

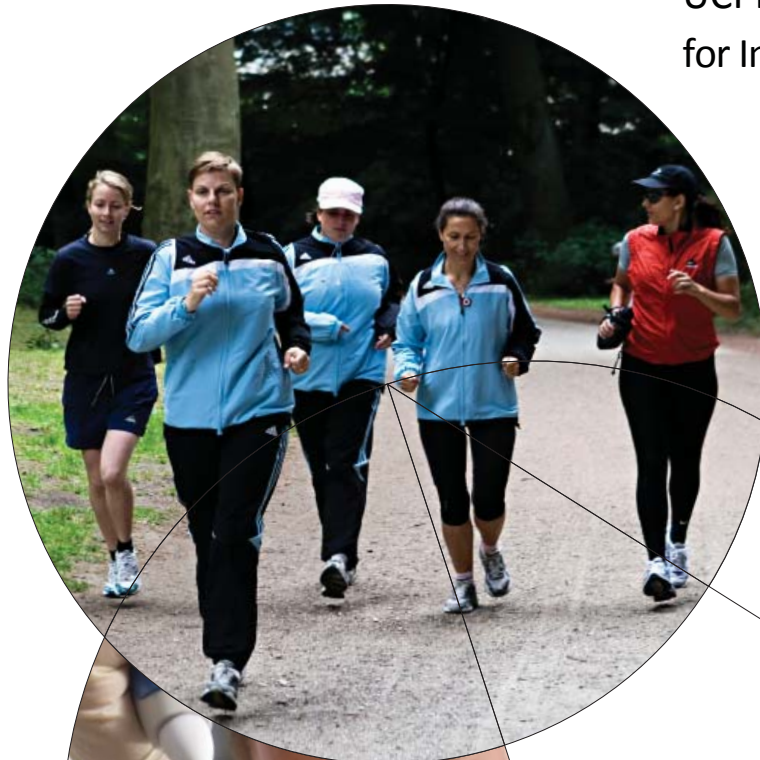


Physical activity and nutrition for improvement of health

Copenhagen Women Study

Final evaluation

UCPH Excellence Programme
for Interdisciplinary Research



Principal investigator

Erik A. Richter

Faculty of Science

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1. Basic Information

<i>PI and Co-PI's</i>	<p>Name, titles and full contact details of the principle investigator: Erik A. Richter, Professor, M.D., D.M.Sci, Department of Nutrition, Exercise and Sports, 13 Universitetsparken, 2100 Copenhagen. E-mail: erichter@nexs.ku.dk, mob: 28751626.</p> <p>Additional names and affiliations (Faculty and Institute), Co-PI's and key VIP's in each Work Package:</p> <ul style="list-style-type: none"> • WP1: Bente Kiens (WP leader), Dept. Nutrition, Exercise and Sports, Faculty of Science. • WP2: Ylva Hellsten (WP leader) and Jens Bangsbo, Dept. Nutrition, Exercise and Sports, Faculty of Science. Bente Stallknecht, Dept. Biomedical Sciences, Faculty of Health and Medicine. • WP3: Henning Langberg (WP leader), Dept. Public Health, Faculty of Health and Medicine. • WP4: Jørn Wulff Helge (WP leader), Dept. Biomedical Sciences, Faculty of Health and Medicine. • WP5: Jørgen Wojtaszewski (WP leader) and Lars Ove Dragsted, Dept. Nutrition, Exercise and Sports, Faculty of Science. • WP6: Reinhard Stelter (WP leader. <i>psychology</i>), Gertrud Pfister (<i>Sociology</i>), Laila Ottesen (<i>Sociology</i>), Lone Friis Thing (<i>Sociology</i>) and Anne-Marie Elbe (<i>Psychology</i>), Dept. Nutrition, Exercise and Sports, Faculty of Science. In WP6 researchers work in humanities despite their positions at Faculty of Science. The respective fields are indicated in italics. <p>Also we express our gratitude for the work done by Lene Otto from Saxo Institute, Faculty of Humanities who passed away in 2014.</p>
<i>Project title</i>	Physical activity and nutrition for improvement of health
<i>Amount granted</i>	25.358.000 d. kr.

2. Research excellence and international impact of the project

The 2016 initiative “Physical activity and nutrition for improvement of health” provides a platform and infrastructure for researchers at UCPH to conduct cutting-edge interdisciplinary research projects in order to improve physical and mental health, prevent disease and facilitate treatment and rehabilitation based on solid evidenced-based recommendations in regard to physical activity and nutrition. The first major research initiative is entitled “The Copenhagen Women Study (CWS)” and is anchored in 4 intervention studies of women at risk of metabolic disease or suffering from loss of dexterity after a stroke (WP 1-4) supported by a molecular (WP5) and sociological and psychological (WP 6) exploratory division that develop and test own hypotheses as well as provide complimentary studies/testing to explain and interpret the observations in WP 1-4 (for more information on background, aim and hypotheses see www.cws.ku.dk). Due to the fundamentally different research questions addressed in the different work packages the overview of the most important scientific discoveries so far, potential significance as well as requirement of interdisciplinary collaboration is presented for each work package individually.

WP1: PCOS STUDY

Key results

- 1) Four months of exercise training improves aerobic capacity and reduces the circulating concentration of male sex hormone in lean PCOS patients and matched control subjects, however the reduction in male sex hormone is markedly greater in PCOS patients.
- 2) The exercise training induced an increase in insulin sensitivity in the controls but not in women with PCOS. The lack of a training induced increase in insulin sensitivity in PCOS seems to be due to the absence of an increase in insulin stimulated glucose uptake in muscle tissue. A mechanistic explanation for this finding seems to be attributable to key proteins within the glucose transport pathway in skeletal muscle. The key proteins were increased in the controls with exercise training but remained unchanged in the PCOS.
- 3) The plasma concentration of the androgen testosterone decreased markedly in women with PCOS with exercise training bringing the levels closer to the values in the control group.
- 4) Exercise training improves the mood of both PCOS women and controls, but more so in PCOS and only in these patients is self-esteem improved by training.
- 5) The plasma HDL-cholesterol concentration, a key component in cardiovascular disease prevention, increased significantly in women with PCOS following exercise training

Implications for the research field

PCOS is believed to be caused by hormonal disturbances (including increased concentrations of male sex hormone) that may result in a cluster of symptoms of a personal (e.g. reduced mood and self-esteem), visual (e.g. acne and excess hairiness) and clinical (e.g. impaired insulin sensitivity, infertility) character. It is well known that for overweight PCOS patients, weight loss can reduce the clinical signs of PCOS, however since ~40% of women with PCOS are normal weight this is not a preferable option for this population. In WP1 the first well controlled training study of lean PCOS patients that are kept weight stable has been performed. Based on the findings so far it seems evident that exercise training per se can improve both clinical and personal symptoms of the disease and hence not only health but also well-being. Based on these observations physical training should be recommended as an effective non-medical approach to improve physical health and life quality of lean women with PCOS. Furthermore, the lesser improvement in insulin sensitivity after training in PCOS patients could lead to novel insight regarding molecular mechanisms controlling insulin sensitivity and we are pursuing this.

WP2 MENOPAUSE STUDY

Key results

- 1) Despite only four years of difference in age between the pre- and post-menopausal groups of women, the post-menopausal women have a reduced function of the blood vessels, more reactive platelets and higher blood pressure.
- 2) Intense physical activity for 12 weeks can effectively oppose the impairment in blood vessel and platelet function and improve cardiac function, which seem related to changes in nitric oxide and prostacyclin metabolism.

Implications for the research field

This study is unique by the invasive nature and breadth of measurements in this subject population. Also, we have managed to compare groups (pre vs. post menopause) with a mean age span of only 4 years which minimizes the confounding effect of aging in interpreting the data – an inherited bias in most other studies of menopause. The findings so far clearly show that the hormonal change at menopause rapidly impairs cardiovascular health, and that physical training is an effective way to oppose this development.

WP 3: STROKE STUDY

Key results

- 1) Tablet-based motor practice with a specialized application improves motor performance and is accompanied by high levels of interest and enjoyment in healthy subjects.
- 2) Thirty minutes of fine-motor practice requiring accurate and fast finger movements with incremental task difficulty results in changes in the cortico-muscular coherence. This has not been demonstrated before and contributes to our understanding of the mechanism behind improved motor performance after practice.
- 3) For some stroke patients similar improvements are observed but optimization of the application towards more daily living task-oriented exercises and more user-friendly training would likely improve the effect for this group of patients.
- 4) Corticomuscular coherence and intermuscular coherence are reduced in acute and subacute stroke compared to healthy controls.
- 5) Corticomuscular coherence is localized above the contralateral sensorimotor cortex in both patients and controls.
- 6) Improvement of hand motor performance did not require changes in corticomuscular coherence and intermuscular coherence.
- 7) Intra- and inter-hemisphere coupling differences were observed in patients compared to healthy controls during early rehabilitation primarily from the γ -band to the β -band.

Implications for the research field

- Approximately half of stroke survivors require a long rehabilitation process but even after intensive therapy, only 10-20% regain the full functional use if the upper extremity is affected. Treatment of these patients relies on intensive rehabilitation, where compliance is made difficult by the repetitive nature of traditional therapies. Tablet-based motor practice involving specialized apps might be a potential motivating and effective training tool to practice manual dexterity at home and enhance neural plasticity.
- This study supports that with sufficient optimization, tablet based training programs may become a clinically relevant, low cost and motivating way to practice fine-motor skills at home for stroke patients suffering from loss of dexterity.
- In order to optimise recovery in the future we also need a better understanding of the mechanisms and pathways responsible for reorganisation of brain function after brain lesions. Improvement of hand motor performance did not require changes in coherence suggesting that coherence is not sensitive enough to measure adaptations in the corticospinal tract. Alternatively, adaptations responsible for improved

performance following stroke may partly occur at other sites such as inter- and intra-hemispheric adaptations. Importantly, these findings highlight that EEG/EMG measurements are able to capture insights of the underlying mechanism responsible for behavioral changes and thus have the potential to become valuable low cost methods to measure neural adaptations in various environments

WP4: OBESITY STUDY

Key results

- 1) Repeated life style interventions over time (4 -5 yrs.) lead to marked and maintained weight loss.
- 2) Maintenance of clinically relevant weight loss (>10%) over time (>5 yrs.) after an intensive lifestyle intervention leads to significant improvements in cardiovascular risk factors and metabolic health compared to a moderate (1-10%) weight loss.
- 3) Volitional, motivational as well as certain biographical factors are related to and can predict weight loss maintenance as well as the upkeep of regular physical activity in an obese population.

Implications for the research field

Based on cross-sectional, retrospective as well as longitudinal evaluations this work package so far has markedly improved our overall understanding of what psychological and sociological mechanisms are determining the ability to maintain weight loss after an intense 12 weeks intervention in a live setting. Furthermore, the role of weight loss and importantly maintained weight loss on physical and mental health is currently being unravelled. Currently, the majority of physiological data are being generated which will greatly improve our mechanistic understanding.

WP5: MOLECULAR PHYSIOLOGY

Key results

- 1) By state-of-the-art global phosphoproteomic analyses of human skeletal muscle it was revealed that an acute bout of exercise regulates 1,004 unique exercise-regulated phosphosites on 562 proteins.
- 2) Proteomic analysis of exosomes purified from human plasma showed increased release of exosomes from human muscle during exercise and follow up studies in mice showed their uptake in various organs, primarily the liver, indicating that secretion of exosomes leads to inter-tissue communication.
- 3) WP5 researchers managed to establish a method to evaluate muscle signalling in single muscle fibre preparations and used this method to illustrate that type 1 fibres (compared to type 2 fibres) have a higher glucose-handling capacity but a similar sensitivity for phosphoregulation by insulin.
- 4) Using a rodent model it was shown that activation of the energy sensitive enzyme AMPK is essential for acute regulation of a range of metabolically relevant genes in response to exercise and importantly that AMPK regulates substrate metabolism in recovery from exercise.
- 5) Metabolic profiling methods and dietary study designs have been established for detecting food intake and lifestyle biomarkers and these methods are applied particularly for determining various sources of protein, including red and white meats, dairy and vegetable proteins.
- 6) The methods have been applied in meal studies and longer-time dietary interventions with target foods and interventions with high/low protein and moderate/high physical activity (collaboration with H2020 project ending 2018).
- 7) Data fusion methods have been established to work with complex big data and these methods have been published and will be applied for the new datasets generated when the dietary studies have terminated.

Implications for the research field

1) The effort undertaken to map the exercise phosphorylation landscape in human muscle has filled a crucial gap in our understanding of muscle exercise signaling. For example, the breadth of signaling pathways and kinases modulated by exercise is far greater than previously appreciated. By using this approach in other organs and studying other protein modifications in a temporal fashion will further ex-

pand our knowledge. Importantly, the combination of these data may provide a blueprint for future studies aimed at developing exercise mimetic therapies for metabolic disease treatment or prevention.

2) Inter-organ communication by exosomal secretion opens up new horizons for how exercise leads to health benefits in the entire organism.

3) Developing this method has allowed for evaluation of tissue signaling in very small sample preparations including individual muscle fibers. Based on observations so far using the method indicates that patients with type 2 diabetes have fewer type I fibers and a higher number of type IIX fibers in their muscles which likely contributes to the impaired insulin sensitivity associated with type 2 diabetes.

4) Within the last 20 years the role of AMPK in regulation of muscle metabolism and function has been intensely investigated. Work performed by WP5 and importantly collaborations allowing for use of unique genetically modified mouse strains have resulted in a shift in our understanding of AMPK towards being a more important enzyme in regulation of metabolism in recovery from exercise rather than during exercise.

WP6: HUMAN AND SOCIAL SCIENCES

Key results

1) Results derived from collaborative work with other work packages in CWS so far have been highlighted in the overview of WP 1, 2 and 4.

2) Researchers in WP6 have developed questionnaires, interview guides and coaching strategies directed specifically toward the subject populations in WP1-4.

Implications for the research field

1) Exercise training results in marked improvements in mood and self-esteem for women suffering from PCOS, exceeding the impact in healthy control subjects. From a human and social science perspective this suggests that exercise training known to improve many aspects of mental health may be even more beneficial when mental health is reduced or compromised.

2) As demonstrated volitional, motivational as well as certain biographical factors are related to and can predict weight loss maintenance as well as the upkeep of regular physical activity in an obese population. This implicates that human and social science screening of subjects may help to customize efforts during intense lifestyle interventions in order to facilitate weight loss and importantly maintenance of weight loss after the intervention.

3) Middle-aged women's (lack of) prioritizing exercise participation in everyday life is highly connected to the dynamic power relations between the societal ideologies of work life, family life, and leisure time. Hence, work and family have a predominant status in many of the middle-aged women's everyday lives which constrain their adherence to sufficient health-promoting exercise.

4) The goal of the health coaching project was to support women in their attempts to remain physically active and to develop and maintain a healthy lifestyle. A theoretical basis and intervention guidelines were developed. The 3 month intervention helped to reduce a number of stress factors, but had no direct impact on higher PA participation.

2.2 Plans for future activities or embedment related to the project

Based on the overall very positive midterm evaluation of CWS, we aimed for a full embedment of the program, "with an amount equal to 50 per cent of what the project received in funding for a period of four years". To fulfill this compulsory criterion for financial embedment of CWS, the following has been achieved.

- Two junior research positions have been established at NEXS, in research groups heavily involved in the CWS project (WP2 and WP5) in order to strengthen research within "physical activity and nutrition for improvement of health". This investment is equivalent to 5 million DKK within a 4 year period and the positions were occupied primo 2017.

- CWS researchers (WP1 and WP5) have established collaborative research project with Novo Nordisk on exercise and health for 6 million DKK (including 44% overhead). This project started 1/4 2017.
- CWS researchers (WP1 and WP5) have established collaborative research project with Pfizer on mechanism in exercise-induced health for which ~12 million DKK (including 44% overhead) is allocated to UCPH. This project started 1/2 2018.
- A Semper Ardens grant (13.8 mio. DKK) was awarded at the end of 2015 by the Calsberg Foundation for work building on achievements in WP5 on development of metabolic profiling methods to be applied in research on low-dose alcohol intake and diabetes risk.
- At the Faculty of Health and Medical Sciences, CWS researchers are planning an interdisciplinary research project with the title “FitMum”, directed at training for pregnant women. This has attracted 50.000 DKK from the Danish Diabetes Academy to support a symposium on the subject as well as 75.000 DKK from the Beckett-foundation, 1.000.000 DKK from Copenhagen Center for Health Technology and 100.000 DKK from Aase and Ejnar Danielsens Foundation. Applications for app. 10 mio. DKK have been submitted for The Independent Research Fund Denmark and Trygfonden.
- An interdisciplinary aging centre has been established at NEXS. Funding was applied for from Innovation-foundation last year and continuous efforts, including an application to the Tryg-foundation is made to secure funding for relevant projects in the centre, in part by CWS researchers.
- Since May 2016 a close collaboration on clinical metabolomics and systems medicine has been established with the metabolomics group at Steno Diabetes Center, Copenhagen Region. This has resulted in additional methods development, including improved plasma, liver and faecal lipidomics and GCxGC-TOF profiling methodology and building on these developments several Steno collaborative grant applications have been submitted.

Based on the summary above we have currently invested and/or received funding equivalent to ~38 million DKK to continue and strengthen the interdisciplinary research efforts within “physical activity and nutrition for improvement of health”, including efforts from the key faculties involved in the CWS program. Furthermore, we aim to continue these efforts.

2.3 Publications

As illustrated in appendix 1 (publication list) the project so far has resulted in 56 publications in peer reviewed journals. The nature of the publications encompasses collaboration *between* research fields (e.g. physiology/psychology/sociology) but also *within* research fields (e.g. cardio-vascular/tissue/molecular physiology) as well as by alliances with different public or private entities (e.g. hospitals, patient groups etc). In order to conduct the studies related to CWS, apart from collaboration between researchers within CWS a wide range of external collaborations (both national and international) have been required. The majority of publications should be considered *within* research fields and particularly within the field of physiology owing to the nature of the intervention studies. Part of the reason for this is a lack of high impact interdisciplinary journals allowing for publications combining data related to both physiology and human and social sciences. However, we have managed to generate ~10 publications that can be characterised as being *between* research fields disregarding the journal impact and importantly with regard to dissemination of results toward municipalities and the public these types of interdisciplinary evaluations are expected to have significant impact.

Top 5 publications:

Phosphoproteomic Analysis of Human Skeletal Muscle Reveals a Network of Exercise-Regulated kinases and AMPK Substrates. (Hoffman NJ. et al. Cell Metab. 2015 Nov 3;22(5):922-35.

In this Cell Metabolism paper, several CWS researchers participated in an international collaboration to elucidate the signaling complexity in muscle in response to exercise by a novel combination of systems biology and molecular physiology. We expect that this novel molecular mechanistic break-through will help

us identify key signaling components that confer the long-term beneficial effects of exercise training in CWS.

Maintaining a clinical weight loss after intensive lifestyle intervention is the key to cardiometabolic health. Dandanell S, Skovborg C, Præst CB, Kristensen KB, Nielsen MG, Lionett S, Jørgensen SD, Vigelsø A, Dela F, Helge JW. *Obes Res Clin Pract.* 2016 11(4):489-498.

In this study researchers from WP4 (study of obese women) have shown that the magnitude of weight loss (kilos lost) and importantly the ability to maintain weight loss (>5 yrs.) after an intensive lifestyle intervention are determinants of the improvements in cardiovascular risk factors and metabolic health. This has important implications for how weight loss should be endorsed with regard to health promotion.

Changes in corticospinal drive to spinal motoneurons following tablet-based practice of manual dexterity. Lisbeth H. Larsen et al. *Physiological Reports* ISSN 2051-817X.

Larsen et al. from WP3 (female stroke survivors) have successfully demonstrated that tablet-based motor practice is associated with changes in the common corticospinal drive to spinal motoneurons involved in manual dexterity in healthy subjects. This observation is instrumental before using tablet-based motor practice as a motivating training tool for stroke patients who struggle with loss of dexterity in WP3.

Enhanced Muscle Insulin Sensitivity After Contraction/Exercise is Mediated by AMPK

Rasmus Kjøbsted, Nanna Munk-Hansen, Jesper B. Birk, Marc Foretz, Benoit Viollet, Marie Bjørnholm, Juleen R. Zierath, Jonas T. Treebak, Jørgen F.P. Wojtaszewski. *Diabetes.* 2017 Mar;66(3):598-612

In this publication, WP5 (molecular physiology) researchers have shown that the marked improvement in insulin sensitivity observed after acute exercise in muscle is mediated by activation of the energy sensor enzyme AMPK. This observation is ground breaking towards understanding the molecular background behind the beneficial effect of physical activity on metabolic regulation.

Early Postmenopausal Phase Is Associated With Reduced Prostacyclin-Induced Vasodilation That Is Reversed by Exercise Training: The Copenhagen Women Study. Nyberg M, Egelund J, Mandrup CM, Nielsen MB, Mogensen AS, Stallknecht B, Bangsbo J, Hellsten Y. *Hypertension.* 2016; 68(4):1011-20.

In this paper researchers from WP2 have shown that recently postmenopausal women have impaired blood vessel function compared to premenopausal women but that a period of exercise training can counteract this impairment. The findings of this study, which also provides mechanistic insight, have important implications for the prevention and treatment of cardiovascular disease.

2.4 Prizes, prestigious grants and awards [præpopuleres pba. midtvejsevaluering]

CWS researchers have not obtained any of the prizes, grants or awards indicated in the report template. However, Henning Langberg (WP3) has been awarded the Ove Bøje Award in 2016 for “significantly improving practices of clinical sports medicine by his research contributions”. The PI Erik A. Richter has been invited to present the Solomon Berson Distinguished Lectureship for the American Physiological Society at the Experimental Biology meeting in San Diego, April 2018.

2.5 International research collaboration

In appendix 2, a complete list of national and international collaborators is listed by the criteria that collaborators should be directly associated with aspects of the research in CWS and consequently appear as co-authors on at least one publication directly related to CWS projects.

Currently the list encompasses 21 international and 24 national research groups with whom collaboration has been established either directly or partly as a consequence of research in CWS. The majority of international collaborations have been within research fields in order to adapt novel state-of-the-art methods and technologies that will increase the impact of our studies – and importantly to allow young researchers to gain experience from stays in foreign research environments as part of the research education. In this context, all of the international collaborations have included visits either from the international collabora-

tor and/or visits from CWS researchers to foreign labs and for the majority of collaborations new projects are being established parallel to the work in CWS. Finally, with three of our partners a PhD exchange agreement has been established.

CWS researchers have presented research derived from CWS in conferences and meetings more than 70 times (majority being oral presentations) both nationally and internationally. Finally, an important part of the international networking strategy has involved numerous visits from foreign researchers at UCPH as well visits by CWS researchers abroad.

As highlighted above, researchers in the present 2016 project have made great efforts to generate a very strong interdisciplinary research platform not only to optimize the scientific output of CWS, but also to build on during future projects as part of our embedment strategy.

3. Research based educational activities and research training

As part of the 2016 project “Physical activity and nutrition for improvement of health” senior researchers have been encouraged to engage in research based educational activities directed toward the young researchers. To facilitate this, management (CWS platform) has offered financial and administrative support to arrange journal clubs and scientific meetings within CWS as well as 11 seminars with international speakers, 5 PhD courses, one master class in E-health and Motivation in Rehabilitation as well as 3 symposia of an interdisciplinary nature (see appendix 3: Platform activities). CWS has engaged a total of 13 PhD students and 6 postdocs that have been either fully or partly financed by the 2016 funding. External grants and co-funding from UCPH has allowed us to uphold this number. Importantly, an instrumental part of research in CWS has been the tireless contributions by both bachelor and master’s students that consequently have been educated in a very ambitious scientific environment and also have been introduced to the interdisciplinary nature of research pertaining to the field of physical activity, nutrition and health. Collectively, 20 bachelor and 38 master’s students have graduated within CWS and several of those have continued in science (at masters/PhD level).

4. External funding [præpopuleres pba. midtvejsevaluering]

CWS has collectively managed to attract ~ 14 mio DKK externally to directly support the research.

<i>Source</i>	<i>Grant holder</i>	<i>Project title</i>	<i>Period</i>	<i>Total amount granted</i>	<i>Sub amount (if more than one grant holder)</i>
<i>The Danish Diabetes Academy</i>	<i>Annemarie Lundsgaard Bahnsen (WP1)</i>	<i>Dietary fatty acids and insulin sensitivity – regulatory mechanisms</i>	<i>2016</i>	<i>500.000 DKR</i>	
<i>Danish ministry of culture</i>	<i>Ylva Hellsten (WP2)</i>	<i>Effect of physical activity on functional and molecular changes in muscle and blood vessels in early post menopause.</i>	<i>2013-2014</i>	<i>460.800 DKR</i>	
<i>Danish ministry of culture</i>	<i>Jens Bangsbo (WP2)</i>	<i>Role of menopause on circulation and muscle function – effect of physical activity</i>	<i>2013-2014</i>	<i>342.000 DKR</i>	

<i>Copenhagen centre for team sports and health</i>	<i>Michael Nyberg (WP2)</i>	<i>The role of Physical activity for performance and health in middle aged women</i>	<i>2014-2015</i>	<i>500.000 DKR</i>	
<i>Dr. Johan Boserup og Lise Boserup foundation</i>	<i>Bente Stallknecht (WP2)</i>	<i>Research grant for clinical research</i>	<i>2015</i>	<i>150.000 DKR</i>	
<i>The Oticon foundation</i>	<i>Lisbeth H Larsen (WP3)</i>	<i>Research stay at University of Florida</i>	<i>2016</i>	<i>5.500 DKR</i>	
<i>The Lundbeck foundation</i>	<i>Lisbeth H Larsen (WP3)</i>	<i>Research stay at University of Florida</i>	<i>2016</i>	<i>20.600 DKR</i>	
<i>The Danish diabetes academy</i>	<i>Stine Dam Søndergård (WP4)</i>	<i>The production of reactive oxygen species in response to glutathione supplementation and acute exercise in patients with type 2 diabetes</i>	<i>2015</i>	<i>550.000 DKR</i>	
<i>The Lundbeck foundation</i>	<i>Janne R Hingst (WP5)</i>	<i>Methodological developments in characterizing the role of hexokinase in glucose metabolism</i>	<i>2016</i>	<i>1.050.000 DKR</i>	
<i>The Danish diabetes academy</i>	<i>Jørgen Wojtaszewski (WP5)</i>	Visiting professorship <i>Methodological developments in characterizing the role of hexokinase in glucose metabolism</i>	<i>2014-2016</i>	<i>450.000 DKR</i>	
<i>Danish ministry of culture</i>	<i>L. F. Thing L. Ottesen (WP6)</i>	<i>Experiences of a more active life style for middle aged women.</i>	<i>2015</i>	<i>500.000 DKR</i>	
<i>Danish Innovation Foundation and the Joint Programming Initiative</i>	<i>L. O. Dragsted</i>		<i>2015</i>	<i>3.500.000 DKK</i>	
<i>The independent Research Foundation Denmark- Medi-</i>	<i>Jens Bangsbo</i>	<i>Estrogen related receptor in postmenopausal women: role in essential hypertension</i>	<i>2017</i>	<i>2.300.000 DKK</i>	

<i>cal Sciences</i>					
<i>The independent Research foundation Dnemark-Medical Sciences.</i>	<i>Erik A. Richter</i>	<i>Panthothenate kinase 4 (PANK4): A novel enzyme in metabolic regulation.</i>	<i>2017</i>	<i>2.590.000 DKK</i>	
<i>The Novo Nordisk Foundation</i>	<i>Erik A. Richter</i>	<i>Discovery and validation of muscle signaling related to health</i>	<i>2017</i>	<i>1.000.000 DKK</i>	

5. Private and public sector collaboration, innovation and impact

5.1 Private and public sector collaboration

The overall aims of the 2016 project “Physical activity and nutrition for improvement of health“ are to improve physical health and well-being, facilitate treatment, rehabilitation and prevent certain diseases by means of interventions related to physical activity and proper nutrition. The first major research initiative (CWS) has focused on women at risk of metabolic disease or in rehabilitation from stroke. Thus WP 1-4 have been extensively depending on public sector collaboration (including several hospitals, the Copenhagen municipality and Ubberrup folk high school) with regard to recruitment, characterisation as well as endpoint evaluation of participants undergoing interventions. These collaborations are indicated in appendix 2 (national collaborations).

As part of these University-public sector collaborations, CWS researchers have not only gained valuable experiences and alliances to be used during the remaining funding period as well as during future research initiatives. Importantly, the research platform “Physical activity and nutrition for improvement of health“ is being established as a highly competent and relevant collaborator and source of information for the public sector.

In regard to stakeholder outreach CWS was represented at the UCPH stakeholder event "Price of modern life - How to handle the complex societal challenges of western lifestyle " hosted by HEALTH in 2013. The aim was to address how to target major societal challenges through cross sectorial collaboration. In this context CWS (together with 3 other 2016 projects) presented and discussed interdisciplinary research of excellence at UCPH.

5.2 Application and commercialisation

Currently research in the present 2016 project has not resulted in any patents or other types of commercialisation. However, research in CWS is not aimed at a commercial outcome.

5.3 Societal impact

One of the key aims of the present 2016 project is to create an inter-disciplinary and cross-faculty research platform at the University of Copenhagen that generates and communicates evidence-based life style recommendations ‘tailored’ for population groups at risk of impaired health, well-being and overall quality of life. Thus, a critical aspect of our work is to disseminate results when it can be meaningfully translated to municipalities or the public. Several efforts have been made based on results already published and others are envisioned since results are still under publication. Below is summary of these efforts.

- WP1 (PCOS study): If it is firmly established that physical training not only results in repression of hyperandrogenism but that patients furthermore gain remarkable improvements in mood and self-esteem then we plan to present the findings to the PCO union in Denmark (no English homepage) and hereby de-

termine a suitable dissemination strategy. Also after original peer reviewed publication the observations will be conveyed to the press and popular media.

- WP2 (menopause study): Data from WP2 clearly show that physical activity is an effective means of promoting cardiovascular and metabolic health in the absence of estrogen in postmenopausal women. This information has not only been published in original peer reviewed publications but has also been disseminated in the press around the world and in popular media (radio and television).
- WP3 (stroke study): We have already presented to the Municipality of Copenhagen that tablet-based motor practice involving specialized apps might be a potential motivating and effective training tool to practice manual dexterity at home and enhance neural plasticity. Future findings will be similar presented.
- WP4 (obesity study): In February 2016 Jørn Wulff Helge has lectured at the Folk University entitled (translated from Danish) “physical activity, it is never too late”. WP4 has entertained an information meeting for all subjects that participated in the longitudinal intervention project. In June 2016 WP4 and WP6 researchers participated in the large annual political festival called “Folkemødet (folk meeting)” on Bornholm with a focus on Lifestyle and the inherent problems in maintaining lifestyle changes and weight loss. Future outreach activities are being planned in collaboration with the “Center of healthy aging” at UCPH.
- WP6 (Human and Social Sciences) researchers have been giving a featured talk (1½ hour workshop) at the IOC/Harvard Medical School Conference on Coaching in leadership and health in 2017.

5.4 Public outreach

Apart from initiatives, directly targeting relevant municipalities, scientific approaches and results from CWS has been disseminated in the form of science communication and input to the public debate via Danish television, radio, newspapers and social media. Selected media appearances so far are highlighted below:

- TV2 Lorry 10/9 2014: Interview with WP 4 leader professor Jørn Helge regarding intense life style interventions as a strategy to target obesity.
- TV2 lorry 7/1 2015: Ugens Nørd: Interview with WP2 researcher post doc Michael Nyberg regarding the effect of physical training on health of women during menopause.
- Italian SuperQuark on Rai1 21/08 2015: Interview with WP2 researchers regarding the effect of physical training on health of women during menopause.
- Articles in Nordvest and Diætisten addressing intense life style interventions as a strategy to target obesity.
- Danish national radio news 5/10 2015: Interview with PI Erik Richter regarding progress in determining the molecular landscape activated by exercise in the body.
- Following the finding of AMPK as central player in mediating improved insulin sensitivity and the follow-up study on proof of concept for the use of this mechanism in control of glucose homeostasis, WP5 researchers have appeared in DR2, Radio 24/7, Radio Novo, Politiken as well as in American news to promote AMPK as a potential “exercise pill”.
- Based on the findings in WP2, a press release has been generated resulting in a range of media appearances. Title: Women should be physically active after the menopause”

6. Concluding remarks

Regular physical activity plays an instrumental part in determining health as defined by physical, mental as well as social well-being. As an illustration, physical inactivity is responsible for an average loss of 7 ‘quality’ years of life and particularly in combination with “unhealthy” diet leads to a marked (> 7 years) reduction in the individual’s lifespan. The cost for society – in terms of health-care expenses and working hours lost – is equally massive. A major society challenge in this context is to elucidate the mechanisms by which physical activity can improve health, prevent disease and facilitate treatment and rehabilitation

in a cost-effective manner. Since the majority of intervention studies with regard to physical activity and health are performed in men, this leaves a distinct lack of well-controlled physiological studies relating physical activity to health in women in different phases of adult life. For instance, hormonal changes and disease states unique to women have marked metabolic consequences which predispose them to type 2 diabetes and cardiovascular diseases.

Based on the efforts in CWS we have managed to create a unique interdisciplinary research environment and infrastructure for large human intervention studies as well as important ties to a wide range of national and international collaborators. On this background the CWS initiative has produced 56 publications and significant results with implications for the health and well-being of the targets groups. Importantly, the nature of CWS has challenged both young and senior researchers to work and communicate between disciplines ranging from physiology, sociology and psychology. In that sense this 2016 project has generated a novel breed of researchers that will be even better equipped to target future interdisciplinary research challenges. To support this process the establishment of novel interdisciplinary research positions at UCPH is important as well as continuation of research in the CWS consortium allowing for further career building for young researchers with an interdisciplinary mindset.

In our view the scientific and strategic outcomes outlined in this report is a direct result of the initial investment made by UCPH which has allowed us to initiate very ambitious and long term studies that are not feasible under normal circumstances. This has fostered invaluable alliances within UCPH and internationally as well as with relevant municipalities, which in turn has allowed us to attract substantial additional research funding. Importantly, combining strengths within research disciplines ranging from physiology, psychology and sociology has allowed us to address novel and essential research questions related to healthy living. On that background we can only endorse similar long term strategic initiatives in the future.

Appendix 1: Publications

WP1

1. Circulating FGF21 in humans is potently induced by short term overfeeding of carbohydrates. Lundsgaard,AM, Fritzen,AM, Sjoberg,KA, Myrmel,LS, Madsen,L, Wojtaszewski,JF, Richter,EA, Kiens,B: *Mol Metab* 6:22-29, 2017.
<https://www.ncbi.nlm.nih.gov/pubmed/28123934>
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<https://www.ncbi.nlm.nih.gov/pubmed/28768703>
4. Gender differences in skeletal muscle substrate metabolism - molecular mechanisms and insulin sensitivity. Lundsgaard, A-M and Kiens B. *Font Endo* . s 1-16, 2014
<https://www.ncbi.nlm.nih.gov/pubmed/25431568>
5. Exercise Physiology in Men and Women. Lundsgaard, A-M., Fritzen, A.M. Kiens, B. In: *Principles of Gender-specific Medicine*. Third edition. ED: Legato M.J. s 525-538, 2017.
6. Molecular Regulation of Fatty Acid Oxidation in Skeletal Muscle during Aerobic Exercise. Lundsgaard, A-M., Fritzen, A.M. Kiens B., *Trends in Endo and Metab*, s 7-13, 2017.
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WP2

1. Effects of high-intensity training on cardiovascular risk factors in premenopausal and postmenopausal women. Mandrup CM, Egelund J, Nyberg M, Slingsby MH, Andersen C, Løgstrup S, Bangsbo J, Suetta C, Stallknecht B, Hellsten Y. *Am J Obstet Gynecol*. 2017 Apr;216(4):384.e1-384.e11.
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<https://www.ncbi.nlm.nih.gov/pubmed/27550922>
3. Adaptations with intermittent exercise training in post- and pre-menopausal women. Seidelin K, Nyberg M, Piil P, Jorgensen NR, Hellsten Y, Bangsbo J. *Med Sci Sports Exerc*. 2017;49:96-105.
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4. Biomarkers of vascular function in pre, and recent postmenopausal women of similar age: effect of exercise training. Nyberg M, Seidelin K, Rostgaard Andersen T, Neumann Overby N, Hellsten Y, Bangsbo J. *Am J Physiol Regul Integr Comp Physiol*. 2014;306:R510-517.

<https://www.ncbi.nlm.nih.gov/pubmed/24477543>

5. Leg vascular and skeletal muscle mitochondrial adaptations to aerobic high-intensity exercise training are enhanced in the early postmenopausal phase. Nyberg M, Egelund J, Andersen CB, Hansen K, Hergel I, Valbak-Andersen N, Frikke-Schmidt R, Bente Stallknecht, Bangsbo J, Hellsten Y. *J Physiol*. 2017 May 1;595(9):2969-2983. doi: 10.1113/JP273871.
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6. Cardiac Adaptations to High-Intensity Aerobic Training in Premenopausal and Recent Postmenopausal Women: The Copenhagen Women Study. Egelund J, Jørgensen PG, Mandrup CM, Fritz-Hansen T, Stallknecht B, Bangsbo J, Nyberg M, Hellsten Y. *J Am Heart Assoc*. 2017 Aug 18;6(8).
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7. Aerobic exercise training lowers platelet reactivity and improves platelet sensitivity to prostacyclin in pre- and postmenopausal women. Slingsby MHL, Nyberg M, Egelund J, Mandrup CM, Frikke-Schmidt R, Kirkby NS, Hellsten Y. *Journal of Thrombosis and Haemostasis*. 2017; 15(12):2419-2431.
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WP3

- 1) Changes in corticospinal drive to spinal motoneurons following tablet based practice of manual dexterity coherence changes following tablet based practice. Lisbeth Hoejkjaer Larsen, Thor Jensen, Mark Schram Christensen, Jesper Lundbye Jensen, Henning Langberg, Jens Bo Nielsen. *Physiological Reports* 2016 Vol. 4 no. e12684
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WP4

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- 2) Maintaining a clinical weight loss after intensive lifestyle intervention is the key to cardiometabolic health. Dandanell S, Skovborg C, Præst CB, Kristensen KB, Nielsen MG, Lionett S, Jørgensen SD, Vigelsø A, Dela F, Helge JW. *Obes Res Clin Pract.* 2016, 11(4):489-498.
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- 3) Intact Regulation of the AMPK Signaling Network in Response to Exercise and Insulin in Skeletal Muscle of Male Patients With Type 2 Diabetes: Illumination of AMPK Activation in Recovery From Exercise. Rasmus Kjøbsted, Andreas J.T. Pedersen, Janne R. Hingst, Rugivan Sabaratnam, Jesper B. Birk, Jonas M. Kristensen, Kurt Højlund and Jørgen F.P. Wojtaszewski. *Diabetes.* 2016 May;65(5):1219-30.
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- 6) Global Phosphoproteomic Analysis of Human Skeletal Muscle Reveals a Network of Exercise-Regulated Kinases and AMPK Substrates. Nolan J. Hoffman, Benjamin L. Parker, Rima Chaudhuri, Kelsey H. Fisher-Wellman, Maximilian Kleinert, Sean J. Humphrey, Pengyi Yang, Mira Holliday, Sophie Trefely, Daniel J. Fazakerley, Jacqueline Stöckli, James G. Burchfield, Thomas E. Jensen, Raja Jothi, Bente Kiens, Jørgen F.P. Wojtaszewski, Erik A. Richter, David E. James. *Cell Metab*. 2015 Nov 3;22(5):922-35.
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WP6

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APPENDIX 2: List of collaborators

International collaborations

Professor David James, Charles Perkins Institute, University of Sydney, Australia.

- Evaluating muscle proteomics and phospho-proteomics in WP1 in collaboration with WP5.
- Professor James was visiting in Copenhagen in 2016 as part of the collaboration.
- A joint application to the Novo Nordic Foundation (NNF) Interdisciplinary Synergy Program has been drafted.
- This collaboration has included student exchange.

Dr. Martin Daumer, Director of the SLCMSR, The Human Motion Institute, Germany

- Dr. Daumer is part of the team inventing the novel accelerometers (Acti-belt) used on women in WP2. He will assist in evaluating and interpreting data obtained.
- As part of the collaboration WP2 researchers have visited Dr. Daumer on three occasions.
- Currently one common grant has been applied for to support future collaboration.

Professor Tim Warner, William Harvey Institute, London, UK

- Professor Warner is a world leading expert in platelet function and will support researchers in WP2
- As part of the collaboration Professor Warner has visited Copenhagen twice, and WP2 researchers and students have visited Professor Warner's lab on several occasions.
- Additional collaborative projects have been established with Professor Warner in this time period and several common grants have been applied for.

Professor Jose Calbet, University of Las Palmas, Gran Canaria, Spain

- Collaboration with researchers in WP4 on HIT training study in men and women.
- Prof. Calbet has been in Copenhagen on several occasions, and several mutual projects are in progress.

Professor Ricardo Mora Rodriguez and Assoc. Professor Ignacio Ara, Universidad Castilla-La Mancha, Toledo, Spain.

- Collaboration with researchers in WP4 on training in patients with metabolic syndrome as well as analyses of samples from CWS.
- A PhD exchange agreement has been established.
- As part of the collaboration WP4 researchers have visited Professor Rodriguez and colleagues on several occasions.
- Additional collaborative projects are in progress.

Professor Carsten Lundby, University of Copenhagen, Denmark. Former location: University of Zurich, Zurich, Switzerland.

- Professor Lundby will assist in evaluating mitochondrial regulation and function in WP4.
- A PhD exchange agreement has been established including a 3 month stay for one WP4 researcher in professor Lundby's lab.
- An additional collaborative project has been established and financed with Professor Lundby in this time period
- Prof. Lundby has visited WP4 on several occasions.

Professor Paul Greenhaff, University of Nottingham, Nottingham, England.

- Collaboration on muscle sample analysis and HIT training in WP4.

- As part of the collaboration WP4 researchers have visited Professor Greenhaff and colleagues and on several occasions and Prof. Greenhaff have visited Copenhagen on several occasions.
- Additional collaborative projects are in progress.

Assoc. Professor James King, University of Loughborough, Loughborough, England

- Collaboration on adipose tissue analysis after HIT training in WP4.
- As part of the collaboration Prof. King and colleagues visited Copenhagen.
- Additional collaborative projects are in progress and a research application has been sent by professor King.

Assoc. Professor Marcin Baranowski, Medical University of Bialystok, Bialystok, Poland

- Collaboration of lipid analysis in muscle in particular ceramide and diacylglycerol using lipidomics approach.
- A PhD exchange agreement has been established and a 3 month stay for a Polish PhD student (Monika Ksiazek) is planned in Prof. Helge's lab.

Professor John Hawley, Australian Catholic University, Melbourne, Australia.

- Collaboration on research in low fat diet influence on performance and fat oxidation including science dissemination counterbalancing the present hype on "Low Carb's".
- WP leader in WP4 has spent 3 month as visiting professor at Professor Hawley's lab in 2015.

Professor Olav Royakers, ICU Karolinska Hospital, Stockholm, Sweden.

- Collaboration with WP4 researchers on blood analyses.
- As part of the collaboration WP4 researchers have visited Professor Royakers and colleagues and on several occasions and Prof. Royakers have visited Copenhagen.

Professor Jørgen Jensen, Norwegian School of Sport Sciences, Norway

- Collaboration with WP5 on developing a Hexokinase II activity assay.
- As part of the collaboration professor Jensen will visit Copenhagen 2x1½ month financed by a visiting professorship grant.

Professor Otto Baba, Japan Otto, Medical and Dental University, Tokyo, Japan

- Collaboration with WP5 on generation of an antibody specific to glycogen. This has resulted in a novel antibody based way to measure glycogen content in tissues with marked impact on the research field.

Associate Professor Robyn Murphy, La Trope University, Australia

- Collaboration with WP5 on measuring muscle signalling in single muscle preparations.
- The collaboration has already led to student exchange in one direction and plans are made for students of professor Murphy to visit Copenhagen

Professor Matthias Mann, Max planck Institute, Germany

- Collaboration with WP5 with regard to perform proteomics/phosphoproteomics on single muscle fibre preparation
- This collaboration will include student collaboration

Professor Benoit Violette, Institut Cochin, Frankrig

- The lab of professor Violette has resulted in generation of unique transgenic animal models by which WP5 can study several central hypotheses regarding AMPK.

- Researchers from WP5 have visited the facilities of professor Violette.

Professor Juleen Zierath, The Karolinska Institute, Sweden

- The lab of professor Zierath has been instrumental in generation of unique transgenic animal models by which WP5 can study several central hypotheses regarding the AMPK complexes containing the gamma 3 subunit.
- Researchers from WP5 have visited the facilities of professor Zierath.

Professor Hadi Al-Hasani, German Diabetes Center, Dusseldorf, Germany

- The lab of professor Al-Hasani has made available unique transgenic animal models by which WP5 can study several novel hypotheses regarding TBC1D4
- The collaboration has and will include student exchange

Professor Sandy Gordon, School of Sport Science, Exercise & Health, University of Western Australia

- Collaboration regarding coaching intervention in WP2 performed by researchers in WP6.
- As part of the collaboration WP6 leader has been visiting professor for 3 months with Professor Gordon.
- A collaborative project is currently being prepared and applied for.

Professor Ian MacDonald, Dept. Nutrition, University of Nottingham, United Kingdom

- Collaboration regarding protein intake and diabetes risk, especially on intake assessment biomarkers.

Professor Edith Feskens, Dept. Nutrition, Wageningen Agricultural University, The Netherlands

- Collaboration regarding dietary instruments and biomarker development, especially in coordination with the Food Biomarker Alliance project under the Joint Programming Initiative (JPI-HDHL).

National collaborators

- Professor Anders Juul, Rigshospitalet.
- Professor Peter Krstrup, University of Copenhagen.
- Chief physician Jens Meldgaard Bruun, Randers Hospital.
- Professor, Chief physician Sten Madsbad, Hvidovre hospital
- Chief physician Lisbeth Nilau, Hvidovre hospital
- Associate professor Lotte Hahn Enevoldsen, University of Copenhagen.
- Professor Andreas Kjær, University of Copenhagen.
- Professor Martin Røssel-Larsen, University of Southern Denmark
- Chief physician Karin Magnussen, Hvidovre hospital
- Professor Henrik Larsson, Glostrup hospital.
- Dr. Thomas Fritz Hansen, Gentofte Hospital.
- Professor Lars Bo Nielsen, Rigshospitalet.
- Associate Clinical Research Professor Ruth Frikke-Schmidt, Rigshospitalet.
- Associate Clinical Research Professor Charlotte Suetta, Rigshospitalet
- Professor Niklas Rye Jørgensen, Rigshospitalet
- Dr. Troels Kjær, Roskilde Hospital
- Dr. Troels Wienecke, Roskilde Hospital
- Dr. Ivan Zibrandtsen, Roskilde Hospital
- Physiotherapists Julie Gerding & Tine Lund Uden, Copenhagen Municipality
- Leader and employees at Ubberup Folk high School.
- Senior Researcher Anja Olsen, Danish Cancer Society
- Senior Researcher Louise Hansen, Danish Cancer Society
- Associate professor Jonas T. Treebak, Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen

APPENDIX 3: Platform activities

CWS seminars:

2013

- Professor Ronald M. Evans: Nuclear Receptors and the Hunger Game

2014

- Professor Kurt Højlund: Exercising with the mechanisms of muscle insulin resistance in type 2 diabetes: Past and Future.
- Professor Robert C. Hickner: Estradiol, body fat distribution and insulin sensitivity in women: Am I confused?

2015

- Professor Dudley W. Lamming: Unleashing the therapeutic potential of mTORC1 inhibition for age-related diseases
- Professor Konrad Talbot: A new class of antidiabetics may be broad-spectrum Alzheimer's disease therapeutics
- Professor Sergio Grinstein: Tracking single molecules during phagocytosis: interplay of kinases and phosphatases.
- Professor Amira Klip: Muscle cell chemoattraction of monocytes: effect of lipids and muscle contraction.

2017

- Professor Hadi Al-Hasani: Dissecting the pathophysiology and genetics of type 2 diabetes and obesity with polygenic mouse models.
- Dr. Benjamin L. Parker, PhD: Genetic Regulation of Proteome and Lipidome Diversity and its Contribution to Hepatic Steatosis
- Dr. Adam Rose, PhD: Liver adaptive stress signalling and systemic metabolic control.
- Professor Mark Febbraio: The engineered designer cytokine IC7 protects against obesity-induced metabolic disease

CWS Courses:

2013

- PhD course (Science): Molecular physiology and metabolism in exercise and health

2014

- PhD course (Science): Vascular function and angiogenesis in health and lifestyle related disease.

2015

- PhD course (Health): Mitochondrial Physiology – from Organelle to Organism
- PhD course (Science): Vascular function and angiogenesis in health and lifestyle related disease.
- Masters class (Health): E-health and Motivation in Rehabilitation.

2016

- PhD course (Science): The Saltin International Graduate Course: Exercise Physiology in Health and Disease.

CWS conferences:

- In collaboration with UCPH-LOM: Exercise and physical activity in relation to lifestyle, obesity and metabolic diseases (may 2015).
- In collaboration with UCPH-LOM: Lifestyle and kinds of living - Opportunities, conditions and biology (may 2016).
- In collaboration with UCPH-LOM: Trends in Excellent and Interdisciplinary Lifestyle, Obesity and Metabolic Research (June 2017)