

PUBLICATIONS

Publications included in the thesis

The PhD thesis is based on the following five papers:

Paper I: **Pigsborg K**, Magkos F. Metabotyping for precision nutrition and weight management. Hype or hope? *Curr Nutr Rep*. 2022 Jun;11(2):117-123.

<https://doi.org/10.1007/s13668-021-00392-y>.

Paper II: Aldubayan MA, **Pigsborg K**, Gormsen SMO, Serra F, Palou M, Mena P, Wetzels M, Calleja A, Caimari A, Del Bas J, Gutierrez B, Magkos F, Hjorth MF. Empowering consumers to PREVENT diet-related diseases through OMICS sciences (PREVENTOMICS): protocol for a parallel double-blinded randomised intervention trial to investigate biomarker-based nutrition plans for weight loss. *BMJ Open* 2022;12:e051285. <https://doi.org/10.1136/bmjopen-2021-051285>

Paper III: Aldubayan MA*, **Pigsborg K***, Gormsen SMO, Serra F, Palou M, Galmés S, Palou-March A, Favari C, Wetzels M, Calleja A, Gómez MAR, Castellnou MG, Caimari A, Galofré M, Suñol D, Escoté X, Alcaide-Hidalgo JM, del Bas J, Gutierrez B, Krarup T, Hjorth MF, Magkos F. A double-blinded, randomized, parallel intervention to evaluate biomarker-based nutrition plans for weight loss: The PREVENTOMICS study. *Clin Nutr*. 2022 Aug;41(8):1834-1844.

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Paper IV: **Pigsborg K**, Stentoft-Larsen V, Demharter S, Aldubayan MA, Trimigno A, Khakimov B, Engelsen SB, Astrup A, Hjorth MF, Dragsted LO, Magkos F. Predicting weight loss success on a New Nordic Diet: an untargeted multi-platform metabolomics and machine learning approach. *Under review*. *Frontiers in Nutrition*.

Paper V: **Pigsborg K**, Kalea AZ, De Dominicis S, Magkos F. Behavioral and psychological factors affecting weight loss success. *Accepted*. *Current Obesity Reports* 2023.

Other publications during the PhD period

Pigsborg K, Gürdeniz G, Rangel-Huerta OD, Holven KB, Dragsted LO, Ulven SM. Effects of changing from a diet with saturated fat to a diet with n-6 polyunsaturated fat on the serum metabolome in relation to cardiovascular disease risk factors. *Eur J Nutr.* 2022 Jun;61(4):2079-2089. <https://doi.org/10.1007/s00394-021-02796-6>

Aldubayan MA, Mao X, Laursen MF, **Pigsborg K**, Christensen LH, Roager HM, Nielsen DS, Hjorth MF, Magkos F. Supplementation with inulin-type fructans affects gut microbiota and attenuates some of the cardiometabolic benefits of a plant-based diet in individuals with overweight or obesity. *Front. Nutr. Sec. Nutrition and Microbes* 2023(10).
<https://doi.org/10.3389/fnut.2023.1108088>

Keijer J, Escoté X, Galmés S, Palou-March A, Serra F, Aldubayan MA, **Pigsborg K**, Magkos F, Baker EJ, Calder PC, Góralaska J, Razny U, Malczewska-Malec M, Suñol D, Galofré M, Rodríguez MA, Canela N, Malcic RG, Bosch M, Favari C, Mena P, Del Rio D, Caimari A, Gutierrez B, Del Bas JM; in name of the PREVENTOMICS Consortium: Empowering Consumers to Prevent diet-related diseases through-OMIC sciences. Omics biomarkers and an approach for their practical implementation to delineate health status for personalized nutrition strategies. *Crit Rev Food Sci Nutr.* 2023 Apr 19:1-29.
<https://doi.org/10.1080/10408398.2023.2198605>

Galmés S, Palou-March A, **Pigsborg K**, Aldubayan MA, Gormsen SMO, Calleja A, Trabal J, Marínez V, Gutierrez B, Del Bas J, Magkos F, Serra F. Personalized nutrition to mitigate inflammation in genetically predisposed individuals: a secondary analysis of the Danish PREVENTOMICS intervention. *Under review.* *Molecular Nutrition and Food Research.*

SUMMARY

To combat the increasing prevalence of obesity that has been rising for the last decades, the best diet for optimal weight loss has been investigated. However, studies consistently show large interindividual variation in response to the same dietary treatment, thus a more personalized diet might minimize this variation. Focusing on each and every individual of the population is unrealistic in terms of cost-benefit but grouping individuals into smaller, relatively homogeneous subgroups based on their metabolic phenotype holds great potential for precision nutrition and has been coined as metabotyping. Accordingly, the objective of this thesis was to explore the potential of metabotyping for optimizing weight loss success in response to diet treatment among individuals with obesity.

In **Paper I**, the existing literature on the already utilized metabolotypes in relation to weight loss was reviewed, and it was established that only a very limited number of studies had investigated metabolotypes; and those that did were very heterogeneous and applied different approaches making comparison very difficult.

In **Paper II** and **Paper III** a randomized controlled trial was designed and conducted to test the efficacy of individualized diet treatments driven by literature-defined metabolotypes, compared to generic dietary recommendations, during a 10-week nutrition intervention. Here, the study demonstrated no additional benefit of personalizing dietary plans over a generic approach on the change in fat mass and body weight in individuals with overweight or obesity and elevated waist circumference. Accordingly, personalization of the diet did not significantly improve health parameters beyond the changes induced by the control diet.

In **Paper IV** a prediction model was developed to predict weight loss success for subjects with overweight or obesity following a New Nordic Diet. By utilizing baseline metabolomics data, a model with two metabolites, urinary levels of adipic acid and argininic acid, was identified that in combination provided a predictive signature for discriminating weight loss responders and non-responders at baseline. These metabolites could potentially be a point of direction for new metabolotypes that respond differently on a fiber-rich diet.

In **Paper V** factors other than biological or metabolic variables, such as behavioral and psychological factors, which potentially could influence the outcome of a weight loss intervention were reviewed. Here, it became evident that the variation in weight loss responses may be

partly explained by differences between individuals in a variety of behavioral and psychological factors, which emerged as important parameters for successful weight loss.

Collectively, this work suggests that there is still much work to be done for optimizing personalized approaches to dietary recommendations for successful weight loss. Future studies should be designed with much more careful consideration of the definition of the metabotypes, and target dietary recommendations on the diet level rather than at the level of specific foods and food ingredients. Last but not least, future studies should also track a variety of behavioral and psychological factors that could affect weight loss outcomes.

DANSK SAMMENDRAG

For at bekæmpe den stigende forekomst af svær overvægt, der de seneste årtier har været støt stigende, har jagten på den optimale diæt under vægttab været i afsøgt. Undersøgelser viser nemlig konsekvent stor interindividual variation i respons på den samme kostsammensætning, og derfor kan en mere personaliseret diæt måske minimere denne variation. At fokusere på hvert enkelt individ af befolkningen synes urealistisk med henblik på cost-benefit, men det at gruppere individer i mindre, relativt homogene undergrupper baseret på deres metaboliske fænotype rummer stort potentiale for præcision ernæring og er blevet betegnet som metabotyping. Følgelig er formålet for denne afhandling at undersøge potentialet ved metabotyping som et optimeringsværktøj for at øge successen for vægttab blandt individer med svær overvægt.

I **Artikel I** blev den eksisterende litteratur om allerede anvendte metabotyper i forhold til vægttab gennemgået, og her blev der konstateret, at kun et begrænset antal studier havde undersøgt potentialet af metabotyper i forbindelse med vægttab; og dem, der gjorde, var meget heterogene og havde forskellige tilgange til det, hvilket gjorde det meget vanskeligt at sammenligne dem.

I **Artikel II** og **Artikel III** blev et kontrolleret lodtrækningsforsøg designet og udført for at teste effektiviteten af individualiserede kostanbefalinger baseret på fem litteraturdefinerede metabotyper og testet mod generelle kostanbefalinger, under en 10-ugers periode. Her viste forsøget ingen yderligere fordel ved de individualiserede diæter sammenlignet med de generelle anbefalinger i ændringen af fedtmasse og kropsvægt hos personer med overvægt eller fedme og forhøjet taljeomkreds. Derudover var der ingen yderlige effekt blandt andre sundhedsparametre mellem de to diættyper.

I **Artikel IV** blev der udviklet en model, der var i stand til at forudsige forsøgspersoner med svært overvægts chancer for vægttab ved at følge en Ny Nordisk Kost. Ud fra baseline metabolomics data, blev modellen indeholdende urinniveauer af adipinsyre og argininsyre identificeret, og denne producerede en forudsigende signatur til at skelne mellem de personer der havde et vellykket vægttab fra dem der ikke havde et vellykket vægttab. De to metabolitter kan potentielt være et nyt retningspunkt for nye metabotyper, der responderer forskelligt på en fiberrig kost under et vægttab.

I **Artikel V** blev ikke-biologiske eller metaboliske faktorer, såsom adfærdsmæssige og psykiske parametre, som potentielt kunne påvirke resultatet af et vægttab gennemgået. Her blev det

tydeligt, at variationen i vægttab delvist kan tilskrives forskelle mellem individer i en række adfærdsmæssige og psykologiske faktorer, som fremstod som vigtige faktorer for vellykket vægttab.

Samlet set tyder arbejde fra denne PhD på, at der stadig er meget arbejde at gøre for at optimere en mere personlig tilgange til kostanbefalinger for at sikre et vellykket vægttab. Fremtidige studier bør udformes med større omhyggelig og overvejelse af definitionen af metabotyperne og målrette kostanbefalinger på en kost som helhed snarere end på specifikke fødevarer og fødevaringredienser. Sidst men ikke mindst bør fremtidige studier også indsamle flere informationer om adfærdsmæssige og psykologiske faktorer, der kan påvirke vægttabsresultater.

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