Eat2beNICE

Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing Behaviours

H2020 - 728018

D5.3: Manuscript on the mediation effect of the microbiome composition and metabolism on the brain-(impulsive/compulsive) behaviour relationship

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1. Deliverable report

Note: publishers' policies prevent sharing of detailed results prior to publication in a peer-reviewed journal. Detailed results, tables and uncompromised figures will be made available upon acceptance and/or as soon as the publisher's embargo has been lifted.

Introduction

Insulin resistance negatively impacts cognitive performance in diabetic patients within the PREDIMED Plus study (Mallorqui-Bargue et al., 2018). This relation is also observed in healthy elderly community populations (e.g. Kong et al., 2018). Peripherally originated insulin resistance can result centrally in neuroinflammation, oxidative stress and plaque formation, ultimately resulting in cognitive decline (Folch et al., 2019).

The gut microbiota release nutrients from our diet and is in turn the biggest modulator of gut microbiota composition. Several gut microbiota and metabolites have been associated with insulin resistance; butyrate producing bacteria, mucin degrading bacteria, gut peptides stimulating insulin secretion (determining for ~50% the post-prandial insulin response to glucose), bile acid metabolites and lactic acid bacteria (Gerard and Vidal, 2019). We selected bacteria involved in insulin sensitivity to be tested for their modulatory role between insulin resistance and cognition in the PREDIMED Plus cohort (Martínez-González et al., 2019). In this cohort a sample of elderly (aged 55-75 years for men; 60-75 for women) with overweight or obesity and metabolic syndrome (body mass index 27 to 40 kg/m2) two lifestyle aspects were compared; energy-restricted Mediterranean diet (MedDiet) including recommendations on PA and motivational behaviour changes versus energy-unrestricted MedDiet. Already after 1 year, patients in the intervention group reported significant decreases in BMI and impulsivity compared to the energy-unrestricted MedDiet (Mallorquí-Bagué et al., 2021).

The current project aims to (1) determine whether insulin resistance is associated with cognitive function and/or age-related cognitive decline after two years in elderly with metabolic syndrome in the PREDIMED Plus study (across intervention groups). In case of such a direct relation, this pattern is hypothesized to (2) exert its effect through the gut microbiota, specifically those involved associated with insulin sensitivity (see Figure 1).

Methods

Participants

We included participants from the PREDIMED-Plus cohort for which insulin resistance values, cognitive task data and gut microbiota data was available, n=641. Participants with a depression diagnosis were excluded from the analyses, leading to final sample of n=515 (**See Table 1**).

Measures

Insulin resistance was determined by the Homeostatic model assessment (HOMA) method (Wallace, Levi & Matthews, 2004). HOMA is a method for assessing β-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations.

For the neuropsychological evaluation, we used a battery of six cognitive tests; Global Cognitive Functioning (GCF), the Mini-Mental State Evaluation, the clock drawing test, the semantic verbal fluency test 'animals in one minute', the phonemic verbal fluency test "words in one minute starting with letter 'p' ", the forward and reverse series of digits test (WAIS-III) and the trail making test, that were collected in personal interviews by the study nurses. The Global cognitive function is calculated with the following formula: GCF_v00 = (zMMSE_v00 + zCDT_v00 + zVFTa_v00 + zVFTp_v00 - zTMTa_v00 - zTMTb_v00 + zDSTf_v00 + zDSTb_v00) / 8

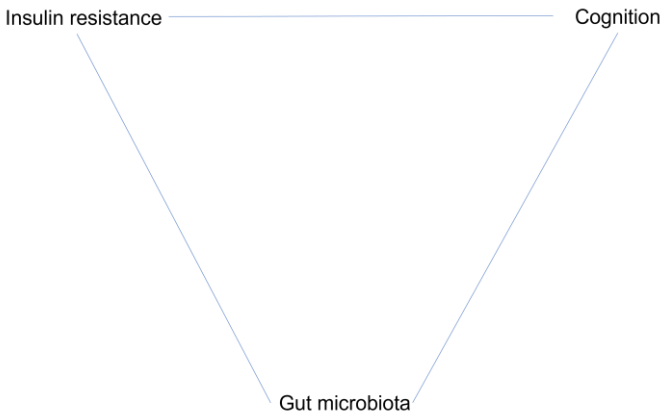

Figure 1. Schematic of mechanistic interrelations considered in this project. As a prerequisite for further analyses, a direct relation between insulin resistance and cognitive performance is evaluated.

Analyses

Normality of insulin resistance and cognitive performance data was assessed by visual inspection of the data distribution. Insulin resistance values were log normalized. We assessed a direct relation between insulin resistance and cognitive performance by using linear regression in R (package lme4), including covariates recruiting center, civil status, smoking status, diabetes, depression, education level, age, sex, bmi, (hyper)cholesterol status, hypertension status. These models were run using baseline cognitive performance and change in cognitive performance after two years.

Results

The direct relation between insulin resistance and cognitive performance did not yield significant associations; not between the baseline measurements or between baseline insulin resistance and the change in cognitive performance after two years (**Tables 2-4**).

Discussion

In the current sample of elderly with metabolic syndrome, cognitive performance and change in cognitive performance after two years did not relate to insulin resistance. As this was the premise to assess a mediating relation by the gut microbiota, the analyses were halted at this point.

References

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2. Tables and other supporting documents where applicable and necessary

Table 1. Descriptive Statistics (N=515)

		Baseline	T1
age (yrs)		64.73	64.73
male:female		305:210	305:210
education level			
	college	102	102
	high school	154	154
	Primary school or less	257	257
smoking status			
	current	71	71
	former	219	219
	never	223	223
Mean Bbody Weight		86.74	83.88
Mean BMI		32.69	31.61
Mean Insulin mesure		17.19	14.77
Mean CQI score		10.86	10.86
Men PDI score		47.00	46.53

Tables 2-4. Association between insulin resistance and cognitive performance

FULL SAMPLE SIZE (N=647)

Cross-sectional — HOMA-IR – cognition

Raw variables

	Coeff.	P value
GCF		
MMSE		
CDT		
VFTa		
VFTp		
TMTa		
TMTb		
DSTf		
DSTb	-.1573801	0.035

Z-scores

	Coeff.	P value
zGCF		
zMMSE		
zCDT		
zVFTa		
zVFTp		
zTMTa		
zTMTb		
zDSTf		
zDSTb	-.3609008	0.032

Longitudinal — changes in HOMA-IR – changes in cognition

Raw variables

	Coeff.	P value
delta_GCF		
Delta_MMSE		
Delta_CDT		
Delta_VFTa		
Delta_VFTp		
Delta_TMTa		
Delta_TMTb		
Delta_DSTf		
Delta_DSTb		

Z-scores

	Coeff.	P value
delta_zGCF		
Delta_zMMSE		
Delta_zCDT		
Delta_zVFTa		
Delta_zVFTp		
Delta_zTMTa		
Delta_zTMTb		
Delta_zDSTf		
Delta_zDSTb		

Longitudinal — baseline HOMA-IR – changes in cognition

Raw variables

	Coeff.	P value
GCF		
MMSE		
CDT		
VFTa		
VFTp		
TMTa		
TMTb		
DSTf		
DSTb		

Z-scores

	Coeff.	P value
zGCF	-.8781788	0.036
zMMSE		
zCDT		
zVFTa	-.3618722	0.019
zVFTp		
zTMTa		
zTMTb		
zDSTf		
zDSTb	-.408182	0.024

EXCLUDING SUBJECTS TREATED WITH INSULIN (-21)

Cross-sectional

HOMA-IR – cognition

Raw variables

	Coeff.	P value
GCF		
MMSE		
CDT		
VFTa		
VFTp		
TMTa		
TMTb		
DSTf		
DSTb	-.1573801	0.035

Z-scores

	Coeff.	P value
zGCF		
zMMSE		
zCDT		
zVFTa		
zVFTp		
zTMTa		
zTMTb		
zDSTf		
zDSTb	-.3609008	0.032

Longitudinal

changes in HOMA-IR – changes in cognition

Raw variables

	Coeff.	P value
delta_GCF		
Delta_MMSE		
Delta_CDT		
Delta_VFTa		
Delta_VFTp		
Delta_TMTa		
Delta_TMTb		
Delta_DSTf		
Delta_DSTb		

Z-scores

	Coeff.	P value
delta_zGCF		
Delta_zMMSE		
Delta_zCDT		
Delta_zVFTa		
Delta_zVFTp		
Delta_zTMTa		
Delta_zTMTb		
Delta_zDSTf		
Delta_zDSTb	.3529386	0.023

baseline HOMA-IR – changes in cognition

Raw variables

	Coeff.	P value
GCF		
MMSE		
CDT		
VFTa		
VFTp		
TMTa		
TMTb		
DSTf		
DSTb		

Z-scores

	Coeff.	P value
zGCF	-.8781788	0.036
zMMSE		
zCDT		
zVFTa	-.3618722	0.019
zVFTp		
zTMTa		
zTMTb		
zDSTf		
zDSTb	-.408182	0.024

Same linear model run in R (full sample size)

Cross-sectional

HOMA-IR – cognition

Raw variables

	Coeff.	P value
GCF	-1.48916	0.000392
MMSE	-0.166356	0.0956
CDT	0.056706	0.662
VFTa	-0.073933	0.0482
VFTp	-0.083582	0.0413
TMTa	0.012745	0.0204
TMTb	0.009775	0.000248
DSTf	-0.12114	0.096131
DSTb	-0.15644	0.071443

Z-scores

	Coeff.	P value
zGCF	-0.93388	0.000392
zMMSE	-0.36419	0.0931
zCDT	0.066329	0.7294
zVFTa	-0.38674	0.0403
zVFTp	-0.424360	0.0260
zTMTa	0.42884	0.011991
zTMTb	0.85680	0.000196
zDSTf	-0.329819	0.0731
zDSTb	-0.37201	0.0587

Longitudinal

changes in HOMA-IR – changes in cognition

Raw variables

	Coeff.	P value
delta_GCF	-1.648e-01	0.7588
Delta_MMSE	7.474e-02	0.49047
Delta_CDT	1.531e-01	0.23311
Delta_VFTa	6.569e-04	0.98332
Delta_VFTp	-5.855e-03	0.87190
Delta_TMTa	1.633e-02	0.00612
Delta_TMTb	3.402e-03	0.21704
Delta_DSTf	-4.493e-02	0.4303
Delta_DSTb	6.793e-02	0.3418

Z-scores

	Coeff.	P value
delta_zGCF	3.507e-01	0.16947
Delta_zMMSE	2.334e-01	0.39662
Delta_zCDT	6.207e-02	0.76159
Delta_zVFTa	6.171e-02	0.67548
Delta_zVFTp	-6.778e-03	0.96404
Delta_zTMTa	-1.928e-01	0.2352
Delta_zTMTb	-1.259e-01	0.5630
Delta_zDSTf	7.639e-02	0.6004
Delta_zDSTb	3.096e-01	0.06226

baseline HOMA-IR – changes in cognition

Raw variables

	Coeff.	P value
GCF	6.984e-01	0.2357
MMSE	1.046e-02	0.9297
CDT	8.680e-02	0.5431
VFTa	-2.140e-02	0.5623
VFTp	-2.805e-03	0.9474
TMTa	-2.801e-03	0.6871
TMTb	-8.028e-03	0.0101
DSTf	-1.590e-02	0.8110
DSTb	2.739e-02	0.7434

Z-scores

	Coeff.	P value
zGCF	-8.226e-01	0.00348
zMMSE	-6.344e-01	0.0330
zCDT	2.522e-01	0.2735
zVFTa	-3.565e-01	0.0391
zVFTp	-3.431e-01	0.0504
zTMTa	0.4645781	0.0137
zTMTb	4.740e-01	0.0604
zDSTf	-3.371e-01	0.04758
zDSTb	-3.294e-01	0.08840

In these tables just significant results are highlighted

3. Acknowledgement and Disclaimer

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 728018.