Investigating insulin resistance in human obesity with transcriptomics

Impact paragraph

Cardiometabolic diseases are the number one cause of death globally. Among them, is **cardiovascular disease** (CVD) (e.g., heart attack, stroke, thrombosis) and **diabetes mellitus** (e.g., type 2 diabetes). Persons with type 2 diabetes have a two times higher chance to develop CVD, and it is the main cause of death in persons with type 2 diabetes (1). **Cardiometabolic risk** describes a person's chance of having a cardiovascular event when one or more risk factors are present. Both **obesity** and **overweight** are associated with **insulin resistance** (IR), which is a risk factor for the development of type 2 diabetes and cardiovascular disease. On that note, a plethora of evidence indicates the importance of adipose tissue mass and function and body fat distribution as important factors determining an individual's risk to develop obesity-associated cardiometabolic diseases, IR and type 2 diabetes.

The World Health Organization (WHO) defines **obesity** and **overweight** as "abnormal or excessive fat accumulation that presents a risk to health", and it is recognised as a disease. A body mass index (BMI) over 25 is considered overweight, and over 30 is obese (2). Obesity is an epidemic, with over 4 million people dying each year because of being overweight or obese, based on the WHO. It is therefore understandable, that treating obesity is very important. In successfully treating obesity, the primary course of action is to reduce weight, as losing weight is associated with a considerable improvement in risk factors associated with obesity. There are several ways to address obesity, from nutritional interventions (e.g., healthier eating habits, diets) to bariatric surgery. In the Netherlands, bariatric surgery, even though an effective treatment, is the last resort in combating severe (BMI over 35) and morbid obesity (BMI over 40) (3).

Nutritional interventions, on the other hand, are non-invasive strategies, which include personalised advice based on general guidelines for a healthy diet and physical activity. They are effective in the reduction of body weight or diabetes risk but are not effective in long-term weight maintenance for the majority of overweight and obese persons. Furthermore, nutritional interventions might improve glucose metabolism, insulin sensitivity and obesity-related health risks despite moderate weight loss, and these effects might be driven by the differential response of a certain subgroup (e.g. based on IR phenotype) to a diet composition. There is growing evidence showing that the severity of IR at the tissue level may play a role in the differential responses to lifestyle and pharmacological interventions that aim to increase insulin sensitivity (4-6). Hence, the effectiveness of an intervention might depend on individual or subgroup pathophysiological factors. This emphasises the need of identifying functional subgroups of obese individuals with different risk profiles, which might lead to a better understanding of the relationship between IR and type 2 diabetes and cardiometabolic risk. This may represent a starting point for future research aimed at identifying novel, more effective **precision-based prevention and treatment strategies** of obesity and its complications, contrary to the population-based strategies.

Relevance of our results towards precision-based prevention and treatment strategies

In this thesis, we have used **network** and **pathway** analysis with **transcriptomics data** as a means to help elucidate the pathways and mechanisms that are altered in human overweight and obese IR phenotypes. We have provided mechanistic insight that the IR phenotypes discussed in this thesis are distinct (**Chapter 2 and 3**), which could help identify functional subgroups of obese individuals with different risk profiles. Furthermore, surrogate insulin sensitivity indexes MISI, HIRI and ATIRI (**Chapters 2 and 3**), are measures that have a great potential in providing relatively easy methods to classify and identify IR phenotypes. This is particularly important when suggesting nutritional intervention strategies for treating or preventing obesity-associated complications, as their effect on an individual might depend on the IR phenotype. In addition to identifying functional subgroups, we have highlighted the added value of knowing/determining cell type composition in the context of human obesity and IR (**Chapters 4 and 5**).

Collectively, our results might represent a starting point for future research aimed at identifying novel, more effective **precision-based prevention and treatment strategies** of obesity and its complications, contrary to the population-based strategies. Notably, future research is needed to first demonstrate that the IR phenotypes respond differentially to diet composition or other interventions. Subsequently, the implications of our findings and the fact that these IR phenotypes may respond differentially to food products or pharmacological agents might be interesting for the nutritional and pharmaceutical industry as it may give leads for product development. Furthermore, the results presented in this thesis may also may be relevant for prevention and give leads for health professionals for guidelines on how to stimulate a healthier lifestyle that will offer a societal benefit in reversing the obesity epidemic. Finally, our results represent a form of knowledge utilization and might be of interest for health professionals and scientists. They have been presented in relevant scientific meetings for obesity and diabetes and have been (or will be) published in academic peer-reviewed journals.

Enabling data sharing and reuse to enhance scientific research

In the era of "Big Data", with increasing costs for data generation, storage and computation, precision-based strategies come with high promises and the potential to be more effective with better understanding of individual factors that predict response. The "Big Data" revolution has enabled the scientific community to recognise the advantages of open and reusable data, while data sharing and reuse are becoming an important part of research, particularly in life sciences. On that note, the scientific community has established guidelines to improve and facilitate data reusability, known as "FAIR data principles" (7); sharing data has undeniable benefits, including minimising costs.

Throughout this thesis, we have used computational tools freely available and accessible to all the scientific community, which provide **helpful insights** for future research, warrant **novel scientific discoveries**, reduce costs but most importantly enable a research community of **accountability** and **reproducibility**. Furthermore, the computational approaches presented in this thesis hold great potential and have provided us with comprehensive and insightful information representing a starting point for future research aimed at identifying precision-based prevention and treatment strategies for obesity and its complications.

As an example, for pathway analysis, we used PathVisio (8) and the human-curated collections from WikiPathways (9), a continuously evolving and growing open community, where researchers can create and curate biological pathways. For network analysis, we used Cytoscape (10), which is an open-source platform for visualizing complex networks and integrating these with any type of attribute data. Importantly, these tools are user friendly, well documented and do not necessarily require experience in programming, therefore they can be useful to scientists without a computational background. Additionally, these tools offered powerful data representation by illustrating complex biological information, in the context of obesity and IR, in an intuitive way, which might represent a starting point for future research aimed at identifying precision-based prevention and treatment strategies.

In **Chapter 4**, we highlight the benefit of publicly available data reuse, which provided helpful mechanistic insight in the context of human obesity and IR. In addition, we have illustrated how other researchers can benefit from our proposed approach. In this way, data sharing and reuse also offers a form of knowledge utilization, which can be beneficial to the scientific community. Furthermore, in **Chapters 4** and **5**, we used two computational algorithms TissueDecoder (11) and EpiDISH (12) to perform computational deconvolution as an alternative to wet-lab experimental approaches for estimating cell type composition. Similarly to other university departments and scientists that mainly use computational we did not have access, sufficient funds, or as a matter of fact expertise to use wet-lab experimental approaches. Nevertheless, the proposed approaches and tooling offered us the opportunity to highlight the added value of knowing/determining cell type composition in the context of human obesity and IR. In those circumstances, publicly available datasets and computational deconvolution can tackle these hurdles and enable researchers without access to wet-lab experimental approaches to develop valid and useful computational approaches and tools that provide comprehensive and insightful information, as we have demonstrated in this thesis.

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