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Effects of a "HEALTHGRAIN" diet on metabolic risk factors in subjects predisposed to type 2 diabetes and cardiovascular disease – a two centre study

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Lund, May 6th, 2010

Association of wholegrain intake with type 2 diabetes

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Table 3. A summary of the cohort- and cross-sectional studies that have assessed the association between intake of whole grain and the risk of type 2 diabetes or indicators of glucose metabolism

Reference	Study	Study population/ cases[a]	Follow-up (years)	Diet assessment[b]	Outcome[c]	Results[d]	Adjustments[e]
Cohort studies							
Pereira et al. (1998)	The CARDIA study	3 627 / NR F/M	7	Diet history	Fasting serum insulin	B^f = -2.44%; P<0.01	Age, sex, BMI, smoking, energy intake, PA, field center, alcohol use, education, race and interaction terms of field center, smoking, education, race and sex
Liu et al. (2000)	The Nurses' Health Study	75 521 / 1879 F	10	FFQ (61 items)	Incidence of DM2	RR=0.73 (0.63–0.85)	Age, BMI, smoking, energy intake, PA, family history of diabetes, alcohol use, supplement use
Meyer et al. (2000)	The Iowa Women's Health Study	35 988 / 1141 F	6	FFQ (127 items)	Incidence of DM2	RR=0.79 (0.65–0.96)	Age, BMI, smoking, energy intake PA, WHR, alcohol use, education,
Fung et al. (2002)	The Health Professionals Follow-up Study	42 898 / 1197 M	12	FFQ (131 items)	Incidence of DM2	RR=0.70 (0.57–0.85)	Age, BMI, smoking, energy intake, PA, Family history of diabetes, alcohol use, fruit and vegetable intakes
Cross-sectional studies							
McKeown et al. (2002)	The Framingham Offspring Study	2941 / NR F/M		FFQ (126 item)	Fasting plasma insulin	Dif=-3%; P=0.03	Age, sex, smoking, energy intake, PA, BP, Alcohol use, FAT, supplement use
Liese et al. (2003)	The Insulin Resistance and Atherosclerosis Study	1600 / NR F/M		FFQ (114 items)	Insulin sensitivity	β=0.04; P = 0.03	Age, sex, BMI, smoking, energy intake, family history of diabetes, WC, ethnicity, clinic, energy expenditure
Esmaillzadeh et al. (2004)	Teheran Lipid and Glucose Study	827 / NR F/M		FFQ (NR)	New DM2	OR=0.88 (0.80–0.94)	Age, sex, smoking, energy intake, BP, energy from fat, estrogen use, diet[g]
McKeown et al. (2004)	The Framingham Offspring Study	2 834 / F/M		FFQ (126 item)	Prevalence of metabolic syndrome	OR=0.67 (0.48-0.91)	Age, sex, smoking, energy intake, PA, alcohol use, FAT, multivitamin use, BP

[a]F = females, M = males, NR = not reported. [b]FFQ = food frequency questionnaire. [c]DM2 = type 2 diabetes. [d]RR = relative risk between the extreme categories of the exposure, β = β coefficient for linear regression for association between dietary exposure and continuous outcome variable, Dif = Difference in fasting insulin between the extreme quintiles of whole grain intake (highest-lowest/highest*100), OR = Odds ratio of type 2 diabetes between the extreme categories of exposure. [e]Adjustments by modeling, BMI = body mass index, PA = physical activity, WHR = waist-to-hips ratio, WC = waist circumference, BP = blood pressure, FAT = intakes of saturated fat and polyunsaturated fat. [f]Repeated measures regression, expected change in fasting insulin (%) per change in intake frequency of the intake. [g]Consumption of meat, fish, fruit and vegetables.

Montonen, Publications of the National Public Health Institute A13/2005

Effects of wholegrains on glucose and insulin homeostasis: evidence from controlled diet intervention studies

Reference	Subjects	Design	Test cereal	Outcome
Leinonen et al 2000	40	2 x 4 weeks crossover	Rye bread	No difference
Saltzman et al 2001	43	2 parallel groups, 6 weeks	Oats	No difference
Jenkins et al 2002	23	2 x 12 weeks crossover	Wheat bran	No difference
Pereira et al 2002	11	2 x 6 weeks crossover	Wholegrain wheat	Improved insulin sensitivity
Juntunen et al 2003	20	2 x 8 weeks crossover	High-fiber rye bread	Enhanced acute insulin secretion
Laaksonen et al 2005	72	2 parallel groups, 12 weeks	Rye bread+pasta	Enhanced early insulin secretion
Östman et al 2006	7	2 x 3 weeks crossover	Wheat, rye, oats	Improved insulin economy
Anderson et al 2007	30	2 x 6 weeks crossover	Wheat, rye, oats	No difference
Giacco et al 2010	15	2 x 3 weeks crossover	Wholemeal wheat	No difference

Outcome parameters: fasting plasma glucose and serum insulin, indices of insulin sensitivity and secretion from FSIGT or clamp test, insulinogenic index from OGTT

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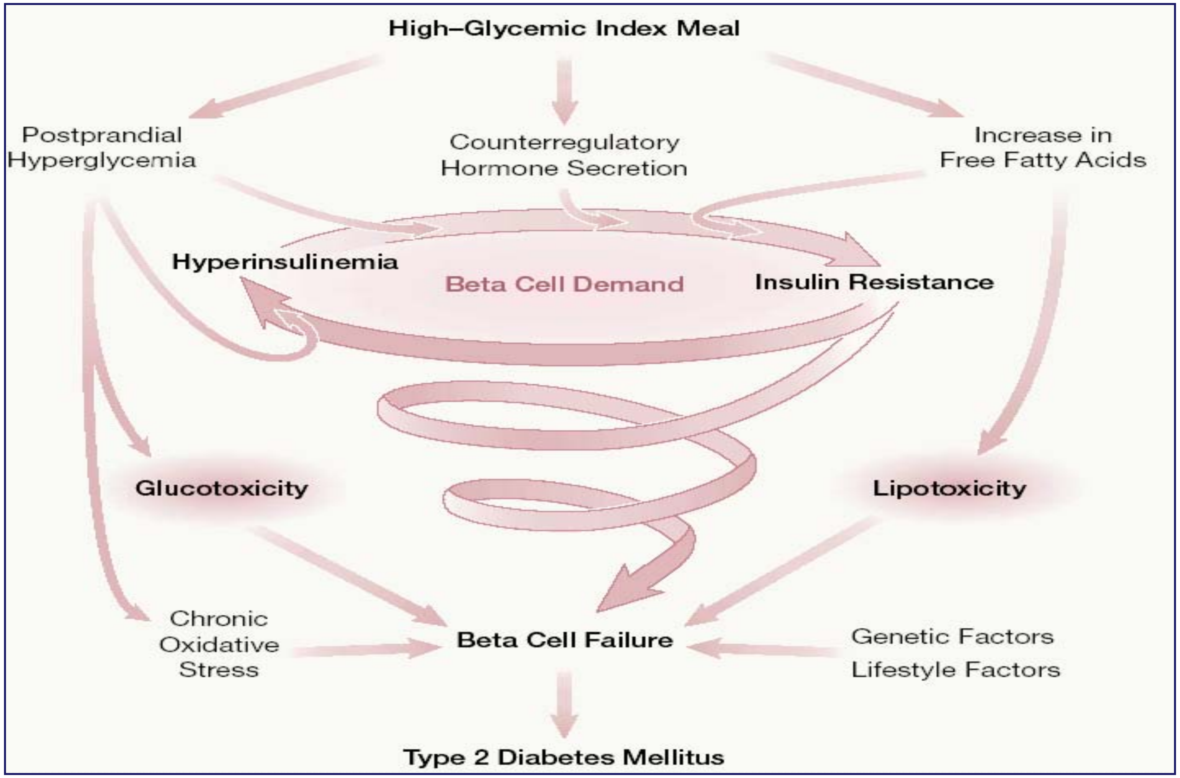
Study objective

- **To determine the effects of a HEALTHGRAIN diet , containing cereals with demonstrated positive effects on glucose and insulin homeostasis, on metabolic risk factors in subjects predisposed to type 2 diabetes and cardiovascular disease in two different dietary settings (Kuopio/Finland and Naples/Italy)**



Ludwig 2002

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Study design

N=30/centre

Control diet: refined cereals

Randomization:
gender, age, BMI,
2h OGTT

4-d/7-d food record

N=30/centre

Experimental diet: mainly wholegrain cereals

0 | 4 wk | 8 wk | 12 wk

4-d/7-d food record | 4-d/7-d food record | 4-d/7-d food record

Anthropometry
FSIGT
OGTT (Kuopio)
Meal study (Naples)
Blood biochemistry
Blood pressure
Gene expression (PBMC, adipose tissue)
Fecal samples/Kuopio
Urine samples/Naples

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Cereal products used in the intervention

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Kuopio

- **Experimental diet**
  - endosperm rye bread (40% share)
  - sourdough wholemeal wheat bread (10%)
  - a selection of commercial rye bread (50%)
  - wholemeal pasta to replace potato and rice
  - oat biscuits
- **Control diet**
  - a selection of refined wheat breads
  - potatoes

Naples

- **Experimental diet**
  - endosperm rye bread (10% share)
  - sourdough wholemeal wheat bread (10%)
  - traditional Italian wholemeal sourdough bread (80%)
  - wholemeal pasta, barley, corn
  - oat biscuits
- **Control diet**
  - a selection of refined wheat breads
  - rice, pizza

Cereal products consumed in the experimental diet have low postprandial glucose and/or insulin response

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Study subjects

- target: 60 subjects/location (30 per diet group)
  - in three lots 2008-2009

- final number of study participants: 69 in Kuopio, 54 in Naples
  - in three lots 2008-2009

Diet	Kuopio	Naples
	Started/Completed	Started/Completed
Experimental	**41/34**	**30/28**
Control	**44/35**	**30/26**

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Inclusion criteria

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- age 40-65 yr
- BMI 26-39
- IGT (2-h glucose 7.8-11.0 mmol/L) or IFG (glucose 5.6-6.9 mmol/L)
- waist circumference >102 (men), >88 (women) cm
- fasting serum triglyceride >1.7 mmol/L
- HDL cholesterol <1.0 mmol/L (men), <1.3 mmol/L (women)
- blood pressure >130/>85 mmHg

(3/5 of the NCEP criteria for the metabolic syndrome)

Characteristics of the study subjects at the baseline

	Kuopio		Naples	
	Test	Control	Test	Control
N (men/women)	34 (17/17)	35 (18/17)	28 (12/16)	26 (11/15)
Age (yr)	58 8	59 7	57 9	58 8
Weight (kg)	90 15	90 13	88 17	86 19
BMI (kg/m^2)	31 3	31 4	32 6	32 6
fS-total chol (mmol/L)	5.1 1.0	5.4 1.0	5.2 1.0	5.1 1.0
fS-LDL-chol (mmol/L)	3.2 0.8	3.4 0.8	3.3 1.1	3.4 0.8

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Fullfilment of the inclusion criteria (% of the participants)

	Kuopio		Naples	
	Test	Control	Test	Control
Fasting glucose ≥ 5.6 mmol/L (<6.9 mmol/L)	91	97	61	58
2-hour glucose ≥ 7.8 mmol/L (<11.0 mmol/L)	27	31	25	27
Waist circumference ≥ 102 cm or ≥ 88 cm	88	91	96	92
Diastolic blood pressure ≥ 85 mmHg	53	71	38	61
Systolic blood pressure ≥ 130 mmHg	59	83	50	64
Fasting HDL-cholesterol ≤ 1.0 mmol/l or ≤ 1.3 mmol/L	41	43	50	81
Fasting triglyceride ≤ 1.7 mmol/L	32	23	36	46

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Consumption of breads (based on daily questionnaire)

Breads	Kuopio		Naples	
	g/d	%	g/d	%
Sourdough whole wheat bread	26	14	18	10
Endosperm rye bread	73	39	18	10
Traditional Italian wholemeal sourdough bread	-	-	140	80
Commercial rye breads	87	47	-	-
Total of breads in experimental diet	185	100	176	100
Total of breads in control diet	194	100	139	100

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Daily intakes of energy and energy nutrients and fiber (mean SD)

	Kuopio		Naples	
	Test (n = 34)	Control (n = 35)	Test (n = 28)	Control (n = 26)
Energy (MJ, kcal)				
Week 0	7.0 2.4	7.3 2.0	1817 520	1780 420
Week 12	7.8 2.8	8.6 2.2	2134 445	1969 286
Carbohydrates (E%)				
Week 0	46 6	48 6	50 ± 5	51 ± 5
Week 12	46 8	47 6	53 ± 5	54 ± 5
Protein (E%)				
Week 0	19 3	19 4	17 ± 3	17 ± 3
Week 12	19 3	19 3	18 ± 1	17 ± 2
Fat (E%)				
Week 0	34 5	31 5	33 ± 5	32 ± 5
Week 12	33 7	33 6	29 ± 5	29 ± 5
Fiber (g)				
Week 0	25 7	23 7	20 6	20 5
Week 12	25 5	18 5	40 9	22 6

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Intake of bioactive compounds of the test breads according to mean consumption of the breads

		Ferulic acid (mg/day)	Folate (µg/day)	Betaine (mg/day)	Choline (mg/day)	Tocols (µg/day)	Alkyl-resorcinols (mg/day)
Kuopio	Breads in experimental diet	64	62	171	25	2964	80
	Breads in control diet (5 commercial refined wheat breads)	17	78	116	24	5445*	7
Naples	Breads in experimental diet	117	116	272	60	4810	220
	Breads in control diet	8	67	115	22	2470	22

*Commercial wheat breads contain vegetable oil, which may explain the higher tocol intake from these breads.

Anthropometry (mean SD)

	Kuopio		Naples	
	Test (n = 34)	Control (n = 35)	Test (n = 28)	Control (n = 26)
Weight (kg)				
Week 0	89 15	89 13	88 ± 17	85 ± 19
Week 12	89 15	90 13	87 ± 16	85 ± 19
BMI (kg/m^2)				
Week 0	31 3	31 4	32 ± 6	32 ± 5
Week 12	31 3	31 4	32 ± 6	31 ± 5
Waist circumference (cm)[a]				
Week 0	106 11	106 10	107 16	106 ± 12
Week 12	106 11	106 10	107 ± 15	105 ± 12
Body fat (%)				
Week 0	37 7	36 9	36 ± 9	34 ± 9
Week 12	37 7	37 9[b]	36 ± 9	33 ± 9

[a]$p<0.05$, General linear model for repeated measures
[b]$p<0.05$, Paired samples T-test

Fasting plasma glucose and serum insulin concentrations (mean SD)

	Kuopio		Naples	
	Test (n = 34)	Control (n = 35)	Test (n = 28)	Control (n = 26)
fP-glucose (mmol/L, mg/dL)				
Week 0	6.1 0.4	6.2 0.5	104 12	105 10
Week 12	6.1 0.5	6.2 0.5	106 13	105 11
fS-Insulin (mU/L)				
Week 0	12.0 6.2	12.8 6.6	17.1 9.8	13.1 5.7
Week 12	13.7 8.0	13.2 6.3	18.2 8.5	12.0 5.2

No significant differences (P>0.05, General linear model for repeated measures)

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Fasting lipid, lipoprotein and adiponectin concentrations (mean SD)

	Kuopio	Naples
Fasting serum cholesterol (mmol/L)	NS	NS
Fasting serum HDL cholesterol (mmol/L)	NS	NS
Fasting serum LDL cholesterol (mmol/L)	NS	NS
Fasting serum triglycerides (mmol/L)	NS	NS
Fasting serum ApoA-1 (g/L)	NS	-
Fasting serum ApoB (g/L)	NS	-
Adiponectin (µg/L)	NS	-

No significant differences (P>0.05, General linear model for repeated measures)

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Indices of insulin sensitivity and secretion based on FSIGT, fasting glucose and insulin, and 2h-OGTT

	Kuopio		Naples	
	Test (n = 34)	Control (n = 35)	Test (n = 28)	Control (n = 23)
S_i (insulin sensitivity/FSIGT)				
Week 0	2.7 1.5	2.8 1.4	2.4 ± 1.7	2.9 ± 2.4
Week 12	2.6 1.2	2.4 1.2	2.6 ± 1.7	2.9 ± 1.8
AIR (acute insulin secretion/FSIGT, Minmod/Kuopio, AUC/Naples)				
Week 0	6.0 6.8	5.1 3.7	914 729	854 615
Week 12	5.9 6.2	5.6 3.8	908 682	837 620
Quicki (insulin sensitivity/fasting values)				
Week 0	0.33 0.02	0.32 0.02	0.32 ± 0.02	0.33 ± 0.02
Week 12	0.32 0.03[a]	0.32 0.02	0.32 ± 0.02	0.31 ± 0.03
Insulinogenic index (early insulin secretion/2h-OGTT)				
Week 0	23.1 16.6	22.6 13.9	-	-
Week 12	24.3 16.3	21.5 12.8	-	-

No significant group x time interaction in General linear model for repeated measures or for univariate analyses, adjusted with baseline weight (kg), baseline level of particular variable and the time of the year when the study started. Time effect was significant for Quicki (p=0.008).

[a] p=0.081 in paired sample t-test

Glucose and insulin curves at the end of intervention (2-h OGTT/Kuopio)

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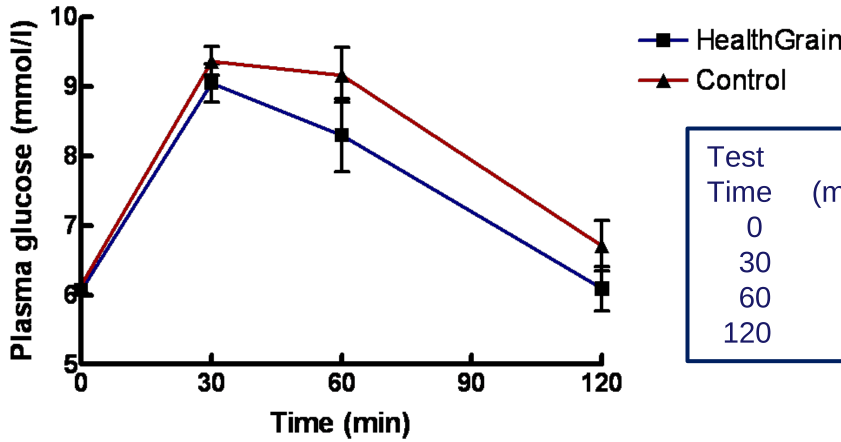
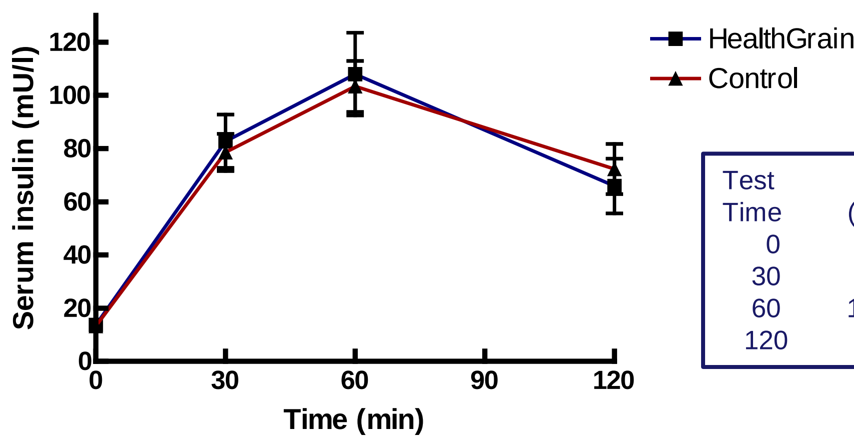


Test Time	(mean ± SD)	n	Control Time	(mean ± SD)	n
0	6,1 ± 0,5	34	0	6,2 ± 0,5	35
30	9,1 ± 1,6	33	30	9,4 ± 1,2	35
60	8,3 ± 2,6	25	60	9,2 ± 2,0	26
120	6,1 ± 1,9	34	120	6,7 ± 2,2	35



Test Time	(mean ± SD)	n	Control Time	(mean ± SD)	n
0	13,7 ± 8,0	34	0	13,2 ± 6,3	35
30	82,7 ± 57,4	33	30	78,6 ± 41,5	35
60	108,0 ± 77,7	25	60	103,4 ± 48,8	26
120	65,9 ± 59,9	34	120	72,3 ± 55,7	35

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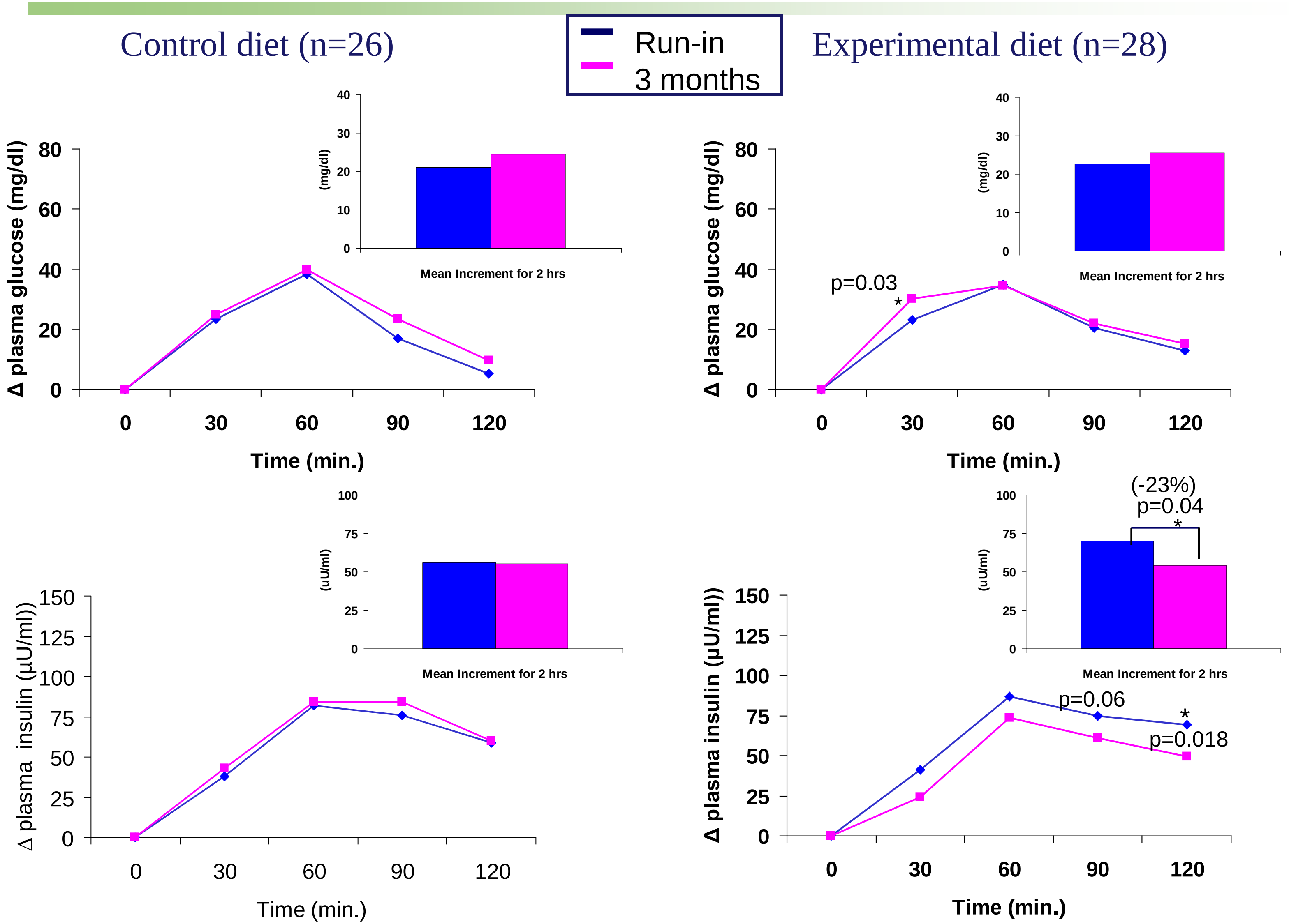
Plasma glucose and insulin responses to the test meals (Naples)



ANOVA *p=0.05 Changes (3 months - Run-in) in mean plasma insulin for 2 hrs postprandial increments between experimental and control diet

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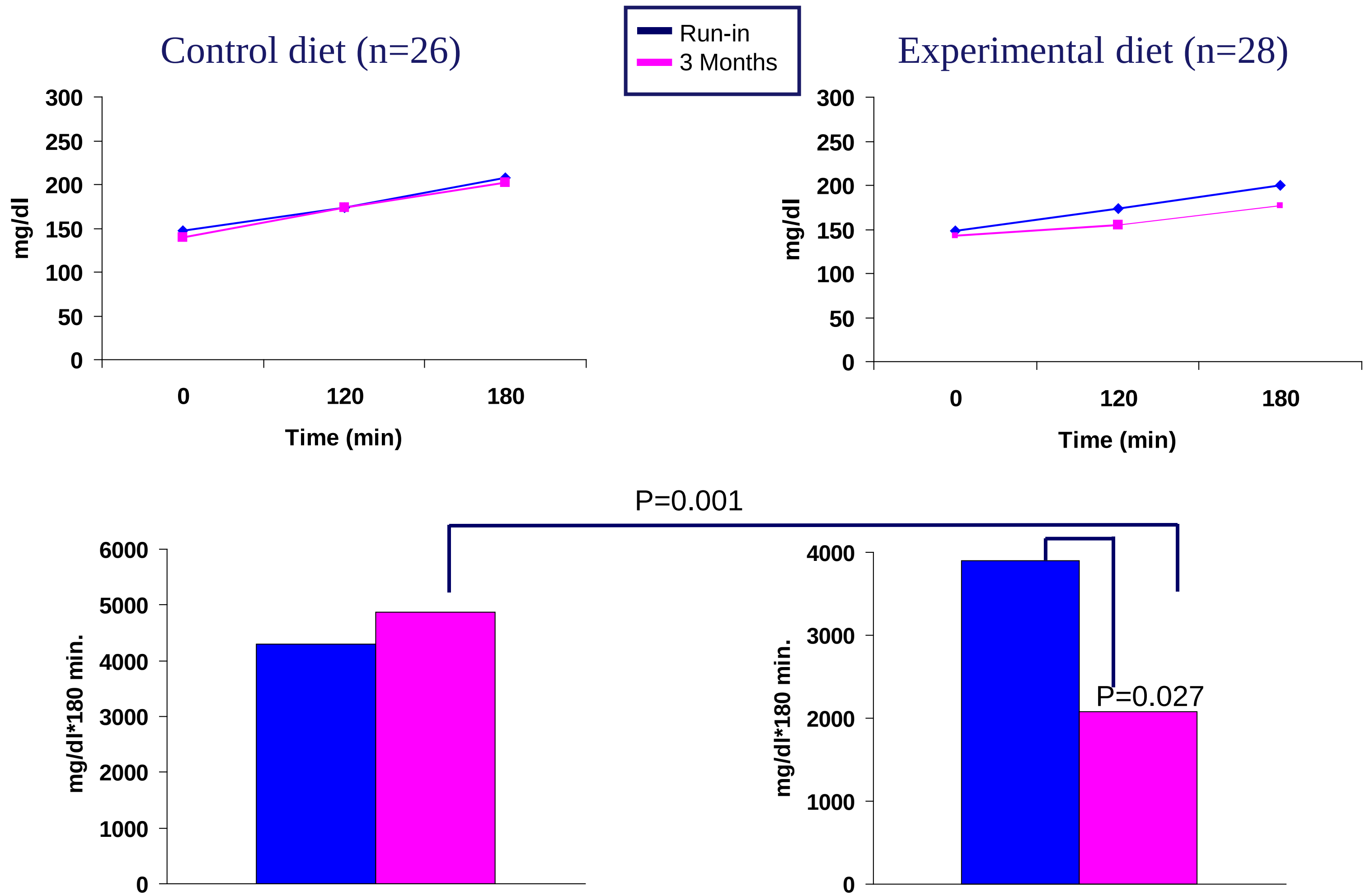
Plasma triglyceride responses to the two test meals (Naples)



ANOVA *p=0.017 Changes (3 months- Run-in) in plasma triglycerides postprandial incremental area between experimental and control diet

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Summary and conclusions

- Subjects filled the criteria of metabolic syndrome
- Good dietary compliance during the intervention period in both groups
- No significant changes in anthropometry, blood pressure, fasting blood glucose, insulin and lipids, and in indicators of insulin sensitivity and secretion
- Tendency towards improved glucose homeostasis during 2-h OGTT and after a test meal, and improved postprandial triglyceride metabolism after a test meal in the group receiving the HEALTHGRAIN diet

- This study suggests that dietary modification will influence primarily the postprandial events related to glucose and triglyceride homeostasis within the gut region