

	GVIF	df	GVIF^{1/(2 · df)}	Interacts With	Other Predictors
Sex	132.404	7	1.418	Age, WHR	FPG
Age	1.000	9	1.000	Sex, WHR, FPG	0.033
WHR	132.404	7	1.418	Sex, Age	FPG
FPG	366.912	3	2.676	Age	Sex, WHR

ESM Table 1 Collinearity analysis using the Generalised variance inflation factor (GVIF) for the model. GVIF^{1/(2 · df)} GVIFs adjusted for degrees of freedom.

	Estimate	Standard error	t value	p value
(Intercept)	-4.668	1.716	-2.720	0.007
Sex	7.875	3.679	2.140	0.033
Age	0.117	0.039	3.024	0.003
WHR	2.878	1.932	1.490	0.138
FPG	0.533	0.219	2.429	0.016
Sex X age	-0.206	0.083	-2.477	0.014
Sex X WHR	-9.000	4.015	-2.241	0.026
Age X WHR	-0.080	0.045	-1.784	0.076
Age X FPG	-0.012	0.004	-2.596	0.010
Sex X age X WHR	0.233	0.089	2.614	0.010

ESM Table 2 Stepwise linear regression model to find the most relevant predictor for hippocampal insulin response (hIResp). Coefficients of selected model using stepwise linear regression hIResp, using the Bayesian Information Criterion to select the most relevant predictors of metabolic health using anthropometric and blood-based clinical parameters ($n=258$, 1 missing value for FPG and 1 missing value for WHR). Effect size adjusted $R^2 = 8 \cdot 10^{-2}$.

	Estimate	Standard error	t value	p value
(Intercept)	-3.840	1.754	-2.189	0.030
Sex	7.264	3.669	1.980	0.049
Age	0.100	0.040	2.522	0.012
WHR	1.949	1.975	0.987	0.325
FPG	0.446	0.222	2.007	0.046
BMI	0.013	0.006	2.013	0.045
Sex X age	-0.188	0.083	-2.262	0.025
Sex X WHR	-8.252	4.008	-2.059	0.041
Age X WHR	-0.068	0.045	-1.504	0.134
Age X FPG	-0.010	0.004	-2.266	0.024
Sex X age X WHR	0.214	0.089	2.393	0.017

ESM Table 3 Coefficients of the stepwise linear regression model for hIResp, using the Bayesian Information Criterion to select the most relevant predictors of metabolic health using anthropometric and blood-based clinical parameters, adjusting for BMI ($n=258$).

FPG	trend	Standard error	df	Lower CL	Upper CL
4.830	-0.009	0.004	248	-0.018	-0.001
5.110	-0.013	0.004	248	-0.021	-0.005
5.540	-0.018	0.005	248	-0.026	-0.009
6.940	-0.034	0.009	248	-0.052	-0.016

ESM Table 4 Simple slope analysis for the results from the stepwise regression model for hIResp with the two-way interaction between FPG and age.

FPG	trend	Standard error	df	Lower CL	Upper CL
4.830	-0.009	0.004	247	-0.017	-0.001
5.110	-0.012	0.004	247	-0.020	-0.004
5.540	-0.016	0.005	247	-0.025	-0.007
6.940	-0.030	0.009	247	-0.048	-0.012

ESM Table 5 Simple slope analysis for the results from the stepwise regression model for hIResp with the two-way interaction between FPG and age, adjusting for BMI.

Sex	WHR	Trend	Standard error	df	Lower CL	Upper CL
Male	0.913	-0.009	0.005	248	-0.019	0.001
Male	0.957	-0.002	0.004	248	-0.010	0.006
Male	0.995	-0.004	0.005	248	-0.007	0.014
Male	1.180	-0.032	0.018	248	-0.004	0.068
Female	0.784	-0.006	0.004	248	-0.014	0.002
Female	0.841	-0.010	0.003	248	-0.017	-0.004
Female	0.885	-0.014	0.004	248	-0.021	-0.006
Female	1.019	-0.024	0.009	248	-0.042	-0.007

ESM Table 6 Simple slope analysis for the results from the stepwise regression model for hIResp with the three-way interaction between WHR × age × sex in female and male participants.

Sex	WHR	Trend	Standard error	df	Lower CL	Upper CL
Male	0.913	-0.008	0.005	247	-0.018	0.002
Male	0.957	-0.002	0.004	247	-0.010	0.006
Male	0.995	0.004	0.005	247	-0.006	0.014
Male	1.180	0.031	0.018	247	-0.005	0.067
Female	0.784	-0.006	0.004	247	-0.014	0.002
Female	0.841	-0.010	0.003	247	-0.017	-0.004
Female	0.885	-0.013	0.004	247	-0.021	-0.005
Female	1.019	-0.022	0.009	247	-0.039	-0.005

ESM Table 7 Simple slope analysis for the results from the stepwise regression model for hIResp with the three-way interaction between WHR × age × sex in female and male participants, adjusting for BMI.

	Estimate	Standard error	<i>t</i> value	<i>p</i> value
(Intercept)	-0.314	0.314	-1.000	0.319
Sex	0.571	0.532	1.074	0.285
Age	0.006	0.008	0.740	0.460
VAT	0.343	0.105	3.254	0.001
Sex X age	-0.015	0.012	-1.225	0.222
Sex X VAT	-0.314	0.142	-2.213	0.028
Age X VAT	-0.007	0.002	-3.096	0.002
Sex X age X VAT	0.007	0.003	2.522	0.013

ESM Table 8 Interaction of hIResp with age, sex and visceral adipose tissue (VAT). Coefficients of the two-sided linear regression model for hIResp and the interactions between sex, age and VAT ($n=180$, 80 missing values for VAT). Effect size adjusted $R^2 = 1.2 \cdot 10^{-1}$.

	Estimate	Standard error	<i>t</i> value	<i>p</i> value
(Intercept)	0.031	0.216	0.142	0.887
Sex	0.211	0.344	0.613	0.541
Age	0.000	0.005	-0.069	0.945
IHL	0.116	0.035	3.291	0.001
Sex X age	-0.005	0.008	-0.619	0.537
Sex X IHL	-0.112	0.050	-2.222	0.028
Age X IHL	-0.002	0.001	-3.524	0.001
Sex X age X IHL	0.003	0.001	2.606	0.010

ESM Table 9 Interaction of hIResp with age, sex and intrahepatic lipid content (IHL). Coefficients of the two-sided linear regression model for hIResp and the interactions between sex $\times$ age $\times$ IHL ($n=177$, 83 missing values for IHL). Effect size adjusted $R^2 = 1.2 \cdot 10^{-1}$.

	Estimate	Standard error	<i>t</i> value	<i>p</i> value
(Intercept)	-0.403	0.360	-1.118	0.265
Sex	0.558	0.533	1.047	0.297
Age	0.005	0.008	0.605	0.546
VAT	0.306	0.129	2.378	0.018
BMI	0.005	0.011	0.506	0.614
Sex X age	-0.015	0.012	-1.191	0.235
Sex X VAT	-0.294	0.147	-1.996	0.048
Age X VAT	-0.006	0.002	-2.619	0.010
Sex X age X VAT	0.007	0.003	2.372	0.019

ESM Table 10 Coefficients of the two-sided linear regression model for hIResp and the interactions between sex $\times$ age $\times$ VAT, adjusting for BMI ($n=180$).

	Estimate	Standard error	<i>t</i> value	<i>p</i> value
(Intercept)	-0.229	0.291	-0.788	0.432
Sex	0.196	0.343	0.571	0.568
Age	-0.002	0.005	-0.383	0.702
IHL	0.101	0.037	2.720	0.007
BMI	0.011	0.008	1.335	0.184
Sex X age	-0.004	0.008	-0.514	0.608
Sex X IHL	-0.103	0.051	-2.038	0.043
Age X IHL	-0.002	0.001	-3.044	0.003
Sex X age X IHL	0.002	0.001	2.418	0.017

ESM Table 11 Coefficients of the two-sided linear regression model for hIResp and the interactions between sex $\times$ age $\times$ IHL, adjusting for BMI ($n=177$).

Sex	VAT	Trend	Standard error	df	Lower CL	Upper CL
Male	3.460	-0.008	0.005	172	-0.018	0.003
Male	5.620	-0.007	0.005	172	-0.017	0.003
Male	7.540	-0.006	0.007	172	-0.020	0.008
Male	14.820	-0.003	0.019	172	-0.040	0.034
Female	2.240	-0.009	0.004	172	-0.018	-0.001
Female	3.400	-0.017	0.004	172	-0.024	-0.009
Female	4.590	-0.025	0.005	172	-0.034	-0.015
Female	8.400	-0.050	0.012	172	-0.073	-0.026

ESM Table 12 Simple slope analysis for the results from the stepwise regression model for hIResp with the three-way interaction between VAT × age × sex in female and male participants.

Sex	IHL	Trend	Standard error	df	Lower CL	Upper CL
Male	2.300	-0.005	0.005	169	-0.014	0.005
Male	5.420	-0.004	0.004	169	-0.012	0.004
Male	11.130	-0.003	0.006	169	-0.014	0.008
Male	29.620	-0.0001	0.017	169	-0.034	0.034
Female	1.890	-0.005	0.004	169	-0.013	0.003
Female	3.570	-0.009	0.004	169	-0.016	-0.002
Female	7.450	-0.018	0.004	169	-0.026	-0.011
Female	22.400	-0.054	0.012	169	-0.079	-0.030

ESM Table 13 Simple slope analysis for the effects of the stepwise regression model for hIResp with the three-way interaction between IHL × age × sex in female and male participants.

Sex	VAT	Trend	Standard error	df	Lower CL	Upper CL
Male	3.460	-0.008	0.005	171	-0.018	0.003
Male	5.620	-0.006	0.005	171	-0.017	0.004
Male	7.540	-0.005	0.007	171	-0.020	0.009
Male	14.820	-0.001	0.019	171	-0.039	0.038
Female	2.240	-0.009	0.004	171	-0.017	-0.001
Female	3.400	-0.016	0.004	171	-0.024	-0.008
Female	4.590	-0.023	0.006	171	-0.034	-0.012
Female	8.400	-0.046	0.013	171	-0.073	-0.020

ESM Table 14 Simple slope analysis for the results from the stepwise regression model for hIResp with the three-way interaction between VAT × age × sex in female and male participants, adjusting for BMI.

Sex	IHL	Trend	Standard error	df	Lower CL	Upper CL
Male	2.300	-0.005	0.005	168	-0.015	0.004
Male	5.420	-0.004	0.004	168	-0.013	0.004
Male	11.130	-0.003	0.006	168	-0.014	0.008
Male	29.620	0.002	0.017	168	-0.033	0.036
Female	1.890	-0.006	0.004	168	-0.014	0.002
Female	3.570	-0.010	0.004	168	-0.017	-0.003
Female	7.450	-0.018	0.004	168	-0.025	-0.010
Female	22.400	-0.050	0.013	168	-0.075	-0.025

ESM Table 15 Simple slope analysis for the results from the stepwise regression model for hIResp with the three-way interaction between IHL × age × sex in female and male participants, adjusting for BMI.

	Estimate	Standard error	<i>t</i> value	<i>p</i> value
(Intercept)	-0.062	0.494	-0.126	0.900
Sex	-0.200	0.764	-0.262	0.793
Age	-0.007	0.011	-0.688	0.493
SAT	0.033	0.027	1.235	0.218
Sex X age	0.011	0.017	0.655	0.514
Sex X SAT	0.005	0.052	0.099	0.921
Age X SAT	0.000	0.001	-0.438	0.662
Sex X age X SAT	0.000	0.001	-0.195	0.846

ESM Table 16 Coefficients of the two-sided linear regression model for hIResp and the interactions between sex × age × SAT (*n*=180, 80 missing values for SAT).

	Estimate	Standard error	<i>t</i> value	<i>p</i> value
(Intercept)	-0.088	0.525	-0.169	0.866
Sex	-0.216	0.773	-0.279	0.780
Age	-0.008	0.011	-0.698	0.486
SAT	0.031	0.030	1.065	0.288
BMI	0.002	0.014	0.151	0.880
Sex X age	0.011	0.017	0.665	0.507
Sex X SAT	0.006	0.052	0.111	0.912
Age X SAT	0.000	0.001	-0.434	0.664
Sex X age X SAT	0.000	0.001	-0.210	0.834

ESM Table 17 Coefficients of the two-sided linear regression model for hIResp and the interactions between sex × age × SAT, adjusting for BMI (*n*=180).

	Trend	Standard error	df	Lower CL	Upper CL
WHR					
premenopausal	0.794	0.775	159	-0.737	2.33
postmenopausal	-3.539	1.192	159	-5.893	-1.18
VAT					
premenopausal	0.113	0.048	104	0.018	0.201
postmenopausal	-0.074	0.048	104	-0.168	0.020
IHL					
premenopausal	0.050	0.017	101	0.017	0.083
postmenopausal	-0.030	0.012	101	-0.054	-0.006

ESM Table 18 Slopes from the linear regression model for hIResp and waist-to-hip ratio (WHR) or VAT or IHL according to menopausal status (*n*=163 (WHR), *n*=108 (VAT), *n*=105 (IHL)).

	Trend	Standard error	df	Lower CL	Upper CL
WHR					
premenopausal	0.219	0.845	158	-1.450	1.890
postmenopausal	-3.795	1.195	158	-6.160	-1.430
VAT					
premenopausal	0.059	0.070	103	-0.080	0.198
postmenopausal	-0.095	0.051	103	-0.197	0.007
IHL					
premenopausal	0.043	0.018	100	0.008	0.078
postmenopausal	-0.032	0.012	100	-0.056	-0.008

ESM Table 19 Slopes from the linear regression model for hIResp and waist-to-hip ratio (WHR) or VAT or IHL according to menopausal status, adjusting for BMI (*n*=163 (WHR), *n*=108 (VAT), *n*=105 (IHL)).

Sex	Cluster (high-risk, low-risk)	Trend	Standard error	<i>df</i>	Lower CL	Upper CL
Female	Low-risk	-0.004	0.005	198	-0.014	0.007
Male	Low-risk	-0.007	0.005	198	-0.017	0.003
Female	High-risk	-0.018	0.004	198	-0.026	-0.009
Male	High-risk	-0.004	0.007	198	-0.017	0.010

ESM Table 20 Slopes from the two-sided linear regression model for hIResp and the interactions between sex × age × Tübingen Prediabetes Cluster category (high-risk or low-risk; *n*=206).

Predictors	Estimate	CI	<i>p</i> value
(Intercept)	-0.040	-1.190 – 1.120	0.950
Sex	0.690	-0.780 – 2.170	0.355
Age	0.000	-0.020 – 0.030	0.886
Cluster 2	0.140	-1.290 – 1.580	0.843
Cluster 3	1.460	-1.530 – 4.450	0.338
Cluster 4	0.540	-0.820 – 1.900	0.438
Cluster 5	0.920	-0.590 – 2.430	0.231
Cluster 6	0.690	-0.580 – 1.970	0.285
Sex X age	-0.020	-0.060 – 0.020	0.297
Sex X cluster 2	-0.760	-2.580 – 1.050	0.407
Sex X cluster 3	-1.920	-5.320 – 1.470	0.265
Sex X cluster 4	-1.020	-2.950 – 0.910	0.297
Sex X cluster 5	-0.640	-2.810 – 1.520	0.558
Sex X cluster 6	-2.020	-4.120 – 0.090	0.060
Age X cluster 2	-0.000	-0.030 – 0.030	0.894
Age X cluster 3	-0.030	-0.090 – 0.020	0.234
Age X cluster 4	-0.010	-0.040 – 0.020	0.519
Age X cluster 5	-0.020	-0.050 – 0.010	0.197
Age X cluster 6	-0.020	-0.050 – 0.010	0.245
Sex X age X cluster 2	0.010	-0.030 – 0.060	0.506
Sex X age X cluster 3	0.050	-0.020 – 0.110	0.152
Sex X age X cluster 4	0.030	-0.020 – 0.070	0.248
Sex X age X cluster 5	0.020	-0.020 – 0.070	0.348
Sex X age X cluster 6	0.050	0.000 – 0.100	0.035

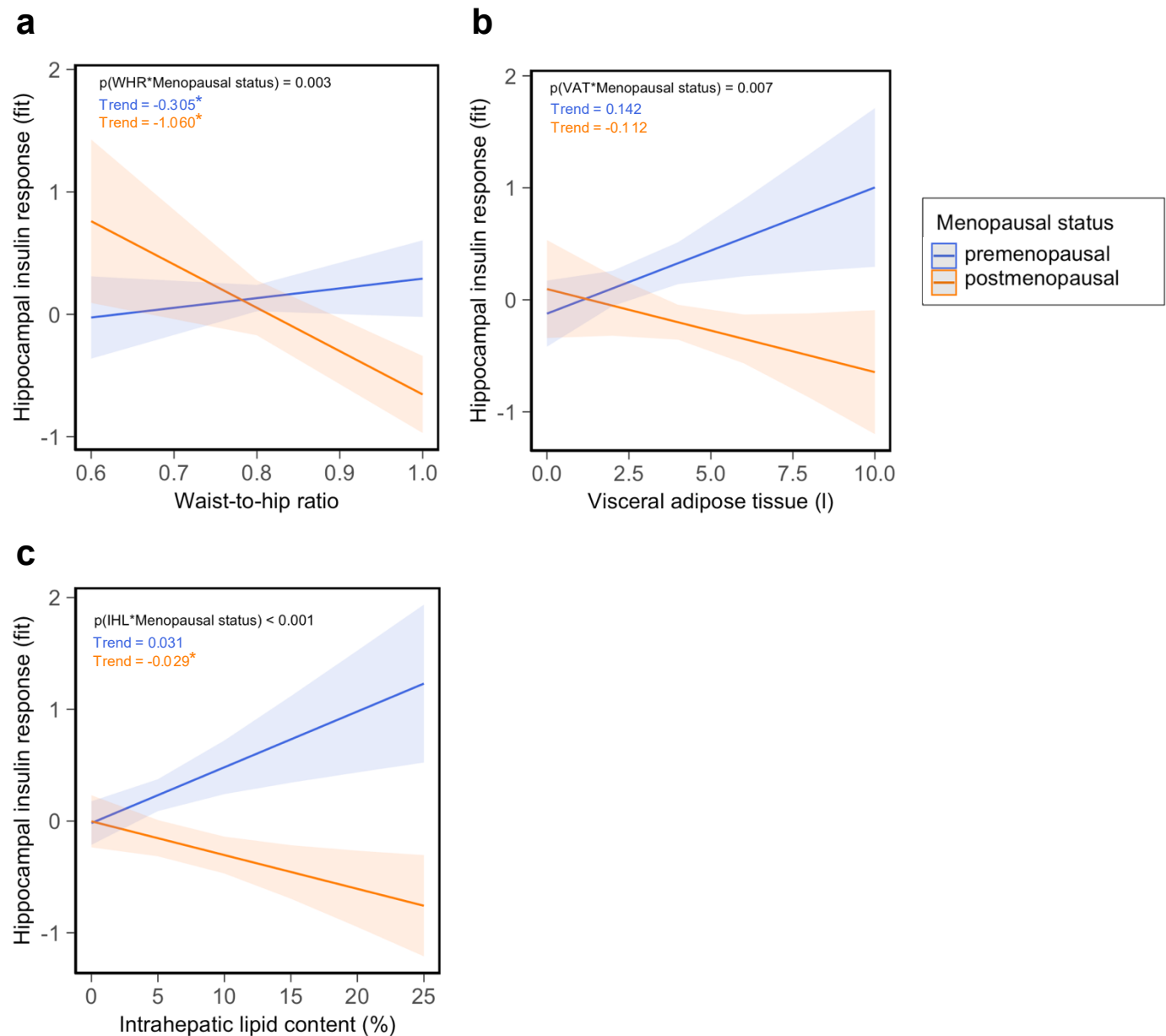
ESM Table 21 Coefficients of the linear regression model for hIResp and the interactions between sex × age × Tübingen Prediabetes Cluster (*n*=206).

	Estimate	Standard error	<i>t</i> value	<i>p</i> value
(Intercept)	89.240	6.352	14.049	0.000
Sex	10.184	11.187	0.910	0.364
Age	0.144	0.138	1.043	0.298
Sex X age	-0.484	0.235	-2.059	0.041

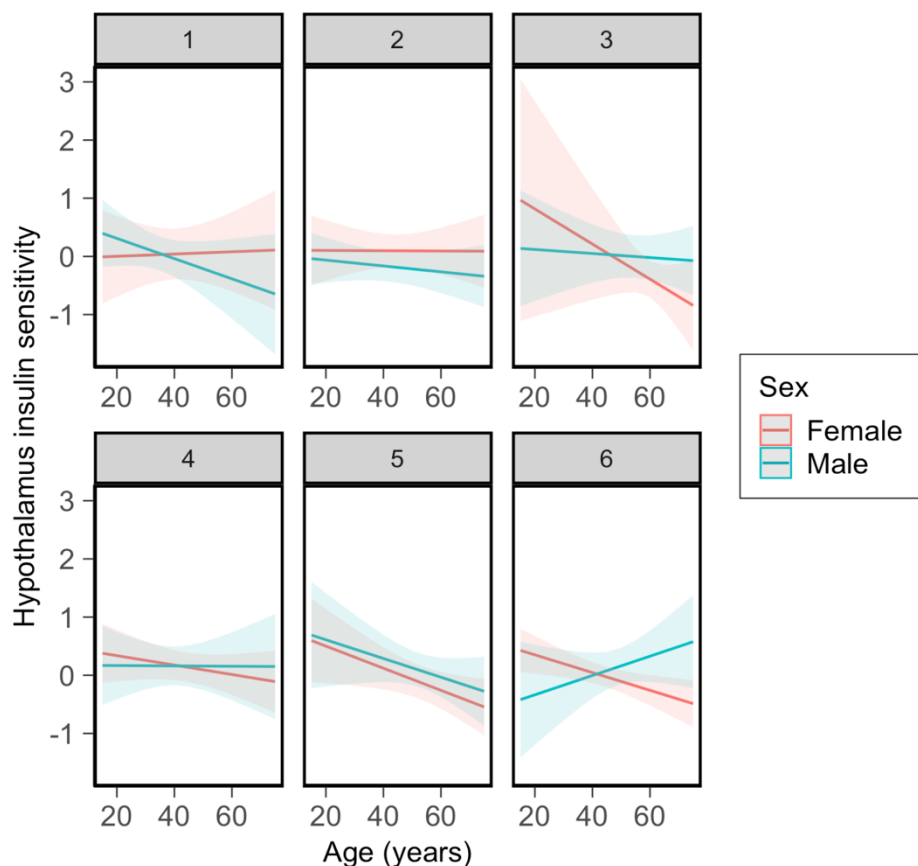
ESM Table S22 Coefficients of the two-sided linear regression model for food craving (trait) and the interactions between sex and age (*n*=227).

Sex	Trend	Standard error	<i>df</i>	Lower CL	Upper CL
female	0.144	0.138	223	-0.128	0.417
male	-0.339	0.190	223	-0.714	0.035

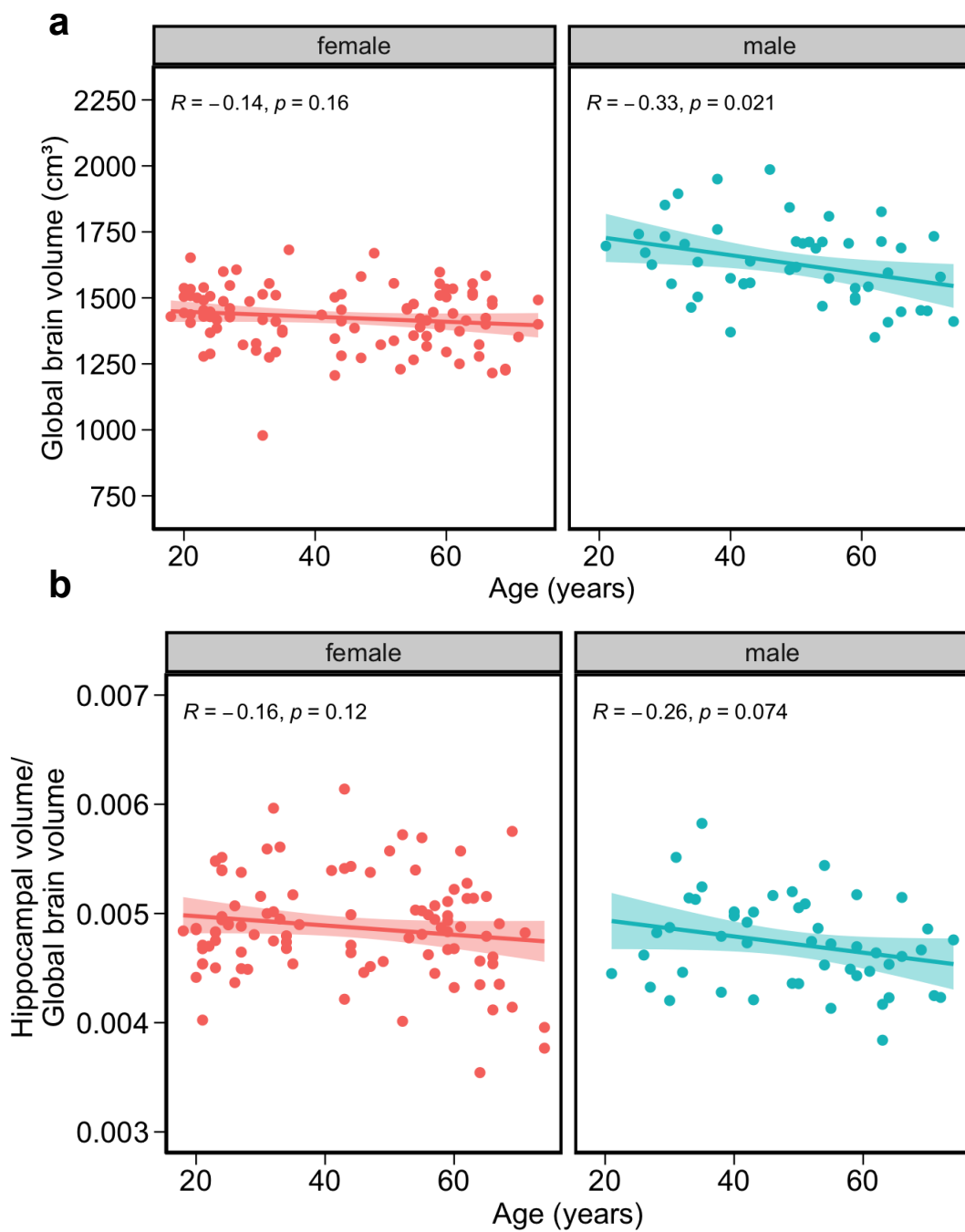
ESM Table 23 Slopes from the two-sided linear regression model for food craving (trait) according to sex (*n*=227).



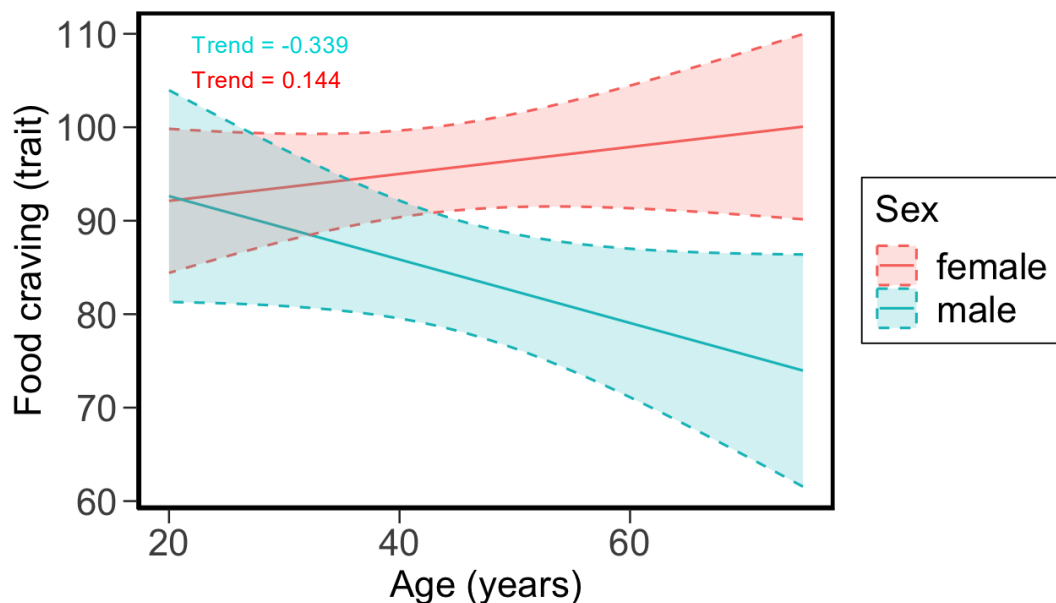
ESM Fig. 1 Association between hIRsp and body fat distribution according to menopausal status. (a) Waist-to-hip ratio ($n=163$, 1 female with hormonal replacement therapy (HRT) was excluded, 1 missing value for WHR), (b) visceral adipose tissue ($n=108$, 1 female with HRT, 56 missing values for VAT) and (c) intrahepatic lipid content ($n=105$, 1 female with HRT, 59 missing values for IHL) show significant interactions with menopausal status on hIRsp. Shaded areas around the line depict the 95% confidence interval. An asterisk (*) denotes a significant simple slope, defined as a 95% CI that did not include 0.



ESM Fig. 2 Age-dependent hIResp in Tübingen Prediabetes Clusters in women and men. Clusters are divided into low-risk (cluster 1, 2 and 4) and high-risk (clusters 3, 5 and 6) separately. Plots show the effects of a two-way interaction between cluster $\times$ sex on hIResp using a two-sided linear regression model ($n=206$). Slopes can be found in Table S21. Shaded areas around the line depict the 95% confidence interval



ESM Fig. 3 Global brain and hippocampal volume in women and men. (a) Global brain volume and (b) normalized hippocampal volume significantly correlates with age in men but not women ($n=150$, 110 missing values for brain volume measurements).



ESM Fig. 4 Food craving score in female and male participants. Plots show the effects of a two-way interaction between age $\times$ sex on the food-craving sum score using a two-sided linear regression model ($n=227$, 33 missing values for FCQ-T). Older women show higher food craving with increasing age than men. Shaded areas around the line depict the 95% confidence interval.

Abbreviations: BMI, body mass index; CI, confidence interval; CL, confidence limit; FCQ-T, Food Cravings Questionnaire–Trait; FPG, fasting plasma glucose; GVIF, generalised variance inflation factor; hIResp, hippocampal insulin response HRT, hormonal replacement therapy; IHL, intrahepatic lipid content; R^2 , coefficient of determination; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WHR, waist-to-hip ratio.