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Abstracts

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EASO Awards

The EASO Young Investigator Awards recognise outstanding scientific achievements in the field of obesity and related metabolic disorders by investigators under the age of 35. Three awards, one for Basic Science, one for Clinical Research and one for Public Health are awarded at each European Congress on Obesity.

EASO Young Investigator Award for Basic Science

Brain-adipose tissue crosstalk: the control of lipid metabolism

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The central nervous system (CNS) plays a key role in the maintenance of energy homeostasis. Neuroanatomical reports have shown that the white adipose tissue is innervated by the sympathetic nervous system, which is well known to control adipocyte metabolism. However, the direct control of adipocyte lipid metabolism by different signals from the CNS was recently discovered. Specifically, central infusion of leptin, melanocortins, glucagon like peptide-1 or central blockade of cannabinoid receptor 1 decreases fat storage. Contrary, central administration of ghrelin, neuropeptides Y, or central blockade of melanocortins promotes fat deposition. Importantly, some CNS pathways control adipocyte metabolism independent of feeding behaviour, suggesting that some signals act through different mechanisms to regulate energy balance. An important challenge will be to decipher the complicated interactions between peripheral signals and neuronal circuits to identify potential targets in the treatment of obesity.

EASO Young Investigator Award for Clinical Research

Anti-melanocortin-4 receptor autoantibodies in obesity

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Introduction: The melanocortin-4 receptor (MC4R) is part of an important pathway regulating energy balance. In a previous study, we have demonstrated that the generation of antibodies (Abs) against the N-terminal domain of the MC4R in rats induced a mild obese phenotype associated with insulin resistance. These findings prompted us to search for functional anti-MC4R autoAbs in sera of obese patients.
Methods: Anti-MC4R autoAbs were detected after screening sera from 216 patients with different body mass index (BMI) by using direct and inhibition ELISA with an N-terminal sequence of the MC4R. Binding to the native MC4R was evaluated by flow cytometry with HEK-293 cells expressing the human MC4R and pharmacological properties of the autoAbs were assessed by measuring adenylyl cyclase activity.
Results: Positive results in all tests were obtained in 5 patients with overweight or obesity (prevalence: 3.6%) but not in normal weight patients. The selective binding properties of the anti-MC4R autoAbs were confirmed by surface plasmon resonance and immunoprecipitation with the native MC4R. Moreover it was demonstrated that these autoAb acted as non-competitive antagonists *in vitro*. One of these autoAbs was evaluated *in vivo* and increased food intake in rats after passive transfer via intracerebroventricular injection.
Conclusion: The fact that functionally active autoAbs were only present in overweight and obese but not in normal weight subjects strongly suggests a possible pathogenic role. Such inhibitory anti-MC4R autoAbs might therefore contribute to the development of obesity in a small subpopulation of patients.

EASO Young Investigator Award for Public Health

Sugar-sweetened beverages and weight gain: a systematic review of the systematic and narrative reviews

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Background: An active debate on the role of sugar-sweetened beverages (SSB) in weight gain or obesity currently exists. Nevertheless, some conflicts of interests may lead to biased scientific conclusions.
Objective: To review if the stated conflicts of interests are related to the main conclusions of the narrative or systematic reviews conducted about this topic so far.
Methods: Medline searches of worldwide literature were used to identify the published reviews (up to January 2009). The relationship between conflicts of interests and conclusions was assessed using a Poisson regression to adjust for year of publication.
Results: We identified 12 reviews. In 3 of them a conflict of interest with beverage industry was disclosed. Among those reviews without any stated conflict of interest 66.6% reported that SSB were associated with increased weight gain. However, none of the reviews disclosing some conflict of interests with the beverage industry reported a positive association. Those reviews with conflict of interests were 3 times more likely to present a non-association conclusion (95% CI: 1.1-7.9) than those without them (RR adjusted for year of publication: 3.9, 95% CI: 1.0-15.9). In addition, one of the studies with conflict of interests presented some methodological flaws described in the corresponding criticizing letters.
Conclusion: Beverage industrial support may bias conclusions in relation to SSB consumption and weight gain or obesity, with potentially adverse consequences for knowledge and public health.

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Plenary Lectures

T1:PL

Inequality: a societal determinant of obesity rates?

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Abstract: Most research on obesity is concerned with individual explanations for what is arguably a societal phenomenon. Using data for rich developed market democracies and for the 50 states of the USA we show that both adult and childhood obesity rates tend to be much higher in more unequal societies – that is in societies where income differences between rich and poor are larger. The association between income inequality and obesity in these two independent settings suggests that part of the explanation for varying societal rates of obesity may lie in the effects of inequality. However, we show that obesity is one of a number of health and social problems (including violence, teenage birth rates, infant mortality, mental illness and drug abuse) which are marked by steep social gradients and are consistently worse in more unequal societies. We suggest that high obesity rates have to be understood as part of a general process of social dysfunction resulting from the effect of inequality on the quality of social relations.

T2:PL

Obesity and cancer

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Obesity is a condition in which excess fat has accumulated in the body. Over the past few decades, the proportion of overweight and obese people has been increasing markedly worldwide along with an adoption of a westernized lifestyle characterized by excessive energy intake and lack of physical activity. Obesity is a well-known risk factor for cardiovascular disease and type 2 diabetes mellitus. Accumulated evidence from a large number of epidemiologic studies indicates that obesity is also an important risk factor for cancer at several sites. There is convincing evidence from meta-analyses that excess body fatness increases the risk of oesophageal adenocarcinoma and cancers of the colorectum, pancreas, gallbladder, breast (postmenopause), endometrium, and kidney (renal cell). Obesity has also been associated with an increased risk of hematopoietic, liver, and aggressive prostate cancer. Several biological mechanisms have been postulated to explain the relationship between obesity and cancer risk, including alterations in circulating concentrations of endogenous hormones such as insulin, sex steroids, and other hormones.

Conflict of Interest: Not disclosed. *Funding:* Not funded.

T3:PL

A cofactor network that controls energy homeostasis

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Introduction: Dysfunctional mitochondrial oxidative phosphorylation and diminished aerobic capacity are associated with metabolic, cardiovascular and neurodegenerative diseases that eventually alter life span.
Results: We will discuss two distinct signalling pathways to control energy expenditure that converge on the coactivator PGC-1a. In a first study we focussed on the polyphenol resveratrol, an activator of the class III HDAC SIRT1, the mammalian Sir2 homolog. Resveratrol significantly increased aerobic capacity as evidenced by the doubling of time that mice run on a treadmill and by the increased oxidative capacity in muscle fibers ex vivo. This enhanced muscle performance was associated with an increase in expression of genes encoding for oxidative phosphorylation and mitochondrial biogenesis. These molecular events were largely explained by the resveratrol-mediated increase in PGC-1a activity, both through an increase in its expression level and a decrease in PGC-1a acetylation, fitting with the fact that resveratrol activates SIRT1. Importantly, the improved mitochondrial activity induced by resveratrol treatment protected mice against diet induced obesity and insulin resistance. In a second study, we characterized the role of SRC-3 in energy metabolism. SRC-1 and -2, two members of the p160 cofactor family were previously shown by us to affect energy homeostasis. Differently from SRC-1 and -2 KO mice, SRC-$3^{-/-}$ animals weigh less under basal conditions, an effect which is accentuated by a high fat diet. This lean phenotype of SRC-$3^{-/-}$ mice is associated with increased energy expenditure in BAT and skeletal muscle subsequent to enhanced mitochondrial activity. The effect on energy expenditure in the SRC-$3^{-/-}$ mice is dependent on the increase in both PGC-1a expression and activity, subsequent to its decreased acetylation.
Conclusion: In combination, these data suggest that SRC-3 and SIRT-1 are critical links in a complex cofactor network that is governed by PGC-1a and that controls energy homeostasis. This work opens up new perspectives for therapeutic and preventive strategies for metabolic diseases.

Conflict of interest: None Disclosed. *Funding:* The research in this abstract was funded by the ERC (EU), NIH, EPFL, and INSERM/CNRS/ULP

T4:PL

What have we learned from genome-wide association studies in obesity?

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Obesity is a common, multifactorial disease that arises through joint actions of genes and environment. Despite high heritability estimates (40%-70%), traditional gene discovery efforts have had limited success. However, genome-wide association studies (GWAs) have changed the pace of gene discovery and have already proven to be successful for various common diseases and traits, including obesity.
This presentation reviews the latest progress and findings in the obesity genetics field and highlights the promise and challenges of the GWA approach.
Last year, GWA led to the discovery of FTO as the first major obesity-susceptibility gene. The second obesity-susceptibility locus mapped near MC4R and was identified through a large-scale GWA meta-analysis including >16,000 individuals as part of the GIANT (Genetic Investigation of ANtropometric Traits) consortium. The most recent extension of the GIANT GWA meta-analysis to >32,000 individuals led to the identification of 6 new loci (*TMEM18*, *KCTD15*, *GNPDA2*, *SH2B1*, *MTCH2*, *NEGR1*) robustly associated with BMI.
Despite consistent replication of the currently 8 obesity susceptibility loci in adults and children, the effect sizes of each of the risk alleles is generally small (0.06-0.33 kg/m^2 per allele), and together the 8 susceptibility loci explain <1% of variation in BMI and their predictive value to obesity is limited. Nevertheless, these recently discovered loci are set to fundamentally improve our insights into the pathophysiology of obesity. Currently, the major challenge is to find more obesity-susceptibility variants, which will require further large-scale data integration and more refined analyses to obtain the power needed for identifying common variants with modest effects.

Conflict of Interest: None Disclosed.

T5:PL

Obesity is an eating disorder

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Eating Disorders are so-called 'mental disorders', and mental disorders by definition refer to a significant impairment of one's cognitive, affective and/or relational abilities or functioning, which may require intervention. The main characteristic of eating disorders is abnormal eating behaviour. In almost all cases, obesity is also characterized by abnormal eating, and it also frequently is related to impairment of cognitive, affective and/or relational abilities or functioning. Obesity with Binge Eating Disorder (BED) is already recognized as an eating disorder but obesity without binge eating is not. Psychological studies into the origin and maintenance of abnormal eating show however remarkable overlap between obesity and eating disorders. It might be concluded that obesity mainly is a psychological problem. Most obese persons know that they should eat less and exercise more; the problem is that they are not able to actually change their behaviour. Behaviour change requires psychological interventions. It will be argued why obesity should be acknowledged and treated as a psychological disorder, i.e. an eating disorder.

T5:PL

Is obesity an eating disorder? The case against

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Obesity is a disease of altered energy storage; if it were an eating disorder, i.e the consequence of an altered energy intake, overeating should be the major cause of obesity; however, most obesities are largely unaffected by dietary behaviour and restrictions. Bulimia or binge eating may play a complementary role in some cases, but the causes of most obesities lie elsewhere. There is a genetic basis for the predisposition to obesity, including the thrifty genes, which activation during development significantly alter the body weight regulation system. The relationship of obesity, insulin resistance and other components of the metabolic syndrome downgraded obesity from a primary disease to just another component of a syndrome encompassing endocrine, energy storage, cardiovascular and behavioural (e.g. depression) pathologic manifestations. Obesity is clearly linked to inflammation, and may result or be directly implicated with the immune response to so far largely unknown stimuli (e.g. diet, stress). The implication of insulin, glucocorticoids and sex hormones in the control of body fat in adipose tissue and muscle, with different sex and site-related pathogenicity suggest that fat storage is not –by itself– the main cause of the metabolic derangements accompanying obesity. However, simple overfeeding does not induce the same tissue metabolic and cell function alterations of obesity; diet seems to play a key role in its development, with fats (particularly saturated, *trans* or long-chain fatty acids) being considered a primary long-term factor for development of the metabolic syndrome. We can thus conclude that obesity is not primarily an eating disease.

PL

The novel adipocyte progenitor niches

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The brown adipose tissue (BAT), due to a unique thermogenic protein, uncoupling protein-1 (UCP1) expressed in its mitochondria is the main effector of adaptative thermogenesis. In humans, it was generally admitted that BAT occurred only in newborns. The white adipose tissue (WAT), on the other hand, is devoted to the storage of lipids. Despite their two diametrically opposed functions, BAT and WAT were considered as close parents.

Since 2007, however, this whole field is in turmoil. First, metabolically active fat depots have been identified by positron emission tomography in adult humans. Second, developmental studies have shown that brown adipocytes share a common origin, not with white adipocytes, but with myocytes. In this context, we have found a brown adipocyte progenitor niche in the vasculature of the human skeletal muscle. Cells expressing the CD34 surface protein, sorted from the human muscle, but not from other tissues, were indeed observed to differentiate in vitro in typical brown adipocytes. Also, UCP1 mRNA was detected in human muscle and its level was increased by administration of the insulin-sensitizer rosiglitazone. Concerning the WAT, a white adipocyte progenitor niche has recently been located in the vasculature of the rodent WAT but not in that of other tissues.

These findings altogether suggest new possibilities to fight human obesity either by stimulating energy dissipation via activation of the recently discovered brown fat depots or muscle CD34 progenitor cells or by slowing down white adipocyte formation by acting on the WAT adipocyte progenitor niche.

Review Sessions

Track 1: Prevention and Health Promotion
T1:RS1 – Interventions in adults

T1:RS1.1

Workplace Interventions

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Introduction: The obesity epidemic is a major public health concern worldwide. Obesity increases the risk of developing many chronic diseases, including cardiovascular disease, Type 2 diabetes, and certain types of cancer. Worksites are important settings for implementing overweight and obesity prevention strategies because of their high percentage of the adult population, their existing channels of communication and social support network, and their controlled environments for implementing policy and environmental change.

Methods: This presentation summarized the results from systematic reviews and reports (1966-2001), research articles and reviews (2001 to present), and cost effectiveness/benefits of worksite interventions for overweight and obesity prevention. Procedures used in previous reviews (e.g., *American Journal of Preventive Medicine*, 18 (Suppl 1):35-43-2000; and www.thecommunityguide.org/obese) provided guidance for this study.

Results: Preliminary results indicated sufficient evidence of effectiveness in the use of combinations of nutrition and physical activity strategies for weight loss. Although few studies used environmental and policy approaches, innovative use of incentives and a combination of individual and environmental strategies appeared promising for improving weight and for reducing cardiovascular disease risk factors. Few studies reported cost benefits or return on investment.

Conclusions: The results from this preliminary analysis suggest the need for long-term studies that include environmental approaches to increase physical activity and improve dietary practices, and studies on workplace weight loss maintenance and cost effectiveness/benefits of interventions in different types of workplaces. Results from further reviews, case examples and recommendations for further research are provided.

Conflict of Interest: None disclosed. *Funding:* None.

T1:RS1.2

Weight gain prevention in Primary Care in Europe

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Primary care physicians are the 'gate-keepers' for good health and an effective European-wide strategy for the prevention of obesity requires their involvement. This could be through an opportunistic approach to engage interest of children and young people, and their parents. The most important factor to those at risk is personal & continuing contact – this may be the primary care physician in some national models whereas a skilled and trained nurse may be an alternative in other models. Irrespective of who fulfils this role, it will depend on existing resources including skills and knowledge of available staff. Training will be a crucial element for such staff to develop a competence framework, supported by quality assurance. The major limitation in primary care is adequate time – priority will be to create time in the primary care setting. Primary care should not be seen in isolation and must be supported by a local 'network' of expertise – this ideally will include dietitians, nurses, physiotherapists, lifestyle coaches, physical trainers, pharmacists and professions other than health such as teaching. National systems for reimbursement must address the necessary resources prior to implementation of any preventive strategy. Potential 'actors' should be identified as part of a preventive network at both national and European level– this may include the development of new types of health professionals to address lifestyle modification that is neither restricted to overweight and obesity nor national boundaries. The active engagement of primary care will be pivotal to the ultimate success of overweight and obesity preventive strategies in Europe.

T1:RS1.3

Dietary counselling and probiotic intervention initiated in early pregnancy modifies maternal adiposity over 12 months postpartum

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Introduction: Excessive weight gain during pregnancy may predispose women to obesity. The aim of the study was to explore the impact of dietary counselling and probiotics on maternal weight and body composition over 12 months postpartum.
Methods: At the first trimester of pregnancy 256 women were randomly assigned to receive dietary counselling aimed to modify dietary intake to conform with that recommended and probiotic capsules (diet/probiotics) or placebo (diet/placebo) or as controls (control/placebo). The preparations used were the combination of Lactobacillus rhamnosus GG, ATCC 53103, and Bifidobacterium lactis or placebo and the randomization in the dietary intervention groups occurred in a double-blind manner. Weights, waist circumferences and skinfold thicknesses were measured.
Results: Dietary counselling resulted in a lower intake of saturated fatty acids and higher intake of monounsaturated and polyunsaturated fatty acids compared to the controls, whilst the energy intake did not differ between the groups. Central obesity defined as waist circumference over 80 cm combined with BMI >30 was detected in 25.0% of the women in diet/probiotics group, 42.9% in diet/placebo group and 40.4% in the controls at 12 months postpartum. Equally, over the postpartum follow-up the proportion of body fat was lowest in the women in diet/probiotics group (mean 27.9%, SD 4.4) compared to those in diet/placebo (28.9%, 5.1) or control/placebo (30.4%, 4.8) groups (p=0.018).
Conclusion: The impact of probiotics-supplemented dietary counselling on body adiposity demonstrated here for the first time may open new angles on the role of gut microbiota in the fight against obesity.

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by Social Insurance Institution of Finland, Academy of Finland and Sigrid Juselius Foundation.

T1:RS1.4

The association between diet composition and diet costs and purchasing differences by level of income in the Netherlands

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Introduction: Food prices and costs of a healthy diet seem major obesogenic factors in our food environment. Food selection may not only be a behavioural issue, but at least partly an economical one. This study examines the association between diet composition and costs in the Netherlands and the role of income on purchasing behaviour.
Methods: Data on dietary intake from two Dutch cohort studies were merged with national food prices and the Dutch Food Composition Database. Energy intake per day; costs per 2,000 kcal; fruit and vegetable intake; and dietary energy density were analysed for different income groups.
Results: High energy dense diets were lowest in fruits and vegetables; provided most kcal per day; and were lowest in costs. There was a significant inverse association between dietary energy density and diet costs. A high energy dense diet could be provided for a minimum of € 4.10 per 2,000 kcal, compared to a maximum of € 6.30 for a diet lowest in energy density. Low income groups had similar food expenses as higher income groups.
Conclusion: Our study confirmed that high energy dense diets are lowest in fruit and vegetables and can be provided for the lowest costs. However, we did not find differences in food purchasing behaviour between income groups. More research is needed on the contribution of price to food purchasing behaviour and whether lower prices can serve as an impulse to consume more healthful products.

Conflict of interest: none. *Funding:* Research related to this abstract was funded by ZonMw.

T1:RS2 – Settings of interventions in children

T1:RS2.1

How do we solve a problem like obesity in childhood disability?

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The dramatic advances in paediatric medicine in the past three decades have led to increased survival rates of children with disabilities. As a consequence, attention has shifted from dealing with mortality towards coping with morbidity with an emphasis on the medical, psychological and social consequences of chronic conditions like cerebral palsy (CP), spina bifida (SB) and other childhood onset conditions. These conditions interfere with the participation (performance) of children with CP in everyday settings, such as home, school and community. Children and adolescents with disabilities tend to show low levels of mobility-related activity in daily life, and their physical fitness is distinctly subnormal. The risk of developing secondary health problems such as obesity is increased and cardiovascular disorders later in life may increase. Although attempts are being made to prevent and to cure childhood disabilities (the ultimate goal), the reality is that these conditions such as CP and spina bifida are lifelong both for the child and the family. The following goals in the management in obesity in childhood disability can be distinguished: i) to prevent obesity, ii) to cure obesity, iii) to improve / optimize activities and (sport) participation and, iv) to manage a life with obesity and childhood disability. In conclusion, obesity and fitness become a more and more important factor in the rehabilitation of youth. The prevention of obesity and a physical inactive lifestyle in both the diseased and healthy population seems a challenge for current and future health-care providers.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T1:RS2.2

Pre-school and day care

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The prevalence of overweight and obesity is increasing dramatically in Europe children and effective prevention and treatment is necessary. However, randomized controlled trials have demonstrated that lifestyle interventions based on nutrition education, physical activity and behaviour therapy have a limited effect and the generalisibility is questionable since long-term success was reported only in specialised treatment centres. Furthermore, primarily families of the upper and middle class lay claim to these lifestyle interventions, while families of lower social status are underrepresented in contrast to the increased risk of obesity in their social class. Therefore, interventions in the school or kindergarten setting with day-care seem meaningful to reach children of all social classes. However, randomized control trials based on education and/or behaviour therapy concerning nutrition and physical activity have shown that health behaviour can be improved in the school and pre-school setting, while the effectiveness on weight status is only moderate: Only a moderate decrease of incidence and no effect on prevalence of overweight were reported. Important disadvantages are the difficulties to reach the parents and the questionable motivation to change health behaviour which is mandatory for any behavioural approach. Arrangement of an anti-obesity environment in the day care setting such as installing of drink water fountains and the prohibition of sweated drinks have the same effects as compared to the behavioural approach but are much cheaper. Further prospective randomized studies are urgently necessary to optimize the interventions.

T1:RS2.3

Diet-related restrictive parenting practices: impact on dietary intake of 2-year-old children and interactions with child characteristics

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This study examined the relationship between diet-related parenting practices, parental characteristics, child characteristics, and 2-year-old child's dietary intake. Cross-sectional data (N = 2578) originated from the KOALA Birth Cohort Study. Principal component analyses revealed two restrictive parenting practice clusters: a cluster characterized by prohibition of the intake of various snacks and soft drinks, and a separate cluster characterized by prohibition of cookies and cake. Regression analyses showed that these clusters were related to the children's behavioural style (i.e. oppositional, depressive and/or aggressive behaviour) and to educational level, age and alternative lifestyle of the mother. The clusters also had a favourable influence on dietary intake (i.e. restrictive parenting practices were related to less consumption of the restricted (unhealthy) items and higher consumption of items considered to be healthy), which was moderated by child characteristics. The parenting practices showed a stronger association with dietary intake in children with a favourable behavioural style (i.e. non-depressed, low anxious, low overactive), a favourable eating style or a lower BMI. The findings suggest opportunities for preventive interventions focussing on parents of young children, and indicate that different approaches to parenting practice interventions are needed for different types of children.

Conflict of interest: None disclosed. *Funding:* The KOALA Birth Cohort Study's conception and follow-up to the age of 2 was financially supported by the Triodos Foundation, Royal Friesland Foods, University Hospital Maastricht, and funds unrelated to commercial organizations (Iona Foundation, Phoenix Foundation, Foundation for the Advancement of Heilpedagogiek), all in the Netherlands. In addition, the research by J.S. Gubbels is financed by the Nutrition and Toxicology Research Institute Maastricht (NUTRIM).

T1:RS2.4

school-based physical activity program increases fitness and decreases adiposity and cardiovascular risk factors in primary school children (KISS): a cluster-randomized trial [ISRCTN15360785]

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Introduction: Childhood obesity and physical inactivity are increasing dramatically worldwide with detrimental effects on physical and psychological health. Schools provide an ideal setting for preventive interventions. We therefore conducted a randomised controlled trial to determine whether a school-based physical activity (PA) program during a full school-year improves physical fitness and cardiovascular risk factors in young schoolchildren.
Methods: Twenty-eight classes were randomly allocated in a single blinded manner to the intervention (16 classes, n=297) and control (12 classes, n=205) groups. The intervention consisted of a multi-component PA intervention program including daily physical education. Primary outcomes included body fat (skinfold thickness), aerobic fitness (shuttle run test), PA (accelerometry), and quality of life (questionnaires). Secondary outcomes included a cardiovascular risk factor score including all components of the metabolic syndrome.
Results: Compared with controls, children in the intervention group showed statistically significant decreases in body mass index z-scores (adjusted difference -0.09; 95%-percent confidence interval [CI], -0.18 to -0.003), sum of four skinfolds (adjusted difference -2·10mm; 95%-CI -3·48 to -0·90), and significant improvements in aerobic fitness z-score (adjusted difference 0·22; 95%-CI, 0·01 to 0·42) and moderate-vigorous PA at school (adjusted difference 14; 95%-CI, 5 to 23). There was also a significant improvement of the cardiovascular risk score (adjusted difference -0.18; 95%-CI, -0.30 to -0.05, intervention: n=227 and control: n=103). Quality of life did not change.
Conclusion: Our findings show that a stringent school-based PA intervention is effective in improving physical fitness and in reducing cardiovascular risk factors in children.

Conflict of interest: None. *Funding:* Swiss Federal Office of Sports (FOSPO). Grant number: SWI05-013.

T1:RS3 – Nutrition and physical activity

T1:RS3.1

Increasing activity or reducing inactivity?

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Obesity is considered as one of the greatest health challenges in the 21st century with increasing prevalence in most parts of the world. Although obesity is multi-factorial, including genetic, biological, cultural, and socio-economic components, it is likely that an imbalance between energy intake and expenditure is the main underlying cause of the current epidemic.

Increasing overall energy expenditure in order to maintain energy balance and thereby a healthy body weight can be achieved by an increase in physical activity and a reduction in time spent sedentary, or a combination of both.

Most previous prospective population based observational studies suggests that individuals who report higher levels of physical activity tend to be less likely to gain body weight, however, the magnitude of association appears to be weak. TV viewing, frequently used as a marker for sedentary behaviour, appears to be related to obesity although this association may be mediated by other behaviours (e.g. snacking) associated with TV viewing. It has also been suggested that obesity predicts self-reported physical inactivity and sedentary behaviour whereas in these studies, there was no evidence for an influence of sedentary behaviour on the development of obesity, a reverse causality argument. Observational studies vary in their conclusion due to issues of confounding and measurement error and leave uncertainties about direction of causality. Dose-response associations can only be properly addressed by studies including objective methods for assessing physical activity and sedentary behaviour. The evidence base on whether increasing physical activity or reducing sedentary behaviour is more important for the prevention of obesity is currently weak.

T1:RS3.2

Quantity Vs Quality of diet

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Obesity—with its comorbidities such as type 2 diabetes, metabolic syndrome and cardiovascular diseases—is a major public health concern. To prevent overweight and its unhealthful effects it is obviously important to reduce the calorie content of the diet. However, the amount of food eaten is not always a good marker of energy intake given the different energy density of each food item; therefore, an appropriate food choice may have a stronger impact on overweight prevention than the sole reduction of portion size. In addition, the composition of the diet may influence satiety and energy expenditure—two important mechanisms of long-term weight changes. While there is no clear evidence that altering the proportion of dietary fat and carbohydrate has major effects on body weigh, there is substantial evidence that carbohydrate-rich foods differ in relation to their impact on body weight. In particular, increased consumption of sugar-sweetened soft drinks is associated with weight gain, particularly in children, since beverages induce less satiety than solid carbohydrates. Conversely, the intake of fibre rich foods like whole-grain cereals, vegetables, legumes and fruits is associated with lower risk of weight gain in observational studies. Other nutrients may also have an impact on body weight: a moderately elevated protein intake stimulates 1) satiety, 2) thermogenesis and 3) lean muscle mass (thus influencing energy expenditure). In conclusion, in populations at risk for obesity multiple small changes in the composition of the habitual diet might be more feasible and effective for overweight prevention than the simple advice to eat less.

T1:RS3.3

Increased energy intake alone virtually explains all the increase in body weight in the United States from the 1970s to the 2000s

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Introduction: The relative contributions of increased total energy intake (TEI) and reduced physical activity (PA) to the obesity epidemic are much debated. We combined biological, epidemiological, and food supply evidence to examine the drivers of weight gain in the US from 1970s to 2000s.

Methods: Data on total energy expenditure (TEE) from doubly labelled water studies in 963 children and 1399 adults were used to derive equations relating stable weight to energy flux (EnFlux=TEE= TEI). The equations were used to predict the increases in weight in the US population using food energy supply data (adjusted for wastage), NHANES surveys (1971-76, 1999-2002), and census data. If predicted equalled observed, then increased TEI was assumed to explain the weight increase; if predicted was higher or lower than observed then changes in PA levels were assumed to have also contributed.

Results: Children: the predicted increase in mean weight (4.0kg) equalled the observed increase (4.0kg). Adults: the predicted increase in mean weight (10.8kg) was higher than the observed (8.6kg) implying that secular increases in PA may have moderated the effect.

Conclusions: The biological relationship between weight and EnFlux predicted that virtually all the observed increase in weight in the US over 30 years could be explained by increases in TEI. This supports the US epidemiological data that shows PA levels have changed little whereas TEI has increased. While reducing the obesogenicity of the food environment should be the dominant focus of strategies to reverse the epidemic, increasing PA and reducing sedentariness are also important.

Conflict of interest: None disclosed. *Funding:* No funding.

T1:RS3.4

Does whole body vibration contribute to reduction in visceral adipose tissue?

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Introduction: Although the use of whole body vibration (WBV) training is described as an alternative way of resistance training, the clinical use of WBV in an obese population remains unclear.

Objective: To determine the effect of WBV training and aerobic exercise, combined with a hypocaloric diet, on weight, body composition and metabolic risk factors in overweight and obese adults.

Methods: A randomized, controlled study in an outpatient clinic with a 6-month intervention period and a 6-month 'no intervention' follow-up. Participants were 79 overweight or obese adults, 61 of them completed the study.

Interventions: A diet only group (DIET), a diet plus fitness group (FITNESS) and a diet plus whole body vibration group (VIBRATION).

Main Outcome Measures: Anthropometric data, body composition and metabolic features were evaluated at baseline and at 3, 6 and 12 months.

Results: Only FITNESS and VIBRATION managed to maintain a weight loss of 5% or more in the long term. Visceral adipose tissue changed most in VIBRATION: -47.8, ±41.2 and -47.7, ±45.7cm² resp. after 6 and 12 months compared to CONTROL (-3.6, ±20.5 and +26.3, ±30.6cm² resp.), DIET (-24.3, ±29.8 and -7.5, ±28.3cm² resp.) and FITNESS (-17.6, ±36.6 and -1.6, ±33.3cm² resp.) (P<0.001).

Conclusion: Adding aerobic exercise or WBV training to a hypocaloric diet, can help to achieve a sustained long-term weight loss of 5-10%. These preliminary data show that WBV training may have the potential to reduce VAT more than aerobic exercise in obese adults, possibly making it a meaningful addition to future weight loss programs.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T1:RS4 – Evidence based prevention and health promotion

T1:RS4.1

Randomised control trials. The only acceptable evidence?

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The importance of evidence-informed policy and practice in public health is well recognised. Much of this discussion has focused on the nature of evidence within public health. Evidence-informed policy and practice helps to identify the potential best buys for health across the broad spectrum of health services from both upstream and downstream perspectives.

A foundational part of the production and utilisation of evidence is the conduct of high quality primary research and evaluation. The nature of research and evidence within public health and health promotion means that study designs, other than randomised controlled trials, which evaluate complex community interventions, and are generally complex and multi-faceted, are vital for informing the evidence base. The importance of utilising multiple methods and data sources, including qualitative and quantitative, experimental and observational research, in developing public health evidence is now well recognised. This emphasis on multiple methods in public health evidence reflects the growing awareness of the importance of contextual, including social, political and organisational, factors in which an intervention is conducted to evaluate design and interpret findings. Consideration of the impact of interventions on health equity, such as differences in outcomes for groups within the intervention population, is also viewed as important when conducting evaluations in health promotion and public health. This recognition of the need to focus on health inequalities provides added weight to the argument for multiple methods in order to ensure that appropriate data are collected to build a comprehensive evidence base.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T1:RS4.2

New paradigms for evidence based prevention.

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Introduction: Randomized controlled trials have been conducted to examine the efficacy or the effectiveness of obesity prevention interventions. A common paradigm has the investigator begin with focus groups, use results from the focus groups to formulate a pilot study, look for positive "signals" of success in the pilot study, and then report trends in the primary outcome that are in the hypothesized direction in a grant proposal to obtain funding for a randomized trial. We believe that obesity prevention research would benefit from additional, intermediate studies that are designed to detect changes in, or associations with, hypothesized mediators or process variables.

Conclusion: Intermediate studies have been called several names by obesity researchers including preliminary, formative, developmental, small efficacy and evidentiary. There currently exists some differences in the type of intermediate research proposed, and this is reflected in the terms, but a consensus seems to be building that more work is needed in intermediate studies prior to the launch of a large, randomized trial to test an obesity prevention intervention. Reductionist thinking, common in laboratory research, may help to move community interventions forward. Existing research has shown that behavioral interventions can improve diet and physical activity levels and reduce body weight; nevertheless, even carefully conducted behavior change interventions are limited in their ability to induce long-term behavioral change in most people. Better behavioral interventions are needed, and their development will depend upon an improved understanding of human behavior, and translation of that understanding into feasible interventions.

Conflict of Interest: Perceived conflict of interest include participation in research funded by Dannon Waters and a Distinguished Professorship funded by the American Institute for Cancer Research. Other current research is funded by the National Institutes of Health. *Funding:* No funding for this presentation.

T1:RS4.3

Identifying priorities for obesity prevention

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Introduction: The Assessing Cost-Effectiveness in Obesity (ACE-Obesity) project used an evidence-based approach to evaluate the cost-effectiveness of interventions for the prevention of unhealthy weight gain in Australian children and adolescents.

Methods: Thirteen interventions across a range of settings were evaluated. To avoid methodological confounding and to provide a balanced approach to priority setting, the ACE-Obesity study used standardised methods. These included: (i) a common setting, target group and decision context; (ii) use of Australian data to calibrate the model; (iii) a two-stage concept of benefit; and (iv) extensive use of probabilistic uncertainty testing. The technical results were reported as cost per disability-adjusted life year saved, using current practice in Australia in 2001 as the comparator. Broader considerations which impinge on resource allocation decisions (level of evidence', 'equity', 'acceptability', 'feasibility', 'sustainability', and 'side effects') were taken into account.

Results: Six interventions (including restriction of TV advertising of high fat/high sugar foods and drinks, and a number of school-based programs) represented excellent 'value for money' and were potentially cost- saving. A further four interventions (including a targeted GP program, orlistat therapy and laparoscopic gastric banding) entailed additional costs, but were still cost-effective.

Conclusion: The ACE-Obesity approach enabled interventions to be ranked in order of economic merit without the normal methodological concerns about results drawn from studies lacking in comparability. It offers a tool for informing decision-makers about both the merit of individual obesity interventions, and the packaging of a strategy of 'best buys' for obesity prevention which fits a particular budget.

Conflict of Interest: None. *Funding:* Research relating to this abstract was funded by the Victorian Department of Human Services

T1:RS4.4

Supporting knowledge transfer into action: A portal for policy-makers, researchers, evaluators and public health practitioners on governmental action plans to tackle obesity

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Introduction: Since the WHO's call for action on obesity in 2004, several countries have adopted governmental action plan (GAP). Due to the novel approaches used in these plans and the paucity of evaluation, stakeholders need to be informed of other countries' GAP. However, having quick access to up-to-date information is challenging. Thus, we developed in 2008 a portal of GAPs on diet, physical activity and obesity and on the grey literature on these topics (www.inspq.qc.ca/pag/).

Methods: Starting from an historical study of the WHO's literature, we identified European countries that planed or developed a GAP. We then searched the websites of the health ministries of European countries that were in French or English, of North America and of Oceanic countries. We only kept GAPs and documents that were published in 2000 or later and were available on a website.
Results: The portal represents 17 countries, 3 states and 2 international organizations. For each GAP, we created a fact sheet providing information about its origin and content and included web links to the full documents and governmental websites. Furthermore, hyperlinks to documents produced by well-know agencies were included for each country, state or international organization as suggested reading. Attention was given to be user-friendly and searchable by topic. Finally, technical papers on GAPs can also be found in the portal.
Conclusion: This portal is a unique, resourceful and practical tool for knowledge transfer to policy-makers, researchers and public health practitioners working on obesity. An evaluation will be done about its utilization.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

Track 2: Epidemiology and the Impact of Obesity
T2:RS1 – Obesity, morbidity and mortality

T2:RS1.1

Assessing the burden of overweight and obesity: an example from the United Kingdom

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Introduction: In this paper I review previous cost studies for overweight and obesity in the UK. I propose a method for estimating the economic and health costs of overweight and obesity in the UK which could also be used in other countries.
Methods: Costs of obesity studies were identified via a systematic search of electronic databases. Information from the WHO Burden of Disease Project was used to calculate the mortality and morbidity cost of overweight and obesity. Population attributable fractions for diseases attributable to overweight and obesity were applied to National Health Service (NHS) cost data to estimate direct financial costs.
Results: We estimate the direct cost of overweight and obesity to the NHS at £3.2 billion. Other estimates range between £480 million in 1998 and £1.1 billion in 2004. There is wide variation in methods and estimates for the cost of overweight and obesity to the health systems of developed countries.
Conclusion: The method presented here could be used to calculate the costs of overweight and obesity in other countries. Public health initiatives are required to address the increasing prevalence of overweight and obesity and reduce associated healthcare costs.

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by the British Heart Foundation.

T2:RS1.2

BMI is an inappropriate marker of obesity related health risks

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Introduction: Many studies find a U-shaped association between body mass index (BMI) and total, as well as coronary mortality indicating that both a low and a high BMI is associated with excess mortality. In fact, several studies document reduced longevity even among lean subjects who never smoked. Likewise, among participants without diagnosed chronic disease, or among those surviving more than 2-8 years subsequent to entering a study, the U-shaped relationship persists. On the other hand, the U-shaped association between BMI and mortality seems to result from a combined risk function of body fat (BF) and fat-free mass (FFM), where mortality increases with high BF and low FFM, making BMI an inappropriate marker of obesity related health risk. Furthermore, the distribution of the fat also has a major impact on health, not accounted for by BMI, and particularly the detrimental effect of excess abdominal fat has been investigated. Indeed, studies show that obesity related health care costs are dependent on excess abdominal obesity and not overall obesity. Less attention has been paid to the potentially protective effects of lower body size e.g. gluteal fat and muscle, and more recent data suggests that both tissue components in this localisation benefit future health. Additionally, these benefits are independent of both overall and abdominally localised obesity. In fact, a small hip-and thigh size carries a great risk of dying prematurely whereas large hips and thighs offer protection – irrespective of BMI and waist size.
Conclusion: It is clear that we need to encourage not only health authorities but also professionals in primary and secondary sectors to monitor the general development of obesity in populations. However, because BMI is an inappropriate obesity marker, and because simple circumference measures seem to capture obesity related health risks more efficiently, a recommendation towards routine measurement of fat distribution should be enforced. In this regard, measurement of lower body size (hip- and or thigh-circumference) should not be omitted.

Conflict of Interest: None Disclosed. *Funding:* No funding.

T2:RS1.3

The mortality after anti-obesity surgery is not different from mortality in a general population cohort, despite higher post-operative co-morbid disease

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Introduction: Several studies have demonstrated that anti-obesity surgery reduces mortality compared to a non-operated obese cohort. However, it is not clear if there remains a difference in mortality compared to the general population.
Methods: Population based cohort study of anti-obesity surgery in Sweden between 1980 and 2006. 13 301 patients (3003 men) over the age of 18 (mean ±SD, 40.0 ±10.3 years of age) who had undergone anti-obesity surgery were indentified in the Inpatient Care Register. For each subject, 10 controls matched for age and gender, were identified in the register of the total population. Censoring occurred at end of study (Dec 31, 2006), date of emigration or date of death (8.9 ±6.5 years of follow-up).
Results: The incidence rate of obesity related co-morbid disease was higher in the surgical cohort compared to the general population cohort. After surgery the hazard ratio (HR) was higher in the surgical cohort for all studied diagnoses (myocardial infarction 1.6 (95% CI 1.3-1.8), angina pectoris 2.0 (1.8-2.3), cerebrovascular lesion 2.0 (1.8-2.3), hypertension 2.4 (2.2-2.6), diabetes 1.7 (1.5-1.8)). The unadjusted HR for all-cause mortality was higher in the surgical group (1.3 (1.2-1.4)). There was no significant difference in adjusted (age, gender, pre-operative co-morbid disease) all-cause mortality (1.0 (0.9-1.1)). However, adjusted all-cause mortality after surgery was increased (1.7 (1.6-1.8)) in the male surgical cohort.
Conclusions: Despite a remaining increased risk of inpatient care for co-morbid disease there is no significant difference in adjusted mortality after anti-obesity surgery compared to the general population except for men.

T2:RS1.4

Impact of cigarette smoking on the relationship between body mass index and coronary heart disease: 3264 stroke and 2706 CHD events in 378579 individuals in the Asia Pacific region

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Introduction: Elevated levels of body mass index (BMI) and cigarette smoking are both well established lifestyle-related risk factors for coronary heart disease (CHD) and stroke. If these two modifiable risk factors have a synergistic impact on cardiovascular risk, rigorous lifestyle modification may contribute to greater reduction in cardiovascular burden than expected.
Methods: Individual participant data were combined from 38 cohorts, involving 378,579 participants (76% Asian) and comprising 1,431,261 person-years of observation. Hazards ratios (HRs) and 95% confidence intervals (CIs) for BMI by cigarette smoking status were estimated using Cox proportional hazard models adjusted for age and stratified by study and sex.
Results: During follow-up, 2706 CHD and 3264 stroke were recorded. There was a log-linear, positive relationship of BMI with CHD and stroke in both smokers and non-smokers. Additionally, there was evidence to support a synergistic effect of smoking on the positive association between BMI and CHD: HRs (95% CIs) associated with a 2 kg/m^2 higher BMI were 1.13 (1.10 – 1.17) in current smokers and 1.09 (1.06 – 1.11) in non-smokers (p-value for interaction = 0.04). In subgroup analyses, similar synergism was observed in both sexes and in both Asians and non-Asians. There was no evidence that smoking status modified the deleterious effect of BMI on stroke.
Conclusions: Cigarette smoking appears to amplify the positive association between BMI and CHD but not stroke. If confirmed, these results suggest that effective strategies that target smoking cessation and body weight optimization are likely to have a greater impact than expected on reducing the burden of CHD.

Conflict of Interest: none disclosed. *Funding:* No funding.

T2:RS2 – Health outcomes in obese subjects

T2:RS2.1

Is overweight beneficial in patients with chronic disease?

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Overweight (body mass index [BMI]=25-30 kg/m2) and obesity (BMI>30 kg/m2) have become mass phenomena with a pronounced upward trend in prevalence in most nations throughout the world and are associated with increased cardiovascular risk and poor survival. Emerging data indicate, however, that traditional risk factors of cardiovascular disease and metabolic syndrome (e.g. obesity and hypercholesterolemia) are paradoxically associated with *better survival* in several distinct populations with chronic disease states and wasting syndrome. In these individuals, a high BMI is incrementally associated with better survival, whereas normal to low BMI is related to worse mortality. At least 10% of the general population suffers from such chronic conditions and exhibit the obesity paradox, including persons with chronic heart failure, chronic kidney disease, chronic obstructive lung disease, rheumatoid arthritis, and malignant disease as well as the geriatric population. These populations apparently have slowly progressive to full-blown wasting and significantly greater short-term mortality than the general population. The survival paradoxes may result from the time differential between the two competing risk factors [i.e. over-nutrition (long-term killer but short-term protective) versus undernutrition (short-term killer)]. Hemodynamic stability of obesity, protective adipokine profile, endotoxin-lipoprotein interaction, toxin sequestration of fat, antioxidation of muscle and survival selection may also contribute to the seemingly counterintuitive risk factor paradoxes. Hence, obesity paradox is the hallmark of chronic disease states or conditions associated with wasting disease. Whereas in such distinct subpopulations obesity may offer survival advantages, esp. if future research should confirm a biological plausibility to that end, the obesity paradox should not lead to confusion about the anti-obesity campaign in the majority of the general population. Research is needed to examine the need for the distinction between different populations and for person-specific recommendations pertaining to anti-obesity interventions and weight reduction in lieu of currently generalized guidelines.

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T2:RS2.2

Is disease occurring at an earlier age as a result of the obesity epidemic?

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Child obesity levels in Europe have risen remarkably in the last two decades, with some surveys showing one third of younger schoolchildren are now overweight or obese. This extraordinary phenomenon is likely to bring with it a range of co-morbidities, but there are few estimates of the extent of the medical problems likely to be faced by paediatric services. In this paper we present some initial estimates of the extent of the disease burden associated with obesity in children in Europe. Co-morbidities include hypertension, altered blood lipid profiles, impaired

glucose tolerance, fatty liver disease and a range of further problems. Of the estimated 6.2m obese children in the European region, over 1.2m children will have three or more metabolic disorders. Indeed, over 1m are likely to be hypertensive, while as many as 1.4m are likely to show hepatic steatosis. Much of this disease burden is hidden from view, and may only come to medical attention after the individual has experienced many years of disordered function, by which time the opportunities to reverse the problem may have already passed. The alternative is to offer screening for metabolic and other disorders to all overweight children, but it is not clear that the paediatric services have the capacity to deal with the screening processes, or to provide medical interventions to all those children identified with the early stages of chronic disease.

T2:RS2.3

Abdominal adipocyte size is a predictor of type 2 diabetes in women independent of age, body fat, BMI and WHR

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Introduction: Enlarged subcutaneous abdominal adipocytes predict development of type 2 diabetes (T2D) in normal glucose tolerant Pima Indians (Weyer et al, 2000). The aim was to investigate the value of subcutaneous abdominal adipocyte size (AAS), and femoral adipocyte size (FAS), as independent predictors of T2D in a Swedish female cohort.
Methods: A representative population sample of 1302 women in five age strata (44, 52, 56, 60, 66 years) was examined in Göteborg 1974-75 for evaluation of health status. T2D status, anthropometry, body composition (total body potassium and total body water) as well as AAS and FAS (needle aspiration) were assessed in a subsample of 245 women with similar age distribution. T2D incidence was followed from 1976 until 2002.
Results: Subjects who subsequently developed T2D had increased AAS and body fat, as well as increased anthropometrical measures at baseline compared with subjects who remained healthy. Multiple Cox regression showed that large AAS was a strong predictor of T2D (age-adjusted hazard ratio for increase of AAS by one standard deviation [AAS-HR] 1.72; $p<0.001$) also when adjusted for percentage body fat (AAS-HR 1.55; $p<0.01$), BMI (AAS-HR 1.45; $p<0.05$), and WHR (AAS-HR 1.56; $p<0.01$). FAS was not an independent predictor of T2D. However, waist circumference, particularly when standardized to height, was the best T2D predictor.
Conclusion: Subcutaneous abdominal, but not femoral, adipocyte size is a predictor of T2D in middle-aged women independent of age, percentage body fat, BMI and WHR. However, waist circumference, and waist to height ratio, are even better predictors of T2D.

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T2:RS2.4

Overweight in early adulthood, life-time weight change and obesity-related diseases in men

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Introduction: Excess body weight is known to increase the risk of morbidity in adulthood, but data on the contribution of weight in early adulthood and subsequent weight change to health status at later ages is limited.
Methods: We prospectively studied the association of recalled body mass index (BMI) at 21 years and subsequent weight change with fatal and non-fatal obesity-related diseases (type 2 diabetes, cardiovascular diseases, obesity-related cancers) among 39,970 Health Professionals Follow-Up Study participants, aged 40 to 75 years in 1986. Cox regression was used to calculate hazard ratios (HR) and 95% confidence intervals (95%CI).
Results: During 18 years of follow-up, 7,074 events of obesity-related diseases were identified. After adjustment for covariates and weight change, compared with a BMI (kg/m^2) at 21 years of 18.5-22.5, the HRs (95%CI) were 1.3 (1.2,1.4) for BMI 22.5-25, 1.7 (1.6,1.8) for BMI 25-27.5, 2.7 (2.4,3.0) for BMI 27.5-30, and 3.6 (3.1,4.1) for BMI ≥30. Compared with a stable weight, the HRs for gaining weight were 1.4 (1.3,1.5) for 5-10 kg, 1.7 (1.6,1.9) for 10-15 kg, and 2.5 (2.3,2.7) for ≥15 kg, whereas weight loss ≥2.5 kg was associated with a decreased risk of 0.7 (0.6,0.9). The relative importance of early weight and weight gain appeared to differ by disease, with weight gain more important for diabetes and early BMI more important for obesity-related cancers.
Conclusion: Overweight and obesity at an early life stage may increase the risks of chronic diseases in adulthood. However, these risks may be modified by weight change during adulthood.

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T2:RS3 - Levels and trends of obesity in Europe

T2:RS3.1

Is the obesity epidemic taking a break?

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The last 3-4 decades have shown a steadily increasing prevalence of obesity in most countries all over the world. However, recent reports from various sites suggest that the increase is levelling off. This raises several questions on the top of the many still unanswered about the rising prevalence. What is specifically causing the rising prevalence remains unknown, although the prevailing belief is that the 'obesogenic environment', defined as an environment that facilitates increased intake of energy dense food and sedentary life style, is the culprit. Is the levelling off in prevalence due to a concurrent levelling off in exposure to the causes or is it due to some additional factors opposing the still operating causes? Has the history of the obesity epidemic shown similar irregularities before, and, if so, what can we learn from these? Is the rising prevalence due to increasing incidence and/or prolonged duration of the condition, and is the levelling off due to opposite changes? Are the changes in prevalence reflecting effects specific to the calendar period, to particular age groups, or to particular birth cohort? Are the changes in prevalence affecting the different types of obesity, i.e. general, abdominal and peripheral obesity, equally? The answers to these questions have obvious implications for where to look for the causes of the changes as well as for the prediction of the future development of the obesity epidemic. There seems to be no reasons to slow down researching causes of obesity and how to prevent and treat the condition.

Conflict of interest: See http://www.ipm.regionh.dk/person/tias/tiasbio.htm, where industrial collaborations are listed. *Funding:* This research is supported by a grant from the Danish Strategic research Council to establish The Danish Obesity Research Centre, DanORC (see http://www.danorc.dk/)

T2:RS3.2

Is obesity an increasing health problem in the aging population?

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The presentation will start with an overview of the current prevalence and recent trends in overweight and obesity in older Europeans. National data show that the prevalence of overweight and obesity is highest in older persons compared to any other age group. Furthermore, Dutch data from a representative sample of older persons showed that the prevalence of obesity of men and women aged 55-65 years has increased from 9.5% and 20.5% in 1992/93 to 18.4% and 27.5% in 2002/03.
In the second part of the presentation some of the negative health consequences of obesity in old age will be discussed, including mobility limitations, pain and incontinence.
In the final part of the presentation results from the Longitudinal Aging Study Amsterdam will be presented on body weight perception, attitude and weight loss strategies among older overweight persons. The results show that most of the overweight persons perceive themselves as overweight. Of the overweight persons less than 10% is satisfied with their body weight, a majority prefers a smaller body size and about a third actively tries to lose weight. Of those who try to lose weight, only 40% used the optimal strategy of eating less and being more physically active. These results suggest many older persons consider their overweight a problem and use potentially harmful strategies to lose weight.
This presentation will clearly show that more attention towards prevention and treatment of obesity in old age is necessary.

Conflict of interest: None. *Funding:* The LASA study is financially supported by the Dutch Ministry of Public Health, Welfare and Sports.

T2:RS3.3

Twenty-five year trends in body mass index by education and income in Finland

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Introduction: Socioeconomic gradient in obesity is amply documented. However, the relative contribution of different socioeconomic indicators over time is less well known. The aim of this study was to investigate the effects of education and income on body mass index (BMI). Especially, we studied whether the associations varied across the years from the late 1970's to the early 2000's.
Methods: Data were derived from nationwide health behavioural surveys carried out annually since 1978. This study comprises 25-year data (1978-2002) including 24584 men and 25339 women aged 25-64 years. BMI was based on self-reported weight and height. Education in years was obtained from the questionnaire and household income per consumption unit from the national tax register. Both education and income was divided into gender-specific tertiles per study year. Log-linear regression analysis was applied.
Results: In men, education had an inverse and stable association with BMI. The most prominent increase in BMI took place in low educated men with the highest income. In women, education showed a stronger inverse association with BMI. In all educational groups, women with the highest income had the lowest BMI.
Conclusion: The socioeconomic gradient, regardless of the indicator used, has stayed stable in women, whereas in men, the effect of income on BMI in men with low education has become more important.

Research relating to this abstract was funded by Academy of Finland.

T2:RS3.4

Trends in Maternal Obesity and Health Inequalities in a Nationally Representative Sample of 619,323 Births in England, UK, 1989-2007

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Introduction: There is an absence of national statistics for maternal obesity in the UK. This study is the first to describe a nationally representative maternal obesity research dataset in England.
Methods: The study was carried out over 2 years, and incorporated an audit of data collection practice in all 243 maternity units in England to establish availability of electronic data required (89% response). 34 maternity units were sampled. The population demographics were nationally representative when compared with national census data. Retrospective data from 1989-2007 were collated, and included 619,323 deliveries. Trends in 1st trimester maternal obesity incidence (BMI>30kg/m^2) were calculated using Chi^2. Demographics of "at risk" women were tested for multicollinearity and logistic regression adjusted for all demographics as confounders.
Results: Maternal obesity is significantly increasing over time, having more than doubled from 7.6% to 15.6% ($p<0.001$, figure 1). There are increased odds of being obese with increasing age (1.02, 95% C.I. 1.02, 1.02), parity (1.17, 95% C.I. 1.16, 1.18), black ethnic group (1.78, 95% C.I. 1.70, 1.87), and deprivation (2.20, 95% C.I. 2.13, 2.28).

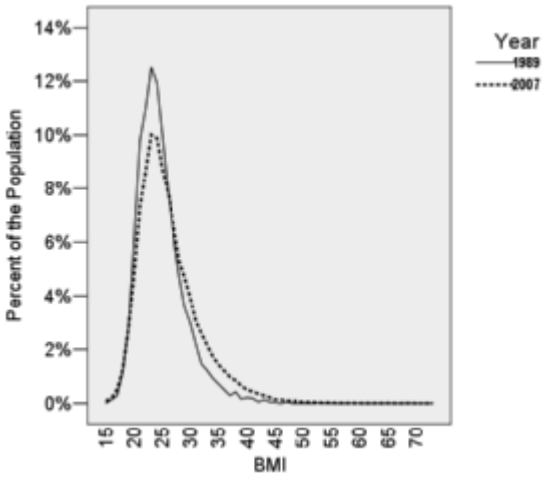

Figure 1: Change in Maternal 1st Trimester BMI Distribution 1989-2007

Conclusion: The increase in maternal obesity has consequences for the health of mothers, infants, and service providers, yielding an additional of 47,500 women per year requiring high dependency care in England (92,500 women in 2007 compared with 45,000 in 1989). The demographics of women most at risk highlight health inequalities associated with maternal obesity which needs to be addressed.

Funding: Research relating to this abstract was funded by the University of Teesside.

T2:RS4 – New determinants of obesity

T2:RS4.1

The impact of sleep loss on obesity and diabetes risk

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Chronic sleep loss due to voluntary bedtime restriction is increasingly common in modern societies. Interestingly, this behavior has developed over the same time period as the recent epidemic of metabolic conditions. In laboratory studies of healthy young lean men submitted to sleep restriction for 2 to 6 days, marked alterations in glucose metabolism including decreased glucose tolerance, impaired ß-cell function, reduced non-insulin dependent glucose utilization, and decreased insulin sensitivity have been demonstrated. The neuroendocrine regulation of appetite was also affected and included a down-regulation of the satiety hormone leptin and an up-regulation of the appetite-stimulating hormone ghrelin. Importantly, these neuroendocrine abnormalities were correlated with increased hunger and appetite, which may lead to overeating and weight gain. Recently, marked alterations in glucose metabolism were observed after experimental induction of a high degree of sleep fragmentation and low amounts of slow wave sleep, without changes in sleep duration. These results indicate that reduced sleep quality *per se* may also play a role in the pathophysiology of diabetes. Consistent with these findings, an ever-increasing number of cross-sectional and prospective epidemiologic studies have provided evidence for an association between short and/or poor sleep, and the prevalence or incidence of obesity and diabetes, after controlling for various confounders. In conclusion, chronic sleep loss and/or poor sleep, conditions that affects millions of individuals, may be important but widely underestimated risk factors for obesity and diabetes. Strategies to improve sleep duration and quality should be considered to prevent or delay the development of these diseases.

Conflict of interest: None Disclosed. *Funding:* Research relating to this abstract was supported by US National Institute of Health grants P01 AG-11412, R01 HL-075079, P60 DK-20595, R01 DK-0716960, R01 HL-075025 and M01 RR000055, by Belgian "Fonds de la Recherche Scientifique Médicale" (FRSM-3.4583.02) and "Fonds National de la Recherche Scientifique" (FNRS), and by INSERM U628 and Claude Bernard University of Lyon, France .

T2:RS4.2

Environmental temperature and obesity

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There is need for information on environmental forces that cause the gradual weight gain in the population. An overlooked but potentially important factor is the reduction in variability in ambient temperature. Traditionally, offices and houses are designed for maximal thermal comfort within the thermal neutral zone (TNZ). However, exposure to ambient temperatures above or below the TNZ increases energy expenditure.
The effect of warm environments on energy balance has not received much attention in the past years. However, on the effect of temperature reduction much information has been gathered. Several studies have confirmed that humans show significant (mild) cold induced thermogenesis, i.e. without shivering. The individual variation in CIT is large. There are indications that CIT is reduced in obese subjects. Tissues shown to be involved in adults are skeletal muscle and brown adipose tissue (BAT). The most likely cellular mechanism in both tissues is mitochondrial uncoupling. Evidence for the involvement of skeletal muscle comes from cellular respiration analyses, showing the level of mitochondrial uncoupling is related to whole body CIT. Evidence that BAT may be an organ of physiological importance in adults comes from nuclear medicine studies using PET/CT scans, and results from uncoupling protein-1 immunofluorescence assays.
Recent studies on molecular level have identified a mechanism by which PRDM16 (a zinc-finger protein selectively expressed in BAT) can induce BAT gene expression while suppressing WAT gene expression, controlling the switch from WAT to BAT. Moreover, it was shown that brown adipose tissue is more related to skeletal muscle than to white adipose tissue. Such factors provide insight into the stem cell origins that lead to brown fat formation and will likely act as targets for obesity-associated therapeutics. It also indicates the importance of both BAT and skeletal muscle as tissues involved in cold induced thermogenesis.

T2:RS4.3

High levels of physical activity can attenuate the effect of FTO (fat mass and obesity associated) gene variant on obesity

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Introduction: Variants in the FTO gene are known to contribute to obesity risk. We examined whether physical activity attenuates the effects of FTO variants on BMI and waist circumference (WC) in the EPIC Norfolk Study, a large-scale population-based cohort.
Methods: We genotyped the FTO variant, rs1121980 (MAF:43%), in 20,374 participants (39-79 years) of European descent. Height and weight were measured to calculate BMI. Physical activity (PA) was assessed by a validated self-reported questionnaire and categorised into 4 groups based on occupational and leisure PA (inactive, moderately inactive, moderately active and active). The association between the FTO variant and BMI and WC was tested using mixed linear models assuming an additive effect and adjusted for age, sex and PA, with the variant-PA interaction term included in the model.
Results: The risk (T)-allele of rs1121980 was significantly associated with BMI (p=2.0E-24, 0.31 $kg.m^{-2}$ increase per allele) and WC (p=2.8E-22, 0.77 cm increase per allele). Interestingly, we found that PA attenuated the effect of the rs1121980 on both BMI and WC. While the risk-allele increased BMI with 0.25 $kg.m^{-2}$ per allele in active individuals, the increase in BMI was ($p_{interaction}$=0.004) more pronounced (76%) in those individuals categorised as inactive (0.44 $kg.m^{-2}$ per risk allele). We observed similar effects for WC ($p_{interaction}$=0.02), where in active individuals, the risk-allele increased WC with 0.64 cm, while in inactive individuals, the risk-allele increased WC with 1.04 cm per allele.
Conclusion: Our results show that PA can attenuate the effect of FTO rs1121980 genotype on BMI and WC.

Conflict of interest: None. *Funding:* The EPIC Norfolk Study is funded by Cancer Research, United Kingdom, and the Medical Research Council.

T2:RS4.4

Mediterranean diet and prospective weight gain in participants of the EPIC-PANACEA project

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Introduction: Greater adherence to a Mediterranean diet has been associated with a reduced risk of developing chronic diseases. However, no large prospective study has assessed whether this dietary pattern may be also protective against the development of obesity.
Objective: To assess the association between adherence to a modified Mediterranean diet, and prospective weight change in European men and women.
Methods: 366,494 individuals (71.8% women) aged 25-70 years from 10 European countries participated in the EPIC-PANACEA project. Diet was assessed at baseline using detailed validated country-specific questionnaires, and a modified-Mediterranean Diet Score (mMDS) was constructed (including high consumption of vegetables, legumes, fruits & nuts, cereals, fish & seafood, and unsaturated: saturated fatty acids ratio; moderate alcohol intake; and low consumption of meat & meat products, and dairy products). Weight was measured at baseline, and self-reported after a mean follow-up time of 5 years. The association between mMDS and annual weight change (kg) was modelled through mixed-effects linear regression, controlling for potential confounders.
Results: Greater adherence to the Mediterranean diet was significantly associated with lower annual weight gain in both men ($P = 0.001$) and women ($P = 0.042$). There was no evidence of heterogeneity among centres, age groups or baseline body mass index.
Conclusion: These results support that Mediterranean dietary patterns can be promoted as a way of maintaining a healthy weight throughout adulthood.

Conflicts of Interest: none declared. *Funding:* Research relating to this abstract was funded by the European Union, in the framework of the Public Health Programme (project number: 2005328).

Track 3: Integrative Metabolism and Homeostasis
T3:RS1 – Obesity and the Gut

T3:RS1.1

Control of the inflammatory tone by gut flora during obesity

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Obesity is characterized by an increased inflammatory tone in adipose tissues. This local inflammation has been suggested to be associated with the enlargement of the adipose depots and the induction of insulin resistance. We have recently demonstrated that the origin of inflammation, during a fat-enriched diet, was associated with dramatic changes in the metagenomic profile of intestinal microflora. A high-fat feeding (HFD) increased the gram negative to gram positive ratio in the gut leading to an increased metabolic endotoxemia i.e. the plasma concentration of LPS which originates from gut flora. We showed that a continuous subcutaneous infusion of low dose LPS increased the count of adipose cells of smaller size when compare to what observed in saline infused mice. The effect of LPS and of a high-fat diet was totally prevented in LPS receptor CD14 knockout mice. In addition, an antibiotic treatment reduced the impact of HFD on the development of inflammation and obesity. To address whether cells in the fat pads could be directly targeted by LPS/CD14 pathway we grafted CD14 knockout mice with fat pads from wild type and CD14 knockout mice. The data showed that adipose tissue inflammation, infiltration, energy metabolism and the antigenic profiles of cells from the stroma vascular fraction were targeted by metabolic endotoxemia. Therefore, adipose tissue plasticity during HFD requires the direct targeting of the adipose fat pads by LPS from intestinal microflora. Hence, the control of the latter by pro- or pre-biotic treatment could reduce the development of obesity.

T3:RS1.2

Nutrient sensing in the gut

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The gastrointestinal tract must balance two ostensibly conflicting tasks: absorption of nutrients and protection against potential harmful pathogenic or antigenic material. Critical for both is the ability to sense luminal content and the orchestration of secretory and motor activity appropriate for either digestion and absorption or dilution and elimination. Recent evidence suggests that the former is linked to mechanisms that control food intake by a complex system of neural and hormonal control mechanisms. In this respect the GI tract has a rich sensory innervation conveying information to the CNS relating to the physical and chemical composition of gut contents, much of it below the level of consciousness. Entero-endocrine cells in the gastrointestinal mucosa are critical for sensory transduction from the lumen to the sensory endings in the lamina propria with a number of mediators released in response to specific macromolecules. CCK released in response to luminal fat and protein digestion products acting on CCK1 receptors on vagal mucosal afferents represents the best understood of the satiety signals. 5-HT is released by enterotoxins and acts via 5-HT3 receptors to trigger nausea and vomiting. However, there is strong evidence that 5-HT may also contribute to glucose-sensing. Other signalling peptides include leptin, ghrelin, orexin, GLP-1 and peptide YY with recent evidence suggesting integration at the level of the vagal afferent neuron. In this respect nodose neurones co-expresses a variety of the receptors that mediate signalling and the relative expression of these receptors alters with nutritional status. These mechanisms integrate nutrient signals to ensure fine-tuning of GI function and regulated food intake.

T3:RS1.3

The effect of site and length of small intestine exposed to fat on satiety, energy intake and satiety hormones in humans

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Introduction: The site of fat delivery affects hunger and food intake, but animal data suggest that the length of intestine exposed to fat might also be important. We tested if increased luminal surface exposed to fat decreases hunger and food intake, versus oral consumption or ileal infusion.
Methods: 15 volunteers intubated with a naso-ileal tube received 4 isocaloric treatments in balanced order on consecutive days. The oral (Oral) control was a Slim·Fast meal replacer (MR) containing 6 g of oil ingested at t=0 min, with saline infusion at t=30-120 min. Experimental treatments were a fat-free MR at t=0, with either 6g oil delivered sequentially (Seq: 2g duodenal t=30-60, 2g jejunal t=60-90, 2g ileal t=90-120 min), simultaneously (Sim: 2g each to all 3 sites t=30-120 min), or ileal only (Ileum: 6g

t=30-120 min). Plasma (in n=9 subset) CCK, GLP-1, PYY, glucose, insulin, gastric emptying (^{13}C-breath test) and hunger were measured until t=180 min, when *ad libitum* food intake was assessed.
Results: Ileum and Sim both reduced hunger versus Oral (P<0.05). Only Ileum reduced food intake versus Oral (P<0.01). Gastric emptying did not differ between treatments. During and after infusion none of the plasma values differed between treatments, except for GLP-1 at t=120 and 180 min when GLP-1 was 70-75% higher after Sim as compared to Oral (P<0.05).
Conclusions: Hunger and food intake are most potently reduced after ileal fat delivery. Hunger-suppressing effects of increased luminal surface exposed to fat are only observed when fat is delivered simultaneously to different intestinal sites.

Funding/Conflict of Interest: Research was funded by Unilever, a commercial manufacturer of meal replacers

T3:RS1.4

Role of gut microbiota in energy metabolism and obesity development in mice

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Introduction: Comparisons of germfree (GF) and conventional (C) mice suggest that the presence of an intestinal microbiota is required for the development of diet induced obesity (Bäckhed et al., 2007). Two groups of bacteria seem to play an important role in the regulation of body weight, the *Bacteroidetes* and the *Firmicutes* (Ley et al., 2005).
Methods: GF and C mice were fed semi synthetic diets differing in their macronutrient composition. Changes in weight, energy homeostasis and in the intestinal microbiota were monitored. In faeces of C mice *Bacteroidetes* were detected with the oligonucleotide probe Bac303, and *Firmicutes* with Erec482 and Lab158. On a molecular level we studied the influence of colonization on the expression of the fasting induced adipose factor (fiaf) in intestinal epithelium, adipose tissue and liver.
Results: Surprisingly, GF mice gained body weight and fat on the semi synthetic high fat diet. They showed a higher energy intake and lower energy expenditure than C mice. We could reproduce the decrease in fiaf mRNA levels in intestinal epithelium of C compared to GF mice observed by Bäckhed et al.. Yet, on the protein level no decrease in intestinal epithelium or plasma was detectable. In faeces of C mice the percentage of bacteria detectable with the three oligonucleotide probes decreased from 70% to around 25% after the switch to semi synthetic diets.
Conclusion: Germfree mice are not generally protected against diet induced obesity. The role of intestinal fiaf in energy metabolism and fat accumulation should be revisited.

T3:RS2 – Obesity and inflammation

T3:RS2.1

Novel adipokines and inflammation

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White adipose tissue is a major endocrine and secretory organ, with white adipocytes releasing a wide range of protein factors and signals. These adipokines are highly diverse in structure and function. The functions encompass appetite control, glucose tolerance, blood pressure regulation, lipid metabolism and angiogenesis. A number of adipokines are directly linked to immunity and the inflammatory response, and these include key cytokines (e.g. TNFα, IL-1β, IL-6), chemokines (e.g. MCP-1, MIF), acute phase proteins (e.g. haptoglobin, serum amyloid A) and inflammation-related factors such as adiponectin and VEGF. The synthesis and release of inflammatory adipokines rises markedly as adipose tissue mass expands in obesity (with the exception of adiponectin which has an anti-inflammatory action), and the tissue contributes to the state of chronic mild inflammation that characterises the disorder. Several novel inflammation-related adipokines, or putative adipokines, have recently been identified, and these include chemerin, IL-18, NGF and members of the matrix metalloproteinase family (e.g. MMP1). In some cases, such as Il-18 and IL-33, gene expression is apparent but evidence that the encoded protein is secreted from adipocytes is equivocal. It is considered that the inflammatory response in adipose tissue underlies the development of the metabolic syndrome and other obesity-associated diseases, with several inflammation-related adipokines being directly linked to insulin resistance. The basis for inflammation in adipose tissue in obesity is uncertain, but we have argued that a key factor is local hypoxia as tissue mass expands, large adipocytes becoming O_2-deprived as their distance from the vasculature increases.

Funding related to this abstract was received from the BBSRC (U.K.).

T3:RS2.2

Inflammatory modulators of the metabolic syndrome

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Introductioin: Metabolic syndrome is the most common disorder associated with coronary artery disease (CAD) based on visceral fat accumulation. To elucidate the molecular link between visceral fat and metabolic syndrome, we analyzed the expressed genes of human visceral fat tissue and found adiponectin, in addition to known proinflammatory molecules.
Methods and Results: Hypo-adiponectinemia was observed in patients with obesity, type 2 diabetes, hypertension and CAD. The genetic hypo-adiponectinemia, I164T mutation, was associated with increased CAD prevalence and the phenotype of metabolic syndrome independent of obesity. In addition, plasma adiponectin levels inversely correlated with C-reactive protein and the metabolites of lipid peroxide in patients with CAD and obesity, suggesting that hypo-adiponectinemia is associated with systemic inflammatory response.
To elucidate the causal relationship between hypo-adiponectinemia and metabolic syndrome, we generated adiponectin deficient (KO) mice, and challenged KO mice with atherogenic diet and the models of metabolic syndrome-related diseases, acute coronary syndrome (ACS), chronic kidney disease (CKD) and nonalcoholic steatohepatitis (NASH). KO mice developed diabetes and hypertension on a high-fat/ high-sucrose diet and a high-salt diet, respectively. In ACS model, KO mice resulted in increased infarct size and tumor necrosis factor-alpha expression. In CKD model, urinary albumin excretion and tubulointerstitial fibrosis were worse in KO mice. In NASH model, hepatic steatosis was enhanced to a greater extent in KO mice. Adiponectin supplementation attenuated these abnormalities in KO mice.
Conclusion: Adiponectin is the key mediator of inflammation, and a therapeutic strategy to increase plasma adiponectin should be useful in metabolic syndrome-related disorders.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T3:RS2.3

Exposure to low barometric pressure mimics obesity-induced hypoxia, inflammation and macrophage infiltration in Wistar rat adipose tissue.

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Introduction: The factors driving obesity-induced massive macrophage recruitment in the adipose tissue are poorly defined. A role for hypoxia has been suggested in obese humans and rodents. Here, we exposed normal rats to low barometric pressure to discriminate the role of hypoxia from obesity.
Methods: Wistar rats were exposed to a simulated altitude of 5,500m in a hypobaric chamber for up to 3 weeks. Pimonidazole labeling was used for the detection of tissue hypoxia. Semi-quantitative RT-PCR-based gene expression analysis was performed in epidydimal and retroperitoneal adipose tissue pads. The number of CD68+ macrophages per 100 adipocytes was quantified on adipose tissue slides.
Results: Pimonidazole positive areas were detected in adipose tissue as early as 6 h of ambient hypoxia. Tissue hypoxia was confirmed by a marked induction of known hypoxia-responsive genes, including VEGF (10-fold), GLUT1 (4-fold) and AngPTL4 (5-fold). Hypoxia was associated with an increased expression of several inflammatory genes. MCP-1 (9-fold), IL-1β (12-fold) and MMP9 (18-fold) were among the most up-regulated genes. In contrast, expression of lipogenic genes and adipose cell size were reduced by hypoxia. Macrophages were virtually absent in normoxic rats and increased to 7 per 100 adipocytes after 3 weeks of hypoxia.
Conclusion: These data suggest that hypoxia induces adipose tissue inflammation, leading to an infiltration of macrophages and potentially other immune cells, even when adipose cell size is not increased; however, the relatively low number of macrophages in hypoxic rat adipose tissue suggests that additional signals, possibly driven by adipocyte hypertrophy, are involved in obesity.

Conflict of interest: None Disclosed. *Funding:* No Funding.

T3:RS2.4

Targeting osteopontin improves obesity-induced adipose tissue inflammation and insulin resistance

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Introduction: Obesity is associated with a state of chronic low-grade inflammation mediated by macrophage accumulation in adipose tissue (AT), which appears to underlie obesity-induced metabolic deterioration including insulin resistance and type 2 diabetes. Osteopontin (OPN) is an inflammatory cytokine, the expression of which is strongly upregulated in the AT upon obesity. Here we studied two murine models to examine the role of OPN in obesity-induced inflammation and insulin resistance.
Methods: Wild-type (WT) and OPN deficient mice ($OPN^{-/-}$) were placed for 24 weeks on high-fat (HF) and low-fat diet. Another group of HF-fed WT mice were intravenously treated or not with an OPN neutralizing antibody. Insulin tolerance and inflammatory alterations in AT and liver were assessed.
Results: After HF-feeding, $OPN^{-/-}$ mice displayed markedly improved insulin sensitivity compared with their WT littermates. Strikingly, interference with OPN action by a neutralizing antibody for only five days significantly improved insulin sensitivity in diet-induced obese mice. Anti-OPN treatment attenuated AT macrophage infiltration and inflammatory gene expression and significantly reduced c-Jun NH_2-terminal kinase phosphorylation. Moreover, anti-OPN treated obese mice exhibited decreased gene expression of hepatic inflammatory proteins and gluconeogenic enzymes.
Conclusion: These findings demonstrate that both genetic OPN deficiency and antibody-mediated neutralization of OPN action improve insulin sensitivity in diet-induced obesity. OPN neutralization abrogates obesity-associated AT and liver inflammation and reverses diet-induced insulin resistance. Hence, targeting OPN could provide a novel approach for the treatment of insulin resistance and related metabolic disorders.

This work was supported by the Austrian Science Fund (P18776-B11, and as part of the CCHD doctoral program, W1205-B09), and by the 7th Framework Programme of the European Commission (grant no 201608; all to T.M.S.).

T3:RS3 – Substrate metabolism

T3:RS3.1

Is lipid oxidation in skeletal muscle impaired with obesity?

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Introduction: With the increasing prevalence of obesity, it is paramount to determine mechanisms that are linked with a propensity for weight gain. Our hypothesis to be tested was that in obese individuals there is a decrement in the ability to oxidize lipid in skeletal muscle which may in turn promote insulin resistance and weight gain.
Methods: Lipid oxidation was determined in human skeletal muscle with a variety of methods (muscle strip incubations, muscle homogenates, primary human skeletal muscle cells) in lean, obese, and very obese (BMI > 40) subjects. Lipid oxidation in muscle was also determined before and after interventions such as weight loss, exercise training, and a high-fat diet.
Results: The ability to oxidize lipid was depressed in skeletal muscle from extremely obese (BMI >40) individuals. This reduction was also apparent in primary muscle cell cultures from extremely obese donors and remained evident after pronounced (50 kg) weight loss (gastric bypass surgery) but was reversed with 10 days of exercise training. The increase in lipid oxidation with exercise may be associated with increased expression of PGC-1α. During a high fat diet, mRNA linked with lipid oxidation were not up-regulated as robustly as in lean individuals, which suggest a possible mechanism involving signaling pathways.
Conclusions: Lipid oxidation in human skeletal muscle appears to be impaired in extremely obese individuals. This defect can be corrected with exercise training but not weight loss. The cellular mechanisms linked with this reduction and the efficacy of exercise training remains to be determined.

Conflict of Interest: None. *Funding:* Funding for these studies was provided by NIH Grants NIDDK RO1-DK56112 and NIA RO1-AG025205.

T3:RS3.2

The physiological function of metabolic lipases in adipose and non-adipose tissues: Lessons from mutant mouse models.

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Metabolic lipases catabolize stored fat in adipose and non-adipose tissues, a process called lipolysis. The released fatty acids are subsequently utilized as energy substrates, for lipid resynthesis, or the generation of lipid signaling metabolites. Currently three enzymes with an established role in lipolysis are known, adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase (MGL). The

phenotypical characterization of mutant mouse lines lacking ATGL and/or HSL provided important insights into the tissue-specific role of these enzymes. Apparently the lipolytic catabolism of stored lipid droplets is not only of central importance in adipose tissue because defective lipolysis due to ATGL and/or HSL deficiency affects lipid- and energy metabolism also in many non-adipose tissues. The presentation will summarize the most important recent findings on tissue-specific effects in response to ATGL or HSL deficiency.

T3:RS3.3

Dietary fat storage in adipose tissue is not upregulated in overweight men: studies in the postprandial state over 24 h

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Introduction: During the postprandial period subcutaneous adipose tissue (AT) stores dietary fat. It is uncertain whether the processes leading to storage of fatty acids (FA) in AT are similar in lean and overweight individuals.
Methods: Abdominal subcutaneous AT FA handling was studied over 24h in 14 age-matched healthy males (seven overweight) using stable-isotope-labelled FA and arterio-venous difference techniques. Three sequential, isocaloric and macronutrient-identical meals were fed 5h apart.
Results: The efficiency of AT FA uptake increased with each meal in lean compared to overweight males. The fractional extraction of chylomicron-TG increased in lean but not overweight males (20±4 to 51±9% (P=0.027) and 37±12 to 35±9% first to last meal, lean and overweight, respectively). With sequential meals, lipoprotein lipase rate of action increased 1.5 fold in lean (P<0.05) but was unchanged in overweight males. AT spillover of chylomicron-derived FAs was remarkably low in overweight males (approximately 3%), whereas lean males showed a marked decrease (20 to 6% P=0.03) with sequential meals.
Conclusion: Lean as compared to overweight males show considerable induction of fat storage capacity in subcutaneous AT. The inability to enhance AT FA uptake after sequential meals in overweight males may expose other tissues to excess FAs leading to ectopic fat deposition.

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by the British Heart Foundation.

T3:RS3.4

Effect of dietary fat modification on skeletal muscle fatty acid handling in the metabolic syndrome; a stable isotope approach

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Introduction: In the metabolic syndrome (MetS), increased fat storage in 'non-adipose' tissue like skeletal muscle may be related to insulin resistance ("lipid overflow" hypothesis). Therefore, we aimed to examine the effects of chronic dietary fat modification on the capacity of skeletal muscle to handle dietary and endogenous fatty acids (FA).
Methods: In a sub-cohort of the LIPGENE study, 39 men (58±2yr, BMI 30.3±0.7kg/m^2) with the MetS were randomly assigned to one of four diets for 12 weeks: a high-fat saturated fat diet (HSFA, n=9), a high-fat mono-unsaturated fat diet (HMUFA, n=10), and 2 low-fat high-complex carbohydrate diets (LFHCC, n=10), one supplemented with 1.24g/d DHA/EPA (LFHCC*n*-3, n=10). Effects on fasting and postprandial skeletal muscle FA handling were examined by measuring arterio-venous differences across skeletal muscle. [$^2H_2$]-palmitate was infused intravenously to label endogenous fat in the circulation and subjects received a high-fat mixed meal (2.6MJ, 61E%fat) containing [U-^{13}C]-palmitate to label chylomicron-TAG.
Results: Postprandial circulating TAG concentrations were significantly lower after dietary intervention in the LFHCC*n*-3 group than the HSFA group (ΔAUC -139±67μmol*240min *vs.* 167±70μmol*240min, P=0.026), together with decreased concentrations of [U-^{13}C]-labelled TAG, representing dietary FA. No differences were observed in skeletal muscle FA handling and glucose uptake between the diets.
Conclusion: The LFHCC*n*-3 diet resulted in decreased postprandial TAG concentrations, explained by lower accumulation of dietary FA in the circulation. This is not accompanied by a higher clearance of dietary FA by skeletal muscle, suggesting that a higher uptake by adipose tissue or a lower intestinal TAG absorption may be responsible for this.

Conflict of Interest: None disclosed. *Funding:* Research relating to this abstract was supported by *Lipgene*, an EU Sixth Framework Programme Integrated Project (Project number: FOOD-CT-2003-505944).

T3:RS4 – Food intake regulation

T3:RS4.1

Endocannabinoids and obesity

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Many different regulatory actions have been attributed to endocannabinoids, and their involvement in several pathophysiological conditions is under intense scrutiny. Cannabinoid receptors [cannabinoid receptor type 1 (CB1) and CB2] participate in the physiological modulation of many central and peripheral functions. The ability of the endocannabinoid system to control appetite, food intake and energy balance has recently received considerable attention, particularly in the light of the different modes of action underlying these functions. The endocannabinoid system modulates rewarding properties of food by acting at specific mesolimbic areas in the brain. In the hypothalamus, CB1 receptors and endocannabinoids are integrated components of the networks controlling appetite and food intake. Interestingly, the endocannabinoid system was recently shown to control several metabolic functions by acting on peripheral tissues such as adipocytes, hepatocytes, the gastrointestinal tract, the skeletal muscles and the endocrine pancreas. The relevance of the system is further strengthened by the notion that visceral obesity seems to be a condition in which an overactivation of the endocannabinoid system occurs, and therefore drugs interfering with this overactivation by blocking CB1 receptors are considered as potentially valuable candidates for the treatment of obesity and related cardiometabolic risk factors.

T3:RS4.2

Roles of taste in feeding and reward

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Palatability is one of the factors that regulate food and fluid intake and contributes to overconsumption in turn contributing to obesity. Taste is unique among sensory systems in its innate association with mechanisms of reward and aversion in addition to its recognition of quality, e.g., sucrose is sweet and preferable, and quinine is bitter and aversive. Taste information is sent to the reward system and feeding center via the prefrontal cortices such as the mediodorsal and ventrolateral prefrontal cortices in rodents and the orbitofrontal cortex in primates. The amygdala, which receives taste inputs, also influences reward and feeding. In terms of neuroactive substances, palatability is closely related to benzodiazepine derivatives and β-endorphin, both of which facilitate

consumption of food and fluid. The reward system contains the ventral tegmental area, nucleus accumbens and ventral pallidum and finally sends information to the lateral hypothalamic area, the feeding center. The dopaminergic system originating from the ventral tegmental area mediates the motivation to consume palatable food. Of six hypothalamic orexigenic neuropeptides, intracerebroventricular administrations of orexin, melanin-concentrating hormone (MCH) and neuropeptide Y (NPY) increased the intake of palatable saccharin solution. Drinking of saccharin in turn elevated the mRNA levels of orexin and NPY, but not MCH. Gastric motor responses were induced by central administration of orexin and NPY, but not MCH. These results suggest that the over-consumption promoted by sweet and palatable tastes is attributed to the activation of the reward system and orexigenic neuropeptides, such as orexin and NPY, together with enhanced digestive functions.

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T3:RS4.3

Acute stress decreases food reward related activation in the brain

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Background: Stress results in overeating without affecting hunger, possibly by a changed rewarding value of food.
Hypothesis: Stress lowers the rewarding value of food.
Aim: Determine the effect of acute stress on food choice reward related brain activity.
Subjects: 10 females (BMI=21.5±2.2kg/m^2, Age=24.3±3.5y).
Procedure: Fasted subjects came twice to randomly complete either the rest or stress (math-test) condition. Per session, two functional MRI scans were made, wherein the subjects chose breakfast/lunch (food images). The rewarding value of the food was measured as liking and wanting. Food characteristics (e.g. crispiness, fullness of taste etc.), energy intake, amount of each macronutrient chosen, plasma cortisol and VAS hunger and satiety were measured.
Results: Fasted state was confirmed by low satiety and high hunger (10.0±10.3, 79.4±15.3 mmVAS). Breakfast energy intake (3±1MJ) and liking were equal in all conditions. Food wanting was lower at lunch (Δ=-.3 items/category, p<.01). Breakfast decreased hunger and increased satiety at rest (-41.5, 50.6 mmVAS, p<.01). At lunch energy intake (-1.1MJ), protein intake (-14.7g), cabohydrate intake (-32.7g) and putamen activity was lower (AUC=-.9%BOLD·sec, all p<.05). Fat intake was not significantly different (-7.3, p=.4). The math-test led to stress (cortisolΔAUC=+2.2·10^{4}nmol·min/l, p<.05). Stress: Satiety was lower after breakfast (-8.0mmVAS, p<0.01). Lunch energy intake, protein intake and carbohydrate intake was no lower than at breakfast. Crispiness and fullness of taste were chosen more. Brain activity was reduced in reward-areas: Amygdala, hippocampus and cingulate cortex (AUC=-4.7,-2.5, -1.4 %BOLD·sec, p<.05).
Conclusion: Reward signaling and reward sensitivity was significantly lower under stress.

Conflict of interest: None disclosed. *Funding:* Research relating to this abstract was funded by Top Institute Food and Nutrition, Wageningen, The Netherlands.

T3:RS4.4

Hepatic fructose-1,6-bisphosphatase: a novel nutrient sensor

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Introduction: The biochemical mechanisms involved in nutrient sensing and body weight regulation are not completely understood. Fructose-1,6-bisphosphatase (FBPase) is a regulatory enzyme in gluconeogenesis that has been shown to be up-regulated in the liver by obesity and fat. We have previously generated liver-specific FBPase transgenic mice with a 3-fold over-expression in the liver. These mice are 10% leaner than the wild-type littermates. We therefore proposed that hepatic FBPase may have an important role in body weight regulation.
Methods: Energy balance parameters including food intake, voluntary physical activity, resting energy expenditure (REE) and fat-pad masses were measured in transgenic and wild-type littermates. Circulating gut hormones, neuropeptide levels and fatty acid oxidation (FAO) parameters were also measured. Hepatic branch vagotomies and specific FBPase inhibitor intervention studies were also performed.
Results: Transgenic mice ate significantly less by 15% and had smaller fat-pad masses compared with wild-type littermates (p<0.005) with no differences in energy expenditure levels (activity or REE). This was associated with elevated FAO, increased levels of carnitine palmitoyltransferase-1a mRNA and increased concentrations of circulating cholecystokinin (CCK), gastrin and leptin. Hypothalamic AgRP and NPY mRNA were reduced in the transgenics (p<0.05). Either hepatic branch vagotomy or direct inhibition of FBPase in the transgenics normalised food intake, body weight and hypothalamic AgRP and NPY expression to those of the wild-type.
Conclusion: This data demonstrates that hepatic FBPase may be a novel nutrient sensor in regulating food intake as over-expression increases FAO and plasma CCK, gastrin and leptin and suppresses hypothalamic neuropeptide levels.

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Track 4: Genes and Tissue Biology
T4:RS1 – Genetics and energy balance

T4:RS1.1

Developmental origins and epigenetics of obesity

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A large number of epidemiological studies have shown that there is a relationship between poor fetal growth and subsequent development of type 2 diabetes, obesity, insulin resistance and other features of the metabolic syndrome. The detrimental effect of poor early growth is increased if it is followed by accelerated postnatal growth. In contrast slow growth during the lactation period appears to be protective against future metabolic disease. The mechanistic bases of these relationships are not known. However, accumulating evidence has emerged to suggest that early environmental factors play an important role. A number of animal models have been established to investigate the mechanisms by which the early environment influences long term metabolic health. The most extensively studied is the maternal low protein model where rodents are fed a low (8 %) protein diet during pregnancy and/or lactation. Offspring born to low protein fed dams have a low birth weight but when suckled by control dams undergo rapid postnatal growth. These

"recuperated" offspring gain excess weight when weaned onto standard laboratory chow and are more susceptible to diet-induced obesity. In contrast offspring of control dams that are suckled by low protein fed dams grow slowly during lactation, gain less weight when weaned onto standard laboratory chow and are resistant to diet induced obesity. These differences in susceptibility to weight gain are associated with changes in expression of genes implicated in regulation of energy balance. Epigenetic mechanisms may contribute to these programmed changes in gene expression.

T4:RS1.2

Obesity and The Metabolic Syndrome – Insights From Nutrigenomics Approaches

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Introduction: The Metabolic Syndrome (Met Syn) is a very common condition that often precedes T2DM and is associated with a greater risk of CVD. It is characterized by abdominal obesity, insulin resistance, dyslipidaemia, hypertension and a chronic, sub-acute pro-inflammatory state which impedes insulin signalling.
Methods: The LIPGENE dietary intervention assigned 417 free-living subjects with the MetS to one of four isoenergetic diets distinct in fat quantity and quality; high-SFA (HSFA); high-MUFA (HMUFA) and two low-fat, high complex carbohydrate (LFHCC) diets, supplemented with 1.24g/day of long chain n-3 PUFA (LC *n*-3 PUFA) or placebo for 12 weeks. Also comprehensive genetic characterisation sought to determine whether common polymorphisms associated with the Met Syn determined responsiveness to dietary intervention.
Results: This presentation will present results from the LIPGENE Human Dietary Intervention Study which sought to determine the effect of dietary fat modification on metabolic and molecular makers associated with the Met Syn. Also common polymorphisms associated with the Met Syn which may determine responsiveness to dietary intervention within the LIGPENE cohort will be explored.
Conclusions: A personalised dietary intervention approach may be most appropriate to achieve effective dietary treatments of the modifiable risk factors associated with the Met Syn.

Conflict of Interest: None. *Funding:* The LIPGENE study was funded by the EU 6 Framework Food Safety & Quality Programme. Contract N0: 505944. 'Diet, genomics, and the metabolic syndrome: an integrated nutrition, agro –food, social and economic analysis.

T4:RS1.3

Large Family-based Genome-wide Association Scan for Early Onset Extreme Obesity

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Introduction: Although heritability for obesity is substantial, the underlying genetic mechanisms are not well understood. We have performed the to our knowledge first family-based genome wide association study (GWA) for early onset (extreme) obesity.
Methods: a) GWA (1000k; Genome-Wide Human SNP Array 6.0 comprising 906,600 single nucleotide polymorphisms) for early onset extreme obesity based on 424 extremely obese young German individuals and both of their parents; transmission disequilibrium tests; b) for confirmation we analysed already available 1000k GWA data on 453 extremely obese children and adolescents (cases) and 435 healthy controls.
Results: Single nucleotide polymorphisms (SNPs) in a novel candidate gene for obesity on chromosome 8 rendered the lowest p-value (nominal $p= 1x10^{-6}$). Surprisingly, the previously described SNPs in the fat mass and obesity related gene (*FTO)* and the melanocortin 4 receptor gene (*MC4R)* gene were not among the best 100 SNPs. The best 20 SNPs of the combined approach (TDT and cases and controls) will be followed up in >20,000 individuals of central European origin of which >2,000 are children and adolescents.
Conclusions: This first family-based GWA for extreme early onset obesity identified variation in a novel candidate gene for obesity. Confirmatory analyses are currently pursued. Parent of origin effects are currently being assessed.

T4:RS1.4

RIP140 expression associates with human obesity

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Introduction: Receptor-interacting protein of 140 kDa (RIP140) knockout mice have reduced body weight and fat content compared to WT-mice. The aim of this work was to elucidate the role of RIP140 in human white adipose tissue (WAT) and obesity.
Methods: RIP140 mRNA levels were quantified with real-time PCR in WAT samples from obese and lean subjects (n=227) and analysed for association with clinical and adipocyte phenotypes. RIP140 expression was knocked down in *in vitro* differentiated adipocytes and changes in glucose transport and mRNA levels of a set of genes were quantified with real-time PCR.
Results: RIP140 mRNA levels in subcutaneous and omental WAT were decreased in obesity (P<0.001 and P<0.01 respectively) and increased by weight-loss (P<0.01). In subcutaneous WAT, low RIP140 mRNA levels were correlated with high amount of body fat (P<0.01). Moreover, subjects with low RIP140 expression displayed low basal lipogenesis, reduced sensitivity for insulin-induced lipogenesis, and low maximum insulin stimulated lipogenesis independent of age and BMI (P<0.001, for all). In preadipocytes, knock down of RIP140 increased glucose transport (P<0.05) and mRNA levels of GLUT4 and UCP-1(fold change vs Scramble: GLUT4, 7.2±1.7; UCP-1, 32.2±14.5).
Conclusion: RIP140 expression is decreased in obese compared to lean subjects independently of age. This may be a compensatory mechanism attenuating the increase in adiposity. In analogy with mouse RIP140, the human homologue appears to have a similar effect on GLUT4 and UCP-1 expression and thereby energy metabolism.

T4:RS2 – Liver pathology in obesity

T4:RS2.1

Pathophysiology of non-alcoholic fatty liver disease

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Several prospective studies have shown that fat accumulation in the liver due to non-alcoholic causes (NAFLD) preceeds and predicts type 2 diabetes and cardiovascular disease independent of obesity and even fat distribution, although individuals with a fatty liver tend to be more abdominally obese than those without. All components of the metabolic syndrome also correlate with liver fat independent of obesity. Both genetic and acquired factors regulate liver fat content. The heritability of liver fat based on twin studies is ~60%. The rs738409[G] allele in the *PNPLA3* (adiponutrin) gene strongly associates with increased liver fat content in 3 different ethnic groups, also in Finns. Of acquired factors, changes in body weight markedly and rapidly change liver fat. Of dietary factors, diets rich in saturated fat and those stimulating de novo lipogenesis appear harmful. Regarding the mechanisms of fat accumulation in the liver, peripheral lipolysis is increased independent of obesity in sub-

jects with NAFLD. In such subjects, adipose tissue in inflamed and insulin resistant and characterized by an excess of ceramides which could be mediators of high fat induced insulin resistance. In the human liver, there is an excess of triglycerides which contain saturated fatty acids, consistent with tracer studies that both increased adipose tissue lipolysis and de novo lipogenesis (which produces saturated fatty acids) contribute to excess fat accumulation in the liver. In the human liver, expression of genes involved in lipogenesis (PPARγ2, ACSL), fatty acid partitioning and binding, lipolysis and monocyte/macrophage recruitment and inflammation are overexpressed. Liver fat content and inflammation can be reduced by PPARγ agonists. This effect is unlikely to be direct s PPARγ2 expression is increased and likely to involve adiponectin which main target is the liver and which circulating concentrations are markedly increased by PPARγ agonist therapy. Indeed patients who are very resistant to insulin because of a fatty liver or who have inflammatory changes in addition to increased fat content (NASH) might form a subgroup which benefit from PPARγ treatment.

T4:RS2.2

Endoplasmic reticulum stress and hepatic lipid metabolism

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Insulin has an key role in the regulation of hepatic metabolism during the nutritional transition from the fasted to the fed state. Insulin inhibits glucose production and activates hepatic glycogen synthesis and lipogenesis. The effect of insulin on the regulation of lipogenesis is mainly transcriptional. Lipogenic gene expression is controlled by SREBP-1c, a transcription factor which is synthetized as a precursor embedded in endoplasmic reticulum membranes and which requires proteolytic cleavage to be activated. Insulin stimulates both transcription and proteolytic cleavage of SREBP-1c. Paradoxically, in obese insulin resistant rodents, there is a loss of the inhibitory effects of insulin on gluconeogenesis whereas lipogenesis, an insulin dependent process, is maximally stimulated. An active lipogenesis in obese insulin resistant rodents suggests that SREBP-1c could be activated by a signal different from insulin. We develop here the idea that an endoplasmic reticulum (ER) stress could be this signal. An activation of the ER stress pathway stimulates SREBP-1c proteolytic cleavage and induces its lipogenic target genes in rat hepatocytes. In genetically obese mice, the hepatic ER stress pathway is activated. Selective inhibition of hepatic ER stress leads to a marked decrease in SREBP-1c processing and expression as well as in a decreased expression of lipogenic genes, a reduced hepatic steatosis and serum triglycerides and improved insulin sensitivity. We conclude that the ER stress pathway has a major role in the development of hepatic steatosis in insulin resistant states by activating SREBP-1c and thus hepatic *de novo* lipogenesis.

T4:RS2.3

Hepatocyte-specific inflammation enhances VLDL production in mice

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Introduction: The low-grade inflammation that is associated with Type 2 Diabetes (DM2) and Cardiovascular Diseases (CVD) plays an important role in their pathophysiology. Shoelson et al have shown that activation of the inflammatory Nf-κB pathway in the hepatocyte induces severe metabolic changes. We questioned whether hepatocyte-specific activation of Nf-κB affects triglyceride and cholesterol metabolism directly.
Methods: The LIKK-mouse has a transgenic hepatocyte expression of constitutive active IkB kinase, IKKβ. We crossbred this LIKK-mouse with the APOE*3Leiden mouse for its human-like lipid metabolism and investigated the effects of this continuous activation of liver Nf-κB on fasted plasma cholesterol, triglycerides and lipoproteins in 12 week old male LIKK.APOE*3Leiden and APOE*3Leiden mouse fed a chow diet (n=6). Livers were collected to determine hepatic steatosis. Furthermore, hepatic VLDL production was measured using Triton WR1339 to block peripheral VLDL lipolysis, in overnight fasted mice (n=8).
Results: Constitutive active IKKβ expression in the hepatocyte induced an increase in basal triglycerides ($p<0.05$) in APOE*3Leiden mice, which was confirmed by elevated levels of VLDL-triglycerides (0.576 vs 0.382 mM). Liver lipid content was not different between both mice. By blocking the VLDL lipolysis with Triton1339, VLDL-triglycerides were accumulating faster in LIKK.APOE*3Leiden mice than APOE*3Leiden mice (0.065 ± 0.017 vs 0.044 ± 0.013 mM min^{-1}, $p<0.05$), thereby showing an increased hepatic VLDL production.
Conclusion: These data show that hepatocyte-specific low grade inflammation directly increased VLDL-TG levels in plasma by upregulation of hepatic VLDL production. We can conclude that chronic low-grade inflammation plays an important role in the pathophysiology of dyslipidemia associated with Cardiometabolic risk.

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T4:RS2.4

Liver-Specific Deletion of Protein-Tyrosine Phosphatase 1B (PTP1B) Improves Glucose and Lipid Metabolism and Attenuates Diet-Induced ER Stress.

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Objective: The protein tyrosine phosphatase PTP1B is a negative regulator of insulin signaling; consequently, mice deficient in PTP1B are hypersensitive to insulin. Because PTP1B-/- mice have diminished fat stores, the extent to which PTP1B directly regulates glucose homeostasis is unclear. Previously, we showed that brain-specific-PTP1B-/- mice are protected against high-fat diet (HFD)-induced obesity and glucose intolerance, whereas muscle-specific-PTP1B-/- mice have increased insulin sensitivity independent of changes in body weight. Our objective was to study the role of liver PTP1B in glucose homeostasis and lipid metabolism.
Research Design and Methods: We analyzed body mass and adiposity, insulin sensitivity, glucose tolerance and lipid metabolism in liver-specific-PTP1B-/- and PTP1Bfl/fl control mice, fed chow or HFD.
Results: Liver-specific-PTP1B-/- mice exhibit improved glucose homeostasis and lipid profiles, independent of changes in body weight. Liver-specific-PTP1B-/- mice have increased hepatic insulin signaling,

decreased expression of gluconeogenic genes PEPCK and G-6-Pase, enhanced insulin-induced suppression of hepatic glucose production, and improved glucose tolerance. Liver-specific-PTP1B-/- mice exhibit decreased triglyceride and cholesterol levels and decreased expression of lipogenic genes SREBPs, FAS, and ACC. Liver-PTP1B deletion also protects against HFD-induced ER stress response *in vivo*, as evidenced by decreased phosphorylation of p38MAPK, JNK, and eIF2a, as well as decreased expression of the transcription factors C/EBP homologous protein (CHOP) and spliced X box-binding protein 1 (XBP1s).
Conclusions: Liver PTP1B plays an important role in glucose and lipid metabolism, independent of alterations in adiposity. Inhibition of PTP1B in peripheral tissues may be useful for the treatment of metabolic syndrome and reduction of cardiovascular risk, in addition to diabetes.

T4:RS3 – The adipose organ

T4:RS3.1

Adipose Stem Cells

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Pioneering work by Arner, Bjorntorp, Hauner, LaFontan, and others initiated studies of what many now refer to as human adipose-derived stromal/stem cells (ASCs). Similar to the bone marrow, adipose tissue contains an adherent population of multipotent stromal/fibroblast-like cells, capable of differentiating along the adipocyte, chondrocytes, hepatocyte, hematopoietic supporting, neuronal-like, and osteoblast lineages *in vitro* [1,2]. Pathologic analyses by Kaplan and Shore of specimens obtained from patients with Progressive Osseous Heteroplasia has confirmed the presence of such multipotent cells *in vivo* [3]. The ASCs can be isolated clonally and demonstrated to retain multilineage differentiation potential, consistent with the definition of a stem cell [4]. With culture expansion *in vitro*, the immunophenotype of the stromal vascular fraction cells of adipose tissue evolves from a heterogeneous mixture to a relatively homogeneous population based on selected stromal associated surface antigens [5,6]. Similar to bone marrow-derived mesenchymal stem cells (BMSCs), the ASCs exhibit immunosuppressive properties *in vitro* in mixed lymphocyte reactions [5,7,8]. In addition to adipokines, the ASCs secrete a number of pro-angiogenic cytokines, including hepatocyte growth factor (HGF) and vascular endothelial factor (VEGF) [9-12]. Based on these observations, a growing number of international laboratories are exploring the utility of human ASCs for tissue engineering and regenerative medicine [2]. In a manner similar to hematopoietic stem cells, both ASCs and BMSCs express mRNAs for the core circadian regulatory proteins (CCRP) in a synchronized oscillatory manner [13,14]. The expression of CCRPs has been associated with adipogenic events [15-18]. This suggests that peripheral circadian clocks may be a etiologic factor in obesity and related metabolic disorders of adipose tissue. Furthermore, the CCRP of the adipose stem cell may provide a mechanistic link accounting for the impact of sleep loss on the risk of obesity and the metabolic syndrome [19-21].

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T4:RS3.2

Causes of macrophage infiltration

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The concept that chronic low-grade inflammation can be the condition linking obesity and associated pathologies is now widely developed. Moreover the evidence that the growth of the fat mass was associated with an accumulation of adipose tissue macrophages (ATM) has raised the hypothesis that the development of inflammatory process within the adipose tissue was a primary event involved in the genesis of systemic metabolic and vascular alterations. Since ATMs originate from the bone marrow/blood compartment, enhanced macrophage recruitment during fat mass increment is suspected. However the mechanisms responsible for blood cell attraction and entry in the adipose tissue remain to be clearly defined. Non-specific events related to tissue growth might play key roles. Increased cell turn-over requires phagocytotic macrophages to eliminate dead cells. Occurrence of local hypoxic area consecutive to tissue expansion, signal for the entry of pro-angiogenic macrophages. Stimulation of angiogenesis regulates endothelial permeability and activation state. In addition, specific AT-dependent mechanisms including adipokines and metabolic products may also contribute to blood cell recruitment. Finally, AT microenvironment may limit ATM emigration while promoting their

proliferation. The present review will summarize the potential causes of macrophage accumulation in adipose tissue. A particular emphasis will be focused on the specie-dependent discrepancies.

Funding for my research is this area has come from INSERM AVENIR, ANR and P Fabre Laboratories with recent investigations supported by FP7 European Community (ADAPT).

T4:RS3.3

Role of the sirtuin SIRT3 in white and brown adipose tissue biology

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Introduction: SIRT3 is a member of the sirtuin deacetylases family, regulatory proteins involved in cell differentiation, metabolism and ageing. SIRT3 is expressed in adipose tissues, preferentially in brown fat. We studied the role of SIRT3 in the control of gene expression in relation to white versus brown adipocyte differentiation and in response to thermogenic stimuli.
Methods: For "loss-of-function" experimental approaches we used SIRT3-knockout (KO) mice. We studied adipocytes differentiated from SIRT3-KO embryonic fibroblasts, brown adipocytes differentiated from SIRT3-KO pre-adipocytes, and brown and white adipose tissues from SIRT3-KO mice. For "gain-of-function" approaches, we used a SIRT3 adenovirus to over-express SIRT3 in cells. Cells were treated with hormonal regulators of white and brown adipogenic differentiation and activity, including noradrenergic stimuli. Gene expression was analyzed by quantitative RT-PCR. Transcriptional regulation was analyzed by transfection of promoter constructs in HIB-1B cells. Transfected cells were exposed to hormonal agonists and/or co-transfected with expression vectors for SIRT3 and other regulators.
Results: The lack of SIRT3 did not impair white or brown adipocyte differentiation but blunted the noradrenergic-mediated induction of the expression of marker genes of brown adipocyte thermogenic activation (i.e. PGC-1alpha, UCP1 or Dio2). Over-expression of SIRT3 into adipocytes activated the expression of brown fat phenotype gene markers and enhanced the noradrenergic-mediated induction of gene expression. Moreover, protein kinase A-mediated induction of PGC-1alpha gene transcription was enhanced by SIRT3.
Conclusions: SIRT3 is essential for the activation of thermogenic gene expression in adipocytes and contributes to drive adipocyte differentiation into a preferential brown fat phenotype.

T4:RS3.4

Human subcutaneous and visceral adipose tissues show distinct pattern of macrophage gene expression according to obesity and metabolic syndrome

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Introduction: We investigated the expression pattern of a set of macrophage-specific genes (MSG) in subcutaneous and visceral adipose tissue (AT) in women with distinct levels of obesity in the presence and absence of the metabolic syndrome (MS).
Methods: A set of 31 MSG was identified by DNA microarray analysis of human AT cell types. 56 women were divided into 4 groups (lean, overweight, obese and obese with MS). Anthropometric measurements, euglycemic hyperinsulinemic clamp, blood analysis and computed tomography scans were performed. Paired samples of subcutaneous and visceral fat were obtained and whole AT was used for gene expression analysis by RT-qPCR. Data were analyzed by ANOVA.
Results: In subcutaneous AT, 25 MSG discriminated between lean, overweight/obese (no difference) and MS subjects and 4 MSG could discriminate the 4 groups. In visceral AT, mRNA levels of the 31 genes significantly differed between the 4 groups. In both AT depots, expression of MSG was the lowest in lean and the highest in MS group. Comparison of visceral/subcutaneous gene expression ratios within each group showed a marked distinction according to obesity but not MS. In the lean group, a majority of genes was expressed more in visceral AT while in the 3 other groups, higher expression was observed in subcutaneous AT. MSG expression in the two depots was correlated with several clinical parameters.
Conclusion: Subcutaneous and visceral AT macrophages show distinct patterns of gene expression according to the metabolic states of the subjects. The phenotypes of macrophages may influence the development of obesity and the MS.

Conflict of interest: None disclosed. *Funding:* Inserm, grants IGA NR 9161-3-2007, GA R 303/07/0840 & MSM 0021620814, Midi-Pyrénées Region and EC Projects HEPADIP and ADAPT.

T4:RS4 – Molecular mechanisms of insulin resistance

T4:RS4.1

Role of stress signaling pathways in different adipose tissue depots

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Introduction: Although accumulation of intra-abdominal fat is accepted as a stronger predictor of insulin resistance than excess subcutaneous adipose tissue, the mechanisms are poorly understood. We reasoned that obesity-associated adipose tissue "stresses" activate signaling cascades in a depot-differential manner, ultimately resulting in whole-body insulin resistance.
Methods: Paired omental (OM) and subcutaneous (SC) adipose tissue biopsies were collected during abdominal surgery, and the protein expression and phosphorylation state of stress kinases and their mRNA levels were determined. Fat distribution was assessed by L_4-L_5 CT.
Results: The amount of phosphorylated forms of kinases tested in 55 persons provided evidence for an activated stress-sensing pathway consisting of the MAP3Ks Ask1 (but not MLK3 or Tak1), the MAP2Ks MKK4,3/6, (but not MKK7), and the MAPKs p38-MAPK and JNK (but not ERK or IKKβ), specifically in OM of obese persons. OM expression of Ask1, and *Ask1*-mRNA were more highly expressed in predominantly intra-abdominally obese persons, with OM *Ask1*-mRNA most strongly correlated with estimated visceral fat (n=196). In OM, Macrophage infiltration strongly correlated with *Ask1*-mRNA ($r=0.885$, $p<0.001$, $n=51$), but the obesity-associated increase in *Ask1*-mRNA could largely be attributed to the adipocyte cell fraction. Finally, multivariate regression analyses adjusted for Age, Sex, BMI, HDL-c, LDL-c, TG, FFA, leptin, adiponectin, and IL-6 revealed OM-*Ask1* as an independent predictor of whole-body glucose uptake in euglycemic-hyperinsulinemic clamps.
Conclusion: An Ask1-MKK4-p38MAPK/JNK pathway may reflect adipocyte stress in response to adipose tissue inflammation specifically in intra-abdominal fat, linking visceral adiposity to whole-body insulin resistance in obesity.

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by the Israel Foundation for the Study of Diabetes, The Israel Science Foundation, the Leslie and Susan Gonda (Goldschmied) Center for Diabetes Research and Education, the Deutsche Forschungsgemeinschaft, and the Interdisciplinary Centre for Clinical Research, Leipzig (Project B24).

T4:RS4.2

Altered mitochondrial function and insulin resistance – is it secondary or primary?

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In the recent 5-6 years, a reduced mitochondrial function in skeletal muscle has been proposed to underlie the development of muscular insulin resistance, one of the earliest hallmarks of type 2 diabetes mellitus. In fact, non-invasive *in vivo* magnetic resonance spectroscopy has revealed a reduced mitochondrial function combined with elevated muscular lipid content in type 2 diabetic patients and in pre-diabetic first-degree relatives. *Ex vivo* measurements have pointed towards reduced intrinsic mitochondrial function, reductions in mitochondrial density and alterations in mitochondrial structure. These mitochondrial abnormalities could be responsible for the accumulation of fat in muscle and thereby be linked to the development of insulin resistance. Alternatively, mitochondrial dysfunction may be the consequence of insulin resistance and/or muscular fat accumulation. Thus, the acute elevation of circulating fatty acids reduces the expression of the transcriptional co-activator PGC1, an important transcription factor in mitochondrial biogenesis. Furthermore, fatty acids that accumulate in skeletal muscle cells may exert deleterious effects to mitochondrial function (lipotoxicity) via the formation of ROS-induced lipid peroxides. Indeed, increased lipid peroxidation has been reported in insulin resistant skeletal muscle. In addition, studies performed in animals fed high-fat diets tend to indicate that muscular fat accumulation precedes the development of mitochondrial dysfunction. In this presentation the current evidence for the role of mitochondrial dysfunction in the etiology of muscular insulin resistance will be discussed.

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by the Dutch Diabetes Research Foundation and the Netherlands Organization for Scientific Research.

T4:RS4.3

Fenretinide prevents high-fat diet induced obesity and associated hyperleptinemia and insulin resistance

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Introduction: Serum RBP4 levels are elevated in insulin resistant humans and in many mouse models of obesity and insulin resistance including high-fat diet. The synthetic retinoid, Fenretinide [*N*-(4-hydroxyphenyl)retinamide] has been shown to lower serum RBP4 levels in rodents and humans. We previously found that Fenretinide treatment of mice on a high fat diet prevented elevations in serum RBP4 levels, ameliorated insulin resistance and normalized glucose tolerance.
Methods: To determine whether Fenretinide treatment alters energy balance and lipid homeostasis, we placed male FVB mice on high-fat diet +/- Fenretinide (HF and FEN-HF) for 34 weeks and compared them to chow fed controls.
Results: FEN-HF treatment for 16 weeks did not affect body weight as compared to HF controls. However, by 22 weeks of diet, FEN-HF mice gained less weight compared to HF controls. Body fat analysis revealed that the reduced weight gain was due to reduced fat mass gain. Visceral (intra-abdominal) and subcutaneous fat masses were not increased in FEN-HF mice but increased 1.5-2 fold in HF mice. Fenretinide treatment prevented hyperleptinemia in FEN-HFD mice after 8 weeks and 22 weeks of treatment. Fenretinide did not have detectable effects on food intake, lipid assimilation or energy expenditure. Similar results were obtained with only 12 weeks of Fenretinide treatment following 22 weeks of HF-diet induced obesity.
Conclusion: Fenretinide partially protected mice from HF-diet induced obesity by inhibiting subcutaneous and visceral fat expansion and hyperleptinemia. Thus, Fenretinide has globally beneficial effects to prevent diet induced obesity, insulin resistance and glucose intolerance.

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T4:RS4.4

Retinoids Regulate Fat Depot-Specific Developmental Gene Expression

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Fat depots vary in growth, function, and potential contribution to metabolic disease. Properties of fat cells and the preadipocytes from which they arise throughout life vary among depots, including capacities for replication and differentiation. Homeobox (HOX) transcription factors regulate replication and differentiation of diverse cell types. We found inherent, distinct HOX expression profiles in human preadipocytes cultured from abdominal subcutaneous compared to omental and mesenteric fat, even after many cell generations in strains made by stably expressing human telomere reverse transcriptase in single preadipocytes. Regulatory pathways changing expression of HOX developmental factors in adults are poorly understood. Vitamin A regulates adipogenesis through its metabolites, all-trans retinoic acid (RA), 9-cis RA and their precursor, retinaldehyde. To test whether they regulate fat tissue HOX genes, we exposed subcutaneous and omental preadipocytes from 4 women to 500 nM all-trans RA, 9-cisRA, and retinaldehyde and determined expression of all 39 HOX genes. We found divergent effects of RA isomers and retinaldehyde in subcutaneous and omental depots. Effects of RA on HOX A3, A5, B4, and B8 were distinct from retinaldehyde 16h after adipogenesis began in subcutaneous adipocytes, but were similar by 46h. In contrast, omental adipocytes responded to retinaldehyde after 46h with selective up-regulation of HOX B genes (B2, B4, B6, B7, B9), while RA isomers had variable effects on HOX expression. These findings demonstrate that RA isomers and retinaldehyde, important mediators of tissue growth and adipogenesis, have a fat depot-dependant impact on expression of developmental genes that regulate progenitor replication, differentiation, and function.

Track 5: Weight and Risk Management – Clinical/ Lifestyle/Weight Loss
T5:RS1 – Obesity management

T5:RS1.1

Family Based Obesity Treatment

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Introduction: More than fifteen percent of children in Europe are overweight; another five percent are obese. The high prevalence of obesity emphasizes the necessity of developing evidence based treatment pro-

grams that are useful in a clinical setting. Management of childhood obesity is commonly based on lifestyle interventions where nutrition, physical activity and behavior modification are the main targets. To incorporate lifestyle interventions, many pediatric obesity treatment models use different psychological models, such as behavior modification, cognitive behavior therapy or family systems therapy.
Methods: Different psychological models are presented from a theoretical point of view. For each theory relevant studies are presented where controlled clinical studies have been performed.
Results: Behavioural therapy, cognitive behavioural therapy and family systems therapy are supported by controlled clinical trials or randomized clinical trials. No comparative study has been performed between different psychological methods regarding efficacy and cost effectiveness. Most clinical trials in childhood obesity reports no clear theoretical framework. One common finding is that family involvement is necessary to achieve a significant improvement regarding the child's obesity or quality of life.
Conclusion: Clinical trials should better describe the psychological framework of the study to improve the possibility to implement successful programs in other areas.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T5:RS1.2

Chronic obesity management - How long should you treat?

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Introduction: The difficulties associated with long-term weight-loss maintenance led to consider obesity a chronic condition requiring continuous care, a strategy adopted by physicians supporting both a pharmacological and a behavioural approach to obesity. However, the evidence in favour of long-term treatments is modest.
Methods: The QUOVADIS study evaluated the weight loss outcome of subjects attending 15 Italian medical centres adopting a continuous care program. 1,000 treatment-seeking obese subjects (785 females, median age 45.1 years, median BMI 37.4 kg/ m^2) were evaluated at baseline and at 36-month follow-up.
Results: Only 157 patients (15.7%) were in continuous treatment at 36 months. The main reasons for attrition were logistics, unsatisfactory results and lack of motivation. The only basal predictor for continuous care was lower Expected One-Year BMI Loss. The mean percentage weight loss was greater in continuers (5.2% vs. 3.0% in dropouts; P = 0.016). However, specific subgroups of dropouts were identified: those satisfied with the results or confident to lose additional weight without professional help reported a mean weight loss of 9.6% and 6.5% respectively.
Conclusion: Not all patients are suitable for a continuous model of care and not all patients need a continuous care approach to obtain long-term favourable results. Research is needed to identify candidates to a long-term treatment, as well as patients who can achieve satisfactory results with shorter and less expensive approach. The Expected One-Year BMI Loss and age must be carefully considered in treatment plans, together with barriers to treatment.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T5:RS1.3

Non-surgical weight loss for extreme obesity: Results of the Louisiana Obese Subjects Study (LOSS)

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Introduction: Little data demonstrates effective non-surgical approaches to extreme obesity. To evaluate a two year intervention for BMI 40-60 Kg/m^2 implemented in primary care settings, we conducted a randomized 2 arm pragmatic clinical trial conducted in 8 sites.
Methods: Eligible participants were randomized into two groups. Usual Care (UC) had access to self-guided internet weight management program. Intensive Medical Intervention (IMI) was delivered in III phases (900 Kcal liquid diet for 12 weeks; group behavioral counseling, a structured diet and pharmacotherapy with sibutramine, orlistat or diethylpropion for the next 4 months; and medications + maintenance strategies for months 8-24)
Results: Of 597 individuals screened, 393 were included in the analysis of IMI (n=200) or UC (n=193). Retention in the IMI group was 60% at one year and 51% at 2 years; for UC, it was 48% and 46%. For IMI, the ITT analysis showed 31%, 21%, 10% and 7% achieved, respectively, 5%, 10%, 15% and 20% weight loss at 2 years, compared to 10%, 4%, 2% and 2% for UC. The last observation carried forward analysis showed weight loss of -8.3$\pm$0.79% for IMI, compared to -0.5$\pm$0.46% for UC. For 119 who completed IMI at 1 year, mean weight loss was -9.7$\pm$1.3%, (-12.7$\pm$1.7 Kg) P<0.0001 vs. baseline. In contrast, the 92 UC completers at 1 year lost -1.5$\pm$0.8 % (-1.7$\pm$0.9 Kg), P=0.28, and at year 2, -1.3$\pm$0.9% (-1.6$\pm$1.1Kg), P=0.4. Many metabolic parameters improved.
Conclusions: This study demonstrates that primary care clinics can implement a successful medical program for extreme obesity.

Conflict of Interest: None to report. *Funding:* The study was funded by the Office of Group Benefits, a provider of health insurance for governmental employees in Louisiana. A portion of the sibutramine used in the study was donated by Abbott.

T5:RS1.4

Lifestyle intervention on top of pharmacological treatment in obese type 2 diabetes mellitus patients.

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Introduction: obesity in type 2 diabetes mellitus (T2DM) patients is often associated with poor blood glucose regulation, decreased quality of life and increased risk of complications (1,2). Pharmacotherapy is often unsuccessful to achieve glucose control and multidisciplinary treatment should be encouraged (3).
Aim: to analyze the longevity of a long-term multidisciplinary lifestyle intervention in the treatment of obese T2DM patients on top of pharmacological treatment.
Methods: we included 93 obese T2DM patients in a 65 week programme containing 32 frequent sessions with a nutritionist, psychologist and physical activity.
Results: After inclusion, mean weight decreased from 112,8 kg to 101,4 kg (p<0,001), mean BMI decreased from 38,8 kg/m2 to 35,1 kg/m2 (p<0,001). HbA1c decreased from 7,6 to 6,6 (p= p<0,001), other metabolic parameters significantly improved. 15% of patients were eventually off medication, 50% decreased their number of tablets needed. Mean number of insulin units decreased from 116 IE to 53 IE (p<0,01). Metabolic parameters remained decreased 2 years after intervention stop. Quality of life, assessed with SF-36 questionnaires, showed significant improvement in self-reported general health, physical functioning, vital-

ity and mental health; all remained significant 2 years after intervention stop.
Conclusion: we have shown that motivated T2DM patients participating in this intervention achieve sustained weight loss and improvement of glucose tolerance and metabolic parameters. Physical and mental quality of life was significantly enhanced and persisted during 2 years follow-up. In our opinion, long-term lifestyle intervention should be a main component in treatment of obese T2DM patients.

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T5:RS2 – Dietary management

T5:RS2.1

The role of Functional Foods: Hype, Help or Hope?

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Whilst susceptibility to obesity is determined largely by genetic factors, the current obesity epidemic is significantly influenced by adverse lifestyle factors. Given our genetic background it is essential infeasible for humans to self-regulate food intake under current obesogenic environment with cheap but tasteful food available mostly in large portions everywhere at all time of the day. The challenge is to reduce the daily energy intake without compromising the consumer liking too much. Science tells us clearly that one should focus in the first place on the macro nutrient composition to reduce energy intake. In this category also the fat and sugar replacers are valuable aids to create low energy alternatives. Addition of specific bioactive food ingredients could be of benefit to enhance satiety or to increase thermogenesis. So far the list of scientifically substantiated ingredients with a successful decrease in body weight over time or prevention of weight regain after weight loss is very short and mostly small related to the effect. The gut seems to be the best target to increase the satiety level and to decrease energy efficiency. With the new EU Health claim regulation, EFSA and the European food industry should come with criteria what could be considered as effective in relation to the weight management. Efficacy should be focused on weight maintenance and not on weight loss as primary end point since we have excellent treatments to reduce body mass by slimming diets.

Conflict of interest: WS works part time as Corporate Scientist at DSM.

T5:RS2.2

How to motivate patients to start and maintain a healthy lifestyle

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I know what I should do, but I don't do it! »Why are our patients so unmotivated to changing their attitude? Why don't we even succeed in convincing them to change their lifestyle?
In order to motivate our patients we have implemented a multidisciplinary approach with a patient education in 5 dimensions. Acquiring new knowledges and skills (cognitive dimension), if it remains a necessary step, isn't enough for improving treatment compliance. A second dimension called "emotional or intentional" is crucial and deeply influences the motivation to change.
A third dimension (infracognitive) should more often be approached by the healthcare provider. It is essential to understand the intimate way of reasoning of the patient. Does he have a tendency to want "all or nothing" or to have negative thoughts? It is also vital to teach the patient to "zoom back" sometimes on what he does or doesn't do (metacognitive dimension). If the patient becomes able to argue on his ambivalence to change, he'll succeed at being more compliant to the treatment.
At last, the fifth dimension is "perceptive", it's the dimension of the sensations of the patient. For example, evaluating a hunger or satiety sensation or feeling the intensity of a physical activity are necessary for a long term weight loss.
This humanistic approach improves greatly the quality of life and the autonomy of the patients. The whole approach is based patients' needs and resources in order to maintain a long-term weight loss.

T5:RS2.3

Eating less, while burning more; acute effects of bioactive components during energy restriction

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Introduction: The aim of the present study was to investigate the possibly synergistic effect of a bioactive mixture containing resistant starch, capsaicin, green tea, and protein on energy expenditure and satiety. Furthermore, to investigate whether an 80% energy requirement diet plus bioactive mixture reaches the same satiety and thermogenesis level as a 100% energy requirement diet without bioactive mixture.
Methods: Sixteen subjects were studied for 2 days in 4 conditions: 1) 100% energy requirement diet plus bioactive mixture (100%H); 2) 100% energy requirement diet, without bioactive mixture (100%C); 3) 80% energy requirement diet plus bioactive mixture (80% H); 4) 80% energy requirement diet, without bioactive mixture (80%C), while appetite profile and energy expenditure were continuously monitored.
Results: Feelings of satiety were significantly higher in condition 80%H (1210±86mm*24h) than in condition 100%C (1022±100mm*24h, $p<0.02$). Total energy expenditure was significantly higher in condition 80%H (9.14±0.32MJ/d) than in condition 100%C (8.90±0.29MJ/d, $p<0.02$). Fat oxidation was significantly higher in condition 80%H (77±4g/d) than in condition 100%C (58±3g/d, $p<0.001$). Carbohydrate oxidation was significantly lower in condition 80%H (248±14g/d) than in condition 100%C (310±15g/d, $p<0.001$). Protein balance was not different between condition 80%H (-1±7g/d) and condition 100%C (-1±2g/d).
Conclusion: A combination of bioactive components added to a 20% energy restricted diet results in higher EE and satiety compared to a control diet in energy balance. A combination of bioactive components may facilitate adherence to an energy deficit diet by sustaining satiety and energy expenditure.

Conflict of Interest: We have no conflicts of interest. *Funding:* This study was funded by DiOGenes (Contract no. FP6-513946).

T5:RS2.4

A 6-months study on body weight regulation and body composition in overweight and obese children following three different diets varying in protein content.

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Background: Overweight among Danish children has risen during recent decades. Studies on adults suggest that high protein intake might be beneficial in promoting weight loss. However, studies on children are conflicting.

Methods: Overweight/obese children (N=65;iso-BMI>25kg*m^{-2};6-17y) was extracted from the Danish Diogenes population. Families were initially randomized to four diets varying in protein content and glycemic index (GI) and a control group. These groups were merged into a low (LO-P), moderate (MO-P) and high (HI-P) protein group, discarding GI. Families were provided with all foods for 6 months. Body fat-percent (%BF), waist circumference (WC), and BMI-z-score (BMIz) were recorded at baseline, 4 weeks (W4), and 6 months (M6). Habitual physical activity level at baseline ($HPA_{baseline}$;N=48;questionnaires) was assessed.
Results: Groups were well matched at baseline, except for $HPA_{baseline}$ (higher for HI-P). No difference in variables between groups was observed from baseline to W4. Between W4 and M6 differences was found between HI-P and MO-P in ΔBMIz (-0.24±0.06 vs. -0.02±0.06,P=0.04) and between HI-P and LO-P in ΔWC (-1.71±0.87cm vs. 1.87±0.89cm;P=0.007). From baseline to M6, differences was found between HI-P and MO-P in ΔBMIz (-0.47±0.09 vs. -0.18±0.06;P=0.03) and Δ%BF (-3.92±1.32pp. vs. -0.41±0.51pp.;P=0.04). Throughout the period, only HI-P showed consistent decreases in variables. $HPA_{baseline}$ confounded the effects on variables leaving no differences between groups except for Δ%BF (baseline-M6).
Conclusion: Our data suggest that high protein intake may reduce body fat in children. Some effects may be accounted for by differences in HPA level. For further insight we await the outcome of the Diogenes multicentre results.

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T5:RS3 – Pharmacotherapy

T5:RS3.1

New leads in pharmacotherapy

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The rising prevalence of obesity and obesity-related co-morbidities increases healthcare costs, and reduced quality of life. Most national healthcare bodies such as the National Institute of Clinical Excellence in the UK recommends pharmacotherapy, in conjunction with lifestyle modification, for obese individuals [i.e. body mass index (BMI) of 30 kg/m2] and for overweight patients with a BMI greater than 27 kg/m2, accompanied by at least one comorbidity. However, the current pharmaceutical treatment available to combat this epidemic remains limited. We will review the efficacy and pharmacology of the anti-obesity agents currently used in clinical practice as well as some of the potential agents in phase II and III trials.

T5:RS3.2

Medication as a cause of weight gain

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Clinically significant weight gain as a consequence of some commonly prescribed drugs does not only contribute to medical comorbidities including cardiovascular disease, insulin resistance and diabetes mellitus, but may also impair the patient's adherence to treatment. The majority of current drug therapies associated with weight gain are used in treatment of diabetes and neurological or psychiatric disorders. In previous research, 9 % of adults attributed weight gain to drugs they were prescribed.
Among antidepressive medication tricyclic antidepressants bear the greatest risk of weight gain, followed by mirtazapine, inhibitors of monoamino-oxidase and selective inhibitors of serotonin-reuptake. Antipsychotic medication, in particular second generation antipsychotics (SGAs), are associated with significant weight gain. For those patients prescribed antipsychotic medication, weight gain is acknowledged as a major cause of non-compliance. Consequently, a consensus development conference convened to classify antipsychotic agents with respect to the substances metabolic risk and issued recommendations on patient screening and monitoring. The SGAs clozapine and olanzapine are considered to carry the highest risk, whereas risperidone and quetiapine are of intermediate risk. The SGAs ziprasidone and amisulpride and the newer agent aripiprazole are less prone to cause weight gain. Baseline screening and regular follow up monitoring are advised. Possible therapeutical strategies for the management of drug induced obesity include conventional approaches, such as lifestyle modification, and pharmacological intervention. Several substances used to treat obesity have shown promising results in the management of psychotropic medication induced weight gain.

T5:RS3.3

The effect of the triple monoamine reuptake inhibitor tesofensine on energy metabolism and appetite in overweight and moderately obese men

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Tesofensine (TE) is under development for the treatment of obesity and has been shown to reduce appetite and produce twice the weight loss compared to weight-reducing drugs currently on the market[1]. In animal models TE increases noradrenaline, dopamine and serotonin neurotransmission, increases energy expenditure and inhibits food intake. Whether it is involved in the regulation of both sides of the energy balance in man is still unresolved.
Thirty-two healthy overweight/obese men (BMI 28-35 kg/m^2) were treated with 2.0 mg TE daily for 7 days, followed by an additional 7 days with 1.0 mg TE daily or placebo. Subjects were instructed to maintain food intake and physical activity levels. Energy expenditure (EE) was measured in a respiration chamber and appetite was evaluated in relation to a standardized meal using Visual Analogue Scales (VAS).
Appetite was strongly affected by TE ($p<0.05$) in a manner likely to result in reduced energy intake. Furthermore, TE-treatment lead to a 1.8 kg [95%CI:1.0;2.5] weight-loss ($p<0.0001$) and 17.7 g [95%CI:1.4;48.9] higher 24-hour fat oxidation compared to placebo ($p<0.05$). EE was maintained, despite a drop in fat-free mass which would theoretically lead to a ~2 % decrease in EE. A significant effect of TE on EE related to FFM when compared to placebo was, however, only found during the night-phase, corresponding to an increase of 16.2 kJ/h [95%CI:2.8;28.2] ($p<0.05$).
In conclusion, we propose that the weight reducing effect of TE is mainly caused by it decreasing appetite, but probably also to some extent by its stimulation of thermogenesis.

Reference

1. Astrup et al. the Lancet online 23 Oct 2008

Conflicts of interest: AA receives a honorarium as a consultant and for membership of the Tesofensine Advisory Board for NeuroSearch. AA and AS own shares in NeuroSearch A/S purchased on the stock exchange. AR, JDM and DM are employees of NeuroSearch A/S and own shares in the company. JKSJ works as a consultant for NeuroSearch A/S. CG is presently employed by Merck Serono, Switzerland while ALHN has no conflict of interest. *Funding:* Research relating to this abstract was funded by NeuroSearch A/S, Denmark

T5:RS3.4

A One-Year Study to Assess the Efficacy, Safety, and Tolerability of Taranabant in Maintaining Weight Loss Induced by Diet in Obese Patients

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Introduction: Taranabant is a cannabinoid-1 receptor inverse agonist that was being developed for the treatment of obesity. This study evaluated the effects of taranabant treatment for 52 weeks on weight regain following low calorie diet (LCD)-induced weight loss.
Methods: This Phase III, randomized, double-blind, placebo-controlled study consisted of a 6-wk LCD-induced weight loss period, including a 2-wk single-blind placebo run-in, followed by 52-wks treatment and 4-wks follow-up. Obese patients (BMI $\geq$30 and $\leq$43 kg/m^2; baseline [Week 0] BMI=32.0 kg/m^2 and body weight [BW]=90.0 kg) with stable BW for $\geq$3 months before study start who lost $\geq$6% of initial BW during the LCD period were randomized to once-daily taranabant 0.5-mg (n=195), 1-mg (n=196), or 2-mg (n=195), or placebo (n=194) with diet/exercise. The primary efficacy endpoint was mean change from baseline in BW.
Results: An average BW loss of 9.6 kg (i.e., 9.5%; initial [Week -6] BMI=35.4 kg/m^2 and body weight=100.5 kg) occurred during the LCD period. The mean BW regain following 52 weeks treatment was -0.1, -0.6, -1.2 and 1.7 kg for the taranabant 0.5-mg, 1-mg, and 2-mg and placebo groups, respectively (all $p<0.01$ versus placebo). The incidences of psychiatric adverse experiences (AE) including irritability were higher for taranabant 1- and 2-mg versus placebo ($p\leq0.038$), while the incidence of gastrointestinal AEs was higher for taranabant 2-mg ($p=0.042$) versus placebo.
Conclusions: Following a 6-wk LCD, all taranabant doses led to significantly less weight regain relative to placebo over 52 wks. Taranabant was associated with increased incidences of psychiatric and gastrointestinal adverse experiences.

T5:RS4 – Surgical treatment

T5:RS4.1

Surgical treatment of diabetes and the effect on insulin sensitivity

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Type 2 diabetes is a growing epidemic that places a severe burden on health care systems. This condition is usually considered a relentless and progressive disease: in fact if medical therapy is suspended, invariably, plasma glucose rises and the disease progresses. This knowledge is now being challenged by a growing body of evidence that remission of diabetes, that is, long-term restoration of normal glycemia and glycated hemoglobin levels without medications, can often be achieved after bariatric surgery. Furthermore, return to euglycemia and normal insulin levels are observed only within days after surgery, suggesting that weight loss alone cannot entirely explain why surgery improves diabetes.
Animal studies have shown that the improved glucose homeostasis after bariatric surgery is not secondary only to decreased food intake, weight loss, or to a reduction in lipid and carbohydrate absorption. Clinical studies have documented rapid postoperative improvement of insulin sensitivity early after procedures that reroute the small bowel, such as Roux-en-y Gastric bypass AND Biliopancreatic Diversion. Recent clinical studies also documented an increase in insulin secretion after gastric bypass. The results of personal studies, consistent with findings of other investigators, point to the exclusion of the duodenum and proximal jejunum from the passage of food as a primary mechanism for the resolution of diabetes. These findings suggest the hypothesis that the proximal small bowel may be contributing to the pathogenesis of the disease, and that insulin resistance may be the result of an aberrant signal originating in the proximal intestine. This alteration could be reversed by bypassing the duodenum-jejunum.

T5:RS4.2

New strategies in surgery

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Introduction: Obesity has become a major health problem in Europe. Bariatric surgery is an effective treatment for patients with clinically severe obesity, offering long-term weight loss and amelioration or significant improvement of obesity co-morbidities.
Methods: In the beginning of the 21st century new strategies in bariatric surgery are aiming at optimizing the morbidly obese patient's management. This can only be achieved when this method of treatment offers long-term sustained weight loss, good life quality, resolution of all major co-morbidities with the lowest possible morbidity and mortality rates.
Results: This difficult target, as several studies have shown, requires adequate training and experience from the surgeon's part, the necessary equipment, facilities and ancillary Institutional services, proper patient's selection criteria, minimally invasive approach, new techniques such as the sleeve gastrectomy, less aggressive operations as the two-stages approach for the super-super obese patients and finally an independent organisation to evaluate Institutions and surgeons and certify that they are offering outstanding patient's cure and provide accreditation as Centres of Excellence.
Conclusions: Better selection criteria for anti-obesity surgical management, new and less invasive techniques and the creation of a network of certified Centres of Excellence in Bariatric and Metabolic surgery would be the new strategies in bariatric surgery in the rise of the new millennium.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T5:RS4.3

Psychological improvement after bariatric surgery

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Introduction: Swedish adjustable gastric banding (SAGB) and Roux- en-Y Gastric Bypass (RYGBP) are surgical procedures aimed to produce a stable weight loss in severely obese subjects. The aim of this study was to evaluate psychological and psychopathological characteristics in obese subjects before and at 6 months after bariatric surgery.
Methods: 110 women (mean age 40.1 ± 10.6 yr, preoperative BMI 42.8 ± 4.8 and postoperative BMI 35.9 ± 4.1) and 54 women underwent (mean age 43.2 ± 8.5 yr, preoperative BMI 52.9± 9.3 and postoperative BMI 39.5 ± 7.8) were administered Minnesota Multiphasic Personality Inventory-2 (MMPI-2), before and after SAGB or RYGBP respectively.
Results: in the SAGB group, at sixth-months follow up, paired sample Student's t-test showed a significant improvement of the following clinical and content scales: Hysteria ($p<0.05$), Paranoia ($p<0.01$), Psychoasthenia ($p<0.001$), Hypomania ($p<0.05$), Social introversion ($p<0.01$), Anxiety ($p<0.001$), Depression ($p<0.0001$), Health Concerns ($p<0.0001$), Bizarre Mentation ($p<0.001$), Cynicism ($p<0.05$), Low Self-Esteem

(p<0.0001), Social Discomfort (p<0.05), Work Interference (p<0.001). in the RYGBP group a significant improvement of the following scales was demonstrated: Hypochondriasis (p<0.001), Depression (p<0.05), Psychopathic Deviate (p<0.05), Paranoia (p<0.01), Psychasthenia (p<0.0001), Schizophrenia (p<0.0001), Hypomania (p<0.01), Social introversion (p<0.0001), Anxiety (p<0.001), Fears (p<0.05), Obsessiveness (p<0.001), Depression (p<0.0001), Health Concerns (p<0.0001), Bizarre Mentation (p<0.05), Anger (p<0.05), Cynicism (p<0.05), Type A (p<0.05), Low Self-Esteem (p<0.001), Social Discomfort (p<0.0001), Family Problems (p<0.05), Work Interference (p<0.0001) and Negative Treatment Indicators (p<0.0001).

Conclusion: at 6 months follow-up, a substantial psychological improvement was demonstrated after both SAGB and RYGBP.

T5:RS4.4

Depression and quality of life after conservative and surgical obesity treatment

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Introduction: Over a period of 4 years, the course of weight in obese individuals was investigated in three different samples within the context of depressive symptoms and QoL

Methods: The course of weight in obese patients was investigated in three different obese samples. 532 individuals were initially included (conservative treatment, CONS): n = 251, obesity surgery (SUR): n = 151, no weight reduction procedures (controls, C): n = 129). QoL (SF-36) and depressive symptoms (HADS-D) were recorded at the onset of treatment (T1), after one (T2), two (T3), 4 years (T4). The drop-out rate after 4 years was 33.8%.

Results: In the SUR- patients, the BMI was reduced from 50.2 to 38.8 kg/m^2; however, the CONS-probands demonstrated their initial weight at T4 after a significant weight reduction during the first year. Physical well-being only improved significantly in the SUR-patients. Solely SUR-patients with clinically relevant depression values (HADS-D > 10) at T1 demonstrated a significant clinical improvement. The extent of weight reduction correlated at all 3 follow-ups to an improvement of physical well-being and reduction of depression values.

Conclusion: A substantial weight reduction, as may be achieved through obesity surgery, improves physical well-being and clinically relevant depressive symptoms; however, for the majority of obese patients with the request for weight reduction this seems to suggest more a state than a trait characteristic of depressive symptoms in obesity.

Conflict of Interest: None Disclosed. *Funding:* the study has been funded by the German Research Council (DFG).

Oral Sessions

Track 1: Prevention and Health Promotion
T1:OS1 – Impact and effectiveness of interventions

T1:OS1.1

Systematic Review of Weight Maintenance Following Weight Loss

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Introduction: Obesity is a complex and challenging problem which impairs the physical and mental health and well-being of millions of people. Treating the associated diseases is estimated to cost the UK health service an extra £45.5billion per year. Weight loss interventions achieve short-term success, but regain is common. The aim of this review was to examine the effectiveness of lifestyle, behavioural, pharmacological and/or surgical interventions for long-term weight maintenance.

Methods: Randomized controlled trials including one or more lifestyle, behavioural, pharmacological or surgical intervention published in 1996 to 2007 were evaluated. All interventions were preceded by initial weight loss periods of at least 4 weeks and were at least 1 year duration. Participants were required to have a baseline BMI of ≥30 and achieved a minimum initial weight loss of 10%.

Results: 11 studies were identified providing a total of 20 intervention groups and a total of 1975 participants. Follow-up ranged from 0 – 23 months. Weight change was analysed. 6 studies, including 2 pharmacological interventions, reported significant between-group differences. Interventions are enhanced by the use of behavioural change techniques which were reported in 9 out of 11 studies. However, reports lack details of techniques used and/or measures of behaviour change.

Conclusion: Overall, long-term weight maintenance strategies are effective in maintaining small weight losses but further work is required to determine which behavioural elements are most effective so that future interventions can be improved.

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T1:OS1.2

The MEND Programme: National effectiveness data

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Introduction: The MEND Programme is the only national multi-component child weight management programme in the UK[1] (www.mendprogramme.org). This study assessed the effectiveness of the MEND intervention beyond the controlled environment of a clinical trial.[2,3]

Methods: Overweight or obese children participated in the MEND Programme at 211 locations across the UK (January-June 2008). The 10-week, community and family-based intervention consisted of twice-weekly group sessions including behaviour change, nutrition education and physical activity. The intervention was delivered by a range of health, exercise, education and social care professionals. Outcomes were assessed pre-intervention and at 3 months.

Results: Of 2506 MEND children participating in the MEND Programme (47% boys; mean age 10.3 years; 73% Caucasian, 34% from single-parent families), 2060 (82%) were measured pre and post intervention. Their mean BMI and waist circumference z-scores decreased by 0.17 (95%CI: 0.16-1.18; p<0.0001) and 0.22 (95%CI: 0.21-0.24; p<0.0001) respectively. These results were very similar to the MEND pilot's results (0.16 and 0.25 z-score reduction for BMI and waist circumference respectively)[4]. Improvements were also noticed for other outcomes: mean change in physical activity levels (+3.6 hours per week, p<0.0001), post-exercise recovery heart rate (-8.3 beats per minute, p<0.0001), sedentary activities (-6.1 hours per week, p<0.0001), and body image (+4 points, p<0.0001). Mean attendance of the MEND Programme sessions was 77% and drop-out rate was 9%.

Conclusion: In accordance with the MEND randomised controlled trial and pilot results[2,5] participation in the MEND Programme was associated with beneficial effects on physical and psychosocial health, suggesting that the programme is replicable and scalable outside of a clinical trial.

Conflict of interest: Sacher PM, Chadwick P and Kolotourou M are all employed part-time by the social enterprise MEND Central. *Funding:* The data collection and evaluation were funded by a combination of Primary Care Trusts (NHS), Local Authorities, Leisure Providers, Sainsbury's Supermarkets Ltd, Big Lottery Fund, Sport England and the National Sports Foundation.

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T1:OS1.3

Watch the label before you watch the movie: Portion-size and Guideline Daily Amounts labeling in the cinema

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Introduction: Portion sizes of soft-drink have increased substantially during the past decades. Although food labelling has received much attention, no experimental studies and studies in real-world settings evaluating the effectiveness of portion-size and calorie Guideline Daily Amounts (GDA) labeling are available. This study assessed the effectiveness of portion-size and calorie GDA labeling on consumers' size choices and consumption of regular soft-drink in a cinema setting.
Methods: The study employed an experimental design with a control condition (N = 49) and an experimental condition (N = 52). Participants, unknowingly of the true purpose of the study, were invited to the cinema. In the control condition, different soft-drink sizes combined with milliliter information were displayed in the cinema. In the experimental condition, portion-size information combined with calorie GDA-information was displayed. Outcome measures were the soft-drink sizes that participants chose and the amount they consumed.
Results: Out of all participants, 59.8% had noticed the displays. Against our hypotheses, participants in the experimental condition were less likely to choose small sizes than participants in the control condition. No effect of labeling was found on the likelihood to choose large sizes, neither on actual soft-drink consumption. Exclusion of participants who had not noticed the displays did not yield different results.
Conclusion: In this study, no effect of portion-size and calorie GDA labeling was found on people's soft-drink intake. Possibly, portion-size choices are determined by habits and multiple exposures to labeling are needed in order to be effective. Further research is required to assess this explanation.

Conflict of Interest: None disclosed. *Funding:* Research related to this abstract was funded by ZonMW (the Netherlands organization for health research and development).

T1:OS1.4

The lifestyle intervention "Obeldicks light" is effective to reduce fat mass in overweight children: preliminary findings in a randomized controlled trial

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Introduction: Randomized controlled trials (RCT) demonstrated the effectiveness of lifestyle interventions in obese (BMI>97th percentile) children. However, no RCT concerning lifestyle interventions have been performed in overweight but not obese children.
Methods: In the ongoing study, 60 overweight (BMI>90th ≤97th percentile) children (mean age 11.2y, mean BMI 23.2±0.2kg/m², 65% female) were randomized into control group (CG) (n=38; no intervention in the course of 6 months) or intervention group (IG) (n=22; 6 months lifestyle intervention "Obeldicks light" based on physical activity, nutrition education, and behavior therapy). Children were examined at baseline (T0), 6 months (T1), and 12 months later (T2). Degree of overweight was calculated as SDS-BMI. Percentage fat mass was determined by skinfold measurements and bioimpedance analyses. All analyses were performed on an intention-to-treat approach.
Results: The drop-out rate was 5% in IG and 11% in CG. At T1, 86% of the children in IG and 21% in CG decreased their SDS-BMI (p<0.001) and 36% of the children in IG were normal-weight. The changes in SDS-BMI differed significantly (p<0.001) between IG and CG at T1 (CG: +0.09±0.04 SDS-BMI; IG: -0.26±0.05 SDS-BMI). At T2, weight loss maintenance was achieved in the IG (T1 to T2: +0.04±0.01 SDS-BMI, p=0.439). The same findings were observed for percentage body fat based on skinfold measurements and bioimpedance analyses.
Conclusions: These preliminary findings suggest that the lifestyle intervention "Obeldicks light" is effective to reduce fat mass in overweight children as compared to a randomized controlled group both at the end of intervention and 6 months later.

Conflict of Interest: None Disclosed. *Funding:* Research related to this abstract was funded by the German Federal Ministry of Research

T1:OS1.5

Increasing fruit and vegetable consumption in children: the Food Dudes programme

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Introduction: The present paper describes an innovative intervention that uses video-based role models (the Food Dudes) and small rewards to help children learn to like fruit and vegetables.
Methods: A whole-school version of the Food Dudes programme was evaluated in two studies. Study 1, in England, compared an experimental school that implemented the intervention with a control school that did not (n = 749 children). Fruit and vegetable intake at lunchtime in school canteens was measured at baseline, intervention, and 4-month follow-up. In Study 2, in Ireland, where food is provided in children's lunchboxes, an experimental school was again compared with a matched control school (n = 435 children). Measurements were taken at baseline, intervention and 1-year follow-up.
Results: In Study 1, lunchtime consumption of fruit and vegetables in the experimental school was substantially higher at intervention and follow-up, compared to baseline ($p < 0.001$), the increases being greatest (from 400 -1400%) in children who ate least to begin with. The control school showed a significant decline in consumption over time. In Study 2, 1 year after the Food Dudes programme, children in the experimental school brought in and consumed significantly more fruit and vegetables from their lunchboxes compared to the control school ($p < 0.001$). There is

now a national roll-out of the programme in Ireland and a regional roll-out has begun in England

Conclusion: The programme produces major and long-lasting increases in children's fruit and vegetable consumption. It could improve the diet and overall health of children internationally.

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by the Horticultural Development Council, Fresh Produce Consortium, Tesco, Sainsbury, Safeway, Co-operative Wholesalers' Society, Asda, Somerfield, Food Standards Agency Wales, Fyffes and Bord Glas.

T1:OS1.6

Leptin intake during lactation prevents diet-induced white adipose tissue leptin resistance in adulthood

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Introduction: We have previously shown that the intake of physiological doses of leptin during lactation in rats protects against later obesity and improves insulin and central leptin sensitivity. Here, we aim to analyze whether leptin-treatment during lactation also affects peripheral leptin sensitivity by affecting the expression of the leptin receptor gene (OB-Rb) in the adipose tissue under high fat (HF) diet.

Methods: A daily physiological oral dose of leptin or the vehicle was given to suckling male rats during lactation. After weaning, animals were fed with a normal fat (NF) or an HF-diet until the age of 6 months. The expression of OB-Rb and other genes involved in lipid metabolism in different adipose depots was measured.

Results: HF-diet feeding resulted in lower OB-Rb expression in visceral adipose tissue in control animals, while levels increased in leptin-treated animals in the different depots studied. This increase was accompanied by an increase in the expression of genes encoding proteins related with energy uptake (GLUT4, CD36) and fatty acid oxidation (PPARalpha, CPT1, UCP3) in different depots. Leptin-treated animals were also protected against the important increase in lipid accumulation occurring in the liver of control animals under HF-diet.

Conclusion: Leptin-treatment during lactation improves peripheral leptin sensitivity in adulthood, which may explain the higher capacity for directing the excess of fat to the adipose tissue, preventing its accumulation in the liver. This, together with the described improvement of central leptin sensitivity, may contribute to the protection of these animals against diet-induced obesity and its metabolic-related disorders.

Conflict of interest: None Disclosed. *Funding:* Research relating to this abstract was funded by the Spanish Government (grant AGL2006-04887/ALI). The *CIBER de Fisiopatología de la obesidad y nutrición* is an initiative of the ISCIII.

T1:OS2 – Determinants of behaviour

T1:OS2.1

Determinants of habitual physical activity level

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Objective: This study investigated which types of physical activity (PA) such as lying, sitting or standing (Sit-Stand), active standing (AS), walking, running, and cycling, determined the physical activity level (PAL).

Methods: Subjects were 15 adults (age: 26-59 years, BMI: 24.4±3 kg/m^2). Habitual PA was measured for five days using one tri-axial accelerometer. Accelerometer output was used to identify 6 types of PA and to assess intensity of walking and cycling (low, moderate, high intensity) by estimating movement speed. PA pattern was described by the average daily duration (ADD) of each activity type. ADD of walking was also quantified in bouts shorter than 5 minutes, longer than 5 minutes and longer than 10 minutes. Simultaneously, average daily metabolic rate (ADMR) was measured using doubly labeled water. PAL was calculated as ADMR divided by sleeping metabolic rate.

Results: Measured PAL was 1.75 ± 0.17. PAL was significantly associated ($p<0.05$) with ADD of Sit-Stand ($R = -0.58$) and walking ($R=0.58$). The other types of activity were not significantly associated with PAL. Moderate intensity walking was positively associated with PAL ($R=0.51$, $p<0.05$). ADD of walks longer than 5 minutes and longer than 10 minutes were significantly related with PAL ($R=0.58$, $R=0.56$, respectively, $p<0.05$).

Conclusion: The time spent sitting or standing and walking are characteristics of the PA pattern that significantly determine PAL. Walking at moderate intensity and engaging in walks longer than 5 minutes contribute to the achievement of a higher activity level.

Disclosure: This work has been funded by Philips Research.

T1:OS2.2

Self-Determination and Exercise Intrinsic Motivation as Mediators of Physical Activity During a Weight Loss Program: One-Year Results from a Randomized Controlled Trial

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Introduction: Few studies have focused on experimentally influencing motivation-related mediators of physical activity/exercise (PA) in the overweight/obese. Our aim was to evaluate changes in PA and psychological mechanisms of PA behavior change during a one year obesity treatment intervention based on Self-Determination Theory (SDT).

Methods: 239 women (37.6±7.1y; 31.5±4.1kg/m2) were assigned to intervention/control groups. The intervention was designed to increase PA and PA motivation, following SDT principles. Assessments included intrinsic motivation-IM; locus of causality-LC, autonomous self-regulation-ASR, psychological motives-PM; and PA: steps/day, moderate+vigorous PA (7-day PAR), and lifestyle activity. Mediation and indirect effects were tested following Preacher and Hayes procedures (2007).

Results: The intervention significantly changed all SDT mediators (ES=0.60-1.08) and increased PA (+147 min/wk moderate+vigorous PA; +1986 steps/day, ES=0.89 for a lifestyle activity index, $p<0.001$ vs controls). At 12 months (86% retention) associations between PA and SDT mediators ranged between $r=.36$ and .50 ($p<0.001$) and IM, ASR, LCE and PM distinguished ($p<0.001$) successful (>150 min/wk PA criteria) from non-successful participants. In the mediated models, direct effects of intervention on moderate-vigorous and lifestyle PA were reduced but remained significant. Significant ($p<0.05$) indirect effects were observed through all 4 SDT variables (IM, LC, ASR, PM), suggesting partial mediation. For steps/day, total mediation for PM (i.e., enjoyment, challenge, energy) was observed ($p=0.003$).

Conclusion: The intervention was successful in affecting theory-driven exercise motivation mediators, which in turn partially explained clinically-significant changes in PA adoption after 1 year. Results are consistent with autonomous self-regulation and intrinsic motivation resting within the causal path of exercise adherence during weight control.

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by Science and Technology Foundation, Calouste Gulbenkian Foundation, Oeiras City Council, IBESA, and Nestlé – Portugal.

T1:OS2.3

Mediators of energy balance related behaviours among children and adolescents.

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Introduction: To prevent excessive weight gain, changes in energy balance-related behaviours (EBRBs), such as dietary intake, physical activity and sedentary behaviours, is required. To change such behaviours by interventions, we need to address changeable mediators that influence the EBRBs. The current paper presents results from two studies exploring potential mediators of environmental influences on different EBRBs among children and adolescents.
Methods: Mediation analyses were conducted. The ENDORSE study among Dutch adolescents and the Pro Children study among European schoolchildren provided data on environmental factors(availability of fruit and vegetables (FV), presence of a TV in the bedroom, presence of sport attributes in the home), cognitive variables (attitude, social norm, perceived behaviour control, intention, habit), engagement in sports, TV viewing and FV intake.
Results: The Pro Children study indicated that mediators of the effect of home availability of FV on FV intake were: attitude towards fruit, liking, perceived barriers and self-efficacy. Likewise, the ENDORSE study showed that the relationship between availability of sports attributes at home and engagement in sport was mediated by attitude towards sports behaviour and intention to increase sports behaviour. Also, the effect of a TV in the bedroom on TV viewing was mediated by attitude, social norm, perceived behaviour control and intention. The latter association lost statistical significance after accounting for the mediators, in contrast to the former two.
Conclusion: As shown, cognitive factors mediate at least partly the associations between environmental factors and important EBRBs such as sports participation, FV intake and TV viewing among children/adolescents.

Conflict of interest: Non disclosed. *Funding:* Research related to this abstract was funded by The Netherlands Organization for Health Research and Development (Zon Mw, 2100.0103), the Commission of the European Communities, SP5A-CT-2006-044128 "Health-promotion through Obesity Prevention across Europe (HOPE), the Fifth Framework Programme of the European Commission, Thematic programme Quality of Life and Management of Living Resources, key action Food, Nutrition and Health (QLK1-CT-2001-00547)and the World Cancer Research Fund (2007/47).

T1:OS2.4

A front-of-pack nutrition logo: a quantitative and qualitative process evaluation

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Introduction: This study aimed to perform a quantitative and qualitative process evaluation of the introduction of the Choices logo, a front-of-pack nutrition logo on products with a favorable product composition, adopted by many food producers, retail and food service organizations, supported by the Netherlands Nutrition Center, conditionally endorsed by the Dutch government, validated by an independent scientific committee of nutrition scientists, and in the process of international dissemination.
Methods: An online questionnaire was sent to adult consumers four months after the introduction of the logo (n=1032) and one year later (n=1127). Additionally, seven consumer focus groups (n=41) were conducted.
Results: Quantitative analyses showed that exposure to the logo had significantly increased. Elderly and obese reported to be more in need of a logo than younger and normal-weight respondents. Women perceived the logo more attractive and credible than men did. Further qualitative analyses indicated that the logo's credibility would improve if it became known that governmental and scientific authorities support it. Elderly indicated to need a logo due to health concerns. Consumers interested in health reported that they used the logo.
Conclusion: Further research focusing on specific target groups, actual food choice and health outcomes is needed to investigate the effectiveness of the Choices logo.

Conflicts of interest: Gerda Feunekes works at the Unilever Food and Health Research Institute, one of the participating food companies in the Choices programme. Léon Jansen works at Schuttelaar & Partners, a consultancy firm that operates as the Foundation's Secretariat. Hans Verhagen Works at the RIVM and is involved in the evaluation of the logo as an independent party, commissioned by the Dutch government. *Funding:* This study was funded by the Choices Foundation.

T1:OS2.5

Contribution of children's consumer behaviour to childhood obesity: a promising target for intervention

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Introduction: The IDEFICS (**I**dentification and prevention of **D**ietary and lifestyle-induced health **EF**fects **I**n **C**hildren and infant**S**) is a five-year multicentre study targeting comprehensively the childhood obesity in the age group 2-10 years. Obesity in childhood is itself a predictor of chronic diseases in adulthood, even if weight is lost later (British Medical Association 2005). Therefore our aim was identifying an intervention point earlier than manifest increase in the child's BMI is detectable, hypothesizing that this mediator could be consumer behaviour.
Methods: We analyzed data of baseline survey of Hungarian IDEFICS sample: the modules of 2509 parental questionnaire referring to consumer behaviour, the BMI measured and ranked according to Cole (2000) and the consumption of the highly promoted so-called 'Big Four' of presugared breakfast cereals, soft-drinks, confectionary and savoury snacks (Hastings, 2006) selected from 50187 food items of the children's in total 4767 24-hour dietary recall.
Results: In the 3-days dietary recall parents reported 6.7 ± 4.02 occasion of consuming "Big Four". This wasn't significantly associated with parental obesity, educational level or most items of parental consumer beliefs. In contrast, „Big Four" was significantly associated ($p<.01$, Spearman) with child's own BMI, child's mental well-being, parenting style and TV viewing time (but no kind of other screen-viewing).
Conclusion: While general family habits resulting in child's obesity are highly influenced by parental (health) literacy and beliefs, the child's own consumer behaviour proved to be not an intermediate step of the above relationship but an independent contributing factor, deserving more attention for targeted intervention.

Conflict of Interest: None. *Funding:* Research relating to this abstract was funded by: EU / FP6 Contract no.: 016181-2 (FOOD)

T1:OS2.6

Television food advertising to children: a global perspective

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Introduction: This study aimed to compare the nature and extent of television food advertising to children in a range of countries.
Methods: An independent collaboration of researchers was established across 12 countries (15 research groups), with representation from Australia, Asia, Eastern and Western Europe, and North and South America. Each group recorded television for two weekdays and two weekend days between 6:00 and 22:00, for the three most popular children's channels (192 hours), between October 2007 and March 2008. Advertisements were coded using predefined criteria. Food advertisements were classified according to three food categories: core/healthy, non-core/unhealthy and miscellaneous. The use of persuasive marketing, including promotional characters and premium offers was also assessed.
Results: For all countries, food advertisements comprised 11 to 23% of advertisements. Non-core foods were the most frequently advertised food products, contributing 53 to 87% of food advertisements. The overall proportion of food advertisements for non-core foods increased during children's peak viewing times, compared to non-peak viewing times ($Å_1$ = 10.80, p<0.001). The majority of food advertisements containing persuasive marketing were for non-core products; 48 to 91% of those containing promotional characters, and 73 to 96% of those containing premium offers.
Conclusion: Internationally, children are exposed to high volumes of unhealthy food and beverage advertising on television. Limiting this food marketing is an important preventive strategy for childhood obesity, and a vital first step is to develop/extend statutory regulations to prohibit unhealthy food and beverage advertising during broadcast periods where a significant number of children are watching.

Conflict of interest: None disclosed. *Funding:* Research relating to this abstract was funded by FAS (Swedish Council for Working Life and Social Research) for the Swedish data.

Track 2: Epidemiology and the Impact of Obesity
T2:OS1 – Alternative measures to BMI and waist circumference

T2:OS1.1

Computed tomography-based validation of abdominal adiposity measurements from ultrasonography, dual X-ray absorptiometry, and anthropometry

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Introduction: Large-scale etiological studies of obesity and its pathologic consequences are often hindered by imprecise assessments of adipose mass, distribution, and subtype. We compared the validity of three methods for the assessment of abdominal adiposity (dual-energy x-ray absorptiometry [DXA], ultrasound, anthropometry) against the gold-standard method of computed tomography (CT).
Methods: Twenty-nine non-diseased middle-aged men (BMI mean 26.5) and women (BMI 25.5) selected as a representative population-sample underwent assessments of adiposity mass (kg) and distribution (total subcutaneous [TSAT], superficial subcutaneous [SSAT], deep subcutaneous [DSAT], and visceral [VAT]).
Results: VAT assessed using ultrasound correlated highly with VAT from CT (r=0.86; P<0.0001), as did abdominal adipose mass measured with DXA (r=0.79; P<0.0001) and waist circumference (r=0.67; P<0.01). Ultrasound yielded the most precise measured of TSAT (r=0.93; P<0.0001). Total adipose mass from DXA was also strongly correlated with CT-assessed TSAT (r=0.72; P<0.001), as was BMI (r=0.67; P=0.01). Although TSAT from ultrasound correlated strongly with the CT measure of SSAT (r=0.78; P<0.0001), the ultrasound SSAT measure was only moderately correlated with the respective CT measure (r=0.58; P<0.05). The best non-ultrasound measure of SSAT was total adipose mass from DXA (r=0.76; P<0.0001). DSAT from ultrasound was strongly correlated with CT-derived DSAT (r=0.88; P<0.0001). DXA total adipose mass (r=0.78; P<0.0001), waist (r=0.74; P<0.0001) and BMI (r=0.72; P<0.0001) were all comparably correlated with DSAT from CT.
Conclusion: Compared with CT, the ultrasound method used in this study can, with a very high level of precision, quantify visceral adipose mass as well as the subcutaneous deep and superficial layers.

Conflict of interest: None disclosed. *Funding:* Research relating to this abstract was funded by Visare Norr Foundation and Swedish Heart and Lung Foundation.

T2:OS1.2

Abdominal obesity and (pre-)diabetes in China

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Objective: To assess the association of indicators of general and abdominal obesity with the prevalence of type 2 diabetes (T2DM) and intermediate hyperglycaemia (IHG) in the Chinese population.
Methods: We used data of 50,905 adults aged 18-79 years in the 2002 China National Nutrition and Health Survey. Recommended Chinese cut-off values were used for BMI (24 kg/m^2) and waist circumference

(WC; 85 cm in men, 80 cm in women). Optimal cut-offs for waist:height ratio (WHtR) were determined from ROC curves.
Results: ROC curve analyses indicated 0.5 as the optimal cut-off value for WHtR in both sexes. High BMI, WC and WHtR were all associated with the prevalence of glucose tolerance abnormalities, with the highest prevalence ratio (PR) for high WHtR (men: PR=2.85, 95%CI 2.54-3.21; women: PR=3.10, 95%CI 2.74- 3.51). When combining BMI and WHtR, in men either a high BMI or a high WHtR alone was associated with increased risk. Among women, a high BMI without a concomitant high WHtR was not associated with increased glucose tolerance abnormalities risk, whereas a high WHtR was associated with risk irrespective of BMI.
Conclusions: Among the Chinese adult population measures of central obesity are better predictors of glucose tolerance abnormalities prevalence than BMI. A WHtR cut-off point of 0.5 for both men and women is as optimum for indicating (pre-) diabetes and may be a useful tool for screening and health education.

Conflict of Interest: None Disclosed. *Funding:* Ministry of Health and Ministry of Science and Technology, China.

T2:OS1.3

The TOFI Phenotype

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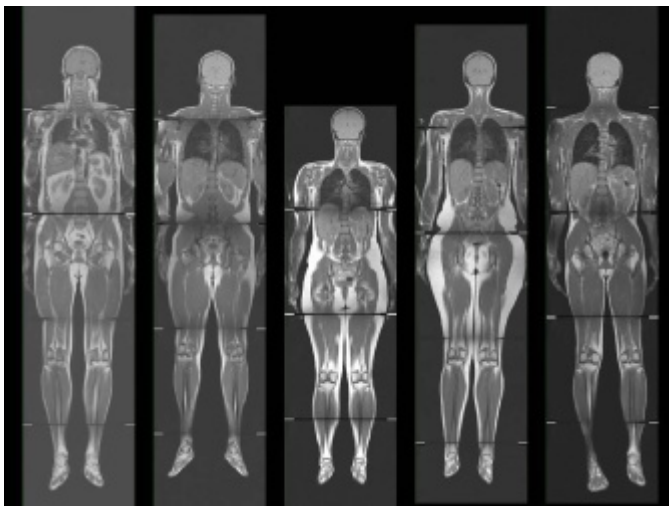
Introduction: We have previously reported subjects with elevated intra-abdominal adipose tissue (IAAT) despite normal BMI. These subjects may be at increased risk of obesity related diseases, despite their 'normal' size. The aim of this study was to determine normal ranges for IAAT in males and females, and define the extent of individuals in a normal population with the TOFI (Thin Outside, Fat Inside) phenotype.
Methods: Whole body MR images were obtained from 535 subjects (286 male, 249 female, BMI range 15.5-57.3 kg/m^2) on a 1.5T Phillips Achiva scanner. Total and regional AT volumes were measured.
Results: Total AT in males ranged from 6.2-79.9 litres (27.0 ± 11.9 mean±SD) and in females from 5.1-109.0 litres (32.6 ± 16.6). However, males carried significantly more IAAT than females (4.0 ± 2.3 [range: 0.2-12.0], vs 2.6 ± 1.8 [range: 0.4-9.8] litres respectively, p<0.001). To establish the TOFI phenotype, IAAT was expressed as a percentage of total AT. The proportion of subjects within the normal BMI range (18-25kg/m^2) in the upper quartile for IAAT/total AT (deemed to be TOFI) was 17.7% for males and 7.3% for females respectively. Example of this is shown in the figure.



Discussion: A significant number of both males and females with normal BMI appear to have the 'TOFI' phenotype. It may be important to identify these individuals, since they may be at particular risk of developing metabolic diseases.

References: Thomas EL, Saeed N, et al .Magnetic J Appl Physiol. 1998 Nov;85(5):1778-85.

Conflict of Interest: None. *Funding:* Research relating to this abstract was funded by the MRC.

T2:OS1.4

Obtaining evidence for higher cut-off values for high-risk waist circumference in older adults

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Introduction: Ongoing debate exists about the applicability of current guidelines for healthy waist circumference (WC) in older adults. Our aim was to compare the currently used cut-offs of WC (as adopted in WHO guidelines) with newly identified cut-offs as assessed in a population-based sample of older adults.
Methods: First, new cut-offs were identified based on the relationship between BMI and WC. ROC curves were used to compare the predictive power of the different categorisations. Furthermore, the association between WC and self-reported mobility limitations was considered using spline regression curves. Data of 1049 participants of the Longitudinal Aging Study Amsterdam (1995-1996), aged 70-88y, were used.
Results: Linear regression analyses showed that the values of WC corresponding to BMIs of 25kg/m^2 and 30kg/m^2 are higher than the current cut-offs. Cut-offs found in men were 97 and 110cm, whereas 88 and 98cm represented the cut-offs in women. Areas under the ROC curves showed that the power to predict mobility limitations improved when the higher cut-offs were applied. The spline regression curve was U-shaped in men, while in women, the risk for mobility limitations increased gradually with increasing WC. At the level of current cut-offs for WC, the odds for mobility limitations were not yet increased in either men or women.
Conclusion: Based on extensive analysis techniques, this study suggests that the current cut-offs for high-risk WC should be higher when applied to older adults. The association of WC with other negative health outcomes needs to be investigated.

Conflict of Interest: None Disclosed. *Funding:* No funding.

T2:OS1.5

Cardiometabolic risk in 'normal' BMI women: Waist circumference standardized to height is the best adiposity marker.

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Background: Higher body fat mass in 'normal' Body Mass Index (BMI<25) women has been associated with higher cardiometabolic risk. The relevance of simple measures such as waist circumference (WC), is of clinical and public health interest. Age effects in this context are less studied. .
Objective: Examine clinical utility of a range of adiposity measures in identifying cardiometabolic risk, within BMI groups and with age.
Methods: 500 women aged 38 and 50 were examined in a population study of women in Gothenburg. The analysis included 307 'normal' and175 'overweight' (BMI>=25) women; 197 and 112 respectively had total body fat mass measurement by Bioelectrical Impedance Spectroscopy.

Results: Explained variability (by Linear regression) in risk scores (Framingham, sum of blood pressure, glucose, lipids scores) in 'normal' and 'overweight' women respectively were, WC (13.7% and 26.1%), Waist-height ratio (WHtR, 18.4% and 29.6%) and body fat mass Index (4.9 and 14.3%); all results were highly significant. Explained variability was greater in younger women in each BMI group.
Positive Predictive Value (PPV) for identifying women with at least one non-adipose component of the IDF criteria at WC>=80cm ranged between 33-60% in the two BMI and age groups. At WHtR>=0.5, PPV was 46-68%. PPV was higher in overweight or older women.
Conclusion: WC or WHtR are at least as good as total body fat, and can identify cardiometabolic risk in 'normal' and 'overweight' women, though with clinical limitations. Adiposity explained variability in risk is limited; absolute clinical gains especially with high-tech methods of measuring adiposity, including central adiposity can therefore be rather limited.

Conflict of Interest: None for any of the authors. *Funding:* The study was supported by grants from the Swedish Council for working life and social research (2005-0794 and 2006-1506).

T2:OS1.6

Utility Of BMI In Screening Children And Adolescent For Clustering Of Cardiovascular Risk Factors: Comparisons of IOTF and CDC References

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Background: BMI cut-offs proposed by the International Obesity Task Force (IOTF) and the US Centers for Disease Control and Prevention (CDC) have been widely used to define childhood overweight/obesity. However, these references have not been thoroughly evaluated in terms of ability to detect clustering of cardiovascular risk-factors.
Objective: To assess the ability of IOTF and CDC BMI cut-offs to successfully screen for children and adolescent with clustering of risk-factors.
Methods: 2836 schoolchildren in the 3rd (8–11 years) and 9th (14–17 years) grade were randomly selected from Denmark, Estonia and Portugal. Risk-factors included in the composite risk-factor score (mean of *Z*-scores) were systolic and diastolic blood pressure, triglyceride, total cholesterol, HDL-cholesterol, insulin resistance and aerobic fitness. Children with a risk score above 1SD of the composite variable were defined as being at risk. Logistic regression and ROC analysis were performed.
Results: Independent of the reference used, the likelihood of having clustering of risk-factors was significantly higher (p-value <0.0001) in the obese (OR: 17.8 IOTF; 18.1 CDC) and overweight groups (OR: 6.4 IOTF; 5.4 CDC) compared to normal-weight group, regardless of age, gender, puberty and country. However, the screening ability of BMI cut-offs was modest. The area under the ROC curves ranged from 0.52 to 0.70 using IOTF reference and from 0.53 to 0.62 using CDC reference. Obesity cut-offs were highly specific, but less sensitive for identifying children at risk.
Conclusion: Current definitions of childhood obesity tend to be conservative, whether the IOTF and CDC references are used.
Keywords: cardiovascular risk factors; childhood obesity; classification systems; screening

Conflict of Interest: None. *Funding:* Research relating to this abstract was funded by the TRYG-foundation, DK

To assess the ability of IOTF and CDC BMI cut-off points to successfully screen for children and adolescent with clustering of risk factors. =23

To determine whether the IOTF or CDC BMI cut-offs for classifying overweight/obesity are more accurate at predicting immediate health risk in childhood. =23

To determine whether the IOTF or CDC BMI cut-offs for classifying overweight and obesity are more accurate at screening children with clustering of risk factors. =25

T2:OS2 – Determinants over the lifespan

T2:OS2.1

The preterm baby as a young adult: effect of prematurity on intrahepatocellular lipid.

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Introduction: Abnormal fat distribution, including intrahepatocellular lipids (IHCL), is associated with insulin resistance and type 2 diabetes. We have previously shown that preterm babies at term have increased IHCL. While it is unknown if this persists into adult life, blood pressure and insulin resistance have been shown to be increased in ex-preterm adults. Here we used MRI/MRS to test the null hypothesis that there is no difference in IHCL between ex-preterm adults and control adults born at term.
Methods: 36 healthy subjects (aged 19-27; BMI 20-24.9), 14 preterms (<33 weeks gestation - 8 males, 6 females) and 22 controls (>37 weeks - 10 males, 12 females) participated in the study. Whole body, regional and liver fat content were measured on a 1.5T Phillips Achiva scanner following an 8-hour fast.
Results: There was no significant difference in total fat between the two groups. However, IHCL was significantly higher in the ex-preterm adults (2.22%) than in the term controls (0.23%), 95% CI p<0.01. Levels of intra-abdominal adipose tissue were lower in the control population, although this did not reach significance (p<0.08). There were no significant differences between genders within each group.
Discussion: The demonstration of elevated IHCL in ex-preterm adults is a novel finding. This adds to the accumulating evidence indicating that this group is at risk of poor metabolic health and warrants close follow-up.

References

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Conflict of Interest: None. *Funding:* Research relating to this abstract was funded by the MRC and Chelsea & Westminster NHS Foundation Trust

T2:OS2.2

Genetic and environmental effects on body mass index during adolescence: A prospective study among Finnish twins

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Introduction: The heritability of BMI is high but BMI is also affected by many environmental factors. Twin studies enable estimating relative contributions of environmental and genetic factors on phenotypes. Few longitudinal twin studies have explored age-changes of these relative

contributions on BMI during adolescence. Longitudinal twin studies are also needed to explore these contributions on BMI phenotypic correlations across ages, i.e., to find out which factors are responsible for the stability of BMI across ages.
Methods: We used twin modeling in a prospective, population-based, twin cohort of 2413 monozygotic and same-sex and opposite-sex dizygotic Finnish twin pairs born in 1983-1987 and assessed by self-report questionnaires at 11-12 (participation rate 92%), 14 (82% of the original sample), and 17 years (74% of the original sample).
Results: The heritability of BMI was estimated to be 0.58-0.69 among 11-12- and 14-year-old boys and girls, 0.83 among 17-year-old boys and 0.74 among girls. Common environmental effects (factors shared by family members such as co-twins) were 0.15-0.23 among 11-12- and 14-year-old boys and girls but no longer discernible at 17 y. Unique environmental effects were 0.15-0.23. Additive genetic factors explained 90-96% of the BMI phenotypic correlations across adolescence, whereas unique environmental factors explained the rest. Common environment had no effect on BMI phenotypic correlations.
Conclusions: The genetic contribution to BMI is strong during adolescence, and it mainly explains BMI phenotypic correlations across adolescence. Common environmental factors have an effect on BMI during early adolescence, but that effect disappears by late adolescence.

Conflict of interest: None Disclosed. *Funding:* Data collection in FinnTwin12 has been supported by NIH/NIAAA (grants AA-09203 and AA-12502) to Richard J. Rose, by awards from the Academy of Finland (grants 100499, 118555, 108297) and Yrjö Jahnsson Foundation to Jaakko Kaprio, Karri Silventoinen and Lea Pulkkinen, and by grants from Helsinki University Hospital to Aila Rissanen. Data analysis was also part of the GENOMEUTWIN project, which is supported by the European Union Contract No. QLG2-CT-2002-01254. The Finnish twin studies are part of the Academy of Finland Centre of Excellence in Complex Disease Genetics. Hanna-Reetta Lajunen is a student of Helsinki Biomedical Graduate School.

T2:OS2.3

Dietary fatty acids and the relationship to visceral and subcutaneous fat content in humans

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Introduction: Whether the type of fat in the diet plays a role in body fat accumulation and adipose tissue distribution is unknown.
Methods: In a population-based sample of 260 men and women (aged 70) of the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS), we investigated cross-sectional relationships between fatty acid (FA) composition in plasma cholesterol esters and subcutaneous (SAT), visceral (VAT) and total adipose tissue, respectively. Dietary biomarkers of FA intake were assessed by gas chromatography. SAT and VAT by MRI and total fat by DXA scan. Univariate correlations and multivariate linear regression were performed (multivariate model adjusting for total energy intake and physical activity level).
Results: The saturated fatty acids 16:0 and 18:0 were positively correlated to VAT ($r=0.19$, $p<0.05$ and $r=0.19$, $p<0.01$, respectively), but not to SAT or total fat. These associations remained in multivariate model ($p<0.01$ and $p<0.05$, respectively). Conversely, 18:2n-6 was inversely related to SAT, VAT and total fat ($r=-0.17$, $p<0.01$; $r=-0.25$, $p<0.001$; and -0.27, $p<0.001$, respectively), associations that persisted in multivariate analyses ($p<0.05$, $p<0.001$ and $p<0.001$, respectively). Long chain n-3 FA (20:5n-3 and 22:6n-3) showed weak positive associations to VAT and total fat in multivariate analyses (all $p<0.05$).
Conclusion: High proportions of plasma n-6 polyunsaturated FA, but not n-3 FA, were related to lower fat content in all adipose tissue depots, whereas saturated FA was positively related to visceral fat. These results accord with a recent study indicating a diet high in polyunsaturated fat and low in saturated fat may decrease abdominal fat.

Conflicts of interest: None disclosed. *Funding:* This work was supported (UR and HP) by NordForsk as a part of the Nordic Centre of Excellence in Food, Nutrition and Health (SYSDIET consortium).

T2:OS2.4

Risk factors for overweight and obesity in adulthood: Results from the Quebec Family Study

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Introduction: The identification of risk factors for obesity is crucial for prevention and for future health promotion strategies. However, evidence on the independent contribution of these risk factors to obesity is limited at present. Thus, the aim of this study was to determine the relative contribution of potential risk factors for adult overweight/obesity.
Methods: A cross-sectional (n = 537) and a longitudinal (n = 283; 6-year follow-up period) analysis was performed for seven risk factors for overweight/obesity assessed in adult participants (aged 18-64 years) of the Quebec Family Study. The main outcome measure was overweight/obesity, defined as a body mass index (BMI) ≥ 25 kg/m^2.
Results: Using logistic regression analysis adjusted for age and sex, short sleep duration (OR = 3.51, 95% CI 2.01-5.21), high dietary restraint behavior (OR = 2.98, 95% CI 1.91-4.61), low dietary calcium intake (OR = 2.33, 95% CI 1.51-3.36), absence of vigorous physical activity (OR = 1.51, 95% CI 1.08-2.28), high dietary lipid intake (OR = 1.50, 95% CI 1.08-2.07), non-consumption of multivitamin and dietary supplements (OR = 1.49, 95% CI 1.09-2.02), and high alcohol intake (OR = 1.27, 95% CI 1.05-1.66) were all significantly associated with overweight/obesity. The analysis of covariance adjusted for age and all other risk factors revealed that only individuals characterized by short sleep duration, low dietary calcium intake, and absence of vigorous physical activity had significantly higher BMI compared to the reference category in both sexes. Over the 6-year follow-up period, short-duration sleepers, low calcium consumers, and those having a high dietary restraint trait score were significantly more likely to gain weight and develop obesity.
Conclusion: These results show that excess body weight or weight gain results from a number of obesogenic behaviors that have received considerable attention over the last decade. They also indicate that the three factors which have the best predictive potential of variations in BMI, be it in a cross-sectional or a longitudinal analytical design, do not have a "caloric value" per se.

Conflict of Interest: None disclosed. *Funding:* Research relating to this abstract was funded by the financial support over 20 years of the Medical Research Council of Canada through several grants for the Quebec Family Study as well as other agencies from the governments of Quebec and Canada.

T2:OS2.5

Sleep duration and quality associated with obesity among Arab children

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Introduction: The link between sleep duration and obesity has been well established in adults, but several epidemiological studies revealed inconsistent findings in adolescents and younger children. This study aims to investigate the relationship between sleep length and obesity in Saudi students.

Methods: A total of 5887 Saudi students, boys (55.2%) and girls (44.8%), aged between 10 and 19 years were randomly selected from elementary, intermediate, and secondary schools in different regions of Riyadh. A questionnaire on sleep behavior was given. Anthropometry included BMI, waist and hip circumferences.
Results: Hours of sleep were inversely correlated with BMI among girls 16-18 y and ≥ 18 y Sleeping < 7 hours significantly increases the risk of obesity in both boys and girls (all age categories) (OR=1.25 – 1.38, 95% confidence intervals=1.02-1.89)**.** Prevalence of overweight and obese were higher among those having interrupted sleep compared to those sleeping continuously (18.7% versus 14.5% respectively).
Conclusion: Short sleep duration and poor sleep quality are significantly associated with obesity among Arab youth. Further studies need to employ more objective measures of sleep, such as actigraphy, and examine the mechanism of these associations.

Conflict of Interest: None disclosed. *Funding:* No funding related to this abstract submission.

T2:OS2.6

Total dietary fiber and cereal fiber intake in relation to subsequent weight change among Europeans: the DiOGenes study

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Introduction: Dietary fiber is recommended to promote a healthy body weight, but epidemiological studies investigating the association between fiber intake, fiber sources, and subsequent weight gain are sparse.
Methods: A total of 89,432 participants, aged 20-78 years at baseline (mean = 53 years), were included in this prospective cohort study. Participants came from five European countries and were followed for an average of 6.5 years (range: 1.9-12.5 years). Total dietary fiber and cereal fiber were assessed using data collected by country specific food frequency questionnaires. Associations between fiber and annual weight change were investigated using multiple linear regression analyses. Analyses were adjusted for baseline anthropometrics, demographic and lifestyle factors, follow-up duration and other dietary variables.
Results: Total fiber was inversely associated with weight change in both men and women, although the association in women was not statistically significant. Each 10 g increase of total fiber intake was associated with an annual weight change of - 38 g/year [95% confidence interval (CI): - 70, - 7] in men and - 36 [95% CI: - 83, 11] in women. Cereal fiber was inversely and significantly associated with weight change in both men and women; 10g cereal fiber was associated with an annual weight change of - 103 g/year [95% CI: - 135, - 71] in men and - 102 g/year [95% CI: - 161, - 42] in women.
Conclusion: Our results support the beneficial role of dietary fiber, and especially cereal fiber, on preventing weight gain.

Conflict of Interest: None. *Funding:* DiOGenes is supported by the European Community (Contract no. FOOD-CT-2005-513946).

Track 3: Integrative Metabolism and Homeostasis
T3:OS1 – Energy and substrate metabolism

T3:OS1.1

Cardiac lipid content after twelve weeks of endurance and strength training in overweight subjects

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Background: Lipid storage in cardiac muscle is associated with diminished systolic and diastolic function in animal studies and recently also in man. 'Lipotoxic' pathways have been suggested to lead to cardiomyopathy and heart failure. Physical training is known to improve cardiac function, however it is unknown whether it affects cardiac lipid content.
Objective: To investigate whether a 12-week endurance and strength training program decreases (non-invasively assessed) cardiac lipid content.
Subjects and methods: Fourteen overweight healthy male subjects (age: 58.4±1.2 years, BMI: 31.1±1.2 kg/m^2) followed a training program (three sessions of 45 min/week). Oxygen uptake (VO_2max) was measured by an incremental cycling test. Cardiac lipid content was determined *in vivo* by image–guided Magnetic Resonance Spectroscopy on a whole body MRI-scanner (Intera, 1.5T, Philips Healthcare). Signal acquisition was restricted to a volume of interest of 6 cm^3 in the septum of the heart, signal acquisition was ECG-triggered to end-systole and respiratory-gated.
Results: Whole body maximal oxygen uptake was improved after training (from 27.7±1.6 to 29.3±2.0 ml*min^{-1}kg^{-1}, p=0.04) and cardiac lipid content was decreased (from 0.78±0.12% to 0.43±0.04% (intensity of CH_2-resonance of lipids relative to water resonance) (p=0.02)).
Conclusion: Twelve weeks of endurance/strength training lead to significant metabolic changes, reflected by an improved maximal whole body oxygen uptake. The training intervention resulted in reduced cardiac lipid content in this group of overweight subjects. As physical activity is well known to beneficially affect cardiac function, these findings are in line with the notion that keeping cardiac lipid storage low may be important.

Funding: This study has been funded by the European Foundation for the study of diabetes (EFSD).

T3:OS1.2

How to characterize impaired metabolic flexibility in type 2 diabetes in the postprandial phase?

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Introduction: Impaired metabolic flexibility has been highlighted in type 2 diabetic subjects using a euglycemic hyperinsulinemic clamp. This study aimed at determining whether such an impaired metabolic flexibility could be characterized in the more physiological postprandial state.

Methods: Metabolic flexibility was evaluated postprandially for 6 hours after an oral glucose load in 11 type 2 diabetic subjects and 12 healthy subjects, by using indirect calorimetry and the percent relative cumulative frequency curve (PRCF) analysis for respiratory quotient (RQ). In parallel, insulinemia, glycemia and non-esterified fatty acids (NEFA) concentration were assessed.
Results: Metabolic flexibility (H: slope of PRCF curve of RQ) was positively correlated to fasting insulinemia and glycemia (r=0.79, p<0.0001 and r=0.49, p=0.02 respectively) as well as to the postprandial glycemic peak (r=0.83, p<0.0001). Glycemia, insulinemia and RQ were significantly different between groups at baseline. Insulin concentration kinetics differed dramatically between groups, with no first acute phase but a longer-lasting response in the diabetic group, associated to a prolonged inhibition of lipolysis, characterized by NEFA concentration follow-up. Hyperglycemia was accentuated and prolonged in the diabetic group.
Conclusion: Despite the reduction in NEFA furniture and the parallel increase in glucose availability due to prolonged hyperglycemia, the capacity to switch from lipid oxidation to glucose oxidation remained impaired in the diabetic group in response to a glucose load. H is a novel and relevant marker of metabolic flexibility in postprandial conditions as it reflects the intrinsic inability to match fuel availability and fuel utilization in type 2 diabetic subjects.

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T3:OS1.3

Mitochondrial determinants of energy metabolism in C57Bl/6 mice

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Introduction: Considerable variation, for which the origin is unknown, in energy expenditure (EE), even after adjustment to body weight, is reported in genetically similar C57Bl/6 mice fed high-fat diets. Here, we combined whole-body and *ex vivo* muscular mitochondrial respiration to investigate if muscle mitochondrial capacity explains the variation in EE.
Methods: Twenty male C57Bl/6 mice consumed a 45-en% HF diet. Metabolic cages were used to examine whole body EE and substrate selection. Animals were grouped based on average EE (adjusted to body weight). At day 7, mitochondria were isolated from the tibialis anterior. Using high-resolution respirometry, ADP-stimulated state 3 respiration and maximal respiration on FCCP (state U) were determined using glycolytic (pyruvate), TCA cycle (glutamate + succinate) and fatty-acid derived (palmitoylCoA + carnitine) substrates. Fibertyping (immunohistology) and Oxphos protein content (western blot) were analyzed.
Results: Energy expenditure in the high EE group was 0.55±0.01 kcal/h and in the low EE group 0.50±0.01 kcal/h. Surprisingly, on palmitoylCoA and pyruvate, the high EE group had lower state 3 (57.0±5.2 vs 98.5±9.9 nmol/mg/min, P<0.01 and 300.0±25.6 vs 388.6±18.8 nmol/mg/min, P=0.01.) and state U respiration (99.2±11.4 vs 146.0±10.4 nmol/mg/min, P=0.01 and 394.3±46.5 vs 515.7±18.6 nmol/mg/min, P=0.02, resp.). The high EE group showed higher percentage IIa fibers (74.8±2.7 vs 60.4±4.9%, P=0.03) at the expense of type IIb (25.3±2.7 vs 38.8±4.6, %, P=0.03).
Conclusion: We confirm the large variability in EE in C57Bl/6 mice upon consumption of a HF diet. Mice with the highest EE were characterized by highest % oxidative muscle fibers, but also the lowest mitochondrial function. The underlying mechanism needs further examination.

This study was supported by the Dutch Organisation for Health Research & Development (ZonMw).

T3:OS1.4

Impaired hepatic mitochondrial function in patients with type 2 diabetes.

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Introduction: The role of mitochondrial dysfunction for the development of fatty liver disease (NAFLD) in type 2 diabetic patients (T2DM) is yet unclear. We developed a technique for absolute quantification of phosphorus metabolites in human liver using phosphorus magnetic resonance spectroscopy (^{31}P MRS).
Methods: We assessed hepatocellular lipids (HCL), absolute concentrations of γATP and inorganic phosphate (Pi) in the liver (n=27) and insulin-suppressed endogenous glucose production (iEGP) with euglycemic-hyperinsulinemic clamps and stable isotopes (n=15) in T2DM (3f/6m age: 58±2 years BMI: 27±1 kg/m^2), age and BMI-matched (mCON) (4/5; 61±4; 25±1) and young healthy humans (yCON) (3/6; 25±3; 22±1; p<0.005 vs. T2DM and mCON).
Results: T2DM had ~30% lower Pi and ~25% lower γATP than CON (0.96±0.01; 1.3±0.1; 1.4±0.2 mmol.L^{-1}; p<0.05; 1.68±0.11; 2.26±0.20; 2.20±0.09 mmol.L^{-1}; p<0.05). HCL (10.6±3.1; 8.2±3.8; 1.6±0.9%) and liver transaminases were comparable. T2DM had 37% lower iEGP than mCON (0.48±0.12;-0.04±0.15; 0.34±0.21 mg.kg^{-1}.min^{-1}; p<0.05 T2DM vs. mCON). iEGP, fasting plasma glucose (r~-0.6, p<0.05), HbA1c and BMI (r~-0.5, p<0.05) related negatively to Pi and γATP. HCL related negatively to γATP (r~0.4, p<0.05). Alanine-aminotransferase related negatively to HCL (r~0.6, p<0.005) and Pi (r~-0.5, p<0.01).
Conclusion: Despite comparable liver fat and transaminases, T2DM show lowered heaptic phosphate compounds which related to metabolic control and iEGP. Thus, hepatic mitochondrial dysfunction could promote development of NAFLD and insulin resistance.

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T3:OS1.5

Association of cardiac fat with liver fat and insulin sensitivity after diet-induced weight loss in overweight nondiabetic women

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Introduction: Cardiac adipose tissue (CAT) is positively associated with fatty liver and obesity-related insulin resistance. Because CAT is a well known marker of visceral adiposity, we investigated the impact of weight loss on CAT and its relationship with liver fat and insulin sensitivity independently of body fat distribution.
Methods: 30 overweight nondiabetic women (BMI 28.2-46.8 kg/m^2, 22-41 y) followed a 14.2±4-wk low-calorie diet. CAT, abdominal subcutaneous (SAT) and visceral fat volumes (VAT) were measured by MRI, total fat mass, trunk and leg fat by DXA and intrahepatocellular lipids (IHCL) by (1)H-magnetic resonance spectroscopy. Euglycemic hyperinsulinemic clamp (M) and HOMA2 model were used to assess insulin sensitivity.

Results: At baseline, CAT correlated with VAT (r=0.82; P<0.001), IHCL (r=0.46), HOMA-IR (r=0.46) and M-value (r=-0.40; all P<0.05). During intervention, body weight decreased by -8.5%, accompanied by –12% CAT, -13% VAT, -44% IHCL, -10% HOMA2-%B and +24% as well as +15% increases in HOMA2-%S and M, respectively. Decreases in CAT were only correlated with baseline CAT and the loss in VAT (r=-0.56; P<0.01; r=0.42; P<0.05). Improvements in HOMA2-%B were related to the decrease in IHCL only (r=0.65, P=0.002) and decreases in IHCL correlated with the decrease in VAT only (r=0.61, P=0.004).
Conclusions: Cross-sectional CAT is correlated with both, liver fat and insulin resistance. Longitudinally, the association between CAT and liver fat was explained by VAT whereas the relationship between CAT and insulin resistance was explained by liver fat.

Conflict of interest: None disclosed. *Funding:* Deutsche Forschungsgemeinschaft DFG Mü 714/8-3.

T3:OS1.6

The effect of UCP1 expression in skeletal muscle on lifespan, substrate and energy metabolism in mice

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Introduction: HSA-mUCP1 transgenic mice have an ectopic expression of uncoupling protein 1 (UCP1) in skeletal muscle. They show a phenotype of increased energy expenditure and improved glucose tolerance [Katterle et al. 2008; Klaus et al. 2005]. Also mild uncoupling through UCPs affects cellular mitochondrial ROS production and might therefore impact aging.
Methods: We investigate lifespan, energy and glucose metabolism under different diets in HSA-mUCP1 mice. Body composition, energy assimilation, activity, metabolic rate and insulin sensitivity were measured at 12 weeks of age. Then mice are fed semisynthetic diets with different macronutrient ratios (energy % carbohydrate:protein:fat): HCLF (41:42:17), HCHF (41:16:43); LCHF (11:45:44) until they die. Measurements are repeated after 20 and 46 weeks. At specific time points mice are killed for analysis of substrate metabolism and oxidative stress parameters.
Results: The HSA-mUCP1 mice had an increased respiratory quotient (RQ) during night time but displayed a rapid drop of RQ in the morning, indicative of a rapid switch from glucose to fat oxidation, i.e. a higher metabolic flexibility. They showed increased insulin sensitivity irrespective of the diet and differences in lifespan and body composition compared to the wt mice. Interestingly, gene expression analysis pointed to increased levels of lipogenesis in white fat of HSA-mUCP1 mice but also increased lipolysis.
Conclusion: Taken together, these data suggest that skeletal muscle mitochondrial uncoupling leads to a "healthy" obese phenotype by preserving insulin sensitivity and a high metabolic flexibility.
Also it leads to profound overall changes in energy and substrate metabolism.

Katterle Y, et al. (2008) Physiol. Genomics 32: 352-359

Klaus S, et al. (2005) Physiol. Genomics. 21:193-200.

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T3:OS2 – Inflammation and stress

T3:OS2.1

Haploinsufficiency of the pRb gene reduces diet-induced obesity, insulin resistance and hepatosteatosis in mice

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Introduction: Lack of the retinoblastoma protein tumor suppressor (pRb, encoded by the Rb gene) affects adipogenesis and promotes a switch from white to brown adipocyte differentiation in adipocyte cell models. The objective is to assess the significance of these effects in the whole animal, by studying the impact of germ-line Rb haploinsufficiency on the adipose tissue phenotype and the response to high fat diet feeding in mice.
Methods: 7-week-old male and female $Rb^{+/-}$ and $Rb^{+/+}$ mice were fed with a high fat diet (HFD) with 60% of the energy as fat for 18 weeks. Body weight and energy intake courves, insulin resistance, glucose tolerance, rectal temperature and circulating metabolites were assessed. Tissue gene expression, composition and morphometric analysis were performed.
Results: $Rb^{+/-}$ mice gained less body weight and body fat than wild-type ($Rb^{+/+}$) littermates after long-term HFD feeding, coupled to reduced feed efficiency and increased rectal temperature. Rb haploinsufficiency ameliorated insulin resistance and hepatosteatosis after HFD in male mice, in which these disturbances were more marked than in females. The expression of peroxisome proliferator activated receptor γ and of genes involved in energy metabolism/mitochondrial function, brown adipocyte determination and tissue vascularization was increased in adipose depots of $Rb^{+/-}$ mice after HFD. $Rb^{+/-}$ mice maintained on regular chow had normal adiposity and displayed signs of increased energy metabolism and enhanced insulin sensitivity.
Conclusion: These findings support a role of pRb in modulating adipocyte function and the metabolic plasticity of the adipose organ in vivo, with implications for the development of obesity.

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T3:OS2.2

Growth Hormone Deficiency Compromises the Expression of the Potential Anti-inflammatory STAMP2 Gene in Human Subcutaneous Adipose Tissue.

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Introduction: The potential coordinator of nutrient and inflammatory response, six-transmembrane protein of prostate 2 (STAMP2), was shown to be associated with obesity and insulin sensitivity (IS). We investigated the effect of growth hormone deficiency (GHD), known to be associated with metabolic dysregulation, increased inflammation and compromised growth and differentiation of adipose tissue, on STAMP2 in human abdominal subcutaneous adipose tissue (SAT).
Methods: The study cohort consisted of 20 GHD patients (age 30.7±7, M/F 12/8, BMI 21.7-36.8 kg/m^2) and 19 healthy age, gender and BMI-matched controls. IS was measured by euglycemic hyperinsulinemic clamp. Abdominal fat mass was determined by MRI. Samples of SAT were taken by needle biopsy and fat cell size (FCS) was assessed by light microscopy. Gene and protein expressions were measured by qRT-PCR and immunoblotting, respectively.
Results: GHD patients displayed lower IS, increased FCS and body fat. GHD was associated with a significant decrease of STAMP2 gene and protein expressions, the change in mRNA being more pronounced during the clamp (2.2-fold, $p<0.0001$) compared to the fasting state (1.42-fold, $p<0.05$). STAMP2 was positively correlated to the protein expression of adipokines regulating growth and differentiation (PDGF, SDF1, GRO; r=0.59, r=0.41, r=0.62; $p<0.05$; n=24). Furthermore, a positive association was found between STAMP2 and adiponectin gene expression during fasting state and the clamp (r=0.52, r=0.67; $p<0.01$; n=34).
Conclusion: Our results demonstrate that STAMP2 is decreased in GHD associated with whole-body metabolic derangements. The relationships of STAMP2 to adipokines regulating adipose tissue growth, differentiation and inflammation support a positive role this protein might play in human metabolic health.

Conflict of Interest: None disclosed. *Funding:* Research relating to this abstract aws funded by APVV 51-040602, VEGA 217110/27, COST BM0602 and COST FA0602

T3:OS2.3

Differential activation of inflammatory and hypoxic pathways in visceral and subcutaneous adipose tissue in obese women

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Introduction: The activation of pathways related to inflammation and hypoxia response is involved in the pathophysiology of cardiovascular and metabolic complications of obesity, and the visceral adipose tissue seems to play a key role.
The aim of this study was to compare the expression of genes involved in inflammation (endoplasmic reticulum stress, proinflammatory adipokines) and hypoxia response (angiogenic and antioxidant factors) in visceral (VAT) and subcutaneous (SAT) adipose tissue.
Methods: Quantitative mRNA expression of forty-four genes involved in inflammation, hypoxia, adipogenesis and gluco-lipidic metabolism was measured by RT-PCR on VAT and SAT samples obtained from 10 obese women undergoing bariatric surgery.
Results: We found increased expression of TNF-α (+3.3 fold change), PRKC (+3.1), methallotionein-3 (+7.9) and decreased expression of WISP2 (-3.8) and leptin (-2.5) in VAT as compared to SAT. When considering group of genes related to specific pathways, such as hypoxia (EPAS1, VEGFA, MT-3, ANGPTL4, HIF-1α), endoplasmic reticulum stress (ERN1, JUN, MAPK8, IKBKB) and insulin resistance (PRKCΔ, IRS1, IKBKB, JUN, TNF-α), a multivariate analysis showed significant difference ($p<0.05$, at least) between the two depots. Moreover, a positive correlation ($p<0.01$) between plasma insulin levels and genes related to endoplasmic reticulum stress, macrophage infiltration, proinflammatory adipokines and hypoxic response was found only in VAT.
Conclusion: In obese women, activation of inflammation, hypoxia response and insulin resistance related pathways is greater in VAT than SAT. Our findings support the hypothesis that VAT may exert its influence on the comorbidities associated with obesity at least in part through pathways related to inflammation and hypoxia

T3:OS2.4

Glucocorticoids, stress and food choice

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Introduction: The relationship between cortisol, stress and food have been obtained in rodents. Few studies conducted in humans demonstrated that subjects with higher levels of cortisol, in response to stress, showed a tendency to eat more than controls or to less reactive counterparts. We want to investigate the relationship between HPA axis activity, food choice and main anthropometric, metabolic and hormonal parameters.
Methods: This study evaluated 160 obese women and 21 normal weight controls. Each subject underwent an OGTT and a basal assay for metabolic and hormonal parameters. Cortisol excretion was assessed on 24 hours urine collection Daily caloric intake was calculated, as well as intake of macronutrients, and of cholesterol, satured fats, oligosaccharides and fibres.
Results: UFC/24 hrs were significantly higher in obese than in controls. UFC/24 hrs was significantly correlated to both BMI and waist circumference. However, the relationship with the latter was lost after adjusting for BMI. No correlation was found between UFC/24hrs and metabolic and hormonal parameters. UFC/24 hrs was significantly and positively correlated to daily total calories and to daily fibres intake. These relationships remained significantly different even after adjustment for BMI. UFC/24 hrs was significantly and positively correlated to weekly frequency of starchy foods, legumes and ice-cream consumption.
Conclusion: To our knowledge this is the first study performed in humans in which a close relationship between HPA axis and food choice has been demonstrated, independently of obesity. Our data seem to support the hypothesis that obesity may represent an escape mechanism against stress.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T3:OS2.5

Effect of continuous and cyclic CB1 antagonist treatment on body weight and inflammatory markers in lean rats.

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Introduction: The cannabinoid system has recently attracted a lot of focus since it has been shown that cannabinoid receptor 1 (CB1) antagonists were able to induce weight loss. Recent studies have indicated that besides central effects CB1 antagonism has direct, peripheral effects. We investigated whether the tolerance development on food intake and weight loss could be minimized by cyclic treatment and at the same time

investigating eventual peripheral effects on adipose tissue metabolism and inflammation.
Methods: We allocated 40 male Wistar rats into 4 groups for 4 weeks:
Group 1: control group, with free access to standard chow.
Group 2: continuously given CB1-receptor antagonist (10mg/kg) every day.
Group 3: pair fed so they lost the same amount of weight as group 2 thereby enabling us to separate effects from just the weight loss from the ones by CB1-receptor antagonist treatment.
Group 4: receiving cyclic CB1-receptor antagonist in repeated intervals of three days.
Weight and food intake was continuously measured. After 4 weeks the rats were sacrificed, blood and tissue samples were collected for determination of inflammatory markers.
Results: Groups 1-3 ended up weighing almost the same (320±2g). Group 4 weighed significantly less (305g). We found a significant increase in epididymal adipose tissue of adiponectin, CRP, TNF-α, MCP-1 and IL-8 mRNA expression in group 4. Serum leptin levels were lower in both treated groups.
Conclusion: Our study indicated that tolerance development during CB1 antagonist treatment could be prevented by intermitted administration but that this seemed to induce inflammation in the adipose tissue.

Conflict of interest: None disclosed. *Funding:* Research relating to this abstract was supported by the Danish Research Council, the Danish Diabetes Association, the Novo Nordisk Foundation and by Aarhus University.

T3:OS2.6

Corticotrophin Realising Factor affects the expression of TLR4 receptor in adipocytes

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Introduction: Adipocytes **share common characteristics with macrophages i.e. they respond to** LPS **via TLR4 receptor to produce cytokines (1)**. Macrophages and adipocytes also express the corticotrophin-releasing factor (CRF) neuropeptides and their receptors which affect macrophage function. Aim of the present study was to examine if CRF also affects adipocytes.
Methods: The mouse 3T3L1 cell line was used. The experiments were held on pre-adipocyte cells and fully differentiated adipocytes as per published protocol.
Results: 3T3L1 pre-adipocytes were incubated with CRF (10^{-8} M) and/or LPS (10 ng/ml) for 5h, 10h and 15h and levels of TLR4 were measured by FACS analysis. Cells incubated for 5 or 10 h with CRF and/or LPS revealed a markedly decrease of TLR4 (Figure 1). LPS plus CRF suppressed TLR4 by Real Time PCR (Figure 2).

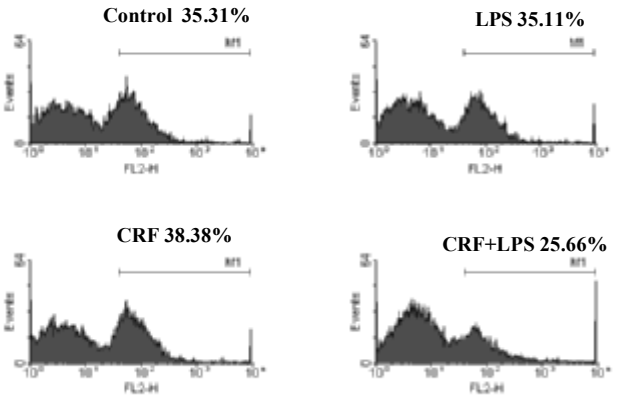

Figure 1: 3T3L1 cells incubated with CRF (10^{-8} M) and/or LPS (10 ng/ml) for 10h and the levels of TLR4 measured by FACS.

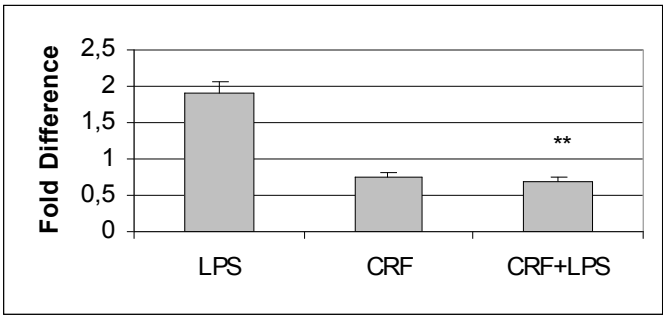

Figure 2: Fully differentiated 3T3L1 cells incubated with CRF (10^{-8} M) and/or LPS (10 ng/ml) for 10 days and the levels of TLR4 measured by RealTime PCR. (**) statistical significance compared to cells exposed to LPS alone.

Conclusion Our data suggest that CRF suppresses TLR4 expression in adipocytes, an effect containing their pro-inflammatory activity.

Conflict of Interest: None. *Funding:* No Funding.

T3/T4:OS1 - Energy metabolism and insulin sensitivity

T3/T4:OS1.1

Acute and Chronic Hypoxia Selectively Modulates the Expression of Glucose Transporters (GLUTs) In Human Adipocytes

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Introduction: Adipose tissue hypertrophy in obesity leads to impaired oxygen supply to adipocytes resulting in hypoxia, and consequently in altered glycolytic metabolism. In this study we have analyzed the effect of acute and chronic hypoxia on the expression of different glucose transporters (GLUT) in human adipocytes, the reversibility of the phenomenon and the role of the hypoxia-inducible transcription factor (HIF-1) in hypoxia-related changes in GLUT expression.
Methods: Mature human adipocytes (SGBS cells) were cultured under 1% O_2 or 21% O_2 for different times. The hypoxia-mimetic, $CoCl_2$, was used to determine the role of HIF-1 in changes of GLUT expression. Expression was determined at both the mRNA (real-time qPCR) and protein (Western blotting) levels.
Results: Hypoxia exerted a significant and specific effect on GLUT expression, upregulating GLUT-1 and -3 mRNA levels, while down-regulating GLUT-4 and -5 levels. The effects of hypoxia on GLUT-1 were largely reversed on returning the cells to normoxia, while partial reversion of GLUT-4 was observed. Treatment with $CoCl_2$, like hypoxia, also induced GLUT-1 gene expression and decreased GLUT-4 expression.
Conclusion: Hypoxia, both acute and chronic, modulates the expression of different glucose transporters in human adipocytes, in a time- and type-dependent manner, and these effects appear to be mediated by the transcription factor HIF-1. Furthermore, hypoxia-induced changes in GLUT expression can be reversed when cells are returned to normoxic conditions. These results raise the possibility that hypoxia may underlie the loss of insulin sensitivity in adipose tissue in obesity.

Conflict of interest: There is no conflict of interest.

T3/T4:OS1.2

Hypoxia decreases insulin signaling pathways in adipocytes

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Objective : Obesity is characterized by an overgrowth of adipose tissue that leads to the formation of hypoxic areas within this tissue. We investigated if this phenomenon could be responsible for insulin resistance by studying the effect of hypoxia on insulin signaling pathway in adipocytes.
Research design and Methods: Hypoxic signaling pathway was modulated in adipocytes from human and murine origins through incubation under hypoxic condition (1% O_2) or modulation of HIF expression. Insulin signaling was monitored through the phosphorylation state of several key partners of the pathway and glucose transport.
Results: In both human and murine adipocytes, hypoxia inhibits insulin signaling as revealed by a decrease in the phosphorylation of insulin receptor. In 3T3-L1 adipocytes, this inhibition of insulin receptor phosphorylation is followed by the decrease in the phosphorylation state of PKB and AS160, as well as an inhibition of glucose transport in response to insulin. These processes were reversible under normoxic conditions. The mechanism of inhibition seems independent of protein tyrosine phosphatases activities. Overexpression of HIF-1α or HIF-2α, or activation of HIF transcription factor with $CoCl_2$ mimicked the effect of hypoxia on insulin signaling while downregulation of HIF-1α and HIF-2α by siRNA inhibited it.
Conclusion: We have demonstrated that hypoxia creates a state of insulin resistance in adipocytes which is dependent upon HIF transcription factor expression. Hypoxia could be envisioned as a new mechanism which participates in insulin resistance in adipose tissue of obese patients.

T3/T4:OS1.3

Adipose tissue lipid and fatty acid compositions change substantially in acquired obesity

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Introduction: We have previously shown in a rare sample of monozygotic (MZ) twins discordant for obesity (4-10 kg/m^2 BMI difference) that acquired obesity is characterized by several metabolic aberrations in the adipose tissue (AT) independent of genetic influences. In particular, we have shown that the obese co-twins' AT had a 47% reduction in mitochondrial DNA copy number, significant downregulation of mitochondrial and upregulation of inflammatory pathways in global transcriptomic arrays (PLoS Med 2008). In the present study, we performed lipidomics analyses to further expose AT lipid changes and their relationships with gene expression and insulin sensitivity in acquired obesity.
Methods: All healthy obesity-discordant MZ pairs (TwinA BMI≥30, TwinB BMI≈25) from birth cohorts 1975-1979 (MZ n=658) were invited to the study. Of the eligible 18 pairs, 14 participated. AT lipidomics measurements were done by liquid chromatography/mass spectrometry, fatty acid (FA) analyses by gas chromatography, and transcriptomics arrays by Affymetrix chips. Insulin sensitivity was assessed by the euglycemic clamp technique.
Results: The obese co-twins had profound alterations in AT lipid and FA composition. Ten most significantly changed lipids all belonged to phospholipid molecular species. Obese co-twin's fat had an overrepresentation of lipogenic palmitoleic and proinflammatory arachidonic acids, and a depletion of essential linoleic and α-linolenic acids. These changes correlated with the inactivation of mitochondrial and the overactivation of inflammatory transcription pathways, as well as whole body insulin resistance.
Conclusion: Our findings suggest that AT membrane lipid changes may be associated in the development of metabolic aberrations in obesity independent of genetic effects.

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by National Institute on Alcohol Abuse and Alcoholism (grants AA-08315, AA-00145 and AA-12502), the European Union Fifth Framework Program GenomEUtwin (www.genomeutwin.org) (QLG2-CT-2002-01254), the Academy of Finland (Grant 44069, 100499 and 201461), the Academy of Finland Centre of Excellence in Complex Disease Genetics and in Mitochondrial Disease and Aging (FinMIT), Sigrid Juselius Foundation, Biocentrum Helsinki Foundation and Helsinki University Central Hospital grants.

T3/T4:OS1.4

Metabolic changes after sleep restriction in rats.

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Introduction: There is a correlation between sleep disturbances and an increased risk in obesity and type 2 diabetes. It has also been found that acute sleep restriction is accompanied with increased appetite, hyperglycemia, decreased leptin and increased ghrelin levels. We are interested in the underlying mechanisms and decided to investigate the metabolic consequences of sleep restriction in a controlled laboratory study in rats.
Methods: Rats were cannulated to allow stress free blood sampling and subjected to 8 days of sleep restriction in which we allowed the animals to sleep for 4h per day. We performed intravenous glucose tolerance tests (IVGTT) during the baseline period, after 8 days of sleep restriction and after 5 days of recovery. Plasma hormone levels were measured during sleep restriction and after recovery. Body weight and food intake were measured daily.
Results: Eight days of sleep restriction led to a reduction in body weight (despite increased food intake), anhedonia and decreased leptin levels. This was accompanied by elevated glucose and reduced insulin profiles during the IVGTT. Food intake remained increased during recovery.
Conclusion: Eight days of sleep restriction leads to marked alterations in energy metabolism that are associated with an increased risk for the development of several aspects of the metabolic syndrome.

1: no conflict of interest. 2: no funding.

T3/T4:OS1.5

Sex differences in the storage of free fatty acids in ntramyocellular triglycerides

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Introduction: To assess whether known gender differences in free fatty acid (FFA) release and energy expenditure also occur in muscle FFA trafficking we measured systemic FFA flux and storage rates into intramyocellular triglyceride (imTG) pools in 61volunteers (age 20-50, BMI 18-38 kg/m^2).
Methods: VO_{2max}, regional body fat and fat free mass (FFM) (DEXA, abdominal CT) were measured. Following a 6 hr [U-^{13}C]palmitate infusion (0.6 nmol•kg FFM^{-1} • min^{-1}), blood and muscle samples were collected for measurement of plasma palmitate and FFA concentrations, imTG concentrations, and [U-^{13}C]palmitate enrichment (mpe) in plasma FFA palmitate and imTG-palmitate.
Plasma [U-^{13}C]palmitate accumulation into imTG (= imTG (µmol/gram wet weight) × Δ imTG-[U-^{13}C]palmitate mpe over 6 hr) was divided by plasma [U-^{13}C]palmitate mpe to calculate FFA storage rates into imTG (µmol FFA/gram muscle/hr). The proportion of FFA flux stored in imTG (PCTFX-TG) was calculated by extrapolating FFA storage per gram muscle per hour to total muscle mass (53% and 47% of FFM in men and women) and dividing this by total FFA flux.
Results: In women, PCTFX-TG correlated with plasma FFA concentrations only (r=0.54, p=0.004); contrastingly, in men, PCTFX-TG correlated with VO_{2max} only (r=0.54, p=0.005). Regional and total fat mass were not associated with PCTFX-TG.

	Female	Male
imTG (µmol/g)	2.75 ± 1.22	1.78 ± 1.58*
FFA flux (mmol/hr)	24.5 ± 1.6	23.0 ± 1.8
PCTFX-TG	11 ± 6%	10 ± 9%

*P=0.01

Conclusion: We find significant sex differences in imTG trafficking. PCTFX-imTG is correlated with plasma FFA concentrations in women, but with cardiovascular fitness in men.

Conflict of Interest: None. *Funding:* Research relating to this abstract was funded by NIH DK40484.

T3/T4:OS1.6

"Adipose" gene (Adp) expression in human subcutaneous adipose tissue is inversely related to fatness and insulin resistance

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Introduction: *Adipose* (*Adp*) inhibits *in vitro* lipid accumulation and mice overexpressing *Adp*
are leaner and show improved metabolic profile. Whereas, *Adp*+/- mice are obese and glucose intolerant. Since the role of *Adp* in humans is unknown, we evaluated *Adp* expression in nondiabetic and type-2 diabetic (T2DM) individuals and related it to metabolic parameters.
Methods: Obese, non-diabetic (16 M/20 F) and BMI-, race- and gender-matched T2DM (26
M/30 F) volunteers were studied. After an overnight fast, an abdominal subcutaneous adipose tissue sample was obtained followed by a 3-h hyperinsulinemic clamp during which fuel oxidation was measured. Adipose tissue *Adp* expression was determined by qRT-PCR and normalized for cyclophilin B.
Results: *Adp* expression was not influenced by the presence of diabetes (p=0.18) but was
higher in males vs. females (1.21 ± 0.04 vs. 1.08 ± 0.03; p<0.01). However, the sex difference disappeared after controlling for percent body fat since *Adp* expression was negatively correlated with %fat (r=-0.25; p=0.02). *Adp* expression correlated inversely with IR-HOMA (r=- 0.33; p<0.01) in all subjects and insulin-stimulated glucose disposal rate (GDR) in diabetics only (r=0.28; p=0.04) independent of gender and body fat. *Adp* expression correlated (p<0.05) with fasting (r=0.43) and insulin-stimulated (r=0.29) respiratory quotient independent of gender, %fat and GDR.
Conclusion: Higher *Adp* expression related with insulin sensitivity and lower adiposity which is consistent with animal studies. *In vitro* studies will disentangle the effect of insulin on adipose *Adp* expression. This aspect is currently under study and these results will be presented at the conference.

Conflict of interest: None. *Funding:* DK060412-06A

Track 4: Genes and Tissue Biology
T4:OS1 – Adipose organ, inflammation and lipid metabolism

T4:OS1.1

Analysis of the metabolic turnover of mitochondrial fatty acid oxidation in undifferentiated and differentiated adipocytes

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Introduction: Development of obesity-associated type 2 diabetes mellitus seems to be related to mitochondrial dysfunction and reduced capacity for fatty acid oxidation, potentially resulting in intramuscular lipid accumulation and insulin resistance. The pathophysiological role of mitochondrial fatty acid oxidation in adipose tissue, however, is not entirely clear. In order to analyze metabolic disturbances of fatty acid oxidation quantitatively, a highly sensitive ESI-MS-MS assay was established in the murine 3T3-L1 preadipocyte cell line.
Methods: Adipose precursor cells were induced for differentiation with an adipogenic cocktail. *In vitro* differentiated adipocytes were permeabilized with digitonin and subsequently incubated with oleic acid and L-carnitine. Extraction of acylcarnitines from cells and incubation medium was followed by desalting of the template using silicagel columns. The purified metabolites were then quantified using ESI-tandem-mass spectrometry. Citrate synthase (CS) activity was measured to correct for mitochondria number.
Results: Mitochondrial CS activity increased significantly during adipose differentiation. Analysis of the metabolites upon oleic acid incubation revealed a reproducible panel of acylcarnitines (C0:0 – C18:2) under different conditions (adipose differentiation, various substrate concentrations, different incubation times). On day 10 after induction of differentiation, fatty acid oxidation capacity was reduced. Use of etomoxir or bezafibrate resulted either in an attenuation or stimulation of intramitochondrial fatty acid flux.
Conclusion: This highly sensitive metabolite flux assay is a valuable tool to study adipocyte fatty acid turnover and may provide new insights in the alterations in obesity associated lipid disturbances. The assay is suitable for investigations of pharmacological effects on fatty acid oxidation.

Conflict of Interest: None Disclosed. *Funding:* The work was supported by the Else Kröner-Fresenius-Foundation, Bad Homburg, Germany.

T4:OS1.2

Hypoxia-independent cold-induced angiogenesis in brown and white adipose tissues: mutually opposing roles of VEGF receptor-1 and -2 in regulating metabolism

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The molecular mechanisms of angiogenesis in relation to adipose tissue metabolism remain poorly understood. Cold exposure markedly induced angiogenesis in inguinal white and interscapular brown adipose tissues. In the inguinal depot, cold exposure resulted in a 500-fold increase in expression of uncoupling protein-1 (UCP1) and increases in other brown-fat associated proteins, such as PGC-1•, as well as in proangiogenic proteins, particularly VEGF. In wild-type mice, both the inguinal and the interscapular tissues became markedly hypoxic during cold exposure; in UCP1(-/-) mice, hypoxia did not occur but the augmented angiogenesis was remarkably unaltered and was thus hypoxia-independent. The regulatory role of VEGF for angiogenesis was demonstrated by antibody treatment during cold exposure: anti-VEGFR2 abolished the induced angiogenesis and resulted in heat-conserving thermoregulatory behavior and reduced nonshivering thermogenesis capacity, whereas anti-VEGFR1 treatment augmented nonshivering thermogenesis capacity. This study thus demonstrates marked metabolic effects of intervention in angiogenesis in adipose tissues.

T4:OS1.3

Local Subcutaneous Lipoatrophy In Type 1 Patients Under Insulin Pump Therapy: The Adipose Tissue Point Of View.

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Introduction: Lipoatrophy (LA) during insulin therapy is characterized by loss of subcutaneous fat at the sites of repeated insulin injections. The pathogenesis of LA is not clear and immune cell involvement, mechanical injuries by needles and contaminants in insulin preparation have been suggested.
Aim: we aimed to characterize the residual adipose tissue present in LA areas.
Research design and methods: we studied 3 type 1 diabetic patients under insulin pump therapy for several years with lispro insulin. The NMR confirmed the subcutaneous adipose tissue reduction at LA areas. We compared tissue biopsies in LA area with adipose tissue biopsies from the same anatomical region of each patient by means of optical and electronic microscopy. We quantified the adipose-specific genes expression by qPCR .
Results and conclusions: The microscopy analysis showed that the residual adipose tissue in LA areas was characterized by smaller perilipin positive adipocytes with an increased vasculature and wide inter-cellular spaces. No inflammatory cell infiltration was observed. We found several adipoblasts and mature "skinny" adipocytes which have lost their lipid contents, as during starvation. Perilipin, adiponectin, *FABP4* and *PPARγ2* were expressed in the LA areas at low or normal levels while leptin was quite absent. We also observed an important increase in the expression of *AEBP1*, a preadipocyte marker with transcriptional repression activity.
Our results seem to exclude an immune-mediated mechanism in the pathogenesis of LA and suggest that prolonged presence of elevated concentration of insulin could induce morphological and functional changes in the adipose tissue.

T4:OS1.4

RAB18, A Molecular Switch Related To Lipid Metabolism In Adipocytes

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Introduction: In adipocytes, lipid metabolism takes place within highly specialized organelles named lipid droplets (i.e. LDs). Recent studies have shown that LDs present a large number of proteins at their surface. One of these is Rab18, a small GTPase involved in the regulation of intracellular membrane trafficking. Rab18 has been shown to interact with LDs, suggesting a link between this GTPase and the metabolic state of adipocytes. However, its specific function and the molecular mechanisms that regulate it, remain unexplored. Thus, we aimed at further investigating Rab18 function in adipose tissue.
Methods: We have analyzed Rab18 mRNA levels in white adipose tissue from rats under different physiological conditions by real-time PCR and endogenous and exogenously-expressed Rab18 intracellular localization in 3T3-L1 adipocytes.
Results: We found that Rab18 transcript levels increased in hypophysectomized and hypothyroid rats. On the other hand, Rab18 mRNA levels were significantly decreased in 48-h fasted rats. In 3T3-L1 adipocytes, both Rab18 gene expression and protein content increased upon stimulation with the lipogenic factor insulin and the lipolytic factor isoproterenol. Furthermore, these treatments induced activation and translocation of Rab18 to the surface of LDs, an effect that was abolished in the presence of inhibitors of insulin and isoproterenol intracellular signalling pathways.
Conclusion: Our results indicate that pituitary regulates Rab18 gene expression in rat adipose tissue, likely through the hypothalamus-pituitary-thyroid axis. Moreover, Rab18 expression is affected by opposite metabolic conditions (i.e. lipogenesis/lipolysis), further supporting the view that Rab18 is linked to the regulation of intracellular lipid trafficking.
Support: FIS/ISCIII (CIBEROBN CB03/06), MEC/FEDER (BFU2007-60180/BFI), and J. Andalucía (CVI-0139, P07-CTS-03039, CTS-1705), Spain.

T4:OS1.5

Intense Increase of Brown Adipose Tissue Glucose Uptake by Cold in Healthy Humans

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Introduction: Our preliminary data show that healthy adults have functional brown adipose tissue (BAT). However, its importance in the energy balance is unclear.
Methods: We studied ten healthy subjects after overnight fasting using $[^{15}O]H_2O$ and [^{18}F]fluoro-deoxy-glucose ([^{18}F]FDG) PET/CT. The subjects were scanned twice, during cold exposure and in warm conditions. Energy expenditure was measured with indirect calorimetry. Perfusion and glucose uptake (GU) rates in the supraclavicular adipose tissue and pectoral muscles were quantified using graphical analysis. Supraclavicular adipose tissue mass was determined using CT.

Results: Five subjects showed intense cold-induced metabolism in the supraclavicular adipose tissue (GU rate 11.8 ± 4.5 umol/100g/min) being 15-fold higher than in warm conditions (1.0 ± 0.5 umol/100g/min, $p = 0.003$). No major cold-induced increase in activity was detected in pectoral muscles. In five subjects we found no BAT activity during cold exposure (GU rate 1.4 ± 0.9 umol/100g/min). Mass of supraclavicular BAT ranged from 7 to 60 g. Respiratory quotient was 0.81 ± 0.02 being similar in both groups regardless of BAT activity.
Conclusion: BAT GU can be increased 15-fold by cold exposure in healthy adults. Thus, the quantified metabolic rate of BAT with measured mass is able to burn the amount of energy equivalent up to 4 kg of adipose tissue over a year. This suggests that human BAT, when activated, has the potential to significantly contribute to human energy expenditure.

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T4:OS1.6

Molecular signature of visceral obesity in antiretroviral treated HIV-1 patients

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Introduction: Visceral obesity, in addition to subcutaneous lipoatrophy, occurs in the lipodystrophy syndrome often appearing in HIV-1-infected patients under antiretroviral treatment. Our aim was to compare gene expression alterations in both visceral (VSA) and subcutaneous (SCA) adipose depots in order to get insight in their differential responsiveness to HIV-1 infection and antiretroviral treatment.
Methods: Biopsies of abdominal SCA from 10 and omental VSA from 7 lipodystrophic HIV1-patients, as well as from 10 non-infected healthy controls, were studied. Mitochondrial DNA content and expression of marker genes of mitochondrial function, adipogenesis and inflammation were analyzed by quantitative real-time PCR, immunoblot and multiplex analysis.
Results: Mitochondrial DNA and mRNA levels were decreased in SCA and VSA from patients respect to controls, although a compensatory increase in mitochondrial protein content was observed. In contrast, expression of adipogenic marker genes (PPARgamma, lipoprotein lipase, GLUT4) was lowered in SCA whereas it remained unaltered in VSA from patients respect to controls. Concerning markers of inflammation, gene expression of TNFalpha and CD68 was induced both in SCA and VSA but other markers (IL-18, IL1Ra, MCP-1) were only induced in SCA but not in VSA.
Conclusion: The lack of impairment of adipogenic gene expression in VSA highlights the relevance of the adipogenic differentiation processes in adipose tissue physiopathology in adult humans. Despite the similar increase in markers of overall inflammation in visceral and subcutaneous adipose depots, the differential behavior of several specific inflammation-related pathways may contribute to the opposite (hypertrophic versus atrophic) outcome of adipose tissue in patients.

T4:OS2 – Nutrients and tissue metabolism

T4:OS2.1

Differential gene expression in adipose tissue from obese human subjects during weight loss and weight maintenance

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Aim: To identify differentially expressed genes during weight loss and weight maintenance after weight loss.
Methods: Subcutaneous abdominal adipose tissue biopsies were obtained from nine obese subjects at baseline, after a low calorie diet (LCD) supported weight reduction and after group therapy to remain at a stable weight. Differences in gene expression were analyzed using Affymetrix HG-U133 Plus 2.0.
Results: Subjects lost 18.8 ± 5.4% of their body weight (BW) during the LCD-period (101 ± 26 days) and maintained this weight (-17.7 ± 5.5% of baseline BW) during the weight maintenance phase (167 ± 37 days). Insulin sensitivity improved during weight loss with no further improvement during weight maintenance (HOMA 2.4 ± 1.3, 0.8 ± 0.5 and 1.3 ± 0.6, respectively; p_{ANOVA}=0.0024). More genes were down- (n=163) than upregulated (n=70) as a result of weight loss. 61 of these genes showed sustained regulation during weight maintenance, 16 upregulated and 45 downregulated. *CDKN2B* and *JAZF1*, both recently shown to associate with type 2 diabetes, were downregulated. We confirm the downregulation of tenomodulin and matrix metallopeptidase 9 with weight loss. The expression of *CIDEA* and *SCD* was upregulated during weight loss but returned to baseline during weight maintenance.
Conclusion: Adipose tissue genes that show sustained regulation during weight loss and weight maintenance, such as *CDKN2B* and *JAZF1*, may be of potential interest as markers of the beneficial effects of weight loss whereas others, such as *CIDEA* and *SCD*, seems to be primarily involved in the process of weight loss itself.

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T4:OS2.2

Adipose tissue mRNA biomarkers of macronutrient dietary intake in weight reduced obese humans

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Introduction: The outcome of dietary interventions to reduce weight is highly variable. Little is known on the molecular adaptations of adipose tissue during weight maintenance and the relationship with macronutrient composition. The present study within the frame of the European program DioGenes aimed at characterizing biomarkers of dietary intervention in obese subjects using transcriptomic analyses of human adipose tissue (AT).

Methods: Subjects who reached at least 8% of weight loss after a hypocaloric diet were randomized in 4 weight stabilization diets differing in protein content and glycemic index for 6 months. Subcutaneous AT biopsies were taken at the beginning (CID2) and the end (CID3) of the weight maintenance phase. Pangenomic cDNA microarrays were used to determine adipose tissue gene expression profiles at CID2 and CID3 of 6 subjects per diet succeeding in weight maintenance and 6 subjects regaining weight.
Results: Analysis of gene expression changes between CID2 and CID3 (CID3/CID2), showed 1818 genes that were differentially expressed between successful and unsuccessful subjects and 391 genes that were modulated by diet composition. Fatty acid metabolism, immunity and defense, apoptosis and cell proliferation were the main functions of genes discriminating between successful and unsuccessful groups. Diet-sensitive genes were mainly modulated by protein dietary content rather than glycemic index. High protein diets up-regulated genes from metallothionein family while low protein diets up-regulated ubiquinone gene family.
Conclusion: The capacity to maintain weight and the macronutrient composition of the diets are reflected in specific patterns of AT gene expression.

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T4:OS2.3

Gender specific differences in the consequences of elevated circulating asymmetric dimethylarginine

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Introduction: Plasma levels of asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, are raised in conditions associated with increased risk of cardiovascular disease including obesity. ADMA is primarily catabolised by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). We hypothesised that DDAH dysfunction would exacerbate obesity-associated changes in nitric oxide-mediated insulin resistance, energy expenditure and adipose tissue accumulation.
Methods: We used male and female DDAH1$^{+/-}$ mice to investigate the effect of standard diet and high-fat feeding on body mass, percentage body fat, food intake, daily energy expenditure (DEE), glucose tolerance, serum and explant adipokines. Mice were maintained on standard or high fat diet (10% or 45% kcal from fat respectively), from 8 months of age, for 15 weeks.
Results: Male DDAH1$^{+/-}$ mice had increased body fat, elevated serum glucose 2h post oral glucose challenge and lower adipose release of adiponectin compared to wild-types on high fat diet. In contrast, in female DDAH1$^{+/-}$ mice DEE was elevated and despite being hyperphagic, they showed no significant increase in body fat with age or in response to high fat diet. These mice were significantly less glucose intolerant, had decreased serum and adipose release of leptin, as well as higher adiponectin release compared to wild-type females.
Conclusion: DDAH1$^{+/-}$ mice exhibit marked gender differences in response to high-fat feeding. Female mice were protected from both age- and diet-associated fat accumulation, which may be partially explained by elevated DEE, and were less glucose intolerant. The mechanisms by which this occurs, and an equivalent human phenotype, are under investigation.

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T4:OS2.4

Effects of diet and exercise on circulating levels and adipose tissue mRNA levels of Retinol Binding Protein 4 in obese subjects

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Background: Retinol-binding protein 4 (RBP4), a protein secreted by adipocytes, has recently been associated with insulin resistance, and may have a causative role in the development of type 2 diabetes. In this study we examined the effect of diet, exercise, or a combination of both on circulating levels of RBP4 and expression levels of RBP4 in subcutaneous adipose tissue (SAT).
Methods: 61 obese but otherwise healthy males (n=30) and females (n=31) (age:36.5±7.2 yrs.; BMI:34.5±3.9 kg/m2) were randomized into three groups a) Exercise-only (12 weeks), b) Diet-only (8 weeks VLED 600 + 4 weeks weight maintenance) and c) Diet+exercise. Blood samples and biopsies from SAT were collected at baseline, after week 8 and week 12. S-RBP4 was quantified using a commercial ELISA kit, and expression levels were quantified using rt-PCR.
Results: After the 12-week-intervention the weight loss was 3.6 kg in the exercise-only-group and ≈ 12 kg in the diet-only-group and diet+exercise-group. S-RBP4 was significantly reduced to approximately 75%($p<0.001$) in both diet-groups at week 8, and remained significantly reduced throughout the study. SAT expression levels of RBP4 was significantly reduced after week 8 in the diet-only-group (≈-45%, $p<0.05$) and in the diet+exercise-group (≈-32%, $p<0.05$). However, expression levels increased during the weight maintenance period, and were unchanged after 12 weeks compared to baseline. Exercise without diet, did not change s-RBP4 levels or expression levels in this study.
Conclusion: Diet alone or in combination with exercise reduces s-RBP4 and RBP4 mRNA in subcutaneous adipose tissue, whereas exercise alone does not change RBP4 levels.

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T4:OS2.5

Intestinal STC-1 cell satiety hormones release is controlled by the five basic tastants

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Introduction: The small intestine plays an import role in food intake. Recent data have shown that the small intestine expresses taste receptors. In this study, the effects of the five basic tastants on the release of satiety hormones cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1) were investigated in a dose- and time dependent manner.
Methods: STC-1 cells were incubated with different concentrations of the bitter (denatonium benzoate, quinine), sour (HCl, HAc), sweet (sucrose, sucralose, erythitol), salty (NaCl), and umami (monosodium glutamate) tastants, respectively. After incubation with different concentrations and after different time periods, respectively, the supernatant was collected and the CCK and GLP-1 concentrations were measured using RIA.
Results: All tastants increased the release of CCK both in a dose and time dependent fashion, ranging from 7pM to 68pM with the highest concentration. GLP-1 release increased after addition of all tastants in a dose dependent fashion, ranging from 0.5pM to 600pM with the highest concentration, with the exception of HAc. GLP-1 was released in a time dependent manner after addition of sweet, salty, sour, and umami tastants, but bitter tastants stimulated GLP-1 release only during the

first 15 minutes of exposure. After this period the release of GLP-1 decreased.
Conclusion: Tastants control the release of satiety hormones to approximately the same extent as dietary proteins. Its use as dietary ingredients in the prevention or treatment of obesity, possibly in combination with a weight reduction programme needs, however, to be established in future research.

T4:OS2.6

The increased sensitivity to the deleterious effects of high fat diet in old rats is related to an increase in muscle ceramide levels during aging.

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Introduction: Obesity and aging are characterized by an increase in insulin-resistance state. Ceramides have been implied in insulin-resistance during obesity. The aim of this study was to measure the synergistic effect of obesity and aging on tissue ceramide level, and its consequence on insulin sensitivity and muscle protein synthesis.
Methods: During 10 weeks, 34 Wistar young and old rats received a control (YC, OC) or a high fat diet (YHF, OHF). Insulin sensibility was measured by intra peritoneal glucose tolerance test. Ceramide levels were measured in the *tibialis anterior* and *soleus* muscle. Fractional synthesis rate (FSR) was estimated by the rate of incorporation of ^{13}C-Valine in muscle proteins.
Results: OHF was the most insulin resistant group ($p \leq 0.05$ *vs*. YC, YHF and OC). Ceramide concentrations are given in table 1. FSR was decreased by 19% in OHF ($p \leq 0.05$) compared to OC. No modification of muscle FSR related to diet was seen in the younger groups.

Table 1: Ceramide concentration (nmol/mg) in tibialis anterior and soleus muscles

	YC	YHF	OC	OHF	Anova
soleus	0.213 ± 0.040^{a}	0.272 ± 0.063^{a}	0.378 ± 0.136^{a}	1.048 ± 0.416^{b}	A
tibialis anterior	0.605 ± 0.177^{a}	0.465 ± 0.047^{a}	$0.932 \pm 0.110^{a,b}$	1.145 ± 0.416^{b}	A

A: age effect

Conclusion: Muscle ceramide concentration is increased in aged rat, even under a control diet. This observation may explain the greater sensitivity of aged rats to the HF diet, notably concerning insulin action and muscle protein synthesis.

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Track 5: Weight and Risk Management – Clinical/ Lifestyle/Weight Loss
T5:OS1 – Dietary management and lifestyle

T5:OS1.1

Effect of a hypo-caloric diet rich in whole grain foods on weight loss, body composition and cardiovascular risk in postmenopausal women: A 12 weeks randomised clinical trial.

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Introduction: In observational studies, a high intake of whole grain foods is associated with a lower body mass index and lower cardiovascular disease risk. However, only few clinical trials have investigated if these associations are causal.
Objective: We studied whether inclusion of wheat based whole grain foods in an individualized hypo-caloric diet enhances weight loss and improves CVD risk factors.
Design: In this open-labelled randomised trial, 79 overweight postmenopausal women with metabolic syndrome features were prescribed a hypocaloric diet with a daily deficit of min. 1,250kJ/d. After a 2 weeks run-in period the subjects were randomly assigned to 12 weeks supplementation with refined wheat (RW) or wholemeal wheat (WW) products corresponding to 25% of their daily energy requirement or 2000 kJ/d. Blood samples and anthropometric measures were assessed at 0, 6 and 12 weeks.
Results: After 12 weeks, body weight decreased significantly in the RW and WW groups ($P<0.01$) (-2.8±0.3 and -3.6±0.5kg in the RW and WW group, respectively), but did not differ between the groups. Changes in body fat percentage assessed by DXA scanning was larger in WW group compared to the RW group (-6.8% vs.-4.8%) ($P=0.03$). Total- and LDL-cholesterol increased by 5% in the refined group but remained unchanged in the whole grain group ($P<0.05$), but insulin, glucose, and C-reactive protein levels did not change in either group.
Conclusions: Both hypo-caloric diets were effective in inducing weight loss, but whole grain foods were more effective to reduce body fat and LDL-cholesterol, two important risk factors of cardiovascular disease.

Conflict of interest: None disclosed/The authors declare no conflict of interest. *Funding:* The study was supported by the European Commission in the Communities 6th Framework Programme, Project HELATHGRAIN (FOOD-CT-2005-514008), University of Copenhagen, Faculty of Life Sciences and LMC FOOD research school.

T5:OS1.2

Long term effects of weight loss from a very-low-carbohydrate diet on endothelial function in subjects with abdominal obesity.

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Background: Although low carbohydrate diets are commonly used the long term effects on endothelial function are unknown.
Objective: To compare the effects of an energy reduced very low carbohydrate, high saturated fat diet (LC) and an isocaloric conventional high carbohydrate, low fat diet (HC) on lipids and endothelial function after 12 months.
Design: 49 overweight and obese patients (age 50.0±7.7 yrs, body mass index 33.7±4.1 kg/m^2) were randomly assigned to either an energy restricted (~6-7MJ, 30% energy deficit), isocaloric LC or HC for 52 weeks.
Outcomes: Weight loss was similar in both groups (LC -14.9±10.5, HC -11.5±7.4 kg; P=0.20). There was a significant time x diet effect for FMD (P= 0.045), such that FMD decreased in LC diet (5.7±3.6% to 3.7±2.7%, P=0.001) but remained unchanged in the HC diet (HC 5.9±2.5% to 5.5±3.5%; P=0.60). PWV improved in both groups but AIx did not change. LDL cholesterol increased by 0.6 mmol/L in the LC group (19%) and did not change in the HC group. Despite a fall of triglyceride in the LC group of 0.58 mmol/L,apoB increased by 3% in the LC group and fell by 6% in the HC group. HDL cholesterol increased by 21% in the LC group and 5% in the HC group.
Conclusion: Both diets achieved similar reductions in body weight and were associated with improvements in PWV. However, LC impaired FMD, suggesting the long-term consumption of LC may have detrimental effects on cardiovascular risk and this is related to higher LDL cholesterol.

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T5:OS1.3

Relation of Fatty Acid Composition of Adipose Tissue to Weight Change in Obese Subjects after 6 Month Controlled Weight Maintenance Diets. DIOGENES Study.

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Introduction: Aim of this study was to evaluate the relationship of weight maintenance after low calorie diet (LCD) with fatty acid composition in adipose tissue in subjects undergoing weight maintenance diets with strictly controlled proportion of protein and glycemic index of food obtained in special supermarkets.
Methods: 87 adult subjects (weight 98.6±15.6kg, BMI 33.8± 4.1kg/m^2, age 44.0±5,4 yr) after 8 week LCD period followed for 6 months strictly controlled weight maintenance diets. Anthropometric parameters were examined and adipose tissue biopsy was obtained before start of LCD, after LCD and after 6 months of weight maintenance.
Results: The mean total weight loss was 9.4±5.7kg and BMI loss 3.2±1.83. During the weight maintenance period the mean weight gain was +1.1±4,1kg, BMI change was +0.4±1.4. Significant correlation was found between body weight or BMI change and change in proportion of saturated (SFA), monounsaturated (MFA), trans fatty acids and n-6 and n-3 polyunsaturated fatty acids (R squared 28,51, P=0.001). Significant positive correlation of change of BMI with change in SFA proportion (P<0.05) and significant negative correlation of weight and BMI change with change in MFA proportion (P <0.005) was found.
Conclusion: The results suggest that the effect of the six month-weight maintenance diet are influenced by change in fatty acid composition of adipose tissue; this change can be result of dietary fat composition and of individual metabolic processing.

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T5:OS1.4

Good long-term results with the "Södertälje model" treating obese children at a general outpatient paediatric single-centre according to the Stockholm County Council action plan against childhood obesity.

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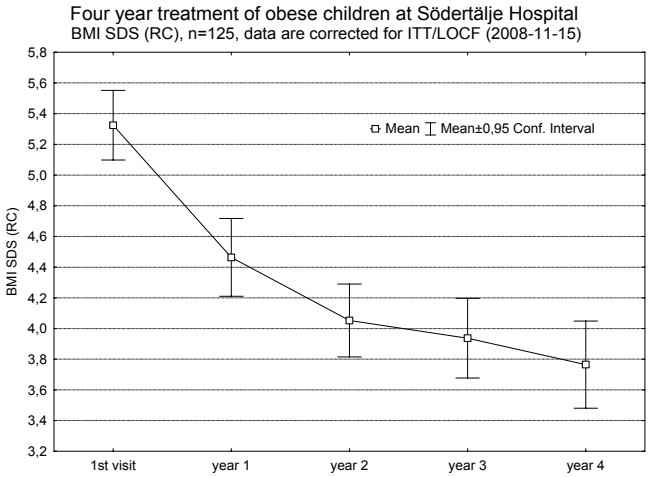
Introduction: The Stockholm County Council action plan (2004) against obesity is based on activities at different health-care levels. 1st line is primary health-care in child-care centres and schools, 2nd line is community based general paediatricians and 3rd line the paediatric hospitals. The paediatric unit at Södertälje Hospital is a community based general outpatient paediatric unit. Since 2002 obese children (ISO BMI >30, Cole et al 2000) 6-12 years, have been offered a structured treatment based on lifestyle interventions (e.g. physical activity, nutrition and behaviour modifications).
Methods: Data on all children included since 2001 has been collected and reported to the Swedish national quality register for childhood obesity (BORIS). All patients included up to 2004 (n=125) were included in the analysis.
Results: In the group treated for > 4 years there are 67 boys and 58 girls with a mean age at 1st visit of 9.8 years (5,8-14,6). 29 children (23%) are considered lost to follow up (19 have quit the treatment, 8 moved away and 2 have passed age limit 18). All are included as ITT/LOCF. There is a decline in mean BMI-SDS from 5.3 ±1.3 at the first visit to 3.8 ±1.6 after four years (Figure). There is no significant difference comparing for boys and girls.
Conclusion: This is the first long-term results from a general paediatric outpatient clinic with a treatment program for childhood obesity based on Stockholm County Council action plan. These encouraging results with an overall reduction of obesity are very good but needs to be followed up by further analyses and comparisons with other treatment groups and untreated controls.

Figure:



Conflict of Interest: None disclosed. *Funding:* Research relating to this abstract was funded by Swedish Association of Local Authorities and Regions / The National Board of Health and Welfare.

T5:OS1.5

The effects of Sugar-Sweetened Beverages (SSB) intake in an ad libitum 6 months low-fat high carbohydrate diet on energy intake.

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Introduction: The increased incidence of obesity coincides with an increased SSB's consumption. The present study investigated the effects of SSB's intake in an ad libitum 6 months low-fat high carbohydrate diet on energy intake in a reanalysis of the CARMEN data*.
Methods: 47 overweight-to-obese men and women participated in the Maastricht centre of the CARMEN study**.** They were allocated to a Control (habitual) Diet group (CD), a low-fat (-10 En%) high Simple Carbohydrate (SCHO) or low-fat high Complex Carbohydrate group (CCHO) (Ratio Simple vs. Complex CHO 1.5 and 0.5 resp.) using a controlled laboratory shop system. Reanalyses were made for the energy, amount, density of all drinks and SSB's. The SCHO and CD group could select regular SSB's, including soft drinks and fruit juices, while the CCHO group received light SSB alternatives.
Results: Energy intake reduced in the CCHO and SCHO group versus the CD group (-2.7±0.4 MJ/d CCHO group vs -0.2±0.5 MJ/d CD group; p<0.01 and -1.4±0.4 MJ/d SCHO group, NS). Simple carbohydrate intake increased significantly with +10.8±1.6 En% in the SCHO group versus the CCHO and CD group (-2.0±0.9 and -0.5±1.1 En%; p<0.001). The

SCHO and CD group significantly increased energy intake of SSB's with +187±114 and +101±83 kJ/d versus the CCHO group (-432±72 kJ/d; p<0.001).
Conclusion : Simple carbohydrate intake (En%) increased through enhanced intake of regular SSB's in the SCHO group. However fat reduction in an ad-lib situation has a much greater impact on total energy intake than a change in SSB intake using light alternatives.
* Saris et al Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs. complex carbohydrates on body weight and blood lipids: the CARMEN study. Int. J. Obes. 2000; 24: 1310 - 1318

Funding: EU-FAIR program PL95-0809 and the Dutch Sugar Foundation.

T5:OS1.6

Cost Effectiveness of a Family Practice Based Weight Management intervention: The Counterweight Programme

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Background: The Counterweight programme is an effective weight management programme delivered within UK family practice[1]. We have examined the cost effectiveness of the programme, to determine 'value for money' within a national healthcare system.
Method: We used an adapted simulation model, originally developed to provide input to the UK National Institute for Health and Clinical Excellence (NICE) guideline on obesity, using data on the cost of delivery of Counterweight and observed 12 month weight change outcomes from the pilot phase of the programme. Outcome data for completers (n= 642) and the intention to treat population is included (n= 1419).
Results: Total cost of delivery of Counterweight is estimated at approximately £60 per patient and includes all costs for the Counterweight project team, training costs, materials, all clinician time required to deliver the programme and cost of additional interventions such as pharmacotherpay. Analysis of data from programme completers (n= 642) shows that the programme results in cost savings over a patient life time when compared with no intervention (i.e. economically dominant). Sensitivity analyses suggests that in a scenario where12m weight loss is immediately regained, cost per QALY is estimated to be £57 (2% of the cost/QALY threshold NICE uses to 'approve' treatments). Intention to treat analysis (n=1419) suggests a cost per QALY of £180 where weight loss is regained in the subsequent 2 years.
Conclusion: The findings suggest that the Counterweight Programme is a cost effective intervention to manage obesity.

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1. Counterweight Project Team. Evaluation of the Counterweight Programme for obesity management in primary care: a starting point for continuous improvement. 2008; **58:** 548-554.

T5:OS2 – Obesity management

T5:OS2.1

Laparoscopic adjustable gastric banding in morbid obese patients with type 2 diabetes.

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Introduction. Interest in bariatric surgery as an effective method for long-term metabolic control of morbid obese patients with type 2 diabetes is increasing. We analyzed weight loss and changes in use of anti-diabetes medications in obese patients treated with laparoscopic adjustable gastric banding (LAGB).
Methods. Between 1993 and 2005, 1791 morbid obese patients underwent LAGB at our Institution. 394/1791 (22.0%) patients had type 2 diabetes at baseline and 52/394 were treated with anti-diabetes medications. Mean follow-up in drug-treated diabetic patients were 3.3±2.0 years (range: 0.25-9 years).
Results. Drug-treated diabetic patients were older (age: 47.6±7.5 vs 37.5±10.7 years, P<0.001), heavier (BMI: 49.1±9.5 vs 45.6±7.5 kg/m^2, P<0.001) and more frequently affected by comorbidities than non-diabetic patients at surgery. Percent of excess weight loss (%EWL) 1 years after surgery was lower (32.4±14.1 vs 41.1±19.9%, P<0.01) in drug-treated diabetic patients than in non-diabetic patients and this difference was maintained over 5 years of follow-up. Both the use of oral anti-diabetic medications and insulin significantly declined after surgery (patients treated with oral anti-diabetic drugs: 52/52 at baseline and 32/52 at the end of follow-up; patients treated with insulin: 6/52 and 2/52). The use of anti-diabetic medications at the end of follow-up was increased in 2/52 (3.8%) patients, unchanged in 9/52 (17.3%), reduced in 16/52 (30.8%), and suspended in 25/52 (48.1%).
Conclusion. Weight loss after LAGB was lower in drug-treated diabetic patients than in non-diabetic patients. However, weight loss was associated to a sustained reduction in the use of anti-diabetic medications in 78.9% of patients.

Conflict of interest: Busetto L declared payments received from Allergan as a conference speaker. *Funding:* No funding relating to this abstract.

T5:OS2.2

Functional impairment of the pancreatic polypeptide receptor (NPY4R) through naturally occuring point mutations: Implications for obesity susceptibility and the use of pancreatic polypeptide as an anti-obesity drug

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Introduction: Gut hormones play a pivotal role in the regulation of food intake in humans. Both PYY and PP were shown to be potent inhibitors of food-intake. These hormones signal through related receptors belonging to the NPY receptor family, specifically NPY4R for PP. However, little is known about the genetics of NPY4R, despite the fact that PP has stirred considerable interest as a potential anti-obesity agent.
Methods: Following positive linkage results at the NPY4R locus, the gene was screened by direct sequencing. We identified several non-synonymous mutations in the receptor. Association analysis was performed between mutations and BMI. Functional studies of the mutations investigated binding affinity and intracellular signaling of wild type and mutant receptor transiently cloned into COS-7 cells.
Results: Mutations showed preferential segregation with obesity (p= 0.004). Binding affinity was decreased in mutatnt receptors. Maximum decrease was observed for mutant R240C, (Ki wild type= 2.31 ± 0.04 nM vs Ki R240C= 19.0±6.59 or 8-fold increase).
All allelic variants of the NPY4R were tested with regard to IP turnover stimulation. A 2-3 fold decreased potency for PP was observed for several mutations (R240C, R239W, R239Q L287P). A similar 2-3 fold decrease in potency was observed for NPY and PYY.
Conclusion: The observed association and reduction in receptor function is in agreement with decreased PP signaling leading to increased food-

intake thus participating to obesity. Moreover, it is anticipated that the reduction in binding and signaling has implications for the efficacy of the use of PP as an anti-obesity agent.

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T5:OS2.3

Does metabolically normal obesity exist?

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Introduction: Although obesity is recognized as a risk factor for cardio-metabolic diseases, the existence of metabolically normal obesity has been claimed. The aim of our study was to investigate the cardio-metabolic characteristics of obese subjects with normal glucose and lipid metabolism parameters. In these subjects, insulin sensitivity and carotid intima-media thickness were evaluated.
Methods: We investigated a sub-group of the RISC (Relationship between Insulin Sensitivity and Cardiovascular Disease) participants with blood pressure (BP) <140/90 mmHg, fasting glucose <5.6mM, 2 hours OGTT glucose <11.0mM, total cholesterol <5.0mM, LDL-cholesterol <3.0mM and triglycerides <1.7mM. The study group was composed of 370 females and 171 males with a BMI ranging between 18 and 41 kg/m^2. Glucose uptake was assessed by the clamp technique, whereas carotid intima-media thickness (IMT) was echographycally evaluated.
Results: When compared to the lean counterpart, obese men and women showed significantly increased plasma insulin ($p<0.0001$) and triglycerides ($p<0.001$). Insulin sensitivity ($p<0.001$) and HDL-cholesterol ($p<0.001$) were significantly lower. Obese women also showed higher LDL-cholesterol ($p<0.01$), glycemia ($p<0.0001$) and systolic and diastolic BP ($p<0.0001$). In both sexes, no differences were observed in IMT, after adjustment for age, BP and lipidemia.
Even when matched for age and insulin sensitivity, obese females had higher systolic ($p<0.01$) and diastolic ($p<0.05$) BP as well as LDL-cholesterol ($p<0.01$), whereas obese males showed higher triglycerides ($p<0.0001$).
Conclusion: Although metabolically normal, obese people show a less favorable cardio-metabolic profile, suggesting that these subjects need a closer surveillance of the metabolic parameters associated to the risk of diabetes and CVD.

T5:OS2.4

Early effect of Roux-en-Y gastric bypass on insulin-resistance in morbidly obese diabetic subjects

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Weight loss after bariatric surgery improves insulin resistance (IR). Recent evidence has shown that biliopancreatic diversion, a predominantly malabsorptive procedure, restores peripheral insulin sensitivity early after surgery before important weight loss. Roux-en-Y gastric bypass (RYGB), a predominantly restrictive surgery, also has been associated with hormonal changes and improved IR – as estimated by HOMA – prior to substantial weight loss. However, there are no data regarding the early effect of RYGB on insulin sensitivity as measured by the gold standard method. The aim of this work was to evaluate, using the euglycemic hyperinsulinemic (240 pmol·m^{-2}·min^{-1}) clamp technique, the effect of RYGB on insulin sensitivity in diabetic subjects early after surgery before any effect of weight loss might occur.

We studied eleven (3male/8female) diabetic morbidly obese subjects (age 49±2 years, BMI=49±2 kg·m^{-2}) before and 18±1 days after RYGB. After surgery, body weight had decreased by 6.8±0.6% (131±9 *vs* 122±8 kg, p=0.003). At this time, fasting plasma levels of glucose (7.9±0.6 *vs* 6.8±0.4 mmol/l, p=0.01) and fasting plasma insulin levels (162±26 *vs* 92±13 pmol/l, p=0.003) were significantly reduced. However, on the clamp insulin sensitivity was only marginally increased (M value=23.0±4.2 *vs* 28.9±2.7µmol·min^{-1}·kg$_{FFM}^{-1}$, p=0.1)

We conclude that in morbidly obese diabetic subjects, undergoing RYGB both plasma insulin and plasma glucose are reduced prior to substantial weight loss, with only minor change in peripheral insulin sensitivity.

T5:OS2.5

Eating Behaviour and Adjustment Post Weight Loss Surgery: A Patient Perspective

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Introduction: The results of weight loss surgery are not equal for all. The present qualitative study explored patients' 'real lived' accounts of their eating behaviours following restrictive weight loss surgery (WLS), and any psychological consequences that impacted on their ability to adjust to new eating styles. The research was patient-led by a researcher with personal experience of WLS.
Methods: Computer Mediated Communication was used throughout. Stage 1 adopted a descriptive phenomenological approach examining the nature and voracity of reported post-surgical eating behaviours and related psychological constructs. Documentary analysis was undertaken of over 300 messages posted asynchronously to topic specific forums on a WLS support website retrospectively over six months. Stage 2 adopted an Interpretive Phenomenological Approach (IPA) gaining a deeper understanding of behaviours/constructs observed, considering contextual features that might have a direct bearing on their nature and existence. Online semi-structured text-based synchronous interviews were undertaken with 12 women and 4 men.
Results: Patients described post-surgical eating behaviours e.g. grazing, craving and perceived binging emerging over time with their ability to cope being dependent on their ability to deal with stress/emotional or situational triggers and hunger. Feelings of a lack of control and the return of maladaptive pre-surgical eating patterns and behaviours were a central theme throughout, regardless of type of restrictive surgery.
Conclusion: The findings suggest the need for improved interventions including access to psychological therapies to help patients adopt adaptive eating styles post-surgery. Assessment of eating behaviour pre and post-surgery is pivotal to identifying those who need support.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

T5:OS2.6

Associations between physical activity level, cardiorespiratory fitness and cardiovascular diseases risk factors among obese children and their mother

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Introduction: The aim of this study is to compare physical activity level, cardiorespiratory fitness and cardiovascular diseases (CVD) risk factors among obese children and their mother, and to evaluate child-mother relationships.
Methods: This is a prospective study including 90 pre-pubertal obese children and their mother assessed at baseline before to participate in a family-based behavioral intervention. Measures: 7- day physical activity count (accelerometer Actigraph); cardiorespiratory fitness (VO_2max) by

a maximal treadmill test in children and a Chester Step Test in mothers; BMI; waist circumference; waist-to-height ratio, body fat by DXA; resting blood pressure (BP); fasting blood lipids, glucose, insulin, HOMA-IR and high-sensitive C-reactive protein (hs-CRP) levels.
Results: Our preliminary data included 14 obese children (female 57%, 9.6±1.1 year), 5 mothers with BMI>25 and 2 with BMI> 30 (39.1±5.1 year). Physical activity level (111.2±12.3 vs 115.6±17 cpm), BMI (24.5±2.5 vs 25.6±3.9), body fat (42.6±5.6 vs 44.8±3.8%), systolic BP (111.1±11.7 vs 117.3±15.6 mmHg), blood lipids, glucose and hs-CRP levels were similar between obese children and their mother. The mothers spent more time in moderate-to-vigorous intensities, but their VO_2max was lower (31.5±6.0 vs 37.5±6.4 $ml.kg^{-1}.min^{-1}$). Waist-to-height ratio, insulin and HOMA-IR were higher in children than mothers. Child-mother relationships were significant for physical activity count and intensity (r=0.65-0.74, P<.05), diastolic BP (r=0.66, p=.02), waist-to-height ratio (r=0.64, p=.01), HDL-cholesterol (r=0.65, p=.02) but not VO_2max.
Conclusion: We showed that physical activity, central adiposity, blood pressure and lipids are closely related among obese children and their mother. Therapeutic interventions focusing on mother's lifestyle changes might be promising.

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Surgery Sessions

SS:OS1 Surgical treatment of obesity and Type 2 diabetes

SS:OS1.1

Long-term Effects of Bariatric Surgery on type 2 DM and overall mortality; results from the SOS study.

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Background: Several studies have demonstrated that bariatric surgery improves recovery from diabetes but controlled, prospective long-term interventions on diabetes incidence and mortality have been lacking.
Methods: SOS involved 2010 obese subjects treated with bariatric surgery and 2037 contemporaneously matched obese controls obtaining conventional treatment. Follow up is currently ranging from 6 to 20 years. At the date of mortality analysis the follow up rate was 99.9 percent.
Results: After 2 years follow up, recovery from diabetes at baseline was 21% in the control group and 72% in the surgery group (OR=8.42, 95% CI 5.7 to 12.5, p<=.001). After 10 years the corresponding figures were 13 and 36% (OR=3.45, CI 1.7 to 7.3, P<0.001). The diabetes incidence rate after 10 years was 24% in the control group and 7% in the surgery group (OR=0.25, CI 0.17 to 0.38, p<0.001). Glucose and insulin were markedly more reduced in gastric bypass than in banding and VBG patients. However, at similar weight loss the three techniques gave similar metabolic improvements. Bariatric surgery reduced mortality with 29% (HR= 0.71, CI0.54-0.92, p=0.01). The relative mortality reduction after surgery was not significantly larger in diabetics than in non-diabetics (p=0.50) and not more pronounced after gastric bypass than after VBG and banding.
Conclusions: Bariatric surgery is worthwhile both in diabetic and non-diabetic subjects and banding may have the lowest long-term mortality.

SS:OS1.2

Short and long term effects of adjustable gastric banding on type 2 DM

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Background: A large number of studies has demonstrated that bariatric surgery has a beneficial effect on obesity related comorbidities, such as T2DM, metabolic syndrome, hypertension, sleep apnea, and others. This is often considered as a secondary effect of bariatric surgery and induced weight loss. However there is an evidence that the mode of action of bariatric surgery might be directly connected to the metabolic changes triggered by the surgery itself, in addition to a secondary consequence of the weight loss.
Methods: 409 patients (291 undergoing Adjustable Gastric Banding (AGB), 118 undergoing another, laparoscopic upper-GI elective procedure) were evaluated. Out of which T2DM 110 (37.8%) in the bariatric, and 10 (8.5%) in control group have been investigated repeatedly within 48 hours after the operation, 1 week, 6-8 weeks, and at 6 months after.
Results: The fasting plasma glucose decreased significantly within 24 hours of operation. However, this trend has been maintained even when ingestion of food has been initiated.
The follow-up showed beneficial effect of AGB on glycaemic control, leading to a normalisation in oGTT in > 50% of subjects.
Remission of T2DM (defined by fasting glucose level < 126 mg/dL [7.0 mmol/L] and glycated hemoglobin [HbA1c] value < 6.2%) while taking no glycemic therapy was achieved in 73% in the bariatric surgery group.
Discussion: There may be differences in the degree of effectiveness achieved by the different methods of bariatric surgery. It has been proposed that different methods of surgery may act through different pathways, but all types of bariatric surgery have been shown to be significantly effective in T2DM treatment.

SS:OS1.4

Preliminary results of biliopancreatic diversion in bmi 25-35 patients with type 2 DM

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Background: BPD is known to have specific actions which cause very long term resolution of type 2 diabetes in near totality of morbidly obese patients. Since these actions are independent of weight changes, the operation should work as well in diabetic patients with BMI <35.
Methods: 27 T2DM patients with BMI <35 were submitted to BPD. There were 18 males, mean age 57 (44-69) yrs, BMI 30.9 (25.3-34.9) kg/m2, diabetes duration 13 (3-28) yrs. All patients were on antidiabetic drugs, and 9 on insulin. All have reached the one, four, eight, and 12 the twelve month follow-up.
Results: There was one postoperative bleeding and no late complications. All patients were on totally free diet after operation. A few patients required hypoglycemic treatment during the first postoperative month, and 3 of them still needed it until the twelfth month. Mean fasting serum glucose (FSG) dropped from preoperative 221 (129-361) mg/dl to 144 (83-302) at 12 months, and mean glycosilated hemoglobin (HbA1c) fell from preoperative 9.6 (7.5-13.5)% to 6.6 (4.7-9.6) at twelve months. When the 15 patients with initial BMI >30 were considered separately from the 12 with BMI <30, the first group showed significantly lower FSG and HbA1c mean values at 4, 8 and 12 months. Mean BMI was 27.1 (22.9-32-4) at one, 25.9 (22.9-30.4) at four, 25.5 (22.1-30.8) at eight, and 25.3 (22.1-30.8) at twelve months.
Conclusion: BPD resolves type 2 diabetes in patients with BMI <35 kg/m2, without causing any excessive weight loss. Patients with BMI <30 appear more difficult to treat, and need further evaluation.

SS:OS1.5

Novell minimal and non invasive techniques and their effect on type 2 DM (Endobarrier)

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The potential of bariatric procedures to improve and even cure type 2 diabetes has been recognized many years ago. In particular bypass procedures have an almost instant effect on insulin sensitivity and control of blood glucose levels. Experimental models in rodents has shown that the duodenum plays a crucial part in this effect. A novel device the Endobarrier™ Liner is a 60 cm sleeve that is placed in the duodenum and kept in place by a retinol anchor. It results in a bypass of the duodenum preventing contact of nutrients with the duodenal wall and in part mimics a gastric bypass procedure. Worldwide a number of studies have been performed with the device.

In Chili a randomized study was performed with the completely endoscopic duodenal-jejunal bypass sleeve (Endobarrier Liner) to specifically treat T2DM. Methods: In a single blind ongoing 52 week study, 18 T2DM patients were prospectively randomized to receive either the DJBS (n=12) or a sham endoscopy (n=6). Both groups were maintained on their baseline caloric intake for the first two weeks and were equally counseled about low calorie diet at each subsequent visit. The primary endpoint was reduction of HbA1c from baseline at 12, 24 and 52 weeks. Select secondary endpoints include safety, fasting plasma glucose (FPG), 7 point glucose profile, total body weight loss (TBWL) and change in the area under the curve after meal tolerance testing (MTT AUC) as compared to baseline. Results: One week data was analyzed for all patients. At week 1, the mean change in MTT AUC was -18.6% and +10.1% in device and sham groups respectively (p=0.05), FPG was -51.6 + 43.5mg/dl and +16.5 + 77.7mg/dl (p=0.17), and the aggregate reduction in 7 point glucose profile was -54.8 + 54.5mg/dl and +1.1 + 45.7mg/dl (p<0.05). TBWL between groups was similar with -4.5 + 1.3kg and -3.9 + 1.3kg for device and sham respectively (p>0.05).

Similar results were found in a study in the Netherlands. In this study the safety and efficacy of the Endobarrier Liner was tested in a randomized fashion. In this study 8 individuals with type 2 DM were included with similar effects on the DM.

Conclusions: These results highlight the ability of bypassing the duodenum to rapidly restore glycemic control independent of weight loss or diet. The durability of glycemic control with the Endobarrier Liner requires further study, which is ongoing at this time.

SS:OS1.6

Nutritional status in super-obese patients after gastric bypass and duodenal switch: a randomised study

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Background: Bariatric surgery is widely performed to induce weight loss. We examined changes in nutritional status after two bariatric surgical procedures.

Methods: Randomised controlled trial conducted in two Scandinavian university hospitals. Participants were 60 super-obese patients (BMI 50 to 60 kg/m^2) from public healthcare treatment programmes. Surgical interventions were laparoscopic long-limb Roux-en-Y gastric bypass (alimentary limb 150 cm) or laparoscopic biliopancreatic diversion with duodenal switch (alimentary limb 200 cm, common channel 100 cm). All patients received standardised daily supplementation with multivitamins, iron, calcium, and vitamin D; gastric bypass patients received additional vitamin B-12 supplements. Patients were examined before surgery and 6 weeks, 6 months, and 1 year after surgery. Self-reported use of multivitamin supplements was 10% before surgery and on average 92% at postoperative visits.

Results: BMI loss 1 year after gastric bypass and duodenal switch was mean 16.3 (SD 4.3) kg/m^2 and 22.8 (4.7) kg/m^2, respectively ($P < 0.001$). Duodenal switch patients had significantly lower mean concentrations of vitamin A and 25-hydroxyvitamin D, significantly higher rates of anemia and hypocholesterolemia, and tended to have higher rates of hypoalbuminemia postoperatively compared with gastric bypass patients. Following both procedures, mean concentrations of vitamin B-1 decreased significantly, whereas mean concentrations of other water soluble vitamins (B-2, B-6, B-12, C, folate) were either similar to or significantly higher than baseline values.

Conclusion: Duodenal switch surgery was associated with greater weight loss and higher rates of nutritional deficiencies as compared with gastric bypass surgery in super-obese patients during 1 year follow-up. ClinicalTrials.gov identifier: NCT00327912

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SS:OS1.7

Food cravings post weight-loss surgery: A quasi-prospective study

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Introduction: Although weight-loss surgery is broadly effective in reducing weight and improving health outcomes, up to a quarter of patients experience post-surgical disordered eating of various types and degrees. The present study investigated the incidence and characteristics of food craving experiences after gastric bypass (RnY) and gastric banding, and by time post-surgery.

Methods: Participants were 21 women: mean age=43 yrs, pre-surgical BMI=48.4 kg/m^2. Of these, 13 had RnY bypass and 8 gastric banding, and 10 were within one year of surgery. Each completed a food craving record (Hill & Heaton-Brown, 1994) after every food craving and a daily mood assessment over a 7-day period.

Results: Savoury foods were the most commonly craved (53% of craving events) followed by chocolate (24%). Patients more than a year post-surgery (PS) had marginally more cravings than those less than a year PS (5.27 vs. 2.90, p<.07). Craving characteristics such as target food, craving strength, resistibility, disappearance, pre-craving mood and subsequent eating did not differ by time PS or surgery type. However, daily ratings showed the RnY group were significantly more hungry, tense, irritable and emotionally vulnerable on days they had food cravings than the gastric band patients.

Conclusion: Craving frequency was higher than observed in previous studies of dieters and non-dieters and directed at different foods. PS time differences in frequency, and surgery-type differences in links with hunger and negative mood, indicate the value of further research into cravings and the routine clinical assessment of eating behaviour pre- and for an extended period post-surgery.

Conflict of Interest: None disclosed. *Funding:* No funding.

European Association for the Study of Obesity

EASO Childhood Obesity Task Force (COTF) Workshop
Integrated prevention and management of childhood obesity

Sustainable prevention and management of overweight and obesity in children: crossing traditional boundaries

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One of the objectives of the Dutch Ministry of Health, Welfare and Sports is to reduce the prevalence of overweight, obesity and related chronic diseases in The Netherlands. Development of programs for improving the prevention and management of overweight and obesity can contribute to this objective. For this purpose, a comprehensive system needs to be developed based on the principles of chronic disease management. In order to facilitate the development and implementation of such a system, the Ministry initiated the formation of the Partnership Overweight Netherlands (PON). in 2008. The partners of the PON are 17 organizations of health care providers, health insurance companies and patient organizations. The chronic disease management model for overweight and obesity involves strategies for diagnosis and early detection of high risk individuals as well as appropriate integrated lifestyle interventions for those who are overweight and obese and , when appropriate, additional medical therapies.

The PON works towards an integrated health care system that transgresses traditional boundaries of conventional health care systems and health care professions but, instead, focuses on competences of groups of health professionals who organize care from a patient oriented perspective.

The PON covers selective and targeted prevention in individuals. There is close collaboration with the Covenant Overweight in The Netherlands which deals primarily with universal and selective prevention in populations and groups. The boundaries between care, cure and prevention therefore also become less strict than is conventionally the case.

These national activities are linked to local demonstration projects. For instance, in the town of Zwolle there is a closely monitored and evaluated program of community intervention approaches of universal and selective prevention of overweight and obesity. These programs target schools, home environments and neighborhoods. In the same town there is a demonstration project of integrated prevention and management of overweight and obese individuals and those who are high at risk. In addition, the cost-effectiveness is studied for an inpatient intensive combined lifestyle treatment program for morbidly obese children and adolescents. Psychological determinants of treatment outcomes are part of the evaluation.

The PON collaborates with organizations responsible for prevention and management of other chronic noncommunicable diseases such as type 2 diabetes mellitus and cardiovascular disease and thus also transgresses the boundaries of chronic diseases specific health care systems.

Further information: www.partnerschapovergewicht.nl

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Management of Childhood Obesity – Lessons from a Business Case

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Introduction: Although health care professionals are aware of effective treatment regimes for obese children, the prevalence of obesity in childhood is still raising in The Netherlands. Apparently there is a mismatch between professional advice (offer) and the parental support for the necessary life style changes (need). Business companies perform marketing studies to determine need, before releasing their offer. According to principles of chronic disease management, we decided to use business models to make a better match between offer and need, potentially leading to a more successful treatment approach.

Hypothesis: Families with obese children, who are motivated for treatment, are capable to determine their needs for successful life style change.

Methods: All obese children are seen by a paediatrician to determine etiological and prognostic factors of obesity. The level of co morbidity is guiding for intensity of treatment. Once child and family are ready for treatment, a specialized nurse will discuss different options in the local obesity treatment network. Group sessions with parents help clarifying their specific needs. A personal (not-health care related) coach will help the family to implement theory into practice. All health care professionals download their standardized data in a central database for evaluation. Quality of life assessments are a leading tool for patient motivation.

Discussion: First pilot results will be presented. Business model approach might help adjusting a personalized health care offer to the patient needs. Personalized treatment may facilitate self-management and stimulate long-term compliance to treatment.

Conflict of Interest: None Disclosed. *Funding:* No Funding.

WHO Growth Chart and daily utility

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Introduction: During the eighties' it was acknowledged that the available growth curves did not match with the normal pattern of growth of breastfed infants. The WHA thus decided to start the Multicentre Growth Reference Study (MGRS) to assess the physiological growth pattern of children from birth to 5 years of age.

Methods: The standards have been built on a prescriptive approach in a sample of about 8500 children from four continents. The sample has been collected according strict rules to assure the highest level of homogeneity.

Only breastfed children from wealthy, educated, and willing to follow the protocol procedures families were included in the study. The children were divided in two groups: a longitudinal one from birth to 24 months and a cross-sectional one from 18 to 60 months. The anthropometric measurements were taken by local experts with a strong standardized

protocol. The statistical analysis of all the data was performed at WHO headquarters using specific and new programs. The growth curves were validated in 4 different countries, comparing the clinical evaluation of the children nutritional status performed by pediatricians and other professionals with the standards.

Results: In 2006 WHO released the new standards from birth to 5 years of age. The astonished result was that the growth pattern was similar in all the children participating to the MGRS, regardless the ethnicity. The validation confirmed the reliability of the standards.

Conclusion: The new WHO standards can be a useful and simple tool to correctly assess the nutritional status of children worldwide

Conflict of Interest: None Disclosed. *Funding:* Research relating to this abstract was funded by WHO.

Non alcoholic fatty liver disease in obese children/ adolescents

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Nonalcoholic fatty liver disease (NAFLD) is one of the most frequent liver disorders. It's dramatic rise is most probably directly related to the increased prevalence of obesity in preadolescence and adolescence.

The estimated prevalence of NAFLD in the general population ranges from 3-24%. There are estimations showing that about two thirds of obese adults and half of obese children may be affected with fatty liver. The diagnosis of that disorder is usually done by means of elevated AST or ALT and/or typical signs within ultrasonography. Fatty liver has been reported in the age of 27 months, pediatric NAFLD is not identical to NAFLD in adults.

Pediatric subjects affected with NALFD tend to have higher plasma TG, total and LDL-cholesterol and lower HDL-cholesterol concentrations. Most patients with NAFLD will develop impaired glucose tolerance, progression of liver fibrosis is associated with more pronounced IR and significant weight gain.The association between metabolic syndrome (MS) and NAFLD is well established in adults, however in children the definition of MS is not really acknowledged.

In regard to the "two hit" model it seems very likely that the excessive hepatocyte TG accumulation resulting from insulin resistance (1st hit) is followed by an inflammatory insult to the liver(2nd hit). In this regard it has been shown that serum adiponectin is reduced in children with elevated ALT, however proinflammatory cytokine levels are not elevated. On the other hand it has been shown that NASH is associated with mitochondrial structural defects. The hepatic glucose production is lowered, however the insulin mediated HGP is suppressed similar to that in type 2 diabetes patients.

NAFLD in obese children and adolescents is very common, however the etiology is not very well understood. Factors who are characteristic for the MS in the adult are oft present, the main etiologic factor being insulin resistance. Longterm observations of children with NAFLD which has been clearly characterized by histology will contribute to the better understanding of the disease.