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Publications

The foundation of this PhD thesis lies in three scientific publications as follows:

1. **Aldubayan MA**, Pigsborg K, Gormsen SMO, Serra F, Palou M, Mena P, et al. 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(3):e051285. doi: 10.1136/bmjopen-2021-051285.

2. **Aldubayan MA**[*], Pigsborg K[*], Gormsen SMO, Serra F, Palou M, Galmés S, et al. A Double-Blinded, Randomized, Parallel Intervention to Evaluate Biomarker-Based Nutrition Plans for Weight Loss: The Preventomics Study. *Clin Nutr* (2022) 41(8):1834-44. Epub 20220630. doi: 10.1016/j.clnu.2022.06.032.
   [*]*Contributed equally. This paper is also included in the PhD thesis of Kristina Pigsborg*

3. **Aldubayan MA,** Mao X, Laursen MF, Pigsborg K, Christensen LH, Roager HM, et al. 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.* (2023) 10. doi: 10.3389/fnut.2023.1108088.

During my PhD period, I co-authored three other papers not included in this thesis:

1. Keijer J, Escoté X, Galmés S, Palou-March A, Serra F, **Aldubayan MA**, et al. Omics Biomarkers and an Approach for Their Practical Implementation to Delineate Health Status for Personalized Nutrition Strategies. *Crit Rev Food Sci Nutr* (2023):1-29. Epub 20230419. doi: 10.1080/10408398.2023.2198605.

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

3. Pigsborg K, Stentoft-Hansen 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 " to be considered for publication in Frontiers in Nutrition, section Nutrigenomics (Under review in Frontiers in Nutrition).

Summary

Combating the obesity epidemic is one of the greatest challenges of modern era. Despite that weight loss diets have been used for more than 2,500 years, they have not yielded significant success given the persistent global rise in rates of overweight and obesity in recent decades.

For years, scientists have debated the ideal dietary plan for weight loss in terms of macronutrient composition. However, no singular dietary approach has been conclusively established to outperform others. Irrespective of the type of diet, people react differently to the same dietary treatment. This ranges from individuals who lose very little weight to others who lose a lot, and there are even some who may gain weight. The reasons for this large interindividual variability can be attributed to various factors such as distinctive genetic makeup and diverse mechanisms of food absorption and metabolism in the body, or even behavioural and psychological factors. It is believed that tailoring dietary intervention strategies according to an individual's metabolic profile holds considerable potential in the treatment of obesity, as opposed to relying solely on generalized dietary recommendations for the whole population.

Accordingly, the H2020 PREVENTOMICS project (Empowering consumers to PREVENT diet-related diseases through OMICS sciences), coordinated by Eurecat in Spain, has developed a direct-to-consumer platform on the basis of integrating genetic, nutritional, biochemical and behavioural factors to assess the unique metabolic profile of individuals using metabolomics and machine-learning techniques, aimed at delivering personalized nutritional plans to ultimately drive sustainable behaviour change to tackle obesity and thereby, prevent nutrition-related chronic diseases.

The current PhD thesis is based on three publications out of the PREVENTOMICS project with an overall aim to investigate the efficacy of using such a platform to deliver personalized nutrition plans for reducing body fat mass and subsequently improving health outcomes. The three objectives and corresponding papers are summarized below.

1. To review the existing literature on precision nutrition for weight loss and design a study to assess such a personalized nutrition approach.
2. To investigate the efficacy of personalizing dietary plans, using genetic and health biomarkers, in producing more favourable health outcomes over dietary plans based on general recommendations.

3. To explore the impact of consuming an *ad libitum* high-fibre plant-based diet on gut microbiota composition and its associations with different metabolic biomarkers, in addition to whether baseline enterotypes can predict weight loss outcomes.

Paper 1 describes in detail the protocol used in the 10-week PREVENTOMICS randomized controlled trial conducted in Denmark, where an algorithm was developed with a priori definition of five distinct metabotypes associated with compromised metabolic processes related to (1) carbohydrate metabolism, (2) lipid metabolism, (3) oxidative stress, (4) inflammation, and (5) microbiota-related metabolism.

In **Paper 2**, we found that personalizing dietary plans did not provide additional benefits compared to a conventional approach on the primary outcomes (change in fat mass and body weight), or on improving health parameters beyond the changes induced by the control diet. Both predominantly plant-based diets were equally effective in improving body weight and health outcomes in individuals with overweight or obesity.

In **Paper 3,** we concluded that consuming *ad libitum* plant-based diet reduces body weight and exerts several health benefits. The addition of inulin-type fructans prebiotics to this naturally fibre-rich diet selectively modifies gut microbiota composition and attenuated some of the realized cardiometabolic biomarkers. In addition, classifying participants based on their baseline *Prevotella*/*Bacteroides* ratio did not predict weight loss outcomes.

In summary, based on the approaches presented in this PhD thesis, metabotyping to provide tailored dietary advice did not support the hypothesis that personalized nutrition is superior to general dietary guidelines for successful weight loss and improved health outcomes. Future studies should focus on the effectiveness and cost-effectiveness of such precision nutrition approaches using more simplified methods while validating biomarkers for weight loss before integrating more complex omics of several markers at once. Moreover, future interventions should address both behaviour change and the surrounding obesogenic environment influences for better maintenance of weight loss outcomes. To combat obesity effectively, a comprehensive holistic and interdisciplinary approach is key requirement.

Summary in Danish

Bekæmpelse af fedmeepidemien er en af de største udfordringer i den moderne tid. Selvom vægttabsdiæter har været anvendt i mere end 2.500 år, har de ikke givet betydningsfuld succes, givet den vedvarende globale stigning i overvægt og fedme de seneste årtier.

I årevis har forskere debatteret den ideelle kostplan til vægttab med hensyn til makronæringsstofsammensætning. Dog er der ingen entydig kostsammensætning der præsterer bedre end de andre. Uanset hvordan kosten er sammensat responderer mennesker forskelligt på samme kostplan. Nogle taber meget lidt vægt, mens andre taber meget, og der er endda nogle, der tager på i vægt. Årsagerne til denne store variation mellem individer kan tilskrives forskellige faktorer såsom genetisk sammensætning, forskellige absorptionsmekanismer af næringsstoffer og stofskifte i kroppen samt adfærd og psykologiske faktorer. Det menes, at målretning af kostinterventioner i overensstemmelse med et individs metaboliske profil har stort potentiale i behandling af fedme, i modsætning til udelukkende generelle diætanbefalinger til hele befolkningen.

Som følge heraf har H2020 PREVENTOMICS-projektet (Styrkelse af forbrugere til at FOREBYGGE kostrelaterede sygdomme gennem OMICS-teknologi), koordineret af Eurecat i Spanien, udviklet en direkte-til-forbruger-platform baseret på integration af genetiske, ernæringsmæssige, biokemiske og adfærdsmæssige faktorer for at vurdere den unikke metaboliske profil hos individer ved hjælp af metabolomics og maskinlæringsmetoder. Formålet er at levere personaliserede kostplaner, der i sidste ende fremmer bæredygtig adfærdsændringer for at bekæmpe fedme og forebygge ernæringsrelaterede sygdomme.

Denne ph.d.-afhandling er baseret på tre publikationer fra PREVENTOMICS-projektet med det overordnede mål at undersøge effektiviteten af at bruge sådan en platform til at levere personaliserede kostplaner med henblik på at reducere kropsfedtmassen og sekundært at forbedre helbredsmæssige parametre. De tre formål og tilhørende artikler er opsummeret nedenfor.

1. At gennemgå den eksisterende litteratur inden for præcisionsernæring i kostinterventioner målrettet vægttab, og designe en undersøgelse for at vurdere en sådan personlig ernæringstilgang
2. At undersøge effektiviteten af personaliserede diætplaner baseret på genetiske og sundhedsmarkører for at opnå bedre sundhedsresultater sammenlignet med diætplaner baseret på generelle anbefalinger.

3. At undersøge virkningen af at indtage en *ad libitum* plantefibre-rig kost på ændringer i tarmmikrobiota og dens sammenhænge med forskellige metaboliske sundhedsmarkører og om vægttab kan forudsiges ud fra basale enterotyper.

Artikel 1 beskriver detaljerne for protokollen, der blev brugt i det 10-ugers PREVENTOMICS randomiserede kontrollerede studie, der blev udført i Danmark, hvor der blev udviklet en algoritme med a priori-definition af fem forskellige metabotyper af kompromitterede metaboliske processer relateret til (1) kulhydratmetabolisme, (2) lipidmetabolisme, (3) oxidativt stress, (4) inflammation og (5) mikrobiota-relateret metabolisme.

I **artikel 2** fandt vi ingen yderligere fordele ved at personalisere kostplaner sammenlignet med en generel tilgang, hvad angår primære resultater (ændring i fedtmassen og kropsvægten) hos personer med overvægt eller fedme. Ej heller observerede vi forbedringer af andre sundhedsparametre ud over ændringerne induceret af kontrolkosten. Begge hovedsageligt plantebaserede kostplaner var lige effektive til at forbedre kropsvægten og helbredsmæssige resultater.

I **artikel 3** konkluderede vi, at indtagelse af en *ad libitum* plantebaseret kost reducerer kropsvægten og har flere sundhedsmæssige fordele. Tilsætningen af inulin fructaner som kosttilskud til en naturligt fiberholdige kost ændrer selektivt sammensætningen af tarmmikrobiot og mindsker visse kardiometabolske markører. Derudover kunne klassificering af deltagerne baseret på deres udgangs-*Prevotella*/*Bacteroides*-ratio ikke forudsige deltagernes vægttab.

Samlet set, baseret på de tilgange, der er præsenteret i denne ph.d.-afhandling, understøttede metabotyping til at give målrettet kostvejledning ikke hypotesen om, at personaliseret ernæring er overlegen i forhold til generelle kostanbefalinger til succesfuldt vægttab og i forbedring af sundhedsresultater. Fremtidige studier bør fokusere på effektiviteten og omkostningseffektiviteten af sådanne personaliserede tilgange ved brug af mere forenklede metoder samtidig med validering af biomarkører til vægttab, før de integreres mere komplekse omics-analyser af flere markører på én gang. Desuden bør fremtidige interventioner adressere både adfærdsændring og indflydelsen fra det obesogene miljø for at opnå bedre vedligeholdelse af vægttabsresultater. For effektivt at bekæmpe fedme er en omfattende, holistisk og tværfaglig tilgang afgørende.