Sex differences in causes and consequences of type 2 diabetes

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Impact paragraph

The goal of scientific research is to establish new facts and reach new conclusions, and subsequently, to make impact on society. Therefore, new knowledge needs to be suitable and/or available for social and/or economic use. In this addendum, we will address how the results of this thesis may benefit society as a whole.

Results and relevance of this thesis

Diabetes mellitus is a chronic, metabolic condition that emerged as one of the major health problems in the last decades worldwide.\textsuperscript{1} To date, approximately 463 million individuals are diagnosed with diabetes mellitus. This number is expected to rise to 700 million by 2045.\textsuperscript{2} Those with diabetes are at increased risk of developing a wide range of diabetes-related complications, including CVD\textsuperscript{1}, classic microvascular complications (i.e. nephropathy, neuropathy, and retinopathy)\textsuperscript{3}, heart failure\textsuperscript{3}, cancer\textsuperscript{1}, non-alcoholic fatty liver disease\textsuperscript{4}, depression\textsuperscript{1} and dementia.\textsuperscript{5} In 2019, an estimated 4.2 million deaths were attributed to diabetes or diabetes-related complications, and 10\% of all healthcare expenditures is currently spent on diabetes.\textsuperscript{5} Cardiovascular disease (CVD) is the most common adverse outcome of diabetes. On average, people with diabetes have about twice the risk of CVD compared to those without diabetes. However, not everyone with diabetes has the same degree of excess risk.\textsuperscript{7} Meta-analyses have demonstrated that diabetes confers a greater excess risk of CVD in women than in men.\textsuperscript{8,9} Moreover, it has also been observed that diabetes is a stronger risk factor for vascular dementia in women than in men\textsuperscript{5}, which suggests that the sex differences in the consequences of diabetes reach further than macrovascular disease alone. Although progress has been made towards identifying sex differences, many uncertainties remain with regard to possible sex differences in the causes and consequences of type 2 diabetes, and in the underlying mechanisms of the observed sex differential in diabetes-associated CVD.

Results of the present thesis imply that type 2 diabetes is not a stronger risk factor for microvascular complications, cognitive decline, depression or poor quality of life in women than in men. Although many individuals with diabetes in our study population had been diagnosed with type 2 diabetes for several years, they were generally relatively healthy. Therefore, we cannot exclude sex differences with regard to more advanced stages of the investigated complications.

Furthermore, results of this thesis are consistent with the concept that women, as compared to men, have a greater deterioration in cardiovascular risk factors, even before the onset of type 2 diabetes. This could contribute to their greater relative risk of diabetes-associated CVD. Additionally, we observed that there are sex differences in body composition associated with type 2 diabetes, which imply that there is a sex-specific role of body composition in the development of type 2 diabetes. The conclusions of this thesis provide an important contribution to the knowledge of sex differences in the causes and consequences of type 2 diabetes and to the current
understanding of the sex differential in diabetes-associated CVD. In practice, tailoring cardiovascular risk management could already benefit from the insight that women’s cardiovascular risk factors deteriorate to a greater extent, even before the onset of type 2 diabetes. In general, the findings of this thesis are not yet sufficient to implement changes in health care guidelines. To establish more refined clinical guidelines that appropriately address clinically meaningful sex differences in (vascular) consequences of diabetes, more research is required. Knowledge needs to be gained from sex-related comparisons in the associations of type 2 diabetes with advanced-stage microvascular complications, mental health aspects, and/or other possible consequences of diabetes. Moreover, further insights need to be provided about the underlying biological mechanisms of the observed sex differential with regard to CVD. In the next paragraphs will be outlined what is needed in order to reach these goals.

**Future research**

Until now, with regard to sex differences in diabetes-associated complications, most is known about CVD. However, before studies on sex-specific prevention of and intervention for diabetes-associated CVD can be conducted, the complex interplay between sex, body composition, type 2 diabetes and CVD needs to be understood. More research of sex differences in the pathophysiology of body composition in the development of type 2 diabetes is required. For example, investigating sex differences in subcutaneous adipose tissue (superficial and deep subcutaneous adipose tissue), visceral adipose tissue, and total and peripheral fat and lean mass, associated with liver and pancreas fat, insulin resistance and beta cell function would help to understand the role of body composition, and sex differences therein, with regard to diabetes development. More specifically, future studies are needed to evaluate, e.g. by mediation analyses, whether sex differences in body composition can explain the sex-specific effects of 1) dysglycemia on cardiovascular risk factors and of 2) diabetes on CVD. Additionally, longitudinal studies are necessary to investigate possible sex differences in complications and/or other consequences of type 2 diabetes. More specifically, future studies are required to investigate whether there are sex differences in more advanced-stage microvascular complications, mental health aspects, and in quality of life, associated with diabetes.

**General impact and future goals**

Ultimately, investigating and understanding sex differences in the causes and consequence of diabetes has the potential to develop new strategies for prevention and avert the onset of diabetes, optimize health service delivery nation-wide, reduce disparities, and improve the lives of women and men currently living with diabetes. For now, results of this thesis are particularly important for scientists, so that new
knowledge can be implemented and can be used for more targeted research. Three articles of this PhD projects are openly accessible in scientific journals and two others will be submitted for open access publication. In addition, this thesis will be distributed to interested parties. Additionally, the findings have been presented at scientific conferences and reported in the media. In general, it is important to incorporate the determination of sex differences in research, as also outlined in the introduction. In The Maastricht Study, it has been standard procedure, from the beginning, to test for interaction with sex and to perform sex-specific analyses. In this thesis, we noted that investigating sex differences sometimes involve complicated conceptual and statistical problems, as outlined in the general discussion. We did find solutions for these problems, which contributes to the field of studying sex differences in biomedical research. We strongly advise, for all researchers, to incorporate the determination of sex differences in their research and to create more awareness with regard to possible differences. During this PhD traject, we also aimed to increase awareness, by sharing knowledge to patients, and the general public, about the presence and implications of clinically meaningful sex differences in the areas of diabetes and CVD. For example, we have collaborated with relevant organizations such as the Harteraad and Diabetes Vereniging Nederland (DVN) to communicate our findings to the general public. Our patient representatives from the Harteraad advised us on communication, seen from the patient's perspective. In collaboration with the Harteraad and DVN, a public webinar on the theme 'Women, type 2 diabetes and cardiovascular diseases' was also organized. Over 250 people attended this webinar, mostly patients with CVD and/or type 2 diabetes. By continuing performing research and creating awareness about diabetes-associated sex differences, we can hopefully reach the abovementioned goals.

**Conclusion**

The findings of the present thesis provide a comprehensive framework on sex differences in the causes and consequence of type 2 diabetes and it contributes to a better understanding of sex differences in the risk of diabetes-associated CVD. It provides new insights for future, more targeted, research. Future research is required to translate our findings into clinical practice.
References


