# SUPPLEMENTAL APPENDIX

## A targeted proteomics investigation of the obesity paradox in venous thromboembolism

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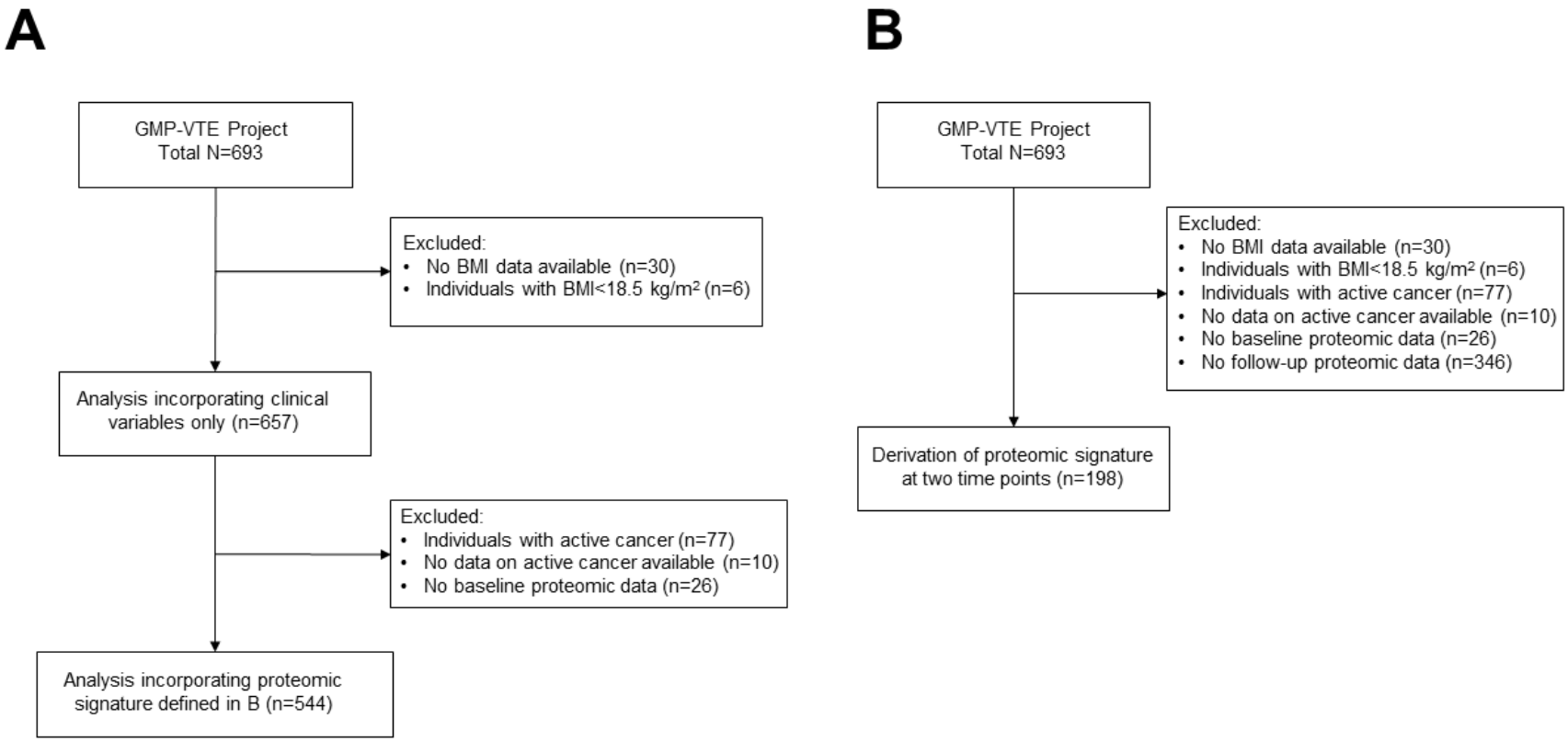
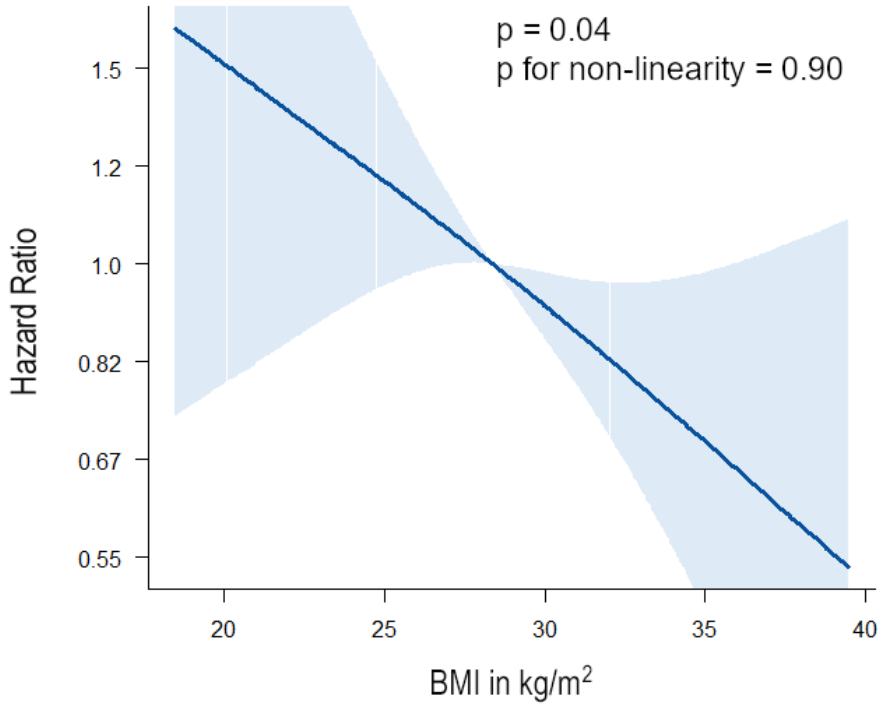
**Supplemental Figure 1.** Analysis flowchart




A: Overall analysis flowchart. B: Derivation of proteomic signature at two time points (baseline and 12 months follow-up).

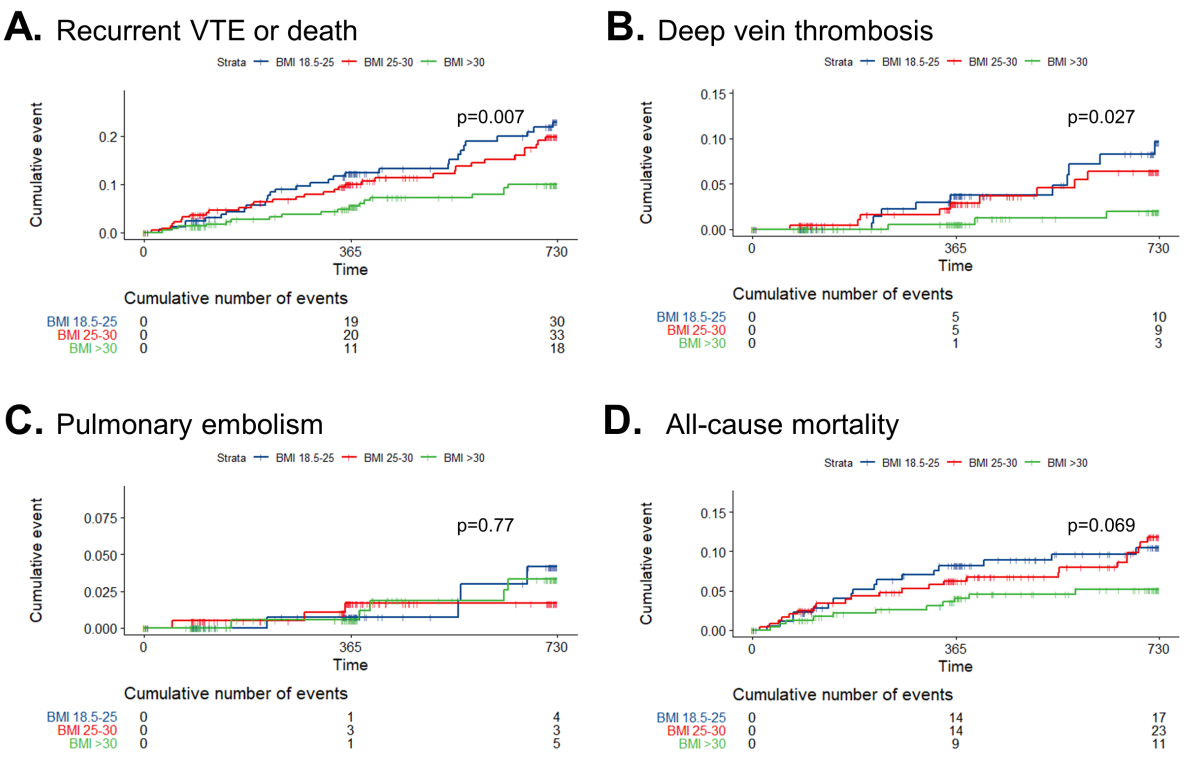
Abbreviations: BMI, body mass index.

**Supplemental Figure 2.** Shape of relationship body mass index and recurrent VTE or death




Hazard ratio by body mass index, as derived from a Cox proportional hazards regression model with recurrent VTE or death as the outcome variable. This figure depicts the hazard ratio by BMI, modeled with restricted cubic splines (3 degrees of freedom). The top p-value signifies the overall p-value for the relationship between BMI and the outcome. The p-value for non-linearity was based on a Wald $\chi^2$ 'chunk' test, using the anova.rms function from the R package 'rms'. The shaded blue region indicates the 95% confidence region. This figure shows that there is no evidence for non-linearity in the inverse relationship between BMI and recurrent VTE or death in this patient cohort. Abbreviations: BMI, body mass index.

**Supplemental Figure 3.** Relationship of weight classes with individual endpoints




This figure shows the cumulative incidence of the aggregate endpoint recurrent VTE or death (A) and the individual endpoints incident deep vein thrombosis (B), pulmonary embolism (C), and all-cause death (D). The p-values shown were calculated with the log-rank test.

**Supplemental Text:** Additional information regarding the regularized regression models

For the derivation of the proteomic signature, LASSO (L1)-regularized regression was used to identify proteins associated with body mass index at both plasma measurement time points (i.e., during the acute event and at 12 months post-index event), incorporating only individuals who had blood samples available at both time points. The model covariates included all 444 proteins as well as the adjustment covariates mentioned in the Methods section in the main manuscript. All variables were transformed using fractional polynomial transformations (^-2, ^-1, ^-0.5, ln, ^0.5, ^1, ^2, ^3) prior to inclusion in the model, and the best fitting transformation(s) was/were subsequently selected by the L1 regularization. A non-linearity penalty factor of 1.025 was used to reduce the unnecessary inclusion of weakly non-linear transformations.

The optimal regularization parameter λ was selected using 10-fold cross-validation, minimizing the mean squared error (MSE). The predictive robustness of selected variables was expressed in terms of the Lambda Ratio (LR), the ratio of the λ at which the coefficient for a given variable was shrunk to zero (i.e., omitted from the model) to the optimal cross-validated λ. For proteins selected in this manner to be part of the proteomic signature, the transformation associated with the highest lambda ratio was applied in subsequent analyses.

**Supplemental Table 1.** Protein names and abbreviations for all measured proteins (N=444)

| Abbreviation | Full name |
|---|---|
| **4E-BP1** | Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) |
| **ACE2** | Angiotensin-converting enzyme 2 (ACE2) |
| **ADA** | Adenosine Deaminase (ADA) |
| **ADAM-TS13** | A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAM-TS13) |
| **ADM** | ADM (ADM) |
| **AGRP** | Agouti-related protein (AGRP) |
| **ALCAM** | CD166 antigen (ALCAM) |
| **AMBP** | Protein AMBP (AMBP) |
| **ANG** | Angiogenin (ANG) |
| **ANG-1** | Angiopoietin-1 (ANG-1) |
| **ANGPTL3** | Angiopoietin-related protein 3 (ANGPTL3) |
| **AOC3** | Membrane primary amine oxidase (AOC3) |
| **AP-N** | Aminopeptidase N (AP-N) |
| **APOM** | Apolipoprotein M (APOM) |
| **AREG** | Amphiregulin AR (AREG) |
| **ARNT** | Aryl hydrocarbon receptor nuclear translocator (ARNT) |
| **ARTN** | Artemin (ARTN) |
| **AXIN1** | Axin-1 (AXIN1) |
| **AXL** | Tyrosine-protein kinase receptor UFO (AXL) |
| **AZU1** | Azurocidin (AZU1) |
| **BACH1** | Transcription regulator protein BACH1 (BACH1) |
| **Beta-NGF** | Beta-nerve growth factor (Beta-NGF) |
| **BIRC2** | Baculoviral IAP repeat-containing protein 2 (BIRC2) |
| **BLM hydrolase** | Bleomycin hydrolase (BLM hydrolase) |
| **BMP-6** | Bone morphogenetic protein 6 (BMP-6) |
| **BNP** | Natriuretic peptides B (BNP) |
| **BTN3A2** | Butyrophilin subfamily 3 member A2 (BTN3A2) |
| **C1QTNF1** | Complement C1q tumor necrosis factor-related protein 1 (C1QTNF1) |
| **C2** | Complement C2 (C2) |
| **CA1** | Carbonic anhydrase 1 (CA1) |
| **CA3** | Carbonic anhydrase 3 (CA3) |
| **CA4** | Carbonic anhydrase 4 (CA4) |
| **CA5A** | Carbonic anhydrase 5A, mitochondrial (CA5A) |
| **CASP-3** | Caspase-3 (CASP-3) |
| **CASP-8** | Caspase-8 (CASP-8) |
| **CCL11** | Eotaxin (CCL11) |
| **CCL14** | C-C motif chemokine 14 (CCL14) |
| **CCL15** | C-C motif chemokine 15 (CCL15) |
| **CCL16** | C-C motif chemokine 16 (CCL16) |

| Abbreviation | Full name |
|---|---|
| **CCL17** | C-C motif chemokine 17 (CCL17) |
| **CCL18** | C-C motif chemokine 18 (CCL18) |
| **CCL19** | C-C motif chemokine 19 (CCL19) |
| **CCL20** | C-C motif chemokine 20 (CCL20) |
| **CCL23** | C-C motif chemokine 23 (CCL23) |
| **CCL24** | C-C motif chemokine 24 (CCL24) |
| **CCL25** | C-C motif chemokine 25 (CCL25) |
| **CCL28** | C-C motif chemokine 28 (CCL28) |
| **CCL3** | C-C motif chemokine 3 (CCL3) |
| **CCL4** | C-C motif chemokine 4 (CCL4) |
| **CCL5** | C-C motif chemokine 5 (CCL5) |
| **CD163** | Scavenger receptor cysteine-rich type 1 protein M130 (CD163) |
| **CD244** | Natural killer cell receptor 2B4 (CD244) |
| **CD28** | T-cell-specific surface glycoprotein CD28 (CD28) |
| **CD4** | T-cell surface glycoprotein CD4 (CD4) |
| **CD40** | CD40L receptor (CD40) |
| **CD40-L** | CD40 ligand (CD40-L) |
| **CD46** | Membrane cofactor protein (CD46) |
| **CD5** | T-cell surface glycoprotein CD5 (CD5) |
| **CD59** | CD59 glycoprotein (CD59) |
| **CD6** | T-cell surface glycoprotein CD6 isoform (CD6) |
| **CD83** | CD83 antigen (CD83) |
| **CD84** | SLAM family member 5 (CD84) |
| **CD93** | Complement component C1q receptor (CD93) |
| **CDCP1** | CUB domain-containing protein 1 (CDCP1) |
| **CDH1** | Cadherin-1 (CDH1) |
| **CDH5** | Cadherin-5 (CDH5) |
| **CDSN** | Corneodesmosin (CDSN) |
| **CEACAM8** | Carcinoembryonic antigenrelated cell adhesion molecule 8 (CEACAM8) |
| **CES1** | Liver carboxylesterase 1 (CES1) |
| **CFHR5** | Complement factor H-related protein 5 (CFHR5) |
| **CHI3L1** | Chitinase-3-like protein 1 (CHI3L1) |
| **CHIT1** | Chitotriosidase-1 (CHIT1) |
| **CHL1** | Neural cell adhesion molecule L1-like protein (CHL1) |
| **CKAP4** | Cytoskeleton-associated protein 4 (CKAP4) |
| **CLEC4A** | C-type lectin domain family 4 member A (CLEC4A) |
| **CLEC4C** | C-type lectin domain family 4 member C (CLEC4C) |
| **CLEC4D** | C-type lectin domain family 4 member D (CLEC4D) |
| **CLEC4G** | C-type lectin domain family 4 member G (CLEC4G) |
| **CLEC6A** | C-type lectin domain family 6 member A (CLEC6A) |
| **CLEC7A** | C-type lectin domain family 7 member A (CLEC7A) |
| **CNDP1** | Beta-Ala-His dipeptidase (CNDP1) |
| **CNTN1** | Contactin-1 (CNTN1) |

| Abbreviation | Full name |
|---|---|
| **CNTNAP2** | Contactin-associated protein-like 2 (CNTNAP2) |
| **COL18A1** | Collagen alpha-1XVIII chain (COL18A1) |
| **COL1A1** | Collagen alpha-1I chain (COL1A1) |
| **COMP** | Cartilage oligomeric matrix protein (COMP) |
| **CPA1** | Carboxypeptidase A1 (CPA1) |
| **CPB1** | Carboxypeptidase B (CPB1) |
| **CR2** | Complement receptor type 2 (CR2) |
| **CRTAC1** | Cartilage acidic protein 1 (CRTAC1) |
| **CSF-1** | Macrophage colony-stimulating factor 1 (CSF-1) |
| **CST3** | Cystatin-C (CST3) |
| **CST5** | Cystatin D (CST5) |
| **CSTB** | Cystatin-B (CSTB) |
| **CTRC** | Chymotrypsin C (CTRC) |
| **CTSD** | Cathepsin D (CTSD) |
| **CTSL1** | Cathepsin L1 (CTSL1) |
| **CTSZ** | Cathepsin Z (CTSZ) |
| **CX3CL1** | Fractalkine (CX3CL1) |
| **CXADR** | Coxsackievirus and adenovirus receptor (CXADR) |
| **CXCL1** | C-X-C motif chemokine 1 (CXCL1) |
| **CXCL10** | C-X-C motif chemokine 10 (CXCL10) |
| **CXCL11** | C-X-C motif chemokine 11 (CXCL11) |
| **CXCL12** | Stromal cell-derived factor 1 (CXCL12) |
| **CXCL16** | C-X-C motif chemokine 16 (CXCL16) |
| **CXCL5** | C-X-C motif chemokine 5 (CXCL5) |
| **CXCL6** | C-X-C motif chemokine 6 (CXCL6) |
| **CXCL9** | C-X-C motif chemokine 9 (CXCL9) |
| **DAPP1** | Dual adapter for phosphotyrosine and 3-phosphotyrosine and 3-phosphoinositide (DAPP1) |
| **DCBLD2** | Discoidin, CUB and LCCL domain-containing protein 2 (DCBLD2) |
| **DCN** | Decorin (DCN) |
| **DCTN1** | Dynactin subunit 1 (DCTN1) |
| **DDX58** | Probable ATP-dependent RNA helicase DDX58 (DDX58) |
| **DECR1** | 2,4-dienoyl-CoA reductase, mitochondrial (DECR1) |
| **DEFA1** | Neutrophil defensin 1 (DEFA1) |
| **DFFA** | DNA fragmentation factor subunit alpha (DFFA) |
| **DGKZ** | Diacylglycerol kinase zeta (DGKZ) |
| **Dkk-1** | Dickkopf-related protein 1 (Dkk-1) |
| **DLK-1** | Protein delta homolog 1 (DLK-1) |
| **DNER** | Delta and Notch-like epidermal growth factor-related receptor (DNER) |
| **DPP10** | Inactive dipeptidyl peptidase 10 (DPP10) |
| **DPP4** | Dipeptidyl peptidase 4 (DPP4) |
| **EDAR** | Tumor necrosis factor receptor superfamily member EDAR (EDAR) |
| **EFEMP1** | EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1) |

| Abbreviation | Full name |
|---|---|
| **EGFR** | Epidermal growth factor receptor (EGFR) |
| **EGLN1** | Egl nine homolog 1 (EGLN1) |
| **EIF4G1** | Eukaryotic translation initiation factor 4 gamma 1 (EIF4G1) |
| **EIF5A** | Eukaryotic translation initiation factor 5A-1 (EIF5A) |
| **ENG** | Endoglin (ENG) |
| **EN-RAGE** | Protein S100-A12 (EN-RAGE) |
| **Ep-CAM** | Epithelial cell adhesion molecule (Ep-CAM) |
| **EPHB4** | Ephrin type-B receptor 4 (EPHB4) |
| **F11** | Coagulation factor XI (F11) |
| **F7** | Coagulation factor VII (F7) |
| **FABP2** | Fatty acid-binding protein, intestinal (FABP2) |
| **FABP4** | Fatty acid-binding protein, adipocyte (FABP4) |
| **FAM3B** | Protein FAM3B (FAM3B) |
| **FAP** | Prolyl endopeptidase FAP (FAP) |
| **FAS** | Tumor necrosis factor receptor superfamily member 6 (FAS) |
| **FCGR2A** | Low affinity immunoglobulin gamma Fc region receptor II-a (FCGR2A) |
| **FCGR3B** | Low affinity immunoglobulin gamma Fc region receptor III-B (FCGR3B) |
| **FCN2** | Ficolin-2 (FCN2) |
| **FCRL3** | Fc receptor-like protein 3 (FCRL3) |
| **FCRL6** | Fc receptor-like protein 6 (FCRL6) |
| **FETUB** | Fetuin-B (FETUB) |
| **FGF-19** | Fibroblast growth factor 19 (FGF-19) |
| **FGF2** | Fibroblast growth factor 2 (FGF2) |
| **FGF-21** | Fibroblast growth factor 21 (FGF-21) |
| **FGF-23** | Fibroblast growth factor 23 (FGF-23) |
| **FGF-5** | Fibroblast growth factor 5 (FGF-5) |
| **Flt3L** | Fms-related tyrosine kinase 3 ligand (Flt3L) |
| **FS** | Follistatin (FS) |
| **FXYD5** | FXYD domain-containing ion transport regulator 5 (FXYD5) |
| **Gal-3** | Galectin-3 (Gal-3) |
| **Gal-4** | Galectin-4 (Gal-4) |
| **Gal-9** | Galectin-9 (Gal-9) |
| **GALNT3** | Polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) |
| **GAS6** | Growth arrest-specific protein 6 (GAS6) |
| **GDF-15** | Growth/differentiation factor 15 (GDF-15) |
| **GDF-2** | Growth/differentiation factor 2 (GDF-2) |
| **GDNF** | Glial cell line-derived neurotrophic factor (GDNF) |
| **GH** | Growth hormone (GH) |
| **GIF** | Gastric intrinsic factor (GIF) |
| **GLB1** | Beta-galactosidase (GLB1) |
| **GLO1** | Lactoylglutathione lyase (GLO1) |
| **GNLY** | Granulysin (GNLY) |
| **GP1BA** | Platelet glycoprotein Ib alpha chain (GP1BA) |

| Abbreviation | Full name |
|---|---|
| **GRN** | Granulins (GRN) |
| **GT** | Gastrotropin (GT) |
| **HAOX1** | Hydroxyacid oxidase 1 (HAOX1) |
| **HB-EGF** | Proheparin-binding EGF-like growth factor (HB-EGF) |
| **HCLS1** | Hematopoietic lineage cell-specific protein (HCLS1) |
| **HEXIM1** | Protein HEXIM1 (HEXIM1) |
| **HGF** | Hepatocyte growth factor (HGF) |
| **HNMT** | Histamine N-methyltransferase (HNMT) |
| **HO-1** | Heme oxygenase 1 (HO-1) |
| **hOSCAR** | Osteoclast-associated immunoglobulin-like receptor (hOSCAR) |
| **HSD11B1** | Corticosteroid 11-beta-dehydrogenase isozyme 1 (HSD11B1) |
| **HSP 27** | Heat shock 27 kDa protein (HSP 27) |
| **ICA1** | Islet cell autoantigen 1 (ICA1) |
| **ICAM1** | Intercellular adhesion molecule 1 (ICAM1) |
| **ICAM-2** | Intercellular adhesion molecule 2 (ICAM-2) |
| **ICAM3** | Intercellular adhesion molecule 3 (ICAM3) |
| **IDUA** | Alpha-L-iduronidase (IDUA) |
| **IFN-gamma** | Interferon gamma (IFN-gamma) |
| **IFNLR1** | Interferon lambda receptor 1 (IFNLR1) |
| **IGFBP-1** | Insulin-like growth factor-binding protein 1 (IGFBP-1) |
| **IGFBP-2** | Insulin-like growth factor-binding protein 2 (IGFBP-2) |
| **IGFBP3** | Insulin-like growth factor-binding protein 3 (IGFBP3) |
| **IGFBP6** | Insulin-like growth factor-binding protein 6 (IGFBP6) |
| **IGFBP-7** | Insulin-like growth factor-binding protein 7 (IGFBP-7) |
| **IgG Fc receptor II-b** | Low affinity immunoglobulin gamma Fc region receptor II-b (IgG Fc receptor II-b) |
| **IGLC2** | Ig lambda-2 chain C regions (IGLC2) |
| **IL-1 alpha** | Interleukin-1 alpha (IL-1 alpha) |
| **IL10** | Interleukin-10 (IL10) |
| **IL-10RA** | Interleukin-10 receptor subunit alpha (IL-10RA) |
| **IL-10RB** | Interleukin-10 receptor subunit beta (IL-10RB) |
| **IL-12B** | Interleukin-12 subunit beta (IL-12B) |
| **IL12RB1** | Interleukin-12 receptor subunit beta-1 (IL12RB1) |
| **IL-13** | Interleukin-13 (IL-13) |
| **IL-15RA** | Interleukin-15 receptor subunit alpha (IL-15RA) |
| **IL16** | Pro-interleukin-16 (IL16) |
| **IL-17A** | Interleukin-17A (IL-17A) |
| **IL-17C** | Interleukin-17C (IL-17C) |
| **IL-17D** | Interleukin-17D (IL-17D) |
| **IL-17RA** | Interleukin-17 receptor A (IL-17RA) |
| **IL-18** | Interleukin-18 (IL-18) |
| **IL-18BP** | Interleukin-18-binding protein (IL-18BP) |
| **IL-18R1** | Interleukin-18 receptor 1 (IL-18R1) |

| Abbreviation | Full name |
|---|---|
| **IL-1ra** | Interleukin-1 receptor antagonist protein (IL-1ra) |
| **IL1RL2** | Interleukin-1 receptor-like 2 (IL1RL2) |
| **IL-1RT1** | Interleukin-1 receptor type 1 (IL-1RT1) |
| **IL-1RT2** | Interleukin-1 receptor type 2 (IL-1RT2) |
| **IL-2** | Interleukin-2 (IL-2) |
| **IL-20** | Interleukin-20 (IL-20) |
| **IL-20RA** | Interleukin-20 receptor subunit alpha (IL-20RA) |
| **IL-22 RA1** | Interleukin-22 receptor subunit alpha-1 (IL-22 RA1) |
| **IL-24** | Interleukin-24 (IL-24) |
| **IL-27** | Interleukin-27 (IL-27) |
| **IL2-RA** | Interleukin-2 receptor subunit alpha (IL2-RA) |
| **IL-2RB** | Interleukin-2 receptor subunit beta (IL-2RB) |
| **IL-33** | Interleukin-33 (IL-33) |
| **IL-4** | Interleukin-4 (IL-4) |
| **IL-4RA** | Interleukin-4 receptor subunit alpha (IL-4RA) |
| **IL5** | Interleukin-5 (IL5) |
| **IL6** | Interleukin-6 (IL6) |
| **IL-6RA** | Interleukin-6 receptor subunit alpha (IL-6RA) |
| **IL-7** | Interleukin-7 (IL-7) |
| **IL7R** | Interleukin-7 receptor subunit alpha (IL7R) |
| **IL-8** | Interleukin-8 (IL-8) |
| **IRAK1** | Interleukin-1 receptor-associated kinase 1 (IRAK1) |
| **IRAK4** | Interleukin-1 receptor-associated kinase 4 (IRAK4) |
| **IRF9** | Interferon regulatory factor 9 (IRF9) |
| **ITGA11** | Integrin alpha-11 (ITGA11) |
| **ITGA6** | Integrin alpha-6 (ITGA6) |
| **ITGAM** | Integrin alpha-M (ITGAM) |
| **ITGB1BP2** | Melusin (ITGB1BP2) |
| **ITGB2** | Integrin beta-2 (ITGB2) |
| **ITGB6** | Integrin beta-6 (ITGB6) |
| **ITM2A** | Integral membrane protein 2A (ITM2A) |
| **JAM-A** | Junctional adhesion molecule A (JAM-A) |
| **JUN** | Transcription factor AP-1 (JUN) |
| **KIM1** | Kidney Injury Molecule (KIM1) |
| **KIT** | Mast/stem cell growth factor receptor Kit (KIT) |
| **KLK6** | Kallikrein-6 (KLK6) |
| **KLRD1** | Natural killer cells antigen CD94 (KLRD1) |
| **KPNA1** | Importin subunit alpha-5 (KPNA1) |
| **KRT19** | Keratin, type I cytoskeletal 19 (KRT19) |
| **LAG3** | Lymphocyte activation gene 3 protein (LAG3) |
| **LAMP3** | Lysosome-associated membrane glycoprotein 3 (LAMP3) |
| **LAP TGF-beta-1** | Latency-associated peptide transforming growth factor beta-1 (LAP TGF-beta-1) |

| Abbreviation | Full name |
|---|---|
| **LCN2** | Neutrophil gelatinase-associated lipocalin (LCN2) |
| **LDL receptor** | Low-density lipoprotein receptor (LDL receptor) |
| **LEP** | Leptin (LEP) |
| **LIF** | Leukemia inhibitory factor (LIF) |
| **LIF-R** | Leukemia inhibitory factor receptor (LIF-R) |
| **LILRB1** | Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1) |
| **LILRB2** | Leukocyte immunoglobulin-like receptor subfamily B member 2 (LILRB2) |
| **LILRB4** | Leukocyte immunoglobulin-like receptor subfamily B member 4 (LILRB4) |
| **LILRB5** | Leukocyte immunoglobulin-like receptor subfamily B member 5 (LILRB5) |
| **LOX-1** | Lectin-like oxidized LDL receptor 1 (LOX-1) |
| **LPL** | Lipoproteine lipase (LPL) |
| **LTBP2** | Latent-transforming growth factor beta-binding protein 2 (LTBP2) |
| **LTBR** | Lymphotoxin-beta receptor (LTBR) |
| **LY75** | Lymphocyte antigen 75 (LY75) |
| **LYVE1** | Lymphatic vessel endothelial hyaluronic acid receptor 1 (LYVE1) |
| **MARCO** | Macrophage receptor MARCO (MARCO) |
| **MASP1** | Mannan-binding lectin serine protease 1 (MASP1) |
| **MB** | Myoglobin (MB) |
| **MBL2** | Mannose-binding protein C (MBL2) |
| **MCP-1** | Monocyte chemotactic protein 1 (MCP-1) |
| **MCP-2** | Monocyte chemotactic protein 2 (MCP-2) |
| **MCP-3** | Monocyte chemotactic protein 3 (MCP-3) |
| **MCP-4** | Monocyte chemotactic protein 4 (MCP-4) |
| **MEGF9** | Multiple epidermal growth factor-like domains protein 9 (MEGF9) |
| **MEPE** | Matrix extracellular phosphoglycoprotein (MEPE) |
| **MERTK** | Tyrosine-protein kinase Mer (MERTK) |
| **MET** | Hepatocyte growth factor receptor (MET) |
| **MFAP5** | Microfibrillar-associated protein 5 (MFAP5) |
| **MGMT** | Methylated-DNA--protein-cysteine methyltransferase (MGMT) |
| **MILR1** | Allergin-1 (MILR1) |
| **MMP-1** | Matrix metalloproteinase-1 (MMP-1) |
| **MMP-10** | Matrix metalloproteinase-10 (MMP-10) |
| **MMP-12** | Matrix metalloproteinase-12 (MMP-12) |
| **MMP-2** | Matrix metalloproteinase-2 (MMP-2) |
| **MMP-3** | Matrix metalloproteinase-3 (MMP-3) |
| **MMP-7** | Matrix metalloproteinase-7 (MMP-7) |
| **MMP-9** | Matrix metalloproteinase-9 (MMP-9) |
| **MPO** | Myeloperoxidase (MPO) |
| **NCAM1** | Neural cell adhesion molecule 1 (NCAM1) |
| **NCR1** | Natural cytotoxicity triggering receptor 1 (NCR1) |

| Abbreviation | Full name |
|---|---|
| **NEMO** | NF-kappa-B essential modulator (NEMO) |
| **NF2** | Merlin (NF2) |
| **NFATC3** | Nuclear factor of activated T-cells, cytoplasmic 3 (NFATC3) |
| **NID1** | Nidogen-1 (NID1) |
| **Notch 3** | Neurogenic locus notch homolog protein 3 (Notch 3) |
| **NOTCH1** | Neurogenic locus notch homolog protein 1 (NOTCH1) |
| **NRP1** | Neuropilin-1 (NRP1) |
| **NRTN** | Neurturin (NRTN) |
| **NT-3** | Neurotrophin-3 (NT-3) |
| **NTF4** | Neurotrophin-4 (NTF4) |
| **NT-proBNP** | N-terminal prohormone brain natriuretic peptide (NT-proBNP) |
| **OPG** | Osteoprotegerin (OPG) |
| **OPN** | Osteopontin (OPN) |
| **OSM** | Oncostatin-M (OSM) |
| **OSMR** | Oncostatin-M-specific receptor subunit beta (OSMR) |
| **PADI2** | Protein-arginine deiminase type-2 (PADI2) |
| **PAI** | Plasminogen activator inhibitor 1 (PAI) |
| **PAM** | Peptidyl-glycine alpha-amidating monooxygenase (PAM) |
| **PAPPA** | Pappalysin-1 (PAPPA) |
| **PAR-1** | Proteinase-activated receptor 1 (PAR-1) |
| **PARP-1** | Poly [ADP-ribose] polymerase 1 (PARP-1) |
| **PCOLCE** | Procollagen C-endopeptidase enhancer 1 (PCOLCE) |
| **PCSK9** | Proprotein convertase subtilisin/kexin type 9 (PCSK9) |
| **PDGF subunit A** | Platelet-derived growth factor subunit A (PDGF subunit A) |
| **PDGF subunit B** | Platelet-derived growth factor subunit B (PDGF subunit B) |
| **PD-L1** | Programmed cell death 1 ligand 1 (PD-L1) |
| **PD-L2** | Programmed cell death 1 ligand 2 (PD-L2) |
| **PECAM-1** | Platelet endothelial cell adhesion molecule (PECAM-1) |
| **PGF** | Placenta growth factor (PGF) |
| **PGLYRP1** | Peptidoglycan recognition protein 1 (PGLYRP1) |
| **PI3** | Elafin (PI3) |
| **PIgR** | Polymeric immunoglobulin receptor (PIgR) |
| **PIK3AP1** | Phosphoinositide 3-kinase adapter protein 1 (PIK3AP1) |
| **PLA2G7** | Platelet-activating factor acetylhydrolase (PLA2G7) |
| **PLC** | Perlecan (PLC) |
| **PLTP** | Phospholipid transfer protein (PLTP) |
| **PLXNA4** | Plexin-A4 (PLXNA4) |
| **PLXNB2** | Plexin-B2 (PLXNB2) |
| **PON3** | Paraoxonase (PON3) |
| **PPP1R9B** | Neurabin-2 (PPP1R9B) |
| **PRCP** | Lysosomal Pro-X carboxypeptidase (PRCP) |
| **PRDX1** | Peroxiredoxin-1 (PRDX1) |
| **PRDX3** | Thioredoxin-dependent peroxide reductase, mitochondrial (PRDX3) |

| Abbreviation | Full name |
|---|---|
| **PRDX5** | Peroxiredoxin-5, mitochondrial (PRDX5) |
| **PRELP** | Prolargin (PRELP) |
| **PRKCQ** | Protein kinase C theta type (PRKCQ) |
| **PROC** | Vitamin K-dependent protein C (PROC) |
| **Protein BOC** | Brother of CDO (Protein BOC) |
| **PRSS2** | Trypsin-2 (PRSS2) |
| **PRSS27** | Serine protease 27 (PRSS27) |
| **PRSS8** | Prostasin (PRSS8 ) |
| **PRTN3** | Myeloblastin (PRTN3) |
| **PSGL-1** | P-selectin glycoprotein ligand 1 (PSGL-1) |
| **PSIP1** | PC4 and SFRS1-interacting protein (PSIP1) |
| **PSP-D** | Pulmonary surfactant-associated protein D (PSP-D) |
| **PTH1R** | Parathyroid hormone/parathyroid hormone-related peptide receptor (PTH1R) |
| **PTPRS** | Receptor-type tyrosine-protein phosphatase S (PTPRS) |
| **PTX3** | Pentraxin-related protein PTX3 (PTX3) |
| **QPCT** | Glutaminyl-peptide cyclotransferase (QPCT) |
| **RAGE** | Receptor for advanced glycosylation end products (RAGE) |
| **RARRES2** | Retinoic acid receptor responder protein 2 (RARRES2) |
| **REG1A** | Lithostathine-1-alpha (REG1A) |
| **REG3A** | Regenerating islet-derived protein 3-alpha (REG3A) |
| **REN** | Renin (REN) |
| **RETN** | Resistin (RETN) |
| **SAA4** | Serum amyloid A-4 protein (SAA4) |
| **SCF** | Stem cell factor (SCF) |
| **SCGB3A2** | Secretoglobin family 3A member 2 (SCGB3A2) |
| **SELE** | E-selectin (SELE) |
| **SELL** | L-selectin (SELL) |
| **SELP** | P-selectin (SELP) |
| **SERPINA12** | Serpin A12 (SERPINA12) |
| **SERPINA5** | Plasma serine protease inhibitor (SERPINA5) |
| **SERPINA7** | Thyroxine-binding globulin (SERPINA7) |
| **SH2B3** | SH2B adapter protein 3 (SH2B3) |
| **SH2D1A** | SH2 domain-containing protein 1A (SH2D1A) |
| **SHPS-1** | Tyrosine-protein phosphatase non-receptor type substrate 1 (SHPS-1) |
| **SIRT2** | SIR2-like protein 2 (SIRT2) |
| **SIT1** | Signaling threshold-regulating transmembrane adapter 1 (SIT1) |
| **SLAMF1** | Signaling lymphocytic activation molecule (SLAMF1) |
| **SLAMF7** | SLAM family member 7 (SLAMF7) |
| **SOD1** | Superoxide dismutase [Cu-Zn] (SOD1) |
| **SOD2** | Superoxide dismutase [Mn], mitochondrial (SOD2) |
| **SORT1** | Sortilin (SORT1) |
| **SPARCL1** | SPARC-like protein 1 (SPARCL1) |

| Abbreviation | Full name |
|---|---|
| **SPON1** | Spondin-1 (SPON1) |
| **SPON2** | Spondin-2 (SPON2) |
| **SPRY2** | Protein sprouty homolog 2 (SPRY2) |
| **SRC** | Proto-oncogene tyrosine-protein kinase Src (SRC) |
| **SRPK2** | SRSF protein kinase 2 (SRPK2) |
| **ST1A1** | Sulfotransferase 1A1 (ST1A1) |
| **ST2** | ST2 protein (ST2) |
| **ST6GAL1** | Beta-galactoside alpha-2,6-sialyltransferase 1 (ST6GAL1) |
| **STAMBP** | STAM-binding protein (STAMBP) |
| **STC1** | Stanniocalcin-1 (STC1) |
| **STK4** | Serine/threonine-protein kinase 4 (STK4) |
| **TANK** | TRAF family member-associated NF-kappa-B activator (TANK) |
| **TCN2** | Transcobalamin-2 (TCN2) |
| **TF** | Tissue factor (TF) |
| **TFF3** | Trefoil factor 3 (TFF3) |
| **TFPI** | Tissue factor pathway inhibitor (TFPI) |
| **TGF-alpha** | Transforming growth factor alpha (TGF-alpha) |
| **TGFBI** | Transforming growth factor-beta-induced protein ig-h3 (TGFBI) |
| **TGFBR3** | Transforming growth factor beta receptor type 3 (TGFBR3) |
| **TGM2** | Protein-glutamine gamma-glutamyltransferase 2 (TGM2) |
| **THBS2** | Thrombospondin-2 (THBS2) |
| **THBS4** | Thrombospondin-4 (THBS4) |
| **THPO** | Thrombopoietin (THPO) |
| **TIE1** | Tyrosine-protein kinase receptor Tie-1 (TIE1) |
| **TIE2** | Angiopoietin-1 receptor (TIE2) |
| **TIMD4** | T-cell immunoglobulin and mucin domain-containing protein 4 (TIMD4) |
| **TIMP1** | Metalloproteinase inhibitor 1 (TIMP1) |
| **TIMP4** | Metalloproteinase inhibitor 4 (TIMP4) |
| **TLT-2** | Trem-like transcript 2 protein (TLT-2) |
| **TM** | Thrombomodulin (TM) |
| **TNC** | Tenascin (TNC) |
| **TNF** | Tumor necrosis factor alpha (TNF) |
| **TNFB** | TNF-beta (TNFB) |
| **TNF-R1** | Tumor necrosis factor receptor 1 (TNF-R1) |
| **TNF-R2** | Tumor necrosis factor receptor 2 (TNF-R2) |
| **TNFRSF10A** | Tumor necrosis factor receptor superfamily member 10A (TNFRSF10A) |
| **TNFRSF10C** | Tumor necrosis factor receptor superfamily member 10C (TNFRSF10C) |
| **TNFRSF11A** | Tumor necrosis factor receptor superfamily member 11A (TNFRSF11A) |
| **TNFRSF13B** | Tumor necrosis factor receptor superfamily member 13B (TNFRSF13B) |
| **TNFRSF14** | Tumor necrosis factor receptor superfamily member 14 (TNFRSF14) |
| **TNFRSF9** | Tumor necrosis factor receptor superfamily member 9 (TNFRSF9) |
| **TNFSF13B** | Tumor necrosis factor ligand superfamily member 13B (TNFSF13B) |
| **TNFSF14** | Tumor necrosis factor ligand superfamily member 14 (TNFSF14) |

| Abbreviation | Full name |
|---|---|
| **TNXB** | Tenascin-X (TNXB) |
| **t-PA** | Tissue-type plasminogen activator (t-PA) |
| **TPSAB1** | Tryptase alpha/beta-1 (TPSAB1) |
| **TR** | Transferrin receptor protein 1 (TR) |
| **TRAF2** | TNF receptor-associated factor 2 (TRAF2) |
| **TRAIL** | TNF-related apoptosis-inducing ligand (TRAIL) |
| **TRAIL-R2** | TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) |
| **TRANCE** | TNF-related activation-induced cytokine (TRANCE) |
| **TR-AP** | Tartrate-resistant acid phosphatase type 5 (TR-AP) |
| **TREM1** | Triggering receptor expressed on myeloid cells 1 (TREM1) |
| **TRIM21** | E3 ubiquitin-protein ligase TRIM21 (TRIM21) |
| **TRIM5** | Tripartite motif-containing protein 5 (TRIM5) |
| **TSLP** | Thymic stromal lymphopoietin (TSLP) |
| **TWEAK** | Tumor necrosis factor Ligand superfamily, member 12 (TWEAK) |
| **UMOD** | Uromodulin (UMOD) |
| **uPA** | Urokinase-type plasminogen activator (uPA) |
| **U-PAR** | Urokinase plasminogen activator surface receptor (U-PAR) |
| **VASN** | Vasorin (VASN) |
| **VCAM1** | Vascular cell adhesion protein 1 (VCAM1) |
| **VEGF-A** | Vascular endothelial growth factor A (VEGF-A) |
| **VEGFD** | Vascular endothelial growth factor D (VEGFD) |
| **VSIG2** | V-set and immunoglobulin domain-containing protein 2 (VSIG2) |
| **vWF** | von Willebrand factor (vWF) |
| **XCL1** | Lymphotactin (XCL1) |
| **ZBTB16** | Zinc finger and BTB domain-containing protein 16 (ZBTB16) |

| | Normal weight (n=181) | Overweight (n=239) | Obese (n=237) |
|---|---|---|---|
| *Medication intake* | | | |
| Cardiovascular medication (C), % (n) | 57.9 (95) | 69.8 (148) | 73.2 (153) |
| Antithrombotic medication (B01), % (n) | 91.5 (150) | 95.3 (202) | 92.8 (194) |
| Vitamin K antagonists (B01AA), % (n) | 4.3 (7) | 8.5 (18) | 6.2 (13) |
| Heparin group (B01AB), % (n) | 60.4 (99) | 70.8 (150) | 61.7 (129) |
| Antiplatelet agents (B01AC), % (n) | 25.6 (42) | 27.4 (58) | 32.1 (67) |
| Enzymes (B01AD), % (n) | 0 (0) | 1.4 (3) | 1 (2) |
| Direct thrombin inhibitors (B01AE), % (n) | 0.6 (1) | 2.4 (5) | 1.9 (4) |
| Direct factor Xa inhibitors (B01AF), % (n) | 26.8 (44) | 22.2 (47) | 27.8 (58) |
| Other anticoagulants (B01AX), % (n) | 2.4 (4) | 1.4 (3) | 1.4 (3) |
| NSAIDs (M01), % (n) | 5.5 (9) | 4.7 (10) | 5.2 (12) |
| Corticosteroids (H02), % (n) | 6.1 (10) | 14.2 (30) | 5.3 (11) |
| Contraceptives (G03), % (n) | 7.9 (13) | 3.3 (7) | 3.3 (7) |

Normal weight was defined as body mass index (BMI) between 18.5 and 25 $kg/m^2$; overweight as BMI equal to or greater than 25 and below 30 $kg/m^2$, and obese as BMI of 30 $kg/m^2$ or greater. Anatomical Therapeutic Chemical (ATC) codes are given behind each medication class in parentheses.

**Supplemental Table 3.** Robustness of the obesity paradox against adjustment by potential clinical confounders

| | Age and sex-adjusted | Additionally adjusted for clinical profile | Additionally adjusted for medication |
|---|---|---|---|
| Obesity (BMI ≥ 30), Hazard ratio [95% CI] | 0.46 [0.28-0.79] | 0.51 [0.30-0.90] | 0.54 [0.31-0.94] |
| BMI per 5-point increment, Hazard ratio [95% CI] | 0.77 [0.62-0.95] | 0.79 [0.63-0.99] | 0.80 [0.63-1.02] |

The above hazard ratios were computed with Cox proportional hazards regression models predicting recurrent VTE or death as the outcome. The clinical profile was defined as presence of cardiovascular disease (any of: atrial fibrillation, coronary artery disease, peripheral artery disease, congestive heart failure, history of stroke), history of VTE, active cancer, active smoking, diabetes, and/or arterial hypertension. Medication was defined as baseline intake of antithrombotics, cardiovascular medication, oral contraceptives, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

Abbreviations: BMI, body mass index; CI, confidence interval.

**Supplemental Table 4.** Proteomic analysis: baseline LASSO regression model

| **Model information** | |
|---|---|
| Type of model | LASSO-regularized linear regression with fractional polynomial terms |
| Dependent variable | BMI |
| Covariates | Age, sex, smoking status (yes/no), history of VTE, cardiovascular disease, D-dimer, C-reactive protein, cardiovascular medication, antithrombotic therapy, NSAID therapy, corticosteroid therapy, contraceptive therapy, all 444 proteins |
| $R^2$ | 0.77 |
| 10-fold cross-validation $R^2$ | 0.33 |
| Optimal λ | 0.07 |
| Non-linear term penalty | 1.025 |
| Sample size | 198 |
| Number of selected variables | 69 |
| Number of selected unique proteins | 64 |

| **Variable** | Transformation | Sign of coefficient | Effect direction | Lambda Ratio |
|---|---|---|---|---|
| **LEP** | ^1 | + | ↑ | 9.18 |
| **MASP1** | ^3 | + | ↑ | 4.88 |
| **PAPPA** | ^1 | + | ↑ | 4.43 |
| **SCGB3A2** | ^1 | - | ↓ | 4.29 |
| **MCP3** | ^3 | + | ↑ | 4.19 |
| **Age** | ^3 | - | ↓ | 3.65 |
| **STC1** | ^3 | + | ↑ | 3.54 |
| **FGF21** | ^3 | + | ↑ | 3.50 |
| **AMBP** | ^-2 | + | ↓ | 3.46 |
| **TNXB** | ^3 | + | ↑ | 3.46 |
| **VEGFD** | ^1 | - | ↓ | 3.39 |
| **IGFBP2** | ^1 | - | ↓ | 3.32 |
| **THBS2** | ^1 | + | ↑ | 3.28 |
| **PAPPA** | ^-1 | - | ↑ | 2.81 |
| **FGF23** | ^3 | + | ↑ | 2.76 |
| **IL2** | ^1 | + | ↑ | 2.73 |

| | | | | |
|---|---|---|---|---|
| **FABP4** | ^3 | + | ↑ | 2.68 |
| **D-dimer** | ^-2 | - | ↑ | 2.57 |
| **Age** | ^2 | - | ↓ | 2.57 |
| **DDX58** | ^-2 | - | ↑ | 2.53 |
| **PARP1** | ^3 | + | ↑ | 2.51 |
| **IL17C** | ^1 | + | ↑ | 2.39 |
| **IL27** | ^-2 | + | ↓ | 2.16 |
| **ITGAM** | ^-0.5 | - | ↑ | 2.11 |
| **ST2** | ^3 | + | ↑ | 2.08 |
| **CLEC4C** | ^2 | + | ↑ | 2.07 |
| **TRIM21** | ^-2 | - | ↑ | 2.02 |
| **NRP1** | ^-2 | - | ↑ | 1.97 |
| **PRDX1** | Log | + | ↑ | 1.85 |
| **C-reactive protein** | ^3 | + | ↑ | 1.72 |
| **LAMP3** | ^3 | - | ↓ | 1.72 |
| **IGFBP2** | ^-2 | + | ↓ | 1.70 |
| **IGFBP7** | ^3 | + | ↑ | 1.69 |
| **TRANCE** | Log | + | ↑ | 1.68 |
| **TSLP** | ^-2 | - | ↑ | 1.65 |
| **STK4** | ^-2 | - | ↑ | 1.64 |
| **BMP6** | ^1 | + | ↑ | 1.61 |
| **FLT3L** | ^1 | - | ↓ | 1.60 |
| **CNTNAP** | ^3 | - | ↓ | 1.56 |
| **VSIG2** | ^-2 | - | ↑ | 1.51 |
| **KPNA1** | ^-2 | + | ↓ | 1.49 |
| **CA5A** | ^3 | + | ↑ | 1.49 |
| **LEP** | ^3 | + | ↑ | 1.44 |
| **TRAF2** | ^-2 | - | ↑ | 1.43 |
| **LY75** | ^1 | + | ↑ | 1.42 |
| **TNFRSF10C** | ^1 | + | ↑ | 1.42 |
| **THPO** | ^0.5 | - | ↓ | 1.40 |

| | | | | |
|---|---|---|---|---|
| **SLAMF1** | ^0.5 | + | ↑ | 1.39 |
| **PLXNA4** | ^-2 | - | ↑ | 1.37 |
| **TCN2** | ^1 | - | ↓ | 1.37 |
| **CTSL1** | ^1 | - | ↓ | 1.35 |
| **IL20RA** | log | - | ↓ | 1.34 |
| **LTBP2** | ^-2 | + | ↓ | 1.32 |
| **PRSS27** | ^3 | - | ↓ | 1.32 |
| **EpCAM** | ^-2 | + | ↓ | 1.32 |
| **VSIG2** | ^-1 | - | ↑ | 1.32 |
| **THBS4** | ^1 | + | ↑ | 1.27 |
| **IL33** | ^3 | - | ↓ | 1.27 |
| **IL17C** | ^3 | + | ↑ | 1.27 |
| **IL17D** | ^-2 | - | ↑ | 1.23 |
| **ARNT** | ^1 | + | ↑ | 1.22 |
| **Contraceptives** | ^1 | - | ↓ | 1.20 |
| **IL4** | ^1 | + | ↑ | 1.19 |
| **CD163** | ^1 | + | ↑ | 1.18 |
| **ITGAM** | log | + | ↑ | 1.16 |
| **FGF23** | ^1 | + | ↑ | 1.11 |
| **CXCL5** | ^3 | - | ↓ | 1.11 |
| **GDNF** | ^1 | - | ↓ | 1.11 |
| **TPSAB1** | ^-2 | - | ↑ | 1.10 |
| **PCSK9** | ^1 | - | ↓ | 1.09 |
| **ENRAGE** | ^1 | - | ↓ | 1.09 |
| **Smoking status** | ^1 | + | ↑ | 1.08 |
| **GP1BA** | ^-2 | + | ↓ | 1.07 |
| **PTH1R** | ^-0.5 | - | ↑ | 1.02 |
| **NTF4** | ^-2 | - | ↑ | 1.02 |
| **CKAP4** | ^-2 | - | ↑ | 1.00 |
| **LYVE1** | ^1 | + | ↑ | 1.00 |

Note: transformations and coefficient signs should be interpreted in conjunction to obtain the final effect direction. For instance, a negative transformation with a negative coefficient yields a positive effect.

**Supplemental Table 5.** Proteomic analysis: 12-month follow-up LASSO regression model

| **Model information** | |
|---|---|
| Type of model | LASSO-regularized linear regression with fractional polynomial terms |
| Dependent variable | BMI |
| Covariates | Age, sex, smoking status (yes/no), history of VTE, cardiovascular disease, D-dimer, C-reactive protein, cardiovascular medication, antithrombotic therapy, NSAID therapy, corticosteroid therapy, contraceptive therapy, all 444 proteins |
| $R^2$ | 0.61 |
| 10-fold cross-validation $R^2$ | 0.24 |
| Optimal λ | 0.11 |
| Non-linear term penalty | 1.025 |
| Sample size | 198 |
| Number of selected variables | 39 |
| Number of selected unique proteins | 38 |

| **Variable** | **Transformation** | **Sign of coefficient** | **Effect direction** | **Lambda Ratio** |
|---|---|---|---|---|
| **LEP** | ^2 | + | ↑ | 5.43 |
| **FABP4** | ^-2 | - | ↓ | 3.59 |
| **PON3** | ^3 | - | ↓ | 3.52 |
| **SIT1** | ^1 | + | ↑ | 2.85 |
| **FGF19** | ^-2 | + | ↓ | 2.74 |
| **CDH5** | ^1 | + | ↑ | 2.63 |
| **ST2** | ^1 | + | ↑ | 2.51 |
| **THBS2** | ^1 | + | ↑ | 2.35 |
| **IL20** | ^-0.5 | - | ↑ | 2.24 |
| **RAGE** | ^-2 | + | ↓ | 2.15 |
| **Age** | ^3 | - | ↓ | 2.14 |
| **LEP** | ^3 | + | ↑ | 1.90 |
| **CR2** | ^1 | + | ↑ | 1.88 |
| **PADI2** | ^3 | + | ↑ | 1.85 |

| | | | | |
|---|---|---|---|---|
| **Flt3L** | ^3 | - | ↓ | 1.81 |
| **LYVE1** | ^3 | + | ↑ | 1.70 |
| **PRSS2** | ^-2 | + | ↓ | 1.62 |
| **KLK6** | ^-2 | + | ↓ | 1.60 |
| **CXCL9** | ^1 | - | ↓ | 1.59 |
| **FS** | ^-2 | - | ↑ | 1.58 |
| **DAPP1** | ^-0.5 | + | ↓ | 1.58 |
| **IGFBP3** | ^1 | - | ↓ | 1.54 |
| **THBS4** | ^3 | + | ↑ | 1.54 |
| **GH** | ^3 | - | ↓ | 1.51 |
| **CLEC4G** | ^3 | + | ↑ | 1.49 |
| **TIMD4** | ^1 | + | ↑ | 1.39 |
| **PCOLCE** | ^-2 | + | ↓ | 1.36 |
| **TSLP** | ^3 | + | ↑ | 1.28 |
| **CCL23** | ^1 | - | ↓ | 1.25 |
| **DNER** | ^-2 | + | ↓ | 1.22 |
| **CLEC4C** | ^0.5 | + | ↑ | 1.18 |
| **BLM hydrolase** | ^3 | - | ↓ | 1.13 |
| **APOM** | ^-2 | + | ↓ | 1.10 |
| **AZU1** | ^-0.5 | - | ↑ | 1.10 |
| **TR** | ^3 | + | ↑ | 1.09 |
| **DLK1** | ^1 | - | ↓ | 1.05 |
| **MASP1** | ^3 | + | ↑ | 1.04 |
| **IL17C** | ^1 | + | ↑ | 1.04 |
| **CA1** | ^-2 | + | ↓ | 1.03 |
| **TIMD4** | ^3 | + | ↑ | 1.00 |
| **CXCL12** | log | - | ↓ | 1.00 |

**Supplemental Table 6.** Inclusion of the body mass-related proteomic signature does not significantly alter the estimate for obesity in relation to recurrent VTE or death

| | Hazard ratio [95% CI] | p |
|---|---|---|
| Obesity (BMI ≥ 30), adjusted for clinical profile | 0.39 [0.18-0.85] | 0.02 |
| Obesity (BMI ≥ 30), adjusted for clinical profile and the proteomic signature | 0.43 [0.20-0.92] | 0.03 |
| *Model comparison* | $\chi^2$ (df) | p |
| Likelihood Ratio (LR) test | 7.7 (11) | 0.74 |

The above results are from two (nested) Cox regression models, predicting the outcome variable 'recurrent VTE or death'. The clinical profile was defined as presence of cardiovascular disease (any of: atrial fibrillation, coronary artery disease, peripheral artery disease, congestive heart failure, history of stroke), history of VTE, active smoking, diabetes, and/or arterial hypertension, as well as baseline intake of antithrombotics, cardiovascular medication, oral contraceptives, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. The proteomic signature incorporated CLEC4C, C-type lectin domain family 4 member C; FABP4, Fatty acid-binding protein; Flt3L, Fms-related tyrosine kinase 3 ligand; IL-17C, Interleukin-17C; LEP, leptin; LYVE1, Lymphatic vessel endothelial hyaluronic acid receptor 1; MASP1, Mannan-binding lectin serine protease 1; ST2, ST2 protein; THBS2, Thrombospondin-2; THBS4, Thrombospondin-4; TSLP, Thymic stromal lymphopoietin. The Likelihood Ratio (LR) test indicates that the model including the proteomic signature does not significantly improve the fit compared to the model containing only clinical variables, while the lack of change in estimate for obesity upon inclusion of this signature indicates that these proteins do not mediate its protective effect against recurrent VTE or death.

Abbreviations: BMI, body mass index; CI, confidence interval; df, degrees of freedom.

**Supplemental Table 7.** Mouse/human interspecies protein sequence similarity: leptin and MMP-2

*UniProt Accession numbers*

| | Leptin | MMP-2 |
|---|---|---|
| Human | P41159 | P08253 |
| Mouse | P41160 | P33434 |

*EMBOSS Stretcher settings and results*

| | Leptin | MMP-2 |
|---|---|---|
| Gap penalty | 3 | 3 |
| Extend penalty | 3 | 3 |
| Align format | pair | pair |
| Length | 167 | 662 |
| Identity | 139/167 (83.2%) | 633/662 (95.6%) |
| Similarity | 152/167 (91%) | 645/662 (97.4%) |
| Gaps | 0/167 (0%) | 2/662 (0.3%) |
| Score | 704 | 3528 |

Protein sequences for leptin and MMP-2, for humans and mice, were taken from UniProt (http://uniprot.org) and aligned with EMBOSS Stretcher (http://www.ebi.ac.uk/Tools/psa/emboss_stretcher/). Abbreviations: MMP-2, matrix metalloproteinase.

**Supplemental Table 8.** Interaction model: high leptin concentrations and body mass index

*Interaction with high body mass index (BMI > 28.4)*

| | β-estimate [95% CI] | Hazard ratio [95% CI] | p |
|---|---|---|---|
| High leptin | -1.41 [-2.60, -0.22] | 0.24 [0.07, 0.80] | 0.02 |
| High BMI | -1.37 [-2.20, -0.54] | 0.25 [0.11, 0.58] | 0.001 |
| High leptin × high BMI | 2.14 [0.60, 3.69] | 8.54 [1.82, 40.16] | 0.007 |

*Interaction with low body mass index (BMI ≤ 28.4)*

| | β-estimate [95% CI] | Hazard ratio [95% CI] | p |
|---|---|---|---|
| High leptin | 0.74 [-0.25, 1.72] | 2.09 [0.78, 5.61] | 0.14 |
| Low BMI | 1.37 [0.54, 2.20] | 3.95 [1.72, 9.06] | 0.001 |
| High leptin × low BMI | -2.14 [-3.69, -0.60] | 0.12 [0.02, 0.55] | 0.007 |

The above two tables show the results of two identical Cox regression models, with the reference category for the BMI category (high/low) alternated to show the effect of high leptin in both conditions. High leptin was defined as a leptin concentration in the top tertile. High BMI was defined as a BMI above the median BMI of 28.4, and low BMI as a BMI equal to or below the median BMI. The main effect of high leptin in the presence of the interaction term signifies the BMI-adjusted effect of high leptin, given that the BMI condition is opposite to the one shown. In other words, these models show that high leptin is protective only when the BMI is below or equal to 28.4. Abbreviations: BMI, body mass index; CI, confidence interval.

**Supplemental Table 9.** Interaction model: high leptin concentrations and MMP-2

*Interaction with high (above median) MMP-2 concentrations*

| | β-estimate [95% CI] | Hazard ratio [95% CI] | p |
|---|---|---|---|
| High leptin | -2.34 [-4.36, -0.33] | 0.10 [0.01, 0.72] | 0.02 |
| High MMP-2 | -0.04 [-0.70, 0.62] | 0.96 [0.49, 1.86] | 0.90 |
| High leptin × high MMP-2 | 2.66 [0.50, 4.81] | 14.23 [1.65, 122.37] | 0.02 |

*Interaction with low (equal to or below median) MMP-2 concentrations*

| | β-estimate [95% CI] | Hazard ratio [95% CI] | p |
|---|---|---|---|
| High leptin | 0.31 [-0.44, 1.06] | 1.37 [0.65, 2.89] | 0.42 |
| Low MMP-2 | 0.04 [-0.62, 0.70] | 1.04 [0.54, 2.02] | 0.90 |
| High leptin × low MMP-2 | -2.66 [-4.81, -0.50] | 0.07 [0.01, 0.60] | 0.02 |

The above two tables show the results of two identical Cox regression models, with the reference category for the BMI category (high/low) alternated to show the effect of high leptin in both conditions. High leptin was defined as a leptin concentration in the top tertile. High MMP-2 was defined as a MMP-2 concentration above the median concentration, and low MMP-2 as a MMP-2 concentration below or equal to the median concentration. Abbreviations: CI, confidence interval; MMP-2, matrix metalloproteinase 2. The main effect of high leptin in the presence of the interaction term signifies the MMP-2-adjusted effect of high leptin, given that the MMP-2 condition is opposite to the one listed. In other words, these models show that high leptin is protective only when the MMP-2 concentration is below or equal to the median MMP-2 concentration.