Report of the Danish Consultation Process
- Obesity research towards 2020
Preface

On behalf of representatives of the Danish Research field in obesity, we are pleased to present the outcome of the Danish Consultation Process on Obesity Research towards 2020.

The Danish Consultation Process was initiated by Danish Obesity Research Centre (DanORC) and the UNIK research initiative ‘Food, Fitness & Pharma’ together with Capital Region Denmark EU Office (creoDK) and have engaged more than 50 researchers, building on the collective Danish capacities within individual areas of obesity research, as well as the multi-disciplinary approach.

The ambition of the Danish Consultation Process was to describe the research challenges, potentials and priorities to meet the needs of society towards tackling obesity and associated co-morbidities including type-2 diabetes, metabolic syndrome and cardiovascular disease, as well as cancer, infertility and musculoskeletal disorders. Further, we wanted to explore the potentials for developing common long-term priorities in obesity research, and hereby strengthening the platform for interaction with stakeholders.

Through the last decades, high expertise of separate research areas has undergone significant progress in the direction of understanding individual factors that play a part in the development of obesity. In particular, the role of genetic and physiological mechanisms involved in regulation of body weight and the beneficial effects of physical activity, certain diets and food components have been explored. Less attention has been devoted to understanding the obesity epidemic in the light of social and historical conditions of the European society, and addressing the future balancing of, on the one hand, the responsibility and actions of society and policy makers in changing the environment and living circumstances and, on the other hand, the responsibility, empowerment and autonomy of the individual to choose their own lifestyle.

Now, following decades of primarily mono-disciplinary approaches towards understanding, preventing and treating obesity and related diseases, there is a growing ambition to integrate the research approaches and methods in assessing the gaps in the current knowledge. Evidently, the scale and the complexity of the challenge posed by the obesity epidemic calls for collaboration across disciplines, across institutions and across borders.

THE DANISH CONSULTATION PROCESS

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For further information on the full process and the participants at the Danish Workshop please visit www.foodfitnesspharma.ku.dk/DCP

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Summary of the Danish Consultation Process –
Obesity research towards 2020
Summary of the Danish Consultation Process - Obesity Research towards 2020

The Danish Obesity research community is working actively with the European Association for the Study of Obesity (EASO) to develop priorities for obesity related research towards 2020. The initiative is known as EuroObesity. The scale of the challenge posed by the obesity epidemic calls for collaboration across borders, disciplines, and institutions. This summary, and the accompanying report1, outlines the strategic priorities for this effort as identified by the leading Danish researchers through an intensive consultation process culminating in a workshop held at the University of Copenhagen the 18th of August 2011.

State of the art and major issues of the obesity challenge

The prevalence of childhood and adult obesity is high and increasing in both Europe and worldwide. Obesity is representing a heavy burden on the individual, on the health and care systems, on the efficiency of the workforce and on society at large. At the same time, no other lifestyle condition has the same level of visibility and attention for the individual, the society and from the media. Tackling obesity is a cornerstone in preventing and treating type-2 diabetes, metabolic syndrome and cardiovascular disease, as well as cancer, infertility, musculoskeletal disorders.

Through the last decades, high expertise of separate research areas has offered significant progress towards understanding factors involved in the development of obesity. In particular, the role of genetic and physiological mechanisms involved in regulation of body weight and the beneficial effects of physical activity, certain diets and food components have been explored. Less attention has been devoted to understanding the obesity epidemic in the light of social and historical conditions of the European society, and addressing the future balancing of, on the one hand, the responsibility and actions of society and policy makers in changing the environment and living circumstances and, on the other hand, the responsibility and autonomy of the individual to choose their own lifestyle.

At this point, the frontline knowledge and challenges can be summarised as follows:

- The effect of physical activity and healthy diets are in many cases superior to the effect of pharmaceutical intervention. A high amount of evidence is available on isolated positive effects of exercise and certain diet compositions in preventing and treating obesity, but there is limited knowledge on the effects of integrated lifestyle patterns such as the interaction between diet, physical activity and sleep patterns.

- The platform for development of novel foods, food additives and probiotics are growing and holds a high innovative potential. However, there is scarce knowledge about consumer acceptance and priorities towards food, and a need for addressing sustainability in food productions and availability.
Summary of the Danish Consultation Process

1. Heritability of obesity is estimated between 40-70%, but very few of the involved genes and pathways have been identified. This leaves a large potential for reclassification of obesity for further exploring candidate genes and pathways involved in regulation of body weight, and for drug target identification as the involved genes and pathways are identified.

2. The few anti-obesity drugs on the market have limited effect. Several have recently been withdrawn and the pipeline has dried out, as late-stage drug candidates have failed due to limited efficacy or adverse effects. Further, little is known about how to increase compliance and ways to balance pharmaceutical treatment with changes in diet and physical activity.

3. Gastric bypass surgery is currently the only truly efficacious and long-lasting cure, but it is re-served for severe cases of obesity, and is associated with substantial side effects and ethical considerations. At the same time, there is limited knowledge about long-term effects and no available tools for predicting response vs. non-response prior to surgery.

To answer this question, we needed to address the following issues:

1. Who becomes obese, who develop related diseases, under which circumstances and in which situations?

2. Why and how do people become obese and develop co-morbidities?

3. How can obesity be prevented, managed and treated and what are the potential constraints and adverse consequences of the different approaches?

The impact, potentials and opportunities of the research

Following decades of primarily mono-disciplinary approaches towards understanding, preventing and treating obesity and related diseases, there is a strong platform of knowledge, disciplines and stake-holders, and a high willingness to integrating the research approaches and methods in assessing the gaps in the current knowledge, by asking novel questions that provides novel answers. This is the platform for cross-disciplinary research, for translational research and innovation, and for addressing obesity as a complex phenomenon.

We know that disciplines such as social epidemiology, microbiology and toxicology will be strongly involved in the next decade of obesity research, and new collaborations and partnerships of research should be established. Social sciences and humanities need to play a central role in development of novel interventions at both micro- and macro-level, and also in a strong consulting relationship to the field of genetics, food and diet, and physical activity research.

By establishing a closer connection between science and stakeholders, the products of the research will be properly implemented towards a significant impact at political, societal and individual level. The research priorities are identified based on the expected needs of the stakeholders in terms of efficiency, readiness, innovation, growth and competitiveness. The stakeholders include politicians and policy makers, the health and care sector and the private sector including food, pharmaceutical, medical technology sectors, as well as the organisational levels (communities, schools, and families) and the individual citizens.

By doing this, the next decade in obesity research has the potential for making the following possible:

- Supporting the consumer in making the healthy choices, recognized as affordable, easy, attractive and familiar choices, and taking into account the potential negative side-effects of campaigns and interventions.

- Advanced assessment and classification of obesity, and ability for early diagnostic and cost-efficient, target prevention and treatment for groups and individuals who are prone to develop co-morbidities.

- Sustainable messages from public and private actors and complementary technological approaches for empowering self-managing consumers by including physical activity and healthy eating habits as central elements in everyday life across ages and social classes, in ‘high-risk’ sub-groups, and during critical phases in life.

- Means to consider and avoid the adverse effects of policies, regulations, recommendations, interventions and classifications in terms of stigmatization and counterproductive reactions.

- Development and marketing of healthy food products and concepts for physical activity which are accepted, attractive and chosen by the consumers.

- Development of novel drugs, with minimal adverse effects, mimicking the beneficial effects of gastric bypass or counter-acting the obesogenic effects of genetically affected metabolic or neuro-physiologic regulatory mechanisms - combined with strategies for tailor made pharmaceutical treatments.

- Improved tools for supervision and follow-up on implementation of prevention and treatment approaches, and for monitoring broader impact on physical, mental and psychosocial functions, rather than just weight loss.

- Optimized European infrastructures and platforms for surveillance and prediction of obesity development and lifestyle of the European citizens, and for testing novel food components or drug candidates in animal models and in humans with the latest techniques in phenotyping, functional imaging, and ‘omics.

To optimally deliver the outcome above, these roadblocks related to frames and conditions for undertaking the suggested research should be addressed:

- The restrictive approach of regulatory authorities regarding approval of drugs targeting obesity, and the need for refining the approvals, allowing for approval of use in subgroups who are (or will be) suffering from severe co-morbidities.

- Establishing infrastructures for developing and generating ‘omics data. Current data mining techniques, multivariate evaluation methods and bioinformatics are not strong enough to handle the wealth of data generated from phenotyping, imaging, ‘omics and data related to psycho-social and environmental characteristics.

- Financial support for the health and care sector is often imbalanced, prioritising surgical and pharmacological treatment higher than the development of novel integrated regimes for promoting health and treating diseases.

- Establishing, operating and maintaining large-scale European cohorts will be challenging in terms of logistics, and in particular in terms of long-term financing of maintenance, follow-up, management and use of data and biological samples. Further, legal and ethical aspects needs to be taken into consideration.

- The structural bottlenecks to scale up research across disciplines related to e.g. publication, dissemination and teaching hampers the development of ambitious and full scale multi-disciplinary.
Specific priorities in research identified from the Danish consultation process

1. Examining social and societal factors complicating healthy lifestyle combined with experiences from collective, individual and real-life interventions will make it possible to map actors, frames, organisations, cultures and discourses and determine effects of prior interventions. With an optimised knowledge foundation, we can address the gaps in transferring interventions from controlled settings to changes in diet and exercise habits in the population level. This would facilitate developing effective policies, frames and legislations as well as infrastructures and urban planning, and aid the development of strategies for changing the habits of different societal groups, reducing health disparities and developing tailored treatments.

The development towards an aging obese population should be illuminated involving social sciences and humanities, actors from the health and care sector, political actors, non-governmental organisations (NGOs), businesses and the media. This could lead to new ways to manage and combat obesity that do not stigmatise or infringe the citizens considering values of empowerment and self-realisation and self-understanding for the individual other than just the value of being healthy.

By optimising and developing social technologies and services, information and communication technologies (ICT), ‘robots’, radio frequency identification tags (RFID) and other supportive tools, it will be possible to develop intelligent technologies and tools, meeting public beliefs, understanding, intuition and behaviour. These tools should be developed to support the citizens in making informed decisions and to motivate a physically active lifestyle. By monitoring different citizens groups in everyday settings, and potentially combining the data with existing and future cohorts and registers, we can address the effects of different recommendations and preventive measures to optimise future interventions.

2. Refining and integrating dietary recommendations and developing new foods and diets

The effects of diet composition, specific foods and food components on weight regulation, gut signalling, and metabolic health should be addressed in interventions, animal models and via epidemiological approaches. This should be integrated with cross-European data on eating patterns, food preferences and indicators of how dietary recommendations and food products have affected consumer behaviour and development of obesity in the past. The interaction between diet and physical activity, environmental, cultural and genetic factors should be taken into account when formulating dietary recommendations. This will allow for development of foods to support dietary recommendations and consumer acceptance, preferences and access. New production systems should be developed to achieve sustainability in the general food production.
The mechanisms and structural settings between actors should be addressed across Europe, including private sectors parallel interests in marketing of products and in corporation’s social responsibility (CSR). Research should explore how actors could collaborate towards sustainable messages and complementary approaches for changing the public behaviour towards a healthier lifestyle. This would lead to development of new and viable business models and incorporating CSR.

3. Optimal use of existing population data and establishing novel European cohorts

European cohorts, such as the EPIC cohort, have led to marked progress in understanding the genetic and lifestyle factors related to obesity and diseases. Follow-up examinations and data from these co-horts, which are now ageing, should be priorities for comprehensive studies of gene-environment interactions. The marked progress in the field of genetics and epigenetics, metabolomics, gut microbiota, and the perspectives of refined phenotyping calls for the establishment of novel European cohorts for extensive biological samples of relevant tissues and with insight into parental and gestational factors, including possible follow-up across generations. Social epidemiology should be strongly involved in the establishing of cohorts, and in exploring the use of the existing cohorts. Novel technologies and information systems should support the recording of lifestyle patterns, psycho-social data, and environment of the living condition including exposure to chemicals, food contaminants and use of over the counter medicine. Human Test Centre Facilities, platforms for phenotyping, and data management and statistics platforms should be central facilities of the cohorts, assuring continuity, development and technology transfer in optimal collection, handling and use of data.

Interventions in ‘high-risk’ obese individuals identified from the established cohorts could be a first step towards tailor-made prevention and treatment based on genetic predisposition to obesity and related diseases. A thorough assessment of potential adverse effects and diabetics related to classifying ‘high-risk’ individuals is crucial step towards implementing a ‘tailor-made’ approach.

4. Identifying early markers of susceptibility to development of obesity-related diseases, towards a reclassification of obesity, and targeting of prevention and treatment

Integrated approaches should be applied to mapping the genotypes, epigenetics, gut microbiota, metabolic and endocrine profiles, socio-economic, psychological and environmental factors associated with subsequent diseases development in overweight and obese individuals (including metabolic syndromes, diabetes, cancer, infertility and musculoskeletal disorders). Hereby paving the way for earlier diagnosis, for prioritising and targeting prevention and treatment, for increased cost-efficiency, and balancing beneficial and potential adverse effects of treatment. Potential negative effects of identifying ‘high risk’ individuals and groups should be addressed and tackled, including stigmatization, legal and ethical dilemmas and unwanted counterproductive consequence.

5. Developing concepts for refined phenotypic characterisation of body composition, insulin sensitivity and other metabolic and endocrine parameters of specific tissues in humans and animals is a central priority. Behavioural and psychological phenotyping methods should be developed, and the extent to which behavioural phenotypes can be assessed in animal models and transferred to humans should be explored.

The current low rate of associations between genotypes and phenotypes are expected due to the use of few, relatively unspecific phenotypes such as BMI and waist-hip ratio. More complex and refined phenotypes will pave the way for identifying the specific genes and pathways involved in regulating body weight through brain signalling, behavioural and metabolism etc. The methods will further be important in reclassification of obesity and targeting of prevention and treatment in the development of novel animal models and establishing of novel European cohorts to be followed over the coming decades.

6. Novel approaches for addressing the role of the brain in relation to obesity

The brain controls behaviours, preferences and responses related to food intake, exercise and stress, sleeping patterns, stress and computer games. Brain signalling is responsible for a large part of genetically determined differences in body weight, and signalling from the peripheral tissues including the gut, adipose tissue, liver and muscles are expected to play a crucial role in the regulation of body weight and well being. As an example, the effects of gastric bypass surgery on type-2 diabetes and obesity appear to involve altered signals from the gut to the brain, providing decreased appetite and altered food preference. Increasing evidence further suggests that physical activity has noticeable effects on brain function including cognitive functions, executiveness, reduction in depression and improved appetite regulation. Finally, the majority of candidate drugs works via the brain, and understanding brain functions paves the way for reducing the side effects though more indirect targeting of the relevant brain centres only.

Close interdisciplinary partnerships between physicists, psychologists, sensory-, behavioural- and neuro-physiologists, biologists and computer science, should move beyond the limited resolving power of current brain imaging techniques such as Functional MRI (fMRI). Refined methods should be developed for objective, non-invasive, real-time, in vivo monitoring of brain functions. The neuro-biology of addiction, reward, food preference, overeating and exercise, as well as response/lack of response to a given treatment, can then be explored in animal models and in humans, in combination with clinical, psycho-social and societal data.

7. Establishing animal models with high translational potential is a top priority in terms of investigating physiological and behavioural patterns related to obesity and co-morbidities, and will allow building on the large similarities between the human and animal genome. Animal test facilities will work as platforms for controlled interventions addressing the effects of specific genotypes, diet composition, energy expenditure, environmental and chemical exposures, testing of surgical procedures, and for obtaining refined phenotyping and biological sampling over time to address omics and epi-genetic changes. This will further be useful in developing improved foods and food ingredients, novel phenotypic characterisations, and for studying brain functioning and gut-brain signalling in obesity. These facilities will thus be a platform for both basic research, and for the business sector testing novel candidates and products.
Report of the Danish Consultation Process
- Obesity research towards 2020
The Danish Obesity research community is working actively with the European Association for the Study of Obesity (EASO) to develop priorities for obesity related research towards 2020. The scale of the challenge of the obesity epidemic calls for collaboration across borders, disciplines, and institutions and this initiative is now known as EurObesity.

The priorities for this effort have been discussed by the leading Danish researchers through an intensive consultation process culminating in a workshop held at the University of Copenhagen the 18th August 2011. The present document presents all the inputs collected from the Danish consultation process, and should be seen as a background paper for ‘Summary of the Danish Consultation Process’ and should be read in context herewith.

The Danish consultation process
More than 50 scientists from Denmark, as well as representatives from larger German research initiatives on obesity, representatives from EASO, the European Parliament, the Danish Agency for Science, Technology and Innovation, the Capital Region of Denmark and the Deans of the faculty of Health Sciences University of Copenhagen, all attended the workshop the 18th of August 2011.

Prior to the workshop, a first inspiration document was developed based on input from 10 of the leading environments in Danish obesity research. All attendants in the workshop were asked to actively contribute to further development of this document, with particular focus on describing the future research in a more long-term perspective, exploring the potentials for cross-disciplinary research, strengthening the platform for interaction with stakeholders and meeting the needs of the society in order to tackle the challenge of obesity.

The outcome of the consultation process appears to be well aligned with the research areas and priorities identified by the EASO and NIH, as well as a recent review series on obesity research in the Lancet, which indicates that a consultation of leading experts in obesity research, whether on the national, EU or American level leads to concurrent identification of research ideas and potentials.

The Danish consultation process was initiated and coordinated by the Scientific Advisory Committee and the Strategy and Organizing Committee for the initiative.

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Preamble

2. Strategic Plan for NIH Obesity Research, March 2011
The first part of this document, which presents the research potentials and priorities in a table, is a summary that visualises the impact of the proposed research and the progress beyond current state of the art. Further the table systematically outlines the needs and potentials for inclusion of other disciplines in the proposed research as well as the stakeholders who will be awaiting and using the results and who should be consulted and integrated in the research. Finally the table lists the infrastructures need, and the roadblock that should be addressed in order to fully pursue the subsequent proposed research and the societal impact and innovation.

The second part is a full length description of the research topics, providing the details on the suggested research areas and the impact and innovation potential of this research.

In both the table and the full length description, the research areas are described thematically. There are several possible constellations of combining these areas in novel large scale cross disciplinary research initiatives targeting the obesity epidemic (as indicated in figure 1, page 19). It therefore appears counterproductive to outline one combination across themes at this point.

Outline of Report of the Danish Consultation Process

The following table gives, for each of the major research topics, an overview of the following:

1. The current major issues and related state of the art (box to the left)
2. The major research topics, priorities and possibilities for the future (box in the middle)
3. Impact and innovation potential of the discoveries foreseen from the proposed research (box to the right)
4. The needs and potentials for inclusion of other disciplines and stakeholders (horizontal box below each topic)
5. Infrastructures need, and the roadblock* to be addressed in order to fully pursue the subsequent proposed research and the societal impact and innovation (horizontal box below each topic).

* The roadblocks described here are the identified obstacles and the ‘bumps on the road’ towards doing the research and implementing the results. The section lists roadblocks which can be alleviated by other lines, methods or disciplines of research or by strengthened infrastructures for research, as well as roadblocks related to political, regulatory, societal or consumer aspects.
1. Identifying individuals that will end up developing obesity-related diseases

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<tr>
<th>STATE OF THE ART</th>
<th>FUTURE RESEARCH POTENTIAL</th>
<th>IMPACT</th>
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<tr>
<td>Overweight and obesity leads to a range of diseases. There are few means to identify the individuals that will end up developing obesity-related diseases.</td>
<td>1.1 Mapping the genotypes, metabolotypes, enterotypes, socio- and environmental factors that lead to disease development in overweight and obese individuals. Include more refined phenotyping regarding body composition, adipose- and muscle tissue functioning, refined measures of insulin resistance and other endocrine and neurophysiologic functions. Assessing socio-economic, psychological, and environmental factors.</td>
<td>Means to identify overweight and obese individuals who are disease prone (even before obesity onset) and derive therefrom, to prioritise and administer the correct and necessary treatments hereby increasing cost-efficiency in obesity management. Evaluation of the younger generation proneness to disease based on both physiological and social and behavioural factors as well as epigenetic. Potential to identify focus groups for national and international interventions on the basis of systemic risk assessment.</td>
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Research collaboration: Involving all research areas, close collaboration with clinicians and other representatives from the health care sector who are involved in prevention and treatment of obesity. Strong involvement of statistical multivariate evaluation methods and bioinformatics. Social science will address the adverse effects of identifying ‘high risk’ individuals and groups, including presumed efficacy of interventions, stigmatisation and unwanted counterproductive reactions. Link to other research themes: Related to the majority of the outlined research themes, in particular 1.1, 2.1, 2.3, 3.2, 4.4, 5.4, 6.3, 7.2, 8.1. Collaboration with stakeholders: Public sector including health care sector, diagnostic and pharmaceutical industry. Infrastructure: Human and animal test facilities and access to existing and novel cohorts. Roadblocks: Lack of refined phenotyping and transferable animal models. Need for novel approaches to data analyses. Lack of knowledge on systemic interaction between biological and non-biological factors. Possible stigmatisation and counterproductive reactions in relation to the concept of identifying ‘at risk’ individuals.

2. Food & Diet

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<th>STATE OF THE ART</th>
<th>FUTURE RESEARCH POTENTIAL</th>
<th>IMPACT</th>
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<tr>
<td>Dietary regimes of high-protein and low glycemic index (GI) have been shown to improve bodyweight regulation in controlled experimental settings.</td>
<td>2.1 Clinical intervention studies, as well as community based studies, addressing effect and mechanism of protein sources, GI, whole grain, resistant starch and other food components in preventing obesity and promoting weight loss in children, adults and the elderly population. Effects of diet on insulin resistance, other markers of metabolic syndrome and gut microbiota should be addressed in intervention studies. Explore the acceptance of these diets by the public in cross-European observational and intervention studies. Testing of dietary recommendations at the public level.</td>
<td>A solid basis of evidence for dietary recommendations to the public. Targeted recommendations for the public and for people with, or at risk for, overweight and type 2 diabetes. Development of new sustainable food products which are attractive to the consumer and addressing the avenues for sustainability in production of high protein foods.</td>
</tr>
</tbody>
</table>

Research collaboration: Food research, including development of novel food products and ingredients, sustainable productions systems, social, cultural and economic sciences. Sensory science, food economics. Link to other research themes: 2.2-5, 3.2, 4.1, 4.3, 4.4, 5.2, 5.4, 5.6, 6.3, 6.4, 7.1, 7.2, 7.3, 7.4, 8.1. Collaboration with stakeholders: Food and agriculture industry, public sector and organizations working with health recommendations related to nutrition. Infrastructure: Need for establishing cohorts and human test centres for thorough phenotyping. Metabolomics techniques. Roadblocks: High protein diets are not sustainable if the main protein source is meat.
Certain food components, foods and diet compositions can enhance satiety and satiation. Little is known about the specific components of the foods responsible for these effects, or the physiological signaling behind this.

2.2 The role of gut and gut-brain signalling, in satiation and satiety, and the effect of different foods and nutrients should be addressed in animal and human models. Sensors for detection of dietary components in the gut should be identified.

Foods should be identified and designed to promote satiety based on their potential to stimulate release of satiety signals from the gut.

The CNS control of appetite, food intake, food preference, food addiction and food reward needs to be addressed in animal and human models.

Development of new and more effective food ingredients, foods, diet regimes and recommendations that enhance the success rate for weight loss and weight control.

Novel tools to overcome addiction to high fat and/or high sugar foods.

The generally implemented dietary advice that are the norm today in obesity treatment, are not producing optimal weight loss and weight maintenance.

2.3 Cross disciplinary approach to addressing the complexity of obesity and identify the broad spectrum of factors which should be included in novel validated tools for individualised or subgroup-based treatment programmes.

Intervention trials in several EU countries in selected groups with a high prevalence of obesity.

Toolboxes of efficient and cost-effective instruments of treatment to combat obesity and associated complications.

Develop and incorporate new validation and treatment methods for the public and private sector.

The role of the public and private sector in influencing the lifestyle of the citizens is not integrated into preventive strategies and little is known about which aspects of preventive initiatives works.

Sustainable recommendations to the public across actors, and sustainability in public beliefs, perception, understanding and behaviour towards fighting obesity as a collective.

Well informed self-regulated, healthier and satisfied consumers.

Research collaboration:
The food industry, social sciences and humanities for heightened acceptance of novel foods, (including attention to the fact that food is eaten for safety as well as for pleasure) and socio-economic aspects of implementation of novel foods and eating patterns, genetics and metabolomics.

Link to other research themes: 1.1, 2.1, 2.2, 3.1, 3.2, 3.3, 3.4, 4.1, 4.3, 5.1, 5.6, 7.1, 7.2, 7.3.

Collaboration with stakeholders: Public and private sector including health care sector, food and food ingredients industry and pharmaceutical industry.

Infrastructure: Human and animal test facilities, facilities for fMRI and novel imaging techniques for addressing neurophysiology of gut and brain signalling.

Roadblocks: The fact that the health care sector gets money for doing surgery, but not for developing novel integrated treatment regimes, and thus the lack of incentives for improving non-surgical approaches to obesity.

Research collaboration: Social science, humanities, psychology, genetics, physiology.

Collaboration with stakeholders: Industry, healthcare system, organizations (incl. schools, workplace).

Link to other research themes: 1.1, 2.1, 2.2, 3.1, 3.2, 3.3, 3.4, 4.1, 4.3, 5.1, 5.6, 7.1, 7.2, 7.3.

Infrastructure: Core facilities for doing large scale interventions of controlled diet and thorough phenotyping. Access to cross-European epidemiological data and ability to conduct intervention trials across Europe e.g. in cross-European Human Test Centres.

Roadblocks: The high costs of well managed large scale intervention trials. Statistic and bioinformatics to handle the data and to handle the between-country factors in observational and intervention trials. The novel dietary advice may not be broadly applicable for every community and needs to be specialized to work in different environments.

2.4 Address strategies for changing the habits of the general public and different population groups, avoiding adverse effects of preventive measures.

Explore cost-effectiveness of general vs. dedicated preventive regimes.

New forms of collaborating between public organisations, non-governmental organizations (NGOs), the private sector and media regarding strategies for changing the public behaviour towards a healthier lifestyle.

Research collaboration: Social sciences and humanities including sociology, anthropology, ethnology, economy, law and political and organizational studies. NGOs, public and private sectors including food industry and the media.

Link to other research themes: 2.1, 3.1, 3.2, 3.3, 3.4, 5.1, 7.1.

Collaboration with stakeholders: Food industry and other NGO’s, public and private sectors.

Infrastructure: Monitoring and following citizens groups and cohorts addressing the effect of different recommendations and preventive measures.

Roadblocks: Countering interests from the actors influencing public and societal behaviour.

Weight loss interventions are effective in controlled settings but challenging to get to the population at large.

2.5 Address the means to successfully bring the knowledge from lab to society in collaboration with the expertise from the humanities and social sciences.

Explore the use of Information and Communication Technologies (ICT) and robots for supporting the citizens and for assessing lifestyle parameters at a large scale.

Continuous refinement of recommendations and ways of providing support for a healthy lifestyle, based on the integrated experience on population level.

Research collaboration: Social science and humanities at large, communication, media and computer science, physical activity, mathematics and data handling experts.

Link to other research themes: 2.1, 3.1, 3.2, 3.3, 3.4, 5.1.

Collaboration with stakeholders: ICT, food and fitness industry, healthcare system, organizations (incl. schools, workplace).

Infrastructure: Take advantage of access to data across Europe, flat rate for using tools.

Roadblocks: Costs related to developing and using the tools, and need of collaboration with public and private stakeholders to make the tools work. Challenges to reduce inaccessiveness of measurements of physical activity.
### STATE OF THE ART

#### Interventions on a collective level such as campaigns, regulations and incentives, are often initiated with the best intentions, but without sufficient understanding of societal factors which may determine their success or failure.

Concurrently, the effect of past and current prevention strategies is difficult to pinpoint, as a variety of other factors are contributing to an increase in the prevalence of obesity.

Although many biological mechanisms of obesity are well-understood, the occurrence of an ‘obesity epidemic’ under the present particular social and historical conditions are not. Accordingly, the current prevention strategies are not systematically utilize insights into social-psychological causes, mechanisms and intervention forms, and at the same time, there is shortage of high quality literature and science journals describing which approaches are most effective in different environments.

In particular, studies with sufficient follow-up, realistic settings, and translational knowledge of real-world implementation, cost and benefits are limited.

Consequently, the option of socially and psychologically based intervention remains vague and complicated to put in use as a supplement and addition to biomedical interventions.

### FUTURE RESEARCH POTENTIAL

#### Interventions

3.1 Identify and examine how institutional set-ups and actors at national and European level interact and frame the development of healthy life styles.

Identify various interventions at macro-level (economic incentives, market regulation, public information and education, urban planning etc.) and examine theoretically and empirically how such interventions can affect, and has affected, population health.

Examine how framing and interaction of various policies and interventions (e.g. agricultural policies and health policies) may equally hamper /promote healthy lifestyles.

Examine how different stakeholders and organisations can collaborate for a global solution towards preventing obesity. The influence of public and private sectors on life style and behaviour should be explored.

**Research collaboration:** Psychology, history, economy, political science, social science, law, philosophers, physical activity, communication science, social epidemiologists, food science and human nutrition, architecture and urban planning.

**Link to other research themes:** 1.1, 2.1, 2.3, 2.4, 2.5, 3.4, 4.3, 5.1, 5.2, 7.2.

**Collaboration with stakeholders:** Policy makers, public sector, health sector, various industries (pharmaceutical, food, agriculture) and NGO’s (consumer, citizens and patients organizations).

**Infrastructure:** Cohorts and data mining resources.

**Roadblocks:** Potential conflicting interests of the actors influencing public beliefs and behaviour.

#### Novel evidence based and coherent public health actions, tools and interventions which are customised to meet the various needs of different target groups (children, adolescents, elderly persons, working population, immigrants etc).

Development of new intervention technologies and new platforms for policy-making and regulatory measures on macro-level, supporting both individuals and groups in achieving higher level of maintained success by respecting societal and social diversity.

Implementing general policies that can effectively modify life style related behaviours.

Outlining novel strategies and investing in new methods for the public and private sector to e.g. incorporate programs on corporate social responsibility (CSR) geared towards preventing obesity.

**Research collaboration:** Psychology, social science, philosophy, law, physical activity, human nutrition experts and clinical researchers.

**Link to other research themes:** 1.1, 2.1, 2.3, 2.4, 2.5, 3.4, 4.3, 5.1, 5.2, 7.2.

**Collaboration with stakeholders:** Primary and secondary health sector.

**Infrastructure:** Human Intervention Centre.

**Roadblocks:** Acceptance and financing from the public sector to support alternative treatment and preventions of obesity other than today’s traditional approaches.
3.3 Different obesity prevention interventions should be studied in terms of exploring the effect of people’s attitudes towards obese people, mapping the effects on social and ethnic inequality in health, investigating to which extent interventions are compatible with different values and goals, and looking at policy processes revealing power relations between different interest groups in developing the policies, industry, agriculture, professional and patient organisations.

The research will provide input to the public debate and raise awareness about the values guiding obesity prevention and provide tools to balance health goals with other societal goals and values.

4. Gut-Brain axis in Obesity and drug development

**STATE OF THE ART**

The brain central in the control of body weight. Several genetic pre-dispositions work through the brain and the brain controls behaviours, preferences and responses to food intake and exercise.

**FUTURE RESEARCH POTENTIAL**

4.1 Development and implementation of novel FMRI and other techniques for non-invasive real-time monitoring of brain functions.

Animal models for studying neurobiology of obesity.

Addressing the brain mechanisms involved in appetite regulation, food preferences, reward, addiction etc.

Addressing the beneficial effect of exercise on cognitive functions, executive, depression etc.

**IMPACT**

Novel regimes for treatment and prevention of obesity based on understanding the neurobiology of physiological and behavioral aspects of obesity

Identification of novel drug targets and candidates.

**Research collaboration:** Psychology, nutrition, food science, sensory science, neurology, metabolomics, pharmaceutical industry.

**Link to other research themes:** 1.1, 2.2, 2.3, rest of section 4.1, 5.1, 5.2, 5.3, 6.1, 6.2. section 7. 8.1.

**Collaboration with stakeholders:** Food and medical technologies and pharmaceutical industry.

**Infrastructure:** Access to dedicated human and animal test centres.

**Roadblocks:** Bioinformatics and data management platforms, limitations of current imaging techniques.

Gastric bypass surgery is an efficacious and long lasting cure for obesity and cures type-2 diabetes immediately, unrelated to weight loss.

The effect of surgery is caused by altered signals from the gut – providing decreased appetite and altered food preference.

4.2 Understanding the mechanism of gut-brain signalling in response to gastric bypass based on human studies and animal models.

Understanding the control of these mechanisms through food component, metabolites, secretory product and integration with signals from adipose tissue, muscle, liver in specific centres of the brain.

This should be addressed in good and poor responders to gastric bypass and combined with clinical and psychosocial data.

Non-surgical interventions mimicking the beneficial effects of bariatric surgery, without side effects.

Novel pharmaceuticals as well as other therapeutic means, to control gut signalling to treat and prevent type-2 diabetes and obesity.

Ability to predict good or poor response to gastric bypass surgery and developing more cost-efficient approaches to obesity surgery.

**Research collaboration:** Clinical and social sciences, Omics research, Neurophysiology and sensory sciences.

**Link to other research themes:** 1.1, 2.2, 4.1, 4.3, 4.4, 7.1, 8.1.

**Collaboration with stakeholders:** Pharmaceutical companies, health care sector and politicians, food industry.

**Infrastructure:** Access to dedicated human and animal test centres. Cohorts and biobanks of gastric bypass patients.

**Roadblocks:** Side-effect of gastric bypass, lack of knowledge of the long term effects and ability to predict responders/non-responders. Politically determined criteria of eligibility to gastric bypass rather than the medical and science based decisions.

Limited quality and usability of evidence concerning real-life interventions on an individual as well as group, organizational and societal levels.

Documentation of interventions to treat or prevent obesity often has one or several shortcomings in terms of the formal requirements of evidence and usability in health science, on terms of transferability, feasibility, cost-effectiveness and social, cultural and ethical soundness.

As a consequence, real-life intervention experiences rarely contribute to the systematic development of knowledge about ‘best practice’ of obesity treatment, prevention and health promotion.

3.4 Developing theories, new constructs and tools at different levels for drawing evidence based conclusions about effects of real life interventions, which cannot always meet all standard criteria for clinically controlled trials (e.g. individual randomization).

Studies in existing methodologies such as pragmatic trials and MTA and their interaction with knowledge dissemination networks and decision processes.

Developing and systematizing such methods and tools for evaluating economical, social, cultural and ethical implications and feasibility of clinically controlled interventions.

New methodologies of broad-spectrum evidence assessment allowing for a more systematic utilization of results from real-life experiments and interventions.

Developing well-described and well-grounded methodological ‘catalogues’ to support high standards of evidence and usability for interventions and policies in real-life on pragmatic trials and other effect evaluations.

Exploring more general systematic assessments (MTA) of consequences of translating research results into policies, services and products.

Identifying of novel drug targets and candidates.

Research collaboration: Collaboration between social sciences, political science, law and economy, philosophers, ethicists, public health science and social epidemiology, mathematical science, computer science, natural sciences and clinicians with expertise in prevention and intervention trials.

Link to other research themes: 1.1, 2.3, 2.4, 2.5, 3.4, 5.1, 6.4, 7.2.

Collaboration with stakeholders: Policy makers, public sector, health sector, industry, professional and patient organizations and other NGOs.

Infrastructure: No specific needs.

Roadblocks: Countering interest from stakeholders with professional and financial interests in specific interventions.

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Collaboration with stakeholders: Policy makers, public sector, health sector, industry, professional and patient organizations and other NGOs.

Infrastructure: No specific needs.

Roadblocks: Countering interest from stakeholders with professional and financial interests in specific interventions.
The gut microbiota has recently been identified as a potential key factor in the development of obesity and the metabolic syndrome.

4.3 Mapping the specific species, combinations and signals of the human gut microbiome predicting obesity, and early onset of type-2 diabetes and other co-morbidities.

Interventions of healthy gut bacteria replacement therapy in subsets of high-risk individuals.

Address the effect of diet, physical activity and other lifestyle factors on the microbiome.

Development of a new line of prevention and treatment of obesity and metabolic impairment by reshaping the gut microbiome through lifestyle interventions, replacement therapies, probiotics or drugs.

Identification of individuals who possess 'high risk' microbiome composition for development of obesity and co-morbidities, and providing tailor-made intervention regimes.

The few anti-obesity drugs on the market have limited efficacy and duration of action and the pipeline for new drugs is rapidly drying out.

The industry knows how to get efficacious drugs acting through the gut - which may not even enter the brain but acts locally in the gut.

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Exercise reduces obesity and co-morbidities by very complex physiological mechanisms, as the effects of exercise are more than just “burning off calories”.

5.3 Identifying the mechanisms whereby exercise influences the size and the function of various fat depots, muscle tissue, metabolic processes as well as mental health and wellbeing.

Interaction between exercise and drug action should be addressed with particular focus on obesity and co-morbidities.

Refined recommendations for physical activity to the population at large and to ‘at risk’ individuals.

Novel tools for adjusting medication to changes in physical activity and limiting adverse effects.

New nutrient and drugs supporting or mimicking the effect of physical activity.

Many factors contribute to an impaired metabolic phenotype. The individual contribution of these factors, and the cellular and molecular mechanisms, is not known.

5.4 Human and animal models, as well as experiments in cells and tissue, should address how physical activity/inactivity, obesity, fasting, short term overfeeding, low birth weight, gender and ageing affects muscle and fat tissues.

Epigenetic effects should be a particular focus.

Focused regimes for diagnosing, treating and preventing the metabolic syndrome by identifying ‘at risk’ individuals and providing tailored interventions.

New drug development based on increased insight into molecular mechanisms of the impaired metabolic phenotype.

Decreased insulin sensitivity and accumulation of lipids and lipid metabolites, known as lipotoxicity in muscles are suspected to be common cause for the ailments related to the metabolic syndrome.

5.5 Elucidating the molecular mechanisms responsible for regulating insulin sensitivity in muscle.

Elucidate regulation of lipid transport, oxidation and lipolysis and lipogenesis in skeletal muscle, and the effect of physical activity, gender and ageing.

New refined phenotypes and surrogate measures of insulin sensitivity addressing insulin sensitivity in relation to fat handling.

Muscle and fat cells are regenerated via resident stem cells (SC), and exercise can induce renewal of MSC pool in skeletal muscles.

5.6 Address whether differentiation potential of MSC to muscle and brown fat is influenced by obesity, type 2 diabetes, low birth weight as well as physical activity and diet.

Novel avenues for combating obesity and its associated diseases by targeting SC and controlling their proliferation and differentiation in vitro as well as in vivo.
6. Liver and Adipose tissue in Obesity research

<table>
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<tr>
<th>STATE OF THE ART</th>
<th>FUTURE RESEARCH POTENTIAL</th>
<th>IMPACT</th>
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<td>Non-alcoholic fatty liver disease is increasing in incidence and is related to obesity and insulin resistance. Insulin inhibits the hepatic glucose release and stimulates hepatic lipogenesis in healthy subjects. In insulin resistance the inhibitory effect on glucose release is decreased while the stimulatory effect on lipogenesis seems to be unaffected or even enhanced.</td>
<td>6.1 To elucidate the basis for this paradox effect of insulin resistance on hepatic lipid metabolism on the whole body physiological level, and the cellular and intracellular signaling levels. In addition to elucidate the interplay between adipose tissue and liver metabolism postprandially with focus on meal composition and the combined effects of incretin hormones, insulin, and the autonomic nervous system. Prevention of progression of hepatic steatosis to inflammatory steatohepatitis, and cirrhosis by proper treatment of combinations of novel pharmaceuticals with incretin hormone effects, and novel food products with less lipogenic effect, thus promoting a better balance between adipose tissue and hepatic lipid metabolism.</td>
<td>There is a known relation between obesity and the development of diseases such as metabolic and cardiovascular diseases as well as cancer, and neurodegenerative diseases including dementia. 6.3 Unravelling the molecular and endocrine mechanisms behind the role of obesity in the development of age-related diseases using novel in vivo and systems biology techniques and novel approaches to characterizing adipose tissue and cell function as well as the early stages of disease development. Addressing adipose tissue throughout lifespan in large scale cohorts, including genetic, epigenetics and prenatal factors, birth weight and lifestyle in the development, prevention and treatment of obesity and metabolic syndrome. Novel means of predicting, who will suffer from a poor health due to their obesity and if preventing and treating these conditions which are widespread and increasing in the obese and ageing society.</td>
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<td>Adipose tissue plays an important metabolic and endocrine role for whole body lipid and glucose homeostasis. Recently we it has become clear that different types of white fat cells diverge in their metabolic and endocrine function and sensitivity to hormones. Furthermore, brown adipocytes are fundamentally different from white fat cells in that they can be stimulated to uncouple their mitochondria and thereby energy release.</td>
<td>6.2 Major effort should be devoted to developing novel technologies for characterizing adipose tissue and adipocytes in human and animal models, as well as in vitro, including dynamic responses and crosstalk between different tissues and cell types. Adipocytes and adipocytokines from different anatomical origins should be characterised to understand the differential effect on health. Determining factors for brown fat development in humans should be identified. Adipocytes, adipocytokines, stem cells and hepatocytes and muscle cells from subjects with different stages of the metabolic syndrome should be compared with cells from healthy subjects to understand mechanisms of the impact of obesity on these tissues and the mechanisms of adipogenesis, insulin resistance and fat oxidation.</td>
<td>Recent research strongly indicates that environmental chemicals may affect metabolic and endocrine functions as well as adipose tissue function and signalling. 6.4 Unravelling the effect on adipose tissue of food contaminants, environmental chemicals and over the counter drugs. Effects on adipocyte differentiation and adipose tissue hormones caused by individual chemicals and ‘real-world’ mixtures should be prioritized. Cell as well as animal models will be important tools. A platform for regulations and precautions to prevent harmful effects of environmental pollutions and toxicants. Generation of knowledge on factors that are involved in obesity development, thereby providing means for preventing disruptions of metabolic and endocrine functions.</td>
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Adipose tissue plays an important metabolic and endocrine role for whole body lipid and glucose homeostasis. Recently we it has become clear that different types of white fat cells diverge in their metabolic and endocrine function and sensitivity to hormones. Furthermore, brown adipocytes are fundamentally different from white fat cells in that they can be stimulated to uncouple their mitochondria and thereby energy release. The relative contributions from the different types of fat cells may not only affect the risk of development of obesity but risk of obesity-related complications.
7. Genetics, Epigenetics and Metabolome

**STATE OF THE ART**

The aetiology of obesity has a strong genetic component. Less than 10% of the genetic effects can be attributed to known gene variants, and genetic predispositions appear to be caused by additive effects and interplay between many gene variants.

Several large scale cohorts addressing obesity and related diseases have been established across Europe. These cohorts are ongoing.

**FUTURE RESEARCH POTENTIAL**

- **7.1 Whole genome sequencing**: Studies in existing and new large well described cohorts followed over time, to discover the cumulative load of multiple rare and common gene variants across the whole genome predicting changes in weight and in a broad spectra of complex phenotypes reflecting obesity and metabolic dysfunctions.

- **Comprehensive gene-environment interaction studies using follow up from large ageing cohorts.**

- **Establishing new cross-European cohorts with advanced measures of lifestyle, anthropometrics and biobanks ready for the omics analyses of the coming decades.**

**IMPACT**

- **Identification of subgroups of the population with particular high risk genetic constellations and providing tailor-made regimes for prevention and treatment.**

- **Development of new drugs based on the identification of key pathways determining bodyweight control.**

- **Novel regimes for prevention and treatment though identification of specific aspects or patterns of lifestyle which are beneficial or harmful in different genetic makeup.**

- **Higher success rate and higher compliance to recommendations.**

**Research collaboration:** Animal models, physiologists for advanced phenotyping, imaging techniques, neurophysiology, data mining and bioinformatics.

**Link to other research themes:** 1.1, 2.1, 2.2, 2.3, 2.4, 2.5, 3.2, 3.3, 4.1, 4.2, 4.4, 5.1, 6.3, 8.1.

**Collaboration with stakeholders:** Public and private sector including the health care sector and the food, diagnostic and pharmaceutical industry.

**Infrastructure:** Well described cohorts, and associated biobanks and databases. Follow up data on weight development and development of co-morbidities.

**Roadblocks:** High expenses of continued follow up on existing cohorts and establishment of novel cohorts using the front line biological sampling techniques, anthropometrics and metabolic characterisation. Data handling and bioinformatics.

**With the increasing knowledge of the genetic constellations of obesity, attempts should be made to target interventions in ‘high risk’ segments of the population.**

- **7.2 Clinically controlled trials to evaluate the efficacy of specific lifestyle or pharmacological interventions in high risk obese adults and children carrying numerous or few adiposity-conferring gene variants.**

**Specific interventions matched for the genetic constellations of obesity.**

- **Moving beyond “one-size-fits-all” interventions and recommendations.**

**Aspects of lifestyle including diet and physical activity can cause lasting changes in the genome through epigenetic mechanisms, and such changes can be passed on to offspring.**

**Research collaboration:** Intervention studies related to diet and exercise, animal models.

**Link to other research themes:** Related to the majority of the outlined research themes, in particular 1.1, 2.1, 2.2, 2.3, 2.4, 4.1, 4.4, 5.4, 5.6, 6.2, 6.3, 8.1.

**Collaboration with stakeholders:** Public and private sector.

**Infrastructure:** Animal model facilities for controlled feeding, exercise and other relevant exposures.

**Roadblocks:** Identifying the relevant tissues for studying the epigenetic modifications which has a functional effect on obesity and co-morbidities.

**Metabolomics:** Methods are maturing. They can be used to assess markers of and whole body responses to, lifestyle as well as risk of development of lifestyle diseases.

**Pathways responsible for the effects of genetics and lifestyle components can be identified using these methods.**

**Aspects of lifestyle including diet and physical activity can cause lasting changes in the genome through epigenetic mechanisms, and such changes can be passed on to offspring.**

- **7.3 Tracking down the role of early epigenetic modifications in the pathogenesis of human obesity.**

- **Address, in human and animal models, whether and how physical activity, diet and other components of lifestyle and metabolic impairment induces epigenetic changes of importance for obesity and for the metabolic health.**

- **Identify the relevant tissues in which the epigenetic modification affects the normal gene expression and physiology.**

**Research collaboration:** Intervention studies related to diet and exercise, animal models.

**Link to other research themes:** Related to the majority of the outlined research themes, in particular 1.1, 2.1, 2.2, 2.3, 2.4, 4.1, 4.4, 5.4, 5.6, 6.2, 6.3, 8.1.

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**7.4 Using metabolomics in observational studies to identify metabolic markers of lifestyle, overweight, obesity, gut microbiota. Response to interventions and gene – diet interactions should be addressed and markers of subsequent risk of obesity-related disease should be identified.**

**Research collaboration:** Intervention and clinical research, genetics and epidemiology, neurophysiology and psychology.

**Link to other research themes:** Related to the majority of the outlined research themes, in particular 1.1, 2.1, 2.2, 2.3, 2.4, 4.1, 4.4, 5.3, 6.2, 6.3, 6.4, 8.1.

**Collaboration with stakeholders:** Pharmaceutical and diagnostic industry involved in development of screening and analytical tools and kits as well as drug development.

**Infrastructure:** Biobanks for exploratory analyses of samples collected in well characterised cohorts or intervention trials.

**Animal models and test facilities.**

**Roadblocks:** Bioinformatics and data handling.

**Improved treatment and prevention regimes for obesity and metabolic diseases, with possible effect on the next generation.**

**Earlier identification of high risk individuals and more efficient tailor-made interventions.**

**Aspects of lifestyle including diet and physical activity can cause lasting changes in the genome through epigenetic mechanisms, and such changes can be passed on to offspring.**

**Research collaboration:** Intervention studies related to diet and exercise, animal models.

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**Infrastructure:** Animal model facilities for controlled feeding, exercise and other relevant exposures.

**Roadblocks:** Identifying the relevant tissues for studying the epigenetic modifications which has a functional effect on obesity and co-morbidities.

**Metabolomics:** Methods are maturing. They can be used to assess markers of and whole body responses to, lifestyle as well as risk of development of lifestyle diseases.

**Pathways responsible for the effects of genetics and lifestyle components can be identified using these methods.**

**Aspects of lifestyle including diet and physical activity can cause lasting changes in the genome through epigenetic mechanisms, and such changes can be passed on to offspring.**

**7.3 Tracking down the role of early epigenetic modifications in the pathogenesis of human obesity.**

- **Address, in human and animal models, whether and how physical activity, diet and other components of lifestyle and metabolic impairment induces epigenetic changes of importance for obesity and for the metabolic health.**

- **Identify the relevant tissues in which the epigenetic modification affects the normal gene expression and physiology.**

**Research collaboration:** Intervention studies related to diet and exercise, animal models.

**Link to other research themes:** Related to the majority of the outlined research themes, in particular 1.1, 2.1, 2.2, 2.3, 2.4, 4.1, 4.4, 5.3, 6.2, 6.3, 6.4, 8.1.

**Collaboration with stakeholders:** Public and private sector.

**Infrastructure:** Animal model facilities for controlled feeding, exercise and other relevant exposures.

**Roadblocks:** Identifying the relevant tissues for studying the epigenetic modifications which has a functional effect on obesity and co-morbidities.

**Metabolomics:** Methods are maturing. They can be used to assess markers of and whole body responses to, lifestyle as well as risk of development of lifestyle diseases.

**Pathways responsible for the effects of genetics and lifestyle components can be identified using these methods.**

**Aspects of lifestyle including diet and physical activity can cause lasting changes in the genome through epigenetic mechanisms, and such changes can be passed on to offspring.**

**Research collaboration:** Intervention and clinical research, genetics and epidemiology, neurophysiology and psychology.

**Link to other research themes:** Related to the majority of the outlined research themes, in particular 1.1, 2.1, 2.2, 2.3, 2.4, 4.1, 4.4, 5.3, 6.2, 6.3, 6.4, 8.1.

**Collaboration with stakeholders:** Pharmaceutical and diagnostic industry involved in development of screening and analytical tools and kits as well as drug development.

**Infrastructure:** Biobanks for exploratory analyses of samples collected in well characterised cohorts or intervention trials.

**Animal models and test facilities.**

**Roadblocks:** Bioinformatics and data handling.

**Improved treatment and prevention regimes for obesity and metabolic diseases, with possible effect on the next generation.**

**Earlier identification of high risk individuals and more efficient tailor-made interventions.**

**Aspects of lifestyle including diet and physical activity can cause lasting changes in the genome through epigenetic mechanisms, and such changes can be passed on to offspring.**
Animal models, in particular rodent models, have been a cornerstone in addressing the genetics and physiology of obesity, appetite and energy expenditure. However, there is a lack of good animal models in terms of high transferability of the results to humans.

Of particular importance is the ability to conduct controlled interventions addressing specific genotypes, breeding, food, energy expenditure, to test surgical procedures, and to obtain refined phenotyping and tissue and cell samples.

### 8.1 Developing and implementing new animal models regarding genetics, patterns of eating and exercise, development of obesity and co morbidities, building on the large similarities between the human and animal genome.

- Behavioural and physiological phenotyping methods should be developed.
- Specifically models of identifying and studying the relevant tissues for epigenetic changes in response to lifestyle and playing a role in development of obesity and metabolic diseases.
- Identification of genetic and epigenetic mechanism of obesity and metabolic diseases.
- Identification of physiological mechanisms behind the effect of genes and lifestyle.
- Development of novel regimes for predicting, diagnosing, treating and preventing obesity.

**Research collaboration:** Experts from the area of human research regarding phenotyping and translational aspects including comparative genomics. Data mining and bioinformatics.

**Link to other research themes:** All other themes except theme nr 3.

**Collaboration with stakeholders:** Food, diagnostic and pharmaceutical industry.

**Infrastructure:** Core facilities for state of the art animal models of obesity and metabolic diseases.

**Roadblocks:** Limitations of the current techniques of phenotyping and imaging.

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### 8. Animal models for obesity and metabolic diseases with high translational potential

<table>
<thead>
<tr>
<th>STATE OF THE ART</th>
<th>FUTURE RESEARCH POTENTIAL</th>
<th>IMPACT</th>
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<tbody>
<tr>
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**Schematic overview of possibilities for collaboration across research themes**

The figure below outlines some of the possible constellations of collaboration across research questions, disciplines, methods and approaches in the proposed research. The table reflects the identified 'Link to other research themes' in the table above, and should not be seen as a complete overview, but an early indication of possible synergies and collaborations.

![Schematic overview of possibilities for collaboration across research themes](image-url)
1.1 Reclassification of obesity according to risk of developing co-morbidities

The need for methods, tools and knowledge allowing for early screening and identification of obese (and pre obese) individuals who will develop co-morbidities and impaired health (and the identification of factors and accelerators that puts individuals at risk), is a cross disciplinary and cross thematic challenge. There is a need for tools to assess risk of developing metabolic syndrome, diabetes and cardiovascular diseases, but also to assess risk of impaired fertility as well as psychological conditions. There is further a strong need for addressing the ethical and social consequences related to identifying ‘high risk’ subjects, to allowing this mode to be implemented optimally and without unwanted side effects (see 3.2, 3.3).

Mapping the genotype, metabotypes, enterotypes, weight gain patterns, eating behaviour and physical activity, as well as socio-psycho-economic factors and living conditions, which lead to disease development, will pave the way for getting a clearer picture of the ‘high risk’ group in the population of overweight and obese individuals. Further, evaluating if the younger generation are more prone to disease can lead to early prediction and counteraction of the raise in obesity related diseases. For identification of high risk individuals prone to develop obesity and associated co-morbidities, the most powerful factors should be taken into consideration, including both physiological and non-physiological factors. While physiological factors might relate to nutrition, physical activity, the intestinal microbiota, gender, genetic factors, non-physiological factors might include socio-economic status, psychological profile, gender, stress, environment, culture, and others. Including all of these factors guarantees the best possible power of prediction in adequate mathematical models.

Human studies and animal models are crucial in approaching this area of research (see 8.1) as is the high need for refined phenotyping regarding anthropometrics, metabolic functions and dysfunctions including insulin sensitivity, neurophysiology etc (see 4.1, 5.3-5, 7.1-4).

Identify the individuals who are disease prone is the major step towards developing, administering and improving adherence to the correct necessary treatment, whether regimes for diet and exercise, novel psychosocial and complex treatment platforms (see 2.3, 2.5, 5.1 surgical (see 4.2) or pharmaceutical (see 4.4) in a targeted and individual manner and, and to prioritise prevention and treatment according to disease risk. Drugs and surgery can thus be restricted to groups of patients from whom this is relevant from a medical point of view and where the side effects are tolerable compared to the benefit and the effects of not intervening.

Full length description of the research topics

The following section is a full length description of the research topics, providing the details on the suggested research areas and the impact and innovation potential of this research.

1. Identify the individuals that will end up developing obesity-related diseases
2. Food & Diet

2.1 Determination of the optimal diet in the management of body weight regulation including the risk factors for type-2 diabetes

Both clinical and community based intervention studies are needed to get novel insights to optimal diet composition for prevention of excess weight gain, for inducing weight loss and for modulating risk factors for the metabolic syndrome and type-2 diabetes. These studies should address the effect in infants, children, adults and in the elderly population.

High-protein diets and low Glycemic Index (GI) diets have been shown to improve weight loss and prevent weight gain in controlled trials. Specific components, such as different protein sources, amino acids, wheyprotein, fibre, resistant starch etc. are expected to be responsible for these effects. Future research in human and animal models (see 2.1) should address these components, and identify other food components, which affects insulin sensitivity and other risk factors for the metabolic syndrome and type-2 diabetes (see 2.2). Understanding how the dissemination of study results on health-promoting diets affects the long-term development of obesity prevalence in population seems a necessary step to take before general advice promotion. This will allow for development of feasible platform of dietary advice to be communicated to the public in general and especially for people at high risk for or with, overweight and pre-diabetes.

Further the interaction between diet and physical activity (see 5.2) and diet and genes (see 7.2) as well as psycho-social, environmental, and cultural factors (see 3.1,3.2) should be addressed and the effect of different dietary regimes on gut-microbiota and gut-brain signalling in relation to obesity development should also be explored (see 2.2). Understanding how the dissemination of study results on health-promoting diets affects the long-term development of obesity prevalence in population seems a necessary step to take before general advice promotion. This will allow for development of feasible platform of dietary advice to be communicated to the public in general and especially for people at high risk for or with, overweight and pre-diabetes.

Novel food products and production systems should be developed to achieve sustainability in the diet (including promoting the use of vegetable protein), palatability, acceptability, consumer access, development of healthy processed foods etc., international aspects of nutrition such as the double burden of disease aspect should further be taken into consideration.

2.2 Appetite, satiety and addiction – food components and gut-brain signalling

Certain food ingredients, foods and diet compositions are known to enhance satisfaction and safety. This includes high-protein foods, wheyprotein and fibre products, resistant starch etc. (see 2.2). There is a need to further explore the particular components of the foods and the physiological mechanisms and signalling of the brain and the gut behind these effects (see 4.1, 4.2, 4.3, 4.4). Moreover, the interaction between the setting of meal consumption (both physical and social), and the nutrient intake should be addressed. Foods that can be modified or designed to target satiation and satiety should be identified. Animal and human experiments should address the role of gut hormones, and gut-brain signalling and gut microbiota, in satiation and safety, and the effect of different foods and nutrients on these mechanisms (see 4.1, 4.2, 4.3, 4.4). There is a need for determining “optimal combinations” (doses, mixture, timing etc.) of hormones and other signals from the gut that will lead to meal termination (satiation) and to safety between meals.

The Central Nervous System (CNS) control of appetite and food intake, food preference and reward needs to be addressed in humans and in animal models (see 4.2). The molecular and physiological mechanism behind the apparent ability to develop an ‘addiction’ towards foods rich in carbohydrate and/or fat – but not protein – should be revealed. Further, genetically determined differences in gut-brain responses to nutrients should be addressed using genetics and metabolomics methods (see 7.1 and 7.4).

This field of research paves the way for novel and more effective diet regimes, recommendations and foods that enhances the success rate for weight loss and weight control and possibly also for the prevention of weight gain as well as the metabolic syndrome. Further, it will lead to novel openings in production of food and food ingredients with high satiating power.

2.3 Individualized dietary treatment regimes of obesity

It is not possible to predict whether a person responds well to a given dietary regime or should be transferred another regime. The standardised diet regimes for treatment of obesity, such as limited energy intake, high-protein-low fat diets etc., are typically supplemented with individualised advice on how to adjust lifestyle, habits, attitudes towards eating etc. The personalised aspect contributes to a better compliance and outcome of treatment, but is often based on the individual experiences in a given treatment centre. This represents limited knowledge, lacking transferability and on-going optimisation, and may not be cost efficient.

Novel treatment strategies should build on current knowledge about the beneficial effects of reducing energy density, portion size, increasing protein intake, avoid eating alone, etc. This should be combined with a complex and holistic model of obesity developed in collaboration between nutritional, physiological, psychological and social sciences and humanities.

Through historical analysis, observation studies and in-depth interview it should be addressed how the following components are related to weight loss success under different regimes and can be addressed by novel approach-
Research should identify aspects of lifestyle that promotes and prevents obesity (see 3.1, 3.2, 5.1) and strategies for changing the habits of the public. In relation to the latter these questions should be addressed through a cross-disciplinary approach:

- What are the effects of the current preventive strategies? What works and what do not?
- How can we move from informing and educating the consumers to actually changing their habits? Addressing the differential effects for prevention strategies in children, adolescents, adults and elderly and during critical periods of life such as moving away from home, childbirth, divorce and retirement.
- Priorities should be addressed in consumer groups defined by age, gender, socioeconomic status etc. when making choices about lifestyle (health, identity, it is easy, pleasure, prestige).

- Possibilities, limitation and cost-effectiveness of general public prevention approaches versus more targeted prevention regimes in schools, workplaces, organisations, local communities etc.
- The ability to transfer knowledge gained from individualised treatment regimes to more generalised prevention strategies.
- Avoiding adverse effects of preventive initiatives in terms of counter reaction such as unhealthier lifestyle, developing of orthoaxia and anorexia nervosa.

Collaboration with NGO's, public and private sectors should be intensified, recognizing that these sectors are important actors which may support or counterbalance the approaches of the health care system. The role and strategies of the private sector towards food choices, eating habits and diets should be addressed, and novel avenues for public-private or other collaborations should be outlined, recognizing that these sectors are stakeholders for this line of research and is a central actor in relation to public information, believes and habits. Creating a level of sustainability in the recommendations to the public and in the public understanding of, and action in response to these recommendations, will be a core element towards prevention of obesity and towards well informed self-regulative, healthier and satisfied consumers (see also section 3.1).

Future preventive initiatives should build upon the abilities of the private sector to influence the pattern of the consumers, and the increasing priority of Corporate Social Responsibility versus public health legislations, combined with evidence based knowledge about prevention and treatment of obesity.

2.4 How to change behaviour and eating habits and prevent obesity at the population level

The factors that predispose to obesity such as physical inactivity, easy access to varied and attractive foods etc. are increasing as is the prevalence of obesity. The effect of current prevention strategies are therefore difficult to pinpoint, as is the nature of aspects that may work to reduce energy intake and increase energy expenditure to prevent obesity. Especially, the transferability of results coming from controlled trials to public health recommendations is not well understood.

2.5 How can we use make use of novel technologies in getting from the lab to the population

We need to be able to apply the knowledge from intervention trials to the population in general and in large scale population based interventions with a long follow-up time.

The possible use of new social technologies and services, information and communication technologies (ICT), ‘bots’, radio frequency identification tags (RFID) and other supportive tools, should be explored, both with respect to supporting the consumer in making healthy choices, in increasing quality of life and compliance to a healthy lifestyle, and with respect to the monitoring of lifestyle habits in the large scale population studies, including assessment of food purchases, eating patterns, physical activity etc. (see section 2.4, 5.1 and section 7.1). The potential of the different technologies should be explored in relation to guiding and monitoring healthy choices and to promote communication and social interaction in relation to lifestyle interventions, campaigns etc. Real-time feedback to the individual about status and achievements on eating healthy and exercising may be a core component.

Social sciences, humanities and communication experts should collaborate with clinical teams involved in treatment and prevention of obesity in outlining these studies addressing consumer attitude, and the studies to guide and increase readiness towards these types of technologies as well as development of platforms for communication, social interaction and behaviour.

This approach will provide a whole new platform for improving as well as addressing long term compliance and effect of intervention regimes in free living individuals, family settings etc. and will bring front line technologies into use and improve the future refinement for this purpose (see 5.1).
3. Social Science and Humanities: Interventions, assessment methods and philosophical clarifications

4Cs moving obesity: Causes, Cures, Constraints and Consequences

Causes

Everyday life habits of different population groups, age groups and personality types are deeply intertwined with social, psychological, cultural and economic realities. These factors form a complex jigsaw puzzle of biological, psychological, and social influences. It is important to mobilize the scientific resources specialized in addressing these kinds of factors. Social science and humanities can make essential contributions to obesity research by offering models of these very complex socio-economic levels of causation which strongly affect the development of obesity through daily life habits and possibly through other causal pathways (e.g. influence of mood on metabolism). A better understanding of such causes will be essential for the development of effective interventions for countering or modifying them, and for understanding why certain ways of shaping an intervention may result in small or lacking real-life effects. Analyzing the parts played by social contexts and environments in relation to changing levels of obesity can help identify new actors and social networks with a key role in the development or overcoming of obesity and type-2 diabetes, e.g. institutions, economy, and market characteristics, communities, social contexts, physical environments and technologies.

Furthermore, there is a largely untapped resource in the cooperation of social sciences and humanities with other disciplines involved in obesity research, identifying respective roles of hunger, reward, stimulation, pleasure, social belonging in eating and other related aspects which cross traditional limits between the fields of physiology, anthropology, sociology and psychology. This could reveal, for instance, how different kinds of causal factors overlap, interact and combine in eating patterns: appetite regulation, food availability, social psychological structures, social peer pressure, traditions, culture and myths.

Cures

To address the causes outlined above, we need to mobilize psychological, social, cultural, political, economic and regulatory structures, forces, actors and interventions to promote healthy lifestyle habits in society, such as, in particular groups of citizens at risk of obesity and related diseases and organisations such as schools or workplaces.

Intervention studies addressing obesity must be adapted to the specific environment and the individual’s situation, rather than the norm today where you treat overweight and obese people as a collective unit rather than a diverse group of individual people. The consequence is that the same tools and methods of interventions may be used on all citizens across all European countries. The cultural and behavioral differences between the population groups across countries are usually not taken into account. Comparative studies across borders and cultures should be conducted to promote novel insight to the challenge of obesity. It should be addressed, that the same recommendations for lifestyle may be implemented completely differently in different cultural settings and that this may account for differences in weight loss success, quality of life and motivation. Thus, the fact that ad libitum low-fat diet and calorie restriction may result in similar weight loss but differences in motivation and liking of the diet should be seen as a first example of obtaining an overall favorable effect by adjusting the guidelines and recommendations. Social epidemiology, natural interventions and public health sciences insights into how people, or cultures, with high success rate from a given intervention have managed the intervention in practice is foreseen to serve as a strong platform for reeting and tailoring future interventions. One of the key questions is: what is the measurable outcome of different interventions and how do we successfully take intervention studies from the research lab to the public?

The possibilities of developing new and more effective means for prevention and treatment of obesity through mass-intervention methods should be addressed by novel research in psychology and sociology and by including the collective experience from successful group intervention studies. Possibilities should be explored for creating regimes allowing for interventions to expand from the closed environments for individuals, to various levels and in different settings.

Novel strategies should be developed for structuring and organizing society more effectively, so that it invites people to a healthy lifestyle (and hence fighting obesity) on a daily basis e.g. exercise more or eat more healthy on a voluntary basis rather than through coercion and the exercise of power. Novel strategies for urban planning, reduced taxes on healthy foods combined with increased taxes on the unhealthy counterpart or examining the possibilities of establishing groups that can support the healthy lifestyle habits in society as such, in particular groups of citizens at risk of obesity and related diseases and organisations such as schools or workplaces.
Social epidemiology should create the basis for developing preventive measures on population- or organizational level and development of new psycho-social treatments.

Today’s treatment for severe obesity, gastric bypass surgery or compulsory hospitalization with strict diets can have varying amount of negative impact and side effects on the obese individual. Cross-disciplinary research should approach the development of new treatments that are more cost-effective and less invasive. The possibilities for making intelligent interventions with high success rate should be explored in collaboration between social sciences, psychologists, clinicians, physiologists and ICT experts.

By developing new and more individualized and nuanced approaches to obesity prevention through empowerment, psychology treatment, mindfulness, life coaching or other regimes, it would be possible to develop more personalized services for the prevention and treatment of obesity that has a much larger success-rate and can reach more people than today’s prevention strategies. Biologically based obesity research may develop and test interventions effective in treating or preventing obesity under ideal conditions. But in real life conditions it is often insufficient to merely inform or advice citizens or prescribe cures. There is a need of new methods supporting the implementation of this knowledge in real life, effective support for the actual change of habits and lifestyles while increasing quality of life. Here, the social sciences and humanities will play a major role in mapping the challenges and road blocks that prevent successful interventions and treatment options.

To address the issue of responsibility, is it possible to develop new business models for the different industries playing a part in relation to obesity so that they get a more diverse and healthy perspective and business base through corporate social responsibility? By getting new insight on the needs that is satisfied by eating, we can pave the way for novel prevention and treatment strategies which deals with all the different needs that are covered by compulsive eating and overweight. Is it possible to find new methods to address the responsibility that makes the different actors collaborate to fight obesity instead of neglecting the common responsibility?

Social peer pressure, traditions, culture and myths should be addressed in social epidemiological studies at group- and population level in order to assess the role of these factors in underlying causes, motivators and indicators of the obesity epidemic. The focus should not only be on obese individuals, but also on the overall compliance of citizens based on population composition, society, market and environment.

Constraints
In order to successfully combat the obesity epidemic and the following negative consequences for the individual and society, cross-disciplinary collaborations across the broad range of social sciences and humanities in partnership with the clinical and natural sciences should address the constraints related existing and novel approaches towards tackling obesity.

This includes:
- Social, cultural, psychological, economic and institutional barriers for effective and acceptable obesity prevention.
- Ethical aspects and interaction with other actors e.g. schools, educational institutions and public institutions.
- Peoples priorities in determining lifestyle and health behaviour and the priority of fitness, leanness and health in the general healthy public, and in subgroups defined by age, gender, social and socio-economic status.
- The influence and role of structural barriers and physical constraint together with political and economic barriers and opportunities.
- The way of perceiving obesity as a phenomenon and how this creates additional problems and constraints that could be avoided by examining and changing the discourse of obesity (e.g. stigmatization and obesity as a disease vs. obesity as living conditions in the late modern society).

Consequences
High focus on prevention and treatment of obesity at the individual level may lead to the perception that the individual is responsible for their obesity and co-morbidities which in turn may lead to exclusion and stigmatization by the society in several ways:
- Obese individuals that cannot be helped from conventional treatments have to live with obesity.
- Self-esteem and self-worth are affected.
- When the society make interventions e.g. introduce differentiated tax on unhealthy food or payment for bringing cars into city centres, the obese individuals who are not able to comply suffer financially without the opportunity to receive the right kind of support.

Research should therefore identify alternatives to giving advices and food recommendations for tackling problems for the obese individuals, addressing the fact that people are confronted with food and eating every day, and hereby with the aspects of lifestyle often seen as the main cause of obesity.
In order to prepare society for an ageing and obese population, social science and humanities should (in a cross-disciplinary setting) address the social, cultural and economic consequences of the ‘obesity-epidemic’ in terms of quality of life, lowered productivity, increased healthcare costs and other societal costs, to approach a better understanding of consumer’s choice and attitudes towards means of treating and preventing obesity. Further, this will reinforce the healthcare, public and private sector to cope with the societal changes of tomorrow including an ageing obese population through higher level of compliance.

Obesity has consequences on different society levels which should all be addressed and examined by accurate in depth analyses. The consequences should be physical activity need by multiple scientific perspectives to get the best possible basis for decision making on both societal and national level. This should be in terms of consequences for the healthcare sector, the work force, the culture around food and exercise which could lead to development of a multi-factorial impact and consequence calculator for better understanding and calculation of measures and or new instruments or recommendations to decrease the lack of compliance.

Implementation and innovation

It is vital that the research being addressed by social sciences and humanities should reflect on the research outcome in terms of impact and innovation potential for the society at large. As other research lines focus on basic research, it is important to notice the direct transferability and spill over effect that new instruments, recommendations, methods, interventions or guidance’s could have on different actors and collaboration partners.

This includes:

**Impact on the citizens**

- Ways of supporting well informed, self-regulative, empowered citizenship, engaged in developing and maintaining healthy habits.
- Context-sensitive recommendations beyond just ‘diet and exercise’.
- New concepts, criteria and measures to serve as inspiration and guidelines in improving quality of life and health for citizens at all ages (combining social, psychological and existential dimensions to biometric and physiological measures), and for particular subgroups such as adolescents, elderly or citizens on different socio-economic levels.

**Impact on policy makers and society**

- Context-sensitive instruments for making healthy habits easy, available and attractive across social, cultural and economic status through novel social and material technologies and economical and regulatory instruments and innovations, for society and ‘third sector organisations’.
- A strengthened platform for policy-making and regulatory measures on society level which systematically secure values and ends of ethical as well as health economical nature.
- More consistent messages and guidance to the citizens, and platforms supporting the compliance to these messages by making them easy and attractive.

**Impact on the health and care sector**

- Intervention technologies supporting individuals and groups in achieving higher level of maintained success in the treatment of obesity through higher level of compliance.
- A platform for creating new forms of prevention and treatment aimed at individuals and groups (socio-economic or cultural) to whom present-day prevention, treatments and technologies are unavailable or useless.
- Insights to help reinforce the health and care sector to cope with the societal changes of tomorrow including an ageing obese population.

**Impact on the industry**

- Context-sensitive knowledge on what guides the citizens choices in terms of diet, exercise regimes and pharmaceuticals, with the possibility to tailor products towards higher compliance and quality of life for consumers.
- Novel platforms for a closer collaboration between private sector: public sector: health and care sector and NGO’s for implementing new regimes of corporate social responsibility.

4. Gut-Brain axis in Obesity and drug development

It can be suggested that for obesity, ‘the disease is in the brain, but the cure can be in the gut’. Insight into gut-brain signaling is foreseen to pave the way for novel means of prevention and treatment of obesity, and related co-morbidities. Expectably this knowledge may lead to different targets and strategies, for prevention and treatment.

4.1 The brain

The brain is a central actor in determining body weight. This includes regulation of voluntary behaviour of food intake, physical activity, reward, and non-reward in relation to food intake, response to stress, sleep, and stimuli from TV and computer games etc. The signaling from the peripheral tissues including the gut (see 2.2 and rest of section 4), adipose tissue (see 6.2), liver, muscles (see 6.2 and 5.2) and other tissues to the brain is crucial in the regulation of energy homeostasis. Further, a large part of the genetic predisposition to obesity appears to be caused by gene variants affecting brain signaling (see section 7). Our knowledge about, and ability to examine the functions of the brain in relation to obesity is very poor at this stage.

There is a need for development of better, integrated in vivo neurophysiological methods for objective and non-invasive studying of the brain as a whole, separate structures and areas, and signaling within the brain and from the peripheral organs including the blood-brain barrier.

Functional MRI (fMRI) has been quite disappointing, though it appears to be used to its fullest potential. There is a need for sophistication and specification of methods which allows for a more detailed, real time mapping of brain functions. The development of and novel techniques should be driven by diseases, and should be based on close interdisciplinary collaborations between physiologists, pathologists, behavioural- and neuropsychologists, bioinformatics and computer and data technologists. With these techniques the neurobiology of overt eating and exercise should be addressed on the individual level. Also, neurobiological differences between responders and non-responders to a given treatment should be explored.

Animal models are central in studying the brain functions, signaling and relation to behaviour. Animal models should be developed to allow translation from animal to humans regarding genetics, brain functions, and behavioural patterns as well as the development of overweight, obesity, related co-morbidities and response to given treatment or human models (see 6.1).

The role of exercise, food and eating patterns and adiposity on mental functions including food choice, appetite, mental health, cognitive functions, executiveness (see 6.2).

4.2 Gastric bypass as a platform for development of novel drugs and foods

The only truly effective and long lasting cure for obesity is gastric bypass surgery. Importantly, surgery works not because of malabsorption or physical restriction, but through decreased appetite and possibly altered, healthy food preference. That is, bariatric surgery alters brain function through altered signaling from the gut, which can cure obesity and also cures type-2 diabetes, immediately unrelated to weight loss.

We need to understand the molecular cellular and physiological basis for how the gut signals to the brain - how food components, metabolites, secretory products etc control these signals - how these signals reach the brain and how they are integrated with signals from adipose tissue, muscle, liver and other centres in the brain. The precise nature of the connections between the brain and the gut, including the blood-brain barrier, needs to be emphasised and studied in detail. Animal models are crucial for this area of research, as only these allow for complete control of food intake and studying the complex physiology an interaction in different organs including the brain (see 4.1, 7.1, 8.1).

These mechanisms should be addressed in good and poor responders to gastric bypass, and novel models for prediction of good respond should be developed with input from the clinical and social sciences. This will allow for developing more cost-effective approaches to obesity surgery, offering the surgery to those who will truly benefit and for whom side effects are tolerable in comparison to the beneficial effects (see 1.1).

This knowledge will pave the way for non-surgical interventions mimicking the beneficial effects of bariatric surgery, without the side effects hereof. This can include novel pharmaceuticals, food (see 2.2) and probiotic products (see 4.3) which can control gut signaling to prevent and treat obesity and type-2 diabetes.

4.3 Gut microbiota

The gut microbiome has recently been discovered as a potential key factor in the development of obesity and
the metabolic syndrome. Part of this effect is expected to be due to metabolites, generated by the bacteria, which function as fuel for the body but importantly also controls gut signaling (see 2.2 and rest of section 4).

There is a need for mapping the specific species of the human gut microbiome that are related to obesity, and early-onset of type-2 diabetes and other co-morbidity (see 1.1). Early studies in animals and humans have indicated beneficial effects of interventions of healthy gut bacteria replacement therapy in subsets of high-risk individuals. This should be addressed further both regarding the mechanisms whereby the gut microbiota can be reshaped or replaced by probiotics or drugs (see 7.5). A particular focus could be critically controlled interventions of repetitive healthy gut bacteria replacement therapy in subsets of high-risk juvenile-onset obesity characterized by a gut microbiome composition known to increase risk of premature cardio-metabolic complications.

The spontaneous effects of diet (see 2,1,2,2,3), physical activity (see 6.2) and other lifestyle factors, and the role of gut brain signaling in the microbiome, should be addressed in human and animal studies (see 8.1).

The perspective should be developing a new line of regimes prevention and treatment of obesity and metabolic impairment by reshaping the gut microbiome through lifestyle interventions, replacement therapies, probiotic or drugs. Symbiosis between the different bacteria and the effect of viruses and antibiotic treatments should further be addressed. Social sciences should be closely involved addressing the citizens and patients attitudes towards such treatment regimes, approaching a stronger platform for development and implementation of novel treatment regimes, recommendations and probiotic products (section 3).

4.4 Novel drug targets based on insight into gut –brain signalling and functions

The few anti-obesity drugs on the market have limited effect and especially limited duration of action. Several anti-obesity drugs have recently been withdrawn and the pipeline has dried out as almost all late stage drug candidates have failed due to limited efficacy or adverse effects. The pharmaceutical industry appears to have lost its momentum and is disillusioned regarding obesity treatment. One main reason is that the major genetic component predisposing to obesity is working via brain – i.e. in centres regulating appetite and energy expenditure. However, drugs acting directly in the brain generally have adverse effects, which are not tolerated in anti-obesity drugs today.

Mimicking the effect of bariatric surgery by altering the signals from the gut and thereby indirectly control the brains function is a very promising avenue for novel drugs. Based on insight into the altered gut brain signaling following bariatric surgery (see 4.2), drugs should be developed which do not actually enter the body but are sensed in the gut like nutrients and metabolites. Novel drugs should also target the food-reward system and thus mimic both the satiety and the pleasure that results from eating (see 4.3). Effects of novel drug candidates on and role of microbiota should be addressed (see 4.3).

Methods should be developed for predicting response and to identify the individual who will benefit from a given drug treatment and predicting interactions between drugs and lifestyle (see 6.3). Further, with the implementation of refined anthropometrics and phenotyping and refined methods for identifying those obese subject that will develop severe co-morbidities (see 1.1) it should be possible to develop and approve drugs for this subgroup of individuals, and thus assure that anti-obesity drugs are only used for medical and not for cosmetic purposes, only used in subjects who are expected to be benefit from the treatment, and not in subjects who would respond just as well to a change in lifestyle.
5. Physical activity and related muscle and adipose tissue physiology

If compliance to a physically active lifestyle can be accomplished, this will have a major impact on public health and thereby society and the cost of treating lifestyle diseases. Further, physical activity is expected to increase quality of life and mental health for citizens of all ages. Physical inactivity can be both a cause and a consequence of obesity, and physical activity should therefore be part of every human life and must be implemented in daily life in the population as a whole, and in particular in the already obese person who may have strong barriers towards physical activity, combined with the many adverse effects of inactivity.

5.1 Reinforcing and targeting physical activity throughout life

Introduction of, and compliance to, a physically active lifestyle in the population, from child to old age, is important in the battle against obesity. Research should address how physical activity can be reinforced in the public in general, and in individuals with specific risk of obesity, inactivity and of developing the metabolic syndrome.

There is a need for translational, cross-disciplinary research converting physical activity to community actions. Research areas of physiology, medicine, social epidemiology, ethnology, psychology, environmental and political sciences should collaborate to identify and grade factors, critical periods (such as adolescence, retirement, etc) and life events predisposing to physical inactivity; barriers towards physical activity and strategies for increasing physical activity (see section 3). This should be addressed in the general public, in obese subjects, in patients suffering from chronic diseases including depression, in children, adolescents and elderly (see 1.1).

Cross-European observational and interventional studies should address the inter-cultural and inter-group differences in level and type of physical activity, to identify societal and cultural mechanisms for improving physical activity.

The different notions of physical activity should be addressed including how exercise is perceived as high level activity, hereby possibly overseeing the physical activity in everyday life, in relation to social contexts and activities, which may be more attractive and achievable in obese individuals. Strategies should be outlined for raising awareness about the effect of physical activity on the many aspects of physical and mental health and brain functioning, including reinforcing executiveness – i.e. the general ability to act on ideas, and not just stay passive (see 4.1).

Stakeholders and actors should be identified and included actively in the research towards implementation of the results. These appear much less prominent than the food industry and other stakeholders in the area of food and diet behaviour. The whole spectre of community based to individual approaches should be addressed including city planning, infrastructures for transport, workplace initiatives, etc. Research should address how such initiatives can be designed and implemented in a way that also activate overweight/obese persons, as many such initiatives may be taken up most readily by those who are already active. The potentials in promoting the use of nature in relation to physical activity and optimising urban planning and transport infrastructures to support an active lifestyle in children and adults, should be addressed in collaboration with the relevant stakeholders.

The potential of technological advances to improve translational value of physical activity should be pursued, including segmental differentiation, individualisation based on age, weight, barriers towards physical activity etc. Technological tools to be developed for illustrating health and effects of exercise and made accessible (price, manageable, low invasiveness) to inspire people to make healthy lifestyle (see 2.5). User-driven innovation should address how the internet and other virtual platforms and social networks can strengthen the pleasure of, and compliance to, exercise and physical activity. Further research should address how to optimise the continued development of new popular forms of exercise and address what turns some forms of exercise into trends, and what can make them more sustainable, in order to make a physical active lifestyle part of the routines of everyday life.

Finally, it should be addressed how health information and campaigns may help motivate people, and whether there are different effects in normal weight and obese subjects, across age groups, gender, and socioeconomic status (see section 3).

5.2 Optimized combination of diet and physical activity for promoting health and prevention and treatment of obesity

Weight loss in healthy overweight or obese people induced by dieting has been shown to result in increased mortality compared to individuals maintaining body weight. However, when weight loss involves physical activity this increase in mortality does not occur. The biological mechanisms for this effect should be addressed with the ambition to optimise the regimes for weight loss through diet and exercise.

Caloric restriction often leads to fatigue preventing physical activity. This can probably be counteracted by an optimal diet, and there is therefore a need to elucidate the interaction between diet and physical activity in relation to weight loss.

The whole spectre of basic physiology (in human studies...
and animal models), clinical intervention and epidemiological studies should address changes in muscle mass and function in response to weight loss through different regimes of diet, (see section 2) and physical activity, in order to identify means to avoid loss of muscle mass, optimize muscle functioning, and minimize other adverse effects for weight loss. Advanced phenotypic measures should be developed and included to define and measure healthy muscle and adipose tissue and monitor the effect of intervention regimes. (see 5.4 and 6.2).

Further, the possible effect of physical activity on gut microbiota should be addressed, acknowledging that physically fit persons have a shorter mean transit time of food through the bowel. (see 4.3).

5.3 The physiology of health benefits from physical activity

Physical activity is not only a means to “burn calories”, and should be recognized for its many positive effects in relation to maintaining a healthy body weight and metabolic health throughout life. Research should address the physiological mechanisms behind the positive effects on metabolic health as well as appetite regulation, mental functions and side effects or unexplainable responses to inactivity and activity. (see 4.1). The interaction between exercise and drug action should be addressed with particular focus on obesity and comorbidities (metformin, NSAID’s, cholesterol-lowering pharmaceuticals) in order to limit adverse effect and adjust medication to changes in physical activity. (see 4.4).

5.4 Physical Activity – a determinant of healthy muscle and fat tissues

Regular physical exercise is a powerful, non-pharmacological tool to maintain a healthy muscle mass and fat distribution, with effects superior to pharmacological treatment. Exercise appears to protect against accumulation of visceral fat and helps maintain a healthy and large muscle mass.

Research should identify how the development and maintenance of healthy muscle and fat tissues (see 6.2, 6.3) is influenced by physical activity/inactivity, obesity, fasting, short term overfeeding, low birth weight, gender, ageing and other factors. All of these factors may contribute to an impaired metabolic phenotype, ultimately resulting in type-2 diabetes and increased risk of multiple chronic disorders. However, the individual contribution of each of these factors needs to be addressed in dedicated interventions in humans and animal models and in epidemiological studies.

The sensitivity to lipolytic action of exercise-induced hormones in visceral and subcutaneous fat should be addressed. In vitro studies of human primary muscle and adipocyte cell cultures will further serve as a unique basis to unravel the mechanisms, whereby lifestyle factors influence our development and maintenance of muscle tissue. (see 4.1) should be addressed at the molecular level only. Epigenetic lasting changes in gene activity (see 7.3) and metabolomics changes, (see 7.4) should be addressed in animal, (see 8.1) and human models, in terms of the effect of physical activity/inactivity, importance for metabolic and cardiovascular health, and the extent to which such changes can be passed on to the offspring.

5.5 Insulin sensitivity and lipid accumulation in muscles

Decreased insulin sensitivity in muscle is a major problem in obesity and probably is a common-cause for the ailments related to the metabolic syndrome. (see 1.1). Therefore, elucidation of the molecular mechanisms responsible for regulating insulin sensitivity in muscle is very important.

Accumulation of lipids and lipid metabolites in muscle (lipotoxicity) are suspected to induce insulin resistance. Therefore regulation of lipid transport, oxidation and lipolysis and lipogenesis in skeletal muscle needs to be clarified. Further, we need to address how physical activity can prevent or treat lipotoxicity in skeletal muscle at the molecular level.

Research, in animal models (see 4.1) and in humans, should identify new molecular mechanisms of importance for regulation of insulin sensitivity and lipid oxidation in muscle which is of major importance for diagnosing and treatment of obesity-related disorders.

New refined phenotypes and surrogate measures of insulin sensitivity should be developed to address insulin sensitivity in relation to handling of sugar as well as fat, and to address the impaired insulin sensitivity in adipose and muscle tissue separately instead of at whole body level only.

5.6 Differentiation potential of stem cells in muscle and brown fat is influenced by weight, type-2 diabetes and physical activity

Many factors determine if an individual is prone to accumulate visceral fat including age, gender, sex hormones, birth weight, and physical activity level. Inversely, the same factors are involved in maintaining a large and healthy muscle mass.

Muscle and fat cells are regenerated by proliferation and differentiation of resident stem cells (SC) belonging to human mesenchymal SC (hMSC), and exercise can induce renewal of hMSC (satellite cell) pool in skeletal muscles. From conception and throughout life physical activity and nutrition influence the risk of obesity, type-2 diabetes, and the metabolic syndrome. The balance between the amount and intrinsic activities of white versus brown fat and muscle may determine the tolerability to a lifestyle with an excessive energy intake. Low birth weight is associated with an increased risk of developing metabolic syndrome, including type-2 diabetes, and immature muscle and fat development may mediate these associations. While it is known that SC proliferation and differentiation is influenced by the in-vitro micro-environment, it is not known how lifestyle factors affect the biology of hMSC. The knowledge generated may contribute to combat obesity and its associated diseases by targeting SC and controlling their proliferation and differentiation in vitro as well as in vivo (see 8.1).
6. Liver and adipose tissue in Obesity research

6.1. Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease is increasing in incidence and is related to obesity and insulin resistance. Insulin inhibits the hepatic glucose release and stimulates hepatic lipogenesis in healthy subjects. In insulin resistance the inhibitory effect on glucose release is decreased while the stimulatory effect on lipogenesis seems to be unaffected or even enhanced.

Future research should elucidate the basis for this paradox effect of insulin resistance on hepatic lipid metabolism on the whole body physiological level, and the cellular and intracellular signaling levels. In addition the interplay between adipose tissue and liver metabolism post prandially should be addressed with focus on meal composition and the combined effects of incretin hormones, insulin, and the autonomic nervous system.

Understanding the mechanisms behind hepatic lipid metabolism and the role of diet and the interplay with adipose tissue will pave the way for prevention of progression of hepatic steatosis to inflammatory steatohepatitis, and cirrhosis by proper treatment of combinations of novel pharmaceuticals with incretin hormone effects, and novel food products with less lipogenic effect, thus promoting a better balance between adipose tissue and hepatic lipid metabolism.

6.2. Adipose tissue development and function

The multifactorial and complex origin of human obesity calls for a thorough characterization of the role of adipose tissue, and its interaction with other organs and functions in the body, on the populations, individuals, tissue level, as well as addressing the role of genetic and epigenetic factors (see 7.3), early foetal events and the ageing process in adipose tissue functioning. Addressing the link between amount, distribution, type, function of adipose tissue and development of metabolic diseases, cardiovascular diseases, and cancer is a central task.

Research should address the mechanisms of generation and the characterization and function, of subtypes of brown and white adipose tissue, pre-adipocytes and stem cells, adipose tissues from different anatomical origins, and muscle and liver tissues with storage of excess fat.

Addressing different stages from healthy physiology to metabolic syndrome, and in the processes of ageing, will lead to a better understanding of the mechanisms behind adipogenesis, insulin resistance and to the development of new drug targets, including stimulation of ‘brown adipose like’ mechanisms resulting in burning of excess fat in the adipose tissue (see 4.4). Addressing mechanisms for adipocyte turnover is central as the average lifespan of an adipocyte is approximately 10 years, indicating that changes in turnover rate could be a cornerstone in metabolic disturbances and ageing.

Characterization of dynamic responses of adipose tissue and the link to responses of other tissues and crosstalk between tissues and cell types will be an important step (including liver, brain, muscles, beta cells etc.) (see 4.1, 5.4, 5.5, 6.1). New projects should aim at moving beyond effects of simple weight loss and calorie restriction, to address the effect of consecutive periods of weight loss and gain, effects of changes in physical activity, and diet composition and patterns on the change in size and function of adipose tissue at different sites.

In this line of research there is a great need for novel and advanced technologies in humans and animal models (see 8.1) to address:

- Characterization of number, size, type etc. of adipocytes and characterization of adipose tissue and ectopic fat in different tissues and organs.
- Novel non-invasive methods of in vivo imaging, characterizing, and markers of adipocytes in their natural site, to address function, dynamic changes and the mechanism of the dysmetabolic conditions by parallel observations and characterization of the organs affected. By strengthening the platform for in vivo research in humans and animals, the impact of novel drugs and other treatment regimes can be monitored.
- Differentiation of insulin sensitivity by supplementing the current approach addressing glucose metabolism with approaches that target lipid metabolism and by developing methods for assessing insulin resistance on organ and tissue level, moving away from the highly simplified approach of assessing whole body insulin resistance (see 5.5).

6.3. Adipose tissue and disease development

There is a known relation between obesity and the development of metabolic and cardiovascular diseases as well as cancer, and neurodegenerative diseases including dementia (see 2.1). Functioning and signaling of adipose tissue as well as muscles (see 5.4-5.5) are expected to play a key role in disease development and thereby also to hold strong perspectives for early diagnostics and novel approaches for treatment and prevention.

The role of adipose tissue and obesity in the development of cancer is of central importance, and the link between adipose tissue function, insulin resistance, and anti-diabetic drugs in cancer should be addressed.

Unraveling the molecular and endocrine mechanisms behind the role of obesity in the development of age-related diseases will be a step towards better prevention and treatment. The impact of obesity on related diseases and conditions such as insulin resistance and fat in the liver (see 6.1) should be addressed in human and animal models and should move beyond weight loss (see 6.1).
6.4 Environmental chemicals, stress and adipose tissue

Increasing evidence suggests that developmental exposure to environmental chemicals could play a role in the increase in incidence of obesity. Animal studies have suggested that dietary exposure to low doses of environmental chemicals in early periods of vulnerability may increase the risk of obesity in adult life. Many of the chemicals also accumulate in fat tissue, which is of great concern since it is now known that body fat is not merely a depot for storage of triglycerides, but an endocrine gland crucially involved in energy regulation. Therefore it is plausible, that environmental chemicals in adipose tissue could disrupt such functions as fat storage, fat distribution, and appetite signaling.

Research should address the influence from environmental pollution on adipose tissue function and signaling, as well as the overall development of obesity in children and adults. This should include food contaminants as well as environmental toxins, Bisphenol A etc. A novel and important approach will be investigating the mixtures of pollutants as they are found in a normal environment (as opposed to investigate them one by one), hereby increasing the impact and applicability of the results in terms of novel regulations and precautions.

7. Genetics, Epigenetic and Metabolomics

7.1 Identifying candidate genes though combining advanced genotyping and phenotyping

The current identification of genetics contributing to obesity has been somewhat disappointing. Only approx. 10% of the genetic variation in BMI is explained from the known obesity genes, and one of the obvious explanations for these small effect sizes is the fact that we use weight, BMI and waist hip ratio as a measure for obesity, and not more refined and physiologically relevant measures.

More refined and defined phenotype measures should be developed and addressed in animal models (see § 4.1) and human clinical studies and cohort studies. These refined phenotypes should cover brain functions and responses (see § 4.1) as well as refined anthropometrics and physiological responses combined with extensive collection of biological samples. In addition behavioural phenotypes will be crucial, as the genetic contribution to obesity is expected to partly work through the brain by influencing behaviours related to food preference, appetite regulation, physical inactivity etc. (see section 2 and 5).

Large scale genome deep sequencing studies in cohorts of adolescents and adults with 10-20 years of follow-up, should address the cumulative load of multiple rare and common gene variants across the whole genome, which predicts weight changes. Further comprehensive gene-environment interaction should be addressed using follow-up from large cohorts, especially in the ageing cohorts such as EPIC and in the combined national mother-child cohorts. Research will move away from the paradigm of seeing the lean and healthy subjects as a ‘control group’ towards identifying the genotypes and behaviour determining the ‘healthy phenotype’.

The limited phenotyping and biosampling of the existing cohort’s calls for establishing supplementary cohorts developed to meet the state of the art analytical platforms and to follow-up over time and even over generations. The enormous environmental pressure on the DNA, and the induced mutations through generations, should be addressed and novel strategies should be developed to take such knowledge into account.

New mathematics and biostatistics tools should be developed to handle the massive amount of phenotypic and genotypic data which are now generated from refined phenotyping, data from national registers, omics techniques and sequencing of the human genome and the metagenome. The methods today are too simple and we lack the mathematical ideas of finding true interactions.

7.2 Clinically controlled trials to evaluate the efficacy of specific lifestyle or pharmacological interventions in subsets of high-risk obese individuals

The already established cohorts is a platform to locate individuals with specific genotypes and phenotypes to be challenged with different regimes for exercise and diet interventions and novel interventions addressing neurophysiological, cognitive and psychological aspects of eating and exercise behaviour. (see section 2 and 5 and 4.1)

Further, clinically controlled trials should evaluate the effect of specific lifestyle or pharmacological interventions in ‘high risk’ obese children and adults carrying numerous or few adiposity-conferring gene variants. The insight from this type of experiment will allow for moving beyond ‘one-size-fits-all’ interventions and recommendations by developing specific interventions matched for the genetic constellations of obesity (see 1.1 and 2.3).

The social, psychological and ethical aspects of classifying people into subgroups based on their genetic profile should be addressed to explore extent of positive and negative behavioural effects. Further, there is a need to address the dilemma that identifying and labelling people based on their genetic profile should not be done until a tailor made treatment is available, but at the same time these regimes can only be developed using the above mentioned platform.

7.3 The role of epigenetic modifications in the pathogenesis of human obesity

The role of epigenetics events occurring in foetal life, or even at the time of conception, associated with the later development of dysmetabolic states should be addressed in order to understand mechanisms involved in cell differentiation and proliferation using human preadipocytes and stem cells. Differently programming of stem cells through epigenetic modifications should be addressed (see § 5.6).

Whole epigenome sequencing studies of oocytes from female monogygotic twins who are discordant for obesity should be used for tracking down the role of early epigenetic modifications in the pathogenesis of human obesity. Animal models should be developed for addressing epigenetic changes of importance for obesity and metabolic health, in response to diet, exercise and other exposures and lifestyle aspects (see § 4.1). The relevant target tissues should be identified and examined including the extend of passing on lifestyle to offspring’s through epigenetic modifications. These models should be used as strategies for obtaining similar data from human studies and for translating the knowledge from animal studies to human studies.

These lines of results can lead to improved prevention and treatment regimes for obesity and metabolic diseases,
of which part of the beneficial effect could possibly be passed off to the next generation. Further, it may open for new approaches to identification of high risk individuals and tailor-made interventions (see 1.1 and 7.2).

7.4 Metabolomics
Metabolomics is now a maturing tool for exploring the alterations in metabolites and metabolic pathways caused by specific dietary regimens (see 2.1), medical treatments (see 4.4) or conditions such as overweight or weight loss (see 1.1). The methodology has already improved our insight into the changes at the whole body level in response to meal challenges with specific carbohydrates, fats, and proteins and has been used to explore the changes in blood plasma composition following gastric bypass operations. These studies have brought attention to the importance of bile acids and branched-chain amino acids as early messengers of change in the metabolism and also to the metabolites from the gut microbiome as potential physiological effectors (see 4.3).

However, metabolomics still evolves and new developments in separation technology as well as next generation equipment will take the technology to further detail in the level of specific messengers that occur at very low levels or have structures which have so far escaped identification. The promise for this technology in obesity and diabetes research is therefore huge and the application of the technology should be increased to involve diet-gene interactions, large-scale intervention studies of diet and physical activity and observational studies.

Using metabolomics in observational studies to identify metabolic markers of overweight, obesity and study their relationship with subsequent risk of obesity-related disease is an example of a promising new application that would give new insight and more targeted hypotheses regarding the mechanisms underlying sustained weight gain.

Using metabolomics analysis of body fluids (including cerebrospinal fluid from clinical bio banks), to identify phenotypic characteristics related to weight gain and depression is another example that would take advantage of the well known interactions between depression, anti-depressive drugs and sudden weight gain or loss. The mechanisms behind these actions are not well understood and metabolomics could help to shape better hypotheses in this research area.
8. Animal models for obesity and metabolic diseases

8.1 Animal models for obesity and metabolic diseases with high translational potential

There is a need for strong, predictive animal models across the whole field of obesity. In particular there is a need for models that can be translated into human genetics, epigenetics, physiology, pathology and behaviour.

Rodent models continue to be a cornerstone of studying these aspects, but there is a strong need for models using larger animals with a higher resemblance to humans regarding genetic makeup, food intake patterns, anatomy, and in particular development of obesity related co-morbidities. Such models can be developed in dogs, cats and pigs etc. These models can be central in identifying candidate genes (see section 7) determining the behavioural and physiological phenotypes, based on the well know, but sparsely explored, inter-breed difference in for instance body composition, eating patterns, response to changes in diet, drug tolerance, predisposition to obesity and co-morbidities. Research should build on the large similarities between the human and animal genome and the ability to conduct controlled trials and obtain a broad phenotyping and biological sampling in animal models.

Facilities for conducting controlled interventions and observations of diet, physical activity, and other lifestyle exposures in larger animal models are crucial. Further, the effect of existing and novel surgical and pharmaceutical procedures can be addressed with respect to tissue and brain function, crosstalk as well as behaviour, weight regulation and development of co-morbidities. There is a particular need for establishing behavioural phenotypes based on animal models and translating these into human clinical studies and, when applicable into cohort studies, to reflect and assess differences in taste perception and preference of food, differences in physical activity, drug response, revised mechanism, real time functional imaging of CNS regions (see 4.2) and other key tissues including gut, muscles and different types of adipose tissue (see section 4, 5 and 6). There is further a need for elaborated sampling techniques and building up biobanks to address metabolomics, gene expression and epigenetic in the relevant tissues.

Finally there is a need to developing and implementing stronger models for addressing the effect of being obese, i.e. longer time of maintained overweight, in terms of development of obesity related co-morbidities and changes in behaviour and neurophysiology in response to obesity.