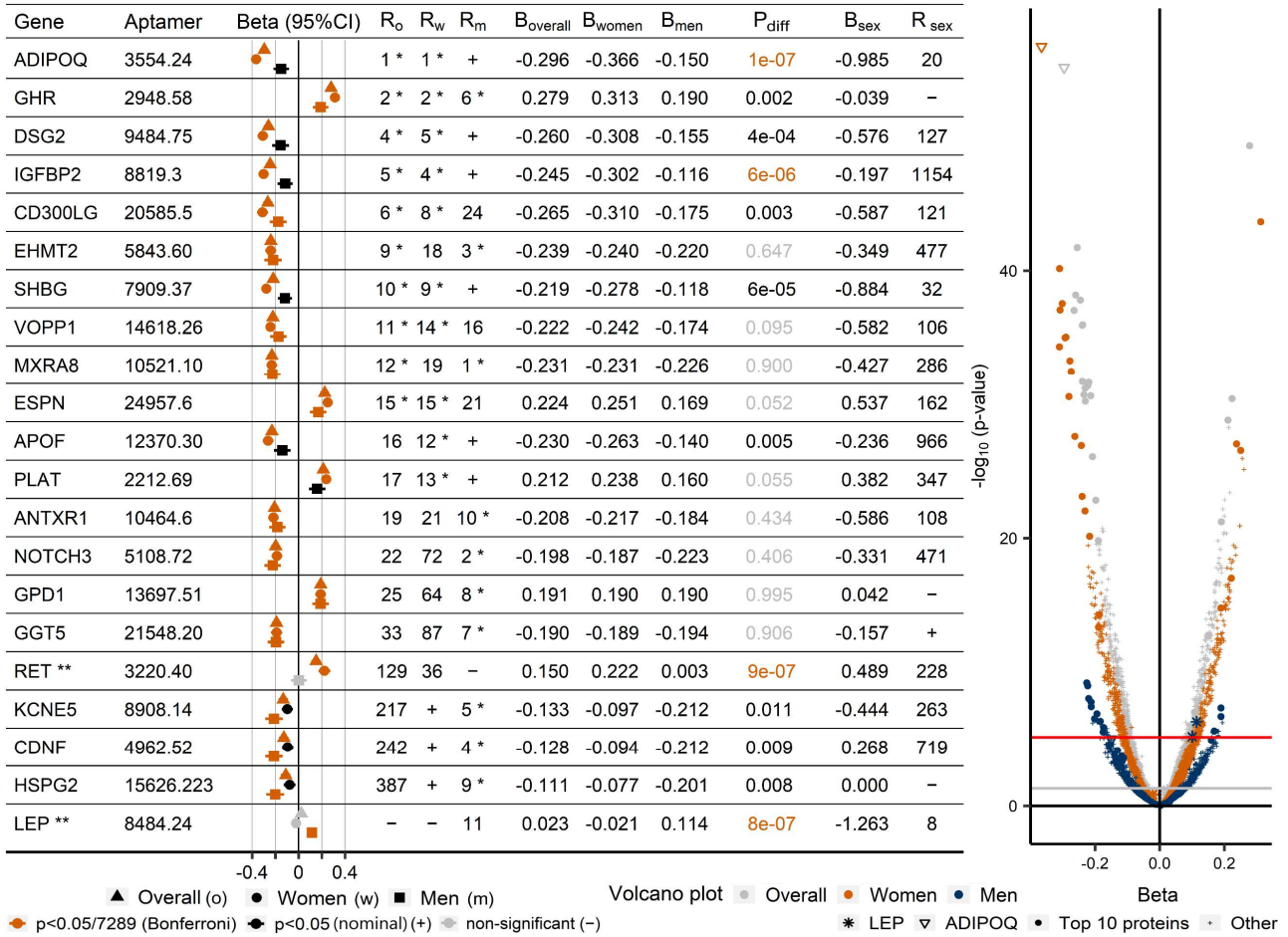
Supplementary Figure S9B Sex differences − top ten proteins for BMI by sex

Gene	Aptamer	Beta (95%CI)	R_o	R_w	R_m	$B_{overall}$	B_{women}	B_{men}	P_{diff}	B_{sex}	R_{sex}
GHR	2948.58		1 *	2 *	5 *	0.239	0.274	0.178	0.010	-0.039	–
ADIPOQ	3554.24		2 *	1 *	+	-0.228	-0.305	-0.080	2e-09	-0.985	20
INHBC	6408.2		3 *	8 *	10 *	0.209	0.241	0.155	0.026	0.203	1086
PLAT	2212.69		4 *	10 *	11 *	0.196	0.217	0.169	0.203	0.382	347
IGFBP2	22985.160		5 *	3 *	+	-0.195	-0.252	-0.075	2e-06	-0.200	1134
MXRA8	10521.10		6 *	15 *	16	-0.201	-0.220	-0.159	0.122	-0.427	286
EHMT2	5843.60		7 *	18	20	-0.204	-0.216	-0.166	0.218	-0.349	477
SHBG	7909.37		8 *	4 *	+	-0.187	-0.242	-0.089	3e-05	-0.884	32
ESPN	24957.6		9 *	16	9 *	0.195	0.216	0.170	0.229	0.537	162
F9	5307.12		11 *	12 *	+	0.206	0.248	0.125	0.003	0.388	396
VOPP1	14618.26		17	13 *	+	-0.178	-0.211	-0.109	0.007	-0.582	106
DSG2	9484.75		18	11 *	+	-0.186	-0.235	-0.092	3e-04	-0.576	127
GPD1	13697.51		25	45	8 *	0.174	0.178	0.179	0.973	0.042	–
LEP	8484.24		45	+	1 *	0.096	0.048	0.200	9e-10	-1.263	8
RARRES2	3079.62		61	209	4 *	0.154	0.135	0.199	0.127	-0.332	542
KCNE5	8908.14		62	242	3 *	-0.153	-0.129	-0.202	0.079	-0.444	263
FABP3	5437.63		189	+	7 *	0.093	0.069	0.151	0.011	-0.827	30
IGFBP5	19581.15		344	+	6 *	-0.100	-0.053	-0.211	3e-04	-0.101	+



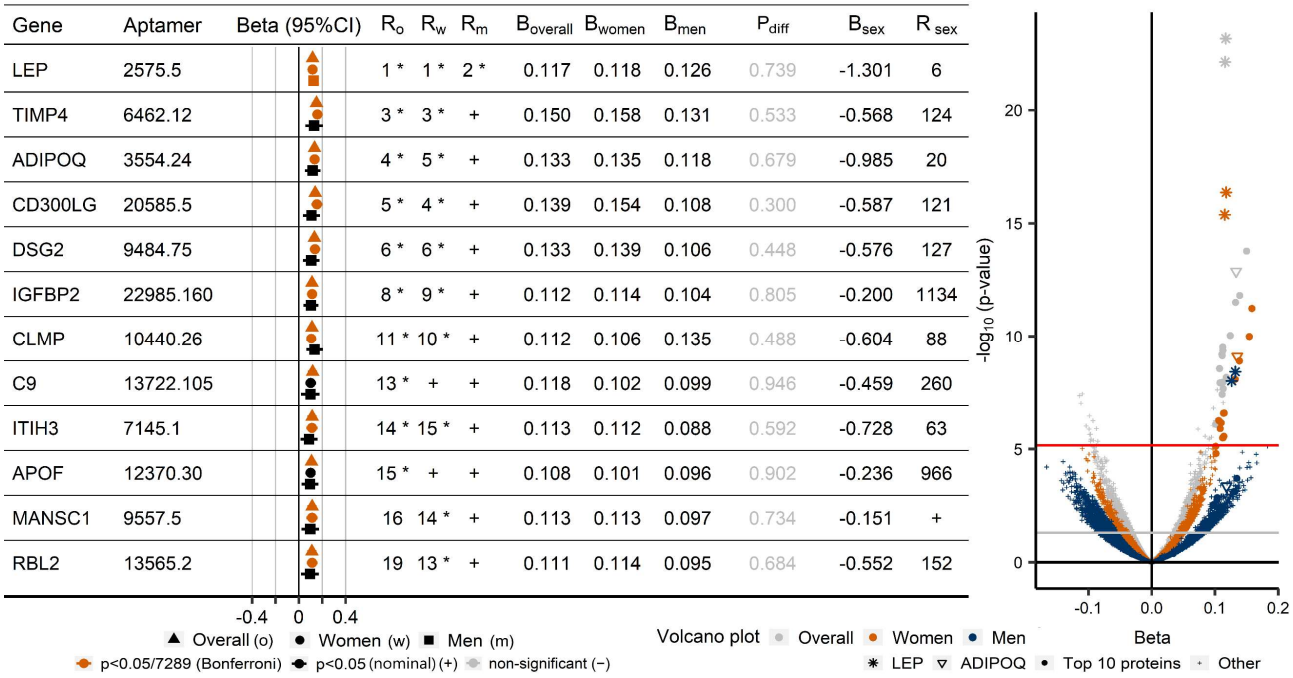
Supplementary Figure S9C Sex differences − top ten proteins for ABSI by sex

Gene	Aptamer	Beta (95%CI)	R_o	R_w	R_m	$B_{overall}$	B_{women}	B_{men}	P_{diff}	B_{sex}	R_{sex}
ADIPOQ	3554.24		1 *	1 *	+	-0.296	-0.366	-0.150	1e-07	-0.985	20
GHR	2948.58		2 *	2 *	6 *	0.279	0.313	0.190	0.002	-0.039	–
DSG2	9484.75		4 *	5 *	+	-0.260	-0.308	-0.155	4e-04	-0.576	127
IGFBP2	8819.3		5 *	4 *	+	-0.245	-0.302	-0.116	6e-06	-0.197	1154
CD300LG	20585.5		6 *	8 *	24	-0.265	-0.310	-0.175	0.003	-0.587	121
EHMT2	5843.60		9 *	18	3 *	-0.239	-0.240	-0.220	0.647	-0.349	477
SHBG	7909.37		10 *	9 *	+	-0.219	-0.278	-0.118	6e-05	-0.884	32
VOPP1	14618.26		11 *	14 *	16	-0.222	-0.242	-0.174	0.095	-0.582	106
MXRA8	10521.10		12 *	19	1 *	-0.231	-0.231	-0.226	0.900	-0.427	286
ESPN	24957.6		15 *	15 *	21	0.224	0.251	0.169	0.052	0.537	162
APOF	12370.30		16	12 *	+	-0.230	-0.263	-0.140	0.005	-0.236	966
PLAT	2212.69		17	13 *	+	0.212	0.238	0.160	0.055	0.382	347
ANTXR1	10464.6		19	21	10 *	-0.208	-0.217	-0.184	0.434	-0.586	108
NOTCH3	5108.72		22	72	2 *	-0.198	-0.187	-0.223	0.406	-0.331	471
GPD1	13697.51		25	64	8 *	0.191	0.190	0.190	0.995	0.042	–
GGT5	21548.20		33	87	7 *	-0.190	-0.189	-0.194	0.906	-0.157	+
RET **	3220.40		129	36	–	0.150	0.222	0.003	9e-07	0.489	228
KCNE5	8908.14		217	+	5 *	-0.133	-0.097	-0.212	0.011	-0.444	263
CDNF	4962.52		242	+	4 *	-0.128	-0.094	-0.212	0.009	0.268	719
HSPG2	15626.223		387	+	9 *	-0.111	-0.077	-0.201	0.008	0.000	–
LEP **	8484.24		–	–	11	0.023	-0.021	0.114	8e-07	-1.263	8



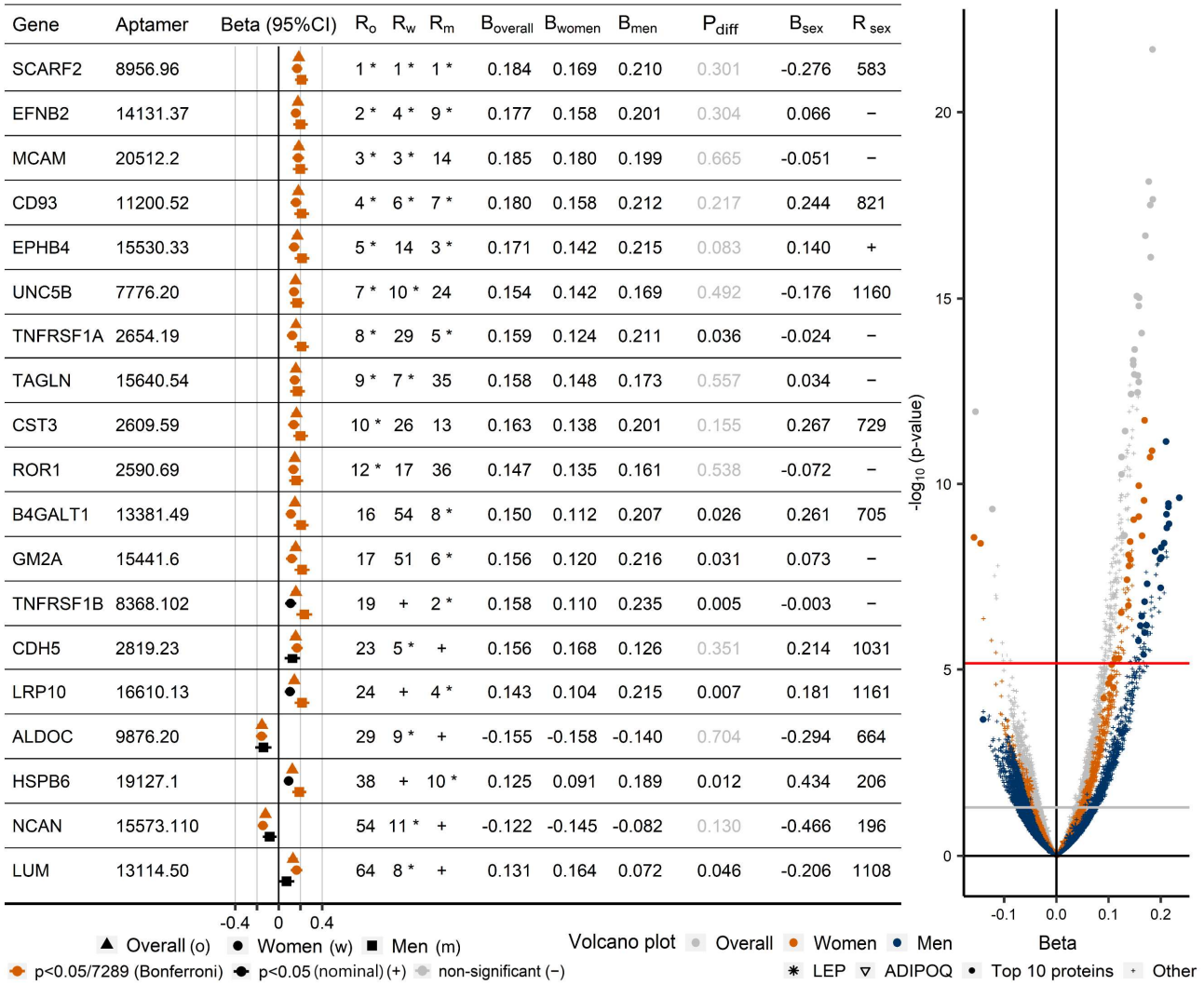
Supplementary Figure S9D Sex differences − top ten proteins for WHI by sex

Gene	Aptamer	Beta (95%CI)	R_o	R_w	R_m	$B_{overall}$	B_{women}	B_{men}	P_{diff}	B_{sex}	R_{sex}
LEP	2575.5		1 *	1 *	2 *	0.117	0.118	0.126	0.739	-1.301	6
TIMP4	6462.12		3 *	3 *	+	0.150	0.158	0.131	0.533	-0.568	124
ADIPOQ	3554.24		4 *	5 *	+	0.133	0.135	0.118	0.679	-0.985	20
CD300LG	20585.5		5 *	4 *	+	0.139	0.154	0.108	0.300	-0.587	121
DSG2	9484.75		6 *	6 *	+	0.133	0.139	0.106	0.448	-0.576	127
IGFBP2	22985.160		8 *	9 *	+	0.112	0.114	0.104	0.805	-0.200	1134
CLMP	10440.26		11 *	10 *	+	0.112	0.106	0.135	0.488	-0.604	88
C9	13722.105		13 *	+	+	0.118	0.102	0.099	0.946	-0.459	260
ITIH3	7145.1		14 *	15 *	+	0.113	0.112	0.088	0.592	-0.728	63
APOF	12370.30		15 *	+	+	0.108	0.101	0.096	0.902	-0.236	966
MANSC1	9557.5		16	14 *	+	0.113	0.113	0.097	0.734	-0.151	+
RBL2	13565.2		19	13 *	+	0.111	0.114	0.095	0.684	-0.552	152



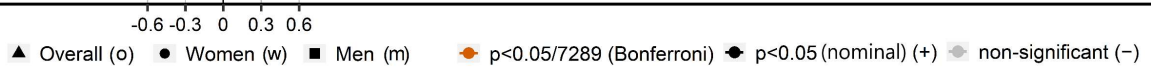
Supplementary Figure S9E Sex differences − top ten proteins for HI by sex

Gene	Aptamer	Beta (95%CI)	R_o	R_w	R_m	$B_{overall}$	B_{women}	B_{men}	P_{diff}	B_{sex}	R_{sex}
SCARF2	8956.96		1 *	1 *	1 *	0.184	0.169	0.210	0.301	-0.276	583
EFNB2	14131.37		2 *	4 *	9 *	0.177	0.158	0.201	0.304	0.066	−
MCAM	20512.2		3 *	3 *	14	0.185	0.180	0.199	0.665	-0.051	−
CD93	11200.52		4 *	6 *	7 *	0.180	0.158	0.212	0.217	0.244	821
EPHB4	15530.33		5 *	14	3 *	0.171	0.142	0.215	0.083	0.140	+
UNC5B	7776.20		7 *	10 *	24	0.154	0.142	0.169	0.492	-0.176	1160
TNFRSF1A	2654.19		8 *	29	5 *	0.159	0.124	0.211	0.036	-0.024	−
TAGLN	15640.54		9 *	7 *	35	0.158	0.148	0.173	0.557	0.034	−
CST3	2609.59		10 *	26	13	0.163	0.138	0.201	0.155	0.267	729
ROR1	2590.69		12 *	17	36	0.147	0.135	0.161	0.538	-0.072	−
B4GALT1	13381.49		16	54	8 *	0.150	0.112	0.207	0.026	0.261	705
GM2A	15441.6		17	51	6 *	0.156	0.120	0.216	0.031	0.073	−
TNFRSF1B	8368.102		19	+	2 *	0.158	0.110	0.235	0.005	-0.003	−
CDH5	2819.23		23	5 *	+	0.156	0.168	0.126	0.351	0.214	1031
LRP10	16610.13		24	+	4 *	0.143	0.104	0.215	0.007	0.181	1161
ALDOC	9876.20		29	9 *	+	-0.155	-0.158	-0.140	0.704	-0.294	664
HSPB6	19127.1		38	+	10 *	0.125	0.091	0.189	0.012	0.434	206
NCAN	15573.110		54	11 *	+	-0.122	-0.145	-0.082	0.130	-0.466	196
LUM	13114.50		64	8 *	+	0.131	0.164	0.072	0.046	-0.206	1108



Supplementary Figure S9F Sex differences − top ten proteins for height by sex

Gene	Aptamer	Beta (95%CI)	R_o	R_w	R_m	$B_{overall}$	B_{women}	B_{men}	P_{diff}	B_{sex}	R_{sex}	Index
CYP3A4	2943.5		830	1194	437	0.145	0.121	0.195	0.051	0.508	213	BMI
CYP3A4	2943.5		128	64	−	0.137	0.184	0.056	0.003	0.508	213	ABSI
CYP3A4	2943.5		96	50	+	0.169	0.213	0.083	0.006	0.508	213	WHI
EEF1A1	25256.153		2183	+	−	0.062	0.066	0.036	0.285	0.039	−	BMI
HSD11B1	21967.20		406	435	530	-0.171	-0.164	-0.165	0.981	0.394	333	BMI
NR3C1	2857.70		2331	+	+	-0.083	-0.087	-0.082	0.910	0.070	−	BMI
PPA2	18307.71		2085	+	+	0.076	0.080	0.056	0.471	0.038	−	BMI
RSPO3	13094.75		2103	1509	−	-0.086	-0.106	-0.037	0.071	-0.189	+	BMI
RSPO3	13094.75		173	+	+	0.104	0.069	0.169	0.031	-0.189	+	Height
STAR	10085.25		1752	+	751	0.100	0.078	0.151	0.058	0.163	+	BMI
STAR	10085.25		348	311	−	0.102	0.130	0.052	0.080	0.163	+	ABSI
STAR	10085.25		309	402	+	0.125	0.130	0.119	0.824	0.163	+	WHI



Supplementary Figure S9G Sex differences − cortisol related proteins by sex

ABSI – allometric body shape index; **Beta (B_{group})** – proteomic regression coefficient; **B_{diff}** – sex difference in proteomic regression coefficients (men − women); **B_{sex}** – sex difference in protein levels (men − women); **BMI** – body mass index; **CI** – confidence interval; **HI** – hip index; **P_{diff}** – p-value for sex difference in proteomic regression coefficients − orange $p<(0.05/7289)\approx7*10^{-6}$ (Bonferroni significance level); black $p<0.05$ (nominal significance level); grey $p\geq0.05$ (non-significant); **R** – aptamer rank order (lowest p-value first) − numerically defined for $p<(0.05/7289)\approx7*10^{-6}$ (Bonferroni significance level), + $p<0.05$ (nominal significance level), – $p\geq0.05$ (non-significant); **WHI** – waist-to-hip index.

***** – top ten proteins (single aptamer per protein) with Bonferroni significance level in the corresponding group.

****** – LEP and RET are included to show all heterogeneity by sex for WHI at Bonferroni significance level.

Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable. All models were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre. Regression models for BMI were additionally adjusted for height. Regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.

Sex differences in proteomic regression coefficients (**B_{diff}**) were tested with Wald test for the interaction term between the corresponding anthropometric index and sex (**P_{diff}**) from fully adjusted interaction models with sex in participants overall.

Association estimates for sex (**B_{sex}**) were obtained from models including a variable with categories women (reference) and men, fully adjusted for other covariates (provides information for the difference in protein levels on a standard deviation scale between men and women).

Figure S9A includes proteins with **P_{diff}** for BMI at Bonferroni significance level and regression coefficients at Bonferroni significance level in participants overall or separately in women or men.

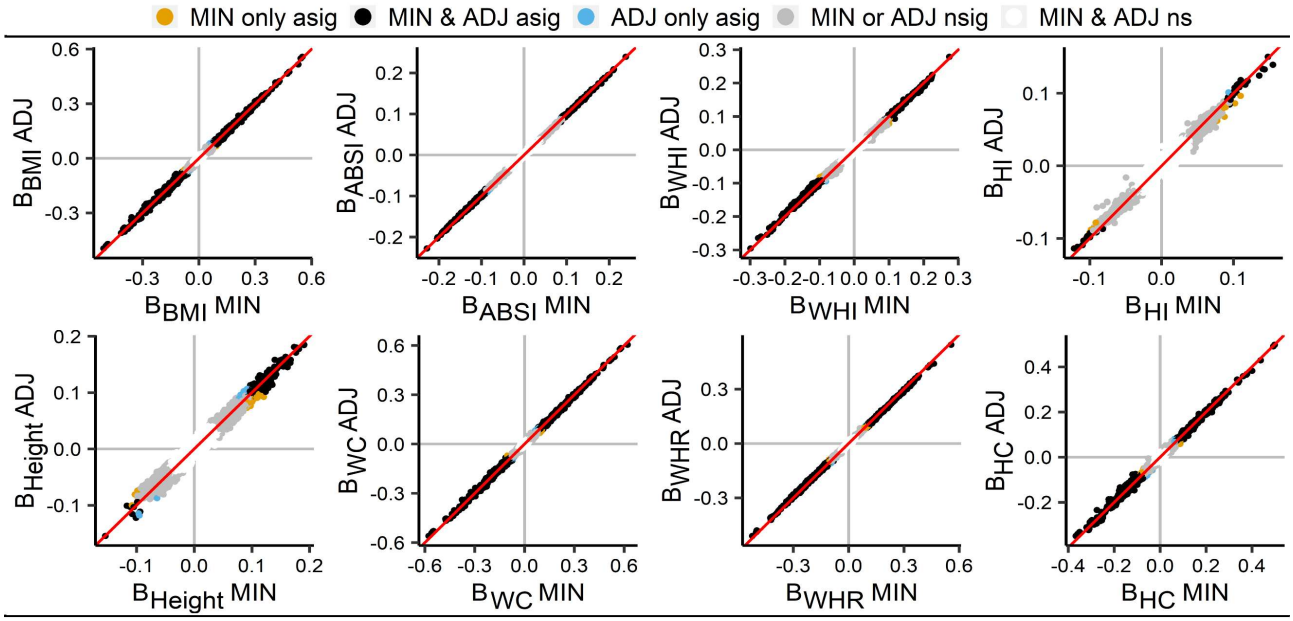
Figure S9G includes cortisol related proteins and anthropometric indices with regression coefficients at Bonferroni significance level in participants overall or separately in women or men.

(continues)

Supplementary Figure S9 Sex differences – top-ranked and cortisol-related proteins

(*legend continued*)

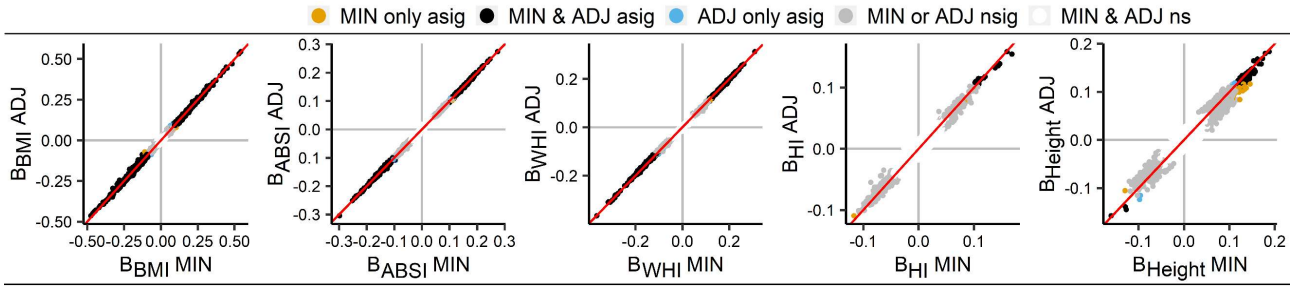
ADAMTSL2 − ADAMTS-like protein 2; **ADH1A** − Alcohol dehydrogenase 1A; **ADIPOQ** − Adiponectin; **AFM** − Afamin; **ALDOC** − Fructose-bisphosphate aldolase C; **ANTXR1** − Anthrax toxin receptor 1; **APCS** − Serum amyloid P-component; **APOF** − Apolipoprotein F; **B4GALT1** − Beta-1,4-galactosyltransferase 1; **C9** − Complement component C9; **CBLN4** − Cerebellin-4; **CD300LG** − CMRF35-like molecule 9; **CD93** − Complement component C1q receptor; **CDH5** − Cadherin-5; **CDNF** − Cerebral dopamine neurotrophic factor; **CGA|FSHB** − Follicle stimulating hormone; **CLMP** − CXADR-like membrane protein:Extracellular domain; **CRP** − C-reactive protein; **CST3** − Cystatin-C; **CYP3A4** − Cytochrome P450 3A4; **DEFB104A** − Beta-defensin 104; **DSG2** − Desmoglein-2; **EEF1A1** − Elongation factor 1-alpha 1; **EFNB2** − Ephrin-B2:Extracellular domain; **EHMT2** − Histone-lysine N-methyltransferase EHMT2; **EPHB4** − Ephrin type-B receptor 4; **ESPN** − Espin; **F9** − Coagulation factor IXab; **FABP3** − Fatty acid-binding protein, heart; **FABP4** − Fatty acid-binding protein, adipocyte; **GAS2** − Growth arrest-specific protein 2; **GDF11|MSTN** − Growth/differentiation factor 11/8; **GFRA1** − GDNF family receptor alpha-1; **GGT5** − Gamma-glutamyltransferase 5; **GHR** − Growth hormone receptor; **GM2A** − Ganglioside GM2 activator; **GPD1** − Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic; **HSD11B1** − Corticosteroid 11-beta-dehydrogenase isozyme 1; **HSPB6** − Heat shock protein beta-6; **HSPG2** − Basement membrane-specific heparan sulfate proteoglycan core protein; **IGFBP1** − Insulin-like growth factor-binding protein 1; **IGFBP2** − Insulin-like growth factor-binding protein 2; **IGFBP5** − Insulin-like growth factor-binding protein 5; **IGFBP7** − Insulin-like growth factor-binding protein 7; **INHBC** − Inhibin beta C chain; **ITIH3** − Inter-alpha-trypsin inhibitor heavy chain H3; **KCNE5** − Potassium voltage-gated channel subfamily E regulatory beta subunit 5:Cytoplasmic domain; **LEAP2** − Liver-expressed antimicrobial peptide 2; **LEP** − Leptin; **LRP10** − Low-density lipoprotein receptor-related protein 10; **LUM** − Lumican; **MANSC1** − MANSC domain-containing protein 1; **MCAM** − Melanoma-associated antigen MUC18; **ME1** − NADP-dependent malic enzyme; **MXRA8** − Matrix-remodeling-associated protein 8:Extracellular domain; **NCAN** − Neurocan core protein; **NOTCH3** − Neurogenic locus notch homolog protein 3; **NR3C1** − Glucocorticoid receptor; **OLFML3** − Olfactomedin-like protein 3; **PLAT** − Tissue-type plasminogen activator; **PPA2** − Inorganic pyrophosphatase 2, mitochondrial; **PPP1R1A** − Protein phosphatase 1 regulatory subunit 1A; **PTN** − Pleiotrophin; **RARRES2** − Retinoic acid receptor responder protein 2; **RBL2** − Retinoblastoma-like protein 2; **RET** − Proto-oncogene tyrosine-protein kinase receptor Ret; **ROR1** − Inactive tyrosine-protein kinase transmembrane receptor ROR1; **RP9** − Retinitis pigmentosa 9 protein; **RSPO3** − R-spondin-3; **SCARF2** − Scavenger receptor class F member 2:Extracellular domain; **SEZ6L** − Seizure 6-like protein; **SHBG** − Sex hormone-binding globulin; **SLITRK3** − SLIT and NTRK-like protein 3; **STAR** − Steroidogenic acute regulatory protein, mitochondrial; **TAGLN** − Transgelin; **THBS2** − Thrombospondin-2; **TIMP4** − Metalloproteinase inhibitor 4; **TNFRSF1A** − Tumor necrosis factor receptor superfamily member 1A; **TNFRSF1B** − Tumor necrosis factor receptor superfamily member 1B; **UNC5B** − Netrin receptor UNC5B; **VOPP1** − Vesicular, overexpressed in cancer, prosurvival protein 1.



	MIN total		ADJ total		MIN only	MIN & ADJ	ADJ only	r_{beta}
	nsig (neg−pos)	asig (neg−pos)	nsig (neg−pos)	asig (neg−pos)	asig (neg−pos)	asig (nn−pp−pn−np)	asig (neg−pos)	
BMI	4730 (2039−2691)	2516 (936−1580)	4708 (2021−2687)	2476 (918−1558)	100 (50−50)	2416 (886−1530−0−0)	60 (32−28)	1.00
ABSI	2490 (932−1558)	468 (248−220)	2459 (929−1530)	459 (248−211)	16 (5−11)	452 (243−209−0−0)	7 (5−2)	1.00
WHI	2608 (1083−1525)	569 (301−268)	2536 (1056−1480)	535 (288−247)	36 (15−21)	533 (286−247−0−0)	2 (2−0)	1.00
HI	1430 (671−759)	62 (28−34)	1344 (621−723)	44 (16−28)	19 (12−7)	43 (16−27−0−0)	1 (0−1)	0.99
Weight	4254 (1781−2473)	1973 (697−1276)	4193 (1744−2449)	1964 (707−1257)	55 (13−42)	1918 (684−1234−0−0)	46 (23−23)	1.00
WC	4730 (2005−2725)	2524 (921−1603)	4673 (1961−2712)	2447 (890−1557)	114 (49−65)	2410 (872−1538−0−0)	37 (18−19)	1.00
WHR	4333 (1724−2609)	1827 (719−1108)	4256 (1685−2571)	1704 (690−1014)	142 (38−104)	1685 (681−1004−0−0)	19 (9−10)	1.00
HC	4128 (1772−2356)	1853 (625−1228)	4072 (1727−2345)	1832 (632−1200)	84 (26−58)	1769 (599−1170−0−0)	63 (33−30)	1.00
Height	2486 (1369−1117)	220 (15−205)	2056 (1023−1033)	192 (11−181)	43 (7−36)	177 (8−169−0−0)	15 (3−12)	0.99

asig − p<(0.05/7289) (Bonferroni) nsig − p<0.05 (nominal) ns − p≥0.05 (non-significant) equivalence line

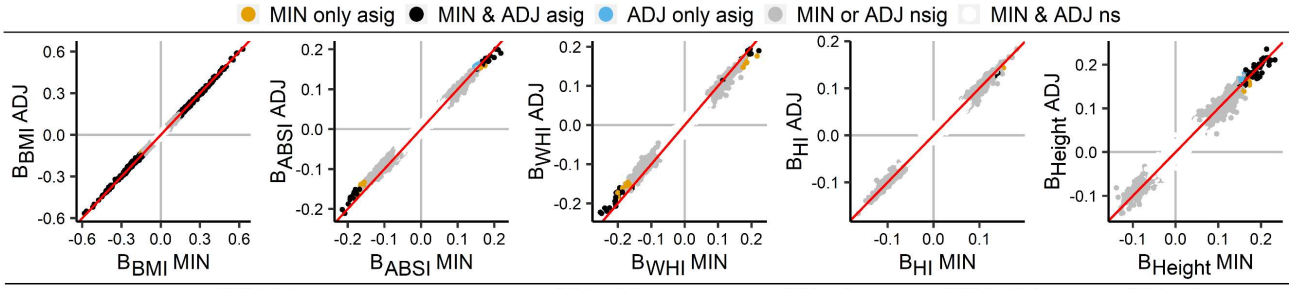
Supplementary Figure S10A Comparison of minimally and fully adjusted models − overall



	MIN total		ADJ total		MIN only	MIN & ADJ	ADJ only	r_{beta}
	nsig (neg−pos)	asig (neg−pos)	nsig (neg−pos)	asig (neg−pos)	asig (neg−pos)	asig (nn−pp−pn−np)	asig (neg−pos)	
BMI	4468 (1861−2607)	2142 (7−8−1344)	4318 (1795−2523)	2022 (757−1265)	152 (60−92)	1990 (738−1252−0−0)	32 (19−13)	1.00
ABSI	2715 (1047−1668)	458 (246−212)	2640 (1000−1640)	446 (244−202)	22 (8−14)	436 (238−198−0−0)	10 (6−4)	1.00
WHI	2533 (1078−1455)	472 (256−216)	2467 (1059−1408)	458 (248−210)	20 (12−8)	452 (244−208−0−0)	6 (4−2)	1.00
HI	906 (367−539)	18 (1−17)	850 (328−522)	15 (0−15)	3 (1−2)	15 (0−15−0−0)	–	0.99
Height	1751 (970−781)	81 (4−77)	1219 (582−637)	58 (5−53)	29 (1−28)	52 (3−49−0−0)	6 (2−4)	0.98

asig − p<(0.05/7289) (Bonferroni) nsig − p<0.05 (nominal) ns − p≥0.05 (non-significant) equivalence line

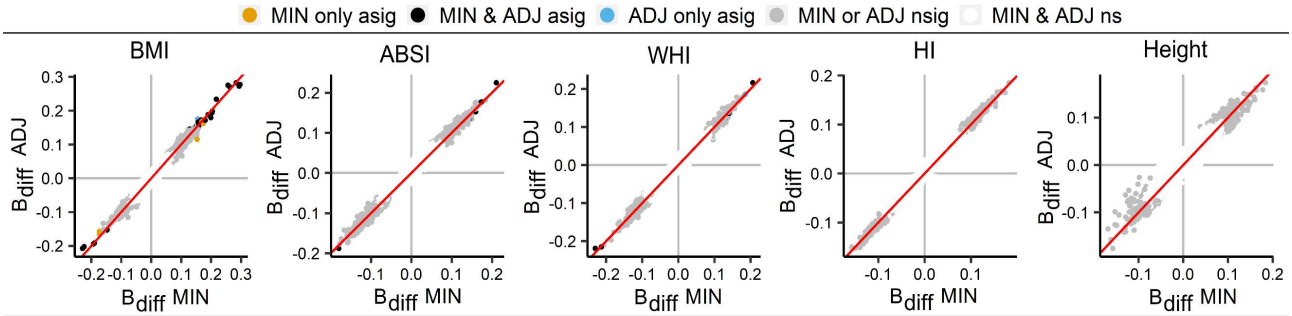
Supplementary Figure S10B Comparison of minimally and fully adjusted models − women



	MIN total		ADJ total		MIN only	MIN & ADJ	ADJ only	r_{beta}
	nsig (neg–pos)	asig (neg–pos)	nsig (neg–pos)	asig (neg–pos)	asig (neg–pos)	asig (nn–pp–pn–np)	asig (neg–pos)	
BMI	3216 (1348–1868)	864 (384–480)	3222 (1355–1867)	871 (380–491)	37 (15–22)	827 (369–458–0–0)	44 (11–33)	1.00
ABSI	987 (447–540)	48 (26–22)	949 (404–545)	35 (14–21)	16 (12–4)	32 (14–18–0–0)	3 (0–3)	0.99
WHI	1016 (521–495)	57 (38–19)	842 (423–419)	33 (22–11)	24 (16–8)	33 (22–11–0–0)	–	0.99
HI	1356 (815–541)	3 (0–3)	1507 (927–580)	2 (0–2)	1 (0–1)	2 (0–2–0–0)	–	0.99
Height	1527 (740–787)	76 (0–76)	1608 (791–817)	70 (0–70)	13 (0–13)	63 (0–63–0–0)	7 (0–7)	0.98

asig – p<(0.05/7289) (Bonferroni) nsig – p<0.05 (nominal) ns – p≥0.05 (non-significant) equivalence line

Supplementary Figure S10C Comparison of minimally and fully adjusted models – men



	MIN total		ADJ total		MIN only	MIN & ADJ	ADJ only	r_{beta}
	nsig (neg–pos)	asig (neg–pos)	nsig (neg–pos)	asig (neg–pos)	asig (neg–pos)	asig (nn–pp–pn–np)	asig (neg–pos)	
BMI	843 (383–460)	31 (7–24)	747 (313–434)	24 (5–19)	9 (2–7)	22 (5–17–0–0)	2 (0–2)	0.98
ABSI	1031 (536–495)	6 (1–5)	1195 (656–539)	6 (1–5)	–	6 (1–5–0–0)	–	0.99
WHI	505 (222–283)	5 (2–3)	518 (233–285)	6 (2–4)	–	5 (2–3–0–0)	1 (0–1)	0.99
HI	598 (337–261)	–	741 (436–305)	–	–	–	–	0.99
Height	371 (150–221)	–	499 (269–230)	–	–	–	–	0.96

asig – p<(0.05/7289) (Bonferroni) nsig – p<0.05 (nominal) ns – p≥0.05 (non-significant) equivalence line

Supplementary Figure S10D Comparison of minimally and fully adjusted models – sex differences

Index	ENG total		ADJ total		ENG only	ENG & ADJ	ADJ only	r_{beta}
	nsig (neg–pos)	asig (neg–pos)	nsig (neg–pos)	asig (neg–pos)	asig (neg–pos)	asig (nn–pp–pn–np)	asig (neg–pos)	
BMI	4717 (2021–2696)	2470 (917–1553)	4708 (2021–2687)	2476 (918–1558)	8 (5–3)	2462 (912–1550–0–0)	14 (6–8)	1.00
ABSI	2458 (931–1527)	452 (243–209)	2459 (929–1530)	459 (248–211)	1 (0–1)	451 (243–208–0–0)	8 (5–3)	1.00
WHI	2529 (1054–1475)	533 (287–246)	2536 (1056–1480)	535 (288–247)	1 (0–1)	532 (287–245–0–0)	3 (1–2)	1.00
HI	1359 (633–726)	43 (15–28)	1344 (621–723)	44 (16–28)	–	43 (15–28–0–0)	1 (1–0)	1.00
Weight	4191 (1743–2448)	1965 (697–1256)	4193 (1744–2449)	1964 (707–1257)	6 (2–4)	1959 (707–1252–0–0)	5 (0–5)	1.00
WC	4681 (1966–2715)	2447 (890–1557)	4673 (1961–2712)	2447 (890–1557)	3 (1–2)	2444 (889–1555–0–0)	3 (1–2)	1.00
WHR	4257 (1687–2570)	1701 (690–1011)	4256 (1685–2571)	1704 (690–1014)	1 (0–1)	1700 (690–1010–0–0)	4 (0–4)	1.00
HC	4065 (1722–2343)	1834 (632–1202)	4072 (1727–2345)	1832 (632–1200)	4 (0–4)	1830 (632–1198–0–0)	2 (0–2)	1.00
Height	2003 (987–1016)	192 (10–182)	2056 (1023–1033)	192 (11–181)	2 (0–2)	190 (10–180–0–0)	2 (1–1)	1.00

asig – p<(0.05/7289) (Bonferroni) nsig – p<0.05 (nominal) ns – p≥0.05 (non-significant)

Supplementary Figure S10E Comparison of energy adjusted and fully adjusted models – overall

Supplementary Figure S10 Comparisons with minimally and energy adjusted models *(legend)*

ABSI – a body shape index; $\mathbf{B_{diff}}$ – sex difference in proteomic regression coefficients (men − women); $\mathbf{B_{INDEX}}$ – proteomic regression coefficient; **BMI** – body mass index; **HC** – hip circumference; **HI** – hip index; **WC** – waist circumference; **WHI** – waist-to-hip index; **WHR** – waist-to-hip ratio.

neg−**pos** – number of aptamers with negative & positive associations at nominal (nsig) or Bonferroni significance level (asig).

Overlaps at Bonferroni significance level:

nn – number of aptamers with negative associations for both MIN or ENG and ADJ
pp – number of aptamers with positive associations for both MIN or ENG and ADJ
pn – number of aptamers with positive association for MIN or ENG negative for ADJ
np – number of aptamers with negative association for MIN or ENG positive for ADJ

Correlation (MIN–ADJ or ENG–ADJ index pairs):

$\mathbf{r_{beta}}$ – Spearman rank correlation coefficient between proteomic regression coefficients

Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable.

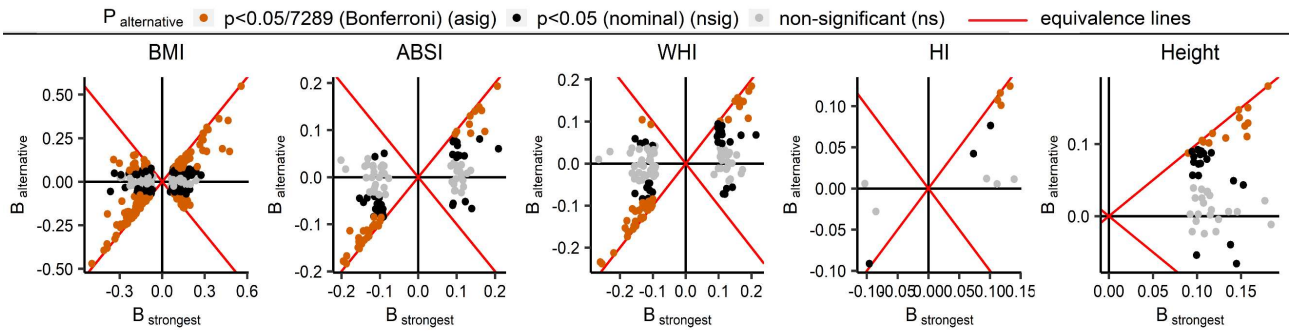
MIN – minimally adjusted regression models – adjusted for age, sex, and study centre.

ADJ – fully adjusted regression models – adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre.

ENG – energy adjusted regression models – fully adjusted models with additional adjustment for energy intake (kcal) calculated based on dietary questionnaires in the EPIC Nutrient Database and categorised as tertiles. Median (2.5^{th}-97.5^{th} centile) overall 2141 (1183 to 3747); women 1937 (1139 to 3177); men 2568 (1509 to 4146) kcal/day.

All regression models for BMI were additionally adjusted for height and all regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.

Sex differences $\mathbf{B_{diff}}$ were tested with Wald test for the interaction term between the corresponding anthropometric index and sex from fully adjusted interaction models with sex in participants overall.



Index	Total	Alternative total	Concordant asig	Concordant nsig	Null ns	Discordant nsig	Discordant asig
BMI	2476	442 (18)	128 (29)	87 (20)	134 (30)	58 (13)	35 (8)
ABSI	459	114 (25)	36 (32)	28 (25)	44 (39)	6 (5)	–
WHI	535	135 (25)	44 (33)	22 (16)	59 (44)	8 (6)	2 (1)
HI	44	12 (27)	4 (33)	3 (25)	5 (42)	–	–
Height	192	53 (28)	13 (25)	16 (30)	21 (40)	3 (6)	–

$r_{aptamer}$					
BMI	0.73 (0.34 to 0.86)	0.23 (0.08 to 0.50)	0.10 (−0.03 to 0.28)	−0.02 (−0.15 to 0.11)	−0.06 (−0.13 to 0)
ABSI	0.82 (0.73 to 0.90)	0.56 (0.34 to 0.79)	0.10 (−0.03 to 0.19)	−0.14 (−0.22 to −0.01)	–
WHI	0.81 (0.70 to 0.90)	0.48 (0.33 to 0.72)	0.08 (−0.04 to 0.18)	−0.21 (−0.27 to −0.02)	0.02 & 0.36
HI	0.94 (0.82 to 0.97)	0.20 (0.15 to 0.73)	0.05 (−0.05 to 0.08)	–	–
Height	0.82 (0.73 to 0.88)	0.73 (0.41 to 0.83)	0.10 (−0.06 to 0.21)	−0.23 (−0.31 to 0.01)	–

Supplementary Figure S11A Alternative aptamers for associations with allometric indices & height

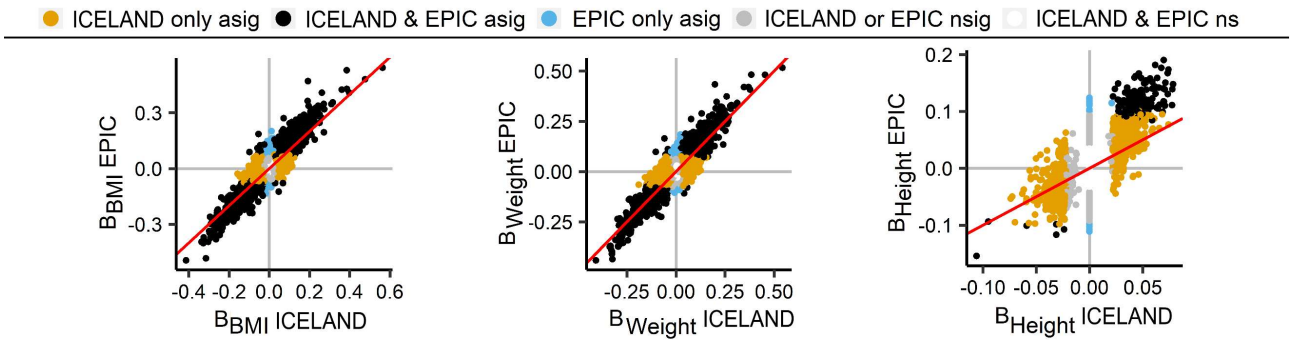
		Strongest						Alternative			
Gene	Aptamer	Beta (95%CI)	R_{BMI}	R_{ABSI}	R_{WHI}	R_{HI}	R_{Height}	Aptamer	Beta (95%CI)	R_{BMI}	$r_{aptamer}$
CD300LG	20585.5		-	21	6	5	163	20585.9		-	0.11
CLMP	10440.26		474	-	-	11	-	9585.80		-	0.06
EFNB2	14131.37		488	321	200	-	2	8772.5		-	0.13
MXRA8	10521.10		70	6	12	-	-	7002.1		1628	-0.06
SCARF2	8956.96		146	129	93	-	1	9925.56		-	0.00

Supplementary Figure S11B Discordant alternative aptamers for top ranked proteins

ABSI − a body shape index; **Beta (B)** – proteomic regression coefficient; **BMI** − body mass index; **CI** – confidence interval; **HI** − hip index; **R** – aptamer rank order (lowest p-value first), numerically defined for Bonferroni significance level; **WHI** − waist to hip index; **asig** – $p<(0.05/7289)\approx7*10^{-6}$ (Bonferroni significance level); **nsig** – p<0.05 (nominal significance level); **ns** – p≥0.05 (non-significant); **$r_{aptamer}$** – pairwise partial Pearson correlation coefficient between protein levels measured with the strongest associated aptamer and the most discordant alternative aptamer – median (25^{th} to 75^{th} centile). **Strongest** – strongest associated aptamer; **Alternative** – most discordant alternative aptamer.

CD300LG − CMRF35-like molecule 9 (same for both aptamers); **CLMP** – CXADR-like membrane protein:Extracellular domain (Strongest); CXADR-like membrane protein:Cytoplasmic domain (Alternative); **EFNB2** − Ephrin-B2:Extracellular domain (Strongest); Ephrin-B2:Cytoplasmic domain (Alternative); **MXRA8** – Matrix-remodeling-associated protein 8:Extracellular domain (Strongest); Matrix-remodeling-associated protein 8:Cytoplasmic domain (Alternative); **SCARF2** − Scavenger receptor class F member 2:Extracellular domain (Strongest); Scavenger receptor class F member 2:Cytoplasmic domain (Alternative).

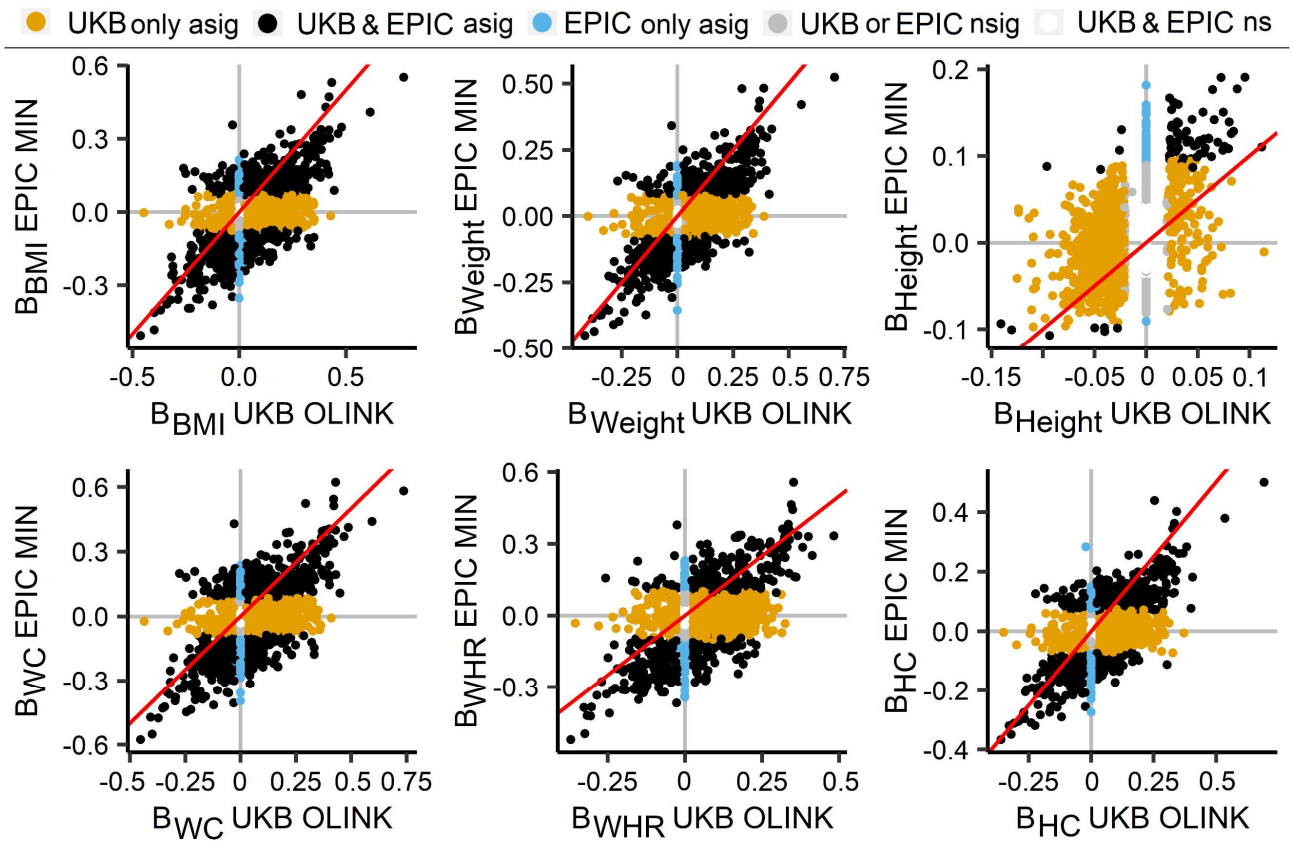
Regression coefficient estimates were obtained from linear regression models examining each anthropometric index individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset individually as outcome variable. All regression models and partial Pearson correlation coefficients were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre (regression) or country (correlation). Regression models for BMI were additionally adjusted for height. Regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.



	ICELAND total		EPIC total		ICELAND only	ICELAND & EPIC	EPIC only	r_{beta}
	nsig (neg–pos)	asig (neg–pos)	nsig (neg–pos)	asig (neg–pos)	asig (neg–pos)	asig (nn–pp–pn–np)	asig (neg–pos)	
BMI	4160 (2226–1934)	3341 (1736–1605)	3270 (1422–1848)	1780 (688–1092)	1720 (1063–657)	1621 (660–945–3–13)	159 (25–134)	0.85
Weight	4184 (2150–2034)	3412 (1722–1690)	2945 (1242–1703)	1404 (516–888)	2097 (1213–884)	1315 (503–804–2–6)	89 (11–78)	0.85
Height	825 (393–432)	756 (333–423)	1741 (934–807)	163 (10–153)	614 (327–287)	142 (6–136–0–0)	21 (4–17)	0.44

asig – p<(0.05/7289) (Bonferroni) nsig – p<0.05 (nominal) ns – p≥0.05 (non-significant) equivalence line

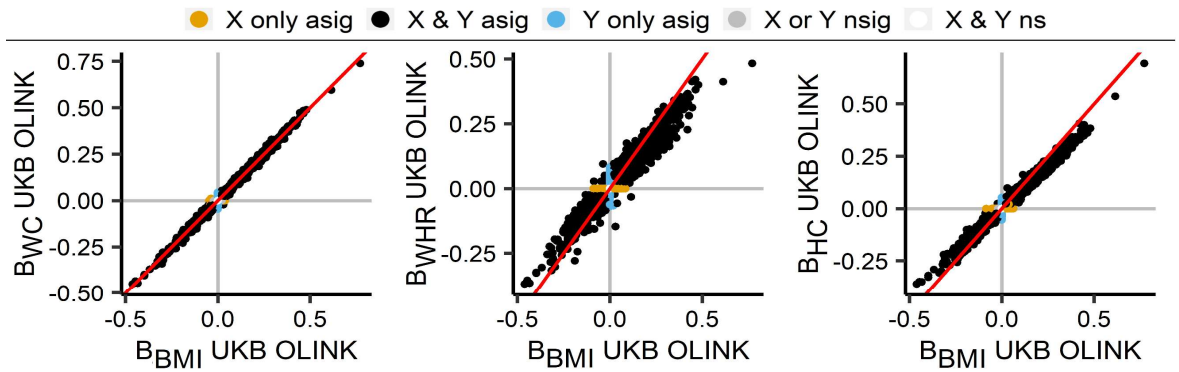
Supplementary Figure S12A Proteomic comparisons of SomaScan in EPIC vs Icelanders



Index	UKB OLINK total	EPIC MIN total	UKB only	UKB & EPIC	EPIC only	r_{beta}
	asig (neg–pos)	asig (neg–pos)	asig (neg–pos)	asig (nn–pp–pn–np)	asig (neg–pos)	
BMI	1746 (343–1403)	887 (408–479)	1023 (125–898)	723 (184–364–141–34)	164 (83–81)	0.38
Weight	1637 (332–1305)	721 (320–401)	1052 (135–917)	585 (172–305–83–25)	136 (65–71)	0.42
Height	1156 (959–197)	121 (8–113)	1087 (948–139)	69 (7–58–0–4)	52 (1–51)	0.37
WC	1786 (336–1450)	890 (406–484)	1053 (120–933)	733 (181–371–146–35)	157 (79–78)	0.39
WHR	1745 (302–1443)	677 (343–334)	1203 (123–1080)	542 (161–261–102–18)	135 (80–55)	0.39
HC	1576 (324–1252)	688 (296–392)	1020 (135–885)	556 (162–294–73–27)	132 (61–71)	0.41

asig – p<(0.05/7289) (Bonferroni) nsig – p<0.05 (nominal) ns – p≥0.05 (non-significant) equivalence line

Supplementary Figure S12B Proteomic comparisons of SomaScan (EPIC) vs Olink (UKB)

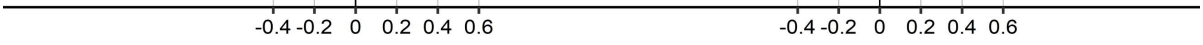


X index	Y index	X total asig (neg−pos)	Y total asig (neg−pos)	X only asig (neg−pos)	X & Y asig (nn−pp−pn−np)	Y only asig (neg−pos)	r_{beta}
BMI	**WC**	2261 (441−1820)	2316 (431−1885)	36 (26−10)	2225 (415−1809−1−0)	91 (15−76)	0.99
BMI	**WHR**	2261 (441−1820)	2267 (383−1884)	156 (83−73)	2105 (348−1743−4−10)	162 (31−131)	0.94
BMI	**HC**	2261 (441−1820)	2014 (412−1602)	285 (48−237)	1976 (392−1583−0−1)	38 (20−18)	0.97

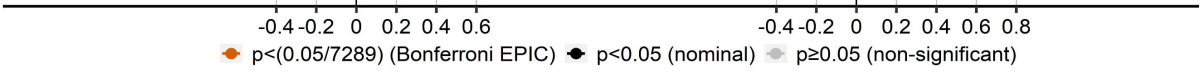
asig − p<(0.05/7289) (Bonferroni) nsig − p<0.05 (nominal) ns − p≥0.05 (non-significant) equivalence line

Supplementary Figure S12C Proteomic comparisons of body shape vs BMI for Olink (UKB)

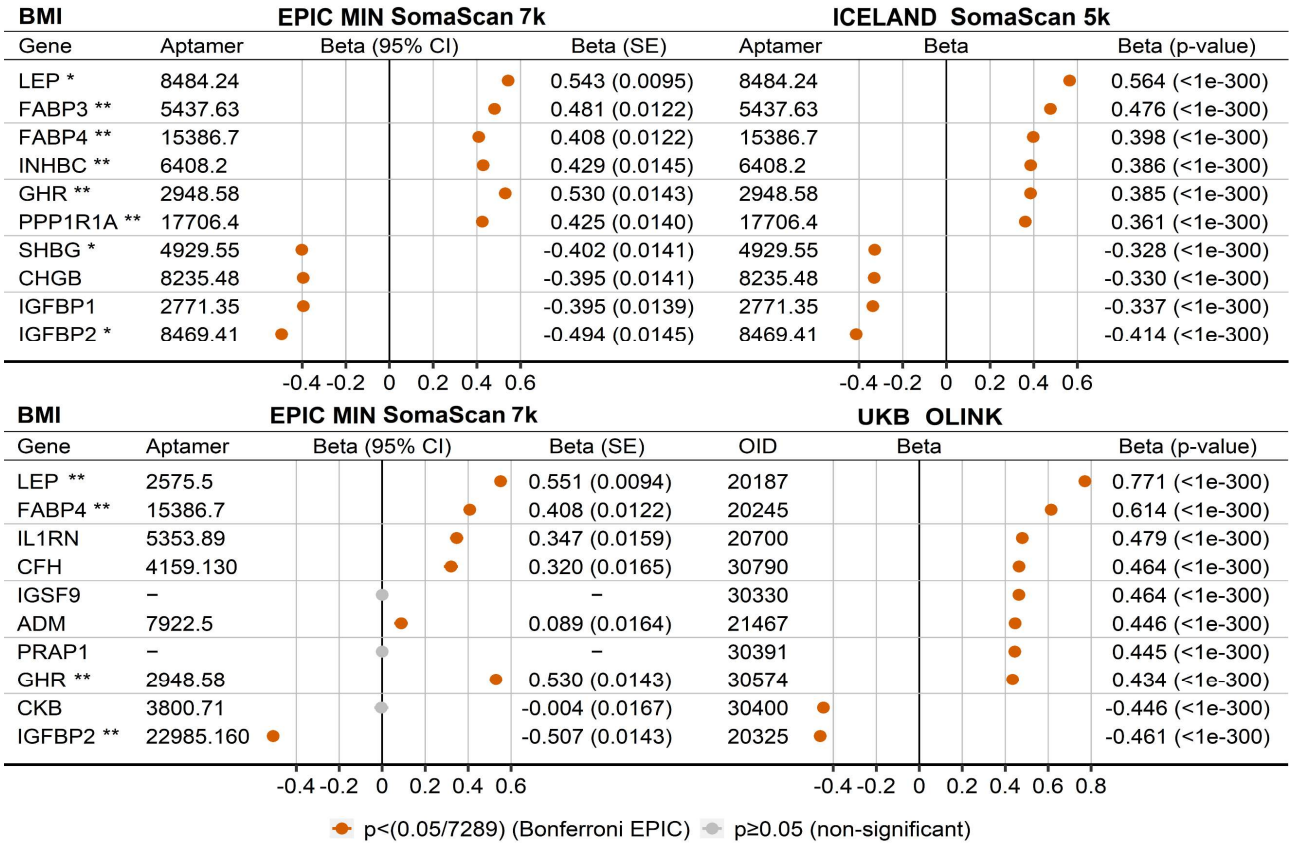
BMI	**EPIC MIN SomaScan 7k**			**ICELAND SomaScan 5k**		
Gene	Aptamer	Beta (95% CI)	Beta (SE)	Aptamer	Beta	Beta (p-value)
LEP *	8484.24		0.543 (0.0095)	8484.24		0.564 (<1e-300)
GHR	2948.58		0.530 (0.0143)	2948.58		0.385 (<1e-300)
FABP3	5437.63		0.481 (0.0122)	5437.63		0.476 (<1e-300)
GPD1	13697.51		0.471 (0.0153)	13697.51		0.192 (8e-261)
INHBC	6408.2		0.429 (0.0145)	6408.2		0.386 (<1e-300)
PPP1R1A	17706.4		0.425 (0.0140)	17706.4		0.361 (<1e-300)
FABP4	15386.7		0.408 (0.0122)	15386.7		0.398 (<1e-300)
PLAT	2212.69		0.315 (0.0144)	2212.69		0.238 (<1e-300)
F9	5307.12		0.299 (0.0158)	5307.12		0.236 (<1e-300)
CLMP	10440.26		0.154 (0.0144)	10440.26		0.173 (1e-210)
TIMP4	6462.12		0.009 (0.0156)	6462.12		0.004 (5e-01)
C9 *	3060.43		-0.059 (0.0168)	3060.43		-0.053 (1e-20)
ITIH3	7145.1		-0.196 (0.0158)	7145.1		-0.111 (1e-86)
ADIPOQ	3554.24		-0.260 (0.0144)	3554.24		-0.295 (<1e-300)
MXRA8	10521.10		-0.283 (0.0152)	10521.10		-0.283 (<1e-300)
DSG2	9484.75		-0.285 (0.0153)	9484.75		-0.178 (5e-224)
VOPP1	14618.26		-0.291 (0.0145)	14618.26		-0.271 (<1e-300)
EHMT2	5843.60		-0.337 (0.0154)	5843.60		-0.299 (<1e-300)
SEZ6L	19563.3		-0.394 (0.0137)	19563.3		-0.303 (<1e-300)
SHBG *	4929.55		-0.402 (0.0141)	4929.55		-0.328 (<1e-300)
APOF	12370.30		-0.484 (0.0151)	12370.30		-0.315 (<1e-300)
IGFBP2 *	8469.41		-0.494 (0.0145)	8469.41		-0.414 (<1e-300)



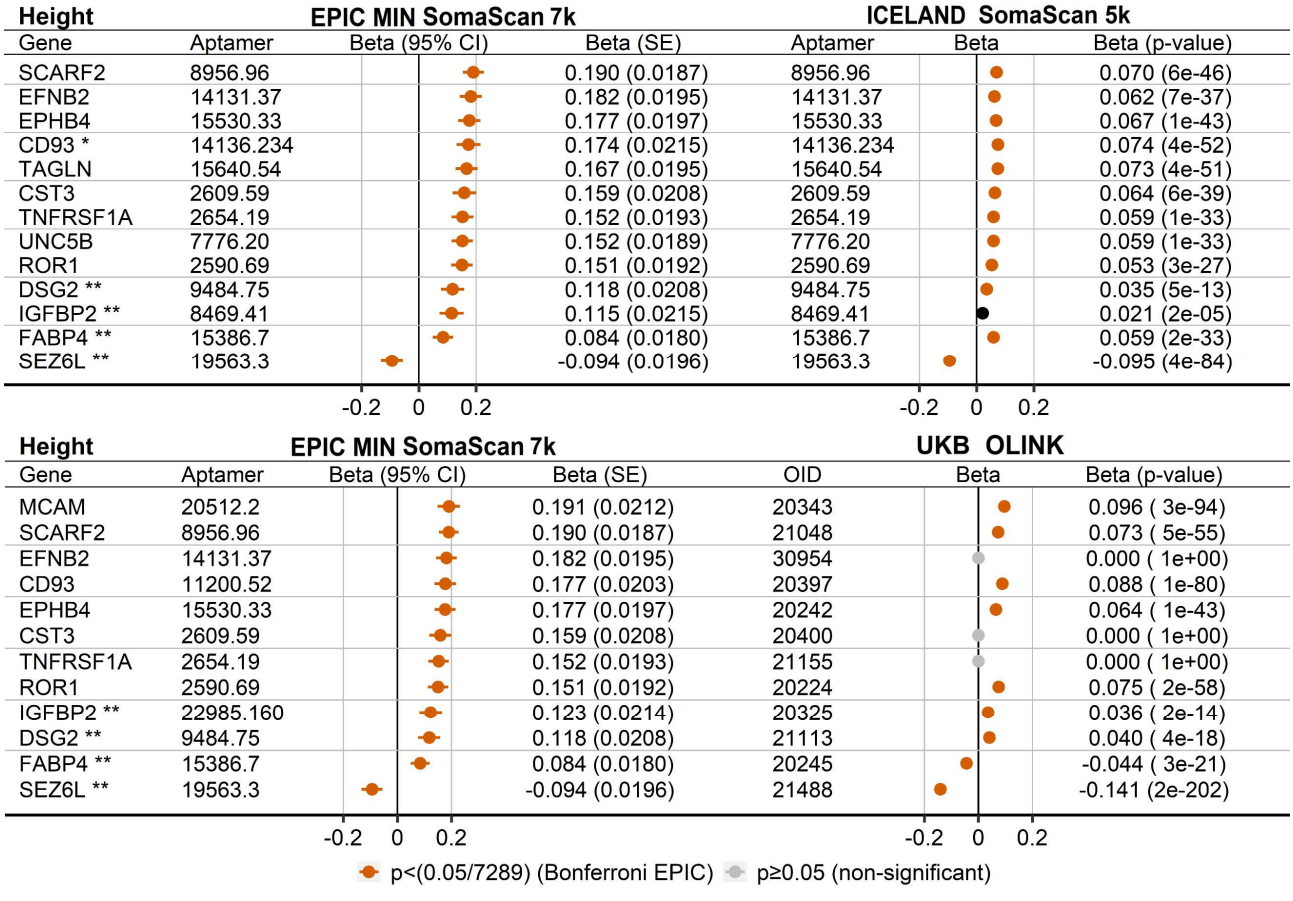
BMI	**EPIC MIN SomaScan 7k**			**UKB OLINK**		
Gene	Aptamer	Beta (95% CI)	Beta (SE)	OID	Beta	Beta (p-value)
LEP	2575.5		0.551 (0.0094)	20187		0.771 (<1e-300)
GHR	2948.58		0.530 (0.0143)	30574		0.434 (<1e-300)
FABP3	5437.63		0.481 (0.0122)	30351		0.291 (<1e-300)
GPD1	13697.51		0.471 (0.0153)	31358		0.421 (<1e-300)
INHBC	6408.2		0.429 (0.0145)	21093		0.406 (<1e-300)
FABP4	15386.7		0.408 (0.0122)	20245		0.614 (<1e-300)
PLAT	2212.69		0.315 (0.0144)	20247		0.378 (<1e-300)
F9	5307.12		0.299 (0.0158)	20349		0.352 (<1e-300)
CLMP	10440.26		0.154 (0.0144)	21419		0.420 (<1e-300)
TIMP4	6462.12		0.009 (0.0156)	21147		0.085 (9e-75)
C9	13722.105		-0.039 (0.0167)	30698		0.000 (1e+00)
CD300LG	20585.5		-0.052 (0.0159)	21130		0.030 (5e-11)
ITIH3	7145.1		-0.196 (0.0158)	20352		-0.088 (3e-81)
ADIPOQ	3554.24		-0.260 (0.0144)	30748		-0.315 (<1e-300)
MXRA8	10521.10		-0.283 (0.0152)	30583		-0.296 (<1e-300)
DSG2	9484.75		-0.285 (0.0153)	21113		-0.174 (<1e-300)
SEZ6L	19563.3		-0.394 (0.0137)	21488		-0.238 (<1e-300)
SHBG	7909.37		-0.396 (0.0142)	30685		-0.368 (<1e-300)
APOF	12370.30		-0.484 (0.0151)	30701		-0.398 (<1e-300)
IGFBP2	22985.160		-0.507 (0.0143)	20325		-0.461 (<1e-300)



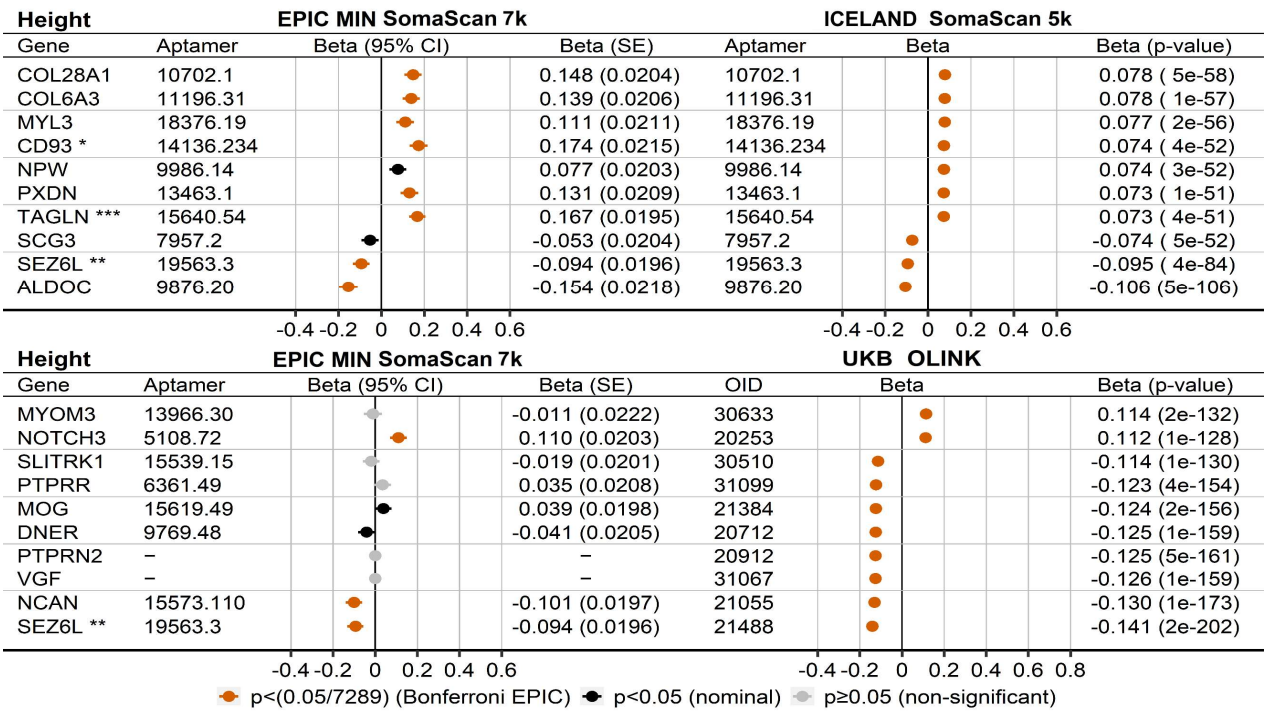
Supplementary Figure S12D BMI associations for top allometric set in EPIC vs Icelanders & UKB



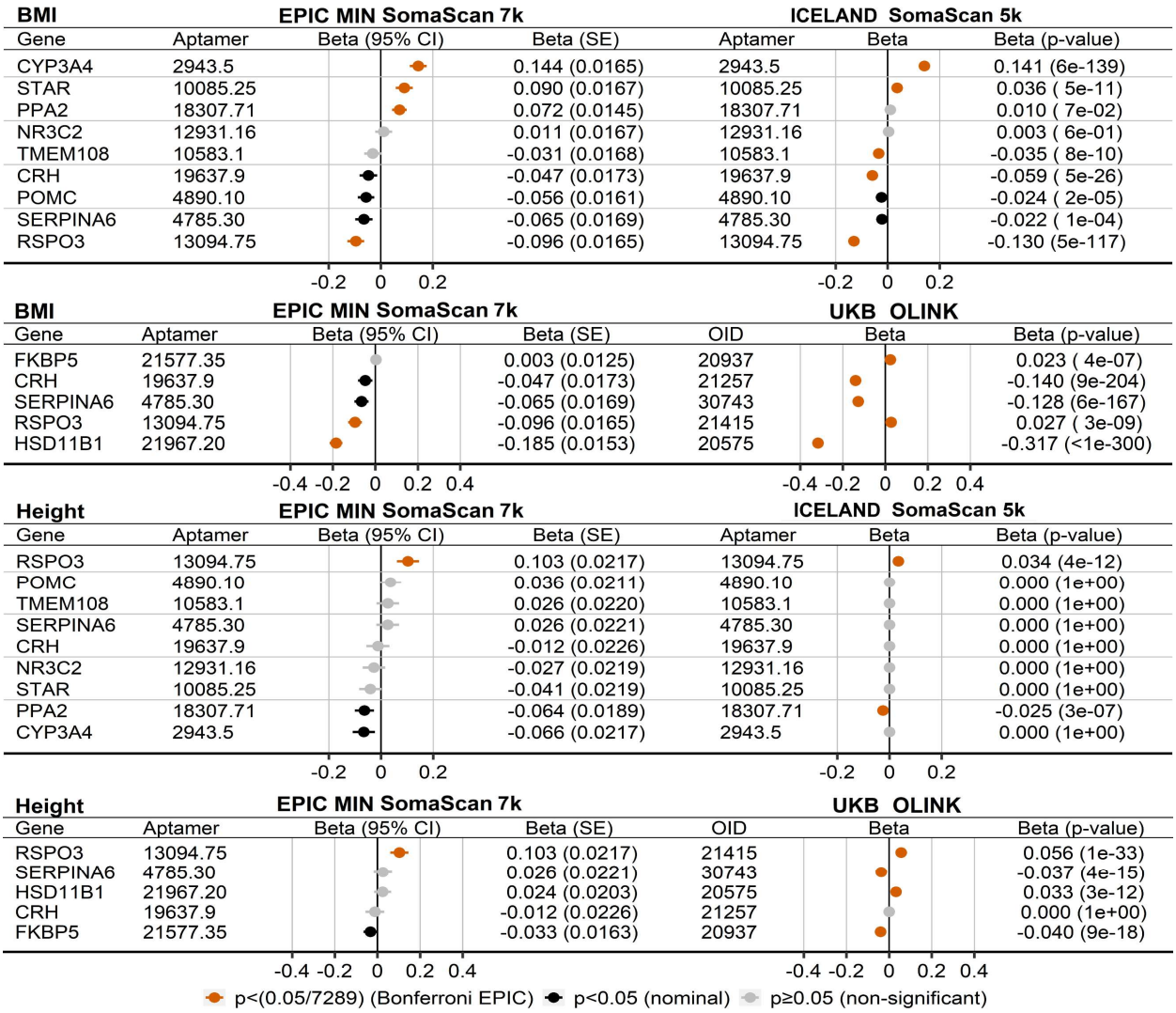
Supplementary Figure S12E Top ten proteins for BMI in Icelanders & UKB vs EPIC



Supplementary Figure S12F Top ten proteins for height in EPIC vs Icelanders & UKB



Supplementary Figure S12G Top ten proteins for height in Icelanders & UK Biobank vs EPIC



Supplementary Figure S12H Cortisol-related proteins in EPIC vs Icelanders & UK Biobank

Supplementary Figure S12 Proteomic associations in EPIC vs Icelanders & UK Biobank *(legend)*

Aptamer – aptamer sequence number for SomaScan; **Beta** ($\mathbf{B_{INDEX}}$) – proteomic regression coefficient; **BMI** – body mass index; **CI** – confidence interval; **EPIC** – European Prospective Investigation into Cancer and Nutrition cohort; **HC** – hip circumference; **OID** – object identifier for assays in the Olink platform; **SE** – standard error; **WC** – waist circumference; **WHR** – waist-to-hip ratio.

ICELAND SomaScan 5k – association estimates for Icelanders (n=28,256 for mean BMI; n=29,994 for median weight; n=36,500 for max height) based on SomaScan v4.0 (5k) aptamer measurements of protein levels previously published in reference [8].

UKB Olink – association estimates for 2925 proteins based on Olink Explore 3072 Proximity Extension Assay protein level measurements for 54,265 UK Biobank participants generated in the UKB Pharma Proteomics Project (UKB-PPP application number 65851) and examined for associations with body mass index, traditional body shape indices, and standing height in reference [8]. Overlapping with SomaScan v4.1 (7k) were 2159 proteins.

EPIC SomaScan 7k – association estimates for the 4037 EPIC participants in our study based on SomaScan v4.1 (7k) aptamer measurements of protein levels with aptamers matching the aptamers included in SomaScan v4.0 (5k) (all 5k aptamers are included in the 7k version).

The **top allometric set** includes the top ten proteins for BMI, ABSI, WHI, and HI.

***** Alternative aptamers used when the SomaScan v4.1 (7k) aptamers included in the top ranked sets in EPIC were not available in SomaScan v4.0 (5k).

****** Proteins from the top allometric set in EPIC marked in **Figure S12E** (showing the top ten proteins for BMI in Icelanders & UK Biobank), **Figure S12F** (showing the top ten proteins for height in EPIC) and **Figure S12G** (showing the top ten proteins for height in Icelanders & UK Biobank).

******* Proteins from the top ten set for height in EPIC marked in **Figure S12G** (showing the top ten proteins for height in Icelanders & UK Biobank).

Regression coefficient estimates were obtained from linear regression models examining BMI, weight or height individually as exposure variable and each aptamer from the sample-normalised (SMP) dataset for SomaScan or each protein target for Olink individually as outcome variable with minimal adjustment for age, sex, and study centre in our study of EPIC participants or for age and sex in the previously published study of Icelanders and UK Biobank participants in reference [8].

Note 1 – for comparability, Bonferroni adjusted p-values correspond to the cut-off used for SomaScan 7k in EPIC $p<(0.05/7289)\approx7*10^{-6}$.

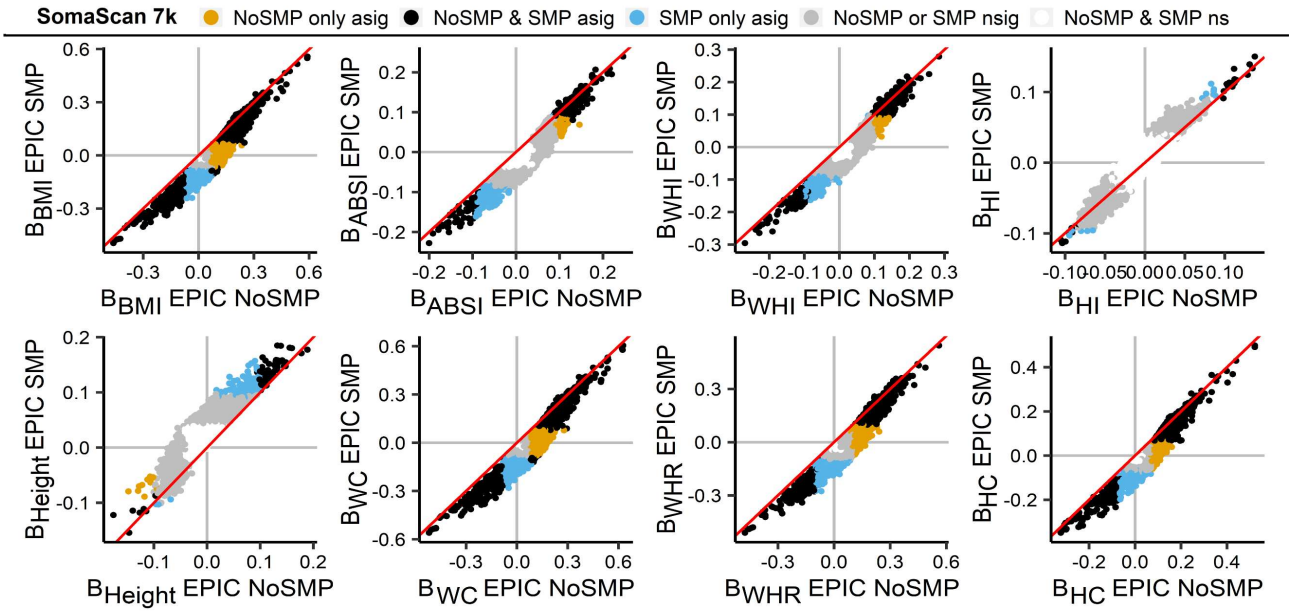
Note 2 – only associations with nominal significance ($p<0.05$) for SMP or NoSMP normalisation were reported in reference [8] (4917 for Mean BMI; 4908 for Median weight; 825 for Max height) and we defined the rest as zero regression coefficients (p-value=1) to complete the 4963 aptamers available in SomaScan v4.0 (5k). Similarly, only proteins with associations significant at $p<1.7*10^{-5}$ were reported in reference [8] for UK Biobank with the Olink platform (2291 for Body mass index; 2142 for Weight; 1515 for Standing height; 2337 for Waist circumference; 2286 for Waist hip ratio; 2037 for Hip circumference) and we defined the rest as zero regression coefficients (p-value=1).

Note 3 – among the 2326 additional aptamers in SomaScan v4.1 (7k) compared to SomaScan v4.0 (5k), 696 were associated with BMI at Bonferroni significance level in EPIC, 560 with weight and 29 with height, which were thus newly identified associations.

Note 4 – comparisons presented in this figure are **not intended as comparisons of the analytical performance of the two versions of SomaScan and Olink** because the analyses were performed not only with different analytical platforms, but also in different times, different samples, different populations and different studies, hence differences are expected but, given these caveats, the similarities are even more remarkable.

Supplementary Figure S12 Proteomic comparisons in EPIC vs Icelanders & UK Biobank
(legend continued)

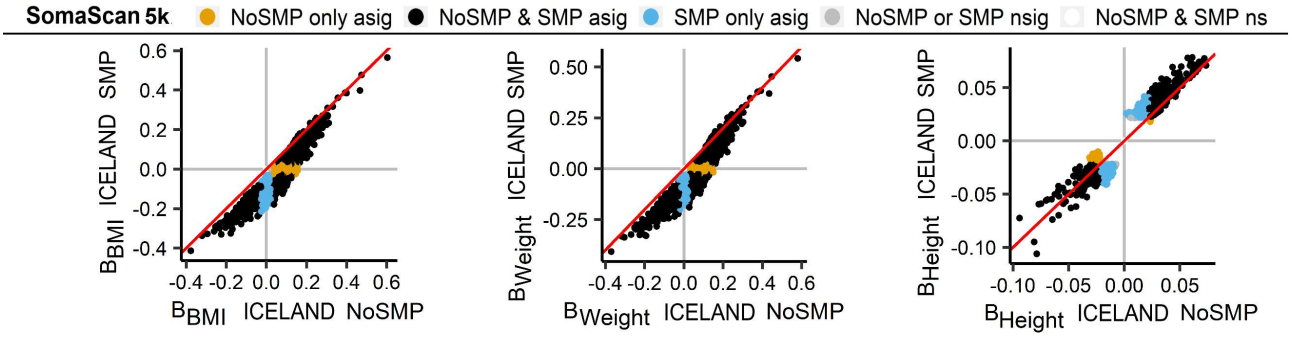
ADIPOQ − Adiponectin; **ADM** − Pro-adrenomedullin; **ALDOC** − Fructose-bisphosphate aldolase C; **APOF** − Apolipoprotein F; **C9** − Complement component C9; **CD300LG** − CMRF35-like molecule 9; **CD93** − Complement component C1q receptor; **CFH** − Complement factor H; **CHGB** − Secretogranin-1; **CLMP** − CXADR-like membrane protein:Extracellular domain; **CKB** − Creatine kinase B-type; **COL28A1** − Collagen alpha-1(XXVIII) chain; **COL6A3** − Collagen alpha-3(VI) chain:Bovine pancreatic trypsin inhibitor/Kunitz inhibitor domain, isoform 1; **CRH** – Corticoliberin; **CST3** − Cystatin-C; **CYP3A4** − Cytochrome P450 3A4; **DNER** − Delta and Notch-like epidermal growth factor-related receptor; **DSG2** − Desmoglein-2; **EFNB2** − Ephrin-B2:Extracellular domain; **EHMT2** − Histone-lysine N-methyltransferase EHMT2; **EPHB4** − Ephrin type-B receptor 4; **ESPN** − Espin; **F9** − Coagulation factor IXab; **FABP3** − Fatty acid-binding protein, heart; **FABP4** − Fatty acid-binding protein, adipocyte; **FKBP5** − FK506-binding protein 5; **GHR** − Growth hormone receptor; **GPD1** − Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic; **HSD11B1** − Corticosteroid 11-beta-dehydrogenase isozyme 1; **IGFBP1** − Insulin-like growth factor-binding protein 1; **IGFBP2** − Insulin-like growth factor-binding protein 2; **IGSF9** − Protein turtle homolog A; **IL1RN** − Interleukin-1 receptor antagonist protein; **INHBC** − Inhibin beta C chain; **ITIH3** − Inter-alpha-trypsin inhibitor heavy chain H3; **LEP** − Leptin; **MCAM** − Melanoma-associated antigen MUC18; **MOG** − Myelin-oligodendrocyte glycoprotein; **MXRA8** − Matrix-remodeling-associated protein 8:Extracellular domain; **MYL3** − Myosin light chain 3; **MYOM3** − Myomesin-3; **NCAN** − Neurocan core protein; **NOTCH3** − Neurogenic locus notch homolog protein 3; **NR3C2** − Mineralocorticoid receptor; **PLAT** − Tissue-type plasminogen activator; **POMC** – Corticotropin (adrenocorticotropic hormone ACTH); **PPA2** − Inorganic pyrophosphatase 2, mitochondrial; **PPP1R1A** − Protein phosphatase 1 regulatory subunit 1A; **PRAP1** − Proline-rich acidic protein 1; **PTPRN2** − Receptor-type tyrosine-protein phosphatase N2; **PTPRR** − Receptor-type tyrosine-protein phosphatase R; **PXDN** − Peroxidasin homolog; **ROR1** − Inactive tyrosine-protein kinase transmembrane receptor ROR1; **RSPO3** − R-spondin-3; **SCARF2** − Scavenger receptor class F member 2:Extracellular domain; **SCG3** − Secretogranin-3; **SERPINA6** – serpin family A member 6 gene (corticosteroid-binding globulin); **SEZ6L** − Seizure 6-like protein; **SHBG** − Sex hormone-binding globulin; **SLITRK1** − SLIT and NTRK-like protein 1; **STAR** − Steroidogenic acute regulatory protein, mitochondrial; **TAGLN** – Transgelin; **TIMP4** − Metalloproteinase inhibitor 4; **TMEM108** − Transmembrane protein 108; **TNFRSF1A** − Tumor necrosis factor receptor superfamily member 1A; **UNC5B** − Netrin receptor UNC5B; **VGF** − Neurosecretory protein VGF; **VOPP1** − Vesicular, overexpressed in cancer, prosurvival protein 1.



Index	NoSMP total		SMP total		NoSMP only	NoSMP & SMP	SMP only	r_{beta}
	nsig (neg−pos)	asig (neg−pos)	nsig (neg−pos)	asig (neg−pos)	asig (neg−pos)	asig (nn−pp−pn−np)	asig (neg−pos)	
BMI	6622 (412−6210)	5093 (251−4842)	4708 (2021−2687)	2476 (918−1558)	3221 (0−3221)	1872 (251−1558−63−0)	604 (604−0)	0.82
ABSI	4490 (300−4190)	452 (71−381)	2459 (929−1530)	459 (248−211)	172 (0−172)	280 (71−209−0−0)	179 (177−2)	0.87
WHI	4668 (313−4355)	491 (88−403)	2536 (1056−1480)	535 (288−247)	159 (0−159)	332 (88−244−0−0)	203 (200−3)	0.86
HI	779 (536−243)	26 (7−19)	1344 (621−723)	44 (16−28)	−	26 (7−19−0−0)	18 (9−9)	0.95
Weight	6366 (365−6001)	4251 (219−4032)	4193 (1744−2449)	1964 (707−1257)	2774 (0−2774)	1477 (219−1257−1−0)	487 (487−0)	0.83
WC	6637 (414−6223)	5209 (252−4957)	4673 (1961−2712)	2447 (890−1557)	3349 (0−3349)	1860 (252−1557−51−0)	587 (587−0)	0.82
WHR	6458 (395−6063)	3980 (231−3749)	4256 (1685−2571)	1704 (690−1014)	2735 (0−2735)	1245 (231−1014−0−0)	459 (459−0)	0.82
HC	6114 (357−5757)	3770 (204−3566)	4072 (1727−2345)	1832 (632−1200)	2366 (0−2366)	1404 (204−1200−0−0)	428 (428−0)	0.84
Height	3142 (2792−350)	79 (20−59)	2056 (1023−1033)	192 (11−181)	13 (13−0)	66 (7−59−0−0)	126 (4−122)	0.84

asig − p<(0.05/7289) (Bonferroni) nsig − p<0.05 (nominal) ns − p≥0.05 (non-significant) equivalence line

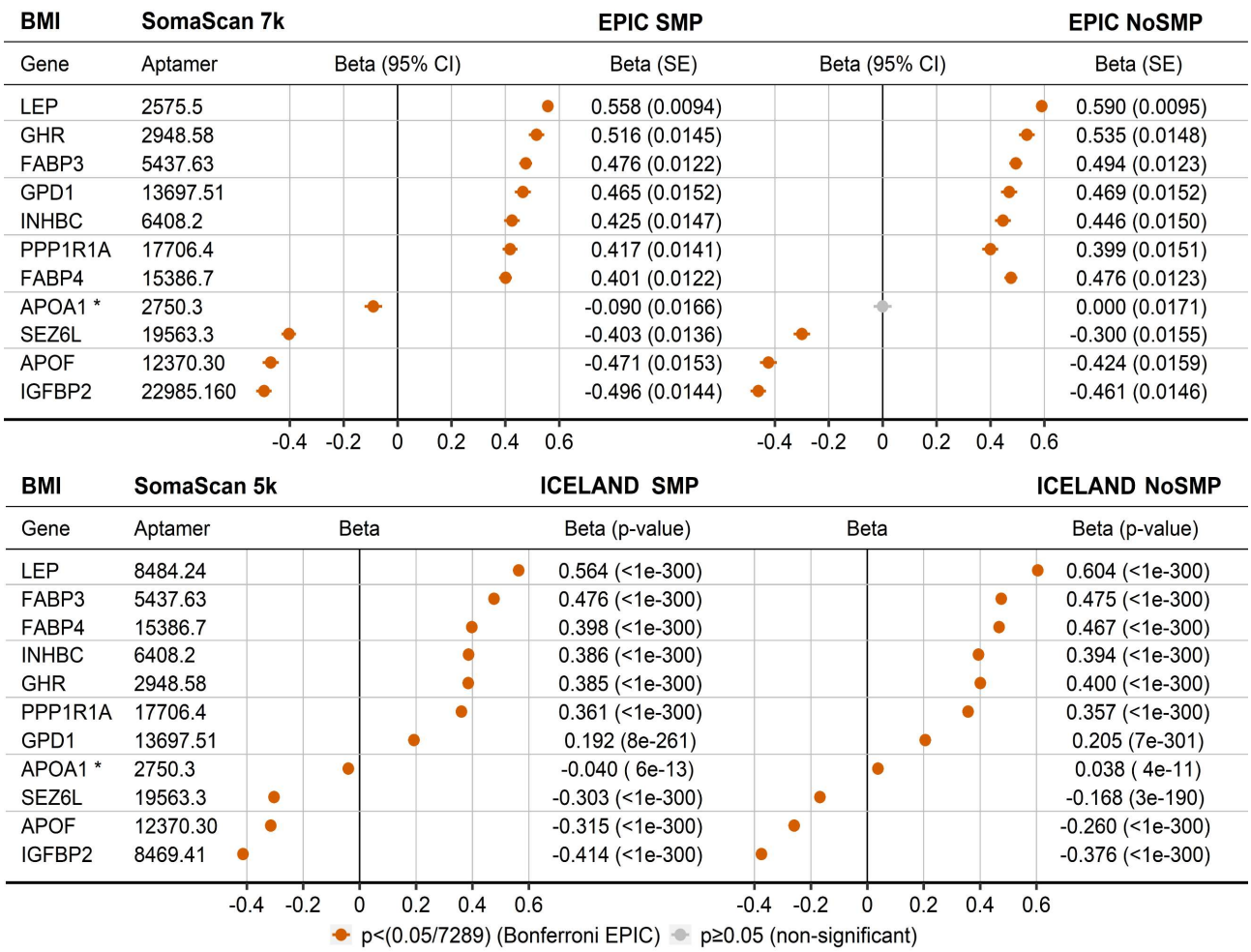
Supplementary Figure S13A SMP vs NoSMP normalisation − EPIC (full adjustment)



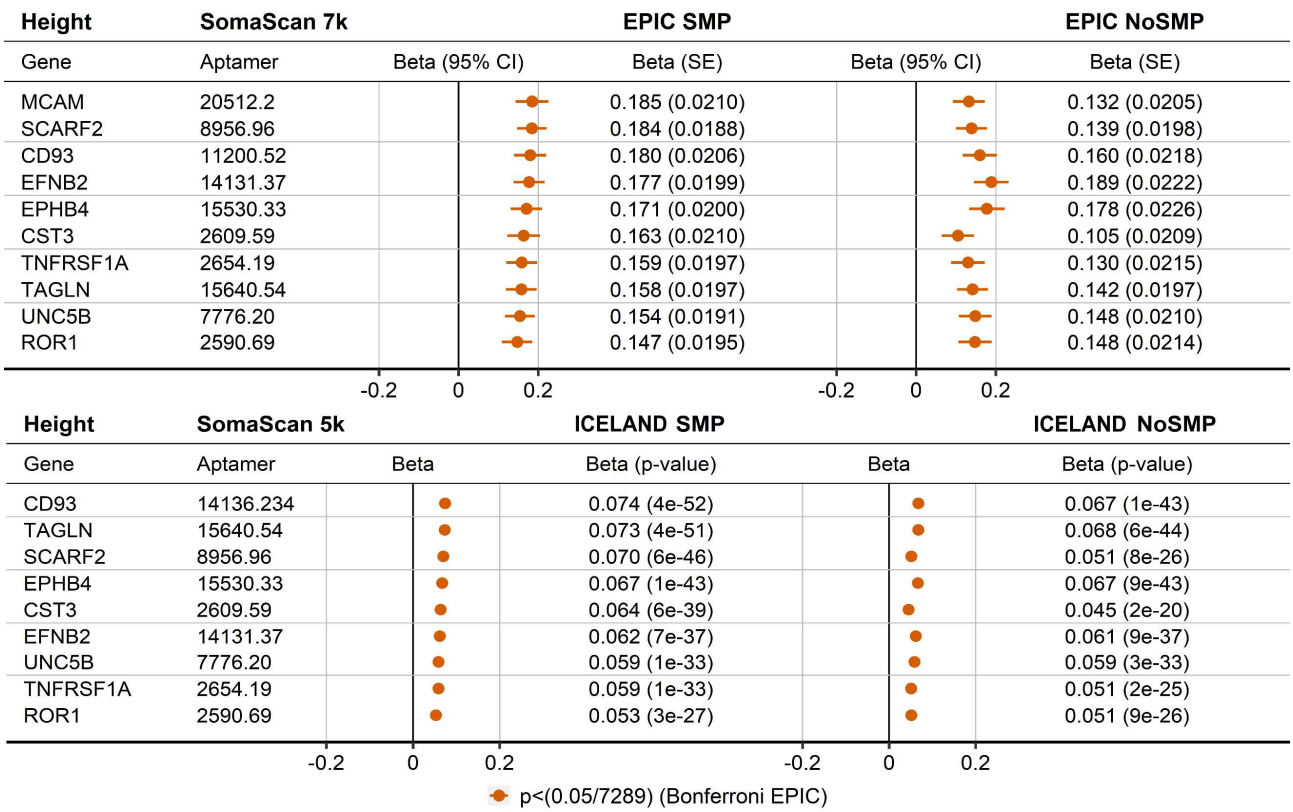
Index	NoSMP total		SMP total		NoSMP only	NoSMP & SMP	SMP only	r_{beta}
	nsig (neg−pos)	asig (neg−pos)	nsig (neg−pos)	asig (neg−pos)	asig (neg−pos)	asig (nn−pp−pn−np)	asig (neg−pos)	
BMI	4726 (316−4410)	4433 (253−4180)	4160 (2226−1934)	3341 (1736−1605)	1566 (0−1566)	2867 (253−1605−1009−0)	474 (474−0)	0.85
Weight	4717 (355−4362)	4438 (290−4148)	4184 (2150−2034)	3412 (1722−1690)	1490 (0−1490)	2948 (290−1690−968−0)	464 (464−0)	0.85
Height	797 (387−410)	503 (210−293)	825 (393−432)	756 (333−423)	48 (44−4)	455 (166−289−0−0)	301 (167−134)	−

asig − p<(0.05/7289) (Bonferroni) nsig − p<0.05 (nominal) ns − p≥0.05 (non-significant) equivalence line

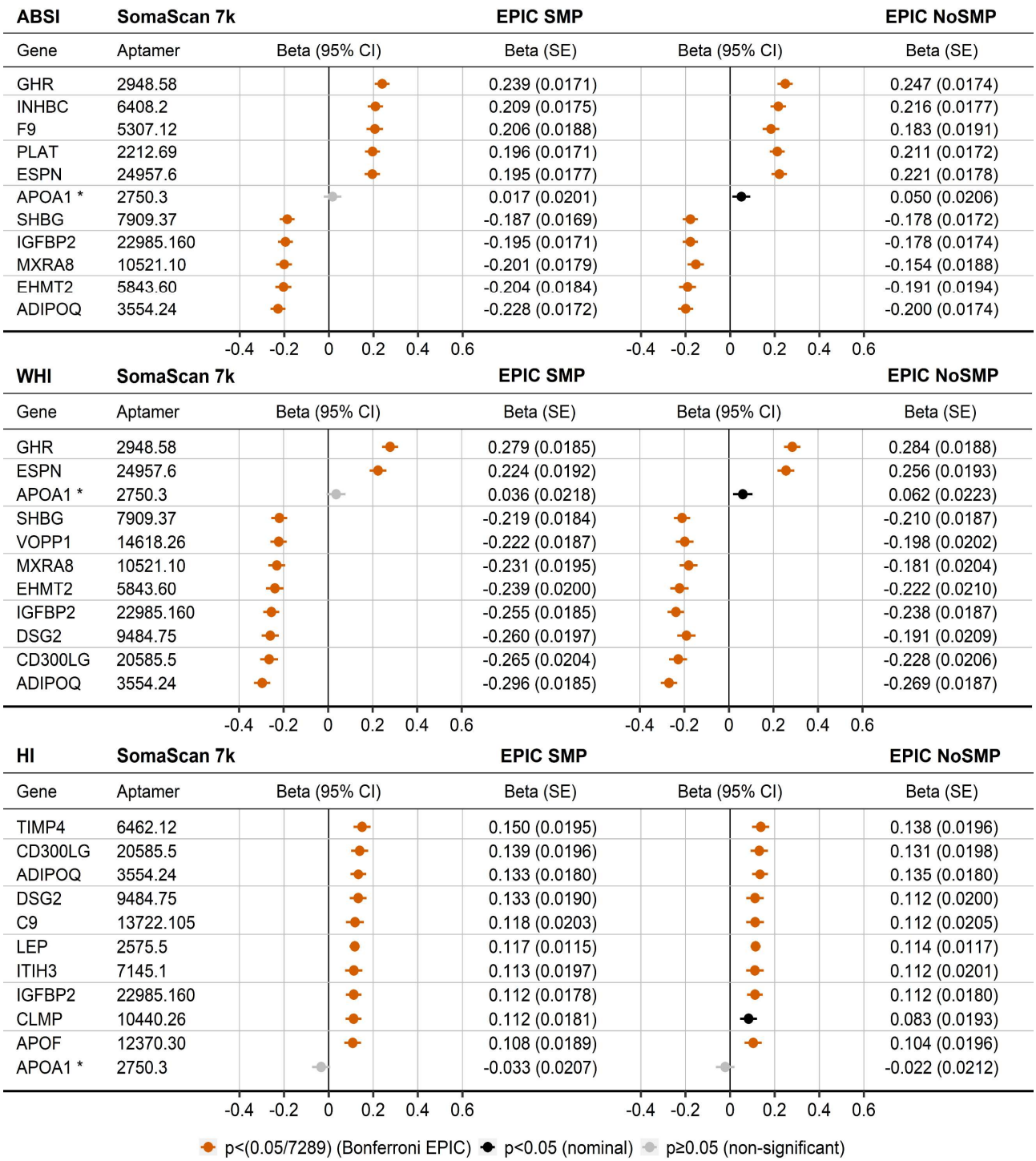
Supplementary Figure S13B SMP vs NoSMP normalisation − Icelanders (minimal adjustment)



Supplementary Figure S13C SMP vs NoSMP normalisation − top ten proteins for BMI



Supplementary Figure S13D SMP vs NoSMP normalisation − top ten proteins for height



Supplementary Figure S13E SMP vs NoSMP normalisation − top ten proteins for body shape

ABSI – a body shape index; **Beta** (B_{INDEX}) – proteomic regression coefficient; **BMI** – body mass index; **CI** – confidence interval; **HI** – hip index; r_{beta} – Spearman rank correlation coefficient between regression coefficients; **SE** – standard error; **SMP** – sample-based normalisation used in SomaScan pre-processing; **WHI** – waist-to-hip index.

Note – for consistency, the Bonferroni cut-off used to evaluate both studies corresponds to SomaScan v4.1 (7k) used in the current study (EPIC).

Association estimates were obtained from linear regression models examining each anthropometric index individually as exposure and each aptamer as outcome with full adjustment for the EPIC study and minimal adjustment for the study of Icelanders, as described below.

Supplementary Figure S13 SMP vs NoSMP comparisons *(legend continued)*

EPIC – 7289 aptamers from SomaScan v.4.1 (7k) examined in 4037 participants from the European Prospective Investigation into Cancer and nutrition cohort (current study). Regression models were adjusted for age, sex (in women also menopausal status and hormone replacement therapy use), smoking status, alcohol intake, physical activity, education, and study centre. Regression models for BMI were additionally adjusted for height. Regression models for ABSI, WHI, and HI were additionally adjusted for BMI and height.

ICELAND – previously reported associations for 4963 aptamers from SomaScan v.4.0 (5k) examined in Icelanders (28,256 participants for Mean BMI; 29,994 for Median weight; 36,500 for Max height) included in Supplementary Table S17 of reference [8]. Note that only regression coefficients with nominal significance ($p<0.05$) for NoSMP or SMP normalisation were available (4917 for BMI; 4908 for weight; 825 for height) and we defined the rest as zero regression coefficients (p-value=1).

neg−pos – number of aptamers with negative & positive associations at nominal (nsig) or Bonferroni significance level (asig).

Overlaps at Bonferroni significance level $p<(0.05/7289)\approx7*10^{-6}$:

nn – number of aptamers with negative associations for both NoSMP and SMP
pp – number of aptamers with positive associations for both NoSMP and SMP
pn – number of aptamers with positive association for NoSMP and negative for SMP
np – number of aptamers with negative association for NoSMP and positive for SMP

Correlation (NoSMP–SMP pairs):

$\mathbf{r_{beta}}$ – Spearman rank correlation coefficient between proteomic regression coefficients − note that, despite the reasonably strong proteomic correlation, the correspondence spindle for all anthropometric indices (except HI in EPIC and height in Icelanders) was distorted in the middle section.

ADIPOQ − Adiponectin; **APOA1** − Apolipoprotein A-I (*); **APOF** − Apolipoprotein F; **C9** − Complement component C9; **CD300LG** − CMRF35-like molecule 9; **CD93** − Complement component C1q receptor; **CLMP** − CXADR-like membrane protein:Extracellular domain; **CST3** − Cystatin-C; **EFNB2** − Ephrin-B2:Extracellular domain; **DSG2** − Desmoglein-2; **EHMT2** − Histone-lysine N-methyltransferase EHMT2; **ESPN** − Espin; **F9** − Coagulation factor IXab; **EPHB4** − Ephrin type-B receptor 4; **FABP3** − Fatty acid-binding protein, heart; **FABP4** − Fatty acid-binding protein, adipocyte; **GHR** − Growth hormone receptor; **GPD1** − Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic; **IGFBP2** − Insulin-like growth factor-binding protein 2; **INHBC** − Inhibin beta C chain; **ITIH3** − Inter-alpha-trypsin inhibitor heavy chain H3; **LEP** − Leptin; **MCAM** − Melanoma-associated antigen MUC18; **MXRA8** − Matrix-remodeling-associated protein 8:Extracellular domain; **PLAT** − Tissue-type plasminogen activator; **PPP1R1A** − Protein phosphatase 1 regulatory subunit 1A; **ROR1** − Inactive tyrosine-protein kinase transmembrane receptor ROR1; **SCARF2** − Scavenger receptor class F member 2:Extracellular domain; **SEZ6L** − Seizure 6-like protein; **SHBG** − Sex hormone-binding globulin; **TAGLN** − Transgelin; **TIMP4** − Metalloproteinase inhibitor 4; **TNFRSF1A** − Tumor necrosis factor receptor superfamily member 1A; **UNC5B** − Netrin receptor UNC5B; **VOPP1** − Vesicular, overexpressed in cancer, prosurvival protein 1.

***** APOA1 was included as an indicative protein because we have previously shown in the large UK Biobank cohort that it was associated inversely with BMI, ABSI, and WHI and positively with HI [77], which is achieved for the SomaScan assays only when SMP normalisation is used.

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