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**Supplementary information**

# Blood-based obesity biomarkers and their relevance for disease risk

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# **Blood-based obesity biomarkers and their relevance for disease risk**

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**Supplementary Table 1:** Summary on the evidence of traditional obesity biomarkers regarding their association with obesity in observational and Mendelian Randomisation studies

| Biomarker | Obesity | | | Weight loss | |
|---|---|---|---|---|---|
| | Obs. Cross-sect. | MR Obesity on biomarker | MR Biomarker on obesity | Lifestyle intervention | Bariatric surgery |
| Adiponectin | ↓[1] | ↔[2] | ↔[2] | ↔[3] | **↑**[4] |
| Leptin | ↑[1] | **↑**[5] | **↑**[6] | **↓**[3] | **↓**[4] |
| FABP-4 | ↑[7,8] | **↑**[9] | **↑**[6] | NA | ↓[10] |
| Omentin | **↓**[11] | NA | NA | ↑[12,13] | ↑[14] |
| Chemerin | **↑**[15] | NA | NA | ↓[16-18] | ↓[16,17,19] |
| Visfatin | ↑[20] | NA | NA | ↔[21] | ↔[4] |
| Resistin | ↔[22] | ↔[6] | ↔[6] | ↔[21] | ↔[4] |
| TNF | ↑[1] | NA | NA | ↔[23] | **↓**[24] |
| IL-6 | ↑[1] | **↑**[25] | ↔[6] | **↓**[23] | **↓**[24] |
| Oestradiol | **↑**(w)[26]<br>↔(m)[27] | **↑**(m)[28] | ↔(m)[28] | ↓(w)[29] | **↓**[30] |
| Testosterone | **↑**(w)[26]<br>**↓**(m)[27] | **↓**(m)[28] | ↔(m)[28] | ↓(w)[29] | **↑**(m)[30]<br>**↓**(w)[30] |

**↑↓** Evidence from meta-analysis or MR

↑↓ Evidence from individual studies

↔ No statistically significant association

*Adjustment for body adiposity not reported in[26,31-33].

m, men; MR, Mendelian Randomisation; w, women; prosp., prospective associations/studies

NA, no corresponding meta-analysis or MR was identified

**Supplementary Box 1: Abbreviations of proteins used in Table 2**

ADA, Adenosine deaminase; ADM, Adrenomedullin; AXIN-1, Axis inhibition protein 1; CCL20, C-C motif chemokine 20; CCL23, C-C motif chemokine ligand 23; CCL28, C-C motif chemokine ligand 28; CC-L3, C-C motif chemokine 3; CFAB, complement factor B; CFAH, complement factor H; CFAI, complement factor I; CRP, C-reactive protein; CSF-1, Macrophage colony-stimulating factor 1; CSF-1, Macrophage colony-stimulating factor 1; CST5, Cystatin-D; CST6, Cystatin-M; CSTB, Cystatin-B; CTSD, Cathepsin D; CXCL-1, Fractalkine; CXL9, C-X-C motif chemokine ligand 9; DKK3, Dickkopf-related protein 3; DNER, Delta and notch-like epidermal growth factor-related Receptor; ESM1, Endothelial cell-specific molecule 1; FABP4, fatty acid binding protein 4; FAS, Tumor necrosis factor receptor superfamily member 6; FGF19, Fibroblast growth factor 19; GAL, Galanin peptides; GDF-15, Growth/differentiation factor 15; GDF2, Growth/differentiation factor 2; GDNF, Glial cell line-derived neurotrophic factor; GHR, Growth hormone receptor; HGF, Hepatocyte growth factor; hK11, Kallikrein-11; IGFBP2, insulin-like growth factor-binding protein 2; IL-12B, Interleukin-12 subunit β; IL-16, Pro-interleukin-16; IL-1ra, Interleukin-1 receptor antagonist protein; IL-6, Interleukin-6; IL-8, Interleukin-8; JAG1, Protein jagged-1; KIM-1, Kidney injury molecule 1; KLK-6, Kallikrein-6; LEP, leptin; IGFBP1, insulin-like growth factor-binding protein 1; LGALS3BP, Galectin-3-binding protein; MB, Myoglobin; MET, Hepatocyte growth factor receptor; MMP10, Matrix metalloproteinase-10 (stromelysin-2); MPO, Myeloperoxidase; NCAM1, Neural cell adhesion molecule 1, 120 kDa isoform, 4498-62_2; NOTCH1, Neurogenic locus notch homolog protein 1; NT 3, Neurotrophin-3; OPG, TNF ligand superfamily member 11; PDL1, Programmed cell death 1 ligand 1; PGF, Placenta growth factor; PRAP, proline-rich acidic protein I; PSGL-1, P-selectin glycoprotein ligand 1; RAGE, Receptor for advanced glycosylation end products; REN, Renin; S10A8, protein S100-A8; S10A9, S100-A9; SCF, Stem cell factor; ; SELE, E-selectin; SERPINC1, Antithrombin-III; SERPINE1, Plasminogen activator inhibitor 1; SHBG, sex-hormone binding globuline; TNF-R1, Tumor necrosis factor receptor 1; TNF-R2, Tumor necrosis factor receptor 2; TNFSF14, Tumor necrosis factor ligand superfamily member 14; t-PA, Tissue-type plasminogen activator; TRAIL, TNF-related apoptosis-inducing ligand; TRANCE, TNF ligand superfamily member 11; TWEAK, TNF ligand superfamily member 12; UNC5D, Netrin receptor UNC5D; U-PAR, Urokinase plasminogen activator surface receptor; VEGF-A, Vascular endothelial growth factor A; VEGF-D, Vascular endothelial growth factor Dh; WFIKKN2, WAP, Kazal, immunoglobulin, Kunitz, and NTR domain-containing protein 2;

**Supplementary Box 2: Footnotes describing the individual associations shown in Table 3**

[a] In observational studies, BCAA were not significantly related to colorectal cancer[34,35] but with a reduced risk of gastric cancer[36]. In MR studies, some BCAA were related to a higher risk of lung cancer[37] but no association of BCAA was found for liver cancer[38].

[b] In some observational studies, tyrosine was related to a higher risk of liver cancer[39], valine to prostate cancer[40], glutamic acid to pancreatic cancer[41], lysine to breast cancer[42], alanine to prostate cancer[43], pyruvate to colorectal cancer[44], and higher glycine related to lower risk of endometrial cancer[45]

[c] In observational studies, higher blood cysteine concentrations were related to a higher risk of breast cancer[46] but to a lower risk of colorectal cancer[47]. Cysteine was not significantly related to CVD risk[48].

[d] In observational studies, triglyceride concentrations were positively related to cancer risk at some sites, such as colorectal cancer[49-51], but results vary for other sites, with studies reporting inverse associations with liver cancer[52] and breast cancer[53,54] and no association with gastric cancer[55]. A systematic review on Mendelian Randomisation studies found an inverse association for breast cancer[56].

[e] In observational studies, HDL cholesterol levels were inversely related to cancer risk at some sites, such as colorectal cancer[49-51,57], liver cancer[52], gastric cancer[55], and, albeit less consistently, with breast cancer[53,54]. Mendelian Randomisation studies found no evidence for HDL cholesterol with regard to colorectal cancer[58] but an inverse association for total cancer risk[56], and a positive association for breast cancer[56].

[f] The diagnosis of diabetes mellitus is based on elevated glucose concentrations.

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