

**Supplementary Table 1:** Human studies investigating the association of irisin with obesity, insulin resistance, diabetes mellitus and metabolic syndrome

| Study             | Study groups                          | Study Type | Subject of study | Irisin levels associated with |              |          | N          | Irisin levels also associated with  |
|-------------------|---------------------------------------|------------|------------------|-------------------------------|--------------|----------|------------|---|
|                   |                                       |            |                  | Obesity (BMI)                 | IR (HOMA-IR) | Diabetes |            |   |
| Schlogl (1)       | Healthy                               | CS         | Nutrition        | NR                            | NR           | NR       | 66         | Higher ad libitum 24 h energy intake associated with lower fasting irisin concentrations the following morning.<br>Fasting irisin concentrations not related to subsequent energy intake. |
| Ko (2)            | Healthy                               | CS         | Nutrition        | NR                            | NR           | NR       | 185        | Fruit consumption (positive)/ Meat consumption (negative)   |
| Anastasilakis (3) | Healthy                               | CS         | Nutrition        | No                            | No           | NR       | 36         | No association with standardized meal, caloric intake or diet quality   |
| Loffler (4)       | Children and young adults             | CS         | Nutrition        | positive                      | NR           | NR       | 189        | No changes after meal or OGTT<br>Fat free mass, muscle mass and WHR (positive)  |
| Pekkala (5)       | Healthy                               | CS         | Exercise         | NR                            | NR           | NR       | 56         | No association with glucose tolerance   |
| Crujeiras (6)     | Obese following diet vs normal weight | PC         | Obesity          | positive                      | NR           | NR       | 142        | Waist circumference, fat mass (positive)<br>Reduction in irisin levels after weight loss<br>Return to baseline irisin after regaining the lost weight                                     |
| Huh (7)           | Healthy vs obese                      | CS         | Obesity          | positive                      | NR           | NR       | 29/<br>117 | Muscle mass, glucose, ghrelin, IGF1 (positive)<br>Age, insulin, cholesterol, adiponectin (negative)<br>Irisin levels were reduced 6 months after bariatric surgery                        |
| Stengel (8)       | Anorectic vs normal vs obese          | CC         | Obesity          | positive                      | NR           | NR       | 40         | Fat mass, body cell mass, fat free mass, insulin (positive)   |
| Pardo (9)         | Anorexic vs                           | CC         | Obesity          | positive                      | positive     | NR       | 145        | Irisin higher in obese vs anorexic or normal weight   |

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|                       | normal vs obese                                   |     |                               |                 |                             |    |     | Fat mass, resting energy expenditure (positive)  |
| Gutierrez-Repiso (10) | Morbidly obese vs nonobese                        | CC  | Obesity                       | <b>positive</b> | NR                          | NR | 45  | % change in waist to hip ratio after bariatric surgery (positive)  |
| Huerta (11)           | Overweight/obese women                            | RCT | Obesity                       | <b>positive</b> | <b>positive</b>             | NR | 73  | Glucose, insulin (positive).<br>No change in irisin levels during OGTT<br>Irisin reduction after weight loss   |
| Li M (12)             | PCOS vs healthy                                   | CS  | PCOS                          | <b>positive</b> | <b>positive</b>             | NR | 301 | WHR, % FAT, TG, TC, LDLC, AUC Insulin, free androgen index (FAI) (positive)  |
| Pukajlo (13)          | PCOS vs healthy                                   | CC  | PCOS                          | NR              | NR                          | NR | 301 | MetS in PCOS and in controls, body fat (positive)  |
| Bostanci (14)         | PCOS vs. matched healthy                          | CC  | PCOS                          | <b>positive</b> | NR                          | NR | 70  | Higher in PCOS women compared to controls<br>Fasting insulin, total cholesterol (positive)   |
| Bluher (15)           | Obese Children                                    | PC  | Obesity                       | NR              | NR                          | NR | 65  | Irisin increase after one year physical activity and diet  |
| Polyzos (16)          | NAFL,NASH, obese, lean                            | CC  | Obesity<br>Liver              | <b>negative</b> | <b>No</b>                   | NR | 68  | Lower irisin in obese, or with NASH/NAFLD vs lean<br>No correlation with cardiometabolic risk factors  |
| Choi (17)             | NAFLD vs healthy                                  | CC  | Obesity<br>Liver              | <b>No</b>       | <b>positive</b>             | NR | 355 | Higher irisin levels in NAFLD compared with healthy<br>No association with obesity   |
| Huth (18)             | Healthy trained /untrained, obese, obese with IGT | CC  | Obesity<br>insulin resistance | <b>positive</b> | <b>positive (M/I index)</b> | NR | 53  | Fat mass (positive)<br>Muscle citrate synthase, fitness (negative)   |
| Crujeiras (19)        | Obese after 8 week diet                           | PC  | Insulin resistance            | NR              | <b>positive</b>             | NR | 136 | Irisin levels paralleled body weight reduction after the dietary treatment (week 8) and returned to the baseline levels at 24 weeks in patients regaining the lost weight. |
| Sesti (20)            | White   | CS  | Insulin                       | <b>positive</b> | <b>positive</b>             | NR | 192 | Fasting and 2h post-load insulin (positive)  |

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|                    | nondiabetic adults                              |    | resistance          | <b>Fat mass</b> | <b>Matsuda index</b>                         |                 |      | Intima media thickness (positive)<br>Insulin stimulated glucose disposal, Matsuda index, insulin clearance (negative)   |
| Reinehr (21)       | Obese, normal weight children                   | PC | Insulin resistance  | <b>No</b>       | <b>positive</b>                              | NR              | 60   | Irisin in obese/IFG > as in obese/NGT or normal weight<br>HDL, fasting glucose, 2h Glucose in OGTT (positive)   |
| Chen (22)          | Healthy, obese, obese with acanthosis nigricans | CC | Insulin resistance  | <b>positive</b> | <b>(positive)<br/>Higher fasting insulin</b> | NR              | 80   | Higher irisin in obese with acanthosis nigricans vs obese without acanthosis nigricans or healthy   |
| Qiu (23)           | Nondiabetic adults                              | MA | Insulin resistance  | NR              | <b>positive</b>                              | NR              | 1912 | The positive association between irisin and insulin resistance was small, but independent of BMI  |
| Norheim (24)       | Prediabetic vs healthy                          | PC | Obesity prediabetes | NR              | NR   | <b>positive</b> | 26   | Higher irisin level in prediabetes vs normal controls<br>No association of irisin with chronic exercise   |
| Sanchis-Gomar (25) | T2DM vs obese vs healthy                        | CS | Obesity prediabetes | <b>No</b>       | NR   | NR              | 153  | Similar irisin levels between morbidly obese patients with atherogenic dyslipidemia vs without, as well as between obese diabetic patients vs nonobese diabetics.<br>Urea, insulin in the nonobese diabetic group (negative)<br>Homocystein, HbA1c in obese diabetic (negative) |
| Kurdiova (25)      | T2DM, IGT, overweight/obese, healthy            | CS | prediabetes T2DM    | <b>No</b>       | <b>No Euglycemic hyperinsuline mic clamp</b> | <b>negative</b> | 99   | Lower irisin levels in T2DM subjects vs lean controls<br>Waist circumference, fasting glucose, AUC glycemic curve, visceral obesity (negative)  |
| Assyov (26)        | NGT, prediabetes, T2DM                          | CC | prediabetes T2DM    | <b>positive</b> | NR   | <b>negative</b> | 160  | Lower irisin levels in T2DM < Prediabetes < NGT<br>Fasting glucose, ALT, AST, GGT (negative)  |

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| Duran (27)     | T2DM vs IFG vs IGT vs NGT   | CS | prediabetes T2DM          | <b>negative</b>       | NR              | <b>negative</b> | 263 | Lower irisin in IFG, IGT or T2DM subjects vs NGT HDLC (positive) / postprandial glucose, LDLC, triglyceride (negative)   |
| Liu (28)       | T2DM vs nondiabetic controls  | CS | T2DM                      | <b>positive NonDM</b> | NR              | <b>negative</b> | 156 | No association with metabolic phenotype in T2DM Total cholesterol, triglycerides, fasting glucose, diastolic pressure in nondiabetic controls (positive)                       |
| Yang (29)      | Healthy without T2DM but with 1 <sup>st</sup> degree relat. with T2DM | CS | T2DM                      | <b>No</b>             | <b>No</b>       | <b>No</b>       | 122 | No association with metabolic parameters in T2DM group HbA1c, eGFR, HOMA $\beta$ in NGT (positive)   |
| Xiang (30)     | Newly diagnos. T2DM, healthy  | CS | T2DM                      | NR                    | NR              | <b>negative</b> | 222 | Flow mediated dilatation( positive)  |
| Zhang (31)     | T2DM with vs without MVD vs healthy                                   | CS | T2DM                      | NR                    | NR              | <b>negative</b> | 94  | Irisin levels in T2DM with MVD < T2DM without MVD < healthy controls   |
| Wang (32)      | NGT vs T2DM   | CS | T2DM                      | NR                    | <b>negative</b> | <b>negative</b> | 140 | No association with beta cell function related variables   |
| Choi (33)      | NGT vs new onset T2DM   | CS | T2DM                      | NR                    | NR              | <b>negative</b> | 208 | Reduced odds of newly diagnosed T2DM (positive) 2 h plasma glucose (negative)  |
| Al-Daghri (34) | T2DM vs controls  | CS | T2DM                      | NR                    | NR              | <b>positive</b> | 164 | Frequency intensity time index (only in control group) (positive) DBP (overall), lean body mass (T2DM group) (negative)  |
| Hu (35)        | T2DM with/ without retinopathy  | CC | T2DM diabetic retinopathy | NR                    | <b>negative</b> | <b>negative</b> | 240 | Lower irisin levels in T2DM group compared with control Fasting glucose, blood urea nitrogen, creatinine, age (negative) Creatinine clearance, ACE/ATII blocker use (positive) |

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| Liu (36)            | T2DM with wide range of renal function                            | CS  | T2DM nephropathy | <b>positive</b> | NR                | NR              | 365  | Higher irisin levels in T2DM with chronic kidney disease compared to T2DM without CKD.<br>Fat mass, % fat mass, eGFR (positive)<br>Age, pulse pressure (in T2DM patients with normal renal function) (negative) |
| Wang (37)           | T2DM vs healthy controls  | CS  | T2DM nephropathy | NR              | NR                | <b>negative</b> | 200  | Irisin in T2DM macroalbuminuria < microalbuminuria < normoalbuminuria.<br>2h blood glucose, urinary albumin excretion (negative)<br>Flow mediated dilation (positive)   |
| Zhang (38)          | Meta-Analysis   | MA  | T2DM             | NR              | NR                | <b>negative</b> | 1110 | Lower irisin levels in T2DM compared to healthy   |
| Espes (39)          | T1DM, healthy   | CS  | T1DM             | NR              | NR                | NR              | 70   | Higher in T1DM compared to healthy controls   |
| Lopez-Legarrea (40) | Excessive obese with MetS after diet                              | RCT | Obesity MetS     | <b>positive</b> | <b>(positive)</b> | NR              | 96   | Fat mass, carbohydrate intake (positive) / Circulating glucose (negative)<br>Higher irisin associated with greater reduction on glucose, insulin, HOMA-IR, triglycerides after diet.                            |
| Park (41)           | Caucasian, African Americans without history of MI, stroke, or DM | CS  | MetS             | <b>positive</b> | <b>positive</b>   |                 | 151  | Increased risk of MetS (positive)<br>Fasting blood glucose, high triglycerides, low HDL, SBP, DBP (positive)<br>Adiponectin (negative)  |
| Moreno (42)         | Active vs sedentary   | CC  | MetS             | <b>positive</b> | <b>positive</b>   | NR              | 428  | Fasting insulin, fasting triglycerides in sedentary individuals (positive)  |
| Hwang (43)          | Seoul Metro City Diabetes   | CS  | MetS             | <b>negative</b> | <b>negative</b>   | <b>negative</b> | 424  | Favorable metabolic income: less obese, lower blood pressure and glucose (positive)   |

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|                    | Prevention Pr.  |          |               |    |          |    |      | Skeletal muscle mass (positive)   |
| Yan (44)           | Chinese with central obesity                                      | CS       | MetS          | No | No       | NR | 1115 | Reduced risk of metabolic syndrome, glucose (positive)<br>Fasting insulin, HbA1c, albumin/globulin ratio (negative)<br>No associations with blood pressure, triglycerides, HDL                          |
| Hirsch (45)        | Prader Willi vs healthy BMI matched                               | CC       | MetS          | NR | negative | NR | 51   | Salivary irisin was higher in Prader-Willi syndrome<br>Total cholesterol, LDL-Cholesterol, leptin, triglycerides in PWS (positive)<br>HDL-Cholesterol in Prader-Willi Syndrome (negative)               |
| Huh (46)           | MetS vs healthy   | PC       | MetS exercise | NR | NR       | NR | 20   | Similar increase of irisin levels in subjects with vs without MetS after exercise   |
| Aronis (47)        | Patient with ACS/ established coronary artery disease vs controls | CC<br>PC | CV            | NR | NR       | NR | 349  | No association between irisin levels and ACS<br>Major adverse cardiovascular events in patients with established coronary artery disease after PCI (positive)<br>Did not predict the development of ACS |
| Emanuele (48)      | Centenarians, young healthy, young with MI                        | CC       | CV            | NR | NR       | NR |      | Irisin in young patients with myocardial infarction < young healthy patients < centenarians   |
| Aydin (49)         | AMI, matched controls   | CC       | CV            | NR | NR       | NR | 25   | Troponin I, CKMB and CK in AMI- Irisin measured in saliva (positive)<br>Gradual decrease of saliva/serum irisin over 48h after AMI  |
| de la Iglesia (50) | Caucasian with MetS in an energy restricted                       | PC       | Lipid profile | NR | NR       | NR | 93   | Total cholesterol, LDL, Apolipoprotein B (positive)   |

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|                 | programme   |    |                           |    |          |          |        |   |
| Panagiotou (51) | Overweight/obese with diabetes or two other CV risk factors | CS | Lipid profile             | NR | NR       | NR       | 39     | HDL, large HDL particles and omentin (negative)   |
| Wen (52)        | CKD vs healthy  | CC | Renal metabolic           | No | NR       | NR       | 57     | Blood urea nitrogen (negative)<br>HDL (positive)  |
| Brondani (53)   | T2DM vs Nondiabetic   | CC | SNPs                      | NR | NR       | NR       | 1440   | FNDC5 gene:<br>SNP rs3480: HbA1c levels in T2DM patients (positive)<br>SNP rs1746661: Increased systolic blood pressure, total cholesterol and LDL (positive)                           |
| Staiger (54)    | German families at increased risk for T2DM                  | CS | SNPs / Insulin resistance | NR | positive | NR       | 1976   | rs16835198 and rs726344 of <i>FNDC5</i> with measures of insulin sensitivity (positive)   |
| Ebert (55)      | General population  | CS | SNPs                      | NR | NR       | NR       | > 1000 | Fat mass, fasting glucose, dyslipidemia (negative)<br>Irisin decreased during OGTT in subjects with NGT, IFG, IGT or T2DM<br>No association of rs726344 <i>FNDC5</i> with irisin levels |
| Tanisawa (56)   | Japanese men  | CS | SNPs                      | NR | No       | NR       | 163    | No association of rs3480 and rs16835198 of <i>FNDC5</i> with circulating irisin   |
| Zhao (57)       | GDM, healthy  | CC | GDM                       | NR | NR       | negative | 122    | DBP, fasting blood glucose (negative)   |
| Yuksel (58)     | GDM, pregnant   | CC | GDM                       | NR | NR       | negative | 40     | No association with maternal age, gestational week at birth, BMI at birth, birth weight, neonatal height, systolic and diastolic blood pressure.  |

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|               |  |    |     |    |                 |                 |     | BMI at birth, as well as with HOMA-IR (negative)  |
| Kuzmicki (59) | GDM, BMI-matched NGT                     | CC | GDM | NR | NR              | <b>negative</b> | 270 | Irisin levels increase in gestation, but this increase is lower in GDM compared to NGT controls.  |
| Erol (60)     | GDM, pregnant                            | CC | GDM | NR | NR              | <b>negative</b> | 50  | Irisin levels lower in GDM vs controls in the first trimester   |
| Ebert (61)    | GDM, pregnant                            | CC | GDM | NR | NR              | <b>No</b>       | 148 | Similar irisin levels between GDM and controls<br>Increased irisin after delivery in GDM compared to normal Fasting insulin during pregnancy (positive)   |
| Garces (62)   | Pregnant vs preeclamptic vs eumenorrheic | CC | GDM | NR | <b>positive</b> | <b>negative</b> | 70  | Irisin was lower in preeclamptic vs pregnant controls in the 3rd trimester of gestation.<br>HOMA IR in the first trimester of normal pregnancy (positive) |

(positive) positive association, (negative) negative association; CC, casecontrol study; CS, crosssectional study; PC, prospective cohort study; RCT, randomized controlled trial; (A)MI, (acute) myocardial infarction; CV, cardiovascular; DBP, diastolic blood pressure; MVD, macrovascular disease; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; SNPs, single nucleotide polymorphism

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