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Sex and gender differences in diabetes care

Hendriks, Steven

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Chapter 9

Discussion

The aim of this thesis was to investigate sex and gender differences in diabetes care for patients treated in primary care in the Netherlands. The results show only small diabetes-related sex and gender differences, which relevance is questionable.

As mentioned in the introduction, the terms sex and gender were both used in this thesis. Sex was used to describe differences between men and women which are mainly caused by biological differences. Gender was used to indicate differences which are mainly caused by psychological and behavioural differences. In this discussion, firstly results of the sex-related studies will be discussed, and secondly results of the gender-related studies. Finally, an overall conclusion with regard to clinical relevance and recommendations for daily practice will be given.

Sex differences

Risk factors

In **chapter 2**, sex differences in the control of cardiovascular risk factors were reported for patients with T2D treated in primary care from 1998 to 2013. This study showed a considerable improvement of quality of care for both men and women with T2D, yet a few sex differences were found. Potentially relevant sex differences in improvement of care were observed for HbA1c, systolic blood pressure, BMI and smoking, whereby the differences between sexes converged throughout the study period. At the end of the study period, men were less frequently obese compared to women. Furthermore, men over 75 years of age had a lower blood pressure. In contrast, women had better cholesterol-HDL ratios, less frequently albuminuria and smoked less compared to men. For HbA1c no difference between sexes was observed anymore in the final years.

In previous published literature, conclusions concerning sex differences were based on results of cross-sectional studies (1,2). In the study in **chapter 2**, trend analyses were performed. The advantage of trend analyses is the possibility to investigate sex differences over time. Therefore, it was possible to investigate whether sex differences in achieving target values were consequently present in each year, or whether converging or diverging trends were observed between sexes in different aspects of diabetes care.

The results of the aforementioned cross-sectional studies generally showed a poorer control of cardiovascular risk factors in women with T2D compared to men (1,2). In the study presented in **chapter 2**, this outcome could only be confirmed for some risk factors, whereas others were poorer controlled in men. The difference between the

results of **chapter 2** and other studies could possibly be explained by the well-organized care for patients with T2D in the Netherlands. The valid guideline on T2D in primary care advised, in the period the study in **chapter 2** was performed, to monitor all T2D patients four times a year. Check-ups were performed to a large extent by practice nurses and were based on protocols. These protocols are based on the guidelines of the Dutch College of General Practitioners and the Dutch Diabetes Federation. In this protocol-based care it is unlikely that women would receive structurally poorer health care. This is reflected by the fact that no sex differences were observed in the process parameters in the study in **chapter 2**.

In order to investigate whether sex differences in risk factor control lead to a difference in the predicted mortality, a risk engine was applied. The Globorisk risk equation was used to predict 10-years mortality risk in patients under 75 years of age without a history of cardiovascular disease (3). The results showed a decrease of cardiovascular mortality risk in both men and women over time. In 1998, more women than men had an intermediate or high mortality risk, but the risk at the end of the study period was comparable between sexes. Nevertheless, this still translates into a relatively higher risk for women, given the fact that women have a lower mortality risk compared to men in the general population.

Despite the fact that quality of care has improved in both sexes from 1998 to 2013, and the 10-years mortality risk decreased in both sexes, some sex differences in clinical parameters are noticeable. The prevalence of microalbuminuria decreased considerably in both sexes less than 75 years of age; however, the prevalence in men was still 17% in 2013, compared to 11% in women. Furthermore, 42% of the men had a cholesterol-HDL ratio > 4 , whereas in women it was 32% in 2013. Although these risk factors were poorer controlled in men, a plateau phase has developed from 2009 onwards for both men and women. Interventions are therefore needed in both sexes in an attempt to further improve these risk factors. This might implicate intensifying drug treatment. However, as the results of **chapter 2** showed that prevalence of smoking and obesity were high in both sexes, improving lifestyle is probably more profitable.

The percentage of smoking men under 75 years of age has decreased from 34% to 22%, whereas in women it remained almost stable at around 18%. More or less the same trend was observed in the general population in the Netherlands (4). Policy efforts to reduce the prevalence of smoking might be focused too much on men, as smoking prevalence was higher in men. However, the smoking prevalence is nowadays almost equal in men and women. This emphasizes the need for more attention to stop-smoking intervention programs for female smokers, irrespective of the diagnosis of T2D.

Concerning body weight, more than 85% of men and women with T2D below 75 years of age had an BMI ≥ 25 kg/m² during the study period. Even more strikingly, in the last decennium, a stable percentage of 50% of the women in our cohort was obese. In men, the percentage of obesity increased from 30% to 40% in the same period. Additional analyses were performed to investigate whether this trend difference between sexes was caused by the cut-off limit for obesity of ≥ 30 kg/m². Analyses for morbid obesity (BMI ≥ 35 kg/m²) showed an increase from 9% to 12% in men and from 19% to 23% in women. This indicates that the prevalence of obesity is becoming more and more similar in men and women with T2D. Though, at the same time the rise in prevalence of morbid obesity continues in both sexes with already half of obese women being morbid obese.

It is questionable whether there is a comparable obesity-related risk of morbidity and mortality in men and women with T2D during life time. In non-diabetic subjects, men have relatively more fat in the abdominal region (visceral fat), whereas premenopausal women store more fat among the hips, buttocks and thighs (subcutaneous fat) (5). Abdominal fat is known to be related to a more unfavourable risk profile; i.e. insulin resistance, glucose intolerance, hyperlipidaemia and hypertension (6,7). This indicates that young men have more risk to develop T2D compared to premenopausal women. Taking this further, premenopausal women who develop T2D might be metabolically different, than other premenopausal women in order to develop T2D; possibly due to conditions like polycystic ovary syndrome. Knowing that in postmenopausal women the amount of intra-abdominal fat increases (8,9), menopause is probably additionally harmful for premenopausal women with T2D compared to women without T2D. Extra attention to lifestyle may therefore important for women with T2D in the menopausal phase.

In the study in **chapter 2**, the existence of sex differences in the improvement of diabetes care was instigated using many clinical parameters. The results show that, besides a potentially sex-specific approach for lifestyle, no different treatment for men and women seems to be needed. However, there are many other diabetes-related factors for which the presence of sex differences should be investigated over time, such as sex differences in macrovascular complications like heart failure and peripheral artery disease. Also, potential differences in gender-related aspects are important to investigate over time, such as differences in well-being, depression and social-economic status. The existence of possible differences in these aspects may result in a further development of more sex-specific diabetes care.

Mortality

Chapter 3 provided a clear insight in the survival of T2D patients relative to the general population in the Netherlands. The results showed that in primary care treated patients with T2D the relative survival was 12% lower in men and 18% lower in women after 14 years of follow-up compared to age-matched men and women in the general population. This could be translated into a median survival, which was 2.2 years lower in men and 3.5 years lower in women with T2D compared to men and women in the general population. Although the impact of T2D on survival seems to be higher in women, no significant difference was found between sexes in the total study population. This is remarkable, as previous studies have shown that the impact of T2D on all-cause mortality is higher among women than men (10,11). Only in the subgroup without a history of cardiovascular diseases (CVD), relative survival rate of women with T2D was significantly lower compared to men with T2D.

One important aspect when comparing absolute loss in life years between sexes, is the fact that women in the general population have a higher life expectancy compared to men. In the introduction of this thesis it was mentioned that life expectancy at birth in 2015 was 79.5 years for men and 83.2 years for women in the Netherlands (12). When the life expectancy was 12% lower in both men and women with T2D, this would consequently result in a higher loss of life years in women than men with T2D (10 years in women and 9.5 years in men). However, survival of men and women with T2D was 12% and 18% lower after 14 years of follow-up compared to men and women in the general population, respectively. So the higher life expectancy of women in the general population only partly explains the sex-related gap in absolute loss of life years.

In literature, especially a relatively higher risk for fatal coronary heart disease is described in women compared to men with T2D (13,14). In **chapter 3** it was not possible to investigate the influence of T2D on fatal coronary heart disease, as only expected survival rates for the control population (the general population in the Netherlands) were available. Therefore it should be investigated whether sex differences in fatal coronary heart disease exist in primary care treated T2D patients in the Netherlands.

Although the relative survival was not significantly different between sexes, it cannot be ruled out for certain that the relative survival of women is lower compared to men with T2D. The results of **chapter 3** showed that in the subgroup of women < 60 years of age, the subgroup of women without albuminuria and the subgroup of women with a BMI between 25-30 kg/m², a significantly lower survival rate in women with T2D was found compared to women in the general population. In contrast, men with T2D had

no significant lower survival rate in any of these subgroups. Furthermore, the relative survival rate of women with T2D without a history of CVD was significantly lower compared to men with T2D. This indicates that the relative mortality is probably higher in specific subpopulations of women with T2D compared to men with T2D.

Cancer incidence and cancer risk

Patients with T2D have an increased risk of developing cancer and even in the pre-diabetes phase a higher cancer risk is described (15). In **chapter 4**, the cancer incidence of men and women with T2D was compared with the cancer incidence of men and women in the general population in the Netherlands in the period 5 years before, around and 5 years after the diagnosis of diabetes. The results showed that cancer incidence peaked around diabetes diagnosis in both men and women. This peak in cancer incidence could probably be explained by increased detection as a result of additional attention, care, and diagnostic tests at the time of diabetes diagnosis.

The results of **chapter 4** showed clear differences between men and women with T2D. Women with T2DM had a higher incidence of cancer than women in the general population, as early as 5 years before diabetes diagnosis. In men, an increase was found around diabetes diagnosis and in the period 5 years after diagnosis. The increased incidence of cancer in women prior to diabetes diagnosis might be attributable to a higher incidence of breast cancer. Postmenopausal breast cancer is described to be related to obesity (16). It is plausible that women put on weight prior to diabetes diagnosis. This may result in a higher detection of breast cancer in screening programs prior to diabetes diagnosis in these women.

Next to postmenopausal breast cancer, a higher BMI is described to be associated with a higher risk of several other types of cancer. According to the World Cancer Research Fund, being overweight or obese is related to oesophageal, stomach (cardia), colorectal, liver, gallbladder, pancreatic and kidney cancer (non sex-specific obesity-related cancers). Furthermore, they have described that being overweight or obese is related to ovarian, endometrial and postmenopausal breast cancer in women and to advanced prostate cancer in men (sex-specific obesity-related cancers) (16).

The incidence of these obesity-related cancers was also investigated in **chapter 4**. The results showed a significantly higher incidence ratio of obesity-related cancers in women with T2D compared to men with T2D. This difference disappeared when sex-specific obesity-related cancers were excluded. Exclusion of the sex-specific obesity-related cancers resulted in an increase of the incidence ratio in men and in a decrease of the incidence ratio in women. This increase in men was caused by exclusion of prostate

cancer, of which a lower risk is described in men with T2D compared to men without T2D (17). The decrease in women was primarily caused by excluding breast cancer which is more prevalent in women with T2D compared to women without T2D (18).

In **chapter 5**, the association between BMI and obesity-related cancers was investigated in both men and women with T2D. Results showed that BMI was associated with obesity-related cancers in men with T2D, except with advanced prostate cancer. In women with T2D, BMI was associated with the total group of obesity-related cancers and with ovarian, endometrial and postmenopausal breast cancer. No association was found with non sex-specific obesity-related cancers in women with T2D.

Apparently, BMI has no predictive value for the risk of non sex-specific obesity-related cancers as a group of cancers in women with T2D. This could mean that T2D and BMI confound each other in their relation with non sex-specific obesity-related cancers in women, whereas BMI is still predictive for the risk of non sex-specific obesity-related cancers in men with T2D. Although the sex difference in intra-abdominal adiposity is reduced in patients with T2D, this intra-abdominal (visceral) fat mass is probably still higher in men. Especially visceral adiposity is associated with many metabolic abnormalities which may increase cancer risk (7). It might therefore be that BMI is not sufficiently accurate to represent the amount of visceral fat especially in women with T2D. Using waist circumference as a marker of visceral fat might have been more accurate (7). Nevertheless, BMI was associated with sex-specific obesity-related cancers in women; i.e. ovarian, endometrial and postmenopausal breast cancer. These cancers are highly related to oestrogen production (19). Adiposity is associated with an increased aromatization of androgens into oestrogens. The association of adiposity with these types of cancer might therefore especially be attributed to an increase in oestrogen production in fat tissue in overweight and obese women with T2D (7). In men, no association between BMI and advanced prostate cancer was found. Although this may be due to the relatively low number of advanced prostate cancer events, it might also be that BMI is indeed no risk factor for advanced prostate cancer, at least in T2D. The International Agency for Research on Cancer (IARC) Working Group has recently described that evidence for a preventive effect of the absence of excess body fatness for fatal prostate cancer is limited (20). Taken this together with the results of **chapter 5**, advanced prostate cancer should be reconsidered as being related to obesity.

In the study in **chapter 5**, 50.800 patients were included and 918 non sex-specific and 745 sex-specific obesity-related events occurred during follow-up. Despite these numbers, the number of events was still too small to investigate each obesity-related cancer type

by its origin. A meta-analysis of cohort studies is therefore recommended for more in-depth analyses.

Overall limitations of the sex-related studies

Some limitations concerning the sex-related studies have to be discussed. In all studies, data from the ZODIAC database were used. These data were collected by practice nurses and GPs and sent to our Diabetes Centre annually. The quality and reliability of the data are therefore dependent on the accuracy of the data acquisition. Furthermore, the ZODIAC database consisted only of patients with T2D who are treated in a shared care setting in primary care. Patients with a very short life expectancy or insufficient cognitive capabilities were excluded from participation in this shared care setting. Patients with T2D who are treated in secondary care were also excluded. Although this implies that the generalizability of our results is limited to the shared-care setting in primary care, it is still representative for a large part of the T2D population due to the fact that the majority (>80%) of the patients with T2D is treated in this shared-care setting in primary care in the Netherlands (21).

Conclusions with regards to sex differences in T2D

With respect to the sex-related differences in treatment of patients with T2D the following conclusions can be drawn:

1. Overall, cardiovascular risk factors are not explicitly poorer controlled in either men or women with T2D.
2. There is no difference in relative survival of men and women with T2D. Only in women with T2D without a history of CVD the relative survival is significant higher compared to men with T2D without a history of CVD.
3. Women have already an increased total cancer incidence in the 5 years prior to diabetes diagnosis, whereas in men an increase in total cancer incidence prior to diabetes is not present.
4. There is a significant higher increased incidence of obesity-related cancer among women compared to men with T2D 5 years before, around and 5 years after diabetes diagnosis. However, there is no higher incidence in women when sex-specific obesity-related cancers are not taken into account.
5. Body Mass Index is a risk factor for obesity-related cancers in men with T2D, except for advanced prostate cancer. Advanced prostate cancer should be reconsidered as being obesity-related.
6. Body Mass Index is a risk factor for the group of ovarian, endometrial and postmenopausal breast cancer in women with T2D.

Gender differences

Gender differences in lifestyle and well-being

In **chapter 6** the relationship between lifestyle factors and emotional well-being in men and women with T2D was described. It was hypothesised that the association of lifestyle and degree of well-being could be different between men and women with T2D as gender differences in lifestyle and in the association of lifestyle with mental health exist (22). The results showed a positive relationship between physical activity and emotional well-being in both men and women. Also, a negative relationship with smoking was found in the total study population with T2D. Furthermore, the explained variance of well-being by all lifestyle factors together did not differ between men and women with T2D.

Although significant associations were found with physical activity and smoking, the clinical relevance of these associations with well-being appears to be low. Well-being was measured with the WHO-5 questionnaire, of which the total score ranges from 0 to 100. The difference between being totally inactive and maximally active was associated with a difference of 8 points on the WHO-5 questionnaire. Since a difference of 10% in WHO-5 is considered as a relevant change, the association between physical activity and well-being is possibly only relevant for patients who have a low level of emotional well-being (23). Smoking (measured as yes or no) was associated with a difference of 3 points on the WHO-5 questionnaire. Taking the same 10% into account, a difference of 3 point is irrelevant.

The relation between physical activity and well-being has also been investigated in intervention studies. One study did not find any effect of physical activity on well-being, whereas three other studies found a higher well-being in the groups which were physically active (24–27). Strikingly, none of these studies indicated a pre-defined clinically relevant difference. It is therefore rather difficult to conclude whether the small improvements of well-being in these studies were clinically relevant (24–26). The highest improvements in well-being were observed in patients who participated in supervised exercise groups (9 points on 0 to 36 scale), whereas only small improvements were observed in patients with self-reported exercise (4 points on a 0 to 36 scale) (26). The study in **chapter 6** also investigated self-reported exercise. Whereas the improvements in supervised exercise groups might be relevant, the improvements of self-reported exercise are negligible. This does therefore not encourage investigating the relation between self-reported physical activity and well-being further. As a consequence, gender differences in the relation between self-reported physical activity and well-being are also less relevant to investigate. However, it remains important to stay focused on gender differences in

well-being and lifestyle separately. As mentioned before, the results of **chapter 2** showed gender differences in smoking and obesity trends, which possibly need a gender specific approach.

Gender differences in patient activation

The results of **chapter 7** showed that the degree of patient activation, which is defined as the confidence, knowledge and skills which are needed for self-management, did not differ between men and women with T2D. Women with T2D have a higher BMI, a lower degree of well-being and a lower health-related quality of life compared to men with T2D (28,29). These factors are also associated with the degree of patient activation in patients with chronic diseases (30). Therefore, the hypothesis of the study presented in **chapter 7** was, that these factors may confound the relation between gender and patient activation. Although BMI, well-being and quality of life differed between men and women, adjusting for these factors did not influence the relation between gender and patient activation.

In line with the results of **chapter 7**, 3 other studies among patients with chronic diseases also did not find a gender difference in the level of patient activation (30–32). On the other hand, Rademakers et al. reported a 2.9 point higher mean score and Hendriks et al. reported a 1.6 point higher mean score in men compared to women with chronic diseases (33,34). Although these differences were indicated as significant, they are not clinically relevant. The patient activation score ranges from 0 to 100 which could be divided in 4 relevantly different patient activation levels. A change in approach is only needed when patients move from one level to the other (35). So, the slightly higher patient activation score which is described in men will only sporadically result in a higher level of patient activation in men compared to women.

Taken this all together, no relevant gender differences in the level of patient activation were found in **chapter 7** and in previous literature. This indicates that men and women could be approached on the same level of patient activation. However, this does not implicate that the same self-care tasks could be given to men and women, as the effectiveness of interventions to promote self-care could still be different in men compared to women and vice versa. This needs to be investigated in intervention studies concerning self-management tasks.

Gender differences in the evaluation of care

Chapter 8 focused on patient-related factors and their association with patient evaluation of care in men and women with T2D. It is important to investigate the association between

patient-related factors and patients' evaluation of care as focusing on patient-related factors might improve patients' evaluation of care. However, improving evaluation is not the final goal. By being aware of factors which are associated with the evaluation of care, the delivered care could possibly be improved (in a gender-specific way).

The results of **chapter 8** showed that there are some gender differences in patient-related factors which are associated with patients' evaluation of care of men and women with T2D in primary care. In men, explanatory factors of the evaluation of care were the use of insulin, having some problems with diabetes-related self-care and coffee consumption. In women, age, well-being, quality of life, following a diet and the use of oral glucose-lowering drugs were associated with patients' evaluation of care. However, the most important finding of this study was that the location where the questionnaire was completed had by far the largest influence on the explained variance of the patient evaluation of care of men and women with T2D. Patients who filled out the EUROPEP questionnaire at home on paper scored relevantly lower compared to patients who filled out the questionnaire at the general practice on a tablet computer. Assistance of a care provider by the use of the tablet computer, may have led to giving desired answers. This is described in literature as the 'yes' saying bias (a culturally based tendency to agree with others) (36).

Associations between well-being, health-related quality of life and EUROPEP scores were found in women only. This might indicate that the evaluation of care is more influenced by personal feelings in women compared to men. However, this suggestion should be interpreted with caution, as these associations were found in an explorative cross-sectional study, and such associations were not described before in literature. More research would have to be carried out to confirm this relationship.

It is, however, questionable whether it is relevant to investigate gender differences in the association between patient-related factors and patients' evaluation of care further in patients with T2D. The degree to which these factors together could explain the EUROPEP score was very low. Up to 8.4% and 16.8% of the variance of the EUROPEP score could be explained by patient-related factors in men and women with T2D, respectively. Almost 65% and 79% of this explained variance was contributable to the location where the questionnaire was completed in men and women, respectively. Two reasons could be given for the low explained variance. It could be that some important explaining factors were not taken into account. For example, it may be that patients' evaluation of care is depending on their perceived self-efficacy and their motivation to play an active role in the care process. These aspects were not investigated in the study in

chapter 8. It could also be caused by high scores on the EUROPEP questionnaire, which resulted in a ceiling effect. In such a homogeneous group it is hard to find predictive factors as there is not much variance that could be explained. Nevertheless, it is certainly possible that this ceiling effect reflects reality since the population used in **chapters 8** was derived from general practices in the Netherlands. The perceived well-being of these patients is high and their evaluation of primary care is quite good. A more sensitive questionnaire might be needed to measure differences in patients' evaluation of care in this population. However, improving patients' evaluation of care in patients who are already satisfied is probably less important.

To conclude, gender differences in the patient-related factors are not clinically relevant. Therefore, in attempts to improve patients' evaluation of care, gender differences are not relevant to take into account.

Limitations of the gender related studies

Chapters 6, 7 and 8 have important limitations in common. The most important limitation is the cross-sectional design of the gender studies. Therefore the results do not allow a conclusion with regards to possible causality. For example, the results of **chapter 6** may indicate that physical activity affects well-being, but it could also be the other way around. Furthermore, the results do not provide evidence for the effect of change, i.e. whether improving physical activity leads to changes in emotional well-being or vice versa.

Conclusions with regards to gender differences

With respect to the gender-related differences in patients with T2D the following conclusions can be drawn:

1. There are no gender differences in the relationship between lifestyle factors and well-being. Furthermore, the associations between smoking, self-reported physical activity and well-being are not clinically relevant in both sexes.
2. There are no gender differences in the level of patient activation. Therefore, there is no justification for approaching men and woman differently with regard to the level of self-management tasks.
3. The evaluation of care is barely related to patient-related aspects. Therefore, in attempts to improve patients' evaluation of care, no different approach for men and women with T2D seems to be needed.

Taken this all together, the results as presented in this thesis do not give direct ground for extending the focus on gender differences in daily practice of diabetes care in the relation

between lifestyle and well-being, the degree of patient activation and patients' evaluation of the delivered care. This can be concluded based on the low the explained variance. However, at the same time these results indicate that well-being, patient activation and patients' evaluation of the delivered care are related to other, probably psychological and sociological related factors and these factors deserve attention in future research.

Overall conclusion and recommendations for daily practice

The aim of this thesis was to investigate whether there are sex and gender differences in patients with T2D who are treated in primary care in the Netherlands. The results as presented in this thesis show small sex and gender differences in several aspects of T2D. However, these differences do not indicate that T2D is specifically poorer controlled in either men or women. Furthermore, most of the differences as described in this thesis do not seem to be clinically relevant. Still, one important question has to be answered: does the care for men and women with T2D need to be changed based on the sex and gender differences which were found in this thesis? As hardly any relevant differences in survival, cancer incidence ratio, well-being, patient activation and evaluation of care were observed, there are overall no clear indications to change care for patients with T2D who are treated in primary care. Nevertheless, there are a few differences between men and women with T2D in lifestyle and cancer incidence which need further attention. In men, weight control should be emphasized to prevent the ever increasing prevalence of obesity, which is approaching the high prevalence of obesity in women. In women with T2D, special attention is needed to reduce smoking, as the proportion of smoking women with T2D is stable for many years, while in men the proportion is decreasing to a level near that of women with T2D. Furthermore, since the prevalence of obesity is high and the prevalence of morbid obesity is still increasing, new strategies have to be developed to help reducing obesity in women and to at least stabilize the increase in morbid obesity. At last, the incidence of sex-specific obesity related cancers is higher among women with T2D compared to women in the general population. An increased awareness for symptoms related to ovarian, endometrial and postmenopausal breast cancer and additional screening for postmenopausal breast cancer might be needed, especially in obese women with T2D. At the same time, there is perhaps no need for an increased attention for prostate cancer in men with T2D, as it seems that the prevalence of prostate cancer not increased in men with T2D and as it seems that advanced prostate cancer is not related to obesity in men with T2D.

It has to be emphasized that the results of this thesis are limited to patients who are treated in primary care in the Netherlands. The question whether there are sex and gender differences in other T2D populations has not been answered. The results are not generalizable to men and women with T2D in secondary care, in whom the prevalence of multi-morbidity is high. Furthermore, it has to be emphasized that this thesis covers not all areas within primary care treated patients with T2D. Therefore, no conclusions can be drawn for sex and gender differences in other aspects of diabetes care, such as differences in the impact of T2D on cardiovascular morbidity and mortality. When sex differences in cardiovascular outcomes exist, this might indicate that sex-specific criteria should be developed for optimal prevention of cardiovascular morbidity and mortality in patients with T2D who are treated in primary care. However, based on the absence of relevant sex and gender differences in areas which are investigated in this thesis, except for lifestyle and sex-specific cancer incidence, it can be concluded that it is not necessary to change care for men or women with T2D in primary care.

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