Sex and gender differences in diabetes care

Hendriks, Steven

Chapter 1

Introduction

Type 2 diabetes

Each year more and more people are diagnosed with diabetes. In 2015 the estimated number of people with type 1 and type 2 diabetes together was 415 million and for 2040 it is estimated that 642 million people will have diabetes worldwide (1). In the Netherlands a comparable trend is seen. In 2013, 5.5% of the total Dutch population was known with diabetes and it is expected that the prevalence will increase to 8% in 2025 (2,3). This is mainly due to an increase in the prevalence of type 2 diabetes (T2D), as this type of diabetes accounts for more than 90% of all diabetes in western countries (3,4). The rising prevalence of T2D and the associated increase in the number of people who are at risk for developing diabetes-related complications, highlights the need for new approaches in diabetes care.

In the Netherlands, 80% of the patients with T2D is treated in primary care (5). The care for these patients is based on nationwide accepted guidelines and protocols and is mostly delivered by practice nurses and general practitioners (6). Since the use of protocol-based care, the quality of diabetes care has improved considerably (7). Although the Dutch care system is among the best in Europe, there is still room for improvement (8). Focusing on individualized care, with specific attention to gender differences, may further improve care for patients with T2D in the Netherlands.

Sex and gender differences in medical research

In many fields of medical research there is an increasing attention to the role of sex and gender differences. Contrary to popular belief, the terms sex and gender are not synonyms and are often mixed up. Sex refers to the biological differences between men and women (i.e. having the genotype of a man or a woman), whereas gender refers to attitudes and behaviours which could be either masculine or feminine (i.e. feeling and behaving as a man or a woman) (9,10). Differences in diseases between men and women are mostly a result of a combination of sex and gender aspects, which makes it almost impossible to use the pure terminology (11). In this thesis, 'sex' will be used to describe differences between men and women which are considered to be mainly caused by biological differences, and 'gender' will be used to indicate differences which are considered to be mainly caused by psychological and behavioural differences.

Investigating sex and gender is argued to be relevant in many ways (12,13). Incorporating sex in research could help to explain differences in the aetiology of diseases. For example,

when a disease occurs more frequently in men compared to women, focusing on the biological differences between men and women may lead to identifying mechanisms that are responsible for the development of this specific disease. Focused attention on sex in research may also help to study the possible differential effect of treatment interventions between men and women. It may be that sex modifies the effect of those interventions, which could potentially lead to sex-specific treatment options. Incorporating gender may result in valuable information as possible differences in health perception among men and women may influence their health outcomes.

Sex differences

Sex differences in the general population

Sex differences have been studied in a variety of fields. In the general population, life expectancy in women is higher compared to men (14). In Europe, women live on average 7 to 8 years longer than men (15). In the Netherlands, this gap is evidently smaller. According to the World Health Organization, the current life expectancy at birth in the Netherlands is 79.5 and 83.2 years for men and women, respectively (15).

A genetic advantage of having two X chromosomes is described as one of the possible contributors to longevity in women (14). It is described as a protector against harmful effects of disadvantageous genes on one of the X chromosomes (14,16). Influences of the primary female sex hormone oestrogen on the cardiovascular and metabolic system is also mentioned as a contributor to the higher life expectancy in women (17). This might be due to various pathophysiological mechanisms, i.e. 1) a direct vasodilatory effect and long-term protective effects on blood vessels, 2) stimulating the production of anti-inflammatory cytokines and inhibiting the production of pro-inflammatory cytokines, and 3) lowering of serum lipid concentrations (14,18,19). Although oestrogen is present in both men and women, the level of oestrogen during the fertile years of life is much higher in women than in men (20).

Whereas vascular changes in men often occur relatively early in life, women are more at risk of these changes from midlife onwards (21). This more pronounced female-specific rise in cardiovascular risk from midlife on is often attributed to the menopausal withdrawal of sex hormones. However, recent data suggest that sex-specific biological ageing may be more important than sex differences in changes of hormonal levels per se (21).

In addition to these cardiovascular differences between men and women, there are sex differences in cancer incidence and mortality as well. In Europe, the estimated incidence of cancer in 2012 was approximately 1.4 million in men and 1.2 million in women. Around 707,000 men and 555,000 women died from cancer in the same year in Europe (22). Smoking is described as the most important risk factor for cancer in both men and women (23). Other important risk factors for men were a deficient intake of fruit and vegetables, work-related exposure and alcohol consumption, whereas for women obesity was the most important other risk factor (23). Although the gender gap in smoking is decreasing in Europe, its prevalence is still higher in men. This may partly explains the higher cancer incidence in men compared to women.

Sex differences in type 2 diabetes

In recent years, more and more researchers in the field of T2D have taken sex differences into account with regard to metabolic syndrome related factors, which has led to some surprising results. When men and women are diagnosed with T2D, the relative female protection from cardiovascular diseases (CVD) seems to disappear (24). In multiple studies a relative higher cardiovascular morbidity and cardiovascular mortality rate is described in women compared to men with T2D in comparison with their non-diabetic counterparts (25–29). The underlying mechanisms for this phenomenon are not entirely clear, but it is likely to be multifactorial. Experimental studies have described that hyperglycaemia negatively modifies the balance of oestrogen receptors in women in the vascular wall. This imbalance is associated with higher oxidative stress, decreased anti-proliferative effects of oestrogen and increased atherosclerosis (30). Furthermore, it is described that women have a more pronounced endothelial dysfunction and a higher rate of hypertension than men when progressing from normoglycemia to pre-diabetes (31). The decrease in morbidity and mortality differences between sexes in T2D is also thought to be the result of sex differences in achieving target values for T2D treatment (32–36). A possible explanation for this might be a systematic undertreatment of women with T2D or a lower response to comparable treatment intensity in women compared to men with T2D (32,35). At last, it is also hypothesised that the relative higher cardiovascular morbidity and mortality rate in women with T2D may not be caused by sex differences influenced by T2D itself, but that it is caused by a larger increase of cardiovascular risk factors in women compared to men during transition to T2D (37,38).

Although striking results were found in previous studies concerning sex differences in cardiovascular risk factors and mortality in T2D, the clinical relevance and generalizability (i.e. with regard to the Dutch population) of the results of some these studies are questionable. Most of the cardiovascular risk factors studies were cross-sectional,

therefore it is unclear whether the differences between sexes increase or decrease over time. Furthermore, most of the knowledge about sex differences in (cardiovascular) mortality in T2D is based on meta-analyses which have used cohorts from the previous century and from other countries than the Netherlands (29,38,39). As mentioned earlier, care for patients with T2D in the Netherlands has improved considerably and is currently one of the best in Europe (7,8). As some explanations for the higher mortality rate in women with T2D are related to the quality of the care of patients with T2D, a well-organized diabetes care system has the potential to reduce sex-related mortality differences in T2D.

In T2D, not only the risk for cardiovascular morbidity and mortality is increased, but also the risk for cancer (40). An increased risk of non-Hodgkin lymphoma, and liver, pancreas, endometrial, colorectal, breast, bladder and kidney cancer is described in patients with T2D (41). Whether this increased risk is directly related to T2D, due to e.g. hyperglycaemia, or indirectly, due to e.g. the use of insulin or common risk factors like obesity, is still unknown (41). It is also not completely clear whether T2D increases cancer risk to the same extent in men and women. In the general population, being overweight or obese is related to oesophageal, gastric-cardia, colorectal, liver, gallbladder, pancreatic and kidney cancer in both sexes (42). The relation between excess body weight and obesity-related cancers is less clear in patients with T2D. Although the evidence is limited, the association between excess body weight in patients with T2D and obesity-related cancers seems to be stronger in men than women (43). This may indicate that obese men with T2D are at a higher risk for developing obesity-related cancers compared to obese women with T2D.

Gender differences

Gender differences in the general population

Men and women differ in many psychological and sociological aspects as well. In the field of psychology it is described that the prevalence of depression and anxiety disorders is higher amongst women compared to men (44,45). Amongst others, this might be a result of gender differences in coping strategies. As compared to men, women tend to more frequently use emotion-focused coping strategies, which are not that effective for reducing distress (45). Sociologically, men and women differ in the roles society assigned to them and in their positions amongst families and communities. This influences risk behaviour in daily life and the way by which they deal with or give attention to their own health. Gender differences in risk taking behaviour are reflected by lifestyle differences

between men and women. The global status report on non-communicable diseases of the World Health Organization reported that in Europe smoking prevalence is higher among men, whereas women are less physically active and more often obese (46). These gender differences in lifestyle, may contribute to differences in health risk and longevity between men and women.

Gender differences in type 2 diabetes

Gender differences are also described in patients with T2D. When focusing on socio-economic background, both a low level of education and a low social-economic-status are related to a higher risk of developing T2D in women, whereas in men this association appears to be less prominent (47,48). When focusing on psychological aspects in the presence of T2D, women with T2D report a lower health-related quality of life compared to men with T2D (49). Also, a higher prevalence of depression and anxiety is described in women compared to men (50,51). Identifying these gender differences in T2D is even more important since a lower quality of life is associated with a higher mortality rate (52).

Much is still unknown about gender differences in psychological aspects related to T2D, especially in the field of lifestyle and self-management. Performing adequate self-management tasks requires patient activation, which comprises knowledge about the disease, skills, and confidence (53). It is unclear whether gender differences in patient activation really exist, as previous studies showed mixed results (54–58). When differences in patient activation between men and women exist, this may indicate that the level of self-management tasks should be more gender-specific to achieve optimal health outcomes in both genders. Furthermore, as mentioned earlier, men and women differ in lifestyle factors, such as BMI, physical activity and alcohol consumption (46). Men and women also differ in their degree of well-being. However, it is unclear whether the relation between these lifestyle factors and perceived well-being differs between men and women. Identifying (gender-specific) lifestyle factors that are associated with degree of well-being, could possibly lead to new strategies in improving well-being of men and women with T2D.

It is also unknown whether there are gender differences in patients' evaluation of care. Patients' evaluation of care is one of the health care delivery aspects which has become increasingly important (59). Variation in patient evaluations could reflect differences between the evaluated general practitioners (GPs) and practices, but it could also reflect differences between patients themselves (60). Insight into these patient-related factors may eventually help to develop methods to achieve a more positive patient experience and thereby improving care for patients with T2D.

General aim

Many aspects of sex and gender differences have already received extensive attention in the field of T2D research. However, there are still many possible sex and gender differences which have not been properly investigated yet.
Differences between men and women with T2D are quite likely caused by a combination of physiological, psychological, sociological or health-related factors. Many of these factors differ between countries and cultures. To identify sex and gender differences in the Dutch population, it is therefore important to perform studies specifically in the Netherlands. Approximately 80% of the patients with T2D in the Netherlands is treated in primary care (5). Whether there are sex and gender differences in this specific population is unknown. Therefore, the general aim of this thesis is to investigate sex and gender differences in primary care treated patients with T2D in the Netherlands.

ZODIAC

A large part of this thesis is based on data from the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) cohort. This cohort started in 1998 as a prospective observational cohort study to investigate the effects of shared care for patients with T2D who are treated in primary care (61). At the beginning of the study, patients were divided in three study groups; two intervention groups in which care for patients with T2D was delegated from general practitioners to practice nurses and/or diabetes specialist nurses and one standard care group in which usual care was delivered. Longitudinal analysis of the first years of this study showed an improvement in clinical parameters and quality of life in the two intervention groups compared with the standard care group (61). Due to these positive results, shared care became the standard care for the Zwolle region in 2002. Further expansion of the shared care initiative to others regions in the Netherlands took place in 2006, 2009 and 2012, respectively. Only T2D patients treated in primary care are included in the ZODIAC project. Patients with a very short life expectancy or insufficient cognitive capabilities are excluded from participation. As part of the ZODIAC initiative, clinical data are collected and sent to the Isala Diabetes Centre for benchmarking and research purposes annually. At the start in 1998, 53 GPs participated in this project, and this number increased to 731 GPs in 2013. The number of patients increased from 2644 to 62,230 patients in 2013.

Content thesis

Part one: Sex differences

Chapter 2 focuses on cardiovascular risk factor control in men and women with T2D. A longitudinal study is used to investigate whether there is a difference between men and women in cardiovascular risk factor control.

The relative survival for men and women with T2D is investigated in **chapter 3.** Whether sex differences in mortality also exist in primary care treated patients with T2D in the Netherlands is studied in this chapter.

Chapters 4 and 5 focus on possible sex differences in cancer risk and cancer risk factors. In **chapter 4**, the cancer incidence of men and women with T2D is compared with the cancer incidence of men and women in the general population in the Netherlands. In **chapter 5**, the association between BMI and obesity-related cancer risk in men and women with T2D is studied.

Part 2: Gender differences

Chapter 6 focuses on the relationship between lifestyle and well-being in men and women with T2D. Identifying gender-specific associations between both could possibly lead to new strategies in improving well-being of men and women with T2D.

Chapter 7 focuses on gender differences in the degree of patient activation in men and women with T2D. Furthermore, factors that are associated with patient activation in men and women are identified.

In **chapter 8** a study is described which focuses on patient-related factors and their association with patient evaluation of care in men and women with T2D. Identifying possible differences in these factors between men and women may call for development of more gender-specific care for patients with T2D.

In **chapter 9** the findings of all studies are summarized and discussed. Finally, recommendations for daily practice and directions for future research are given.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 7th edn. [Internet]. Brussels: Belgium: International Diabetes Federation; 2015. Available from: http://www.diabetesatlas.org
2. Kleefstra N, Landman GWD, Van Hateren KJJ, Meulepas M, Romeijnders A, Rutten GEH, et al. Dutch diabetes prevalence estimates (DUDE-1). J Diabetes. 2015 Dec 22;
3. Baan CA, van Baal PHM, Jacobs-van der Bruggen MAM, Verkley H, Poos MJJC, Hoogenveen RT, et al. [Diabetes mellitus in the Netherlands: estimate of the current disease burden and prognosis for 2025]. Ned Tijdschr Geneeskd. 2009;153:A580.
4. Holman N, Young B, Gadsby R. Current prevalence of Type 1 and Type 2 diabetes in adults and children in the UK. Diabet Med J Br Diabet Assoc. 2015 Sep;32(9):1119–20.
5. InEen. Transparante ketenzorg diabetes mellitus, COPD en VRM rapportage zorggroepen over 2014. 2015 Jun.
6. Rutten G, De Grauw W, Nijpels G, Houweling S, Van de Laar F, Bilo H, et al. The NHG guideline Diabetes mellitus type 2. Huisarts Wet. 2013;56(10):512–25.
7. van Hateren KJJ, Drion I, Kleefstra N, Groenier KH, Houweling ST, van der Meer K, et al. A prospective observational study of quality of diabetes care in a shared care setting: trends and age differences (ZODIAC-19). BMJ Open. 2012;2(4).
8. Health Consumer Powerhouse. Euro Diabetes Index [Internet]. 2014 [cited 2015 Feb 6]. Available from: http://www.healthpowerhouse.com/files/EDI-2014/EDI-2014-report.pdf
9. Schiebinger L. Scientific research must take gender into account. Nature. 2014 Mar 6;507(7490):9.
10. Hammarström A, Annandale E. A conceptual muddle: an empirical analysis of the use of "sex" and "gender" in "gender-specific medicine" journals. PloS One. 2012;7(4):e34193.
11. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocr Rev. 2016 May 9;er20151137.
12. Nieuwenhoven L, Klinge I. Scientific excellence in applying sex- and gender-sensitive methods in biomedical and health research. J Womens Health 2002. 2010 Feb;19(2):313–21.
13. Wieringa NF, Hardon AP, Stronks K, M'charek AA. Diversity among patients in medical practice: challenges and implications for clinical research. Amsterdam: Universiteit van Amsterdam; 2005.
14. Seifarth JE, McGowan CL, Milne KJ. Sex and life expectancy. Gend Med. 2012 Dec;9(6):390–401.
15. World Health Organization. The European health report 2015. Targets and beyond – Reaching new frontiers in evidence. 2015.
16. Short SE, Yang YC, Jenkins TM. Sex, gender, genetics, and health. Am J Public Health. 2013 Oct;103 Suppl 1:S93-101.
17. Harvey RE, Coffman KE, Miller VM. Women-specific factors to consider in risk, diagnosis and treatment of cardiovascular disease. Womens Health Lond Engl. 2015 Mar;11(2):239–57.
18. Salerni S, Di Francescomarino S, Cadeddu C, Acquistapace F, Maffei S, Gallina S. The different role of sex hormones on female cardiovascular physiology and function: not only oestrogens. Eur J Clin Invest. 2015 Jun;45(6):634–45.
19. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. N Engl J Med. 1999 Jun 10;340(23):1801–11.
20. Ober C, Loisel DA, Gilad Y. Sex-specific genetic architecture of human disease. Nat Rev Genet. 2008 Dec;9(12):911–22.
21. Merz AA, Cheng S. Sex differences in cardiovascular ageing. Heart Br Card Soc. 2016 Jun 1;102(11):825–31.
22. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer Oxf Engl 1990. 2013 Apr;49(6):1374–403.
23. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011 Dec 6;105 Suppl 2:S77-81.

24. Barrett-Connor E. The Rancho Bernardo Study: 40 years studying why women have less heart disease than men and how diabetes modifies women's usual cardiac protection. Glob Heart. 2013 Jun 1;8(2).
25. Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia. 2014 Aug;57(8):1542–51.
26. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet. 2014 Jun 7;383(9933):1973–80.
27. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006 Jan 14;332(7533):73–8.
28. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care. 2000 Jul;23(7):962–8.
29. Roche MM, Wang PP. Sex differences in all-cause and cardiovascular mortality, hospitalization for individuals with and without diabetes, and patients with diabetes diagnosed early and late. Diabetes Care. 2013 Sep;36(9):2582–90.
30. Dantas APV, Fortes ZB, de Carvalho MHC. Vascular disease in diabetic women: Why do they miss the female protection? Exp Diabetes Res. 2012;2012:570598.
31. Donahue RP, Rejman K, Rafalson LB, Dmochowski J, Stranges S, Trevisan M. Sex differences in endothelial function markers before conversion to pre-diabetes: does the clock start ticking earlier among women? The Western New York Study. Diabetes Care. 2007 Feb;30(2):354–9.
32. Franzini L, Ardigò D, Cavalot F, Miccoli R, Rivellese AA, Trovati M, et al. Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men: results from the MIND.IT Study Group of the Italian Society of Diabetology. Nutr Metab Cardiovasc Dis NMCD. 2013 Mar;23(3):235–41.
33. Ferrara A, Mangione CM, Kim C, Marrero DG, Curb D, Stevens M, et al. Sex disparities in control and treatment of modifiable cardiovascular disease risk factors among patients with diabetes: Translating Research Into Action for Diabetes (TRIAD) Study. Diabetes Care. 2008 Jan;31(1):69–74.
34. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, et al. Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. J Intern Med. 2013 Aug;274(2):176–91.
35. Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. Diabetes Care. 2005 Mar;28(3):514–20.
36. Kautzky-Willer A, Kamyar MR, Gerhat D, Handisurya A, Stemer G, Hudson S, et al. Sex-specific differences in metabolic control, cardiovascular risk, and interventions in patients with type 2 diabetes mellitus. Gend Med. 2010 Dec;7(6):571–83.
37. Wannamethee SG, Papacosta O, Lawlor DA, Whincup PH, Lowe GD, Ebrahim S, et al. Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. Diabetologia. 2012 Jan;55(1):80–7.
38. Peters SAE, Huxley RR, Sattar N, Woodward M. Sex Differences in the Excess Risk of Cardiovascular Diseases Associated with Type 2 Diabetes: Potential Explanations and Clinical Implications. Curr Cardiovasc Risk Rep. 2015;9(7):36.
39. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA. 1991 Feb 6;265(5):627–31.
40. Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG, et al. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012 Jun;55(6):1607–18.
41. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010 Jul;33(7):1674–85.

42. World Cancer Research Fund. Cancers linked with greater body fatness [Webpage] [Internet]. 2015 [cited 2016 Mar 23]. Available from: http://www.wcrf.org/int/cancer-facts-figures/link-between-lifestyle-cancer-risk/cancers-linked-greater-body-fatness
43. Miao Jonasson J, Cederholm J, Gudbjornsdottir S. Excess body weight and cancer risk in patients with type 2 diabetes who were registered in Swedish National Diabetes Register--register-based cohort study in Sweden. PloS One. 2014;9(9):e105868.
44. Grigoriadis S, Robinson GE. Gender issues in depression. Ann Clin Psychiatry Off J Am Acad Clin Psychiatr. 2007 Dec;19(4):247–55.
45. McLean CP, Anderson ER. Brave men and timid women? A review of the gender differences in fear and anxiety. Clin Psychol Rev. 2009 Aug;29(6):496–505.
46. World Health Organization. Global status report on noncommunicable diseases 2014. 2014.
47. Kautzky-Willer A, Dorner T, Jensby A, Rieder A. Women show a closer association between educational level and hypertension or diabetes mellitus than males: a secondary analysis from the Austrian HIS. BMC Public Health. 2012;12:392.
48. Tang M, Chen Y, Krewski D. Gender-related differences in the association between socioeconomic status and self-reported diabetes. Int J Epidemiol. 2003 Jun;32(3):381–5.
49. Schunk M, Reitmeir P, Schipf S, Völzke H, Meisinger C, Thorand B, et al. Health-related quality of life in subjects with and without Type 2 diabetes: pooled analysis of five population-based surveys in Germany. Diabet Med J Br Diabet Assoc. 2012 May;29(5):646–53.
50. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord. 2012 Oct;142 Suppl:S8-21.
51. Collins MM, Corcoran P, Perry IJ. Anxiety and depression symptoms in patients with diabetes. Diabet Med J Br Diabet Assoc. 2009 Feb;26(2):153–61.
52. Landman GWD, van Hateren KJJ, Kleefstra N, Groenier KH, Gans ROB, Bilo HJG. Health-related quality of life and mortality in a general and elderly population of patients with type 2 diabetes (ZODIAC-18). Diabetes Care. 2010 Nov;33(11):2378–82.
53. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. Health Serv Res. 2004 Aug;39(4 Pt 1):1005–26.
54. Hendriks M, Rademakers J. Relationships between patient activation, disease-specific knowledge and health outcomes among people with diabetes; a survey study. BMC Health Serv Res. 2014;14:393.
55. Bos-Touwen I, Schuurmans M, Monninkhof EM, Korpershoek Y, Spruit-Bentvelzen L, Ertugrul-van der Graaf I, et al. Patient and disease characteristics associated with activation for self-management in patients with diabetes, chronic obstructive pulmonary disease, chronic heart failure and chronic renal disease: a cross-sectional survey study. PloS One. 2015;10(5):e0126400.
56. Rask KJ, Ziemer DC, Kohler SA, Hawley JN, Arinde FJ, Barnes CS. Patient activation is associated with healthy behaviors and ease in managing diabetes in an indigent population. Diabetes Educ. 2009 Aug;35(4):622–30.
57. Rademakers J, Nijman J, van der Hoek L, Heijmans M, Rijken M. Measuring patient activation in The Netherlands: translation and validation of the American short form Patient Activation Measure (PAM13). BMC Public Health. 2012;12:577.
58. Chubak J, Anderson ML, Saunders KW, Hubbard RA, Tuzzio L, Liss DT, et al. Predictors of 1-year change in patient activation in older adults with diabetes mellitus and heart disease. J Am Geriatr Soc. 2012 Jul;60(7):1316–21.
59. Richards T. Patients' priorities. BMJ. 1999 Jan 30;318(7179):277.
60. Heje HN, Vedsted P, Sokolowski I, Olesen F. Patient characteristics associated with differences in patients' evaluation of their general practitioner. BMC Health Serv Res. 2008;8:178.
61. Ubink-Veltmaat LJ, Bilo HJG, Groenier KH, Rischen RO, Meyboom-de Jong B. Shared care with task delegation to nurses for type 2 diabetes: prospective observational study. Neth J Med. 2005 Mar;63(3):103–10.

Part 1

Sex differences