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3. Effective Date (07-August-2008)

04-APRIL-2020

4. Are you the corresponding author?

☐ Yes

☒ No

5. Manuscript Title

Monounsaturated fat rapidly induces hepatic-glucose homeostasis and whole-body insulin resistance

6. Manuscript Identifying Number (if you know it)

134520-INS-CMED-TR-2

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						ADD
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						ADD
11. Stock/stock options	☒	☐	☐			X
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						ADD
6. Payment for lectures including service on speakers bureaus	☐	☒	☐	Boehringer-Ingelheim Pharma Eli Lilly; Prosciento; Sanofi US Fishawade Group; Novo Nordisk Genentech Laboratories; Target NASH		X
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1 Supplemental Material

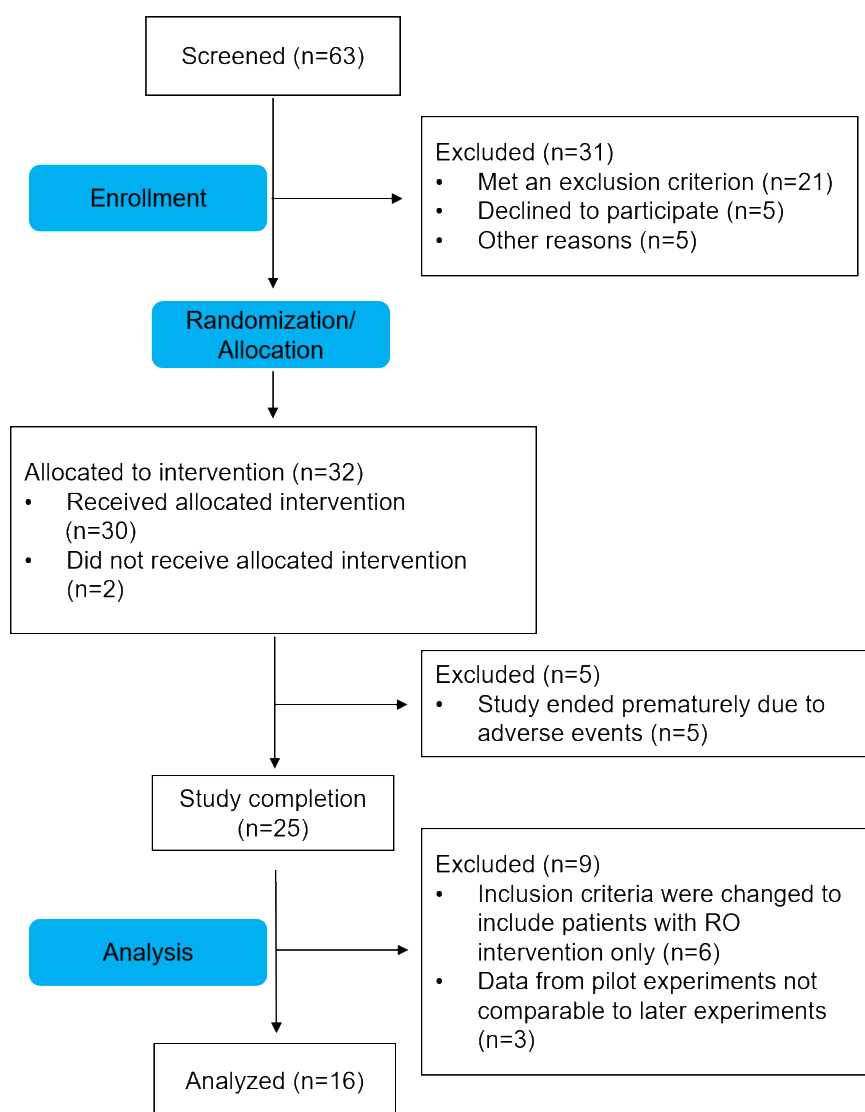


Figure S1. CONSORT flow diagram. Sixty-three patients underwent screening, which included medical history, clinical examination, anthropometry, bioimpedance analysis and a 75-g oral glucose tolerance test. Of the 63 screened volunteers, 32 were allocated to the interventions, and 30 participants received the allocated interventions. Five volunteers were excluded prematurely. In total, 25 participants completed the study. Another 6 participants had to be excluded after a change of inclusion criteria and due to differences in data acquisition in the pilot experiments so that data could not be pooled (n=3). Ultimately, data from 6 female and 10 male participants were analysed. Results of the control experiments of the male volunteers have already been published in a previous publication (1). As there were more drop outs for the rapeseed oil than for the palm oil intervention in the first set of experiments, only results for palm oil vs vehicle were published due to power considerations and additional experiments were performed for canola oil vs vehicle at a later time point to increase patient number.

1 **Table S1. Time course of plasma free fatty acid spectrum after OIL and VCL**

Fatty acid species (µg/ml)	Intervention	Time		
		0 min	+180 min	+360 min
Linoleic acid (18:2)	VCL	17±4	11±2	59±14
	OIL	16±1	19±1	34±3
Myristic acid (14:0)	VCL	3±1	2±1	10±4
	OIL	2±0	2±1	2±1
Oleic acid (18:1)	VCL	42±12	33±7	86±16
	OIL	41±7	59±12	122±13*
Palmitic acid (16:0)	VCL	28±7	18±3	37±15
	OIL	29±4	26±3	35±5
Palmitoleic acid (16:1)	VCL	7±1	5±0.3	16±3
	OIL	6±1	5±1	5±2
Stearic acid (18:0)	VCL	8±0	6±1	17±2
	OIL	11±2	11±2	16±1

2 Concentrations were measured in participants before administration canola oil (OIL) or water (vehicle,
3 VCL) at 0 min and at +180 min and +360 min (pre-clamp period). Data are shown as means±SEM; n=3; *,
4 p<0.05 +360 min OIL vs. +0 min OIL.
5

6

7

1 **Table S2. Time course of adipokines, cytokines and hormones**

Parameter	Intervention	Time			
		0 min	+120 min	+240 min	+360 min
Leptin (ng/ml)	VCL	13.9±3.3	11.5±2.6	11.5±2.6	10.6±2.3
	OIL	12.6±2.9	11.7±2.6	11.1±2.6	10.7±2.4
HMW adiponectin (µg/ml)	VCL	2.3±0.2	2.5±0.3	2.7±0.4	2.1±0.2
	OIL	2.4±0.2	2.6±0.2	2.6±0.2	2.7±0.2
IL-1ra (pg/ml)	VCL	280±28	255±26	284±59	259±27
	OIL	333±33	321±32	359±38	330±28
IL-18 (pg/ml)	VCL	178±15	170±13	169±14	172±14
	OIL	226±46	238±45	235±44	241±48
FABP-4 (ng/ml)	VCL	8.6±1.0	8.2±1.1	7.9±0.9	7.8±1.0
	OIL	8.5±1.1	8.3±1.0	8.1±1.0	7.7±3.3
FGF21 (pg/ml)	VCL	212±43	157±39	134±27	135±21
	OIL	154±23**	99±13**	90±10**	126±20
Cortisol (µg/dl)	VCL	17±1.4	12±1.1	9±1.0	11±1.8
	OIL	16±1.2	14±1.9	12±1.4	11±1.0

2 Concentrations were measured in participants before administration of canola oil (OIL) or water (vehicle,
3 VCL) at 0 min and at +120 min, +240 min and +360 min (pre-clamp period). Data are shown as
4 means±SEM; n=16; **, p<0.005 OIL vs. VCL. IL-1ra: interleukin-1 receptor antagonist; IL-18: interleukin-
5 18; FABP-4: fatty acid binding protein-4; FGF21: fibroblast growth factor 21.

6

Table S3. List of parameters during steady-state conditions (+460 - +480 min)

Parameter	Intervention	Time		
		+460 min	+470 min	+480 min
C-peptide (ng/ml)	VCL			1.5±0.7
	OIL			2.3±0.9**
GIR (ml/h)	VCL	127±58	131±65	127±58
	OIL	94±33	98±34	98±34*
APE (mg/min)	VCL	2.3±0.2	2.5±0.2	2.3±0.2
	OIL	2.4±0.2	2.5±0.2	2.5±0.2

Circulating serum C-peptide concentrations, glucose infusion rate (GIR, 20% glucose infusion) and atom percent enrichment of [6,6-²H₂]glucose in the blood glucose pool (APE) during steady state of the clamp period with canola oil (OIL) or water (vehicle, VCL). Data are shown as means ± SEM; n=16; *, p<0.05 OIL vs. VCL, **, p<0.005 OIL vs. VCL.

1 **References**

- 2 1. Hernandez EA, Kahl S, Seelig A, Begovatz P, Irmeler M, Kupriyanova Y, et al. Acute dietary fat
3 intake initiates alterations in energy metabolism and insulin resistance. J Clin Invest. 2017;127(2):695-
4 708.

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