LIST OF INCLUDED PUBLICATIONS

This thesis includes the following 3 original papers

Paper I **Ruixin Zhu**, Ionut Craciun, Jan Bernhards-Werge, Elli Jalo, Sally D. Poppitt, Marta Silvestre, Maija Huttunen-Lenz, Melitta A. McNarry, Gareth Stratton, Svetoslav Handjiev, Teodora Handjieva-Darlenska, Santiago Navas-Carretero, Jouko Sundvall, Tanja C. Adam, Mathijs Drummen, Elizabeth J. Simpson, Ian A. Macdonald, Jennie Brand-Miller, Roslyn Muirhead, Tony Lam, Pia S. Vestentoft, Kristine Færch, J. Alfredo Martinez, Mikael Fogelholm, Anne Raben. Age-and sex-specific effects of a long-term lifestyle intervention on body weight and cardiometabolic health markers in adults with prediabetes: results from the diabetes prevention study PREVIEW. *Diabetologia*, 2022; 65: 1262–1277. https://doi.org/10.1007/s00125-022-05716-3

Paper II **Ruixin Zhu**, Elli Jalo, Marta P. Silvestre, Sally D. Poppitt, Teodora Handjieva-Darlenska, Svetoslav Handjiev, Maija Huttunen-Lenz, Kelly Mackintosh, Gareth Stratton, Santiago Navas-Carretero, Kirsi H. Pietiläinen, Elizabeth Simpson, Ian A. Macdonald, Roslyn Muirhead, Jennie Brand-Miller, Mikael Fogelholm, Kristine Færch, J. Alfredo Martinez, Margriet S. Westerterp-Plantenga, Tanja C. Adam, Anne Raben. Does the effect of a 3-year lifestyle intervention on body weight and cardiometabolic health differ by prediabetes metabolic phenotype? A *post-hoc* analysis of the PREVIEW study. *Diabetes Care*, 2022; 45:1–11. Online ahead of print. https://doi.org/10.2337/dc22-0549

Paper III **Ruixin Zhu**, Maija Huttunen-Lenz, Gareth Stratton, Teodora Handjieva-Darlenska, Svetoslav Handjiev, Jouko Sundvall, Marta P. Silvestre, Elli Jalo, Kirsi H. Pietiläinen, Tanja C. Adam, Mathijs Drummen, Elizabeth J. Simpson, Moira A. Taylor, Sally D. Poppitt, Santiago Navas-Carretero, J. Alfredo Martinez, Wolfgang Schlicht, Mikael Fogelholm, Jennie Brand-Miller, Anne Raben. Associations of obesity phenotypes with body weight and cardiometabolic benefits during a 3-year lifestyle intervention: a secondary analysis of the randomized trial PREVIEW. (Submitted to *Clinical Nutrition*)

OTHER ACTIVITIES DURING THE PHD PERIOD

Publications:

Zhu R, Larsen TM, Fogelholm M, Poppitt SD, Vestentoft PS, Silvestre MP, Jalo E, Navas-Carretero S, Huttunen-Lenz M, Taylor MA, Stratton G, Swindell N, Drummen M, Adam TC, Ritz C, Sundvall J, Valsta LM, Muirhead R, Brodie S, Handjieva-Darlenska T, Handjiev S, Martinez JA, Macdonald IA, Westerterp-Plantenga MS, Brand-Miller J, Raben A. Dose-Dependent Associations of Dietary Glycemic Index, Glycemic Load, and Fiber With 3-Year Weight Loss Maintenance and Glycemic Status in a High-Risk Population: A Secondary Analysis of the Diabetes Prevention Study PREVIEW. *Diabetes Care* 2021;44:1672-1681. https://doi.org/10.2337/dc20-3092

Zhu R, Fogelholm M, Larsen TM, Poppitt SD, Silvestre MP, Vestentoft PS, Jalo E, Navas-Carretero S, Huttunen-Lenz M, Taylor MA. A High-Protein, Low Glycemic Index Diet Suppresses Hunger but Not Weight Regain After Weight Loss: Results From a Large, 3-Years Randomized Trial (PREVIEW). *Front Nutr* 2021;8:685648. https://doi: 10.3389/fnut.2021.685648

Zhu R, Larsen TM, Poppitt SD, Silvestre MP, Fogelholm M, Jalo E, Hatonen KA, Huttunen-Lenz M, Taylor MA, Simpson L, Mackintosh KA, McNarry MA, Navas-Carretero S, Martinez JA, Handjieva-Darlenska T, Handjiev S, Drummen M, Westerterp-Plantenga MS, Lam T, Vestentoft PS, Muirhead R, Brand-Miller J, Raben A. Associations of quantity and quality of carbohydrate sources with subjective appetite sensations during 3-year weight-loss maintenance: Results from the PREVIEW intervention study. *Clin Nutr* 2022; 41: 219-230. https://doi.org/10.1016/j.clnu. 2021.11.038

Zhu R, Fogelholm M, Poppitt SD, Silvestre MP, Moller G, Huttunen-Lenz M, Stratton G, Sundvall J, Raman L, Jalo E, Taylor MA, Macdonald IA, Handjiev S, Handjieva-Darlenska T, Martinez JA, Muirhead R, Brand-Miller J, Raben A. Adherence to a Plant-Based Diet and Consumption of Specific Plant Foods-Associations with 3-Year Weight-Loss Maintenance and Cardiometabolic Risk Factors: A Secondary Analysis of the PREVIEW Intervention Study. *Nutrients* 2021; 13: 3916. https://doi.org/10.3390/nu13113916

Zhu R, Fogelholm M, Jalo E, Poppitt SD, Silvestre MP, Moller G, Huttunen-Lenz M, Stratton G, Sundvall J, Macdonald IA, Handjieva-Darlenska T, Handjiev S, Navas-Carretero S, Martinez JA, Muirhead R, Brand-Miller J, Raben A. Animal-based food choice and associations with long-term weight maintenance and metabolic health after a large and rapid weight loss: The PREVIEW study. *Clin Nutr* 2022;41:817-828. https://doi.org/10.1016/j.clnu.2022.02.002

Conference:

ePoster: DNSG 2021 - 38th International Symposium on Diabetes and Nutrition of the Diabetes and Nutrition Study Group of the European Association for the study of Diabetes 'Dose-dependent associations of dietary glycemic index, glycemic load and fiber with 3-year weight-loss maintenance and glycemic status: results from the PREVIEW diabetes prevention study'

SUMMARY

The global prevalence of obesity is increasing. Obesity is related to an increased risk of type 2 diabetes and cardiovascular diseases (CVD). Lifestyle-based weight management programmes have been shown to aid weight loss and improve risk factors of type 2 diabetes and CVD in several large-scale, long-term intervention studies. Clinical guidelines from the American Heart Association and American Diabetes Association therefore recommend weight loss for individuals with overweight or obesity to prevent type 2 diabetes and CVD. It is unclear whether the clinical guidelines would benefit specific populations or whether personalized interventions are needed. Several previous studies have investigated the associations of participants' baseline characteristics (e.g. age, sex, prediabetes phenotype, and obesity phenotype) with the effect of lifestyle interventions. Evidence based on the long-term, large-scale interventions, however, is scarce.

This PhD thesis was based on the data from the PREVIEW (PREVention of diabetes through lifestyle interventions and population studies In Europe and around the World) study, a 3-year, large-scale, multinational randomized controlled trial. The overall objective of this PhD thesis was to examine whether age, sex, prediabetes phenotype, and obesity phenotype would influence the effect of a low-energy diet followed by a 3-year lifestyle intervention on health outcomes: body weight, type 2 diabetes incidence, and cardiometabolic risk factors in a large and high-risk cohort.

In **Paper I**, the aim of the study was to examine age- and sex-specific effects of a low-energy diet followed by a long-term lifestyle intervention on body weight, type 2 diabetes incidence, and cardiometabolic risk factors. A total of 2223 participants (783 younger, 25−45 years; 319 middle-aged, 46−54 years; and 1121 older adults, 55−70 years; and 1503 women and 720 men) with overweight and prediabetes were included in the analysis. During the study, participants underwent 8-week rapid weight loss followed by a 148-week lifestyle-based weight-loss maintenance intervention. We found that compared with younger adults, older adults benefited less from a lifestyle intervention in relation to body composition and cardiometabolic risk factors. Compared with men, women benefited less in relation to body composition. Compared with older adults, middle-aged adults had higher 3-year cumulative incidence of type 2 diabetes. There were no differences in type 2 diabetes incidence between other age groups.

In **Paper II**, the study aimed to determine whether the effect of a low-energy diet followed by 3-year lifestyle intervention on body weight, type 2 incidence, and cardiometabolic risk factors would differ

by prediabetes phenotype. In total, 1510 participants with prediabetes were stratified into metabolic phenotypes: isolated impaired fasting glucose (iIFG), isolated impaired glucose tolerance (iIGT), and both iIFG and IGT (IFG+IGT). They were also classified as having normal hemoglobin A_{1c} (HbA_{1c}, <39 $mmol \cdot mol^{-1}$) and having intermediate HbA_{1c} (39–47 $mmol \cdot mol^{-1}$). During the study, participants underwent 8-week rapid weight loss followed by a 148-week lifestyle-based weight-loss maintenance intervention. We found that individuals with iIFG and IFG+IGT had similar improvements in cardiometabolic risk factors after the lifestyle intervention, despite greater sustained weight loss in those with IFG+IGT. There were no differences in 3-year type 2 diabetes incidence among prediabetes phenotypes. Participants with prediabetic hyperglycemia and normal vs intermediate HbA_{1c} had similar weight changes over 3 years. During weight maintenance, those with normal HbA_{1c} levels had greater improvements in cardiometabolic risk factors compared with those with intermediate HbA_{1c}. Individuals with normal HbA_{1c} had lower 3-year 2 diabetes incidence and greater improvements in cardiometabolic risk factors than those with intermediate HbA_{1c}.

In **Paper III**, we compared body weight, type 2 diabetes incidence, and cardiometabolic risk factors during a 3-year lifestyle intervention between adults with baseline metabolically healthy (MHO) vs unhealthy overweight/obesity (MUO). Participants were classified into MHO and MUO, according to baseline characteristics, i.e. waist circumference, fasting triglycerides, high-density lipoprotein cholesterol, blood pressure, and fasting plasma glucose. During the study, participants underwent 8-week rapid weight loss followed by a 148-week lifestyle-based weight-loss maintenance intervention. We found that compared with those with baseline MHO, individuals with baseline MUO benefited more from rapid weight loss in relation to cardiometabolic risk factors. Participants with MHO benefited more from lifestyle intervention than those with MUO. Individuals with MUO had lower 3-year type 2 diabetes incidence than those with MHO after a lifestyle intervention.

In conclusion, based on the data from the PREVIEW study, we found that in a large-scale, multinational, high-risk cohort, the 3-year effect of a lifestyle intervention may differ by age, sex, and metabolic status. After the 3-year lifestyle intervention, older adults benefited less in relation to body composition and cardiometabolic risk factors than younger adults. Women benefited less in relation to body weight and composition than men (**Paper I**). Compared with those with intermediate HbA_{1c}, individuals with normal HbA_{1c} had lower incidence of type 2 diabetes and greater improvements in cardiometabolic risk factors after the lifestyle intervention. (**Paper II**). Individuals with MHO had lower incidence of type 2 diabetes and greater improvements in cardiometabolic risk factors than those with MUO after the lifestyle intervention. (**Paper III**).

SAMMENDRAG (DANISH SUMMARY)

Den globale udbredelse af fedme er stigende. Fedme er relateret til en øget risiko for type 2 diabetes og hjertekarsygdomme (CVD). Livsstilsbaserede vægtreguleringsprogrammer har vist sig at hjælpe til vægttab og forbedre risikofaktorer for type 2 diabetes og hjertekarsygdomme i adskillige store, langvarige interventionsstudier. Kliniske retningslinjer fra American Heart Association og American Diabetes Association anbefaler derfor vægttab til personer med overvægt eller fedme for at forebygge type 2 diabetes og CVD. Det er uklart, om de kliniske retningslinjer vil gavne specifikke populationer, eller om der er behov for personlige interventioner. Adskillige tidligere undersøgelser har undersøgt sammenhængen mellem deltagernes baseline-karakteristika (f.eks. alder, køn, prædiabetes-fænotype og fedmefænotype) og effekten af livsstilsinterventioner. Evidens baseret på langvarige, store studier er dog sparsom.

Denne Ph.D.-afhandling var baseret på data fra PREVIEW (PREVention of diabetes through lifestyle interventions and population studies In Europe and around the World), et 3-årigt, stort, multinationalt, randomiseret kontrolleret forsøg. Det overordnede formål med denne Ph.D.-afhandling var at undersøge, om alder, køn, prædiabetes-fænotype og fedmefænotype ville påvirke effekten af en lavenergidiæt efterfulgt af en 3-årig livsstilsintervention på kropsvægt, type 2 diabetes forekomst og kardiometaboliske risikofaktorer i en stor og højrisiko kohorte.

I **Paper I** var formålet med undersøgelsen at undersøge alders- og kønsspecifikke effekter af en lavenergidiæt efterfulgt af en langsigtet livsstilsintervention på kropsvægt, type 2 diabetes forekomst og kardiometaboliske risikofaktorer. I alt 2223 deltagere (783 yngre, 25-45 år; 319 midaldrende, 46-54 år; og 1121 ældre voksne, 55-70 år; og 1503 kvinder og 720 mænd) med overvægt og prædiabetes blev inkluderet i analysen. I løbet af undersøgelsen gennemgik deltagerne 8 ugers hurtigt vægttab efterfulgt af en 148-ugers livsstilsbaseret vægttabsvedligeholdelsesintervention. Vi fandt, at sammenlignet med yngre voksne havde ældre voksne mindre gavn af en livsstilsintervention i forhold til kropssammensætning og kardiometabolske risikofaktorer. Sammenlignet med mænd havde kvinderne mindre gavn af interventionen i forhold til kropssammensætning. Sammenlignet med midaldrende voksne havde ældre voksne en lavere 3-års kumulativ forekomst af type 2 diabetes. Der var ingen forskelle i forekomsten af type 2 diabetes mellem andre aldersgrupper.

I **Paper II** havde undersøgelsen til formål at afgøre, om effekten af en lavenergidiæt efterfulgt af 3-årig livsstilsintervention på kropsvægt, type 2-forekomst og kardiometaboliske risikofaktorer ville afhænge af prædiabetes-fænotype. I alt blev 1510 deltagere med prædiabetes stratificeret i metaboliske fænotyper: isoleret forhøjet faste glukose (iIFG), isoleret nedsat glukosetolerance (iIGT)

og både iIFG og IGT (IFG+IGT). De blev også klassificeret i grupper med normalt hæmoglobin A_{1c} (HbA_{1c}, <39 $mmol \cdot mol^{-1}$) eller intermediært HbA_{1c} (39-47 $mmol \cdot mol^{-1}$). I løbet af undersøgelsen gennemgik deltagerne 8 ugers hurtigt vægttab efterfulgt af en 148-ugers livsstilsbaseret vægttabsvedligeholdelsesintervention. Vi fandt, at personer med iIFG og IFG+IGT havde samme forbedringer i kardiometaboliske risikofaktorer efter livsstilsinterventionen, på trods af større vedvarende vægttab hos dem med IFG+IGT. Der var ingen forskelle i 3-årig type 2 diabetes forekomst blandt prædiabetes fænotyper. Deltagere med prædiabetisk hyperglykæmi og normalt vs intermediært HbA_{1c} havde sammenlignelige vægtændringer over 3 år. Under vægtvedligeholdelse havde de med normale HbA_{1c}-niveauer større forbedringer i kardiometaboliske risikofaktorer sammenlignet med dem med intermediært HbA_{1c}. Personer med normalt HbA_{1c} havde lavere type 2 diabetes forekomst efter 3 år og større forbedringer i kardiometabolske risikofaktorer end dem med intermediært HbA_{1c}.

I **Paper III** sammenlignede vi kropsvægt, type 2 diabetes forekomst og kardiometabolske risikofaktorer under en 3-årig livsstilsintervention mellem voksne med baseline metabolisk sund overvægt/fedme (MHO) vs usund overvægt/fedme (MUO). Deltagerne blev klassificeret i MHO og MUO i henhold til baseline karakteristika, dvs. taljeomkreds, faste triglycerid, high-density lipoprotein kolesterol, blodtryk og fastende plasma glukose (FPG). I løbet af undersøgelsen gennemgik deltagerne 8 ugers hurtigt vægttab efterfulgt af en 148-ugers livsstilsbaseret vægttabsvedligeholdelsesintervention. Vi fandt, at sammenlignet med dem med baseline MHO, havde personer med baseline MUO større fordel af hurtigt vægttab i forhold til kardiometaboliske risikofaktorer. Deltagere med MHO havde mere gavn af livsstilsintervention end dem med MUO. Personer med MUO havde lavere 3-årig type 2 diabetes forekomst end dem med MHO efter livsstilsinterventionen.

På baggrund af data fra PREVIEW-studiet, kan det konkluderes, at i en stor, multinational, højrisiko-kohorte, kan den 3-årige effekt af en livsstilsintervention variere efter alder, køn og metabolisk status. Efter den 3-årige livsstilsintervention havde ældre voksne mindre gavn i forhold til kropssammensætning og kardiometabolske risikofaktorer end yngre voksne. Kvinder havde mindre gavn i forhold til kropsvægt og sammensætning end mænd (**Paper I**). Sammenlignet med dem med intermediært HbA_{1c} havde personer med normalt HbA_{1c} lavere forekomst af type 2 diabetes og større forbedringer i kardiometaboliske risikofaktorer efter livsstilsinterventionen (**Paper II**). Personer med MHO havde lavere forekomst af type 2 diabetes og større forbedringer i kardiometaboliske risikofaktorer end dem med MUO efter livsstilsinterventionen (**Paper III**).

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