Obesity in Finland
Background and Research in Kuopio

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Research areas

Diet and chronic diseases
- obesity
- diabetes
- cardiovascular diseases

Eating behaviour
- dietary counselling
- weight management

Food and Health
- whole grain
- berries
- fish (fat)
- probiotics
- plant sterols

Safety and health aspects of foods
- lactic acid bacteria
- microbial toxicants and contaminants
- phytochemistry

Nutrition as part of promotion of health
## Obesity in Finland

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI: weight (kg) / Height (m)$^2$</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Normal weight</td>
<td>&lt;25</td>
<td></td>
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<tr>
<td>Overweight</td>
<td>25-30</td>
<td>&gt;60% of the popul.</td>
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<tr>
<td>Obesity (Class I)</td>
<td>30-35</td>
<td>&gt;20% of the popul.</td>
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<tr>
<td>Severe obesity (Class II)</td>
<td>35-40</td>
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<tr>
<td>Morbid obesity</td>
<td>&gt;40</td>
<td>1-2% of the popul.</td>
</tr>
</tbody>
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2007-2012 the increase was less than 2002-2007
How to tackle obesity related problems – contribution in Kuopio

Teaching of Clinical Nutrition
- Nutrionist education essential
- In society to promote health
- Education of doctors, nurses etc.

Research of Clinical Nutrition
- Evidence-based knowledge
- Novel individualized treatments
- Multidiscipl. with food technology

Optimal treatment

Nutrition (and other lifestyle factors)

Molecular level
- Interaction with genes

Metabolic level
- NAFLD important, metabolomics, systemns biology

Traditional treatment

Common diseases (e.g. obesity and diabetes)
## Non-alcoholic Fatty Liver Disease (NAFLD)

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**Adult population: 10-50% have NAFLD**

Szczepaniak 2005; Kallwitz 2009; Vernon 2011

- 50% NAFLD → 10% of the popul.
- 90% NAFLD → 1% of the popul.
Lifestyle change is the best treatment for diabetes risk
Finnish Diabetes Prevention Study

Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS)

J. Lindström · M. Peltonen · J. G. Eriksson · P. Ilanne-Parikka · S. Aunola · S. Keinänen-Kiukaanniemi · M. Uusitupa · J. Tuomilehto · for the Finnish Diabetes Prevention Study (DPS)
Examples of intervention studies with a focus on nutrition
Triacylglycerol Fatty Acid Composition in Diet-Induced Weight Loss in Subjects with Abnormal Glucose Metabolism – the GENOBIN Study

Ursula Schwab¹,²*, Tuulikki Seppänen-Laakso³, Laxman Yetukuri³, Jyrki Ågren⁴, Marjukka Kolehmainen¹, David E. Laaksonen⁴,⁵, Anna-Liisa Ruskeepää³, Helena Gylling¹,², Matti Uusitupa¹, Matej Orešič³* for the GENOBIN Study Group

¹ School of Public Health and Clinical Nutrition, Department of Clinical Nutrition and Food and Health Research Centre, University of Kuopio, Kuopio, Finland, ² Kuopio University Hospital, Kuopio, Finland, ³ VTT Technical Research Centre of Finland, Espoo, Finland, ⁴ Department of Physiology, University of Kuopio, Kuopio, Finland, ⁵ Department of Medicine, Kuopio University Hospital, Kuopio, Finland

Abstract

Background: The effect of weight loss on different plasma lipid subclasses at the molecular level is unknown. The aim of this study was to examine whether a diet-induced weight reduction result in changes in the extended plasma lipid profiles (lipidome) in subjects with features of metabolic syndrome in a 33-week intervention.

Methodology/Principal Findings: Plasma samples of 9 subjects in the weight reduction group and 10 subjects in the control group were analyzed using mass spectrometry based lipidomic and fatty acid analyses. Body weight decreased in the weight reduction group by 7.8±2.9% (p<0.01). Most of the serum triacylglycerols and phosphatidylcholines were reduced. The decrease in triacylglycerols affected predominantly the saturated short chain fatty acids. This decrease of saturated short chain fatty acid containing triacylglycerols correlated with the increase of insulin sensitivity. However, levels of several longer chain fatty acids, including arachidonic and docosahexanoic acid, were not affected by weight loss. Levels of other lipids known to be associated with obesity such as sphingolipids and lysophosphatidylcholines were not altered by weight reduction.

Conclusions/Significance: Diet-induced weight loss caused significant changes in global lipid profiles in subjects with abnormal glucose metabolism. The observed changes may affect insulin sensitivity and glucose metabolism in these subjects.

Trial Registration: ClinicalTrials.gov NCT00621205
Weight reduction modulates expression of genes involved in extracellular matrix and cell death: the GENOBIN study

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¹School of Public Health and Clinical Nutrition, Clinical Nutrition and Food and Health Research Center, University of Kuopio, Kuopio, Finland; ²Institute of Clinical Medicine, Internal Medicine, Kuopio University Hospital, Kuopio, Finland; ³Department of Computer Science, University of Kuopio, Kuopio, Finland; ⁴Institute of Biomedicine, Physiology, University of Kuopio, Kuopio, Finland; ⁵Kuopio Research Institute of Exercise Medicine, University of Kuopio, Kuopio, Finland and ⁶Institute of Clinical Medicine, Clinical Physiology, Kuopio University Hospital, Kuopio, Finland

Objective: Lifestyle and genetic factors interact in the development of obesity and the metabolic syndrome. The molecular mechanisms underlying the beneficial dietary modifications are, however, unclear. We aimed to examine the effect of the long-term moderate weight reduction on gene expression in adipose tissue (AT) and to identify genes and gene clusters responsive to treatment and thereby likely contributing to the development of the metabolic syndrome.

Design: Randomized controlled and individualized weight reduction intervention.

Subjects: Forty-six subjects with impaired fasting glycemia or impaired glucose tolerance and features of metabolic syndrome, aged 60±7 years were randomized either to a weight reduction (WR) (n=28) or a control (n=18) group lasting for 33 weeks.

Measurements: Oral and intravenous glucose tolerance tests and subcutaneous AT biopsies were performed before and after the intervention. Gene expression of AT was studied using microarray technology in subgroups of WR (with weight reduction ≥5%, n=9) and control group (n=10). The results were confirmed using quantitative PCR.

Results: In the WR group, glucose metabolism improved. Moreover, an inverse correlation between the change in S₁ and the change in body weight was found (r=−0.44, P=0.026). Downregulation of gene expression (P<0.01) involving gene ontology groups of extracellular matrix and cell death was seen. Such changes did not occur in the control group. The tenomodulin-gene was one of the most downregulated genes (-39±16%, P<0.0001). Moreover, its expression correlated with insulin sensitivity (r=−0.34, P=0.005) before the intervention and with body adiposity both before (r=0.42, P=0.007) and after (r=0.30, P=0.056) the intervention.

Conclusion: Genes regulating the extracellular matrix and cell death showed a strong downregulation after long-term weight reduction. This likely reflects a new stable state at the molecular level in AT. Further studies are warranted to elucidate the mechanisms of these genetic factors.

Effects of an isocaloric healthy Nordic diet on insulin sensitivity, lipid profile and inflammation markers in metabolic syndrome – a randomized study (SYSDIET)


From the ¹Institute of Public Health and Clinical Nutrition, University of Eastern Finland; ²Research Unit, Kuopio University Hospital, Kuopio, Finland; ³Department of Medicine and Endocrinology MEA, Aarhus University Hospital, Aarhus, Denmark; ⁴Institute of Clinical Medicine, Department of Internal Medicine, University of Oulu, Oulu, ⁵Institute of Clinical Medicine, Internal Medicine, Kuopio University Hospital, Kuopio, Finland; ⁶Biomedical Nutrition, Pure and Applied Biochemistry, Lund University, ⁷Department of Endocrinology, Skåne University Hospital, Lund, Sweden; ⁸Institute of Biomedicine and Biocenter of Oulu, University of Oulu, Oulu, ⁹Department of Psychiatry, Kuopio University Hospital, Kuopio, Finland, ¹⁰Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala University, Uppsala, ¹¹Center for Clinical Research Dalarna, Falun, Sweden; ¹²Eastern Finland Laboratory Centre and Department of Clinical Chemistry, University of Eastern Finland; ¹³Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland; ¹⁴Department of Nutrition, Exercise and Sport, University of Copenhagen, Copenhagen, ¹⁵Department of Epidemiology, School of Public Health, Aarhus University, ¹⁶Department of Cardiology, Aalborg Hospital, Aarhus University Hospital, ¹⁷Department of Animal Science, Aarhus University, Aarhus, Denmark; ¹⁸Department of Medicine (H7), Karolinska Institute, Stockholm, Sweden; ¹⁹Nofima, Norwegian Institute of Food, Fisheries and Aquaculture Research, As; ²⁰Department of Health, Nutrition and Management, Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences, Oslo, Norway; ²¹Unit for Nutrition Research, University of Iceland and Landspítali–The National University Hospital of Iceland, Reykjavik, Iceland; ²²VTT Technical Research Centre of Finland, Espoo, Finland; and ²³Department of Clinical Nutrition, Skåne University Hospital, Lund, Sweden
Fig. 1 Study design in the Healthy Nordic diet intervention study. In four centres, the main outcome measurements were taken at week 18. PBMCs = peripheral blood mononuclear cells.
Sysdimet-study

**Sysdimet:** grain products with low insulin response, fatty fish 3 x wk, bilberries (n=37)

**Health Grain:** grain products with low insulin response (n=34)

**Control:** grain products with high insulin response, no bilberries, fish max 1 x wk (n=35)

0 wk

OGTT, lipidomics, PBMC, adipose tissue biopsy, microdialysis

12 wk

OGTT, lipidomics, PBMC, adipose tissue biopsy, microdialysis
Effects on glucose and insulin metabolism

A Pro12Ala substitution in PPARγ2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity

Samir S. Deeb¹, Lluis Fajas², Masami Nemoto¹, Jussi Pihlajamäki³, Leena Mykkänen³, Johanna Kuusisto³, Markku Laakso³, Wilfred Fujimoto¹ & Johan Auwerx²


GENEDIET study 2011-2012 - differential effect of fatty acid modification on insulin action

Pro12Pro or Ala12Ala

PUFA

SAFA

PUFA

SAFA
Effect of orlistat treatment on body composition and resting energy expenditure during a two-year weight-reduction programme in obese Finns

L Karhunen¹, A Franssila-Kallunki², P Rissanen¹,², R Valve¹, M Kolehmainen¹, A Rissanen²,³ and M Uusitupa¹

OBJECTIVE: To examine the effect of orlistat (Xenical™) treatment on body composition and resting energy expenditure (REE) during a 2y weight-reduction programme in obese Finns.

SUBJECTS: Of initially 96 obese subjects who participated in the weight-reduction programme, those 72 subjects (13 men, 59 women, body mass index (BMI) 35.9 ± 3.9 kg/m², age 43.4 ± 6.0 y, mean ± s.d.) with the complete set of data for 2 y were included in the study.

DESIGN: After a 4-week lead-in period, subjects were randomized with either orlistat 120 mg t.i.d. or placebo t.i.d. in conjunction with a mildly hypoenegentetic balanced diet for 1 y. This was followed by 1 y double-blind period with the subjects within each treatment group re-assigned to receive orlistat 120 mg t.i.d. or placebo t.i.d. in conjunction with a weight maintenance diet.

MEASUREMENTS: Body composition and REE were measured after an overnight fast by a bioelectrical impedance method and indirect calorimeter, respectively. The measurements were performed at the beginning and at 3, 6, 12 and 24 months.

RESULTS: During the first year, the orlistat-treated group had greater reduction of body weight and fat mass but not of fat-free mass or REE as compared to placebo. During the second year, orlistat treatment was associated with smaller regain of body weight and fat mass with no significant differences in the changes of fat-free mass or REE as compared to placebo.

CONCLUSION: In addition to better weight loss and maintenance of reduced weight, orlistat treatment is associated with beneficial changes in body composition but with no excess decrease in resting energy expenditure as compared to that achieved during placebo with a dietary therapy alone.
Examples of intervention studies with psychological aspects
Psychobehavioural Factors Are More Strongly Associated with Successful Weight Management Than Predetermined Satiety Effect or Other Characteristics of Diet

Leila Karhunen,¹ Marika Lyly,²,³ Anja Lapveteläinen,¹ Marjukka Kolehmainen,¹ David E. Laaksonen,⁴,⁵ Liisa Lähteenmäki,²,⁶ and Kaisa Poutanen¹,²

This study aimed to investigate factors associated with weight management, especially whether satiety value of food as a part of a weight-maintenance diet would affect self-regulation of food intake and weight management. Altogether 82 obese subjects completed the study consisting of weight-loss and weight-maintenance (WM) periods. During the WM, subjects were randomized into higher- and lower-satiety food groups. No differences were observed in the changes in body weight, energy intake, or eating behaviour between the groups, even despite the different macronutrient compositions of the diets. However, when regarding all study subjects, success in WM was most strongly associated with a greater increase in the flexible control of eating and experience of greater easiness of WM and control of food intake and a greater decrease in uncontrollable eating and psychological distress. Psychobehavioural factors seem to be more strongly associated with successful weight management than the predetermined satiety effect or other characteristics of the diet.
How does lifestyle intervention affect depressive symptoms? Results from the Finnish Diabetes Prevention Study

A. Ruusunen¹, S. Voutilainen¹, L. Karhunen¹, S. M. Lehto², T. Tolmunen², S. Keinänen-Kiukaanniemi³,⁴,⁵, J. Eriksson⁶,⁷,⁸,⁹,¹⁰, J. Tuomilehto¹⁰,¹¹,¹², M. Uusitupa¹ and J. Lindström¹⁰

Aims To assess the effect of lifestyle intervention on depressive symptoms during a 36-month randomized clinical trial designed to prevent Type 2 diabetes.

Methods A total of 522 middle-aged participants, who were overweight or obese and had impaired glucose tolerance, were randomized to the lifestyle intervention or control group in the Finnish Diabetes Prevention Study. The intervention group received individualized counselling aimed at reducing weight and increasing physical activity. Depressive symptoms were measured using the Beck Depression Inventory among a subgroup of 140 participants.

Results On study entry, the mean Beck Depression Inventory scores ± SD were 6.8 ± 5.6 in the intervention group and 6.7 ± 5.5 in the control group. Beck Depression Inventory scores reduced during the intervention study: the mean ± SD (95% CI) reduction was 0.90 ± 4.54 (–1.99 to –0.19) scores in the intervention group and 0.75 ± 4.47 (–1.80 to 0.31) in the control group, with no difference between the groups. In a stepwise linear multivariate regression analysis, the variables with the strongest associations with the change in Beck Depression Inventory scores were baseline Beck Depression Inventory scores, marital status, weight change and change of total energy intake ($R^2 = 0.209$, $P < 0.001$).

Conclusions Participation in the study lowered depression scores, with no specific group effect. Among the lifestyle changes, particularly successful reduction of body weight was associated with the greater reduction of depressive symptoms. Thus, regardless of the intensity of the treatment, the success in executing alterations in one’s lifestyle and behaviour is associated with beneficial changes in mood.

Examples of experimental studies with a focus on eating behaviour
Serum leptin, food intake and preferences for sugar and fat in obese women

LJ Karhunen1, RI Lappalainen1, SM Haffner2, RH Valve1, H Tuorila3, H Miettinen2,4 and MIJ Uusitupa1

OBJECTIVE: To examine the association of leptin with food intake and preferences for sugar and fat in obese humans.

METHOD: Food intake and preferences for sugar and fat were measured in 35 obese women by a four-day food record and three hedonic tests, respectively.

RESULTS: High fasting serum leptin concentration adjusted for body fat mass and dietary underreporting was associated with low dietary energy and fat intakes. In addition, trends towards lower preference for chocolate as well as for the taste of high-fat, low-sugar mixture were observed in those with higher leptin concentration.

CONCLUSION: High serum leptin concentration could be associated in obese women with lower dietary energy and fat intakes, and possibly with the lower preference for fat. These findings need to be verified in further human studies.
Subjective and Physiological Cephalic Phase Responses to Food in Obese Binge-Eating Women

Leila J. Karhunen
Raimo I. Lappalainen
Liisa Tammela
Anu K. Turpeinen
Matti I. J. Uusitupa

Objective: The subjective and physiological cephalic phase reactivity to food was investigated in obese binge-eating women. Method: Eleven obese binge-eating women and 10 obese nonbinge-eating women participated in a cephalic phase response test consisting of baseline, anticipation, food exposure, and free eating periods. Serum insulin, free fatty acids, and plasma glucose concentrations as well as salivation, feeling of hunger, and desire to eat were repeatedly measured during the test. Results: During the food exposure, the binge eaters reported more desire to eat than did the nonbinge eaters. No differences were found between the groups in the physiological cephalic phase responses except for the lower salivation in the binge eaters during the food exposure. The amount of food eaten after the food exposure was similar in both groups. Discussion: Binge-eating women are characterized by stronger subjective but not stronger physiological cephalic phase reactivity to food. © 1997 by John Wiley & Sons, Inc. Int J Eat Disord 21: 321–328, 1997.
Plasma ghrelin levels after two high-carbohydrate meals producing different insulin responses in patients with metabolic syndrome

Miika V. Heinonen b, Leila J. Karhunen a, Emelia D. Chabot a, Leena K. Toppinen a, Katri S. Juntunen a, David E. Laaksonen c,d, Maritta Siloaho a, Kirsi-Helena Liukkonen e, Karl-Heinz Herzig b,d,f,* , Leo K. Niskanen d, Hannu M. Mykkänen a

Ghrelin is an orexigenic peptide produced in the stomach and its plasma levels are decreased acutely in response to ingested nutrients. To further clarify the role of insulin on ghrelin secretion, the present study was designed to investigate whether circulating ghrelin is affected differently by two mixtures of whole-grain breads known to produce low or high insulin responses in obese non-diabetic subjects with metabolic syndrome. After an overnight fast eight obese subjects with the metabolic syndrome (3 men and 5 women; BMI 33.7±0.7 kg/m²; age 55.6±1.8 y) received two different meals consisting of whole-grain rye or wheat breads. The comparison group (3 men and 5 women; BMI 22.5±0.5 kg/m²; age 26.0±0.9 y) received a wheat bread meal. Blood samples were collected postprandially at time intervals for 2 h. Feelings of hunger and satiety were analyzed using the visual analogue scales. Ghrelin concentrations decreased after bread meals in lean individuals, but not in obese individuals with the metabolic syndrome. Despite the difference in plasma insulin response, there was no difference in plasma ghrelin or feelings of hunger and satiety in patients with metabolic syndrome. After both rye and wheat bread meals, the decrease in ghrelin concentrations seen in normal-weight individuals after wheat bread meal was absent in subjects with metabolic syndrome. Despite the different plasma insulin response in obese patients, ghrelin levels did not change in response to either type of bread meals. In addition, ghrelin levels did not correlate with insulin, glucose, HOMA1-IR and satiety and hunger ratings in either study groups. This indicates that regulation of ghrelin might be altered in obese patients with metabolic syndrome independently of insulin.
Regional cerebral blood flow during food exposure in obese and normal-weight women

L. J. Karhunen,¹,³ R. I. Lappalainen,² E. J. Vanninen,⁴ J. T. Kuikka⁴ and M. I. J. Uusitupa¹,³

Summary
The cerebral responses elicited by the sight of food and food-related cues are poorly known in humans. Therefore, regional cerebral blood flow (rCBF) was measured during food exposure in 11 obese and 12 normal-weight women. The rCBF was mapped while the subject was looking at a picture of a landscape (control) or at a portion of food (food exposure), and was measured by ⁹⁹ᵐTc-ethyl-cysteine-dimer single photon emission computed tomography. In the obese women, the rCBF was higher in the right parietal and temporal cortices during the food exposure than in the control condition. In addition, in the obese women the activation of the right parietal cortex was associated with an enhanced feeling of hunger when looking at food. No such changes or associations were seen in the normal-weight women. In conclusion, exposure to food is associated with increases in the rCBF of right parietal and temporal cortices in obese women, but not in normal-weight women.
Reduced serotonin transporter binding in binge eating women

Abstract Rationale: There is evidence that abnormalities in brain dopamine, norepinephrine and serotonin metabolism may play an important role in binge eating. Serotonin-active antidepressant drugs have also been found to decrease binge eating. Objective: We investigated serotonin transporter binding in obese binge-eating women. Eleven obese binge-eating and seven obese control women participated in the study. The subjects were not taking any medication known to affect serotonin (5-HT) transporters. Methods: We used single-photon emission tomography (SPECT) with the radioligand \(^{123}\)I-labelled nor-\(\beta\)-CIT, which specifically labels 5-HT transporters. Results: Obese binge-eating women showed significantly decreased 5-HT transporter binding in the mid-brain compared with obese controls (2.1±0.5 versus 2.9±0.5, respectively). Conclusions: SPECT imaging with a ligand specific for 5-HT transporters can be used to assess altered serotonin transporter binding in the living human brain. The results tentatively suggest that 5-HT transporter binding is decreased in binge-eating women.
Association of serotonin transporter promoter regulatory region polymorphism and cerebral activity to visual presentation of food

Salla Kaurijoki¹, Jyrki T. Kuikka², Eini Niskanen³⁴, Synnöve Carlson⁵, Kirsi H. Pietiläinen⁶⁷, Ullamari Pesonen⁸, Jaakko M. Kaprio⁶⁷, Aila Rissanen⁹, Jari Tiitonen¹⁰ and Leila Karhunen¹

Recent functional magnetic resonance imaging (fMRI) studies have revealed links between genetic polymorphisms and cognitive and behavioural processes. Serotonin is a classical neurotransmitter of central nervous system, and it is connected to the control of appetite and satiety. In this study, the relationship between the functional variation in the serotonin transporter gene and the activity in the left posterior cingulate cortex (PCC), a brain area activated by visual food stimuli was explored. Thirty subjects underwent serial fMRI studies and provided DNA for genetic analyses. Subjects homozygous for the long allele exhibited greater left PCC activity in the comparison food > non-food compared with individuals heterozygous or homozygous for the short allele. The association between genotype and activation was linear, the subjects with two copies of the long allele variant having the strongest activation. These results demonstrate the possible genetically driven variation in the response of the left PCC to visual presentation of food in humans.
Brain electrical activity during food presentation in obese binge-eating women

Liisa I. Tammela\textsuperscript{1}, Ari Pääkkönen\textsuperscript{2}, Leila J. Karhunen\textsuperscript{4}, Jari Karhu\textsuperscript{3}, Matti I. J. Uusitupa\textsuperscript{1} and Jyrki T. Kuikka\textsuperscript{4,5}

Binge-eating (BE) subjects have shown altered brain activity at frontal regions during food presentation. The aim of this study was to examine the frontal brain electrical activity in obese BE women ($n = 12$) and in obese women without BE (non-BE, $n = 13$). Brain electrical activity was measured using a quantitative electroencephalography during a resting state (eyes-closed) and when the subjects focused (eyes-open) their attention on a picture of a landscape (control experiment) or on a meal (food experiment). The BE showed greater frontal beta activity (14–20 Hz) than the non-BE in both the eyes-closed (on average 52\%) and the eyes-open situations and independently of the stimulus (control experiment: 57\% and food experiment: 71\%). No significant differences between the groups were found in alpha, delta or theta amplitudes. Increased beta activity correlated positively with the disinhibition factor of the Three-Factor Eating Questionnaire. Thus, our results suggest that elevated frontal beta activity may be a marker of dysfunctional disinhibition–inhibition mechanism, which could make the obese BE women more vulnerable or sensitive to food and the environmental cues.
Ongoing studies in Finland (that could be linked with the IOC?)

• Psychological intervention to modify eating behaviour
• An intervention with fish vs fish oil
• Interventions with whole grain (especially rye)
• Large study on metabolic consequences of NASH and obesity surgery
• Strong collaborations with VTT (National Technical Institute)

Other possibilities
• New national Obesity Program in Finland
• Regional program for health promotion
• EU: Horizon 2020?