

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to:

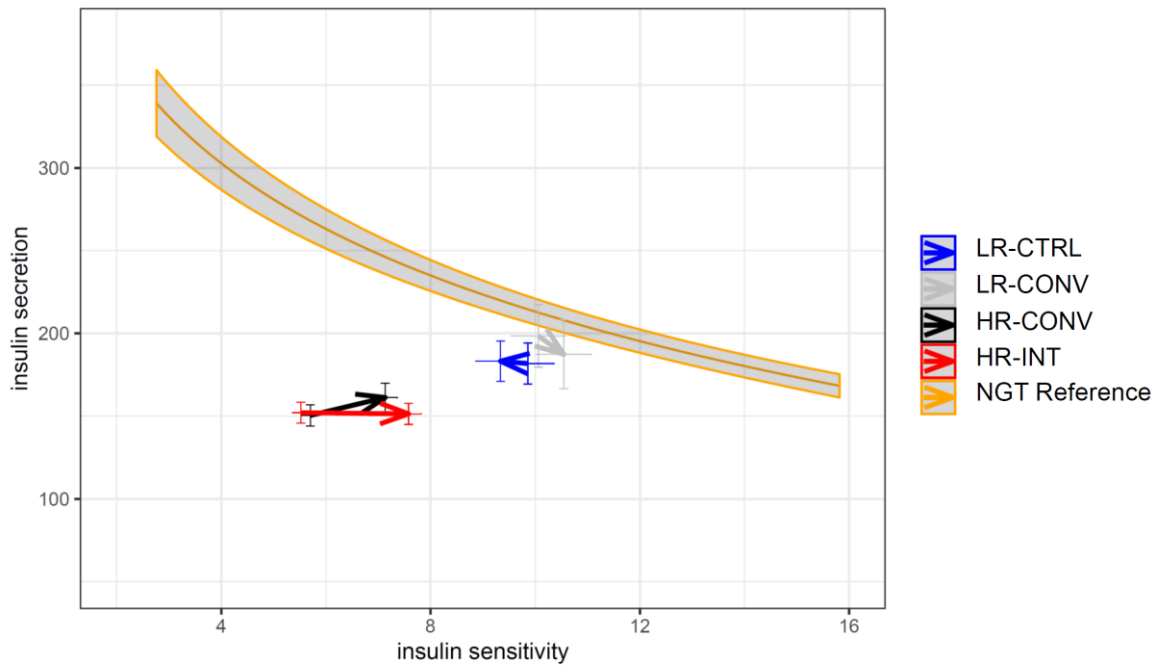
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Different effects of lifestyle intervention in high- and low-risk prediabetes -
Results of the randomized controlled Prediabetes Lifestyle Intervention Study (PLIS)

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Appendix Figure 1

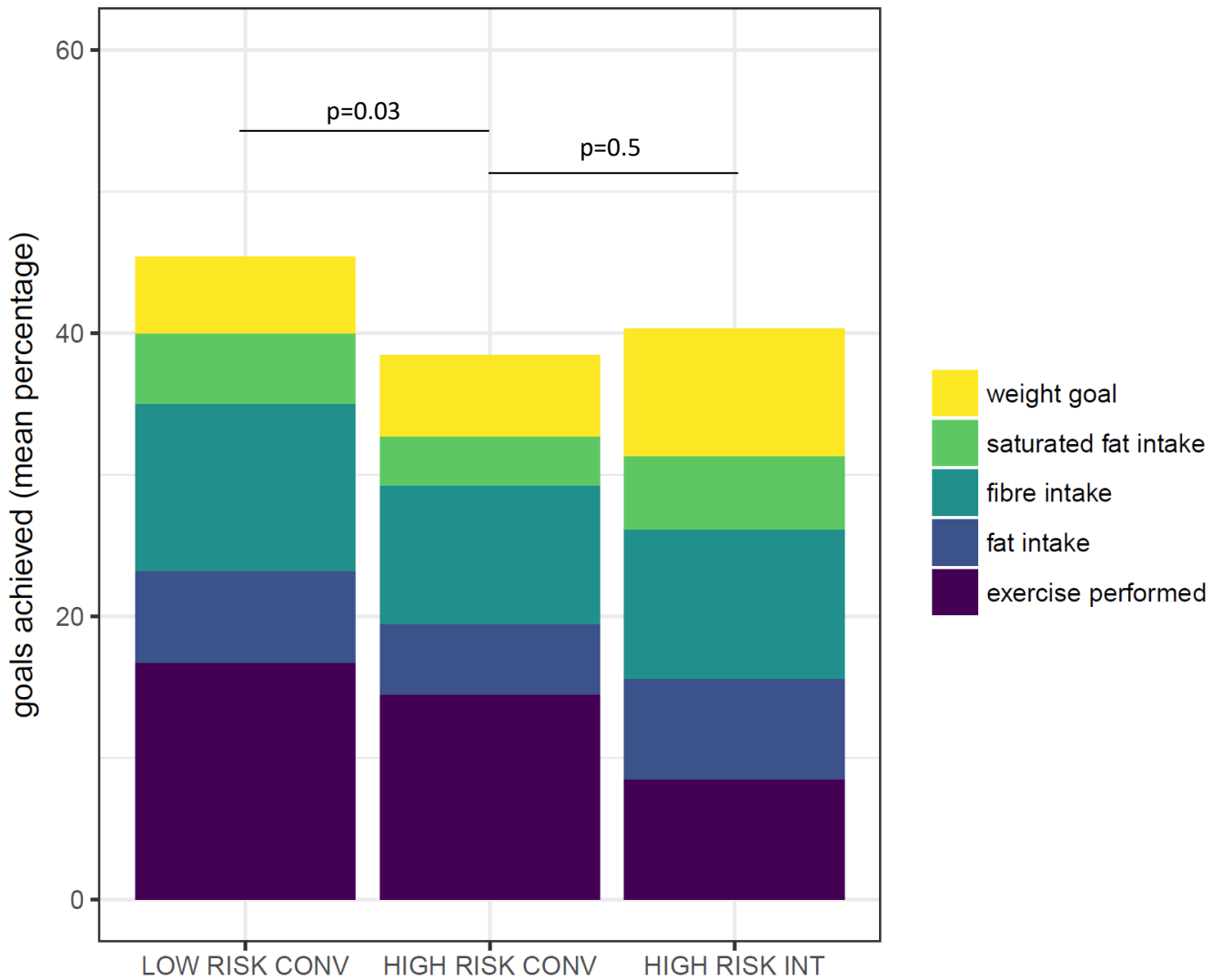


Change in insulin secretion and sensitivity during the study in the different study arms.

Insulinogenic index (arbitrary units) as marker for insulin secretion is shown as hyperbolic function of insulin sensitivity (insulin sensitivity index, arbitrary units, unadjusted values). Subjects with normal glucose tolerance (NGT, age 18-50 years) from the German TUEF study (43) were used to compute the hyperbolic function (n=1421). The arrows represent baseline values (origin) and values after 12 months of intervention (end) in the study arms.

95 % CI are shown, blue: LR-CTRL, grey: LR-CONV, black: HR-CONV, red: HR-INT.

Appendix Figure 2



Aggregate percentage of completed lifestyle goals during the study.

To scale the aggregate percentage of all lifestyle goals to a maximum of 100%, the number of completed individual goals are downscaled by a factor of 5 (number of individual goals). The aggregate percentage of all completed lifestyle goals was higher in the LR-CONV compared to the HR-CONV ($p=0.03$, Wilcoxon-test) and not different between HR-CONV and HR-INT ($p=0.5$).

Appendix Table 1**Participation at different academic diabetes centers where the study was performed.**

From each study center, about 2 fold of actually included individuals with prediabetes were potentially eligible for the study. For all study centers, a total of n=2561 were potentially eligible.

| | Number of participants receiving allocated intervention | Number of participants completing follow up |
|--|---|---|
| University Hospital of Tübingen | 351 | 304 |
| University Hospital of Dresden | 213 | 178 |
| German Institute of Human Nutrition, Potsdam | 175 | 137 |
| University Hospital of Heidelberg | 104 | 80 |
| University of Düsseldorf | 59 | 48 |
| Technical University of Munich | 106 | 82 |
| Ludwig Maximilian University Munich | 49 | 40 |
| University Hospital of Leipzig | 48 | 39 |

Appendix Table 2

Exclusion criteria.

| Criterion | Specific definition |
|-------------------------------------|---|
| Pregnancy | |
| Lactation | |
| Symptomatic coronary artery disease | |
| Active malignant disease | Active malignant disease and/or unintended weight loss > 10% over the last 6 months |
| Elevated liver transaminases | 3 times above the upper limit of normal level |
| Chronic kidney disease | estimated glomerular filtration ratio < 50 ml/min/1.73m ² |
| Systemic infection | |
| Glucocorticoid use | |
| Severe mental illness | |

Appendix Table 3**Full-set analysis on all 1105 participants**

using multivariable imputation performed on a wide-dataset encompassing basic variables (sex, age, BMI, waist circumference, education, study center), and glycemic variables (glucose during OGTT, AUC glucose, HbA1c), variables on insulin secretion and sensitivity (ISI and IGI), disposition index as well as liver fat content at the visits at 6 months and 12 months. Missing data were imputed for all visits. The imputation was performed using the MICE package in R using default settings (predictive mean matching as default algorithm, 5 iterations) and passive imputation for derived variables (disposition indexes).

| | Imputed variables (baseline/follow up) | LOW RISK | | | HIGH RISK | | |
|---|---|---------------------|---------------------|----------------|---------------------|---------------------|----------------|
| | | LR-CTRL | LR-CONV | p-value | HR-CONV | HR-INT | p-value |
| body mass index (kg m ⁻²) | 0/157 | 0 [-0.2;0.2] | -0.6 [-0.9;-0.4] | <0.0001 | -1.1 [-1.3;-1] | -1.6 [-1.8;-1.4] | <0.0001 |
| fasting glucose (mmol l ⁻¹) | 1/159 | -0.13 [-0.21;-0.05] | -0.29 [-0.37;-0.21] | 0.004 | -0.2 [-0.25;-0.15] | -0.29 [-0.34;-0.24] | 0.02 |
| post-challenge glucose (mmol l ⁻¹) | 2/164 | -0.49 [-0.76;-0.21] | -0.45 [-0.73;-0.18] | 0.9 | -0.65 [-0.82;-0.48] | -0.94 [-1.11;-0.77] | 0.02 |
| glucose AUC (mmol min l ⁻¹) | 1/163 | -8 [-32;17] | -14 [-38;11] | 0.7 | -76 [-92;-61] | -105 [-120;-89] | 0.01 |
| glycated hemoglobin (%) | 1/161 | 0 [0;0] | 0 [-0.1;0] | 0.2 | -0.1 [-0.1;-0.1] | -0.1 [-0.2;-0.1] | 0.02 |
| Insulin sensitivity index (AU) | 25/181 | -1.2 [-1.8;-0.6] | -0.2 [-0.9;0.4] | 0.04 | 1.2 [0.9;1.5] | 1.9 [1.6;2.2] | 0.004 |
| Insulin secretion (Disposition ind) (AU) | 26/184 | -236 [-434;-37] | -247 [-446;-48] | 0.9 | 127 [51;203] | 168 [92;244] | 0.5 |
| Liver fat content (%) | 184/437 | 0.1 [-0.3;0.5] | -0.1 [-0.5;0.3] | 0.4 | -3.1 [-3.5;-2.6] | -4.5 [-4.9;-4] | <0.0001 |

Appendix Table 4:

Comparison of baseline parameters (mean±SD), low-risk group control versus conventional intervention and high risk group conventional versus intensive intervention.

| | LR-CTRL | LR-CONV | HR-CONV | HR-INT |
|--|----------------|----------------|-----------------|-----------------|
| sex female/male (%) | 63/38 (62/38) | 61/39 (61/39) | 186/165 (53/47) | 209/147 59/41) |
| age (years) | 57±12 | 58±11 | 59±10 | 59±10 |
| weight (kg) | 80.1±16.1 | 81.3±16.3 | 92±19.7 | 92.4±19.2 |
| body mass index (kg m ⁻²) | 27.9±5.1 | 28.3±5.3 | 31.5±5.9 | 31.9±5.7 |
| waist circumference (cm) | 93±12 | 94±13 | 105±14 | 105±14 |
| waist-to-hip ratio | 0.89±0.09 | 0.89±0.08 | 0.94±0.09 | 0.94±0.08 |
| systolic blood pressure (mmHg) | 135±16 | 135±17 | 140±16 | 139±17 |
| diastolic blood pressure (mmHg) | 84±10 | 85±12 | 86±10 | 86±11 |
| fasting glucose (mmol l ⁻¹) | 5.7±0.5 | 5.7±0.4 | 5.9±0.5 | 6.0±0.5 |
| post-challenge glucose (mmol l ⁻¹) | 6.9±1.4 | 6.7±1.5 | 7.8±1.7 | 7.8±1.7 |
| glucose AUC (mmol min l ⁻¹) | 935±112 | 933±130 | 1131±160 | 1131±161 |
| glycated hemoglobin (%) | 5.7±0.3 | 5.6±0.3 | 5.8±0.3 | 5.8±0.4 |
| glycated hemoglobin (mmol mol ⁻¹) | 38.4±3.6 | 37.8±3.6 | 40.1±3.5 | 39.4±4.1 |
| triglycerides (mmol l ⁻¹) | 1.26±0.96 | 1.24±0.72 | 1.64±0.95 | 1.63±0.98 |
| cholesterol (mmol l ⁻¹) | 5.34±0.86 | 5.22±0.87 | 5.46±1.09 | 5.43±1.02 |
| LDL cholesterol (mmol l ⁻¹) | 3.23±0.83 | 3.12±0.79 | 3.38±0.95 | 3.3±0.87 |
| HDL cholesterol (mmol l ⁻¹) | 1.47±0.4 | 1.56±0.71 | 1.37±0.36 | 1.39±0.41 |
| Liver fat content (%) | 2.85±2.74 | 2.86±3.1 | 10.72±8.76 | 10.18±7.57 |
| Insulin sensitivity index (AU) | 9.86±5.05 | 10.06±5.16 | 5.70±3.12 | 5.52±3.01 |
| Insulin secretion (Disposition index) (AU) | 1440±994 | 1627±1352 | 654±424 | 688±506 |
| Hypertension no/yes (%) | 56/39 (59/41) | 63/33 (66/34) | 155/185 (46/54) | 152/181 (46/54) |

| | | | | |
|---|---------------|---------------|-----------------|-----------------|
| Hyperlipidemia no/yes (%) | 55/38 (59/41) | 58/34 (63/37) | 184/145 (56/44) | 171/145 (54/46) |
| History of myocardial infarction no/yes (%) | 91/3 (97/3) | 97/1 (99/1) | 325/7 (98/2) | 314/10 (97/3) |
| History of stroke no/yes (%) | 90/4 (96/4) | 95/2 (98/2) | 325/4 (99/1) | 311/13 (96/4) |
| peripheral artery disease no/yes (%) | 85/6 (93/7) | 88/7 (93/7) | 288/41 (88/12) | 284/39 (88/12) |
| medication: angiotensine convertase inhibitors no/yes (%) | 89/12 (88/12) | 91/9 (91/9) | 290/61 (83/17) | 303/53 (85/15) |
| medication: angiotensine receptor blockers no/yes (%) | 84/17 (83/17) | 84/16 (84/16) | 276/75 (79/21) | 260/96 (73/27) |
| medication: thiazide diuretics no/yes (%) | 93/8 (92/8) | 92/8 (92/8) | 306/45 (87/13) | 301/55 (85/15) |
| medication: other diuretics no/yes (%) | 98/3 (97/3) | 98/2 (98/2) | 335/16 (95/7) | 341/15 (96/4) |
| medication: beta blockers no/yes (%) | 88/13 (87/13) | 86/14 (86/14) | 272/79 (77/23) | 273/83 (77/23) |
| medication: statins no/yes (%) | 89/12 (88/12) | 86/14 (86/14) | 287/64 (82/18) | 294/62 (83/17) |
| current smoking no/yes (%) | 93/3 (97/3) | 91/7 (93/7) | 324/22 (94/6) | 321/22 (94/6) |
| alcohol consumption n (%) | | | | |
| 1_none | 20 (21) | 11 (11) | 29 (8) | 42 (12) |
| 2_rarely | 30 (31) | 43 (44) | 157 (45) | 147 (43) |
| 3_week-ends | 9 (9) | 5 (5) | 33 (10) | 24 (7) |
| 4_weekely_2-3 | 33 (34) | 27 (27) | 82 (24) | 87 (26) |
| 5_daily | 5 (5) | 13 (13) | 44 (13) | 40 (12) |
| highest education n (%) | | | | |
| 1_none | 1 (1) | 4 (4) | 8 (2) | 11 (3) |
| 2_post_secondary | 46 (47) | 53 (54) | 160 (48) | 154 (45) |
| 3_bachelor_or_equivalent | 18 (18) | 15 (15) | 85 (25) | 89 (26) |
| 4_master_or_equivalent | 34 (34) | 26 (27) | 84 (25) | 88 (26) |

Appendix Table 5

Comparison of baseline variables (mean±SD) non-completers versus completers.

| | Non-completer (n=197) | Completer (n=908) | p-value |
|---|--------------------------|----------------------|---------|
| Riskgroup n (%) | | | 1 |
| 1_low risk | 44 (22) | 201 (22) | |
| 2_high risk | 153 (78) | 707 (78) | |
| Intervention group n (%) | | | 0.91 |
| control | 22 (11) | 101 (11) | |
| conventional | 101 (51) | 451 (50) | |
| intensive | 74 (38) | 356 (39) | |
| sex female/male (%) | 132/65 (67/33) | 519/389 (57/43) | 0.014 |
| age (years) | 54±12 | 59±10 | <0.0001 |
| weight (kg) | 93.1±21.1 | 89.6±19.4 | 0.036 |
| body mass index (kg m ⁻²) | 32.2±6.5 | 30.9±5.9 | 0.0091 |
| waist circumference (cm) | 104±16 | 102±14 | 0.19 |
| waist-to-hip ratio | 0.92±0.09 | 0.93±0.09 | 0.19 |
| systolic blood pressure (mmHg) | 136±16 | 139±17 | 0.048 |
| diastolic blood pressure (mmHg) | 86±10 | 86±11 | 0.98 |
| fasting glucose (mmol l ⁻¹) | 6.0±0.6 | 5.9±0.5 | 0.089 |
| post-challenge glucose (mmol l ⁻¹) | 7.5±1.9 | 7.6±1.7 | 0.7 |
| glucose AUC (mmol min l ⁻¹) | 1084±191 | 1088±173 | 0.79 |
| glycated hemoglobin (mmol mol ⁻¹) | 39.3±4.4 | 39.4±3.8 | 0.72 |
| glycated hemoglobin (%) | 5.7±0.4 | 5.8±0.3 | 0.72 |
| triglycerides (mmol l ⁻¹) | 1.53±0.86 | 1.55±0.95 | 0.83 |
| cholesterol (mmol l ⁻¹) | 5.33±0.98 | 5.41±1.01 | 0.31 |
| LDL cholesterol (mmol l ⁻¹) | 3.26±0.88 | 3.3±0.89 | 0.52 |
| HDL cholesterol (mmol l ⁻¹) | 1.39±0.38 | 1.41±0.44 | 0.59 |
| Hepatic triglyceride content (%) | 9.12±8.21 | 8.75±8 | 0.62 |
| Insulin sensitivity index | 6.38±3.68 | 6.58±4.04 | 0.52 |
| Insulin secretion (Disposition index) (AU) | 882.±660 | 863±781 | 0.73 |
| Hypertension no/yes (%) | 95/84 (53/47) | 426/438 (49/51) | 0.4 |
| hyperlipidemia no/yes (%) | 108/64 (63/37) | 468/362 (56/44) | 0.14 |
| myocardial infarction no/yes (%) | 172/4 (98/2) | 827/21 (98/2) | 1 |
| stroke no/yes (%) | 176/2 (99/1) | 821/23 (97/3) | 0.32 |
| peripheral artery disease no/yes (%) | 154/21 (88/12) | 745/93 (89/11) | 0.83 |
| medication: angiotensine convertase inhibitors no/yes (%) | 171/26 (87/13) | 773/135 (85/15) | 0.62 |
| medication: angiotensine receptor blockers no/yes (%) | 160/37(81/19) | 704/204 (78/22) | 0.3 |
| medication: thiazide diuretics no/yes (%) | 176/21 (89/11) | 792/116 (87/13) | 0.49 |
| medication: other diuretics no/yes (%) | 194/3 (98/2) | 872/36 (96/4) | 0.14 |
| medication: beta blockers no/yes (%) | 156/41 (79/21) | 719/189 (79/21) | 1 |

| | | | |
|--------------------------------|----------------|-----------------|---------|
| medication: statins no/yes (%) | 173/24 888/12) | 756/152 (83/17) | 0.14 |
| current smoking no/yes (%) | 154/26 (86/14) | 829/54 (94/6) | 0.00021 |
| alcohol use | | | 0.025 |
| 1_none | 31 (17) | 102 (12) | |
| 2_rarely | 89 (50) | 377 (42) | |
| 3_week-ends | 13 (7) | 71 (8) | |
| 4_weekely_2-3 | 31 (17) | 229 (26) | |
| 5_daily | 16 (9) | 102 (12) | |
| highest education | | | 0.62 |
| 1_none | 6 (3) | 24 (3) | |
| 2_post_secondary | 95 (52) | 413 (47) | |
| 3_bachelor_or_equivalent | 38 (21) | 207 (24) | |
| 4_master_or_equivalent | 44 (24) | 232 (26) | |

Appendix Table 6

Effect of conventional LI in low risk individuals versus high risk individuals.

*ANCOVA, adjusted for baseline and center.

| | Between-group difference of conventional intervention * (for HR-CONV, reference: LR-CONV beta coefficient (\pmSE)) | p-value |
|---|--|----------------|
| age (years) | -0 (\pm 0) | 0.6 |
| weight (kg) | 0.4 (\pm 0.6) | 0.5 |
| body mass index (kg m ⁻²) | 0.1 (\pm 0.2) | 0.5 |
| waist circumference (cm) | -1 (\pm 1) | 0.6 |
| waist-to-hip ratio | -0.02 (\pm 0.01) | 0.008 |
| lean mass percent | -5.5 (\pm 2.3) | 0.02 |
| fat mass percent | 0.9 (\pm 0.5) | 0.07 |
| habitual physical activity score | 0.1 (\pm 0.1) | 0.5 |
| systolic blood pressure (mmHg) | -3 (\pm 2) | 0.09 |
| diastolic blood pressure (mmHg) | -1 (\pm 1) | 0.3 |
| heart rate (1/min) | -0 (\pm 1) | 0.7 |
| fasting glucose (mmol l ⁻¹) | -0.16 (\pm 0.06) | 0.006 |
| post-challenge glucose (mmol l ⁻¹) | -0.55 (\pm 0.20) | 0.008 |
| glucose AUC (mmol min l ⁻¹) | -33 (\pm 20) | 0.1 |
| glycated hemoglobin (mmol mol ⁻¹) | -0.0 (\pm 0.4) | 1 |
| glycated hemoglobin (%) | -0.0 (\pm 0.0) | 1 |
| triglycerides (mmol l ⁻¹) | 0.11 (\pm 0.07) | 0.1 |
| cholesterol (mmol l ⁻¹) | 0.12 (\pm 0.08) | 0.1 |
| LDL cholesterol (mmol l ⁻¹) | 0.09 (\pm 0.07) | 0.2 |
| HDL cholesterol (mmol l ⁻¹) | 0.04 (\pm 0.03) | 0.2 |
| C-reactive protein (mg dl ⁻¹) | 0.1 (\pm 0.8) | 0.9 |
| Aspartate aminotransferase (Units l ⁻¹) | 0.1 (\pm 1.4) | 0.9 |
| Alanin aminotransferase (Units l ⁻¹) | 0.3 (\pm 1.5) | 0.8 |
| Gamma glutamyltransferase (Units l ⁻¹) | 2.4 (\pm 2.1) | 0.3 |
| Insulin sensitivity index | -0.1 (\pm 0.5) | 0.9 |
| Insulin secretion (Disposition index) (AU) | 226 (\pm 134) | 0.09 |
| Liver fat content (%) | 0.1 (\pm 0.6) | 0.9 |
| Framingham 10-year-CV-risk (%) | -0.4 (\pm 1.0) | 0.7 |

Calculations

$$\text{Insulin sensitivity index (Matsuda - ISI)} = \frac{10000}{\sqrt{(G_0 * I_0) * (G_{mean} * I_{mean})}}$$

$$\text{Insulinogenic Index: IGI} = \frac{\Delta I_{0,30}}{\Delta G_{0,30}}$$

$$\text{Disposition Index: (Insulin sensitivity index) * (Insulinogenic index)}$$

G_{mean} = mean plasma glucose 0,30,60,90,120 min during OGTT

I_{mean} = mean plasma glucose 0,30,60,90,120 min during OGTT

G_0 = fasting plasma glucose, I_0 = fasting plasma insulin

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Data and Resource Availability

Due to ethical regulations, we cannot share individual participant data. Mean values and confidence intervals of all analysed patient-level data are available and maybe shared upon reasonable request. Study protocol, statistical analysis plan and analytic code used to generate results are available upon reasonable request.

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