Review Sessions by Track

TRACK 1

T1:RS1 – Psycho-Social and Cultural Aspects

T1:RS1.1

Obesity and political economics

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Obesity is a complex multifactorial problem that has emerged in affluent societies at different times at differing rates. Macro-level approaches to understanding obesity in such societies have only emerged recently. Among these, political economic explanations include the declining time cost and market price of food (especially of mass prepared foods), increasing social and economic inequality, subordination, stress and myopic bias. Our work attempts to unify some of these approaches. We test the proposition that market-liberal countries have an environment of greater insecurity, and that this is the source of stress that drives higher levels of obesity. The institutional structures that market-liberal societies put in place promote insecurity and inequality, while work-related insecurity, including low income, poor job mobility and absence of union protection, elevates the likelihood of stress and ill-health. Responses to stress include overeating and preferences for high energy-density foods, both of which are implicated in the causation of obesity. In an ecological regression meta-study in which 96 body-weight surveys from 11 countries between 1994 and 2004 are pooled, a composite of declining time cost and market price of food works most strongly in the production of obesity in market-liberal countries. However, economic insecurity is almost twice as powerful as these food effects, while the impact of inequality is weak. The association of insecurity and obesity has a bearing on policy norms, with the economic benefits of flexible and open markets promoted by market-liberalism being offset by costs to personal welfare and public health which are rarely taken into account.

T1:RS1.2

Understanding the relationship between obesity and educational achievement

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Multiple observational studies, conducted during recent several decades, have shown an inverse relationship between duration of education as a measure of educational achievement and prevalence of obesity. This relationship may be added to the long list of impairments of quality of life that come along with obesity, and it may as well be impeding the coping with the obesity problem. A fundamental question in understanding the relationship is whether low educational achievement promotes development of obesity and/or whether presence of obesity causes educational difficulties. If there is a bidirectional causal relationship it may induce a vicious cycle. Another possibility is that both phenomena originate from some common underlying neuro-psychological dysfunction, possibly reflecting transgenerational, genetic and/or environmental effects. The genetic background and the environment in a broad sense, ranging from societal structure through rearing conditions within the family, influence both educational achievement and obesity, and interactions between these influences are possible. The epidemiological evidence suggesting several of these types of relationships will be briefly summarised, and the major challenges in disentangling the mechanisms will be discussed.

T1:RS1.3

Tackling childhood obesity through the education system: opportunities and ethical challenges

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Introduction: In industrialised countries, most children spend significant amounts of time at school. The education system has therefore become an important site for childhood obesity interventions, e.g. through improving food environments, integrating nutrition education into the curriculum and increasing physical activity (Story et al, 2006). This paper identifies ethical challenges school-based interventions face and suggests how these challenges might be approached.
Methods: The paper draws on philosophical literature on the role of education and empirical studies on school-based obesity interventions.
Results: While school-based interventions can contribute to the prevention of ill health among children, they also face ethical challenges. First, health promotion is not necessarily consistent with other goals schools pursue, such as the facilitation of children's autonomy. Many approaches to obesity prevention in schools restrict children's choices, which may bring immediate benefits, but may run counter to the objective of enabling autonomous choices later in life. We outline several considerations that can make interventions more consistent with the pursuit of autonomy. Second, schools are an important mediator in children's ability to obtain jobs or university places. Childhood obesity interventions can improve academic performance (Taras, 2005) but there are concerns that these effects are greater for children from affluent backgrounds than for those from lower-income families (Belot & James, 2009). We outline how concerns about the wider implications of school-based interventions could be integrated into their design and evaluation.
Conclusion: The paper outlines ethical challenges school-based obesity interventions face and suggests how these challenges may be met.
Conflict of interest: none.
Funding: This research is funded by the IDEFICS study.

T1:RS1.4

Seeds of doubt in the media landscape: a backlash against obesity prevention?

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Introduction: The mass media are identified as a key component of the obesogenic environment. New voices argue in the media that: there is no 'obesity epidemic', obesity is not a health hazard, people can be fat and healthy, sedentary habits are not harmful, physical activity can solve obesity-related health problems, and promoting high-fat, high-sugar food to children is not causing obesity.
Methods: Content and discourse analysis were used to examine frames and news angles in all articles published in *The Australian*, *The Sydney Morning Herald*, *The Daily Telegraph*, *The Herald Sun* and *The Age* in 2000 to 2009 mentioning 'overweight' and/or 'obesity' in the headline and/or lead paragraph (Factiva).
Results: The size of the problem and causes of obesity dominated news angles in early coverage and solutions dominated later coverage. More articles focused on health effects in 2005, but fewer did so in 2009. Articles leading on regulation rose in 2005 but fell in

2009. These declines occurred despite rising obesity rates and at the same time as the appearance of a novel news angle: questioning the size or importance of obesity as a problem. Results of the discourse analysis will be presented.
Conclusion: Backlash discourses are making headlines. These elements contribute to public uncertainty echoing campaigns against tobacco control and the promotion of doubt about human induced climate change. Innovative media interventions are required to highlight and counter these potentially anti-health messages.
Conflict of interest: none.
Funding: This research was supported under Australian Research Council's Discovery Projects funding scheme (Project No. 1096251) and by the University of Technology, Sydney's ECRG (Project No. 2009001198). The TV sample was provided by the Australian Health News Research Collaboration.
References are available on request.

T1:RS2 – Policy and Economics

T1:RS2.1
Lessons learnt from tobacco control
Sezginer Dagli E

Industries marketing unhealthy products may use mutual methods therefore there may be lessons to be taken from tobacco control movement. The tactics used by the tobacco industry to resist government regulation of its products include conducting public relations campaigns, buying scientific and other expertise to create controversy about established facts, funding political parties, hiring lobbyists to influence policy, using front groups and allied industries to oppose tobacco control measures, pre-empting strong legislation by pressing for the adoption of voluntary codes or weaker laws, and corrupting public officials. The following conditions should be imposed on companies. (1) Public disclosure should be made in every market of what the companies knew about the harm of the product, (2) Internationally recognized basic consumer rights should be guaranteed (3) All contributions to political parties and politicians should be declared, and all amounts paid to lobbyists, consultants and other groups. (4) Trade associations of the industry and other groupings established in order to deceive the public about the harm should be disbanded. (5) Anti-corruption and anti-trust laws should beenforced.
References:
1. Saloojee Y, Dagli E. Tobacco industry tactics for resisting public policy on health. Bulletin of the World Health Organization, 2000, 78: 902–910.
2. Hurt RD, Robertson CR. Health law and ethics. Prying open the door to the tobacco industry's secrets about nicotine: the Minnesota tobacco trial. Journal of the American Medical Association, 1998, 280 (13): 1173–1181.
3. Ciresi MV et al. Decades of deceit: document discovery in the Minnesota tobacco litigation. William Mitchell Law Review, 1999, 25: 477–566.

T1:RS2.2
Health economics of obesity from a European perspective
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Background: Obesity is associated with large societal costs due to morbidity, mortality and productivity losses. The mere fact that a health condition is associated with large costs does not imply that investments should be made in intervention or prevention. The cost, effectiveness and safety of such efforts also need to be taken into account.
Aim: To critically assess cost and effectiveness data, as well as modelling strategies, used in published cost-effectiveness analyses (CEAs) of bariatric surgery and antiobesity drugs.
Methods: Literature review of the design and inputs used in published CEAs of bariatric surgery and pharmacological antiobesity treatment.
Results: Published economic evaluations indicate that weight loss surgery provides health effects at a reasonable cost, but they generally do not show cost savings (compared with non-surgical interventions). CEAs of antiobesity drugs (compared with diet & exercise alone) also indicate the interventions to be within what is generally regarded as cost-effective. Studies were based on short-term data and extrapolations were made using effects on the surrogate marker BMI, not actual effects on costs and quality-adjusted survival. Studies also included only a limited number of comorbidities, and used assumptions which may have biased the results in any direction. Despite a strong association between obesity status and work loss, most models did not include indirect costs/productivity losses, performing analyses from a healthcare instead of societal perspective.
Conclusion: Systematic and long-term measurement of costs and healthcare outcomes is needed to verify CEA model assumptions and estimate actual (as opposed to modelled) costs, effects and cost-effectiveness.
Funding: Research on use of register-derived outcomes for economic evaluation in health care funded by the Delegation of Clinical Research (www.kurnet.se) and ARTIS; research on the cost-effectiveness of bariatric surgery funded by AFA (www.afa.se).
Potential conflict of interest:
Expert council member of Itrim, a Swedish weight loss franchising company (www.itrim.se).

T1:RS2.3
Internet marketing to children on food/beverage websites in two different policy environments
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Introduction: This study aimed to determine whether there are differences between the child content on English and French food/beverage websites in Canada where there are two advertising policies, self regulation by industry (in Canada with the exception of Quebec), and an advertising ban directed at children under the age of 13 years (in Quebec, a province where the majority speak French).
Methods: A total of 78 English language and 71 French language food/beverage websites were selected based on their prevalence during children's preferred television viewing in a previous study. Twenty-eight (36%) English and 23 (32%) French websites had child directed content. A content analysis was conducted on these sites that included examining the number of marketing features, company created mascots, advergames, and the use of healthy lifestyle messages.
Results: The product logo, the featured food product and the product as you eat it were featured on 96%, 73% and 70% respectively of total websites (n = 51) with child content. Company-created mascots were featured on 53% of sites (X = 34 per site), and advergames were seen on 61% of sites (X = 3.3 per site). Healthy lifestyle messages were present on 49% of the total websites. There were no statistically significant differences between the English and French websites. However, 16% of the total websites restricted access to Quebec residents who were under the age of 13 years.
Conclusion: The advertising ban in Quebec does not appear to be influencing the content of French language food/beverage websites in Canada.
Conflict of interest: none disclosed.
Funding: This research was funded by the Canadian Institutes of Health Research.

T1:RS2.4

Are policy interventions 'good buys' as obesity prevention measures?

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Introduction: The Assessing Cost-Effectiveness (ACE) methodology employs a standardised, evidence-based approach to evaluate the cost-effectiveness of interventions to inform priority setting. This presentation reviews application of the methodology to different policy interventions to ascertain their value-for-money as obesity prevention initiatives.
Methods: A range of policy interventions, covering nutrition and physical activity, were evaluated as part of three separate studies – the ACE-Obesity and ACE-Prevention studies in Australia and the ACE-Obesity America pilot study. Each intervention was modelled against a current practice comparator, the main outcome was change in Body Mass Index, and the technical results were reported as cost per disability-adjusted life years (DALYs) saved over the lifetime of the cohort.
Results: Policy interventions were generally effective, low cost, and offered excellent value at a population level. Food policy interventions (including restriction of advertising of unhealthy food, a tax on sugar sweetened beverages) were typically more cost-effective than policy measures targeting physical activity.
Conclusions: The ACE approach enables policy interventions to be ranked in terms of economic merit both against each other and other non-policy options. Whole-of-population food policy interventions offer excellent value as obesity prevention measures.

TRACK 2

T2:RS1 – Health Outcomes in Early and Later Life

T2:RS1.1

How do early mental and physical health outcomes appear in children?

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Greater numbers of children are becoming heavier at progressively younger ages. As such, potential negative mental and physical health consequences of the excess weight may manifest themselves already in childhood. Studies have reported associations between excess body size in childhood with a wide range of concurrent mental health consequences. Examples of these consequences include bullying, loneliness, low self-esteem, poor body image and social discrimination. Similarly, studies have also reported associations between childhood body size and immediate physical health consequences. Examples of these consequences include heart disease risk factors such as dyslipidaemia, high blood pressure and type 2 diabetes.
The review will synthesise the evidence from the literature on the association between body size and the appearance of mental and physical health conditions in childhood. The strength of the evidence will be evaluated according to the criteria of sample size, the participation rate in the study as well as the comparability in the methods of each study. The methodological comparability will be assessed along the dimensions of the source of the study population, the age of the subjects, the definition of childhood body size, the definition of the outcome, the measurement techniques and the length of follow-up. Particular attention will be given to examining if there is evidence for gender differences in the associations as well as whether the associations change with age within the period of childhood.
Conflict of interest: No conflicts of interest to declare.

T2:RS1.2

Is there an optimal anthropometric measure in younger and older adulthood?

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Abdominal obesity is associated with increased incidence of several chronic diseases such as type 2 diabetes, cardiovascular disease and with increased mortality. It is, however, not feasible to measure abdominal fatness directly in large population-based studies. Several anthropometric indicators have been used to measure abdominal obesity. These include waist circumference, hip circumference, waist-hip ratio, body mass index (BMI) and waist-height ratio. The interpretation of these indicators is complicated since waist and BMI are positively and hip and height negatively associated with disease and death. In addition, several of the indicators are highly intercorrelated. Cut-off points based on these measures have been suggested in the literature and these sometimes vary with gender or age. With age more fat is stored in the body and the grade of abdominal obesity usually increases with age. The results vary depending on whether the studies have been cross-sectional or prospective, the ethnic and age composition of the study population and the outcome measure used. The presentation will elucidate the advantages and disadvantages of these measures and discuss the current evidence when taking into account the history of these measures as well as recent large prospective studies and current reviews in this field.

T2:RS1.3

Associations of waist circumference, overweight and underweight with increased mortality risks in the elderly: a meta-analysis of 15 cohorts involving more than 20,000 65- to -75-year olds

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Introduction: The association between waist circumference (WC) and mortality in elderly remains unclear. The aim of this meta-analysis of 15 prospective cohort studies including elderly aged 65–75 years was to examine the U-shaped association between WC and (cause-specific) mortality, and assess at which WC the mortality risk was at its lowest point (nadir). Additionally, we examined the association between combined WC-BMI categories and mortality.
Methods: We used a bivariate fixed effects model to pool the age, smoking and BMI adjusted relative risks (RRs) of mortality for continuous WC. To pool the age and smoking adjusted RRs of mortality for combined WC-BMI categories, we used a univariate fixed effects model.
Preliminary results: 20,073 Elderly were included in which 1588 deaths occurred during 5 years of follow-up. We found at 112 cm in men and 97 cm in women a significant twofold increased RR of all-cause mortality with the nadirs at 80 and 64 cm, respectively. For CVD mortality in women and cancer mortality in men, we found at 105 cm a twofold increased RR with the nadirs at 69 and 70 cm, respectively. From the results of the BMI-WC categories, we only found high significant mortality RRs ranging from 2.3 to 3.8 for underweight (BMI <20 kg/m^2), except for CVD mortality in women.
Conclusion: Increased WC is associated with increased risk of mortality among elderly. Our results indicate that the internationally accepted WC cut-off points might be too high in elderly. However, elderly with underweight are at great risk of mortality.

T2:RS1.4

Childhood overweight after establishment of the gut microbiota – the role of delivery mode, pre-pregnancy weight, and early administration of antibiotics

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Objective: To investigate whether delivery mode (vaginal vs. by caesarean section), maternal pre-pregnancy BMI and early exposure to antibiotics (<6 months of age) influence the child's risk of overweight at age 7 years, hence supporting the hypotheses that environmental factors influencing the establishment and diversity of the gut microbiota are associated with later risk of overweight.
Design: Longitudinal, prospective study with measure of exposures in infancy and follow-up at age 7 years.
Methods: 28,354 mother–child dyads from the Danish National Birth Cohort (DNBC) with information on maternal pre-pregnancy BMI, delivery mode and antibiotic administration in infancy were assessed. Logistic regression analyses were performed using childhood overweight at the 7-year follow-up as outcome measure.
Results: Delivery mode [OR 1.18, 95% CI (0.95–1.47)] was not significantly associated with childhood overweight. Antibiotics during the first 6 months of life led to increased risk of overweight among children of normal weight mothers [OR 1.54, 95% CI (1.09–2.17)], and a decreased risk of overweight among children of overweight mothers [OR 0.54, 95% CI (0.30–0.98)].
Conclusion: The present cohort study revealed that a combination of early exposures including delivery mode, maternal pre-pregnancy BMI and antibiotics in infancy influences the risk of overweight in later childhood. This could be due to early antibiotic treatment preventing colonization by an obesity-promoting gut flora transferred from the overweight mother, and allowing colonization by such flora in children born to normal weight mothers.
Keywords: gut microbiota, childhood overweight, antibiotics, delivery mode, pre-pregnancy BMI.
Conflict of interest: none disclosed.
Funding: Research related to this abstract was funded by a Female Research Leader grant (no.09-066323) from the Danish Council of Independent Research to Dr. Tine Jess.

T2:RS2 – Methods to Integrate Nutrition and Physical Activity

T2:RS2.1

New methods for integrating diet and physical activity assessment

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Obesity is now recognised as a public health priority (1) and given the consequences of obesity, understanding how best to treat and prevent it remains a research priority. However, the design of potentially effective interventions is hampered by the general lack of good-quality data available (2), and it is accepted that the assessment of dietary intake and physical activity levels remains challenging and is particularly difficult when attempting to carry out these assessments at a population level.
Low burden, cost effective and fit for purpose (including accuracy of measurement) are all attributes which need serious consideration when determining the suitability of particular data collection methods. Currently large-scale surveys rely on self reported accounts of dietary intake and physical activity through an assortment of diary records, frequency and recall questionnaires.
In recent years there have been significant developments in the area of novel assessment methods (3) for both dietary intake, physical activity and a combination of the two behaviours. This presentation will explore the ways in which we can utilise new methods of dietary intake and physical activity assessment as well as examine their limitations, and will showcase some new technologies being developed and tested across the world.
References:
1. Foresight Tackling Obesities: Future Choices (2007) HMSO UK [www.foresight.gov.uk].
2. Wanless D (2004) Securing good health for the whole population. London: HM Treasury.
3. Zhu F *et al.* (2008) Proc IS&T/SPIE Conference on Computational Imaging 6814, 1–10.

T2:RS2.2

Energy balance and determinants in children

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In order to improve and maintain current and future health, it is important that children are physically activity and have health dietary habits. In order to effectively promote healthy behaviours in populations of children, we need to gain a thorough understanding of the factors that are associated with (changes in) these behaviours. This will help identify target populations and modifiable factors that may be changed through interventions. Where previous research has mostly focussed on cross-sectional data on demographic and psychological factors, ecological theory proposes investigating a broader range of influences, including socio-cultural, societal and environmental. Longitudinal studies using appropriate, valid and reliable measures of both the exposure and the behavioural outcome in sufficiently diverse and large samples are still scarce. Using examples from large population-based studies such as SPEEDY (Sport, Physical activity and Eating behaviour: Environmental Determinants in Young people), a broad range of potential influences on children's physical activity and dietary behaviour will be discussed. Moreover, we will explore how this knowledge can contribute to intervention development and what future work is needed in order to increase our understanding of how to improve children's health.
Conflict of interest: no conflict of interest.
Funding: Dr Van Sluijs is funded by the Medical Research Council (UK).

T2:RS2.3

Using observation to compare different accelerometer cut points for sedentary behavior in children

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Introduction: Accurate objective methods for the assessment of sedentary behavior are crucial for population monitoring and evaluation of public health strategies for preventing childhood obesity. Actigraph accelerometers are a commonly used objective physical activity measurement tool. It is hypothesized that accelerometers may also provide a valid method for assessing children's sedentary time. However, there is considerable variation in published accelerometer cut-off points for measuring sedentary time in children. The objective of this study is therefore to compare different accelerometer sedentary cut points with observation of children performing specific sedentary behaviors in free-living conditions.
Methods: Direct observation and Actigraph uniaxial accelerometers were used to measure children's activity intensity while playing com-

puter games, non-electronic sedentary games, watching television and playing outdoors. Direct observation was the criterion for assessing the validity of four different previously published sedentary cut-points: i.e., 100, 300, 800, and 1100 counts per minute (cpm).
Results: The median cpm were lowest for computer games (30 cpm), followed by television viewing (109 cpm) and non-electronic sedentary games (172 cpm) and highest for outdoor play (1452 cpm). The median counts during all sedentary behaviors were below the lowest cut-point of 100 cpm. The 75th percentile values for the sedentary behaviors were always below the cut-point of 300 cpm.
Conclusion: Our results suggest that the Actigraph accelerometry cut-point of <100 cpm is the most appropriate, if not too high, for quantifying the time children spend sedentary.
Conflict of interest: none disclosed.
Funding: no funding.

T2:RS2.4
Differences in prevalence rates of overweight and energy balance-related behaviors across seven European countries: findings from the ENERGY project

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Introduction: To inform obesity prevention interventions, it is important to have up-to-date data on prevalence, identify children who are particularly at risk for overweight and obesity, and to gain further insight in the prevalence and distribution of energy-balance behaviors associated with risk for overweight and obesity.
Methods: A seven-country, school-based survey was conducted. In total 6980 children (mean age 11.6) participated. For all children, weight, height, and waist circumference was measured by trained staff and engagement in physical activity, sedentary and dietary behaviors was reported in questionnaires. All measurements and data handling were standardized across the participating countries. Descriptive analyses were conducted, looking at differences in weight status and risk behaviors according to country, gender and parental education.
Results: Across the seven countries, 25.5 and 5.2% (boys), and 21.4 and 4.1% (girls) were overweight and obese respectively. The highest overweight prevalence, mean BMI and waist circumference were found among Greek boys (46%); the lowest levels were observed in Norway, the Netherlands and Belgium (13–15% t). Large differences between countries were also found in specific diet, physical activity and sedentary behaviors, such as intakes of sugar-sweetened beverages, breakfast habits, active transport to school, and TV and computer time. Across countries and within the countries more favorable behavioral patterns were found in children from higher educated parents than in children from parents with lower levels of education.
Conclusion: Striking difference in weight status and risk behaviors related to overweight and obesity were found among schoolchildren across seven countries in Europe.
Conflict of interest: none.
Funding: The ENERGY project is funded by the Seventh Framework Programme (CORDIS FP7) of the European Commission, HEALTH (FP7-HEALTH-2007-B), grant agreement no. 223254. The content of this abstract reflects only the authors' views and the European Community is not liable for any use that may be made of the information contained therein.

T1/T2:RS1 – Surveillance and Early Life Prevention

T1/2:RS1.1
The two faces of childhood obesity monitoring

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Monitoring childhood obesity is a multifaceted issue that will be discussed from two viewpoints: public health and clinical perspectives.
In public health it is essential to monitor childhood obesity, to address whether policies are effective in promoting healthy weights or whether health planners should modify their policies. To obtain useful data for this purpose, surveillance activities should be conducted in representative sub-samples of the population using standardized measurement protocols and be repeated periodically. A number of key ethical issues involving what to do with the surveillance data will be discussed in this part of the presentation.
In contrast to surveillance, from a clinical perspective it would be ideal to monitor all children from an early age and treat all who are at risk. Children who are overweight are at greater risk of poor health in adolescence and also in adulthood. The clinical perspective focuses on early identification of overweight children in order to promote healthy behaviors and prevent co-morbidities. The treatment should be initiated during childhood to reduce weight gain while growing. Some children have an increased risk of developing premature chronic diseases (cardiovascular diseases, type 2 diabetes) and should be identified early in life.
Fortunately, public health and clinical perspectives can easily meet, with provision of adequate resources. There are about 12 million overweight children (0–14 years old) in Europe and 4.4 million healthcare staff (doctors and others) to treat them. If resources for universal screening are not available, high-risk screening efforts can be conducted via collaboration between surveillance and the clinic. For instance, surveillance data can be used to identify high risk areas for more intensive clinical screening efforts. This solution is a compromise but very much in the spirit of public health prevention paradigms.

T1/2:RS1.2
Obesity interventions in the very young: rationale and evidence

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Introduction: Infant feeding practices influence early intake and eating behaviours which in turn track into childhood and are associated with later obesity risk. Rapid early weight gain is an established risk factor for childhood obesity. Early feeding practices determine infant exposure to food (type, texture, amount) and include parent response (e.g. coercion) to infant feeding behaviour (e.g. food refusal). Feeding practices are influenced by culture and family tradition. They evolved in times of relative food scarcity and have not adapted to the current food environment that is characterised by excess. Early feeding practices fall short of ideal and are a potentially modifiable risk factor for childhood obesity. However, evidence to guide effective early intervention strategies is scarce. This paper aims to present evidence

that obesity prevention should start very early and review the very few obesity prevention intervention trials, including NOURISH, that have commenced prior to age 12 months.
Methods and results: A review (Hesketh *et al.*, 2009) of interventions to impact on weight status of children 0–5 years included 22 studies; only two of the seven studies with children <2 years presented growth data. Only two small RCTs have evaluated very early feeding interventions (Harvey-Berino, 2003; Paul, 2010). Four large RCTs are underway in Australia/New Zealand with a prospective meta-analysis planned (Askie, 2010).
Conclusion: Despite the acceptance of a life course approach to preventing chronic disease, including obesity, the potential of very early interventions has been neglected. Results from four large trials currently underway will redress this evidence gap.

T1/2:RS1.3
Overweight prevention in adolescents by increasing physical activity: 6-year results of the randomized ICAPS study

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Introduction: ICAPS (Intervention Centred on Adolescents' Physical Activity and Sedentary Behaviour), a 4-year multilevel randomized study, has demonstrated that enhancing physical activity with a multilevel program integrating environmental changes prevents excessive weight gain in adolescents. Our aim was to investigate the long-term effects of the program, 2 years after the end of the 4-year intervention.
Methods: Measured body mass index (BMI) and waist circumference (W), reported physical activity (PA) and sedentary behaviours (MAQ questionnaire) were assessed in 556 subjects (mean age 17.7 ± 0.6 years) of the initial cohort (n = 954) between September 2008 and September 2009. Analyses used linear mixed models taking into account cluster randomization, baseline values and repeated individual data over time.
Results: Two years after the end of the intervention, as compared to controls, intervention students spent less time in TV/Video viewing (−29 minutes/day; $P < 0.01$), had higher active school/home or school/work transport levels (+5 minutes/day; $P < 0.01$) and tended to have higher leisure PA levels (+38 minutes/week; $P = 0.10$). They maintained a significantly lower gender- and age- adjusted BMI (−0.37 kg/m^2; $P = 0.02$) and a lower W (−1.6 cm; $P < 0.01$), with differences that tended to be higher in socio-economically less-favoured adolescents as compared to their more advantaged counterparts (−0.58 versus −0.06 kg/m^2; interaction $P = 0.22$).
Conclusion: These results confirm that multilevel prevention strategies based on a global approach of the individual and its environment has the potential to prevent overweight in the long-term, without enhancing social health inequalities.
Conflict of Interest: none.
Funding: French National Research Agency (ANR-08-ALIA); INSERM; INRA; Regional Health Insurance of Alsace-Moselle; French Public Authorities within the National Nutritional Health Program and through the Youth and Sports Ministery; Conseil General du Bas-Rhin; Municipalities of Drusenheim, Illkirch-Graffenstaden, Obernai and Schiltigheim; Wyeth and Lab foundation; CNP assurances.

T1/2:RS1.4
Ethnic differences in maternal perception of offspring's weight: the ABCD study

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Objective: To determine ethnic variation in maternal perception of their child's weight status and the potential explanatory role of socio economic status (SES), level of integration and parental BMI.
Design: A multi-ethnic sample of 2932 children aged 5–6 years was examined (ABCD study) from five ethnic subgroups: Dutch (n = 1787), African descent (n = 128), Turkish (n = 74), Moroccan (n = 122), and other non-Dutch (n = 635). Mothers' perception about their child's weight, SES, level of integration, lifestyle characteristics and the measured children's weight and height were collected. Misperception was defined by comparing the maternal perception with the actual overweight status of her child (IOTF guidelines).
Results: Misperception was more prevalent in the Turkish (26.9%), Moroccan (22.6%) and African descent mothers (14.8%) as compared to the Dutch mothers (5.5%). These differences are for a relevant degree explained by the lower SES, lower level of integration and higher parental BMI in these groups. These risk factors, however did not fully explain the higher prevalence for misclassification. The odds ratios (OR) remained significantly higher in the Turkish (OR: 2.40; 95% CI: 1.20–4.80) and Moroccan (OR: 2.16; 95% CI: 1.17–3.98) groups.
Conclusion: The perception of non-Dutch ethnic mothers on their children's weight status more frequently differed from the actual status than in ethnic Dutch women. The lower SES, level of integration and higher parental BMI in these groups play an important role but also other, probably socio-cultural, factors. Given that weight perceptions may affect weight gain, health professionals should promote a realistic perception of mothers of their children's weight status, particularly in ethnic minority groups.

TRACK 3

T3:RS1 – Energy Balance and its Neuro-Endocrine Regulation

T3:RS1.1
Dietary fat sensing by enterocyte fatty acid oxidation – effects on eating

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Various mechanisms detect the presence of dietary fat in the digestive tract and link fat ingestion to the control of eating. I here present evidence for the existence of a novel fat sensing mechanism based on enterocyte fatty acid oxidation (FAO). Peripheral FAO has long been implicated in the control of eating. The prevailing view was that mercaptoacetate (MA) and other FAO inhibitors stimulate eating by modulating vagal afferent signaling from the liver. This concept has been challenged because hepatic parenchymal vagal afferent innervation is scarce and because experimentally induced changes in hepatic FAO often fail to affect eating. Several recent findings support a role of the small intestine as a FAO sensor that can influence eating. After intrajejunal infusions MA stimulated eating in rats through vagal afferent signaling, and after infusion into

the superior mesenteric artery MA increased the activity of celiac vagal afferent fibers originating in the proximal small intestine. Also, pharmacological interference with triacylglycerol (TAG) synthesis targeting the small intestine induced a metabolic profile indicative of increased FAO and inhibited eating in rats on a high fat diet, but not on chow. Finally, cell culture studies indicate that enterocytes oxidize fatty acids, and that this can be modified pharmacologically. Thus, enterocytes may sense dietary fat-derived fatty acids via FAO and influence eating through changes in intestinal vagal afferent activity. Further studies are necessary to identify the link between enterocyte FAO and vagal afferents and to examine the specificity and potential physiological relevance of such a mechanism.

Conflict of interest: The author has no conflict of interest to declare.

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T3:RS1.2

Gut hormones in the central control of energy metabolism

Field BCT

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Several hormones, including PYY, GLP-1, oxyntomodulin, CCK, pancreatic polypeptide and islet amyloid polypeptide, are released post-prandially by the gut, in proportion to the energy content of ingested food. When administered by intravenous infusion, these hormones induce early satiety in humans. In some instances, chronic treatment results in weight loss, via both reduced appetite and increased energy expenditure. The mechanisms underlying these effects are not yet fully understood.

As pharmaceutical targets, hormones, with their distinct target tissues, have an advantage over classical neurotransmitter pathways, in that off-target adverse effects might be less likely to occur. However, with the exception of GLP-1, gut hormones have yet to demonstrate their full potential as treatments for obesity. This situation arises in part because the mechanisms through which gut hormones act are not yet fully understood. In particular, identification of the relevant target tissues is challenging.

This talk will address the question of how gut hormones influence energy metabolism, concentrating on the identification of target tissues, and on how stimulation of these tissues might lead to alterations in eating behaviour and energy expenditure.

T3:RS1.3

Evidence for a functional adipocyte-nerve axis in the gut

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Introduction: The enteric nervous system (ENS) regulates mucosal and muscle functions through neurons in the submucous and myenteric plexus, respectively. The ENS controls autonomous reflex pathways but is also modulated by mediators released from non-neuronal cells. We hypothesize an adipocyte-nerve axis which may influence ENS activity and may play a role in obesity.

Methods: We used voltage sensitive dye imaging to record activity in colonic sumucosal and myenteric neurons of mice and guinea-pigs. Immunohistochemistry was used to label adipocytes and nerves in the gut wall. Mucosal secretion and muscle activity was measured *in vitro* with Ussing and organ bath techniques, respectively.

Results: We observed a close apposition between adipocytes in the submucosa and enteric neurons. The functional relevance of this finding was supported by actions of leptin (62.5 pM) which excited 15% of submucous and 8% of myenteric neurons. At this low concentration leptin did not affect mucosal secretion or muscle activity suggesting a subtle modulatory action of leptin at the level of the ENS. In obese mice (induced by high fat diet) more myenteric neurons responded to nicotine which mimics fast excitatory neurotransmission in the ENS. This suggested plasticity in cholinergic responses in obese mice.

Conclusion: We present evidence for adipocyte nerve interactions in the gut wall. Enteric neurons are activated by leptin, one of the main mediators released from adipocytes. It remains to be studied whether the increased excitatory action of nicotine in obese mice is a consequence of the enhanced cross talk between adipocytes and nerves.

Conflict of Interest: none disclosed.

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T3:RS1.4

Moderate caloric restriction during gestation in rats alters sympathetic innervation of white adipose tissue and later adiposity in offspring in a gender- and depot-dependent manner

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Maternal prenatal undernutrition predisposes offspring to higher adiposity in adulthood. No data exist about possible programming effects on peripheral nervous system structures involved in white adipose tissue (WAT) development and metabolism. We aimed to evaluate the effects of moderate caloric restriction in rats during early pregnancy on offspring WAT sympathetic innervation and its relationship with adiposity development. For this purpose, inguinal and retroperitoneal WAT (iWAT and rpWAT, respectively) were analysed in male and female offspring of 20% caloric-restricted (from 1 to 12 days of pregnancy) (CR) and from control dams. Body weight and the weight, DNA-content, morphological features and the immunoreactive tyrosine hydroxylase area (TH^+, performed by immunohistochemistry) of both WAT depots were studied at 25 days and 6 months of age, the latter after 2 month exposure to high fat diet. At 25 days of life, CR males, but not females, showed lower TH^+ in the iWAT, but not in the rpWAT, suggesting lower sympathetic innervation. At 6m, CR males, but not females, exhibited greater body weight, and greater weight and total DNA-content in the iWAT, without changes in the size of adipocytes, suggesting the development of hyperplasia in this depot. However, in the rpWAT, CR males showed larger adipocyte diameter, with no changes in DNA content, suggesting the development of hypertrophy. The effects of gestational caloric restriction on later adiposity and on the differences in the adult phenotype between internal and subcutaneous fat depots in the male offspring may be associated in part with specific alterations in sympathetic innervation, which may impact on WAT architecture.

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T3:RS2 – Gut Microbiota

T3:RS2.1

Gut microbiota – state of the art approaches

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Since birth, our gut is colonized by microbes that outnumber our own cells – this gut microbiota, previously termed microflora, consti-

tutes the largest microbial ecosystem that is close to our heart. The collective genome of the gut microbiota, also know as the microbiome, exceeds the coding capacity of our own system and presently more than 3 million genes have been characterized at the sequence level. However, unlike our own genome, the microbiome is not, or not only, vertically inherited and, moreover, this personalized organ can be modified by diet, life style and antimicrobials. Hence, there is great interest in relating the intestinal microbiome to health and disease. This requires a quantitative description of the main microbial community members, their genomes and functions. Moreover, as the intestinal microbes have developed intimate relations with the host, their dynamics and interactions should be analyzed.

This contribution aims to summarize the recent state of the art of the human gut microbiota with specific attention for describing the microbial diversity in time and space, studying the microbial activity by functional metagenomics, notably metaproteomics, and understanding the interaction of intestinal bacteria with the host. Moreover, cause-effect relations are being developed with specific interventions of diet and microbes as well as via microbial transplantations that have unprecedented power and therapeutic potential for a variety of aberrations, including metabolic syndrome.

T3:RS2.2
Animal models of obesity and microbiota

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The human gut is home to a vast number of microorganisms, especially bacteria, which are estimated to outnumber our human cells by an order of magnitude. Thus our human body is an amalgam of eukaryotic and bacterial cells that both affect our metabolism.

Germ-free animal models were developed during the first half of the 20th century and have been extensively used to study the interactions between the host and gut microbiota. We recently identified the gut microbiota as an environmental factor that regulates adiposity by using germ-free C57Bl6 mice, which exhibit reduced adiposity and are resistant to diet-induced obesity compared with conventionally-raised counterparts. The underlying mechanism involves reduced energy harvest from the diet, reduced hepatic lipogenesis, and reduced LPL-mediated triglyceride deposition in adipose tissue. Colonization of germ-free mice with a normal gut microbiota reverses these phenotypes and is associated with a rapid suppression of the LPL inhibitor Angiopoietin-like protein 4 (Angptl4). By rederiving *Angptl4-/-* mice as germ-free we demonstrated that at least part of the resistance to diet-induced obesity in germ-free mice requires Angptl4.

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T3:RS2.3
Gut microbiota: relevance in human metabolism

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The human intestinal tract harbours a complex microbial ecosystem which plays a key role in nutrition and health. Interactions between food constituents, microbes and the host organism derive from a long co-evolution that resulted in a mutualistic association. A specific link between gut microbiota and human metabolism has been suggested from recent work and is being scrutinized in detailed studies relying on high resolution assessment on the microbiota, interfaced with host phenotype.

Current investigations into the human faecal metagenome are delivering an extensive gene repertoire representative of functional potentials of the human intestinal microbiota. The most redundant genomic traits of the human intestinal microbiota are identified and thereby its functional balance. These observation point towards the existence of enterotypes, i.e. microbiota sharing specific traits but yet independent of geographic origin, age, sex etc. It also shows a unique segregation of the human population into individuals with low vs. high gene-counts. In the end, it not only gives an unprecedented view of the intestinal microbiota, but it also significantly expands our ability to look for specificities of the microbiota associated with human diseases and to ultimately validate microbial signatures of prognostic and diagnostic value in immune mediated diseases.

Metagenomics of the human intestinal tract was applied to specifically compare obese versus lean individuals as well as to explore the dynamic changes associated with a severe calorie-restricted diet. Microbiota structure differs with BMI and a limited set of marker species may be used as diagnostic model with a >85% predictive value. The overall phenotypic characteristics are worse in individuals with low gene counts microbiota, including a worse evolution of morphologic features over a period of 10 years, a low grade inflammatory context also associated with insulin-resistance, and the worst response to dietary constraints in terms of weight loss or improvement of biological and inflammatory characteristics.

In gastric bypass surgery, seen as a drastic model of caloric restriction, post surgery alterations in microbiota composition confirmed the above associations and pointed out specific associations of microbial groups with specific features such as a negative correlation between levels of *Faecalibacterium prausnitzii* and the overall inflammatory context.

Finally, functional metagenomics are applied to specifically explore microbes-host crosstalk mechanisms. Molecular patterns associated with commensal microbes and able to modulate cellular pathways pertaining to regulation of immune response or cellular metabolism are hence being characterized.

We are still quite far from delivering causal inter-relations between features of the microbiota and metabolic status of the host but current observations converge towards a general model with physiopathological relevance.

TRACK 4

T4:RS1 – Genetics and Lifestyle–Gene Interactions

T4:RS1.1
Progress in the genetics of common obesity – from genome-wide association studies towards insights in biology

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Over the past 4 years, genome-wide association studies (GWAS) have dramatically increased the pace of gene discovery for common obesity; at least 50 loci have been unequivocally associated with obesity-related traits. This presentation (i) reviews the progress in gene discovery, (ii) discusses how these loci provide new insights into the physiology, and (iii) highlights the major challenges ahead.

GWAS for body mass index (BMI) have identified at least 32 loci. The firstly discovered locus, *FTO*, is ubiquitously expressed in the hypothalamus and may cause obesity through the central regulation

of food intake. Also other BMI-loci are expressed in the brain, further highlighting role of the CNS in obesity-susceptibility. At least four BMI-loci (POMC, MC4R, SH2B1, BDNF) harbour genes previously linked to monogenic obesity and two other loci (NEGR1, GPRC5B) tag copy number variants. GWAS for waist-to-hip ratio have identified 14 loci, seven of which show more pronounced effects in women. Preliminary evidence suggests that these loci modulate body fat distribution independent of overall adiposity through effects on adipose tissue. GWAS for extreme obesity have identified three new loci that are not associated with BMI, suggesting that extreme and common obesity may have a different genetic (and physiological) background. A locus near *IRS1*, identified through a GWAS for body fat percentage, was associated with less body fat, but surprisingly also with an increased T2D and CAD risk, suggesting that this locus might be implicated in the expansion ability of adipose tissue.

The two major challenges ahead are the discovery of more obesity-susceptibility loci, which will require further large-scale data integration and refined analyses, and the fine-mapping of established loci to identify the causal variants and genes, which will allow investigating the physiology that underlies common obesity.

T4:RS1.2

Emergence of microRNA in the field of Nutrigenomic

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Major research efforts have been devoted to find molecular mechanisms that underlie metabolic diseases, like obesity and type 2 diabetes, in particular, how nutrients and hormones are sensed by transcriptional regulators and control biological processes that are potentially dysregulated in these diseases. In recent years, our understanding of complex gene-regulatory networks governing cell physiology has rapidly evolved with the discovery of microRNAs. MicroRNAs belong to a large class of evolutionary conserved non coding RNAs of 21 to 22 nucleotides which act as negative regulators of gene expression either by inhibiting mRNA translation or promoting mRNA degradation through base paring to the 3' untranslated region of target mRNAs. Important roles for these microRNAs have now emerged such as in the control of metabolic pathways involved in fat metabolism, adipocyte differentiation, energy homeostasis, glucose-stimulated insulin secretion and insulin signaling. We recently found that insulin regulates the expression of a large set of microRNAs in human skeletal muscle, both in vivo and in vitro in cultured myocytes. We also found that this regulation is altered in the muscle of insulin resistant type 2 obese diabetic patients, leading to the expression of a modified pattern of microRNAs in muscle of these patients. Dysregulation of microRNA expression has been also described in adipose tissue of obese patients. Until now, regulation of microRNA expression by nutrition has been poorly studied. Understanding the role of microRNA in metabolic disease and their modulation by nutritional factors, as well as identifying their target genes are however of great interest. This may potentially identify new pathways involved in these complex diseases and thus contribute to the development of novel strategies for the treatment of obesity and type 2 diabetes.

T4:RS1.3

Genetic variation near irs1 associates with reduced body fat percentage and an impaired metabolic profile

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Introduction: Genome-wide association studies have identified 32 common variants that associate with body mass index (BMI). BMI does not, however, distinguish between lean and fat body mass. Body fat percentage is a more accurate measure of adiposity, which may help to identify new genetic loci predisposing to adiposity.

Methods: We meta-analyzed GWA data from 29,069 white-European and 7557 Indian-Asian individuals with body fat percentage, and followed up the 14 most significant ($P < 10^{6}$) independent loci in up to 39,576 Europeans.

Results: We confirmed the established adiposity locus in the *FTO* gene ($P = 3 \times 10^{26}$) and identified two new loci, i.e. near-*IRS1* ($P = 4 \times 10^{11}$) and near-*SPRY2* ($P = 3 \times 10^{8}$), to affect body fat percentage. The association of the near-*IRS1* locus with body fat percentage was stronger in men ($P = 3 \times 10^{11}$) than in women ($P = 9 \times 10^{3}$) ($P_{interaction} = 0.02$). This sexual dimorphism was also observed in follow-up analyses which showed that the body fat percentage lowering allele of the near-*IRS1* locus was associated with an impaired metabolic profile, including increased insulin resistance and visceral fat, dyslipidemia, decreased circulating levels of adiponectin, and increased risk of diabetes and coronary artery disease. Although the locus maps 500 kb upstream of *IRS1*, the body fat lowering allele shows decreased *IRS1* expression.

Conclusion: Genetic loci near the *IRS1* and *SPRY2* genes are associated with body fat percentage. The body fat percentage lowering allele of near-*IRS1* is also associated with an impaired metabolic profile, particularly in men. These findings provide new insights into the molecular mechanisms underlying common adiposity and insulin resistance.

T4:RS1.4

A family history of type 2 diabetes is associated with increased body fat and waist circumference in normoglycaemic individuals

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We have recently shown that a non-diabetic group of healthy subjects with a family history of Type 2 diabetes mellitus (T2DM) gained more weight than a matched control group during a voluntary overfeeding protocol (1). We examine here whether a similar but larger group shows differences in body composition consistent with that finding. Anthropometric measurements (height, weight, BMI, hip and waist circumferences) and percent body fat (DXA) were analysed in data from 202 participants in various published and unpublished studies in which family history of T2DM (FH) was documented. Individuals were categorised as FH+ [≥1 first-degree relative with T2DM, 50F/30M, age 45 ± 2 (SE) years] or FH- (71F/51M, age 43 ± 1 years). Fasting blood glucose did not differ between groups (FH+ 4.7 ± 0.1, FH- 4.7 ± 0.1 mmol/l). After adjustment for age and gender, FH+ was associated with significantly higher waist circumference (84 ± 2 versus 80 ± 1 cm, $P = 0.01$) and percent body fat (32 ± 1 versus 28 ± 1, $P = 0.01$). Weight ($P = 0.12$) and BMI ($P = 0.11$) showed similar trends. We conclude that a family history of T2DM is associated with increased adiposity and waist circumference. This finding is consistent with our reported effects of FH on weight gain during voluntary overfeeding (1) and together these results suggest that the risks of later T2DM and of increasing adiposity are linked at an early stage of disease development and are exacerbated by nutrient excess.

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T4:RS2 – Fat Cell Dynamics and Cytokines

T4:RS2.1
Adipocyte turnover and disease risks

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It was previously believed that human fat cells are made up during childhood – adolescence age. However, we recently demonstrated that there is a very high turnover of fat cells in adult humans. About 10% of the fat cells are dying each year and replaced by new ones. This turnover rate, on the whole body level, is two fold enhanced among the obese. Furthermore, despite of the high turnover, the total amount of fat cells in the body is remarkably constant over the whole adult human life span and also resistant to both voluntary and involuntary weight loss. A remarkable feature of human adipose tissue is the large interindividual variation in the size and number of fat cells. Both in lean and obese people the adipose tissue can be composed by many small fat cells (hyperplasia) or few but large fat cells (hypertrophy). The occurrence of these differences of adipose morphologies have clinical consequences. Lean or obese subjects with hypertrophy have decreased insulin sensitivity, in particular if this occurs in subcutaneous fat, whereas hypertrophy in visceral fat is more closely linked to dyslipidemia. Adipose morphology is regulated by fat cell turnover, the turnover rate is twice as high in hyperplasia as in hypertrophy. Local inflammation, usually though to be pernicious linking adipose tissue insulin resistance, is also important for the turnover of fat cells in healthy lean subjects. A novel transcription factor, Twist-1, is a master regulator of the inflammation and the adipose morphology. No conflict of interest is reported.

T4:RS2.2
Microenvironment of adipose cells: remodelling and body weight

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The integrity of the extracellular matrix (ECM) is essential for the proper development of adipose tissue (WAT). Fibrosis is usually characterized by the modification of both the amount and composition of ECM proteins. The tissue accumulation of fibrosis generally disrupts cellular processes and appears detrimental for the normal function of different organs. There are available evidences supporting an important ECM remodeling in obese WAT. This phenomenon was described in rodents and evidences are emerging in humans. Animal models with disruptions in ECM components suggest that fibrosis could limit adipocyte hypertrophy and associate with obesity related metabolic disorders. In humans, together with inflammatory cell accumulation, the evaluation of transcriptomic interactions characterizing human adipose tissue demonstrated the strong relationships linking inflammatory processes to ECM components. We provided insights into the composition in WAT fibrosis showing a different pattern and distinct physiopathological significance in WAT depots. In subcutaneous and visceral depots, fibrosis show differences in organization, quantity, nature and influence in clinical parameters of obese patients. A major finding is the diminished fat mass loss in patients with high level of scWAT fibrosis. More knowledge is nevertheless necessary to understand the contribution of ECM modifications and the consequence of fibrotic depots in obesity development and maintenance.

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T4:RS2.3
Inflammation and the fat depot-specific secretome of human fat cell progenitors

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Introduction: We tested the hypothesis that preadipocytes from different fat depots have distinct secreted protein profiles, which might contribute to the more proinflammatory state of intraperitoneal than subcutaneous fat.

Methods: Abdominal subcutaneous and omental preadipocytes cultured from eight obese adults (female; 46 ± 5.0 years; BMI 45 ± 6.4 kg/m^2) were assayed by label-free quantitative proteomics (both secreted and intracellular proteins), ELISA, and macrophage chemoattraction.

Results: We identified 195 differentially secreted proteins in conditioned medium of preadipocytes isolated from the two depots (over twofold up- or down-regulation; FDR <0.05; hierarchical clustering). Intracellular global protein profiles in cell lysates differed less between depots. Chemokines were the most distinct category of secreted proteins ($N = 8$, $P < 0.001$; GeneGO pathway prediction). Upregulated chemokines in omental preadipocytes were confirmed by ELISA (IL6, IL8, MCP-1, RARRES2, RANTES; $P < 0.005$). Macrophage chemoattractant effects of omental were greater than subcutaneous preadipocytes (chemotaxis of THP-1 macrophages and human primary blood monocytes in response to preadipocyte conditioned medium; $N = 4$; $P < 0.05$). Neutralizing antibodies to MCP-1, RANTES, RARRES2, and their combination reduced macrophage chemoattraction by omental preadipocytes (much less by subcutaneous preadipocytes). Subcutaneous preadipocyte chemokine secretion (MCP-1, RANTES) and macrophage chemoattraction were stimulated by IL-6 treatment, making them more like omental cells. Conversely, reducing IL-6 effects by inhibiting JAK in omental preadipocytes decreased these chemokines and macrophage chemoattraction, making omental more like subcutaneous cells.

Conclusions: The secretome of subcutaneous and omental fat depots is distinct. The omental secretome is more pro-inflammatory and induces macrophage attraction. The IL-6/JAK pathway is implicated in these regional differences in fat tissue inflammation.

Conflict of interest: none disclosed.

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T4:RS2.4
Macrophage-induced expression and release of matrix metalloproteinase 1 and 3 by human preadipocytes is mediated by IL-1B via activation of MAPK and NF-κB

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Introduction: Obesity is associated with low-grade inflammation and increased macrophage infiltration in adipose tissue. Matrix metallo-

proteinases (MMPs) are involved in adipose tissue remodelling in obesity. This study investigated whether macrophage-derived factors modulate MMP1 and MMP3 production in human preadipocytes and the potential mediators and signalling pathways.
Methods: Preadipocytes were incubated with RPMI 1640 medium (control) or THP-1 macrophage-conditioned (MC) medium (25% and 100%) for 24 hours. Preadipocytes were also incubated with IL-1β or TNF-α neutralising antibody in the presence of MC medium for 24 hours.
Results: MMP1 and MMP3 were primarily expressed and secreted by preadipocytes and dramatically reduced post-differentiation. MC medium markedly increased mRNA levels of MMP1 (up to 122-fold) and MMP3 (up to 59-fold) and protein release of MMP1 (up to 378-fold) and MMP3 (up to 10-fold) in a dose-dependent manner. IL-1β or TNF-α induced MMP1 and MMP3 secretion by preadipocytes. IL-1β neutralization abolished the induction of MMP1 and MMP3 in preadipocytes by MC medium while the effects of TNF-α neutralization were modest. MC medium or IL-1β led to the phosphorylation of p38, ERK and JNK MAPKs. Inhibition of p38, ERK and JNK MAPKs reversed the stimulatory effects of MC and IL-1β on MMP1 and MMP3 production. MC medium and IL-1β activated NF-κB p65 subunit whereas reduced IκBα protein expression.
Conclusion: These results suggest that macrophage infiltration into adipose tissue has a central role in stimulating expression and release of MMP1 and MMP3 by preadipocytes; this is mediated partially by IL-1β via activation of the MAPK and NF-κB signalling pathways.
Conflict of interest: none.
Funding: This work was supported by the UK Medical Research Council (87972).

T4:RS3 – Organelle (Dys)Function

T4:RS3.1
Mitochondria dysfunction in white adipose tissue pathophysiology

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Mitochondrial activity has been traditionally considered essential for brown adipocyte function, but only recently mitochondrial activity has also been recognized to be essential for white adipocyte differentiation and metabolism. Mitochondrial biogenesis is associated with white adipocyte differentiation. Thiazolidinediones, key activators of white adipocyte differentiation through the activation of PPAR-gamma, induce mitochondrial biogenesis in white adipocytes. Experimental obesity in rodents models, either of genetic or dietary origin, is associated with reduced mitochondrial mass and function in white fat, although these observations have not been confirmed in humans. In fact, there is data that impaired mitochondrial equipment in adipose tissue is specially related to the insulin-resistant status occurring frequently in obesity. Moreover, impaired mitochondrial function underlies alterations in adipose tissue amounts and distribution in some forms of lipodystrophy. The mechanisms by which mitochondrial activity influence white adipocyte biology are unclear, and simple bioenergetic explanations based in rates of ATP production can hardly explain the multiple disturbances taking place in white fat when mitochondrial function is altered. There is evidence that mitochondrial activity influences the overall program of adipocyte differentiation and function though the so-called ''mitochondrial retrograde signaling'', by which mitochondrial activity provides intracellular signals that modulate nuclear gene expression. The role of mitochondrial activity on adipocyte function may have systemic consequences, especially when the expression of nuclear genes for secreted proteins is involved. In this sense, adiponectin gene expression and adiponectin release by white fat is modulated according to the extent of production of reactive oxygen species by mitochondria.

T4:RS3.2
Mitochondrial energetics (muscle, liver), oxidative stress and diet

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Mitochondria are key organelles in energy metabolism, especially in tissues with high metabolic activity, such as skeletal muscle and liver. Therefore, mitochondrial dysfunction could play an important role in the pathogenesis of metabolic disorders.
By using different physiological approaches, we have shown that a correlation exists between diet and mitochondrial functioning, both in liver and skeletal muscle, that exert a deep impact on glucose homeostasis.
High fat feeding, that leads to obesity and insulin resistance, is deleterious for the liver since it induces mitochondrial oxidative stress and ectopic lipid deposition without affecting mitochondrial respiratory capacity, while catch-up fat after caloric restriction, that also induces insulin resistance and excess body fat deposition, stimulates hepatic mitochondrial respiratory capacity without inducing oxidative stress or ectopic lipid deposition.
In skeletal muscle, high fat feeding is associated with lower mitochondrial oxidative stress while oxidative capacity is unchanged in intermyofibrillar and down regulated in subsarcolemmal mitochondria. Catch-up fat after caloric restriction enhances skeletal muscle mitochondrial oxidative stress while respiratory capacity is increased in intermyofibrillar and decreased in subsarcolemmal mitochondria.
In conclusion ,in the liver, high fat feeding is more deleterious than catch-up fat. On the other hand, in skeletal muscle both high fat feeding and catch-up fat selectively damage subsarcolemmal mitochondria. Given the role of subsarcolemmal mitochondria in the bioenergetic support of insulin signalling and insulin-mediated glucose transport in skeletal muscle, their impairment could play a role in the derangement of glucose homeostasis induced by catch-up fat and high fat feeding.

T4:RS3.3
Mitochondrial dysfunction and oxidative stress

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Insulin resistance in skeletal muscle is a major hallmark of type 2 diabetes and an early detectable abnormality in the development of this disease. Altered lipid metabolism and mitochondrial dysfunction in skeletal muscle are associated with the development of insulin resistance and type 2 diabetes. However, our recent works suggest that mitochondrial alterations in skeletal muscle are not causal in the onset of high fat and high sucrose diet (HFHSD)-induced insulin resistance, but rather a consequence of muscle oxidative stress, due to glucolipotoxicity. In agreement with our observation, several recent studies also questionned the cause-and-effect relationship between mitochondrial dysfunction and insulin resistance. Nevertheless, by promoting lipid accumulation, mitochondrial alterations likely participate to the maintenance or to the exacerbation of impaired insulin sensitivity. In addition, oxidative stress, which precedes mitochondrial alterations in the course of diet-induced insulin resistance, could also play a role in the development of insulin resistance, by activating several serine/threonine kinases (NFkB, JNK, P38MAPK and PKC), leading to subsequent phosphorylation of IRS-1 on serine residues and altered insulin signalling. However, the important unsolved question is to determine whether oxidative stress

is a primary causal factor or a complication associated with the evolution of diabetes. Therefore, I will discuss on (i) the molecular mechanisms by which increased reactive oxygen species (ROS) production in skeletal muscle could alter mitochondria structure and function, (ii) the origin of muscle ROS in glucolipotoxic states and the impact of antioxidant treatment on mitochondria function and (iii) whether increased oxidative stress could participate itself to the development of IR, in parallel to its deleterious effects on mitochondria.

T3/T4:RS1 – Neuronal and Metabolic Programming

T3/T4:RS1.1
Hypothalamic inflammation and diet-induced obesity

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Food intake, energy expenditure and endogenous glucose production are regulated by highly integrated hypothalamic neurocircuits that process input from both hormonal and nutrient-related signals. In response to afferent signals such as insulin and leptin, the brain initiates responses that promote the maintenance of both body fat stores and blood glucose levels. High-fat diet consumption causes excess weight gain in part by generating resistance to these signals, but the mechanisms by which this occurs are incompletely understood. In the periphery, obesity is associated with expansion of the macrophage compartment, generating an inflammatory milieu that promotes insulin resistance. Likewise, long-term high-fat feeding induces inflammation in the hypothalamus; however, this process is implicated as a cause rather than consequence of weight gain since both pharmacological and genetic blockade of hypothalamic inflammation attenuates diet-induced obesity. Our data suggest that interactions between hypothalamic neurons and glia rapidly induced by high-fat feeding have the potential to affect the control of food intake and body weight.

T3/T4:RS1.2
Leptin and neuronal development

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Leptin is well known as an important hormone in the central control of feeding behavior. During development, fetuses and newborns are exposed to leptin and recent evidence has shown that leptin receptors are widespread throughout the developing brain. This lecture will summarize recent findings concerning the developmental effects of leptin on brain pathways involved in feeding regulation. It will show that the actions of leptin in the developing brain are generally permanent and range from neurogenesis in the embryonic neuroepithelium to axon growth in the postnatal hypothalamus. Nutritional manipulation of leptin secretion during perinatal life has generated considerable concern. This lecture will also provide an overview of recent evidence concerning the effects of nutrition in programming the development and organization of hypothalamic circuits that regulate feeding behavior and energy balance.

Supported by research grants from the National Institute of Health (NIH/NIDDK), and the French National Agency for Research (ANR)

T3/T4:RS1.3
Thrifty energy metabolism in catch-up growth trajectories to obesity and the metabolic syndrome

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Catch-up growth (after fetal, neonatal and/or infantile growth retardation) is a risk factor for later obesity, type 2 diabetes and cardiovascular diseases. These risks are generally interpreted alongside teleological arguments that environmental exposures that hinder growth early in life lead to programming of 'thrifty mechanisms' that are adaptive during the period of limited nutrient supply (or growth constraint), but which increase risks for diseases during improved nutrition and catch-up growth later in life. This presentation addresses this notion of adaptive-turned-maladaptive 'thrifty mechanisms' in the light of evidence that catch-up growth is characterized by a disproportionately higher rate of fat gain relative to lean tissue gain, and that such preferential catch-up fat is in part driven by energy-sparing mechanisms operating via suppressed thermogenesis. It reviews emerging insights into the mechanisms that constitute this thrifty 'catch-up fat' phenotype which operate during the phase of catch-up growth to predispose towards obesity and the insulin-resistance (metabolic) syndrome.

Conflict of interest: None.
Funding: Swiss National Science Foundation (SNSF).

TRACK 5

T5:RS1 – Comorbidities of Obesity

T5:RS1.1
Obesity and polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a common and complex disorder characterized by androgen excess, oligo-anovulation and polycystic ovaries on ultrasound. PCOS appears to be closely associated with obesity. Although obesity is not universally observed in PCOS, many women with PCOS are obese, and android fat distribution is common in lean PCOS. Obesity is recognized as a major contributor to considerable variation in severity and expression of PCOS phenotype. Obese women with PCOS have more severe cardiometabolic risk factors compared with their lean counterparts. Increased adiposity, particularly the abdominal type, has significant impact on androgen excess and oligo-anovulation of PCOS through various mechanisms. Although underlying genetic and environmental factors are not fully understood for the linkage between obesity and PCOS, insulin resistance appears to be a common denominator of these disorders. Finally, it is noteworthy that even modest weight loss through diet interventions and increased physical activity has favorable effects on metabolic, endocrine and reproductive outcome in PCOS.

T5:RS1.2
Obesity and kidney

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The last three decades a considerable increase of obesity and chronic kidney disease has been observed. In a recent meta-analysis over-

weight individuals had elevated risk of kidney disease (RR = 1.40; 95% CI: 1.30–1.50) compared to normal-weight individuals; obese subjects were at much higher risk (RR = 1.83; 95% CI: 1.57–2.13). Moreover, multiple epidemiologic studies have linked the development of renal cell carcinoma to obesity. Obesity increases renal sodium reabsorption mainly by activating the renin-angiotensin and sympathetic nervous systems but also by modifying intrarenal physical forces. Visceral obesity leads to hypertension by several mechanisms. This may affect considerably renal function. Moreover, insulin resistance and adipose tissue derived molecules which affect inflammation may lead to hyperfiltration and histological changes in the kidneys. Several studies have shown a relation between obesity and focal segmental sclerosis and hyalinosis. Interestingly lowered adiponectin levels in visceraly obese patients directly affect the renal podocytes and lead to albuminuria. All the above histological and functional changes may provoke progressive decrease of glomerular filtration rate and further increase of arterial pressure. These effects may increase substantially cardiovascular mortality. Dietary treatment of obesity and weight loss decreases proteinuria. Bariatric surgery improves considerably the metabolic parameters and renal function. However, adverse effects may also occur such as oxalate nephropathy which may lead to chronic kidney disease or end-stage renal disease. In conclusion obesity provokes renal disease by several mechanisms and weight loss may be a useful treatment.

T5.RS1.3
Dicker

T5:RS2 – Physical Activity

T5:RS2.1
Physical activity and body composition in school-age youths
Gutin B[1]
[1]*University of North Carolina- Chapel Hill, USA*

Recent research suggests that physical activity PA of a vigorous nature (such as running), more so than moderate PA (such as walking), helps youths to develop bodies that have relatively low amounts of fat mass as a percentage of total body mass. Because vigorously active youths tend to ingest more dietary energy than their sedentary peers, it is easier for them to ingest sufficient amounts of the nutrients needed to support healthy growth. Thus, *preventive* interventions should emphasize promotion of vigorous PA and ingestion of nutrient-rich diets, rather than restriction of dietary energy intake. The minimum dose needed for non-obese youths to develop and maintain healthy body composition and fitness is approximately 60 minutes/day of vigorous activities such as basketball, soccer and dance. For *treatment* of youths who are already obese, it is often necessary to restrict energy intake in order to incur the substantial energy deficits needed to reduce fat mass. For such dieting youths, concurrent participation in PA helps to prevent the loss of lean body mass that often accompanies low-energy dieting. Intervention studies of obese youths that have focused exclusively on PA, with no emphasis on dietary change, indicate that engaging in moderate-vigorous PA 3–5 times/week, for 30–50 minutes/session improves body composition and aerobic fitness. As the youths improve their fitness and body composition, they should increase their dose of PA in both intensity and volume to the levels recommended for non-obese youths.

Reference: Gutin B. Diet versus exercise for the prevention of pediatric obesity: the role of exercise

Conflict of interest/funding: I have no conflict of interest to disclose. My research has been funded mainly by the National Institutes of Health of the USA.

T5:RS2.2
How do we get adults to be more active?
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To get adults to be more active has been recognized as a public health priority by WHO. To achieve this goal, we need to have an understanding of how to define and assess this complex behaviour, what its determinants are and whether the available evidence from intervention studies is generalisable to different settings. Technological developments in assessment of human movement behaviour provide new tools to study the distinct dimensions of activity, inactivity and sedentary behaviour in relation with chronic disease and obesity. New issues are emerging about the respective influence of different sedentary behaviours on weight and health outcomes. Although it is likely that only increasing leisure-time physical activity will not be enough to substantially alter the tendency for weight gain, there is an important body of evidence showing that even light to moderate physical activity has the potential to improve physical capacity and metabolic health. Focusing only on individual-level behavioural factors would however mean missing a major part of the overall picture where broader contextual influences appear so powerful. In this field, refinement of spatial analysis techniques as applied to the field of build environment in relation with physical activity is needed. Based on socioecological models of health behaviour, this should help, at least in part, to better delineate the respective influence of the physical and social environment on physical activity at individual level, and the relationships with body weight outcomes. A key question then is: how do we get the environment to help adults to be more active?

Conflict of interest: None.
Funding: Supported in part by the French National Research Agency (ELIANE ANR-07-PNRA-004).

T5:RS2.3
Time spent in sedentary posture, measured by activPAL, is a robust predictor of waist circumference and cardiovascular risk
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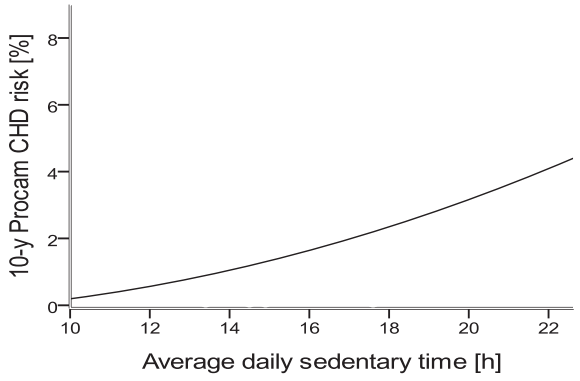
Introduction: The aim was to establish the association between objectively measured time in sedentary posture and coronary heart disease (CHD) risk.
Methods: A total of 74 healthy Glasgow postal workers–36 (3F) office workers and 38 (3F) walking delivery workers – were recruited to wear the activPAL physical activity monitor and to give fasting blood samples for lipid profile and plasma glucose. 10 years PROCAM coronary risk was calculated. Partial correlations and multiple regressions were undertaken to explore the association between daily time spent in sedentary posture coronary risk.



Results: Significant associations between daily sedentary time and coronary risk factors, after adjusting for age, energy intake, complex carbohydrates, dietary fat, saturated fat, sugars, vitamin C, fibre density and daily energy expenditure (MET.hours).
Only age and sedentary time were significant predictors of 10 years PROCAM CHD risk, accounting for 42% of the variability ($R^2 = 0.42$, $P < 0.001$). 10 years PROCAM CHD risk increased by 0.27% for each hour spent sedentary each day (Figure 1), and by 0.26% for each additional year of age.

Regression model shows significant dependence of 10 year PROCAM CHD risk on daily time spent in sedentary posture.

Partial correlations	BMI	Waist	Total chol	Triglycerides	HDL	PROCAM risk
Sedentary time						
r	0.32	0.41	0.13	0.31	–0.35	0.26
P	0.01	0.001	0.31	0.02	0.01	0.04

Conclusion: Time spent sedentary is a valuable, modifiable independent risk factor for CHD in apparently healthy men.
Conflict of interest: None to declare.
Funding: This project was funded by Glasgow Caledonian University, UK.

T5:RS2.4

Associations of cardiorespiratory fitness and physical activity with metabolic risk factors in bedfordshire schoolchildren [happy study]

Bailey DP, Kerr CJ, Savory LA and Denton SJ
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Introduction: Cardiorespiratory fitness (CRF) and physical activity (PA) may be pivotal in the protection and treatment of cardiovascular disease and metabolic risk factors in children and adolescents. However, few studies have investigated this hypothesis. The aim of this study was to explore the associations of CRF and PA with individual metabolic risk factors and the Metabolic Syndrome (MetS).
Methods: One hundred and sixteen boys and girls aged 10–14 years had waist circumference (WC) and blood pressure (BP) measured and also completed a maximal cycle ergometer fitness test and seven consecutive days of minute-by-minute PA monitoring using the RT3® triaxial accelerometer. Eighty-six participants provided blood samples and were fully screened for MetS using Cook *et al.*, (2003) paediatric definition.
Results: When adjusted for age and sex, regression analysis revealed that the odds of having high WC (OR 0.73, $P < 0.001$), high body fat % (OR 0.76, $P < 0.001$), high diastolic BP (OR 0.92, $P < 0.05$), and MetS (OR 0.89, $P < 0.05$) significantly decreased with increasing CRF. Triglycerides, HDL-cholesterol, fasting blood glucose, and systolic BP were not associated to CRF, while PA held no associations with MetS or individual risk factors.
Conclusion: These results suggest that CRF, but not PA, is associated with individual and clustered metabolic risk factors in children and adolescents. Interventions to improve the metabolic profiles of youth should aim to increase CRF.
Conflict of interest: None disclosed.
Funding: Research relating to this abstract was funded by the Bedford Charity (The Harpur Trust).

T5:RS3 – Nutritional Aspects of Treating Obesity

T5:RS3.1

Dietary treatment of obesity – a chronicle of failure?

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The treatment of obesity demands a negative energy balance, which obviously necessitates reducing the *quantity* of food intake. Yet the optimal diet composition *quality* for weight loss is still unclear. The major controversy seems to be between choosing low-fat or low-carbohydrate diets, with additional debates on the importance of the glycemic index and the amounts of dairy products and calcium. It is evident from many large, randomized trials that the 'best diet' that can suit everyone has yet to be identified. The different options for low-calorie diets should be prescribed on an individual basis, in order to best fit each patient's personal preferences. All hypocaloric regimens are suitable (and apparently equally (in)effective[1]), as long as they work for a given subject. The problem, of course, is long-term maintenance and adherence to an altered lifestyle, and the public health challenge is how to learn from the successful 'positive deviants'[2]. Recent work suggests that some 17% of subjects are indeed able to maintain a sustained weight loss of at least 10%, which is of major benefit in combating the metabolic complications of obesity[3].
References:
1 Dubnov-Raz G & Berry EM. Dietary Approaches to Obesity. *Mount Sinai J Med*. 77: 488–98, 2010.
2 Berry EM & De Geest S. 'Diabesity' & Positive Deviance: the challenge of adherence to long-term therapies': Israel National Institute for Health Policy, 2011.
3 Kraschnewski JL *et al*. Long-term weight loss maintenance in the United States. *Int J Obes* 34: 1644–54, 2010.

T5:RS3.2

Dietary management in postsurgical obese patients

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Bariatric surgery is the only proven effective long term efficient weight loss therapy for severe obesity and related commorbidities. Outcomes of malabsorptive and restrictive procedures depend on several factors. Potential nutritional derangements arising from degree of malabsorption, triggered by change of dietary habits, gastrointestinal changes, occasional food intolerance, change in satiety regulation, poor food choice, or simply by restriction of food intake can be avoided through detailed and continuous nutritional education and overall interdisciplinary support is extremely important in achieving long term success and preventing possible serious clinical disorders.
Author will present algorithms for post-surgerical patient follow-up period, timings, meal progression and diet composition as well as relevant clinical, lab and nutritional checks linked to particular bariatric procedures.
Recommended dosages of proteins, micronutrient supplementation after malabsorptive or combined bariatric surgery according contemporary guidelines will be summarized. Compliance with nutritional recommendations contributes to prevention of protein malnutrition, metabolic bone disease and secondary hyperparathyreoidism (calcium, vitamin D), compromised haemopoesis (iron, vitamin B12, folate, copper), central and peripheral neuropathy (thiamin, vitamin B12, copper), night blindness (vitamin A), oxalate nefropathy with

chronic kidney disease and end stage renal disease (calcium, oxalates), worsening of wound healing (vitamin C, Se, Zn, protein malnutrition..) and other potentially serious depletions.
Emphasis is given on review of nutritional management of post-bariatric patient in cases they become critically ill (for non-bariatric reasons), in pre-pregnancy and during pregnancy period, as well as on interdisciplinary management of eating behaviour disorders, frequently presented after bariatric surgery.
Supported by a grant MSM 0021620819 'Replacement of and support to some vital organs' Charles University, Medical School and Teaching Hospital Plzen, Czech Republic.

T5:RS3.3
Is intervention intensity related to dropout rates in diet/supplement randomized weight control trials?

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Introduction: We hypothesized that aspects of interventions related to participant burden or frequency of contact might be related to dropout rates in weight control trials.
Methods: We extracted dropout rate and intervention details and generated an intervention score based on the types and frequencies of activities described in the methods section of 46 studies. Intervention scores consisted of dietary and physical activity tasks such as counselling, keeping food /activity journals and frequency of contact. Contact frequency scores were summed and Pearson's correlations with percent dropouts were calculated. Welch's ANOVA were performed for mean dropout percentages between those requiring food (30 yes, 16 no) and physical activity journaling (22 yes, 24 no).
Results: The mean (SD) dropout percentage = 15.3% (11.1), range 0–41.5%. Correlations between dropout percentages and frequency of contact were not significant ($r = –0.065$, $P = 0.668$). Correlations between diet or physical activity sub-scores were also non-significant (all $P > 0.561$). There was a significantly higher dropout percentage in studies where food journaling was required (M = 17.6%, SD = 11.6) over those where it was not (M = 11.1%, SD = 9.2), F (1,37.251) = 4.354, $P = 0.044$. There was no significant difference in dropout percentage in studies where activity journaling was required (M = 15.9%, SD = 9.4) compared to those where it was not (M = 14.7%, SD = 12.6), F (1,42.528) = 0.125, $P = 0.726$.
Conclusion: Results indicate a relationship between dropout rates and required food journaling in diet/supplement trials. Future studies should examine whether this is a causal relationship.
Conflict of interest: Dr. Allison has received grants and consulting fees from companies with interests in clinical trials design.
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T5:RS3.4
Addiction to highly pleasurable foods as a cause of the childhood obesity epidemic

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Introduction: In December 1999 an interactive, open-access website was launched to help overweight and obese youth. Information on healthy eating, portion control, and exercise, with online community support, was grossly inadequate for most of the thousands of youth using the site to attain and maintain healthy weights.
Methods: A 10 year prospective study was carried out of qualitatively analyzing 134 568 anonymous bulletin board messages posted by overweight youth, ages 8–21, with the goal of elucidating reasons for their weight loss failures and successes.
Results: Thirty-two percent explicitly described turning to food when sad, stressed, or bored and unable to stop. For most, this 'comfort eating' appeared mindless. Most hated being fat, yet they struggled to resist cravings for highly pleasurable foods. The way these youth described their relationship with highly pleasurable foods satisfied nearly all of the WHO substance dependence (addiction) criteria. Their struggle to lose weight was proportional to BMI percentile, where morbidly obese youth struggled the most. Thus, their dependence on highly pleasurable foods appeared to be on a continuum: overweight youth seemed only partially dependent (addicted); obese youth fully dependent (addicted); and morbidly obese youth probably in addictive tolerance mode, where they ate more and higher pleasure-level foods to obtain the same degree of comfort.
Conclusions: Food addiction is an unpopular paradigm among health professionals. Nevertheless, acknowledging addiction to highly pleasurable foods for a segment of the paediatric population and incorporating substance dependence methods into overweight interventions may help improve the success rate in combating the childhood obesity epidemic.

T5:RS4 – Novel Drugs

T5:RS4.1
Pharmacotherapy of obesity: lessons from past and present

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Pharmacotherapy for obesity represents a great failure in translational research. In fact, after the discovery of leptin 15 year ago and the assumption that appetite and energy homeostais are hormonally regulated, a wealth of peptides and factor have been proposed as candidates for antiobesity intervention. The result of that tremendous effort is a failure, we have only orlistat for obesity treatment. All other drug were progressively discontinued and most of them were poorly used before discontinuation. Potential explanations of such situation are: (i) single drugs are unable to work effectively as a therapy, perhaps, only combinations will do it. (ii) the safety limits must be reevaluated and weighted against the risk of no treating the patients. (iii) the ideology of health administration must change to finally accept that obesity is a ''true'' disease and not a will power problem and finally, (iv) regulatory authorities must understand that physicians are capable and may manage the adverse effects of drugs on a reasonable manner.
There is a considerable amount of new drugs in the pipeline of pharmaceutical industries. But only solving the above points may them be incorporated in the future treatment of our patients.

T5:RS4.2
What are the targets of new drugs in the pipeline?

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The antiobesity drug market is characterised by the controversy of increasing prevalence of obesity and limited possibilities of current pharmacotherapy. There are several possible targets of new antiobesity drugs with four mechanisms of action: (i) centraly acting appetite suppressants, (ii) calorie absorption inhibitors, (iii) Gut derived incretine based drugs. The fourth mechanism of metabolism enhencing was never successful in the history of antiobesity drug research and it is not probable that it will be successful in future. Appetite suppressants under clinical development (e.g. lorcaserin, naltrexone, zonisamide, metreleptin, tesofensine) have a large clinical perspective

especially in combination with another drug with additive effect or drug limiting side effect e.g. depression. Cetilistat is perhaps the only new calorie absorption limiting drug with lower side effects then orlistat. The most perspective antiobesity drugs are gut derived incretine analogues (primarily developed for diabetes treatment). The effect of liraglutide in non diabetic patients was twice stronger then the effect of orlistat in a placebo controlled study. Several other drugs from this group (exenatide, exenatide once weekly, albiglutide, taspoglutide, lixisenatide and others) could be successful in inducing weight loss non only in diabetic but also in nondiabetic patiens. Pramlintide, another related drug, is successful in inducing weight loss in combination therapy. Weight can be induces as a secondary effect of drugs for treatment of comorbidities (centrally acting antihypertensive drugs, antidepressants as bupropione and antidiabetic drugs (incretine analogues, gliflozines). The perspectives of antiobesity drug market are promising especially when combining drugs with different mode of action.

Potential conflict of interest: Member of local advisory boards in Czech Republic: Lilly Diabetes, Novartis, and MSD. No funding.

T5:RS4.3

Incidence and effects of nausea on weight loss and quality of life with the glp-1 analogue liraglutide: A 52-week randomised trial

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Introduction: A placebo-controlled 20 week trial (extended to 52 weeks) of liraglutide on weight (primary outcome) was conducted in non-diabetic obese adults.

Methods: Participants (n = 564, 18–65 years, BMI 30–40 kg/m^2) on a 500 kcal/day deficit diet plus exercise were randomised after 2 weeks to once-daily liraglutide (1.2, 1.8, 2.4 or 3.0 mg, evening subcutaneous injection), placebo, or open-label orlistat (120 mg×3 / day). Analyses were post-hoc, with last-observation-carried-forward for weight-change.

Results: Intention-to-treat participants were 561/564 (n = 90–98 / arm, age 45.9(10.3) years, BMI 34.8(2.7) kg/m^2 [mean(SD)]. Mild to moderate nausea/vomiting occurred equally in men and women. More participants reported nausea/vomiting with liraglutide 3.0mg (49/93;53%) than with lower doses, placebo (8/98; 8%) (P < 0.0001, logistic-regression) or orlistat (7/95; 7%), (P < 0.0001). Median durations of nausea episodes were 15 days (placebo, n = 7), 15–31 days (liraglutide 1.2–3.0 mg, n = 23–45) and 35 days (orlistat, n = 8). Most nausea episodes started in weeks 1–4 and none were rated serious. Most liraglutide 3.0 mg recipients experiencing nausea [36/45(80%)] had one episode, with only 4/93(4%) withdrawals over 52 weeks due to nausea/vomiting.

Mean weight-loss with liraglutide 3.0 mg was 10.0 kg for those with nausea/vomiting (n = 49) and 7.3 kg for those without (n = 43) (difference 3.0 kg [95%CI 0.5–5.4]; P = 0.02, ANCOVA). Weight-loss without nausea/vomiting was still 4.2 kg greater than placebo (P = 0.0001) and 2.3 kg greater than orlistat (P = 0.04).

Total quality-of-life scores at 20/52 weeks with liraglutide 3.0 mg improved from baseline, equally in those with and without nausea.

Conclusion: Nausea occurs mainly in weeks 1– 4 in c.50% of individuals on liraglutide 3.0 mg. However, it is well-tolerated, associated with 3.0 kg greater weight-loss without impairing quality-of-life.

Conflict of interest: AA, NF, LN, SR and LVG were Novo Nordisk (NN) advisory board members and received speakers' honoraria. AR was a NN advisory board member. ML, MK, RC, and MJS received research funds from NN. AH and MLL are employed by NN and hold shares in the company.

Funding: Research for this abstract was funded by Novo Nordisk A/S, Denmark.

www.clinicaltrials.gov ID: NCT00480909.

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T5:RS4.4

Cardiometabolic risk reduction is directly related to magnitude of weight loss with low-dose, controlled-release phentermine/topiramate (PHEN/TPM CR)

Rössner S[1], Peterson C[2], and Troupin B[2]

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Introduction: Analysis from a Phase 3 study (CONQUER) assessed effects of different weight loss (WL) categories on cardiometabolic risk factors in overweight/obese subjects with ≥2 weight-related comorbidities treated with PHEN/TPM CR.

Methods: This double-blind, 56-week trial randomized 2487 subjects to receive placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg(15/92).

Results: Subjects had a mean baseline weight of 103.1 kg and BMI of 36.6 kg/m^2. A comparative categorical analysis at week 56 demonstrated that subjects achieving ≥ 10%– < 15% WL or ≥ 15% WL had significantly greater improvements in multiple cardiometabolic parameters than subjects achieving 5% – <10% WL (Table). At week 56, least-squares (LS) mean percent WL was significantly greater for both doses of PHEN/TPM CR versus placebo (P < 0.0001): 1.2%, 7.8%, and 9.8% (ITT-LOCF) for placebo, 7.5/46, and 15/92, respectively. PHEN/TPM CR was generally well tolerated.

Table. LS Mean Change in Cardiometabolic Parameters at week 56.

	Mean Baseline	5% – <10% WL	≥ 10% – <15% WL	≥ 15% WL
Waist circumference (cm)	113.5	−7.9	−12.0*	−18.2*
Systolic blood pressure (mm Hg)	128.4	−4.8	−7.4†	−9.4*
Diastolic blood pressure (mm Hg)	80.6	−3.8	−5.0†	−5.6†
Triglycerides (mmol/L)	1.86	−0.2	−0.5*	−0.7*
HDL-C (mmol/L)	1.26	0.03	0.09*	0.17*
HbA1c (%)	5.8	0.0	−0.1†	−0.3*
Fasting glucose (mmol/L)	5.8	−0.2	−0.4†	−0.6*

*P < 0.0001 versus 5% to < 10% WL; †P ≤ 0.05 versus 5% –< 10% WL

Conclusions: PHEN/TPM CR resulted in greater WL than placebo. Significant improvements in multiple cardiometabolic risk factors occurred with incrementally greater WL.

Conflict of interest: Dr. Rössner has received support from Vivus, Inc., for consultancy work.

Mr. Peterson and Dr. Troupin are employed by Vivus, Inc., the manufacturer of the study drug.

Funding: Research relating to this abstract was funded by Vivus, Inc.

T5:RS5 – Management of Childhood and Adolescent Obesity

T5:RS5.1
Family based interventions for the treatment of obesity

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Only few family based interventions fulfill stringent research criteria thus allowing assessment of their effectiveness. Several issues require consideration:

1) Age of the child; the intervention must appropriately target the respective age group and effects of weight loss programs may be dependent on age.
2) The extent of the involvement of the family differs being minimal in trials that focus on the child only; even in such interventions parents must be motivated to let their child participate and accordingly arrange their schedule. Some studies have targeted only parents. The majority of studies have targeted both parents and their children.
3) The selection criteria for inclusion in a trial are important and include motivation of the child/family (rarely assessed), BMI for age, gender, parental obesity, somatic comorbidity and mental health of the probands/parents and socio-economic status of the family.
4) The type of intervention varies both in qualitative and quantitative terms. Some interventions focus on dietary intake, others on increasing physical activity and decreasing inactivity, and finally on healthy lifestyle changes.
5) Side effects of family based interventions are usually not assessed despite concerns that a subgroup of exposed children may actually develop somatic (e.g. increased weight gain) and/or emotional (reduced self-esteem as a result of the failure to lose weight during the intervention) ''side effects''.
6) Outcome criteria and length of follow-up differ.
7) Finally, cost-effectiveness and generalizability need to be taken into account. We will address the aforementioned aspects based on published randomized controlled trials to treat childhood obesity.

T5:RS5.2
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T5:RS5.3
Management of childhood and adolescent obesity: bariatric surgery

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Background: Results of bariatric surgery in young adolescents are limited in the international literature and choice of operation remains controversial.
Methods: From December 1996 to December 2009, 39 patients ≤ 19 years old with minimum follow-up of 1 year were retrospectively selected from an institutional data base out of 1475 obese operated patients (2.6%). Mean age was 17.7 ± 1.9 years; mean preoperative weight, BMI and %excess weight were 119.7 ± 18.7 kg, 43.9 ± 5.5 kg/m^2 and 75.2 ± 21.9, respectively. 13/39 (33.33%) patients were preoperatively submitted to BIB\intra-gastric balloon placement; 4/13 (30.7%) patients refused to receive any surgical procedure after BIB removal. Laparoscopic Adjustable Gastric Banding (LAGB) was performed with Lap Band System (Allergan) or SAGB (Ethicon), Laparoscopic Gastric Bypass(LRYGBP) was performed by using circular stapler ante-colic ante-gastric anasthomosis, Sleeve Gastrectomy (SG) was performed with a vertical gastric transection reinforced by Peristrip Veritas calibrated on a 40 Fr bougie, Laparoscopic Biliopancreatic Diversion(LBPD) was performed according Scopinaro technique. Weight loss failure was considered BMI > 35.
Results: A total of 18 (12F/6M) patients with LAGB presented a mean weight, BMI and %EWL of 89.9 ± 26.1 kg, 32.8 ± 7.1 kg/m^2, 54.7 ± 32 respectively (mean follow-up:60 ± 37.5months). 5/18 (27.7%) LAGB underwent band removal due to unsatisfactory weight loss and were converted to other procedures; 3 other patients (16%) failed presenting BMI > 35.
A total of 16 (15F/1M) LRYGBP patients (13 primary and 3 secondary procedures) presented a mean weight, BMI and %EWL of 87.8 ± 18.2 kg, 32.4 ± 5.8 kg/m^2 and 65.7 ± 25.1 respectively (mean follow-up: 44.4 ± 27.3 months). 3/16 (18.75%) patients presented BMI > 35.
A total of (2F/1M) SG patients (2 primary and 1 secondary procedures) presented a mean weight, BMI and %EWL of 85 kg, 30 ± 1.2 kg/m^2 and 76.6 ± 1.7 respectively (mean follow-up: 18 months).
LBPD patients (3F of which one affected by Prader Willi's syndrome, two primary and one secondary procedures) presented a mean weight, BMI and %EWL of 99.3 ± 8 kg, 37.6 ± 6.4 kg/m^2 and 51 ± 30.9 respectively (mean follow-up: 30 ± 25 months). Overall follow-up rate was 97.4%. Mortality and complications were absent.
Conclusions: Restrictive procedures for treatment of obese teenagers have a high-rate of failure and conversion to other bariatric operations.

