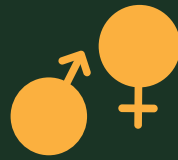


CARDIOVASCULAR RISK AND DISEASE MANAGEMENT IN DIABETES:

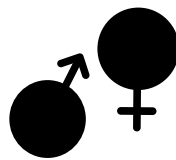
DIFFERENCES BETWEEN WOMEN AND MEN



MARIT DE JONG

CARDIOVASCULAR RISK AND DISEASE MANAGEMENT IN DIABETES:

DIFFERENCES BETWEEN WOMEN AND MEN



MARIT DE JONG

Cardiovascular risk and disease management in diabetes: differences between women and men.

PhD thesis, Utrecht University, with a summary in Dutch.

Author: Marit de Jong

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**Cardiovascular risk and disease management in diabetes:
differences between women and men**

**Cardiovasculair risico en diabeteszorg in patiënten met diabetes:
verschillen tussen vrouwen en mannen**

(met een samenvatting in het Nederlands)

Proefschrift

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Marit de Jong

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te Almelo

Promotoren:

Prof. dr. M.L. Bots

Prof. dr. M. Woodward

Copromotoren:

Dr. S.A.E. Peters

Dr. R.C. Vos

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Chapter 1

General introduction and thesis outline

Relevance of sex- and gender-based research

Sex and gender are major modifiers of disease, and there is an unprecedented need for sex- and gender-based reporting within biomedical research.¹⁻⁵ Historically, women and men were believed to experience disease in the same way, and, accordingly, research findings were assumed to be applicable to both sexes. Following the Thalidomide and Diethylstilboestrol (DES) tragedies, the US Food and Drug Administration (FDA) issued the “General Considerations for the Clinical Evaluation of Drugs” guideline in 1977. This guideline declared that all women of child-bearing potential, including single women, women using contraceptives, and women with sterile partners, should be excluded from early phase drug trials.^{6,7} As a consequence, for decades, women were less frequently included in medical research and research findings were rarely analysed by sex or gender.^{4,8-10} This has limited the identification of relevant sex and gender differences in determinants of health and disease, and may have resulted in suboptimal care or even harm to women and men.^{2,8} Given that women and men are biologically different, and approximately half the population exists of women, any finding of relevant sex or gender differences is likely to have widespread relevance.³

At present, sex and gender are recognized as fundamental drivers of health, and research has established the presence of relevant sex and gender differences across many biomedical areas.^{5,8,9} For example, several well established cardiovascular risk factors, including smoking and diabetes, are associated with higher risk of incident myocardial infarction (MI) in women than in men.¹¹ Among those with MI, women were found to present themselves with different clinical manifestations (i.e. shortness of breath and nausea or vomiting) compared to their male counterparts.¹² Several drugs turned out to be less effective or even harmful in clinical practice as sex- specific effects were not taken into account in translational and preclinical studies.² Between 1997 and 2000, ten FDA-approved drugs were withdrawn from the US market because of serious side effects. Majority of these drugs may have posed greater health risks for women than for men.^{2,13} Recent evidence suggests that the optimal survival in women with heart failure with reduced ejection fraction occurs at half the guideline-recommended doses of β -blockers, angiotensin receptor blockers (ARB), and angiotensin converting enzyme (ACE) inhibitors than in men.¹⁴ Additionally, a systematic review on sex differences in adverse drug reactions to heart failure drugs was published, and, albeit some sex differences in adverse drug reactions were identified, there was a widespread lack of sex-specific data which significantly hindered the identification of sex-specific adverse drug reactions.^{15,16}

Over the years, an increasing number of funding agencies, funding bodies, and journal editors have implemented various strategies to ensure greater focus on sex- and gender-based research.^{8-10,17-21} Publishers are more frequently mentioning sex and gender reporting requirements², and, in 2016, the Sex and Gender Equity in Research (SAGER) guidelines were developed to provide guidance for reporting sex and gender information across all aspects of research from study design to interpretation of the findings.^{8,22} Many funding agencies from Europe and North America have implemented strategies to inform, support, and instruct researchers to consider sex and gender at all levels of biomedical research.^{10,20} Consequently, the inclusion of sex and gender-specific

analyses in biomedical research has progressively increased over time.⁹ Nonetheless, women are still underrepresented in many trials, which does not seem to be due to unwillingness to participate, and researchers often omit to implement sex and gender as important variables in their studies.^{8,15,16,23-26} As a consequence, knowledge gaps regarding sex and gender as determinants of health and disease continue to exist.

From a historical perspective, it was believed that cardiovascular disease (CVD) predominantly affects men.²⁷ However, CVD is the main cause of death worldwide in both women and men, being responsible for one-third of all deaths in 2019.²⁸ Diabetes has long been recognized as an important risk factor for CVD in both sexes. However, there is compelling evidence that women and men do not have the same excess risk of CVD associated with diabetes.²⁹

Diabetes and cardiovascular complications: differences between women and men

Diabetes mellitus, or in short diabetes, is a serious condition characterized by a state of hyperglycaemia which is caused by the inability of the body to produce sufficient amounts of insulin and/or to effectively use the insulin that is produced.³⁰ The three main categories of diabetes are type 1 diabetes, type 2 diabetes, and gestational diabetes, with vast majority of those with diabetes being diagnosed with type 2 diabetes (~90%). Globally, an estimated 463 million adults were living with diabetes in 2019, and the prevalence of diabetes is steadily increasing over time with considerable variation across countries.³¹ Diabetes prevalence increased from 4.6% in 2000 to 9.3% in 2019, among those aged 20-79 years.^{31,32} By 2030, it is estimated that 1 in 10 adults (578 million individuals) will be living with diabetes. By 2045, this number is predicted to rise to 700 million adults (10.9%). Diabetes is a serious threat to public health. Those with diabetes are at increased risk of developing a wide range of diabetes-related complications, including CVD, nephropathy, retinopathy, neuropathy and vasculopathy, resulting in premature comorbidity and mortality. Individuals with diabetes are also more prone to develop respiratory and other infections, physical and mental decline (i.e. dementia), depression, and certain types of cancer.³³ 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.³¹

Diabetes is a strong risk factor for CVD in both sexes. Among adults with type 2 diabetes, the global prevalence of CVD is estimated to be 32%, and CVD was responsible for approximately half of all deaths.³⁴ Although incidence rates of CVD have been reported to be higher in men than in women, with and without type 2 diabetes, there is a growing body of evidence showing that the relative risk of cardiovascular complications conferred by diabetes is considerably larger in women than in men.^{11,35-43} In other words, there is compelling evidence showing that diabetes is a stronger risk factor for the development of major cardiovascular complications in women compared to their male counterparts.^{11,35-43} For example, a large meta-analysis, including 64 cohorts with over 850,000 participants, showed that, compared to those without diabetes, diabetes increased the risk of coronary heart disease (CHD) by approximately 2.8-fold in women, but 2.2-fold in men, which corresponded with an excess risk of 44% in women.³⁸ Likewise, another meta-analysis demonstrated that the relative risk of stroke was 27% higher among women with diabetes than

their male counterparts.³⁷ A sex differential in the consequence of diabetes has also been reported for heart failure, where the relative risk of heart failure, associated with diabetes, was substantially greater in women than in men.³⁶ Less is known about sex differences in the effects of diabetes on microvascular complications such as diabetic retinopathy, neuropathy, and nephropathy, and studies have shown conflicting results. For example, a meta-analysis, including 10 studies with over 5 million participants, demonstrated that women with diabetes experienced 38% excess relative risk of end stage renal disease, while no sex difference was found for the association between diabetes and chronic kidney disease.⁴⁴

Mechanisms underlying the sex differences in cardiovascular risk consequent to diabetes

The mechanisms underpinning the excess risk of major CVD conferred by diabetes in women compared to men have yet to be unravelled, and there is urgent need for a better understanding of these sex differences. Improved understanding of the mechanisms underpinning this sex differential could help to increase the awareness of sex differences in the burden of diabetes-associated CVD among patients, healthcare providers, and policymakers, and may provide targets for more personalized care, thereby reducing the burden of diabetes in both women and men. Numerous studies have speculated about these underlying mechanisms, which are most likely multifactorial.⁴⁵ Mechanisms that contribute to the greater relative risk of major CVD in women, compared to men, may include differences in biology and disparities in the provision and uptake of healthcare. Further detailing these aspects, with a focus on differences in diabetes management, is one of the objectives of this thesis.

Objectives

The overarching objective of this thesis was to provide further insight in the mechanisms underpinning the sex differential observed in the risk of macrovascular disease consequent to diabetes.

The specific aims of this thesis are to:

1. Provide an overview of sex differences in both biological factors and in healthcare provided for the prevention, management, and treatment of diabetes and its cardiovascular complications.
2. Investigate the sex-specific risk of (cardiovascular) events across the glycaemic spectrum, before and after the diagnosis of diabetes.
3. Examine sex disparities in the management of diabetes and diabetes-related complications.

Outline of this thesis

In the **second chapter** of this thesis, an overview is provided of the current knowledge regarding sex differences in both biological factors, with a specific focus on differences in adipose tissue, and management of diabetes. In **chapter 3**, we discuss statistical methods that can be used to obtain sex-specific estimates and estimates of sex differences. In **chapters 4, 5 and 6**, we apply the statistical strategy recommended in **chapter 3** to study the sex-specific effects and

sex differences of diabetes status and glycated haemoglobin (HbA1c) on MI, CHD, and COVID-19 (**chapters 4 and 5**), and to study the sex-specific effects and sex differences of diabetes duration on CVD (**chapter 6**), using data from the UK Biobank. The UK Biobank is a large prospective cohort from the United Kingdom, including detailed phenotypic and genotypic data of over 500,000 participants aged between 40–69 years at study baseline between 2006 and 2010.⁴⁶ In **chapters 7 and 8**, sex disparities in the management of diabetes and cardiovascular complications are being studied using two Dutch cohorts: The Julius General Practitioners Network (JGPN) and the Diabetes Pearl cohort. The JGPN is a large ongoing dynamic cohort of primary care patients that anonymously extracts routine healthcare data from electronic records at one of the included general practices in Utrecht and vicinity, The Netherlands.⁴⁷ The Diabetes Pearl cohort is an observational cohort involving eight Dutch academic medical centres including individuals with type 2 diabetes receiving primary or secondary/tertiary care.⁴⁸ In **chapter 9**, which involves a systematic review, sex disparities in the assessment of cardiovascular risk factors and diabetes-related complications are being explored. In **chapter 10**, we conclude by discussing the main findings of this thesis and explore implications for future research.

Studying sex, gender, or both?

The terms ‘sex’ and ‘gender’ are frequently used interchangeably, and, although sex and gender are closely interrelated and nearly impossible to separate, their meanings are not synonymous. Sex refers to the biological differences between women and men (or intersex), whereas gender refers to socially constructed roles, that is, being a fluid construct influenced by social and cultural context which may vary over time and with age.⁴⁹ Most cohorts used in this thesis reported on a binary variable of being either female or male, without separating sex from gender. To improve readability, the term ‘sex’ is consistently used throughout this thesis, while acknowledging that the work presented in this thesis has both sex and gender elements.

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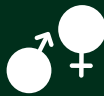
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Part 1

Sex differences in the risk of cardiovascular
disease conferred by diabetes



Chapter 2

Sex differences in the risk of vascular
disease associated with diabetes

Rianneke de Ritter*

Marit de Jong*

Rimke C. Vos

Carla J.H. van der Kallen

Simone J.S. Sep

Mark Woodward

Coen D.A. Stehouwer

Michiel L. Bots

Sanne A.E. Peters

* Authors equally contributed

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Abstract

Diabetes is a strong risk factor for vascular disease. There is compelling evidence that the relative risk of vascular disease associated with diabetes is substantially higher in women than in men. The mechanisms that explain the sex difference have not been identified. However, this excess risk could be due to certain underlying biological differences between women and men. In addition to other cardiometabolic pathways, sex differences in body anthropometry and patterns of storage of adipose tissue may be of particular importance in explaining the sex differences in the relative risk of diabetes-associated vascular diseases. Besides biological factors, differences in the uptake and provision of healthcare could also play a role in women's greater relative risk of diabetic vascular complications. In this review, we will discuss the current knowledge regarding sex differences in both biological factors, with a specific focus on sex differences in adipose tissue, and in healthcare provided for the prevention, management, and treatment of diabetes and its vascular complications. While progress has been made towards understanding the underlying mechanisms of women's higher relative risk of diabetic vascular complications, many uncertainties remain. Future research to understanding these mechanisms could contribute to more awareness of the sex-specific risk factors, and could eventually lead to more personalised diabetes care. This will ensure that women are not affected by diabetes to a greater extent, and will help to diminish the burden in both women and men.

Background

Diabetes is one of the most common chronic diseases globally. In 2017, an estimated 425 million adults, 8.4% of women and 9.1% of men, had diabetes, and an additional 352 million adults were at risk of developing the condition.¹ The prevalence of diabetes is expected to further rise by 48%, to 629 million affected adults aged between 20-79 years by 2045.¹ The two main types of diabetes are diabetes type 1 and diabetes type 2, accounting for 5-10% and 90% of all individuals with diabetes, respectively.^{1,2} Although diabetes type 2 is most often diagnosed at middle or old age, it is increasingly common in children, adolescents, and young adults, often as a consequence of obesity, physical inactivity, and poor dietary habits.^{1,3}

Diabetes is a major contributor to premature mortality. In 2017, an estimated 4 million deaths of people aged between 20-79 years were attributed to diabetes¹, making it the seventh most common cause of death worldwide.⁴ More women than men die of diabetes on a global scale: 2.1 versus 1.8 million in 2017.¹ The only regions where more men than women die from diabetes are North America and the Caribbean region.¹ Individuals with diabetes are at increased risk of cardiovascular complications, chronic kidney disease, certain cancers, physical and cognitive impairment (i.e. dementia), depression, and respiratory and other infectious diseases.^{1,5,6} Cardiovascular disease is the most common complication of diabetes and can be broadly categorized in microvascular complications (classically: neuropathy, nephropathy and retinopathy) and macrovascular complications including coronary artery disease, stroke, and peripheral arterial disease. Individuals with diabetes are two to three times more likely to develop cardiovascular disease compared to individuals without diabetes.¹

However, not everyone with diabetes has the same excess risk of cardiovascular disease. Large-scale systematic reviews with meta-analyses have demonstrated that the excess risk of macrovascular complications associated with diabetes is substantially greater in women than in men.^{7,8} The relative risks of incident coronary heart disease (CHD) and stroke, respectively, associated with diabetes have been estimated to be 44% and 27% higher in women than in men.^{7,8} Likewise, another meta-analysis of 68 prospective studies has shown that, after adjustment for major vascular risk factors, diabetes was associated with a nearly 50% higher occlusive vascular mortality rate among women than men.⁹ The excess risk of vascular mortality among women conferred by diabetes was especially high among those between the age of 35 and 59 years, with almost a six times higher occlusive vascular death rate among women and a nearly two and a half times higher rate among men.⁹ Another meta-analysis demonstrated that diabetes was associated with a 19% higher relative risk of vascular dementia in women than in men.¹⁰ A sex differential in the consequences of diabetes has also been shown for end stage renal disease, where the relative risk of end-stage renal disease was 38% higher among women than men.¹¹ Since 90% of individuals with diabetes have type 2 diabetes, most individuals with diabetes who were included in these meta-analyses had type 2 diabetes. Nevertheless, a meta-analysis that specifically focused on type 1 diabetes has shown that women with type 1 diabetes had almost a 40% higher relative risk of all-cause mortality, and a 200% higher relative risk of fatal and nonfatal vascular events, compared with men with type 1 diabetes.¹² In addition to vascular disease, sex differences may

also exist in the association between diabetes and non-vascular diseases. A recent meta-analysis has shown that women have a 6% greater relative risk of diabetes-associated cancer, with some variation by cancer type.¹³ Sex differences in other non-vascular diseases require further study. Figure 1 summarizes the results from the abovementioned meta-analyses.

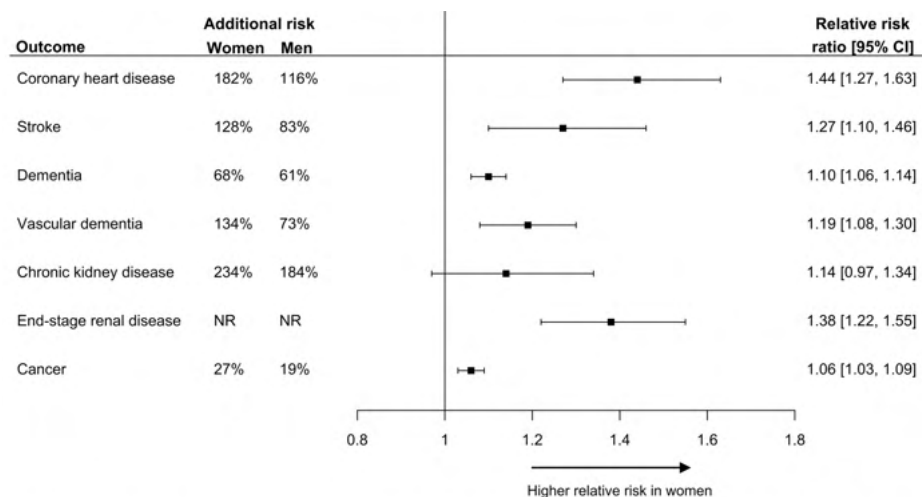


Figure 1. Results from prior meta-analyses of sex differences in the effects of diabetes on vascular outcomes and cancer, expressed as the women-to-men ratio of relative risks and the additional risks.^{7,8,10,11,13} NR = not reported.

While the greater excess risk of vascular complications conferred by diabetes in women compared with men has been well described, mechanisms underpinning the sex difference have not been identified in full. In this review, we will first discuss sex differences in biological factors, with a specific focus on adipose tissue, and secondly, we will discuss sex differences in the uptake and provision of healthcare. These mechanisms may be involved in explaining the sex difference in the vascular consequences of diabetes. Although some aspects may differ by type of diabetes, we shall mainly focus on diabetes in general, while acknowledging that most cases with diabetes would have type 2 diabetes.

1. Biological aspects

Women and men are subject to similar environmental exposures during their life course, but they are biologically different. For that reason, the excess risk of diabetes-associated vascular disease in women compared with men could be due to physiological, such as hormonal or genetic, differences between women and men.

To diagnose diabetes, an arbitrary cut-off value of a continuous trait is used, such as fasting blood glucose (FG) or glycated haemoglobin (HbA1c). Nevertheless, there is compelling evidence of a progressive association between various measures of glycaemia and the risk of vascular disease, both above and below the clinical threshold for diabetes. It has been postulated that, compared

with men, metabolic risk factors in women have to deteriorate to a greater magnitude across this continuous trait for diabetes to develop.^{8,14} As a consequence, the exposure to a hazardous cardiometabolic environment in the development of diabetes may be more pronounced in women.^{8,15} This hypothesis is supported by a study that found that, on average, men have prediabetes for 8.5 years and women for 10.3 years prior to the development of diabetes.¹⁶ Moreover, several studies have found a relatively greater increase in the levels of cardiovascular risk factors, in women with diabetes compared with women without diabetes, opposed to their male counterparts.¹⁷⁻²⁰ Additional to the different impact of risk factors, sex differences in vascular and hormonal pathophysiology could partially explain women's higher relative risk on diabetes-associated vascular diseases.²¹ These potential explanations will be outlined in the next paragraphs.

Diabetes-associated sex differences in adiposity

Sex differences in body anthropometry and patterns of storage of adipose tissue may be of particular importance in explaining the sex differences in the diabetes-associated risk of vascular disease.²² Among 500,000 individuals of the UK Biobank, waist circumference and body mass index (BMI) differed more between women with and without diabetes than between men with and without diabetes.²³ Moreover, when first diagnosed with diabetes, women have a BMI that is nearly 2 kg/m² higher than that of men, despite similar levels of HbA1c.^{24,25} These sex differences in anthropometric characteristics among those with and without diabetes may be linked to differential patterns of fat storage in adipose tissue in women and men.²²

Ample evidence exists to show that excess adipose tissue is causally linked to the development of type 2 diabetes and vascular disease.^{26,27} However, it is becoming increasingly apparent that adipose tissue in different parts of the body has different biochemical profiles. In contrast to (peripheral) subcutaneous fat, excess visceral fat and fat in ectopic tissues, like skeletal muscle and the liver, has specifically been associated with insulin resistance.²⁸⁻³⁰ This interferes with insulin signalling pathways, which eventually could lead to diabetes.²⁸⁻³⁰ Sex differences in the preferred location of fat storage could have an effect on the duration of the development of insulin resistance and diabetes and the consequent deterioration of other related cardiometabolic risk factors. This process is illustrated in figures 2 and 3. Women are more likely to store fat subcutaneously and on their lower extremities, whereas men are more likely to store fat in the abdominal region.³¹ Correspondingly, men have a substantially higher amount of visceral and ectopic fat compared with premenopausal women, independent of BMI and the amount of total body fat.^{32,33} The preferential deposition of excess fat in visceral and ectopic tissues in men could lead to a faster transition to insulin resistance and diabetes, whereas women may need to gain more weight and related metabolic risk factors might need to deteriorate to a greater extent than in men to reach the same levels of visceral and ectopic fat that are required to develop insulin resistance and eventually diabetes (Fig. 3).^{34,35}

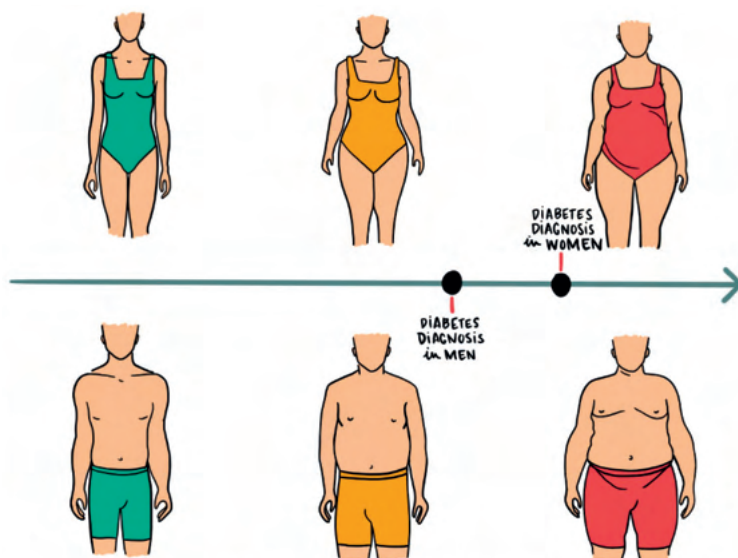


Figure 2. Sex differences in visceral and subcutaneous fat and their association with the time of diagnosis of diabetes

Next to the different metabolic effects of adipose tissue in different parts of the body, abdominal visceral adipose tissue itself seems to have a stronger association with insulin resistance in women than in men, suggesting that excess visceral adipose tissue is more strongly linked to diabetes in women than in men.³⁶ Likewise, recent findings from the UK Biobank demonstrated that higher waist circumferences and waist-to-hip ratio conferred a greater excess risk of myocardial infarction in women than in men.³⁴ These findings suggest that excess adipose tissue in the abdominal region may have more adverse cardiometabolic consequences in women than in men, which may be explained by sex difference in insulin resistance at a given amount of adipose tissue (Fig. 3).

Finally, there is compelling evidence that obesity and its associated metabolic dysfunction suppresses women's protective effect of sex-hormones on cardiovascular disease.³⁷ Adipocytes overfilled with lipids release leptin, which can promote activation of the sympathetic nervous system and the renin-angiotensin system and could stimulate the secretion of aldosterone.³⁸ In turn, aldosterone is associated with excessive mineralocorticoid receptor signalling on endothelial cells, which play a major role in obesity-associated cardiovascular disease.^{37,38} Women may be predisposed to heightened endothelial mineralocorticoid receptor activation. This might be explained by higher endogenous expression of endothelial mineralocorticoid receptors in blood vessels in women than in men, possibly driven by progesterone receptor activation in endothelial cells.³⁷ Moreover, these disadvantageous obesity-associated mechanisms in women may be stronger in the presence of type 2 diabetes, since women have a higher BMI and subsequently more adipose tissue at the moment of diagnosis of diabetes than men.^{24,25}

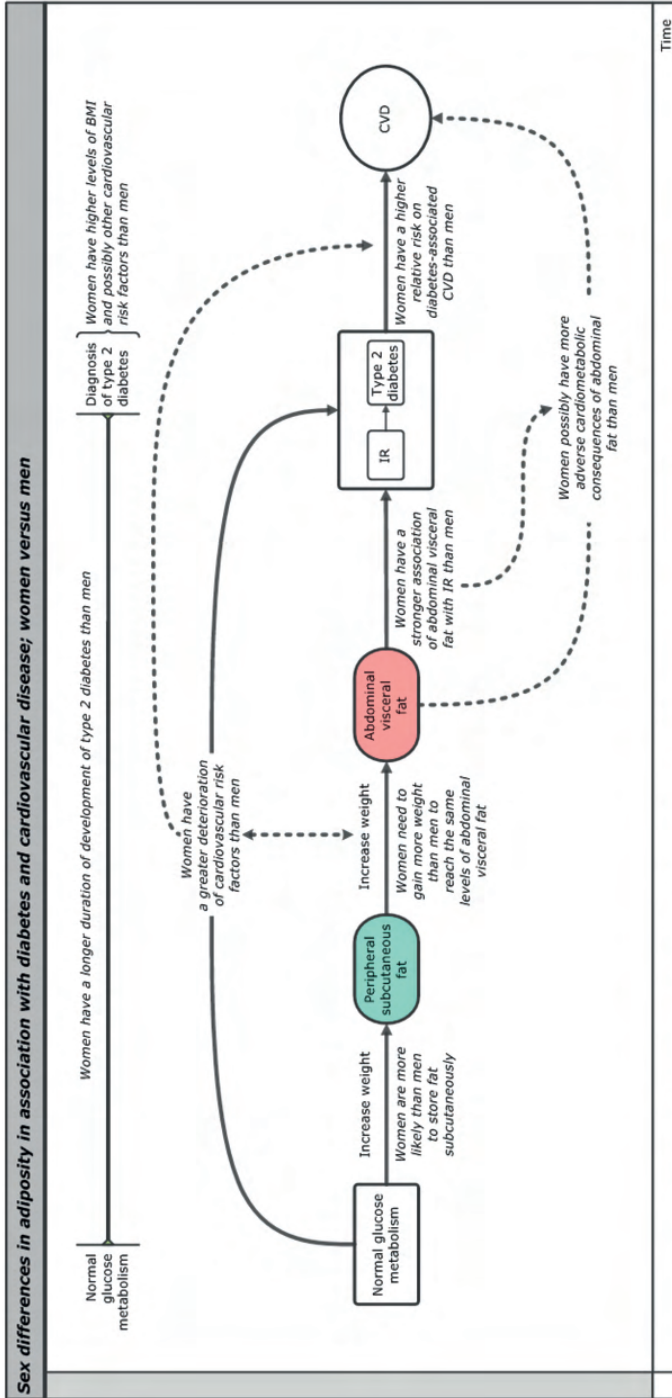


Figure 3. Sex differences in adiposity in association with diabetes and cardiovascular disease. The figure illustrates the associations between adiposity, insulin resistance, type 2 diabetes, and cardiovascular disease in women compared with men. BMI = body mass index; IR = insulin resistance; CVD = cardiovascular disease.

Diabetes-associated sex differences in other cardiovascular risk factors and vascular pathophysiology

As previously mentioned, it has been hypothesized that women have to undergo greater metabolic deterioration to develop diabetes than men. This hypothesis is also supported by studies that found that sex differences in metabolic risk factors already occur in the transition from normoglycaemia to elevated glucose levels and diabetes.^{39,40} During 8 years of follow-up, women who converted to diabetes showed relatively worse levels of total cholesterol, HDL cholesterol, triglycerides, and diastolic blood pressure at baseline than men who converted to diabetes, compared with participants of the same sex who did not develop diabetes.⁴⁰ Correspondingly with the classic risk markers, progression from normal glucose metabolism to elevated levels of fasting glucose in women was associated with relatively greater endothelial dysfunction, a higher prevalence of hypertension, and a greater degree of dysregulated fibrinolysis and coagulation than in male counterparts.³⁹ Compared with men, women generally have higher fibrinolytic potential and a better endothelial function, but these protective effects are diminished in the presence of type 2 diabetes.²¹ Additionally, the coagulation system is in a more pro-thrombotic state in diabetic women compared with diabetic men.²¹ Finally, type 2 diabetes may induce a greater immune response and impairment of cellular defence mechanisms against oxidative stress in women than in men.⁴¹ These sex differences in hyperglycaemia-induced haemodynamics might be explained by complex interactions between insulin and oestrogen signalling.⁴² Whether these differences explain women's higher relative risk on diabetes-associated cardiovascular disease requires further study.

Despite the evidence above regarding traditional risk factors, results from the meta-analyses that demonstrated that sex differences exist in the relative risk of vascular disease associated with diabetes were adjusted for traditional cardiovascular risk factors. Hence, it is conceivable that sex differences in traditional risk factor levels alone cannot fully explain the higher relative risk of women in diabetes-associated vascular disease, even though there may be unmeasured confounding. Moreover, key risk factors for vascular disease, such as total cholesterol, blood pressure and BMI, have each been found to have a continuous log-linear association with occlusive vascular mortality in diabetic and non-diabetic individuals, which does not differ by sex.⁹ Nevertheless, only baseline information about cardiovascular risk factor levels in participants with or without diabetes has been taken into account in the meta-analyses, not the possibly larger deterioration in cardiovascular risk factors levels in the conversion to diabetes. It is therefore conceivable that the risk factor changes in the conversion to diabetes explain some of the higher relative risk of vascular disease in women compared to men.

Future perspective

In future studies, it would be useful to investigate possible sex differences in cardiovascular risk factor levels associated with glucose metabolism status and across levels of glycaemic control. Previous results from The Maastricht Study indicated that there are already sex differences in cardiometabolic risk factors to women's disadvantage before the development of type 2 diabetes, albeit weaker than in type 2 diabetes, with greater differences in systolic blood pressure and

lipid levels among women than men with prediabetes and across levels of HbA1c.⁴³ To further understand the effects of sex differences in adiposity, detailed body composition and body fat distribution measurements conducted by DEXA and MRI can be used. These methods are appropriate to assess the extent to which fat and lean mass, visceral and subcutaneous fat, and the fat content of the liver and pancreas are differentially associated with glucose metabolism status in women and men and how such differences can explain women's greater excess vascular disease risk associated with diabetes.

2. Healthcare aspects

In addition to sex differences in biological aspects, disparities in the uptake and provision of healthcare may in part explain sex differences in diabetes-related vascular complications (Fig. 4).

Diabetes management

One of the primary goals in the management of diabetes is the delay and prevention of vascular morbidity and mortality.⁴⁴ Currently, many guidelines on diabetes management exist. Most of these evidence-based guidelines provide broadly similar recommendations for both sexes on diabetes management and prevention of diabetes-related complications, and target lifestyle factors, including smoking behaviour, physical activity, diet, and weight control, and adequate management of blood pressure, cholesterol, and glucose levels (Table 1).^{3,45}

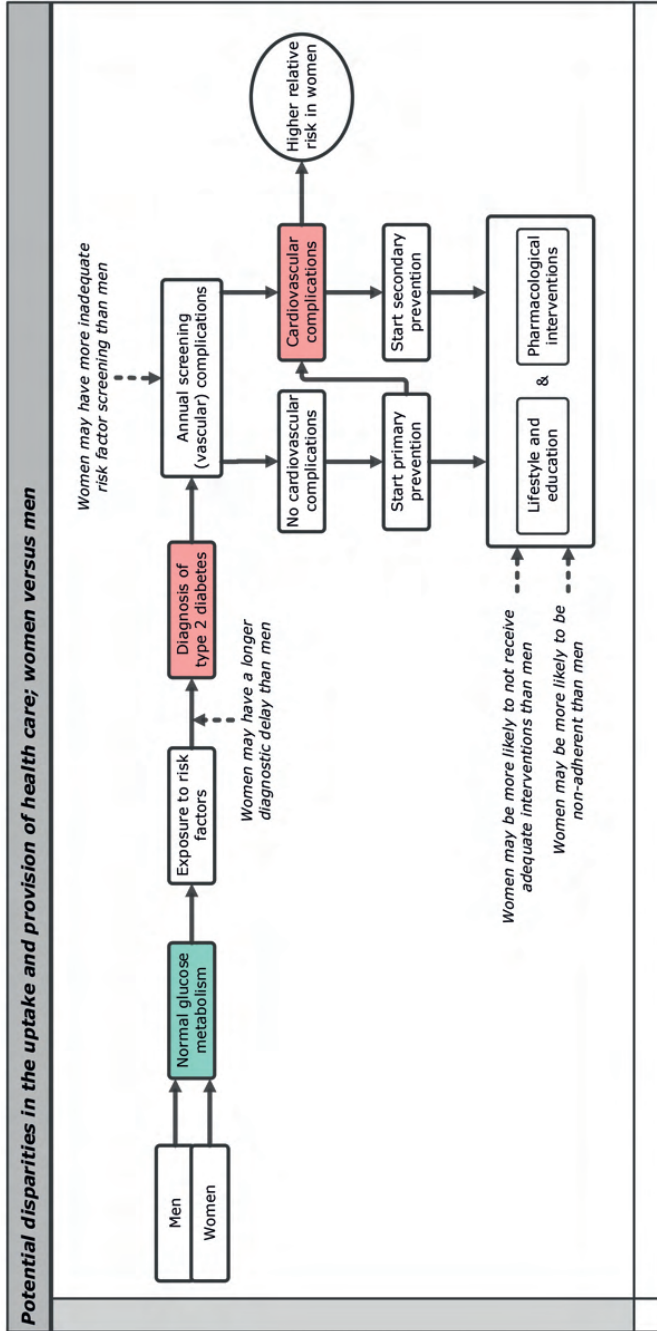


Figure 4. Disparities in the uptake and provision of healthcare may in part explain the excess risk of vascular disease in women with diabetes compared to their male counterparts. Potential differences in the uptake and provision of healthcare between the sexes may occur throughout the pathway - starting with healthy men and women being exposed to certain risk factors, at some point being diagnosed with diabetes, and eventually developing cardiovascular complications - and may include, i.e. diagnostic delay, inadequate risk factor screening, disparities in adequate interventions, and non-adherence as shown by the arrows. The green-coloured box displays normal glucose tolerance, and the red-coloured boxes display negative events (i.e. type 2 diabetes, cardiovascular complications) irrespective of the sexes.

Table 1. Standards of care for the management of diabetes according to the recommendations from the International Diabetes Federation.^{3,45}

Standards of care for the management of diabetes by the International Diabetes Federation^{3,45}		
Risk factor screening	Lifestyle and education	Drug interventions and target values
<p><i>Clinical assessment:</i> weight, BMI, waist circumference, blood pressure, retinopathy screening (every 1 to 2 years) and screening for peripheral neuropathy, feet exam (every year), screening for macrovascular disease (if patient is symptomatic).</p> <p><i>Biochemical assessment:</i> Biochemical assessment: HbA1c, lipid spectrum, renal function (every year)</p> <p><i>Lifestyle assessment:</i> Smoking status, overweight, physical activity, diet</p>	<p><i>Education:</i> - Referral to a diabetes education program</p> <p><i>Diet:</i> - Reduce caloric intake with obesity or overweight, if possible referral to a dietician - Prefer high fibre and low – glycaemic index foods - Avoidance of sugar, sweets and sweetened beverages</p> <p><i>Physical activity:</i> - Increase of physical activity</p> <p><i>Habits:</i> - Avoid smoking - Avoid excess alcohol intake</p>	<p><i>Start lipid-lowering drugs:</i> - T2DM and established CVD - T2DM, no established CVD, ≥40 years and LDL-cholesterol >100mg/dL - T2DM, no established CVD, LDL-cholesterol >70mg/dL may benefit especially with high 10-year CVD risk</p> <p><i>Start glucose-lowering drugs:</i> - General HbA1c target <7%, >8% is generally unacceptable - HbA1c levels between 7.5% and 8% may be acceptable for patients using multiple drugs, if expected survival is limited, cognitive impairment, CKD or severe CVD associated with multiple comorbidities.</p> <p><i>Start antihypertensive drugs:</i> - Diastolic target 80mmHg - Systolic target of 130 to 140 mmHg</p> <p><i>Start ACE-inhibitor or ARB:</i> - Persistent albuminuria</p>

CVD = cardiovascular disease; BMI = body mass index; T2DM = type 2 diabetes mellitus; CKD = chronic kidney disease; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Differences in healthcare provision

Sex differences in healthcare provision can broadly occur at three levels. There may be sex differences in the assessment and monitoring of vascular risk factors, in drug and lifestyle interventions for the management of risk factors, and in risk factor control among those treated. Early detection of suboptimal vascular risk factors and subsequent interventions – either lifestyle or pharmacological – significantly improves clinical outcomes.³ Thus, any potential sex differences in the assessment or monitoring of vascular risk factors or differences in the initiation of lifestyle and/or pharmacological interventions may result in less optimal treatment, inadequate risk factor control, and consequently more severe clinical outcomes.

Two recent studies assessed sex differences in healthcare provision for the prevention of CHD.^{46,47} Within the general population of Australia, women were less likely to receive cardiovascular risk factor screening compared with men. However, high-risk women or women with a history of cardiovascular disease aged 65 years or older were more likely to be prescribed recommended drugs than men.⁴⁶ A large study including 10,000 individuals with CHD across Europe, Asia and the Middle East found that risk factor management of secondary prevention was generally worse in women than in men.⁴⁷ Several studies have been published on sex disparities in the management of diabetes, mainly with respect to screening of risk factors and risk factor control (Supplemental

table 1). Overall, these studies have reported mixed findings regarding the presence, magnitude, and direction of sex differences in diabetes care and no definite conclusion about the impact of differences in healthcare provision on sex disparities in diabetes and its related cardiovascular complications can be drawn. According to most studies, women are less likely to attain risk factor control for LDL-cholesterol compared with men⁴⁸⁻⁵⁸, while risk factor control for HbA1c is more often found to be similar between sexes.^{49-51,54-56,58-61}

The National Diabetes Audit – 2012-2013 studied essential care processes and achievement of treatment targets in 2 million individuals with diabetes living in England or Wales.⁴⁴ Multivariable analyses showed that women were less likely to receive assessment of all eight care processes than men, and that the three recommended target levels were met by 33% and 30% of men and women, respectively. Moreover, women were less likely to receive risk factor assessment of smoking status, BMI, foot surveillance, cholesterol levels, and urine albumin and more likely to receive testing of serum creatinine and blood pressure.⁴⁴ A large population-based study from Italy, including 415,294 individuals with type 2 diabetes, demonstrated that women were less likely to receive recommended care than men.⁵² In particular, women were less likely to receive assessment of kidney function, foot and eye surveillance, and to achieve risk factor control of HbA1c and LDL-cholesterol despite drug intervention, and were more likely to have a BMI ≥ 30 than men. Women were more likely to receive insulin or antihypertensive medication than men when being off target for HbA1c or blood pressure respectively, while women were less likely to receive adequate treatment despite micro/macroalbuminuria compared with men.⁵² In contrast, a large cross-sectional study among 18,000 men and women with diabetes in the US from the Medical Expenditure Panel Survey Household Component, showed that, over a study period of nine years, women were more likely to receive recommended care than men.⁶² In adjusted analyses, women were more likely to receive annual tests for dilated eye exams, blood pressure control, and to visit a doctor than men; no differences were found for HbA1c testing and foot surveillance.⁶²

Although studies are inconclusive about sex differences in diabetes management, implementation of diabetes management can be improved on multiple aspects for both sexes, including assessment of risk factors and risk factor control. Rossi *et al.* reported that women were more likely to be off target for HbA1c and LDL cholesterol than men, despite receiving drug interventions.⁵² Similar results were found in a Dutch primary care population with diabetes, showing that women receiving lipid-lowering drugs were less likely to be on target for LDL cholesterol and more likely to attain treatment targets for blood pressure when prescribed antihypertensive drugs than men.⁶³ Hence, these differences in risk factor control may be caused by differences in drug type, dosage, or adherence, which is not assessed in most studies and should be investigated further.

Differences in drug adherence

Non-adherence to drugs is a frequent, complex, and multidimensional problem, and the World Health Organization (WHO) has described non-adherence as being '*the primary reason for suboptimal benefit of therapy*'.⁶⁴ Inadequate drug adherence results in suboptimal risk factor control and has been associated with adverse cardiovascular outcomes, including premature

mortality.^{65–68,69} Nonetheless, non-adherence remains difficult to define and absence of uniform research methods makes it challenging to study and reduce non-adherence.⁶⁸

Despite the major impact of non-adherence on cardiovascular outcomes, determinants, including sex, that drive non-adherence have not been fully identified. A large meta-analysis, including 53 studies from diverse populations, showed that only about 50% of men and 47% of women were adherent to statins, and that women were an additional 10% more likely to be non-adherent than men.⁷⁰ Several meta-analyses and systematic reviews on non-adherence have shown that adherence rates in individuals with diabetes are also suboptimal.^{71–73} Moreover, individuals with diabetes non-adherent to cardiovascular drugs were reported to have higher rates of all-cause mortality and higher hospital-admission rates compared with adherent individuals.⁶⁹ Only a limited amount of studies have studied sex differences in non-adherence among individuals with diabetes, and these showed inconclusive results.^{74–78}

To further improve healthcare and to prevent and delay vascular complications, it is of major importance to identify sex-specific determinants that may contribute to non-adherence. Most studies on non-adherence rely on pharmacy claims refill data, self-report, pill count, or medication event monitoring systems. The disadvantage of these strategies is that none of these methods measure true medication intake. There is a need for studies that objectively measure medication adherence, which can be done by quantifying, through mass spectrometry, the presence of drug compounds in body fluids. By objectively studying non-adherence, more awareness about this complex and multidimensional problem can be generated and this may help healthcare providers to address this complex problem more easily.

Conclusion

Sex differences in both biological factors as in the uptake and provision of healthcare could contribute to women's higher relative risk of diabetic vascular complications. While progress has been made towards understanding the underlying mechanisms, many uncertainties remain. Further research is recommended to study the impact of sex differences in biological factors and healthcare provision. To that end, it is important to include adequate numbers of women and men in future studies, including in clinical trials. This could contribute to more awareness of the sex-specific risk factors of diabetic vascular complications and could eventually lead to more personalised care, including sex-specific recommendations in clinical guidelines. This will ensure that women are not affected by diabetes to a greater extent than men and will help to diminish the burden in both sexes.

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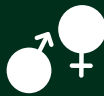
Supplemental table 1. Results from studies reporting on sex differences in screening, risk factor control, and drug interventions for diabetes.

	Women do better	Women do worse	No difference between sexes
Screening (vascular) complications			
Doctor visit	62		
BMI		44	63,79
(Systolic) blood pressure	44,62	59	52,61,63
Retinopathy	54,55,58,62,80	52,57,81,82	79,83
Feet exam		44,52,83	57,62
HbA1c	58,80	55¶,56,61**	44,52,53,54,55†,57,59,61~,62,63,79,81,82,83
Lipid profile/total cholesterol/LDL-cholesterol		44,52,53,55¶,56,59,61**,81,84	54,57,55†,58,61~,63,79,80,82,83
Nephropathy		52,55	58,79
Urine Albumin		44,81,82	53,57
Serum creatinine	44	61**,81	61~
Smoking status	59	44,79	
Screened for diabetes complications	63,80	44,59,85	80,82,83
Risk factor control			
<i>Being on target for</i>			
HbA1c	53,57	50*,51*,52,79,86	49,50,51†,54,55,56,58,59,60,61
(Systolic) blood pressure	50†	49*,50*,51*,52,	49†,51†,57,59,60,61,79
Total cholesterol/LDL cholesterol		48,49*,50,51,52,53,54,55,56,57,58,59	49†,60,61,79
BMI		50,52	
Smoking status (non-smoker)	50		59
<i>Being off target despite drug prescription</i>			
Glucose-lowering drugs		52	
Lipid-lowering drugs		52	
Antihypertensive drugs			52
<i>Receiving drug prescription and being on target</i>			
Glucose-lowering drugs		87	63
Lipid-lowering drugs		63,87	
Antihypertensive drugs	63	87*	87†

Supplemental table 1. Results from studies reporting on sex differences in screening, risk factor control, and drug interventions for diabetes. (continued)

	Women do better	Women do worse	No difference between sexes	
Drug interventions				
<i>Being off target and no prescription</i>				
Glucose-lowering drugs	52			
Lipid-lowering drugs			52	
Antihypertensive drugs	52			
ACE-I or ARB		52		
<i>Being off target and prescription</i>				
Glucose-lowering drugs			49,51,63	
Lipid-lowering drugs		51*,53	49,51†,63	
Antihypertensive drugs			49,51,63	
ACE-I or ARB			53	
1 study	2 studies	3 studies	4 studies	≥5 studies

The numbers in this table refer to the references. The legend at the bottom of the table displays the number of studies that indicate that women do better, women do worse or that no difference between sexes were found on the level of screening, control or drug interventions according to the included studies. For example, the study by Rossi et al., 2013 showed that women were less likely to receive retinopathy screening than men and therefore women do worse on the retinopathy screening compared to men. Only results from adjusted analyses were included. If several models were tested results from the fully adjusted model was included. Some studies stratified study results for cardiovascular disease; * individuals with a history of cardiovascular diseases; † individuals without a history of cardiovascular diseases. Other studies stratified study results for health plans; ‡ Medicare; ¶ Commercial, or contract status; · pre-contract; **post contract. BMI = body mass index; ACE-I = angiotensin converting enzyme-inhibitor; ARB = angiotensin receptor blocker. The table summarizes the results of studies reporting on sex differences in diabetes management, but is not the result of a systematic review. Hence, studies may be lacking from this overview.



Chapter 3

Statistical approaches to assess sex differences
in the association between risk factors and
disease outcomes: an illustrative example

Marit de Jong
Mark Woodward
Sanne A.E Peters

Introduction

Sex is a fundamental driver of virtually all aspects of health and disease. Historically, women have been underrepresented in health research and even when they were represented, results from studies were not analysed separately for women and men.¹ This has led to knowledge gaps and, in some cases, to poorer health outcomes for women and men.¹ Clinically meaningful sex differences can only be identified, and addressed in clinical practice, if the data are reported by sex. In the case of sex differences in risk factors for disease outcomes, this involves the assessment of the sex-specific association between a risk factor, say diabetes, and disease outcome, say myocardial infarction (MI). Sex differences in the diabetes – MI association are ideally quantified by adding an interaction term to the model. Although such sex-specific analyses are increasingly performed, they typically dismiss the potential impact of sex-specific confounding, which potentially leads to erroneous conclusions.^{2,3}

Common statistical approaches to assess sex differences in risk factor – disease associations are (1) stratification by sex and (2) the use of a single interaction term with sex.³ In the first approach, associations are studied in separate strata for men and women. That is, for example,

$$h_i = \exp(b_1 * \text{diabetes} + b_2 * \text{age} + \dots + b_p * \text{cholesterol})$$

where h_1 is the hazard ratio for women and h_2 is the hazard ratio for men.

This stratified approach estimates the association between the risk factor and the disease outcome separately for men and women, and, as such, accounts for sex-specific confounding. However, as two models are used, estimates of sex differences can not be extracted from the same model and involves additional calculations. In the second approach, the single interaction model, an interaction term between sex and the risk factor of interest is included in the model, together with potential confounders. For example, in Cox survival analysis,

$$h = \exp(b_1 * \text{diabetes} * \text{sex} + b_2 * \text{diabetes} + b_3 * \text{sex} + b_4 * \text{age} + \dots + b_p * \text{cholesterol}).$$

where h is the hazard ratio, $\{b_j\}$ are regression coefficients and diabetes is the index exposure variable.

The advantage of the second approach is that estimates of sex differences can be extracted from the same model. However, the second approach does not adjust for sex-specific confounding, that is, sex differences in the impact of confounders on the sex-specific risk factor – disease estimates. A previous simulation study demonstrated that sex-specific estimates obtained from a model with a single interaction term were biased when confounders had sex-specific associations with the outcome.³ This problem can be circumvented by a third approach, the full interaction model, in which interaction terms between sex and each variable are included in the model.^{2,3} That is, for example,

$$h = \exp(b_1 * \text{diabetes} * \text{sex} + b_2 * \text{diabetes} + b_3 * \text{sex} + b_4 * \text{age} * \text{sex} + b_5 * \text{age} + \dots + b_p * \text{cholesterol} * \text{sex} + b_y * \text{cholesterol}).$$

where h is the hazard ratio, $\{b_j\}$ are regression coefficients and diabetes is the index exposure variable.

Using this approach, one adjusts for sex-specific confounding whilst also being able to extract sex-specific effects and sex differences from the same model.^{2,3}

In this report, we illustrate that different conclusions on the presence and magnitude of sex differences in the association between cardiovascular risk factors and MI may be reached by applying different approaches to deal with sex-specific confounding.

Methods

We used data from the UK Biobank, a large prospective cohort of ~500,000 participants aged between 40-69 years at study baseline between 2006 and 2010. Details of the UK Biobank have been described elsewhere.⁴ Participants with a history of cardiovascular disease (CVD) (self-reported or hospital admission of MI, stroke or angina pectoris) at baseline were excluded from the current analyses. The outcome was incident MI, identified by ICD-10 codes. Follow-up started at inclusion and ended on 30/06/2020, date of death, or upon the first (non-)fatal MI. Cox regression models were used to obtain sex-specific hazard ratios (HRs) with 95% confidence intervals (CI) of the association between risk factors and MI, using the three approaches as described above (i.e. stratification, single interaction, full interaction). Sex-specific results for both sexes can be extracted from the single and full interaction by changing the reference category of sex. In models where women are coded as 0, the coefficients for the main effects are female-specific. In models where men are coded as 0, the coefficients for the main effects are male-specific. Women-to-men ratios of HRs (RHRs) were obtained from single and full interaction models. The interaction term between sex and the main effect (e.g. diabetes) in the model where men are coded as 0 can be interpreted as the women-to-men ratio of hazard ratios. All models were adjusted for age. Diabetes and systolic blood pressure were adjusted for each other as well as for smoking status, body mass index (BMI), lipid-lowering medication, antihypertensive medication, cholesterol and socioeconomic status. The models for hypertension, diastolic blood pressure, and atrial fibrillation (AF) were adjusted for these eight variables as well. HbA1c per 1% change was additionally adjusted for glucose-lowering medication. Smoking status was adjusted for socioeconomic status, and models for BMI and weight were adjusted for smoking status and socioeconomic status. Participants with missing data were not included in the relevant model.

Results

Overall, 471,929 participants (56% women) with no history of CVD were included with a mean age of 56 at study inclusion. Over a mean follow-up of 11 years 9,724 (37% women) MI events were documented. As expected, estimates of sex-specific effects were identical in the stratified and full interaction models. However, there were differences between the single and full interaction models. For diabetes, the sex-specific estimates obtained from the single and full interaction models, respectively, decreased in women from a HR of 2.66 (2.33;3.03) to a HR of 2.43 (2.10;2.81) and slightly increased in men from a HR of 1.72 (1.58;1.88) to a HR of 1.79 (1.63;1.96). The corresponding women-to-men RHR was 1.54 (1.33;1.79) in the single interaction model and 1.36

(1.14;1.61) in the full interaction model (Table 1). Similar patterns were seen for some other risk factors (Table 1). For example, the sex difference in the risk of MI associated with a 1% increase in HbA1c seen in the single interaction model (RHR 1.09 [1.04;1.14]) disappeared in the full interaction model (RHR 1.01 (0.96;1.07)). The sex difference in the association between AF and MI was 1.22 (0.78;1.92) in the single interaction model and 1.11 (0.71;1.75) in the full interaction model. No meaningful differences across the three different approaches in the sex differences estimates were found for SBP, DBP, hypertension, smoking, BMI and overweight.

Table 1. Multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios for the association between risk factors and myocardial infarction, using three statistical approaches.

	Stratification by sex*				Single interaction model**				Full interaction model***				
	Women (HR 95% CI)	Men (HR 95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Known diabetes vs. no diabetes	2.43 (2.10;2.81)	1.79 (1.63;1.96)	2.66 (2.33;3.03)	1.72 (1.58;1.88)	1.54 (1.33;1.79)	2.43 (2.10;2.81)	1.79 (1.63;1.96)	1.36 (1.14;1.61)			1.36 (1.14;1.61)		
HbA1c per 1%	1.19 (1.14;1.24)	1.18 (1.14;1.22)	1.24 (1.20;1.28)	1.14 (1.10;1.18)	1.09 (1.04;1.14)	1.19 (1.14;1.24)	1.18 (1.14;1.22)	1.01 (0.96;1.07)			1.01 (0.96;1.07)		
Systolic BP per 20mmHg	1.29 (1.24;1.34)	1.20 (1.16;1.23)	1.30 (1.25;1.35)	1.19 (1.16;1.23)	1.09 (1.04;1.14)	1.29 (1.24;1.34)	1.20 (1.16;1.23)	1.08 (1.03;1.13)			1.08 (1.03;1.13)		
Diastolic BP per 10mmHg	1.16 (1.12;1.21)	1.13 (1.10;1.16)	1.13 (1.09;1.18)	1.14 (1.11;1.17)	0.99 (0.95;1.04)	1.16 (1.11;1.21)	1.13 (1.10;1.16)	1.03 (0.98;1.08)			1.03 (0.98;1.08)		
Hypertension vs. no hypertension	1.75 (1.52;2.01)	1.30 (1.16;1.46)	1.78 (1.55;2.04)	1.31 (1.16;1.47)	1.36 (1.14;1.63)	1.75 (1.52;2.01)	1.30 (1.16;1.46)	1.35 (1.12;1.62)			1.35 (1.12;1.62)		
Current vs. never/ previous smoking	1.48 (1.38;1.60)	1.36 (1.29;1.43)	1.51 (1.40;1.62)	1.33 (1.27;1.40)	1.13 (1.03;1.23)	1.48 (1.38;1.59)	1.36 (1.29;1.43)	1.09 (1.00;1.19)			1.09 (1.00;1.19)		
BMI per 5kg/m ²	1.21 (1.17;1.25)	1.26 (1.22;1.29)	1.21 (1.17;1.25)	1.26 (1.23;1.29)	0.96 (0.92;1.00)	1.21 (1.17;1.25)	1.25 (1.22;1.29)	0.96 (0.92;1.01)			0.96 (0.92;1.01)		
Overweight (≥25kg/m ²) vs. healthy weight(<25kg/m ²)	1.36 (1.26;1.48)	1.43 (1.34;1.52)	1.39 (1.28;1.50)	1.43 (1.35;1.52)	0.97 (0.88;1.07)	1.36 (1.26;1.47)	1.43 (1.34;1.52)	0.95 (0.86;1.05)			0.95 (0.86;1.05)		
History of AF vs. no history of AF	1.55 (1.03;2.32)	1.39 (1.14;1.71)	1.67 (1.12;2.50)	1.36 (1.11;1.67)	1.22 (0.78;1.92)	1.55 (1.03;2.32)	1.39 (1.14;1.71)	1.11 (0.71;1.75)			1.11 (0.71;1.75)		

All models were adjusted for age, Diabetes and systolic blood pressure were adjusted for each other as well as for smoking status, body mass index (BMI), lipid-lowering medication, antihypertensive medication, cholesterol and socioeconomic status. The models for hypertension, diastolic blood pressure, and atrial fibrillation were adjusted for these eight variables as well. HbA1c per 1% change was additionally adjusted for glucose-lowering medication. Smoking status was adjusted for socioeconomic status, and models for BMI and weight were adjusted for smoking status and socioeconomic status. BP = blood pressure; BMI = body mass index; AF = atrial fibrillation; HR = hazard ratio; RHR = ratio of hazard ratio's; CI = confidence interval. * For the stratification approach we assessed the association of risk factors with myocardial infarction in separate datasets for men and women. ** For the multiple-adjusted single interaction model we included sex as an interaction term with the determinant of interest i.e. $h = \exp(b_1 \cdot \text{diabetes} + b_2 \cdot \text{diabetes} + b_3 \cdot \text{sex} + b_4 \cdot \text{age} + \dots + b_5 \cdot \text{cholesterol})$, where h is the hazard ratio, $\{b_i\}$ are regression coefficients and diabetes is the index exposure variable. *** For the multiple-adjusted full interaction model, we included sex as an interaction term with both the determinant of interest and the covariables i.e. $h = \exp(b_1 \cdot \text{diabetes} + b_2 \cdot \text{diabetes} + b_3 \cdot \text{sex} + b_4 \cdot \text{age} + \dots + b_5 \cdot \text{cholesterol} + b_6 \cdot \text{sex} + b_7 \cdot \text{age} + \dots + b_8 \cdot \text{cholesterol} \cdot \text{sex} + b_9 \cdot \text{cholesterol} \cdot \text{age} + \dots + b_{10} \cdot \text{cholesterol} \cdot \text{age} \cdot \text{sex})$, where h is the hazard ratio, $\{b_i\}$ are regression coefficients and diabetes is the index exposure variable.

Conclusion

In the present example, we demonstrate that estimates of sex differences can be biased if sex-specific confounding is not considered in the model or accounted for through stratification. As the majority of studies generally only present one statistical method, the impact of sex-specific confounding on other risk factor – disease estimates is largely unknown. However, it is important to properly account for the possibility of sex-specific confounding when studying sex-specific effects and sex differences. As such, we recommend the use of a full interaction model including interaction terms between sex and each of the variables in the model.

Acknowledgements

This research has been conducted using the UK Biobank Resource (application No 2495). Permission to use the UK Biobank Resource was approved by the access subcommittee of the UK Biobank Board.

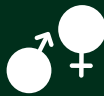
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Part 2

Sex, diabetes, and disease risk



Chapter 4

Diabetes, glycated haemoglobin, and the risk of myocardial infarction in women and men: a prospective cohort study of the UK Biobank

Marit de Jong
Mark Woodward
Sanne A.E Peters

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Abstract

Objective

Diabetes has shown to be a stronger risk factor for myocardial infarction (MI) in women than in men. Whether sex differences exist across the glycaemic spectrum is unknown. We investigated sex differences in the associations of diabetes status and glycated haemoglobin (HbA1c) with the risk of MI.

Research Design and Methods

Data were used from 471,399 (56% women) individuals without cardiovascular disease (CVD) included in the UK Biobank. Sex-specific incidence rates were calculated by diabetes status and across levels of HbA1c, using Poisson regression. Cox proportional hazards analyses estimated sex-specific hazard ratios (HR) and women-to-men ratios by diabetes status and HbA1c for MI during a mean follow-up of 9 years.

Results

Women had lower incidence rates of MI than men, regardless of diabetes status or HbA1c level. Compared with individuals without diabetes, prediabetes, undiagnosed diabetes, and previously diagnosed diabetes were associated with an increased risk of MI in both sexes. Previously diagnosed diabetes was more strongly associated with MI in women (HR 2.33 [95%CI 1.96;2.78]) than in men (1.81 [1.63;2.02]), with a corresponding women-to-men ratio of HRs of 1.29 (1.05;1.58). Each 1% higher HbA1c, independent of diabetes status, was associated with an 18% greater risk of MI in both women and men.

Conclusions

Although the incidence of MI was higher in men than in women, the presence of diabetes is associated with a greater relative risk of MI in women. However, each 1% higher HbA1c was associated with an 18% greater risk of MI in both women and men.

Introduction

Despite significant improvements in prevention and treatment, coronary heart disease (CHD) remains the leading cause of death for both women and men worldwide.¹ Diabetes is a key risk factor for CHD, and large studies and meta-analyses have provided convincing evidence that the magnitude of excess risk of CHD conferred by diabetes is stronger in women than in men.²⁻⁷ For example, previous analyses in the UK Biobank population demonstrated that the excess risk of myocardial infarction (MI) associated with diabetes was 47% greater in women than in men.³

Biological sex is known to affect the pathogenesis of metabolic disorders such as diabetes.⁷ The mechanisms underpinning the excess risk of CHD conferred by diabetes in women compared with men remain uncertain. However, previous studies have demonstrated that the differences in cardiovascular risk factors between people with and without diabetes are greater in women than in men⁸⁻¹² Other studies have shown that women's greater excess risk of diabetes-related CHD is explained by greater cardiometabolic changes before the clinical diagnosis of diabetes.⁸ Diabetes is defined by an, arguably, arbitrary threshold of glycated haemoglobin (HbA1c). However, previous large-scale studies have demonstrated that elevated HbA1c levels are also associated with an increased risk of CHD below the clinical threshold of diabetes. If the sex difference in the cardiovascular complications of diabetes is present across the glucose intolerance continuum, both before and after the clinical diagnosis of diabetes, it could be hypothesised that the association of HbA1c and the risk of CHD is stronger in women than in men¹³ Previous studies of sex differences in the association between HbA1c levels and the risk of CHD are sparse and have been inconclusive.¹⁴⁻¹⁸ As such, it remains unclear whether sex differences in the risk of CHD exist across the glycaemic spectrum. In this study, we used data from the UK Biobank to investigate the sex-specific association and the sex differences between various levels of diabetes status and levels of HbA1c and the risk of MI.

Methods

Study design and participants

The UK Biobank is a large prospective cohort of >500,000 participants aged between 40-69 years at study baseline between 2006 and 2010. Details of the study procedures for the UK Biobank have been described elsewhere.¹⁹ In short, individuals who lived near one of 22 assessment centres across the UK were invited to enter the cohort. Of these, 5.5% agreed to participate and attended the baseline assessment, which included questionnaires on lifestyle and medical history and physical, and functional measurements.^{20,21} In addition, blood, urine, and saliva samples were taken. All participants provided written informed consent. Participants with a history of cardiovascular disease (CVD) (self-reported or hospital admission of MI, stroke, or angina pectoris, n=30,565) at baseline were excluded from the current analyses. We also excluded those with missing data on both self-reported diabetes and HbA1c (n=572).

HbA1c and diabetes status

A medical history of diabetes, including age at first diagnosis of diabetes and the use of medications for diabetes regulation, were self-reported. In 438,259 (93%) of the included participants, HbA1c was measured using high-performance liquid chromatography analysis on a BioRad VARIANT II Turbo.²² We categorised diabetes status into four groups: 1. no diabetes (i.e. no previous diagnosis of diabetes, HbA1c level <5.7% (39mmol/mol), and no use of glucose-lowering medication); 2. prediabetes (i.e. no previous diagnosis of diabetes, HbA1c between $\geq 5.7\%$ (39mmol/mol) and <6.5% (48mmol/mol)²³, and no use of glucose-lowering medication); 3. undiagnosed diabetes (no previous diagnosis of diabetes, HbA1c $\geq 6.5\%$ (48mmol/mol), and no use of glucose-lowering medication); 4. previously diagnosed diabetes (self-reported diagnosis of diabetes and/or the use of glucose-lowering medication). Participants with missing data on HbA1c but without diabetes or glucose-lowering medication and participants with missing data on diabetes but with HbA1c <5.7% (39mmol/mol) and no use of glucose-lowering medication were classified as not having diabetes. Participants with missing data on diabetes but with HbA1c $\geq 6.5\%$ (48mmol/mol) and no use of glucose-lowering medication were classified as having undiagnosed diabetes. Those with missing data on diabetes but with HbA1c $\geq 5.7\%$ - 6.5% (≥ 39 mmol/mol – 48mmol/mol) and no use of glucose-lowering medication were classified as having prediabetes.

Study outcomes

The study outcome was incident non-fatal or fatal MI, defined by codes I21, I22, I23, I24.1 or I25.2 in the tenth edition of the International Classification of Diseases (ICD-10). Outcome adjudication involved linkage with hospital admissions data from England, Scotland, and Wales and the national death register to identify the date of the first known MI after the date of baseline assessment.²⁴ Follow-up started at inclusion in the UK Biobank and ended on February 1 2018, date of death, or upon the first non-fatal or fatal MI, for all participants.

Statistical analyses

Sex-specific baseline characteristics are presented by diabetes status. Although incidence rates are less likely to be translated to, and applied in, other populations because of the background variation in risks across populations, they should be considered when making clinical decisions. Therefore, we examined the sex-specific effects and sex differences in the association of diabetes status and HbA1c with MI both on the absolute and relative scales.

Sex-specific incidence rates and women-minus-men differences of rate differences of MI were calculated by diabetes status and across levels of HbA1c (in participants with previously diagnosed diabetes) using Poisson regression models.²⁵ For diabetes status, the model was adjusted for age, smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, the Townsend social deprivation score, and interaction terms between each variable and sex. The model for levels of HbA1c was additionally adjusted for the use of glucose-lowering medication, again with interaction terms between each variable and sex. The interaction terms of diabetes status and levels of Hba1c with sex were used to obtain the

sex-specific incidence rates and women-minus-men differences of rate differences. Interaction terms of the other variables with sex were included to adjust for sex-specific confounding, which is identical to stratification by sex, with the advantage of extracting sex-specific estimates and sex differences from one model.²⁵

Cox regression models were used to obtain the sex-specific hazard ratios (HRs) and the women-to-men ratio of HRs (RHRs) with 95% CIs of MI by diabetes status.²⁵ In participants with previously diagnosed diabetes, we also estimated HRs and RHRs across levels of HbA1c, using participants without previously diagnosed diabetes as the reference (including prediabetes and undiagnosed diabetes). Three levels of adjustments were used. For diabetes status, the first model was adjusted for age. The second model was additionally adjusted for smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, and the Townsend social deprivation score. The third model included the interaction terms between each variable in the second model and sex. Models for levels of HbA1c were additionally adjusted for the use of glucose-lowering medication, again with sex interactions in the third model. For all three models, an interaction term between the determinant of interest (diabetes status or levels of HbA1c) and sex was used to obtain the sex-specific HRs and women-to-men RHRs. The third model included interaction terms between each variable in the second model and sex to additionally adjust for sex-specific confounding.

Penalized spline models with four degrees of freedom were used to examine the sex-specific association between baseline HbA1c and MI. Adjustments were as in the second model for levels of HbA1c, with additional adjustment for history of diabetes. The sex-specific penalized spline models were obtained using stratification by sex. Therefore, additional adjustments for each variable in the model and sex were not included.

Cox analyses estimated the HRs and RHR between a 1% increase in baseline HbA1c and MI. In prespecified subgroup analyses, results were stratified for age (<60 years and ≥ 60 years), BMI (<25kg/m² and ≥ 25 kg/m²), socioeconomic states (SES) on the basis of the Townsend deprivation index (> -0.56 (lower SES) and ≤ -0.56 (higher SES)), and use of glucose-lowering medication. Two levels of adjustments were used. The first model was adjusted for age, smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, the Townsend social deprivation score, use of glucose-lowering medication, and history of diabetes. The second model included the interaction terms between each variable in the first model and sex. Again, interaction terms between 1% increase in baseline HbA1c and sex in both models were used to obtain the sex-specific HRs and women-to-men RHRs.

To ensure that the association between 1% increase in baseline HbA1c and MI was not explained by diabetes status, the analysis was adjusted for history of diabetes. However, by adjusting for history of diabetes, we may have adjusted away some of the effects of higher HbA1c levels. Therefore, a sensitivity analysis was performed without adjusting for history of diabetes. Furthermore, sensitivity analyses were performed in which analyses were additionally adjusted

for depression and sleep characteristics, again with interaction terms between each variable in the model and sex. Moreover, sex-specific subgroups for depression and sleep characteristics were included in the analyses of 1% increase in HbA1c and MI. Available case analyses were conducted using StataSE13 and RStudio version 1.1.456.

Results

Overall, 471,399 participants were included (56% women). At baseline, 6.0% of men and 3.5% of women were previously diagnosed with diabetes with a median HbA1c of 6.7% (50mmol/mol) in both sexes (Table 1). Over a mean follow-up of 8.9 years, 7,316 (30% women) MI events were documented. The incidence of MI per 10,000 person-years was 9.3 (95% CI: 8.9; 9.7) for women and 27.6 (26.8; 28.3) for men.

Table 1. Baseline characteristics by sex and diabetes status.

	Women				Men					
	All n=263,024	No diabetes n=221,592	Prediabetes n=30,939	Undiagnosed Diabetes n=1,253	Previously diagnosed diabetes n=9,240	All n=208,375	No diabetes n=170,672	Prediabetes n=23,486	Undiagnosed diabetes n=1,801	Previously diagnosed diabetes n=12,416
General characteristics										
Age, years	56.2 (8.0)	55.6 (8.0)	59.8 (6.6)	58.9 (6.9)	58.3 (7.7)	56.3 (8.2)	55.7 (8.3)	58.6 (7.6)	57.3 (7.8)	59.4 (7.2)
Ethnicity										
White	247,983 (95%)	211,266 (96%)	27,885 (91%)	1,003 (81%)	7,829 (86%)	195,940 (95%)	162,750 (96%)	20,864 (90%)	1,519 (85%)	10,807 (88%)
Non-white/mixed	14,006 (5%)	9,569 (4%)	2,872 (9%)	235 (19%)	1,330 (15%)	11,271 (5%)	7,072 (4%)	2,433 (10%)	262 (15%)	1,504 (12%)
Socioeconomic status										
High	177,791 (68%)	152,028 (69%)	19,949 (65%)	698 (56%)	5,116 (55%)	139,662 (67%)	116,866 (69%)	14,636 (62%)	993 (55%)	7,167 (58%)
Low	84,921 (32%)	69,310 (31%)	10,950 (35%)	553 (44%)	4,108 (45%)	68,441 (33%)	53,594 (31%)	8,813 (38%)	803 (45%)	5,231 (42%)
Smoking										
Never	157,131 (60%)	133,337 (60%)	17,631 (57%)	728 (59%)	5,435 (59%)	104,685 (50%)	89,200 (52%)	9,666 (42%)	719 (40%)	5,100 (41%)
Past	81,592 (31%)	69,100 (31%)	9,184 (30%)	378 (31%)	2,930 (32%)	76,900 (37%)	61,270 (36%)	9,175 (39%)	755 (42%)	5,700 (46%)
Current	23,067 (9%)	18,222 (8%)	3,931 (13%)	131 (11%)	783 (9%)	25,752 (12%)	19,499 (11%)	4,452 (19%)	308 (17%)	1,493 (12%)

Table 1. Baseline characteristics by sex and diabetes status. (continued)

	Women				Men					
	All n=263,024	No diabetes n=221,592	Prediabetes n=30,939	Undiagnosed Diabetes n=1,253	Previously diagnosed diabetes n=9,240	All n=208,375	No diabetes n=170,672	Prediabetes n=23,486	Undiagnosed diabetes n=1,801	Previously diagnosed diabetes n=12,416
Diabetes characteristics										
diabetes duration, years	NA	NA	NA	NA	8.4 (10.0)	NA	NA	NA	NA	8.5 (10.1)
Median diabetes duration, years	NA	NA	NA	NA	5 (2-10)	NA	NA	NA	NA	5 (2-10)
Diabetes type 1 ^a	NA	NA	NA	NA	500 (5%)	NA	NA	NA	NA	531 (4%)
HbA1c, %	5.4 (0.5)	5.3 (0.3)	5.9 (0.2)	7.4 (1.5)	6.9 (1.3)	5.5 (0.7)	5.3 (0.3)	5.9 (0.2)	7.7 (1.6)	7.0 (1.3)
Median HbA1c, % (IQR)	5.4 (5.1-5.6)	5.3 (5.1-5.5)	5.8 (5.8-6)	6.9 (6.7-7.5)	6.7 (6.7-5)	5.4 (5.1-5.6)	5.3 (5.1-5.5)	5.9 (5.8-6)	7.1 (6.7-8)	6.7 (6.1-7.6)
HbA1c, mmol/mol	35.7 (5.8)	34.0 (3.0)	41.0 (1.9)	58.0 (16.7)	51.8 (14.1)	36.2 (7.1)	33.9 (3.0)	41.1 (2.0)	60.8 (17.9)	52.8 (13.9)
Median HbA1c, mmol/mol (IQR)	35.1 (32.7-37.6)	34.4 (32.2-36.3)	40.4 (39.5-41.9)	51.8 (49.5-58.5)	49.4 (42.0-58.5)	35.1 (32.7-37.8)	34.3 (32.1-36.2)	40.5 (39.6-42.0)	53.6 (49.9-64.3)	50.1 (43.2-59.2)
Measurements										
BMI, kg/m ²	27 (5.1)	26.5 (4.8)	28.8 (5.7)	32.7 (6.3)	31.8 (6.7)	27.7 (4.2)	27.3 (3.9)	28.9 (4.6)	31.4 (5.2)	30.7 (5.3)
Systolic BP, mmHg	135.2 (19.2)	134.3 (19.1)	140.3 (19.1)	146.74 (19.4)	139.2 (17.7)	141.1 (17.4)	140.5 (17.3)	143.9 (17.8)	147.9 (18.1)	142.6 (16.6)
Diastolic BP, mmHg	80.8 (10)	80.5 (10.0)	82.4 (9.9)	86.3 (10.2)	80.9 (9.7)	84.5 (9.9)	84.4 (9.9)	85.6 (9.9)	88.8 (10.2)	82.6 (9.4)
Cholesterol, mmol/L	5.9 (1.1)	5.9 (1.1)	6.1 (1.2)	6.1 (1.3)	4.8 (1.1)	5.6 (1.1)	5.7 (1.0)	5.6 (1.1)	5.7 (1.2)	4.4 (1.0)

Table 1. Baseline characteristics by sex and diabetes status. (continued)

	Women				Men					
	All n=263,024	No diabetes n=221,592	Prediabetes n=30,939	Undiagnosed Diabetes n=1,253	Previously diagnosed diabetes n=9,240	All n=208,375	No diabetes n=170,672	Prediabetes n=23,486	Undiagnosed diabetes n=1,801	Previously diagnosed diabetes n=12,416
Prescribed medication										
Antidiabetic medication										
No medication	NA	NA	NA	NA	3,588 (39%)	NA	NA	NA	NA	4,397 (35%)
Oral	NA	NA	NA	NA	4,109 (44%)	NA	NA	NA	NA	6,045 (49%)
Insulin	NA	NA	NA	NA	834 (9%)	NA	NA	NA	NA	1,015 (8%)
Oral + Insulin	NA	NA	NA	NA	709 (8%)	NA	NA	NA	NA	959 (8%)
Antihypertensive medication	32,317 (12%)	21,483 (10%)	5,899 (19%)	281 (22%)	4,654 (50%)	32,553 (16%)	20,265 (12%)	4,893 (21%)	384 (21%)	7,011 (57%)
Lipid-lowering medication	23,057 (9%)	12,680 (5-7%)	4,583 (15%)	227 (18%)	5,567 (60%)	29,535 (14%)	16,204 (10%)	4,664 (20%)	315 (18%)	8,352 (67%)

Data are mean (SD) or n (%) unless otherwise indicated. BMI = body mass index; BP = blood pressure; NA = not applicable. [^]Participants with self-reported diabetes onset before the age of 30 and using insulin were considered to have type 1 diabetes. Due to missing data, not all variables included add up to n = 208,375 for men and n = 263,024 for women.

Sex-specific rates of MI according to diabetes status

Following multiple adjustments, women had lower incidence rates of MI per 10,000 person-years than men for no diabetes (8.7 [8.2;9.2] vs. 25.4 [24.5;26.3]), prediabetes (10.9 [9.8;12.0] vs. 29.7 [27.5;31.9]), undiagnosed diabetes (14.3 [8.4;20.1] vs. 38.9 [30.2;47.6]), and previously diagnosed diabetes (20.4 [17.1;23.6] vs. 46.1 [41.4;50.8]) (Figure 1A and Supplemental table I). Similar results were found for individuals without previously diagnosed diabetes and those with previously diagnosed diabetes at different levels of HbA1c (Figure 1B and Supplemental table II).

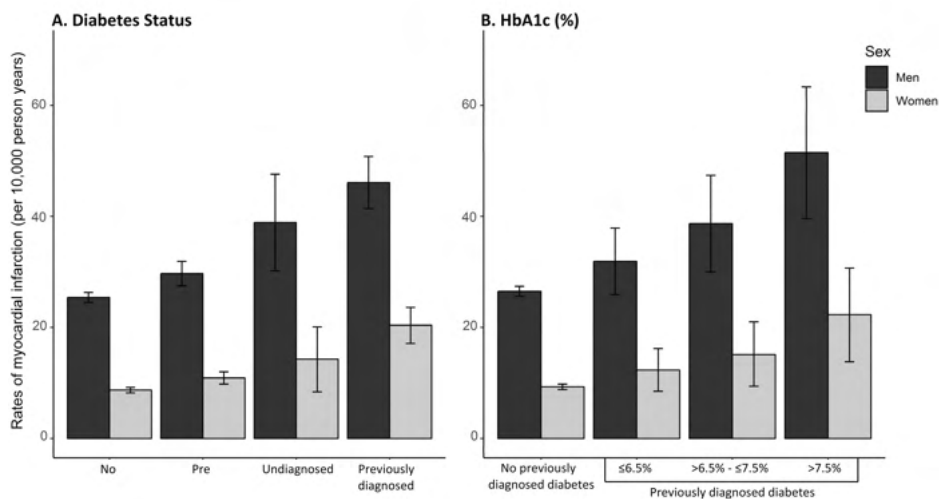


Figure 1. Multiple-adjusted rates of myocardial infarction (per 10,000 person years) by sex for diabetes status (A) and levels of HbA1c (B). Analyses on diabetes status were adjusted for age, smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, and the Townsend social deprivation score, with interaction terms between each variable and sex. Analyses for levels of HbA1c were additionally adjusted for the use of glucose-lowering medication, again with interaction terms between each variable and sex. No previously diagnosed diabetes includes no diabetes, prediabetes, and undiagnosed diabetes. HbA1c 6.5% = 48mmol/mol; HbA1c 7.5% = 58mmol/mol. Pre = prediabetes.

Diabetes status and the risk of MI

Compared with no diabetes, prediabetes, undiagnosed diabetes, and previously diagnosed diabetes were each associated with an increased risk of MI in both sexes in each of the models (Figure 2A and Supplemental table III). Prediabetes was more strongly associated with MI in women than in men in the age-adjusted and multiple-adjusted model without, but not with, sex*confounder interaction terms. In the full interaction model, compared with no diabetes, previously diagnosed diabetes was associated with a greater increased risk of MI in women (2.33 [1.96;2.78]) than in men (1.81 [1.63;2.02]), with a corresponding RHR of 1.29 (1.05;1.58).

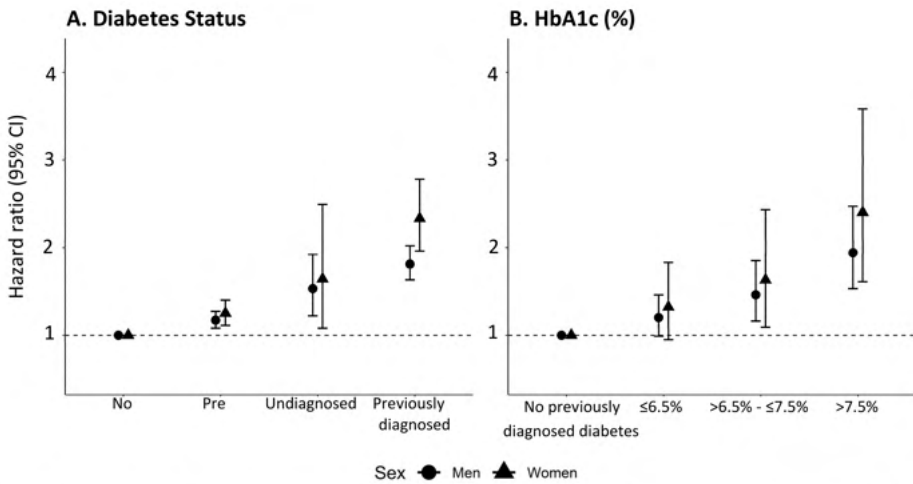


Figure 2. Multiple-adjusted sex-specific hazard ratios for myocardial infarction by diabetes status (reference = no diabetes) (A) and levels of HbA1c (reference = no previously diagnosed diabetes) (B). Analyses on diabetes status were adjusted for age, smoking, BMI, systolic blood pressure, use of antihypertensive medication, total cholesterol, use of lipid-lowering medication, and the Townsend social deprivation score, with interaction terms between each variable and sex. Analyses for levels of HbA1c were additionally adjusted for the use of glucose-lowering medication. No previously diagnosed diabetes includes participants categorized as no diabetes, prediabetes, and undiagnosed diabetes. HbA1c 6.5% = 48mmol/mol; HbA1c 7.5% = 58mmol/mol. Pre = prediabetes.

Levels of HbA1c among people with diabetes and the risk of MI

In the multiple-adjusted model without sex*confounder interactions, compared with those without previously diagnosed diabetes (including prediabetes and undiagnosed diabetes), the risk of MI among people with previously diagnosed diabetes was higher in both women and men at different HbA1c levels, except for men with a HbA1c $\le 6.5\%$ (48mmol/mol). Different HbA1c levels were found to be more strongly associated with MI in women with previously diagnosed diabetes than in men. These sex-differences were no longer statistically significant in the full interaction model. The women-to-men RHRs were 1.39 (1.03;1.88) for $\le 6.5\%$ (48mmol/mol), 1.50 (1.10;2.05) for >6.5 to $\le 7.5\%$ (>48 mmol/mol - ≤ 58 mmol/mol), and 1.69 (1.28;2.23) for $>7.5\%$ (58mmol/mol) in the multiple-adjusted model with main effects for confounders only but were 1.09 (0.75;1.60), 1.11 (0.70;1.77), and 1.24 (0.78;1.97), respectively, in the full interaction model (Figure 2B and Supplemental table IV).

HbA1c among all individuals and the risk of MI

Independent of diabetes status, there was an approximate log-linear association between levels of HbA1c and MI in both sexes (Figure 3A and 3B). In the multiple-adjusted model without sex*confounder interactions, a 1% increase in HbA1c was more strongly associated with MI in women than men: the HRs were 1.24 (1.20;1.28) in women and 1.14 (1.10;1.19) in men, and the women-to-men RHR was 1.09 (1.03;1.14). After including the sex*confounder interactions, the HRs were 1.18 (1.13;1.24) in women and 1.18 (1.13;1.23) in men. The corresponding RHR was 1.00 (0.94;1.07). There was no evidence for differences in the multiple-adjusted association between

HbA1c and MI across sex-specific subgroups in the multiple-adjusted models with sex*confounder interactions. Similarly, no significant differences in women-to-men RHRs by age, BMI, SES, and use of glucose-lowering medication were found (Figure 4 and Supplemental table V).

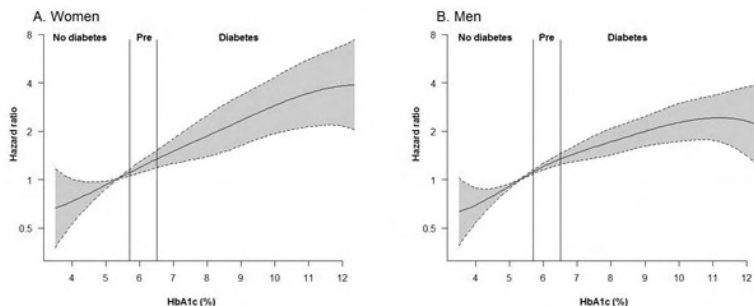


Figure 3. Multiple-adjusted hazard ratios for myocardial infarction according to baseline HbA1c, stratified by women (A) and men (B). Penalized spline models with 4 degrees of freedom and reference HbA1c set at 5.3% (34mmol/mol). Analyses were adjusted for age, smoking, BMI, systolic blood pressure, antihypertensive medication, total cholesterol, use of lipid-lowering medication, Townsend score, history of diabetes (no previously diagnosed diabetes including prediabetes and undiagnosed, diabetes), and the use of glucose-lowering medication. Shaded lines show 95% confidence intervals. Vertical lines at HbA1c 5.7-7% (39mmol/mol) and 6.5% (48mmol/mol) show the threshold for prediabetes and diabetes, respectively. The figure was trimmed at a HbA1c level of 12%.

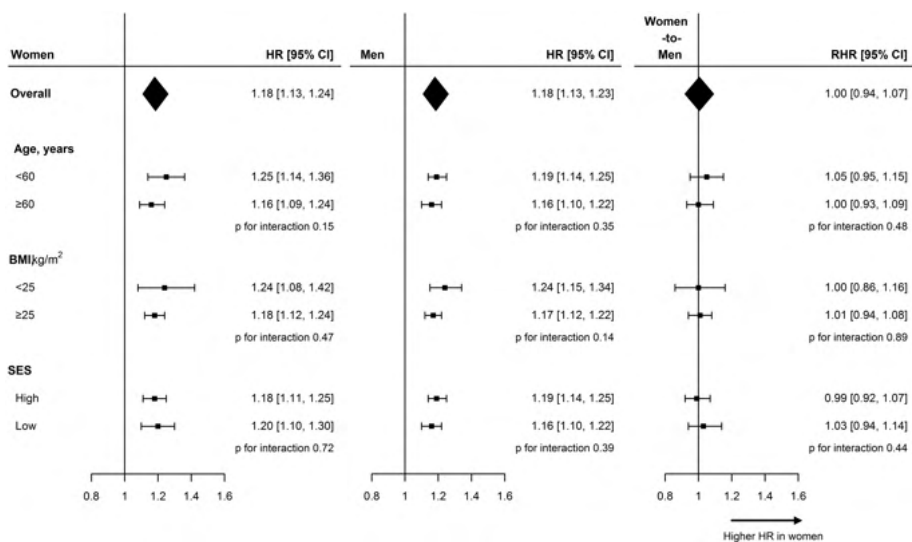


Figure 4. Multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios for myocardial infarction per 1% HbA1c change overall and in subgroups. Analyses were adjusted for age, smoking, BMI, systolic blood pressure, antihypertensive medication, total cholesterol, use of lipid-lowering medication, the Townsend social deprivation score, history of diabetes (no previously diagnosed diabetes including prediabetes and undiagnosed, diabetes), and the use of glucose-lowering medication, with interaction terms between each variable and sex. P-values for the sex-specific hazard ratios represent the two-way interaction terms including HbA1c and the variable that was stratified for. P-values for the women-to-men ratio of hazard ratios represent the three-way interaction terms including sex, HbA1c, and the variable that was stratified for. HR = hazard ratio; RHR = ratios of hazard ratios; BMI = body mass index.

Sensitivity analyses

There was no evidence of a difference in the multiple-adjusted association between HbA1c and MI after excluding history of diabetes from the main analysis (Supplemental table VI). Furthermore, the results of the multiple-adjusted analyses on diabetes status, levels of HbA1c, and 1% HbA1c increase with MI were virtually identical to the main analyses after adjusting for depression and sleep characteristics (Supplemental tables VII – X). Moreover, there was no evidence for sex differences in the multiple-adjusted association between 1% HbA1c increase and MI across sex-specific subgroups for depression and sleep characteristics because there was no evidence of significant differences in women-to-men RHRs by depression and sleep characteristics (Supplemental table XI).

Discussion

This study, which included 471,399 UK Biobank participants without prevalent CVD, showed that although the incidence of MI was considerably higher in men than in women for diabetes status and across levels of HbA1c, the presence of previously diagnosed diabetes was associated with a greater excess relative risk of MI in women than men. Each 1% higher HbA1c, independent of diabetes status, was associated with an 18% greater risk of MI in both women and men.

This study adds to the growing body of evidence on sex differences in the risk of MI, and other CVD phenotypes, associated with diabetes.^{2-6,26,27} Studies assessing sex-specific effects and sex differences in the association between diabetes status by HbA1c thresholds, including prediabetes and/or undiagnosed diabetes, and major cardiovascular events are limited and have provided mixed results.¹⁴⁻¹⁸ A large cohort study including >140,000 Mexican adults showed that both undiagnosed and previously diagnosed diabetes were associated with a higher risk of CVD-related mortality, with higher risks among individuals with poorer glycaemic control.¹⁴ No sex differences in the risk of mortality of vascular, renal and infectious causes according to diabetes status were found.¹⁴ The Atherosclerosis Risk in Communities (ARIC) study, which included 10,844 participants in the US without previously diagnosed diabetes, showed that both men and women with HbA1c-defined prediabetes or undiagnosed diabetes had a higher CVD risk.¹⁵ Although sex-stratified analyses provided some evidence for a stronger association of prediabetes and undiagnosed diabetes with peripheral artery disease in women than men, no statistically significant sex differences were present for CHD and/or ischemic stroke.¹⁵ A cohort study among 22,106 participants in the UK showed that undiagnosed, controlled (HbA1c < 5.7% [< 39 mmol/mol]), and uncontrolled (HbA1c $\geq 6.5\%$ [≥ 48 mmol/mol]) diabetes and diabetes with moderately raised HbA1c (HbA1c 5.7–<6.5% [39 –< 48 mmol/mol]), but not prediabetes, were associated with an increased risk of cardiovascular mortality. After stratification by sex, mixed results were found regarding the presence and magnitude for the association between diabetes status and CVD mortality.¹⁷ Our study also showed that prediabetes was associated with an increased risk of MI in both sexes, with evidence for stronger effects in women than men. However, this sex difference attenuated to unity and was no longer statistically significant in analyses that also accounted for sex-specific confounding effects. Similarly, while our analyses that did not account for sex-specific

confounding showed that the relationship between HbA1c and the risk of MI was stronger in women than men, accounting for sex-specific confounding demonstrated that a 1% increase in HbA1c was associated with an 18% greater risk of MI in both sexes.

Sex differences in the uptake and provision of healthcare for diabetes or differences in underlying biological mechanisms of diabetes may explain the greater excess risk of MI conferred by diabetes in women. The National Diabetes Audit among 2 million individuals with diabetes in England and Wales showed that women were 15% less likely to receive assessment of critical care processes as recommended by the guidelines compared with men.²⁸ In addition, only 30% of women and 33% of men attained all treatment targets for HbA1c, cholesterol and blood pressure.²⁸ A population-based study in Italy also showed that women were less likely to receive recommended care and to attain treatment targets for HbA1c and LDL-cholesterol.²⁹ In contrast, a large cohort study performed in the US among 18,000 individuals with diabetes demonstrated that women were more likely to receive recommended care than men.³⁰ Overall, previous studies on sex differences in the provision of healthcare for diabetes have reported mixed results regarding the presence, magnitude, and direction of sex differences in healthcare provision and no final conclusions about the impact of differences in healthcare provision on sex disparities related to cardiovascular complications can be drawn. Notably, sex differences in healthcare provision are also seen in non-diabetic populations, suggesting that sex differences in care alone are unlikely to be the only cause of the excess cardiovascular risk in women with diabetes.^{31,32}

Biological differences between the sexes may therefore play a key role in explaining these sex differences. Previous studies suggested that the cardiovascular risk profile in women needs to deteriorate further than men before they develop overt diabetes.⁹⁻¹² Consequently, women may be exposed to adverse cardiovascular risk factors over a longer time period. This hypothesis is in line with findings of a study that showed that the average duration of prediabetes was 10·3 years in women and 8·5 years in men.³³ The Asia Pacific Cohort Studies Collaboration, including 161,214 individuals from the Asia-Pacific region, showed that differences in blood pressure, lipids and BMI among individuals with and without diabetes was larger in women than men.³⁴ A recent study among 3,400 Dutch individuals showed that several cardiovascular risk factors were already more elevated in women with prediabetes than men, and these difference were even more pronounced in individuals with type 2 diabetes compared to individuals with a normal glucose metabolism.⁸ In addition, increases in HbA1c among individuals without type 2 diabetes was more strongly associated with systolic and diastolic blood pressure, HDL cholesterol and LDL cholesterol in women than men.⁸ In our study, we found no evidence of a sex difference in the association between increases in HbA1c and the risk of MI. Instead, the notion that the sex-specific effects attenuated after adjustment for sex-specific confounders suggest that other sex-specific pathways may be involved. A recent Mendelian randomization study showed that the higher BMI led to higher risk of type 2 diabetes in women than in men.³⁵ Hence, it may be that the sex differences in the association between diabetes and MI occur before the onset of diabetes.

Another possible explanation for the greater relative risk of MI found in women with diabetes compared to men is that this may simply be a mathematical artefact as a result of the lower cardiovascular risk in women. However, meta-analyses of sex differences in the association between blood pressure and high BMI with CVD showed no sex difference in the relative risks. In addition, for total cholesterol associated with CVD there is some indication of higher relative risks in men. Thus, it seems unlikely that the finding of a greater relative risk of MI associated with diabetes in women compared with men is an inevitable consequence of women's lower absolute rates, compared with men.^{9,36}

It is surprising that while diabetes was associated with a greater relative risk of MI in women than men, increases in HbA1c levels did not show any sex differences. Reasons for this apparent discrepancy warrant further investigation, ideally in studies with repeated HbA1c measurements so as to assess the potential impact of sex differences in glycaemic control post baseline assessment.

The strengths of this study include its prospective design, large sample size, and the extensive phenotypic detail available on all participants. This study also has some limitations. First, people with a higher socioeconomic status and of Caucasian background are overrepresented in the UK Biobank, which may have limited the generalisability of our results. Second, diagnosis of diabetes, CVD, and the use of diabetes medications were self-reported, which may have resulted in some misclassification in both sexes. However, there is no reason to assume that women and men reported differently on these aspects. Third, participants with missing data on self-reported diabetes or HbA1c measurements were allocated to the best fitting diabetes status category by using the available information, this may have resulted in some additional misclassification, most likely resulting in underestimation of the sex-specific effects that were found in this study. Fourth, although we adjusted for several major confounding factors, including sex-specific confounding, residual confounding may be present.

In conclusion, the presence of diabetes is associated with a greater relative risk of MI in women than men. However, each 1% higher HbA1c, independent of diabetes status, was associated with an 18% greater risk of MI in both women and men.

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Supplemental table I. Unadjusted and multiple-adjusted rates of myocardial infarction (per 10,000 person-years) by sex and diabetes status.

	Women	Men	Difference of rate differences (women-men)
Unadjusted			
No diabetes	7.7 (7.3;8.1)	24.0 (23.2;24.8)	Reference
Prediabetes	15.1 (13.7;16.6)	38.2 (35.6;40.8)	-6.8 (-9.9;-3.6)
Undiagnosed diabetes	23.2 (14.3;32.2)	53.0 (41.7;64.3)	-13.5 (-27.9;1.0)
Previously diagnosed diabetes	27.0 (23.4;30.5)	53.6 (49.2;57.9)	-10.3 (-16.0;-4.6)
Multivariable-adjusted*			
No diabetes	8.7 (8.2;9.2)	25.4 (24.5;26.3)	Reference
Prediabetes	10.9 (9.8;12.0)	29.7 (27.5;31.9)	-2.1 (-4.8;0.5)
Undiagnosed diabetes	14.3 (8.4;20.1)	38.9 (30.2;47.6)	-7.9 (-18.5;2.6)
Previously diagnosed diabetes	20.4 (17.1;23.6)	46.1 (41.4;50.8)	-9.0 (-14.8;-3.2)

* The multivariable-adjusted model is adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, and interaction terms between each variable and sex.

Supplemental table II. Unadjusted and multiple-adjusted rates of myocardial infarction (per 10,000 person-years) by sex and HbA1c levels.

	Women	Men	Difference of rate differences (women-men)
Unadjusted			
No previously diagnosed diabetes±	8.7 (8.3;9.0)	25.9 (25.2;26.7)	Reference
≤6.5%	18.9 (14.2;23.5)	42.4 (36.3;48.6)	-6.3 (-14.0;1.44)
6.5 - ≤7.5%	27.1 (20.1;34.1)	52.5 (44.3;60.6)	-8.1 (-18.9;2.6)
>7.5%	41.6 (32.5;50.8)	72.3 (62.2;82.4)	-13.4 (-27.0;0.2)
Multivariable-adjusted*			
No previously diagnosed diabetes±	9.3 (8.8;9.8)	26.5 (25.6;27.4)	Reference
≤6.5%	12.3 (8.5;16.2)	31.9 (25.9;37.9)	-2.4 (-9.7;4.9)
6.5 - ≤7.5%	15.2 (9.4;21.0)	38.7 (30.0;47.4)	-6.3 (-17.0;4.4)
>7.5%	22.3 (13.8;30.7)	51.5 (39.6;63.3)	-12.0 (-26.8;2.8)

* The multivariable-adjusted model is adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, glucose-lowering medication, and interaction terms between each variable and sex. HbA1c 6.5% = 48mmol/mol; HbA1c 7.5% = 58mmol/mol.

Supplemental table III. Age-adjusted and multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction according to diabetes status

	Women, n (%)	Men, n (%)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Age-adjusted model					
No diabetes	1,533 (0.7%)	3,659 (2.1%)	1.0	1.0	NA
Prediabetes	417 (1.4%)	792 (3.4%)	1.58 (1.42;1.77)	1.36 (1.26;1.47)	1.16 (1.02;1.33)
Undiagnosed diabetes	26 (2.1%)	84 (4.7%)	2.55 (1.73;3.76)	2.03 (1.63;2.52)	1.26 (0.81;1.96)
Previously diagnosed diabetes	221 (2.4%)	584 (4.7%)	3.02 (2.62;3.48)	1.85 (1.69;2.02)	1.63 (1.38;1.93)
Multiple-adjusted - main effects model*					
No diabetes	1,404 (0.7%)	3,392 (2.1%)	1.0	1.0	NA
Prediabetes	390 (1.3%)	739 (3.4%)	1.32 (1.18;1.48)	1.14 (1.05;1.24)	1.15 (1.00;1.32)
Undiagnosed diabetes	23 (2%)	78 (4.7%)	1.71 (1.13;2.58)	1.51 (1.20;1.89)	1.13 (0.71;1.81)
Previously diagnosed diabetes	194 (2.3%)	520 (4.6%)	2.66 (2.27;3.11)	1.72 (1.55;1.91)	1.54 (1.29;1.84)
Multiple-adjusted - full interaction model**					
No diabetes	1,404 (0.7%)	3,392 (2.1%)	1.0	1.0	NA
Prediabetes	390 (1.3%)	739 (3.4%)	1.25 (1.11;1.40)	1.17 (1.08;1.27)	1.07 (0.93;1.23)
Undiagnosed diabetes	23 (2%)	78 (4.7%)	1.64 (1.08;2.49)	1.53 (1.22;1.92)	1.07 (0.67;1.72)
Previously diagnosed diabetes	194 (2.3%)	520 (4.6%)	2.33 (1.96;2.78)	1.81 (1.63;2.02)	1.29 (1.05;1.58)

*The main effects model is adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, and the Townsend social deprivation score. **The full interaction model is additionally adjusted for interaction terms between each variable and sex. NA = not applicable; HR = hazard ratio; RHR = ratio of hazard ratios; n (%) = number of events.

Supplemental table IV. Age-adjusted and multiple-adjusted hazard ratios and ratios of hazard ratios of MI according to levels of glycaemia.

	Women, n (%)	Men, n (%)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Age-adjusted model					
No previously diagnosed diabetes \pm	1,976 (0.8%)	4,535 (2.3%)	1.0	1.0	NA
HbA1c \leq 6.5%	64 (1.7%)	183 (3.7%)	1.95 (1.52;2.50)	1.33 (1.14;1.54)	1.47 (1.10;1.97)
HbA1c $>$ 6.5% - \leq 7.5%	58 (2.4%)	160 (4.6%)	2.58 (1.99;3.35)	1.65 (1.41;1.94)	1.56 (1.15;2.12)
HbA1c $>$ 7.5%	80 (3.7%)	198 (6.3%)	4.41 (3.53;5.52)	2.53 (2.20;2.92)	1.74 (1.34;2.27)

Supplemental table IV. Age-adjusted and multiple-adjusted hazard ratios and ratios of hazard ratios of MI according to levels of glycaemia. (continued)

	Women, n (%)	Men, n (%)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Multiple-adjusted - main effects model*					
No previously diagnosed diabetes \pm	1,817 (0.8%)	4,209 (2.3%)	1.0	1.0	NA
HbA1c \leq 6.5%	58 (1.6%)	168 (3.6%)	1.56 (1.18;2.06)	1.12 (0.93;1.35)	1.39 (1.03;1.88)
HbA1c >6.5% - \leq 7.5%	56 (2.5%)	151 (4.7%)	2.02 (1.49;2.74)	1.35 (1.09;1.68)	1.50 (1.10;2.05)
HbA1c >7.5%	73 (3.6%)	179 (6.2%)	3.03 (2.28;4.03)	1.79 (1.44;2.24)	1.69 (1.28;2.23)
Multiple-adjusted - full interaction model**					
No previously diagnosed diabetes \pm	1,817 (0.8%)	4,209 (2.3%)	1.0	1.0	NA
HbA1c \leq 6.5%	58 (1.6%)	168 (3.6%)	1.32 (0.95;1.83)	1.20 (0.99;1.46)	1.09 (0.75;1.60)
HbA1c >6.5% - \leq 7.5%	56 (2.5%)	151 (4.7%)	1.63 (1.09;2.43)	1.46 (1.16;1.85)	1.11 (0.70;1.77)
HbA1c >7.5%	73 (3.6%)	179 (6.2%)	2.40 (1.61;3.58)	1.94 (1.53;2.47)	1.24 (0.78;1.97)

*The main effects model is adjusted for age plus smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, and glucose-lowering medication. **The full interaction model is additionally adjusted for interaction terms between each variable and sex. \pm No previously diagnosed diabetes, including prediabetes and undiagnosed diabetes. NA = not applicable; HR = hazard ratio; RHR = ratio of hazard ratios. n (%) = number of events. HbA1c 6.5% = 48mmol/mol; HbA1c 7.5% = 58mmol/mol.

Supplemental table V. Multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction per 1% HbA1c change, stratified by age, BMI, socioeconomic status, and use of glucose-lowering medication.

	Women, n (%)	Men, n (%)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)	P for interaction
Multiple-adjusted main effects model*						
Overall	1,936 (0.8%)	4,518 (2.5%)	1.24 (1.20;1.28)	1.14 (1.10;1.19)	1.09 (1.03;1.14)	NA
Age						
<60	669 (0.5%)	1,830 (1.7%)	1.33 (1.23;1.43)	1.17 (1.11;1.22)	1.13 (1.04;1.24)	
\geq 60	1,267 (1.3%)	2,688 (3.5%)	1.21 (1.16;1.27)	1.12 (1.07;1.18)	1.08 (1.01;1.15)	0.355
BMI						
<25	606 (0.7%)	891 (1.9%)	1.36 (1.20;1.54)	1.21 (1.12;1.31)	1.12 (0.97;1.30)	
\geq 25	1,330 (1.0%)	3,627 (2.7%)	1.23 (1.19;1.28)	1.13 (1.08;1.18)	1.09 (1.04;1.15)	0.744
Socioeconomic status						
High	1,173 (0.8%)	2,986 (2.4%)	1.22 (1.17;1.28)	1.16 (1.11;1.22)	1.05 (0.99;1.12)	
Low	763 (1.0%)	1,532 (2.6%)	1.27 (1.29;1.37)	1.13 (1.07;1.20)	1.13 (1.04;1.22)	0.197
Use of glucose-lowering medication						
No	1,795 (0.8%)	4,156 (2.4%)	1.21 (1.16;1.27)	1.17 (1.12;1.23)	1.03 (0.97;1.11)	
Yes	141 (3.0%)	362 (5.2%)	1.20 (1.08;1.34)	1.19 (1.11;1.28)	1.01 (0.89;1.15)	0.735

Supplemental table V. Multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction per 1% HbA1c change, stratified by age, BMI, socioeconomic status, and use of glucose-lowering medication. (continued)

	Women, n (%)	Men, n (%)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)	P for interaction
Multiple-adjusted full interaction model**						
Overall	1,936 (0.8%)	4,518 (2.5%)	1.18 (1.13;1.24)	1.18 (1.13;1.23)	1.00 (0.94;1.07)	NA
Age						
<60	669 (0.5%)	1,830 (1.7%)	1.25 (1.14;1.36)	1.19 (1.14;1.25)	1.05 (0.95;1.15)	
≥60	1,267 (1.3%)	2,688 (3.5%)	1.16 (1.09;1.24)	1.16 (1.10;1.22)	1.00 (0.93;1.09)	0.484
BMI						
<25	606 (0.7%)	891 (1.9%)	1.24 (1.08;1.42)	1.24 (1.15;1.34)	1.00 (0.86;1.16)	
≥25	1,330 (1.0%)	3,627 (2.7%)	1.18 (1.12;1.24)	1.17 (1.12;1.22)	1.01 (0.94;1.08)	0.891
Socioeconomic status						
High	1,173 (0.8%)	2,986 (2.4%)	1.18 (1.11;1.25)	1.19 (1.14;1.25)	0.99 (0.92;1.07)	
Low	763 (1.0%)	1,532 (2.6%)	1.20 (1.10;1.30)	1.16 (1.10;1.22)	1.03 (0.94;1.14)	0.440
Use of glucose-lowering medication						
No	1,795 (0.8%)	4,156 (2.4%)	1.19 (1.12;1.25)	1.19 (1.14;1.24)	1.00 (0.93;1.07)	
Yes	141 (3.0%)	362 (5.2%)	1.20 (1.08;1.34)	1.19 (1.11;1.28)	1.01 (0.89;1.15)	0.880

*The main effects model is adjusted for age plus smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, history of diabetes (no previously diagnosed diabetes including prediabetes and undiagnosed, diabetes), and glucose-lowering medication. **The full interaction model is additionally adjusted for interaction terms between each variable and sex. NA = not applicable; BMI = body mass index; HR = hazard ratio; RHR = ratio of hazard ratios; n (%) = number of events.

Supplemental table VI. Multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction per 1% HbA1c change.

	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Multiple-adjusted full interaction model*	1.18 (1.13;1.24)	1.18 (1.13;1.23)	1.00 (0.94;1.07)
Multiple-adjusted full interaction model excl. history of diabetes	1.19 (1.13;1.25)	1.19 (1.14;1.23)	1.00 (0.94;1.07)

*The full interaction model is adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, history of diabetes (no previously diagnosed diabetes including prediabetes and undiagnosed, diabetes), glucose-lowering medication, and interaction terms between each variable and sex. HR = hazard ratio; RHR = ratio of hazard ratios.

Supplemental table VII. Number (%) of women and men with depression and certain sleep characteristics.

	Number (%) of women	Number (%) of men
Use of antidepressants		
Yes	11,548 (4.4%)	4,800 (2.3%)
No	251,747 (95.6%)	203,876 (97.7%)
Told to have depression during the verbal interview¹		
Yes	17,561 (6.7%)	8,466 (4.1%)
No	245,724 (93.3%)	200,210 (95.9%)
Told to have depression during the verbal interview OR using antidepressants		
Yes	22,035 (8.4%)	10,229 (4.9%)
No	241,260 (91.6%)	198,447 (95.1%)
Told to have depression during the verbal interview AND using antidepressants		
Yes	7,074 (2.7%)	3,037 (1.5%)
No	256,221 (97.3%)	205,639 (98.5%)
Told to have sleep apnoea during the verbal interview¹		
Yes	354 (0.1%)	1,025 (0.5%)
No	262,941 (99.9%)	207,651 (99.5%)
Use of medication to treat insomnia - extensive²		
Yes	2,533 (1.0%)	1,277 (0.6%)
No	260,762 (99.0%)	207,399 (99.4%)
Use of medication to treat insomnia - restricted³		
Yes	1,992 (0.8%)	953 (0.5%)
No	261,303 (99.2%)	207,723 (99.5%)

¹“In the touch screen you selected that you have been told by a doctor that you have other (non-cancer) serious illnesses or disabilities, could you now tell me what they are?” asked by a trained nurse during the verbal interview stage of data collection. The nurse used a tree structure organized by system and loosely based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), codes to record a diagnosis of depression or sleep apnoea (UK Biobank field: 20002) using given codes 1286 and 1123 respectively.

²Participants using the following medication were considered to have trouble sleeping (insomnia): Diazepam, Flunitrazepam, Flurazepam, Loprazolam, Lorazepam, Lormetazepam, Nitrazepam, Oxazepam, Temazepam, Zolpidem, Zopiclon and Zaleplon. ³Several drugs used to treat insomnia have multiple treatment indications including panic disorders. The variable “use of medication to treat insomnia – restricted” included medication with a more strict indication for insomnia, including: Flunitrazepam, Flurazepam, Loprazolam, Lormetazepam, Nitrazepam, Temazepam, Zolpidem, Zopiclon, and Zaleplon.

Supplemental table VIII. Multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction according to diabetes status.

	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Multiple-adjusted - full interaction model*			
<i>No diabetes</i>	1·0	1·0	NA
<i>Prediabetes</i>	1·248 (1·112;1·401)	1·170 (1·080;1·269)	1·067 (0·927;1·230)
<i>Undiagnosed diabetes</i>	1·642 (1·084;2·488)	1·533 (1·222;1·922)	1·072 (0·668;1·720)
<i>Previously diagnosed diabetes</i>	2·334 (1·960;2·780)	1·815 (1·630;2·020)	1·286 (1·048;1·579)
+ use of antidepressants			
<i>No diabetes</i>	1·0	1·0	NA
<i>Prediabetes</i>	1·245 (1·109;1·397)	1·168 (1·077;1·268)	1·065 (0·925;1·227)
<i>Undiagnosed diabetes</i>	1·634 (1·078;2·475)	1·535 (1·224;1·926)	1·064 (0·663;1·708)
<i>Previously diagnosed diabetes</i>	2·318 (1·946;2·760)	1·808 (1·624;2·012)	1·282 (1·045;1·574)
+ told to have depression during the verbal interview [†]			
<i>No diabetes</i>	1·0	1·0	NA
<i>Prediabetes</i>	1·247 (1·111;1·400)	1·170 (1·078;1·269)	1·067 (0·926;1·229)
<i>Undiagnosed diabetes</i>	1·637 (1·081;2·480)	1·533 (1·222;1·923)	1·068 (0·665;1·714)
<i>Previously diagnosed diabetes</i>	2·333 (1·959;2·779)	1·814 (1·630;2·020)	1·286 (1·048;1·579)
+ told to have depression during the verbal interview <u>OR</u> using antidepressants			
<i>No diabetes</i>	1·0	1·0	NA
<i>Prediabetes</i>	1·246 (1·110;1·398)	1·169 (1·078;1·268)	1·066 (0·925;1·228)
<i>Undiagnosed diabetes</i>	1·643 (1·085;2·489)	1·533 (1·222;1·923)	1·072 (0·668;1·720)
<i>Previously diagnosed diabetes</i>	2·327 (1·954;2·771)	1·811 (1·627;2·016)	1·285 (1·047;1·577)
+ told to have depression during the verbal interview <u>AND</u> using antidepressants			
<i>No diabetes</i>	1·0	1·0	NA
<i>Prediabetes</i>	1·247 (1·111;1·400)	1·169 (1·077;1·268)	1·067 (0·926;1·229)
<i>Undiagnosed diabetes</i>	1·631 (1·077;2·472)	1·535 (1·224;1·926)	1·063 (0·662;1·706)
<i>Previously diagnosed diabetes</i>	2·329 (1·956;2·773)	1·811 (1·627;2·016)	1·286 (1·048;1·579)
+ told to have sleep apnoea during the verbal interview [†]			
<i>No diabetes</i>	1·0	1·0	NA
<i>Prediabetes</i>	1·248 (1·112;1·401)	1·169 (1·078;1·269)	1·068 (0·927;1·230)
<i>Undiagnosed diabetes</i>	1·642 (1·084;2·488)	1·533 (1·222;1·923)	1·071 (0·667;1·719)
<i>Previously diagnosed diabetes</i>	2·334 (1·960;2·780)	1·813 (1·629;2·019)	1·287 (1·049;1·581)

Supplemental table VIII. Multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction according to diabetes status. (continued)

	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Multiple-adjusted - full interaction model*			
+ use of medication to treat insomnia - extensive ²			
<i>No diabetes</i>	1.0	1.0	NA
<i>Prediabetes</i>	1.252 (1.115;1.405)	1.170 (1.078;1.269)	1.070 (0.929;1.233)
<i>Undiagnosed diabetes</i>	1.648 (1.088;2.497)	1.532 (1.221;1.922)	1.076 (0.670;1.726)
<i>Previously diagnosed diabetes</i>	2.333 (1.959;2.779)	1.815 (1.630;2.020)	1.286 (1.047;1.578)
+ use of medication to treat insomnia - restricted ³			
<i>No diabetes</i>	1.0	1.0	NA
<i>Prediabetes</i>	1.252 (1.116;1.406)	1.170 (1.078;1.269)	1.071 (0.929;1.233)
<i>Undiagnosed diabetes</i>	1.647 (1.087;2.494)	1.532 (1.222;1.922)	1.074 (0.669;1.725)
<i>Previously diagnosed diabetes</i>	2.338 (1.963;2.784)	1.815 (1.630;2.020)	1.288 (1.050;1.582)

*The full interaction model is adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, and interaction terms between each variable and sex. NA = not applicable; HR = hazard ratio; RHR = ratio of hazard ratios.¹“In the touch screen you selected that you have been told by a doctor that you have other (non-cancer) serious illnesses or disabilities, could you now tell me what they are?” asked by a trained nurse during the verbal interview stage of data collection. The nurse used a tree structure organized by system and loosely based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), codes to record a diagnosis of depression or sleep apnoea (UK Biobank field: 20002) using given codes 1286 and 1123 respectively. ²Participants using the following medication were considered to have trouble sleeping (insomnia): Diazepam, Flunitrazepam, Flurazepam, Loprazolam, Lorazepam, Lormetazepam, Nitrazepam, Oxazepam, Temazepam, Zolpidem, Zopiclon and Zaleplon. ³Several drugs used to treat insomnia have multiple treatment indications including panic disorders. The variable “use of medication to treat insomnia - restricted” included medication with a more strict indication for insomnia, including: Flunitrazepam, Flurazepam, Loprazolam, Lormetazepam, Nitrazepam, Temazepam, Zolpidem, Zopiclon, and Zaleplon.

Supplemental table IX. Multiple-adjusted hazard ratios and ratios of hazard ratios of MI according to levels of glycaemia.

	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Multiple-adjusted - full interaction model*			
<i>No previously diagnosed diabetes±</i>	1·0	1·0	NA
<i>HbA1c ≤6·5%</i>	1·319 (0·949;1·833)	1·207 (0·994;1·465)	1·093 (0·746;1·602)
<i>HbA1c >6·5% - ≤7·5%</i>	1·631 (1·095;2·430)	1·465 (1·161;1·849)	1·113 (0·702;1·767)
<i>HbA1c >7·5%</i>	2·404 (1·614;3·583)	1·943 (1·532;2·465)	1·237 (0·778;1·968)
+ use of antidepressants			
<i>No previously diagnosed diabetes±</i>	1·0	1·0	NA
<i>HbA1c ≤6·5%</i>	1·310 (0·943;1·821)	1·203 (0·991;1·461)	1·089 (0·743;1·596)
<i>HbA1c >6·5% - ≤7·5%</i>	1·646 (1·105;2·42)	1·469 (1·164;1·853)	1·121 (0·706;1·778)
<i>HbA1c >7·5%</i>	2·414 (1·619;3·601)	1·942 (1·531;2·464)	1·243 (0·781;1·980)
+ told to have depression during the verbal interview ¹			
<i>No previously diagnosed diabetes±</i>	1·0	1·0	NA
<i>HbA1c ≤6·5%</i>	1·313 (0·945;1·825)	1·206 (0·994;1·465)	1·088 (0·743;1·595)
<i>HbA1c >6·5% - ≤7·5%</i>	1·636 (1·098;2·438)	1·469 (1·164;1·854)	1·114 (0·702;1·768)
<i>HbA1c >7·5%</i>	2·406 (1·614;3·587)	1·947 (1·535;2·470)	1·236 (0·776;1·967)
+ told to have depression during the verbal interview <u>OR</u> using antidepressants			
<i>No previously diagnosed diabetes±</i>	1·0	1·0	NA
<i>HbA1c ≤6·5%</i>	1·308 (0·941;1·818)	1·204 (0·992;1·462)	1·086 (0·741;1·591)
<i>HbA1c >6·5% - ≤7·5%</i>	1·647 (1·105;2·455)	1·469 (1·164;1·853)	1·121 (0·707;1·780)
<i>HbA1c >7·5%</i>	2·415 (1·619;3·603)	1·944 (1·532;2·466)	1·243 (0·780;1·979)
+ told to have depression during the verbal interview <u>AND</u> using antidepressants			
<i>No previously diagnosed diabetes±</i>	1·0	1·0	NA
<i>HbA1c ≤6·5%</i>	1·315 (0·946;1·828)	1·205 (0·993;1·464)	1·091 (0·745;1·599)
<i>HbA1c >6·5% - ≤7·5%</i>	1·634 (1·096;2·435)	1·470 (1·165;1·855)	1·112 (0·700;1·764)
<i>HbA1c >7·5%</i>	2·404 (1·613;3·584)	1·946 (1·534;2·469)	1·235 (0·776;1·966)
+ told to have sleep apnoea during the verbal interview ¹			
<i>No previously diagnosed diabetes±</i>	1·0	1·0	NA
<i>HbA1c ≤6·5%</i>	1·319 (0·949;1·833)	1·206 (0·993;1·464)	1·094 (0·746;1·603)
<i>HbA1c >6·5% - ≤7·5%</i>	1·631 (1·095;2·430)	1·465 (1·161;1·849)	1·113 (0·702;1·767)
<i>HbA1c >7·5%</i>	2·404 (1·614;3·583)	1·940 (1·530;2·461)	1·239 (0·779;1·971)

Supplemental table IX. Multiple-adjusted hazard ratios and ratios of hazard ratios of MI according to levels of glycaemia. (continued)

	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Multiple-adjusted – full interaction model*			
+ use of medication to treat insomnia - extensive ²			
<i>No previously diagnosed diabetes</i> ±	1·0	1·0	NA
<i>HbA1c ≤6·5%</i>	1·315 (0·946;1·828)	1·206 (0·994;1·465)	1·090 (0·744;1·598)
<i>HbA1c >6·5% - ≤7·5%</i>	1·632 (1·095;2·431)	1·465 (1·161;1·848)	1·114 (0·702;1·768)
<i>HbA1c >7·5%</i>	2·416 (1·621;3·601)	1·943 (1·532;2·465)	1·243 (0·781;1·978)
+ use of medication to treat insomnia – restricted ³			
<i>No previously diagnosed diabetes</i> ±	1·0	1·0	NA
<i>HbA1c ≤6·5%</i>	1·315 (0·946;1·827)	1·207 (0·994;1·465)	1·089 (0·743;1·597)
<i>HbA1c >6·5% - ≤7·5%</i>	1·632 (1·095;2·431)	1·465 (1·161;1·849)	1·114 (0·702;1·767)
<i>HbA1c >7·5%</i>	2·412 (1·619;3·595)	1·944 (1·532;2·465)	1·241 (0·780;1·975)

*The full interaction model is adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, glucose-lowering medication, and interaction terms between each variable and sex. ± No previously diagnosed diabetes, including prediabetes and undiagnosed diabetes. NA = not applicable; HR = hazard ratio; RHR = ratio of hazard ratios. HbA1c 6.5% = 48mmol/mol; HbA1c 7.5% = 58mmol/mol. ⁴“In the touch screen you selected that you have been told by a doctor that you have other (non-cancer) serious illnesses or disabilities, could you now tell me what they are?” asked by a trained nurse during the verbal interview stage of data collection. The nurse used a tree structure organized by system and loosely based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), codes to record a diagnosis of depression or sleep apnoea (UK Biobank field: 20002) using given codes 1286 and 1123 respectively. ²Participants using the following medication were considered to have trouble sleeping (insomnia): Diazepam, Flunitrazepam, Flurazepam, Loprazolam, Lorazepam, Lormetazepam, Nitrazepam, Oxazepam, Temazepam, Zolpidem, Zopiclon and Zaleplon. ³Several drugs used to treat insomnia have multiple treatment indications including panic disorders. The variable “use of medication to treat insomnia – restricted” included medication with more strict indication for insomnia, including: Flunitrazepam, Flurazepam, Loprazolam, Lormetazepam, Nitrazepam, Temazepam, Zolpidem, Zopiclon, and Zaleplon.

Supplemental table X. Multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction per 1% HbA1c change.

	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men RHR (95% CI)
Multiple-adjusted full interaction model*	1.184 (1.126;1.245)	1.179 (1.134;1.226)	1.004 (0.942;1.070)
+ use of antidepressants	1.184 (1.126;1.246)	1.179 (1.134;1.226)	1.004 (0.942;1.070)
+ told to have depression during the verbal interview ¹	1.185 (1.127;1.246)	1.180 (1.134;1.227)	1.004 (0.942;1.070)
+ told to have depression during the verbal interview OR using antidepressants	1.185 (1.127;1.246)	1.180 (1.134;1.227)	1.005 (0.942;1.071)
+ told to have depression during the verbal interview AND using antidepressants	1.184 (1.126;1.245)	1.180 (1.134;1.227)	1.004 (0.942;1.070)
+ told to have sleep apnoea during the verbal interview ¹	1.184 (1.126;1.245)	1.179 (1.134;1.226)	1.004 (0.942;1.070)
+ use of medication to treat insomnia - extensive ²	1.185 (1.127;1.246)	1.179 (1.134;1.226)	1.005 (0.943;1.071)
+ use of medication to treat insomnia – restricted ³	1.185 (1.127;1.246)	1.179 (1.134;1.226)	1.005 (0.943;1.071)

* The full interaction model is adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, history of diabetes (no previously diagnosed diabetes including prediabetes and undiagnosed, diabetes), glucose-lowering medication, and interaction terms between each variable and sex. HR = hazard ratio; RHR = ratio of hazard ratios. ¹In the touch screen you selected that you have been told by a doctor that you have other (non-cancer) serious illnesses or disabilities, could you now tell me what they are?² asked by a trained nurse during the verbal interview stage of data collection. The nurse used a tree structure organized by system and loosely based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), codes to record a diagnosis of depression or sleep apnoea (UK Biobank field: 20002) using given codes 1286 and 1123 respectively. ²Participants using the following medication were considered to have trouble sleeping (insomnia): Diazepam, Flunitrazepam, Flurazepam, Loprazolam, Lorazepam, Lormetazepam, Nitrazepam, Oxazepam, Temazepam, Zolpidem, Zopiclon and Zaleplon. ³Several drugs used to treat insomnia have multiple treatment indications including panic disorders. The variable “use of medication to treat insomnia – restricted” included medication with more strict indication for insomnia, including: Flunitrazepam, Flurazepam, Loprazolam, Lormetazepam, Nitrazepam, Temazepam, Zolpidem, Zopiclon, and Zaleplon.

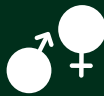
Supplemental table XI. Multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction per 1% HbA1c change, stratified by depression and sleep characteristics.

	Women (HR 95% CI)**	Men (HR 95% CI)**	Women-to-men RHR (95% CI)***
Multiple-adjusted full interaction model*	1.184 (1.126;1.245)	1.179 (1.134;1.226)	1.004 (0.942;1.070)
Use of antidepressants			
Yes	1.196 (1.139;1.255)	1.187 (1.142;1.234)	1.007 (0.946;1.072)
No	1.001 (0.837;1.199)	0.947 (0.789;1.136)	1.058 (0.819;1.366)
<i>P for interaction</i>	0.054	0.015	0.708
Told to have depression during the verbal interview ¹			
Yes	1.190 (1.133;1.250)	1.185 (1.139;1.232)	1.000 (0.943;1.070)
No	1.061 (0.869;1.294)	1.054 (0.898;1.238)	1.006 (0.779;1.298)
<i>P for interaction</i>	0.257	0.155	0.992
Told to have depression during the verbal interview <u>OR</u> using antidepressants			
Yes	1.196 (1.129;1.255)	1.187 (1.142;1.235)	1.007 (0.946;1.072)
No	1.048 (0.897;1.225)	1.043 (0.909;1.197)	1.005 (0.816;1.237)
<i>P for interaction</i>	0.099	0.066	0.985
Told to have depression during the verbal interview <u>AND</u> using antidepressants			
Yes	1.189 (1.132;1.249)	1.185 (1.139;1.231)	1.004 (0.943;1.069)
No	1.005 (0.779;1.297)	0.900 (0.706;1.148)	1.117 (0.785;1.588)
<i>P for interaction</i>	0.197	0.026	0.551
Told to have sleep apnoea during the verbal interview ¹			
Yes	1.185 (1.127;1.245)	1.180 (1.134;1.227)	1.004 (0.943;1.070)
No	0.750 (0.218;2.585)	1.124 (0.854;1.479)	0.667 (0.188;2.370)
<i>P for interaction</i>	0.469	0.730	0.527
Use of medication to treat insomnia - extensive ²			
Yes	1.186 (1.128;1.247)	1.181 (1.1,135;1.228)	1.005 (0.943;1.070)
No	1.134 (0.817;1.573)	1.063 (0.782;1.445)	1.066 (0.681;1.670)
<i>P for interaction</i>	0.787	0.504	0.794

Supplemental table XI. Multiple-adjusted hazard ratios and ratios of hazard ratios of myocardial infarction per 1% HbA1c change, stratified by depression and sleep characteristics. (continued)

	Women (HR 95% CI)**	Men (HR 95% CI)**	Women-to-men RHR (95% CI)***
Use of medication to treat insomnia – restricted ³			
Yes	1.184 (1.126;1.246)	1.179 (1.134;1.226)	1.004 (0.942;1.071)
No	1.260 (0.925;1.716)	1.179 (0.869;1.599)	1.069 (0.692;1.650)
<i>P for interaction</i>	0.696	0.999	0.780

*The full interaction model is adjusted for age plus smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, the Townsend social deprivation score, history of diabetes (no previously diagnosed diabetes including prediabetes and undiagnosed, diabetes), glucose-lowering medication, and interaction terms between each variable and sex. HR = hazard ratio; RHR = ratio of hazard ratios. ⁴In the touch screen you selected that you have been told by a doctor that you have other (non-cancer) serious illnesses or disabilities, could you now tell me what they are?" asked by a trained nurse during the verbal interview stage of data collection. The nurse used a tree structure organized by system and loosely based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), codes to record a diagnosis of depression or sleep apnoea (UK Biobank field: 20002) using given codes 1286 and 1123 respectively. ²Participants using the following medication were considered to have trouble sleeping (insomnia): Diazepam, Flunitrazepam, Flurazepam, Loprazolam, Lorazepam, Lormetazepam, Nitrazepam, Oxazepam, Temazepam, Zolpidem, Zopiclon, and Zaleplon. ³Several drugs used to treat insomnia have multiple treatment indications including panic disorders. The variable "use of medication to treat insomnia – restricted" included medication with more strict indication for insomnia, including: Flunitrazepam, Flurazepam, Loprazolam, Lormetazepam, Nitrazepam, Temazepam, Zolpidem, Zopiclon, and Zaleplon. ******P-values for the sex-specific hazard ratios represent the two-way interaction terms including HbA1c and the variable that was stratified for. *******P-values for the women-to-men hazard ratios represent the three-way interaction terms including sex, HbA1c and the variable that was stratified for.



Chapter 5

Diabetes and COVID-19-related mortality in women
and men in the UK Biobank: comparisons with
influenza/pneumonia and coronary heart disease

Marit de Jong
Mark Woodward
Sanne A.E. Peters

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Abstract

Objective

Whether sex differences exist in the association between diabetes, HbA1c, and risk of COVID-19 mortality is unknown.

Research Design and Methods

Sex-specific associations of diabetes and HbA1c with COVID-19 mortality were studied in the UK Biobank (n=501,884). These were compared with sex-specific associations of death from influenza/pneumonia and fatal coronary heart disease (CHD).

Results

Diabetes was associated with greater risk of death from COVID-19 (HR 1.52 in women vs. 1.73 in men), influenza/pneumonia and CHD in both sexes. No sex differences were found for the association of diabetes and HbA1c with COVID-19 or influenza/pneumonia mortality, while prediabetes, diabetes, and HbA1c were more strongly associated with fatal CHD in women than men.

Conclusions

Diabetes has adverse mortal effects on COVID-19 in both sexes, as it does for influenza/pneumonia and CHD. However, unlike fatal CHD, there are no sex disparities in the effects of diabetes on death from COVID-19 or influenza/pneumonia.

Introduction

There is accumulating evidence that diabetes confers a greater cardiovascular risk in women than men.¹ Individuals with diabetes are also at increased risk of poor outcomes in COVID-19, including death.²⁻¹¹ Whether the excess risk of COVID-19 mortality associated with impaired glucose tolerance and diabetes are different between women and men is uncertain. We used data from the UK Biobank to investigate the sex-specific associations, and sex differences, between diabetes status, HbA1c, and risk of COVID-19 mortality. As comparison, we also examined sex-specific associations and sex differences of death by influenza/pneumonia, a major cause of death from respiratory disease prior to the COVID-19 pandemic, and fatal coronary heart disease (CHD), a condition for which sex differences are well-established.

Research Design and Methods

The UK Biobank is a prospective cohort study including over 500,000 participants aged between 40-69 years at baseline between 2006-2010.¹² Medical history of diabetes, and use of glucose-lowering medications, were self-reported. HbA1c was measured at baseline in 466,493 participants. Diabetes status was categorised into four groups (no diabetes, prediabetes, undiagnosed diabetes, and previously diagnosed diabetes) using available information about self-reported diabetes, use of glucose-lowering medication, and HbA1c (those with missing data for all three variables were excluded).¹³ The primary study outcome was COVID-19 mortality. Secondary outcomes were death from influenza/pneumonia and CHD. Follow-up for cause-specific mortality was conducted up to June 30, 2020 through linkage with the national death register.

Cox regression was used to obtain sex-specific hazard ratios (HRs) and 95% confidence intervals (CI) for mortality from COVID-19, influenza/pneumonia, and CHD for diabetes and HbA1c. For analyses involving more than two groups, 95% CIs were estimated through floating absolute risks.¹⁴ Adjustments were made for age, BMI, socioeconomic status (SES), smoking, systolic blood pressure, antihypertensive medication, total cholesterol, and lipid-lowering medication. Models for levels of HbA1c ($\leq 6.5\%$ ($\leq 48\text{mmol/mol}$), $>6.5\% - \leq 7.5\%$, $>7.5\%$ (58mmol/mol)) were additionally adjusted for glucose-lowering medication, and models for 1% HbA1c change (irrespective of diabetes) were additionally adjusted for glucose-lowering medication and diabetes. Interactions between each variable and sex were added to the model, so as to obtain the women-to-men ratio of HRs (RHRs) for each risk factor. Available case analyses were conducted using StataSE13 and R version 3.3.0.

Results

Overall, 501,884 participants were included (54% women) in the analyses. At baseline, 7.1% of men and 3.9% of women were previously diagnosed with diabetes, with a median HbA1c of 7.0% (53mmol/mol) and 6.9% (52mmol/mol), respectively. Over a mean follow-up of 11.2 years, 408 (36% women) died of COVID-19, 549 (36% women) died of influenza/pneumonia, and 3,347 (19% women) died of CHD.

Diabetes was associated with a greater risk of death from COVID-19, influenza/pneumonia, and CHD in both men and women (Table 1). In both sexes, the magnitude of the association was strongest for CHD with a HR of 3.17 in women and 1.93 in men, followed by influenza/pneumonia (HR 2.06 vs. 1.80), and then COVID-19 (HR 1.52 vs. 1.73). For COVID-19 and influenza/pneumonia, the magnitude of the association with diabetes was similar between the sexes. For CHD, diabetes was associated with a 64% greater excess risk in women as compared with men. Higher levels of HbA1c were not associated with a greater risk of COVID-19 or influenza/pneumonia death in women. In men, a HbA1c >7.5% (58mmol/mol), compared with no diabetes, was associated with a greater risk of COVID-19 or influenza/pneumonia death. Each 1% higher HbA1c was associated with a 9% greater risk of influenza/pneumonia death in men. By comparison, higher levels of HbA1c were associated with a greater risk of fatal CHD in both sexes, and the magnitude of the association between a 1% higher HbA1c and CHD was 9% stronger in women as compared with men.

Table 1. Adjusted hazard ratios (HRs) and women-to-men ratio of HRs for death from COVID-19, influenza/pneumonia or coronary heart disease associated with diabetes status, levels of HbA1c, and HbA1c per 1% change.

	Death from COVID-19				Death from influenza/pneumonia				Death from CHD			
	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men (RHR 95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men (RHR 95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men (RHR 95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men (RHR 95% CI)
Previously diagnosed diabetes vs. not	1.52 (0.82; 2.82)	1.73 (1.19; 2.52)	0.88 (0.43; 1.81)	2.06 (1.30; 3.28)	1.80 (1.32; 2.44)	1.15 (0.66; 2.00)	3.17 (2.51; 3.99)	1.93 (1.73; 2.15)	1.64 (1.27; 2.12)			
Diabetes status												
No diabetes	1.00 (0.77; 1.30)	1.00 (0.82; 1.22)	1.00 (0.72; 1.39)	1.00 (0.79; 1.26)	1.00 (0.84; 1.19)	1.00 (0.75; 1.34)	1.00 (0.87; 1.15)	1.00 (0.94; 1.07)	1.00 (0.86; 1.16)			
Prediabetes	0.93 (0.64; 1.35)	0.94 (0.67; 1.31)	0.99 (0.60; 1.63)	1.15 (0.85; 1.57)	1.11 (0.85; 1.45)	1.04 (0.69; 1.57)	1.55 (1.32; 1.82)	1.26 (1.15; 1.37)	1.23 (1.03; 1.48)			
Undiagnosed diabetes	1.27 (0.32; 5.08)	3.51 (1.82; 6.78)	0.36 (0.08; 1.68)	0.73 (0.10; 5.15)	1.71 (0.71; 4.12)	0.42 (0.05; 3.64)	1.68 (0.80; 3.53)	2.17 (1.69; 2.80)	0.77 (0.35; 1.70)			
Previously diagnosed diabetes	1.51 (0.85; 2.69)	1.80 (1.29; 2.52)	0.84 (0.43; 1.64)	2.17 (1.42; 3.31)	1.89 (1.44; 2.47)	1.15 (0.69; 1.89)	3.76 (3.07; 4.61)	2.12 (1.93; 2.33)	1.78 (1.42; 2.22)			
HbA1c levels												
No previously diagnosed diabetes	1.00 (0.45; 2.21)	1.00 (0.62; 1.61)	1.00 (0.39; 2.53)	1.00 (0.49; 2.05)	1.00 (0.66; 1.51)	1.00 (0.44; 2.30)	1.00 (0.75; 1.33)	1.00 (0.87; 1.15)	1.00 (0.73; 1.38)			
≤6.5%	0.82 (0.28; 2.39)	1.38 (0.85; 2.23)	0.60 (0.18; 1.92)	1.01 (0.52; 1.96)	1.27 (0.86; 1.87)	0.80 (0.37; 1.71)	2.18 (1.62; 2.94)	1.48 (1.29; 1.69)	1.48 (1.06; 2.05)			
>6.5% - ≤7.5%	1.10 (0.35; 3.45)	1.69 (0.93; 3.07)	0.65 (0.18; 2.36)	1.42 (0.77; 2.62)	1.26 (0.78; 2.03)	1.13 (0.52; 2.46)	2.18 (1.53; 3.10)	1.62 (1.38; 1.89)	1.35 (0.92; 1.99)			
>7.5%	2.67 (0.98; 7.22)	2.25 (1.20; 4.24)	1.18 (0.36; 3.85)	0.94 (0.43; 2.07)	1.69 (1.04; 2.74)	0.56 (0.22; 1.40)	3.70 (2.65; 5.15)	2.08 (1.77; 2.45)	1.77 (1.22; 2.57)			

Table 1. Adjusted hazard ratios (HRs) and women-to-men ratio of HRs for death from COVID-19, influenza/pneumonia or coronary heart disease associated with diabetes status, levels of HbA1c, and HbA1c per 1% change. (continued)

	Death from COVID-19			Death from influenza/pneumonia			Death from CHD		
	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men (RHR 95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men (RHR 95% CI)	Women (HR 95% CI)	Men (HR 95% CI)	Women-to-men (RHR 95% CI)
HbA1c per 1%	1.04 (0.76; 1.42)	1.10 (0.98; 1.22)	0.95 (0.68; 1.32)	1.06 (0.83; 1.35)	1.09 (1.00; 1.19)	0.97 (0.75; 1.25)	1.21 (1.14; 1.29)	1.12 (1.09; 1.14)	1.09 (1.02; 1.16)

Analyses by diabetes and diabetes status were adjusted for age, BMI, socioeconomic status, smoking, systolic blood pressure, use of anti-hypertensive medication, total cholesterol, and use of lipid-lowering medication. Models for levels of HbA1c were additionally adjusted for the use of glucose-lowering medication. Similar levels of adjustments were used for the analyses of 1% HbA1c change, additionally adjusted for history of diabetes. For all analyses involving more than two groups, 95% CIs were estimated through floating absolute risks. RHR = women-to-men ratio of hazard ratio's. COVID-19 mortality was defined by the International Classification of Diseases (ICD-10) code U072. Death from influenza/pneumonia was defined by ICD-10 codes J09, J13, J14, J100, J101, J108, J110, J111, J118, J121-J123, J128, J129, J150-J152, J154, J155, J159, J180, J181, and J189. Fatal CHD was defined by ICD-10 codes I200, I209, I213, I214, I219, I232, I248-I255, I258, and I259. HbA_{1c} 6.5% = 48 mmol/mol; HbA_{1c} 7.5% = 58 mmol/mol.

Discussion

This study of over 500,000 UK Biobank participants shows that diabetes is associated with a greater risk of death from COVID-19, influenza/pneumonia, and CHD in women and men. In men, the presence of diabetes was associated with an approximately similar excess risk of mortality across the three endpoints of about 70% to 90%. In women, the excess risks of COVID-19 and influenza/pneumonia mortality were similar to those in men. For CHD, however, diabetes was associated with a 217% excess risk in women, which was 64% greater than that in men. Unlike for CHD, the association between a higher HbA1c and COVID-19 and influenza/pneumonia death was not different between the sexes.

Our finding that diabetes is associated with a higher risk of COVID-19 mortality is consistent with other studies.²⁻¹¹ For example, a study of 61 million individuals in England showed that over a third of all in-hospital COVID-19-related deaths occurred in those with diabetes, and those with diabetes had higher odds of in-hospital COVID-19-related death compared to those without diabetes.³ This study suggested that women with diabetes were at higher risk of in-hospital COVID-19-related mortality than men³, while all HRs for COVID-19-related mortality were found to be lower in women compared to men in our study, with exception of HbA1c > 7.5% (58 mmol/mol). Therefore, sex-specific associations between diabetes status and levels of HbA1c with COVID-19-related mortality need further study in large longitudinal studies across several populations.

Our results suggest that worse glycaemic control might further increase the risk of COVID-19 mortality among those with diabetes. A population-based study including over 17 million English individuals and 11,000 COVID-19-related deaths showed that, compared to those without diabetes, individuals with controlled (HbA1c < 7.5% (58 mmol/mol)) and uncontrolled diabetes (HbA1c ≥ 7.5% (58 mmol/mol)) were at increased risk of COVID-19-related death, with greatest risk found among those with uncontrolled diabetes.⁹ A retrospective, multicentre study, located in the Hubei province (China), including ~7,300 hospitalized individuals with COVID-19, showed that those with type 2 diabetes and poorly controlled blood glucose levels were at increased risk of mortality compared to those with controlled diabetes.¹⁰ Moreover, analyses of the UK Biobank showed that those with uncontrolled diabetes (HbA1c ≥ 8.6% (70 mmol/mol)) were at highest risk of hospitalization with COVID-19 compared to those without diabetes.¹⁵ Collectively, these findings suggest that worse glycaemic control in those with diabetes might be more strongly associated with increased risk of severe COVID-19 infections than those with well-controlled diabetes. Some studies have also reported that individuals with undiagnosed diabetes are particularly at increased risk of severe COVID-19 infections.^{11,15} Although relatively few participants had undiagnosed diabetes in the present study, we showed that undiagnosed diabetes was associated with a 3.5-fold excess risk of COVID-19 mortality in men. Our study adds to these findings by, for the first time, also reporting sex-specific findings. Although we found no evidence for a sex difference in the association between HbA1c levels and COVID-19 mortality, the finding that associations are broadly similar across sexes and diseases with the exception of women with CHD is interesting, and is important when considering mechanistic explanations of the female disadvantage in CHD.

Conclusion

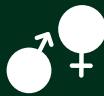
Overall, these findings indicate that strategies to prevent diabetes, to timely identify individuals with diabetes, and to improve glycaemic control among those with diabetes could lead to better COVID-19 outcomes for both sexes.

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Chapter 6

Duration of diabetes and the risk of major cardiovascular events in women and men: a prospective cohort study of UK Biobank participants

Marit de Jong
Mark Woodward
Sanne A.E Peters

Submitted

Abstract

Objective

Diabetes has been associated with a greater excess risk of cardiovascular disease (CVD) in women than men. We investigated whether there are also sex differences in the association of diabetes duration and the risk of CVD.

Research Design and Methods

Data were used from 18,961 (40% women) individuals with type 2 diabetes without a history of CVD in the UK Biobank. Sex-specific incidence rates were calculated by diabetes duration using Poisson regression. Cox proportional hazards analyses estimated multiple-adjusted sex-specific hazard ratios (HR) and women-to-men ratio of HRs (RHR) by diabetes duration categorized (< 5, ≥ 5-< 10, and ≥10 years) and per 5-year increase in duration for CVD, and separately for myocardial infarction (MI) and stroke.

Results

Over a median follow-up of 11 years, 1,506 (29% women) CVD events, 931 (26% women) MIs, and 653 (33% women) strokes were documented. Compared with men, women had lower multiple-adjusted incidence rates of CVD and MI per 10,000 person-years for all categories of diabetes duration. Duration of diabetes was associated with an increased risk of CVD, and MI and stroke separately, in both sexes. Compared with a diabetes duration of <5 years, the HRs for CVD, in women and men, respectively, were 1.25 (95% CI 0.98;1.60) vs. 1.33 (1.13;1.55) for a diabetes duration of ≥5 to <10 years, and 1.71 (1.34;2.17) vs. 1.68 (1.43;1.96) for a diabetes duration of ≥10 years, with corresponding women-to-men ratio of HRs of 0.95 (0.71;1.26) and 1.02 (0.76;1.35) respectively. A 5-year increase in diabetes duration was associated with an approximately similar excess risk of about 20% for each of the three endpoints in both sexes.

Conclusions

The increased risk of CVD associated with longer duration of diabetes is similar in women and men.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide in both women and men; responsible for 33% of deaths (18.6 million) in 2019.¹ Individuals with diabetes are at increased risk of CVD, including stroke and myocardial infarction (MI). Among adults with type 2 diabetes, the global prevalence of CVD is estimated to be 32% and CVD was responsible for 50% of all deaths.² However, not every person with diabetes experiences the same excess risk of CVD; those with a longer duration have a greater risk of a major cardiovascular events.^{3,4} Also, there is compelling evidence that, compared with men, women bear a greater excess risk for the development of major cardiovascular complications.⁵⁻¹⁵ The mechanisms underpinning this sex differential remain uncertain and previous studies typically assessed diabetes as a binary variable without considering the increased risk of CVD associated with longer durations of diabetes. The few studies examining sex differences in the association between diabetes duration and CVD have provided mixed results.¹⁶⁻¹⁹ Therefore, we used data from the UK Biobank to examine whether there are sex differences in the association of diabetes duration with the risk of cardiovascular disease (CVD), and separately for MI and stroke.

Methods

Study design and participants

The UK Biobank is a large prospective cohort study, comprising over half a million participants aged between 40-69 years at study baseline between 2006 and 2010. Details of the study procedures for the UK Biobank have been described elsewhere.²⁰ In short, participants were invited to one of the 22 assessment centres across the UK for baseline assessment, which included questionnaires on lifestyle and medical history, and physical and functional measurements. In addition, blood, urine, and saliva samples were taken. All participants provided written informed consent. Participants with a history of CVD (self-reported or hospital admission of MI, stroke or angina pectoris (n = 30,564)) at baseline were excluded from the current analyses. Analyses were also restricted to those who were considered to have type 2 diabetes; i.e. those with a previous diagnosis of diabetes after the age of 30 years.

Diabetes and duration

A medical history of diabetes, including age at first diagnosis and the use of glucose-lowering medication, were self-reported. Previously diagnosed diabetes was defined as a self-reported diagnosis of diabetes and/or the use of glucose-lowering medication. Diabetes duration was calculated by subtracting age at diagnosis from age at study baseline. Age at diagnosis was obtained through the touch screen question “what was your age when diabetes was first diagnosed?” and a nurse-led interview. Participants indicating they had diabetes only during pregnancy were excluded. A small proportion of the participants with diabetes (0.7%) seemed to have misinterpreted the touch screen question “what was your age when diabetes was first diagnosed?” for “How long ago were you diagnosed?” For those with conflicting data, information from the nurse-led interview was used to obtain information about the age at diagnosis when the

sum of 'age at diagnosis' (touch screen question) and the 'year of diagnosis' (nurse-led interview) corresponded to the year of the baseline visit.

Study outcomes

The primary study outcome was CVD, defined as incident non-fatal or fatal MI or stroke, identified by codes I21-I21.4, I21.9, I22-I22.1, I22.8, I22.9, I23-I23.6, I23.8, I24.1, I25.2 I60-I60.9, I61-I61.9, I63-I63.9, I64.X in the tenth edition of the International Classification of Diseases (ICD-10). Secondary outcomes were incident MI and stroke. Outcome adjudication involved linkage with hospital admissions data from England, Scotland, and Wales and the national death register to identify the date of MI and stroke after the date of baseline assessment.^{21,22} Follow-up started at inclusion in the UK Biobank and ended on June 30 2020, date of death, or date of the event, whichever came first.

Statistical analyses

Baseline characteristics were summarized by sex and diabetes duration, classified into three ordinal groups (<5; ≥5-<10; >10 years). Information on missing data can be found in supplemental table II. Sex-specific incidence rates of CVD, MI, and stroke, and women minus men differences-of-rate differences, were calculated by diabetes duration, using Poisson regression models. Two levels of adjustments were used, each including interaction terms between each variable and sex. The first model adjusted for baseline age. The second model additionally adjusted for smoking, BMI, systolic blood pressure, use of anti-hypertensive medication, total cholesterol, use of lipid-lowering medication, the Townsend (area-level) social deprivation index, and ethnicity.

Cox regression models, with identical adjustments, were used to obtain the sex-specific hazard ratios (HRs) and the women-to-men ratio of hazard ratios (RHR) with 95% confidence intervals (CI) of CVD, MI and stroke per 5 years of diabetes duration and by categories of diabetes duration (<5; ≥5 - <10; >10 years), using diabetes duration of <5 years as reference. In prespecified subgroup analyses, results for CVD were stratified by baseline age (<60 years and ≥60 years), BMI (<30kg/m² and ≥30kg/m²), socioeconomic status (SES) based on the Townsend deprivation index (> -0.56 (SES lower than the national average) and ≤ -0.56), and ethnicity (white vs. non-white). Penalized spline models, with four degrees of freedom, were used to examine the sex-specific shape of the associations. Adjustments were as in the second model. The sex-specific penalized spline models were obtained using stratification by sex. Therefore, additional adjustments for each variable in the model and sex were not included.

Sensitivity analyses were performed to examine the effect of: (1) adjusting for HbA1c and glucose-lowering medication; (2) excluding BMI from the second (main) model; (3) excluding participants who seemed to have misinterpreted the touch screen question ““what was your age when diabetes was first diagnosed?” as “how long ago were you diagnosed?”; (4) excluding participants who used insulin only; and (5) excluding participants who did not use glucose-lowering medication. Available case analyses were conducted using StataSE13 and RStudio version 1:1.456.

Results

Baseline characteristics are presented by sex (Table 1) and diabetes duration (Supplemental Table I). Overall, 18,961 participants were included (40% women), with a median HbA1c of 6.7% (50mmol/mol) and median duration of 5 years in both sexes. Over a median follow-up of 11 years, 1,506 (29% women) CVD events, 931 (26% women) MIs, and 653 (33% women) strokes were documented.

Table 1. Baseline characteristics by sex.

	Women <i>n</i> =7,559	Men <i>n</i> =11,402
General characteristics		
Age, years	59.5 (6.9)	59.6 (7.0)
White ethnicity	6,373 (85%)	9,919 (88%)
Socioeconomic status*		
<i>Higher than average</i>	4,136 (55%)	6,634 (58%)
<i>Lower than average</i>	3,409 (45%)	4,750 (42%)
Smoking		
<i>Never</i>	4,389 (59%)	4,591 (41%)
<i>Past</i>	2,465 (33%)	5,334 (47%)
<i>Current</i>	628 (8%)	1,367 (12%)
Diabetes characteristics		
Median diabetes duration, years (IQR)	5 (2-9)	5 (2-9)
Median HbA1c, % (IQR)	6.7 (6.1-7.5)	6.7 (6.1-7.5)
Risk factors		
BMI, kg/m ²	32.5 (6.6)	30.9 (5.3)
Systolic BP, mmHg	140.1 (17.6)	142.7 (16.6)
Diastolic BP, mmHg	81.2 (9.5)	82.8 (9.4)
Cholesterol, mmol/L	4.7 (1.0)	4.4 (1.0)
Prescribed medication		
Antidiabetic medication		
<i>No medication</i>	2,615 (35%)	4,078 (36%)
<i>Oral</i>	3,854 (51%)	5,802 (51%)
<i>Insulin</i>	481 (6%)	654 (6%)
<i>Oral + Insulin</i>	609 (8%)	868 (8%)
Antihypertensive medication	4,170 (55%)	6,472 (57%)
Lipid-lowering medication	4,995 (66%)	7,733 (68%)

Data are mean (SD) or n (%) unless otherwise indicated. * Socioeconomic status was determined using the postcode-based Townsend deprivation index and dichotomised using the national median Townsend score (high: ≤ -0.56 ; low: > -0.56). IQR = interquartile range; BMI = body mass index; BP = blood pressure. Due to missing data, not all variables included add up to $n=11,402$ for men and $n=7,559$ for women.

Sex-specific rates of CVD, MI and stroke according to diabetes duration

After multiple adjustments, women had lower incidence rates of CVD and MI per 10,000 person-years than men for all categories of diabetes duration. Women-versus-men incidence rates of CVD were 43.8 (36.7;50.9) vs. 73.4 (65.5;81.3) for <5 years, 54.9 (44.5;65.4) vs. 97.1 (85.9;108.3) for ≥ 5 to <10 years, and 74.4 (61.0;87.9) vs. 122.2 (108.3;136.1) for ≥ 10 years. The incidence rates of MI in women versus men were 23.6 (18.4;28.8) vs. 49.8 (43.3;56.3) for <5 years, 29.0 (21.5;36.6) vs. 56.8 (48.3;65.4) for ≥ 5 to <10 years, and 40.7 (30.8;50.6) vs. 80.1 (68.8;91.4) for ≥ 10 years. For stroke, the incidence rates per 10,000 person-years were 21.6 (16.6;26.5) in women vs. 25.6 (21.5;30.2) in men for a diabetes duration of <5 years, 27.1 (19.8;34.4) vs. 42.8 (35.6;50.0) for ≥ 5 to <10 years, and 36.1 (26.9;45.4) vs. 46.1 (37.9;54.3) for ≥ 10 years). (Figure 1 and Supplemental table III).

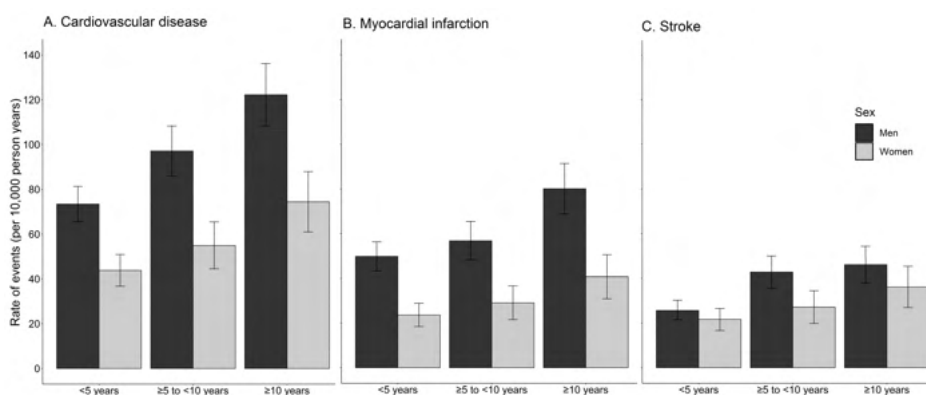


Figure 1. Multiple-adjusted rates of cardiovascular disease (A), myocardial infarction (B), and stroke (C) (per 10,000 person years) by diabetes duration and sex. Analyses were adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, and interaction terms between each variable and sex. Bars show 95% confidence interval.

Diabetes duration and the risk of CVD

Compared to those with a diabetes duration of <5 years, diabetes durations of ≥ 5 to <10 years and ≥ 10 years were associated with ever increasing risk of CVD in both sexes (p for trend < 0.001). The sex-specific HRs, in women and men respectively, were 1.25 (95% CI 0.98;1.60) vs. 1.33 (1.13;1.55) for a diabetes duration of ≥ 5 to <10 years, and 1.71 (1.34;2.17) vs. 1.68 (1.43;1.96) for a diabetes duration of ≥ 10 years. No sex differences were found in the association between diabetes duration categories and CVD, with corresponding women-to-men ratio of HRs of 0.95 (0.71;1.26) for a diabetes duration of ≥ 5 to <10 years and 1.02 (0.76;1.35) for a diabetes duration of ≥ 10 years. (Figure 2A and Supplemental table IV) There was an approximately log-linear association between diabetes duration and CVD in both sexes. (Figure 3A) A 5-year increase in diabetes duration was associated with an 20% and 16% increased CVD risk in women and men, respectively: the HRs were 1.20 (95% CI 1.12;1.28) in women and 1.16 (1.11;1.22) in men, with a corresponding women-to-men RHR of 1.03 (0.95;1.12). (Supplemental table V). There was no evidence for a sex difference in the association between a 5-year increase in diabetes duration and CVD across sex-specific subgroups, with two exceptions. First, the association between diabetes

duration and CVD was stronger among women with a BMI ≥ 30 (HR 1.29 [1.18;1.41]) than those with a BMI < 30 (1.08 [0.97;1.21]) (p for interaction = 0.02). The women-to-men RHR in those with a BMI ≥ 30 was 1.11 (0.99;1.24). Second, the association between diabetes duration and CVD was stronger in non-white men (1.31 [1.17;1.45]) compared to white men (1.13 [1.08;1.19]) (p for interaction = 0.02) without evidence for a sex difference in either of the ethnicity categories. (Figure 4 and Supplemental Table VI).

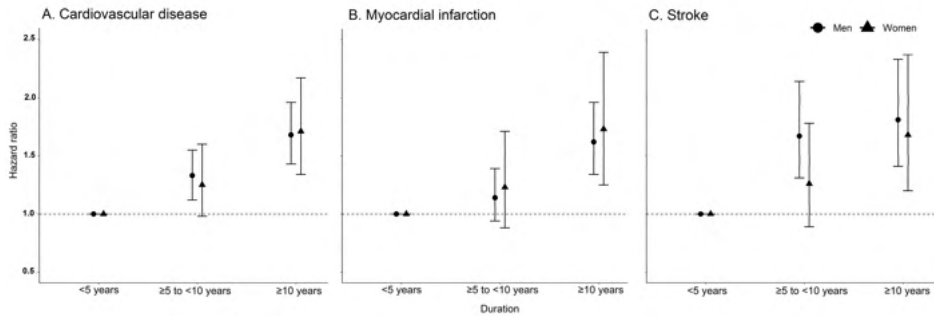


Figure 2. Multiple-adjusted sex-specific hazard ratios of cardiovascular disease (A), myocardial infarction (B) and stroke (C) according to diabetes duration. Analyses were adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, and interaction terms between each variable and sex. Bars show 95% confidence interval.

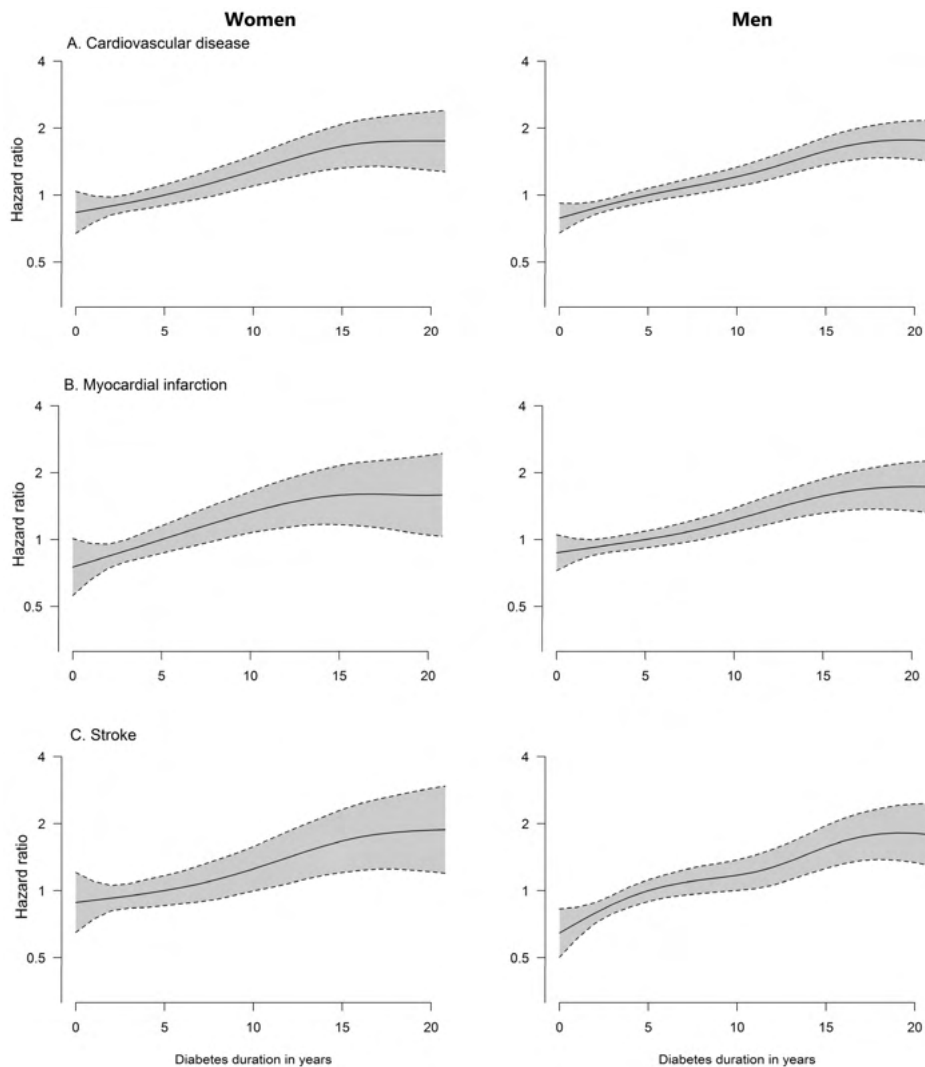


Figure 3. Multiple-adjusted hazard ratios for cardiovascular disease (A), myocardial infarction (B), and stroke (C) according to diabetes duration, stratified by sex. Penalized spline models with 4 degrees of freedom and reference diabetes duration set at 5 years. Analyses were adjusted for age, smoking, BMI, systolic blood pressure, antihypertensive medication, total cholesterol, use of lipid-lowering medication, socioeconomic status, and ethnicity. Shaded lines show 95% confidence intervals. Figure was trimmed at a diabetes duration of 20 years.

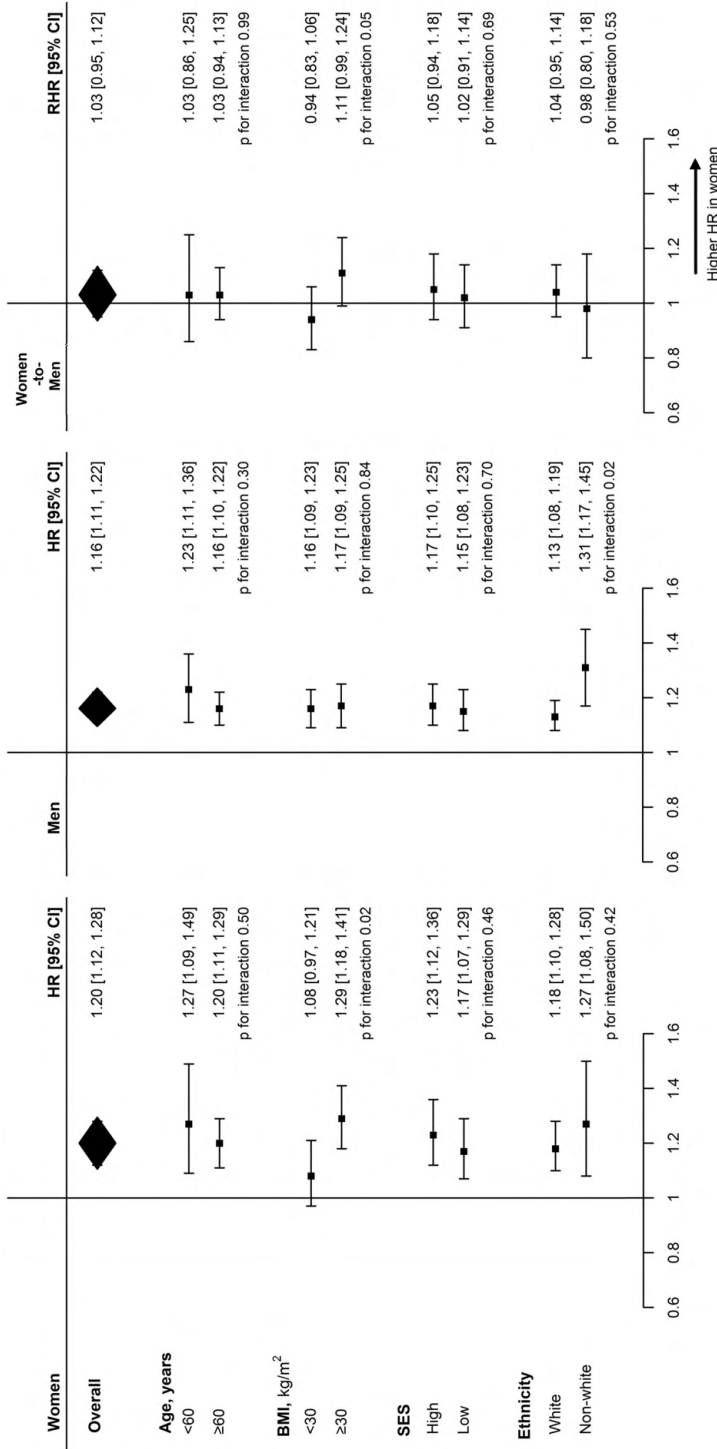


Figure 4. Multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular diseases per 5 years of diabetes duration, stratified by age, BMI, socioeconomic status, and ethnicity. Analyses were adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, and interaction terms between each variable and sex.

Diabetes duration and the risk of MI

Compared to those with a diabetes duration of <5 years, a diabetes duration of ≥ 10 years, but not ≥ 5 to <10 years, was associated with increased risk of MI in both sexes, without evidence for a sex difference. (Figure 2B and supplemental table IV) There was an approximate log-linear association between diabetes duration and MI in both sexes. (Figure 3B) A 5-year increase in diabetes duration was associated with a HR for MI of 1.23 (95% CI 1.12;1.35) in women and 1.16 (1.09;1.23) in men, with a corresponding women-to-men RHR of 1.06 (0.95;1.18). (Supplemental Table V)

Diabetes duration and the risk of stroke

Compared to those with a diabetes duration of <5 years, a diabetes duration of ≥ 10 years, was associated with increased risk of stroke in both sexes. A diabetes duration of ≥ 5 to <10 years was associated with increased stroke risk in men (HR 1.67 [1.31;2.14]), but not in women (1.26 [0.89;1.78]). No statistically significant sex differences were found (Figure 2C and supplemental table IV) There was an approximate log-linear association between diabetes duration and stroke in both sexes. (Figure 3C) A 5-year increase in diabetes duration was associated with a HR for stroke of 1.16 (95% CI 1.05;1.28) in women and 1.17 (1.09;1.26) in men, with a corresponding women-to-men RHR of 0.99 (0.88;1.12). (Supplemental Table V)

Sensitivity analyses

The results from the five sensitivity analyses were broadly similar to the multiple-adjusted analyses, with no evidence of any sex difference in the multiple-adjusted association between CVD and diabetes duration. (Supplemental Tables VII and XI).

Discussion

This study of 19,000 UK Biobank participants with type 2 diabetes shows that duration of diabetes is independently associated with a greater risk of CVD, MI, and stroke in women and men, without evidence of sex differences in the strength of the association. In both sexes, a 5-year increase in diabetes duration was associated with an approximately similar excess risk of CVD, MI, and stroke of about 20%.

Comparison with existing literature

Our finding that duration of diabetes is associated with higher risk of major CVD is consistent with several other studies.^{3,4,16–19,23–26} Studies assessing sex-specific effects and sex differences in the association between duration of diabetes and CVD are limited and have provided mixed results.^{16–19} The study most similar to our study is the ADVANCE-ON study. This study, including 11,000 participants with type 2 diabetes, showed that every 5-year increase in diabetes duration was associated with 24% and 10% increased risk of MI in women and men, respectively.¹⁸ Compared with men, women had a 13% higher excess risk of MI (women-to-men ratio of HRs: 1.13 [1.00;1.26]). After stratifying their results by region of residence, women-to-men ratio of HRs were 1.32 (1.08;1.61) in those living in Asia versus 1.04 (0.90;1.20) in those living in Australia, Europe, or Northern America (p for interaction 0.23).¹⁸ Explanations as to why our study, in contrast to the

ADVANCE-ON study, did not find evidence for sex differences in the strength of the association between duration of diabetes and CVD remain speculative, but might be explained by differences in underlying population characteristics such as ethnicity. In contrast to the UK Biobank cohort, with all participants living in the UK and majority being white, over 37% of the participants in the ADVANCE-ON study were living in Asia.¹⁸ Although subgroup analyses in the ADVANCE-ON study showed consistent estimates of women-to-men ratio of HRs across those living in Asia and those not living in Asia, confidence intervals were relatively wide.¹⁸ Analyses of the 1971-1992 National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES), including 10,871 participants, showed that both women and men with longer diabetes duration (≥ 10 years) without prevalent MI were at increased risk of CHD mortality compared to those without diabetes; the sex-specific hazard ratios were 4.8 in women and 2.6 in men with no statistically significant difference between the sexes.¹⁹ Lastly, a cohort study including 89,443 Ukrainian individuals with type 2 diabetes showed no sex differences in the association between duration of diabetes and cardiovascular mortality.²⁵ In the present study we showed that the increased risk of CVD associated with longer duration of diabetes was similar in both sexes. Our study add to these previous findings by including non-fatal events, and by studying MI and stroke separately and combined.

Underlying mechanisms

Individuals with type 2 diabetes are at increased risk of major cardiovascular complications due to a complex interplay of traditional (i.e. hyperlipidaemia, hypertension, obesity, smoking) and non-traditional risk factors (i.e. microalbuminuria, thrombogenic factors, inflammatory markers, glucose variability) that, among other things, contribute to the progressive development of atherosclerosis.²⁷ However, the Emerging Risk Factor Collaboration meta-analysis showed that the increased CVD risk associated with diabetes is only partially explained by these risk factors, and it has been suggested that other factors, including those yet to be discovered, may be involved.²⁸ Explanations as to why diabetes duration is independently associated with CVD risk are not fully understood but includes chronic exposure to hyperglycaemia, worsening of β -cell function, and increased insulin insufficiency^{16,29} For example, hyperglycaemia is known to induce oxidative stress thereby triggering various pathways involved in vascular damage. Moreover, it is well known that glucose can react with various proteins to form advanced glycaemic end products i.e. glycosylated haemoglobin (HbA1c) and glycosylated albumin.³⁰ These advanced glycosylated end products may result in long-term diabetes-related complications including plaque formation, atherosclerosis, and micro- and macrovascular disease.³⁰ Insulin insufficiency and resistance could also play a role in the development of diabetes-related complications as endogenous insulin is involved in many pathways and tissues beyond glucose-metabolism.¹⁶

Clinical implications

The apparent gradual association between duration of diabetes and the risk of major cardiovascular complications indicate that effective prevention and adequate treatment of cardiovascular complications requires awareness and active screening at all stages of the disease. Moreover, the incidence rates and relative risks were highest in the groups with longest diabetes

duration in both sexes, suggesting that screening for cardiovascular complications should be intensified with increasing diabetes duration.¹⁸

Strengths and limitations

The strengths of this study include its prospective design, large cohort of individuals with type 2 diabetes, and the extensive phenotypic detail available on all participants. In addition, several sensitivity analyses were performed to minimize the impact of potential misclassification of type of diabetes, and all CVD outcomes were adjudicated by the UK Biobank outcome adjudication group. Lastly, sex-specific effects and sex difference were assessed both on absolute and relative scales. Although, incidence rates are less likely to be applicable in other populations, they should be considered when making clinical decisions.

This study also has some limitations. First, people with a higher socioeconomic status and of Caucasian background are overrepresented in the UK Biobank, which may have limited the generalisability of our results. Second, duration of diabetes was self-reported, which may have resulted in some misclassification in both sexes. Especially, for those with longer diabetes duration it may have been more challenging to report the age at diagnosis accurately. However, there is no reason to assume that women and men reported differently on these aspects. Third, although we adjusted for several major confounding factors, including sex-specific confounding, residual confounding may be present.

Conclusions

The increased risk of CVD, MI, and stroke associated with longer duration of diabetes is similar for women and men.

Acknowledgements

This research has been conducted using the UK Biobank Resource (application No 2495). Permission to use the UK Biobank Resource was approved by the access subcommittee of the UK Biobank Board.

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Supplemental table I. Baseline characteristics by sex and diabetes duration.

	Women		Men	
	<5 years n=3,742	≥5 to <10 years n=2,125	<5 years n=5,268	≥5 to <10 years n=3,374
				≥10 years n=2,760
General characteristics				
Age, years	59.0 (7.1)	59.7 (6.9)	58.5 (7.3)	61.3 (6.2)
White ethnicity	3,212 (87%)	1,774 (84%)	4,611 (88%)	2,981 (89%)
Socioeconomic status*				
Higher than average	2,059 (55%)	1,172 (55%)	3,058 (58%)	2,015 (60%)
Lower than average	1,678 (45%)	948 (45%)	2,201 (42%)	1,355 (40%)
Smoking				
Never	2,113 (57%)	1,285 (61%)	2,159 (41%)	1,320 (39%)
Past	1,260 (34%)	650 (31%)	2,435 (47%)	1,619 (48%)
Current	338 (9%)	165 (8%)	631 (12%)	405 (12%)
Diabetes characteristics				
Median diabetes duration, years (IQR)	2 (1-3)	7 (5-8)	2 (1-3)	7 (5-8)
Median HbA1c, % (IQR)	6.5 (6.0-7.1)	6.9 (6.3-7.6)	6.4 (5.9-7.1)	6.8 (6.2-7.6)
Risk factors				
BMI, kg/m ²	32.6 (6.5)	32.6 (6.6)	30.9 (5.2)	31.0 (5.2)
Systolic BP, mmHg	140.2 (17.5)	139.5 (17.2)	142.4 (16.1)	142.5 (16.8)
Diastolic BP, mmHg	82.5 (9.5)	80.9 (9.1)	84.3 (9.2)	82.5 (9.2)
Cholesterol, mmol/L	4.8 (1.1)	4.7 (1.0)	4.5 (1.0)	4.3 (0.9)

Supplemental table 1. Baseline characteristics by sex and diabetes duration. (continued)

	Women		Men			
	<5 years n=3,742	≥5 to <10 years n=2,125	≥10 years n=1,692	<5 years n=5,268	≥5 to <10 years n=3,374	≥10 years n=2,760
Prescribed medication						
Glucose-lowering medication						
<i>No medication</i>	1,861 (50%)	493 (23%)	261 (15%)	2,708 (51%)	944 (28%)	426 (15%)
<i>Oral</i>	1,723 (46%)	1,366 (64%)	765 (45%)	2,345 (45%)	2,053 (61%)	1,404 (51%)
<i>Insulin</i>	74 (2%)	99 (5%)	308 (18%)	86 (2%)	124 (4%)	444 (16%)
<i>Oral + Insulin</i>	84 (2%)	167 (8%)	358 (21%)	129 (2%)	253 (7%)	486 (18%)
Antihypertensive medication	1,869 (50%)	1,279 (60%)	1,022 (60%)	2,580 (49%)	2,059 (61%)	1,833 (66%)
Lipid-lowering medication	2,345 (63%)	1,473 (69%)	1,177 (70%)	3,313 (63%)	2,420 (72%)	2,000 (72%)

Data are mean (SD) or n (%), unless otherwise indicated. *Socioeconomic status was determined using the postcode based Townsend deprivation index and dichotomised using the national median Townsend score (high: ≤ -0.56 ; low: > -0.56). IQR = interquartile range; BMI = body mass index; BP = blood pressure. Due to missing data, not all variables included add up to n = 11,402 for men and n = 7,559 for women.

Supplemental table II. Overview of missing data

	Missing data <i>n = 18,961</i>
Age	0 (0%)
Ethnicity	161 (0.8%)
Socioeconomic status	32 (0.2%)
Smoking	187 (1.0%)
HbA1c	1,502 (7.9%)
Body mass index	196 (1.0%)
Systolic blood pressure	77 (0.4%)
Diastolic blood pressure	77 (0.4%)
Cholesterol	1,311 (6.9%)
Antidiabetic medication	0 (0%)
Antihypertensive medication	0 (0%)
Lipid-lowering medication	0 (0%)

Supplemental table III. Age-adjusted and multiple-adjusted rates of cardiovascular disease, myocardial infarction, and stroke (per 10,000 person-years) by sex and diabetes duration.

	Women	Men	Difference of rate differences (women-men)
CVD			
Model 1			
<5 years	44.9 (38.3;51.5)	71.0 (63.8;78.2)	NA
≥5 to <10 years	56.4 (46.6;66.1)	91.3 (81.4;101.3)	-8.9 (-26.0;8.1)
≥10 years	76.0 (63.3;88.6)	124.1 (111.2;137.0)	-22.1 (-42.7; -1.5)
Model 2			
<5 years	43.8 (36.7;50.9)	73.4 (65.5;81.3)	NA
≥5 to <10 years	54.9 (44.5;65.4)	97.1 (85.9;108.3)	-12.6 (-30.9;5.7)
≥10 years	74.4 (61.0;87.9)	122.2 (108.3;136.1)	-18.2 (-40.1;3.7)
MI			
Model 1			
<5 years	24.0 (19.2;28.9)	47.9 (42.0;53.7)	NA
≥5 to <10 years	30.5 (23.3;37.6)	53.3 (45.7;60.8)	1.0 (-11.9;13.9)
≥10 years	42.7 (33.3;52.1)	80.4 (70.1;90.7)	-13.9 (-29.9;2.1)
Model 2			
<5 years	23.6 (18.4;28.8)	49.8 (43.3;56.3)	NA
≥5 to <10 years	29.0 (21.5;36.6)	56.8 (48.3;65.4)	-1.6 (-15.5;12.3)
≥10 years	40.7 (30.8;50.6)	80.1 (68.8;91.4)	-12.2 (-30.3;3.8)

Supplemental table III. Age-adjusted and multiple-adjusted rates of cardiovascular disease, myocardial infarction, and stroke (per 10,000 person-years) by sex and diabetes duration. (continued)

	Women	Men	Difference of rate differences (women-men)
Stroke			
Model 1			
<5 years	22.0 (17.4;26.7)	25.1 (20.9;29.4)	NA
≥5 to <10 years	27.3 (20.6;34.1)	41.5 (34.8;48.1)	-11.0 (-22.4;0.4)
≥10 years	36.5 (27.8;45.2)	49.3 (41.3;57.2)	-9.7 (-23.1;3.7)
Model 2			
<5 years	21.6 (16.6;26.5)	25.6 (21.5;30.2)	NA
≥5 to <10 years	27.1 (19.8;34.4)	42.8 (35.6;50.0)	-11.6 (-23.7;0.5)
≥10 years	36.1 (26.9;45.4)	46.1 (37.9;54.3)	-5.9 (-19.9;8.1)

Model 1: Analyses were adjusted for age. Model 2: model 1 + smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, Townsend score, ethnicity, and interaction terms between each variable and sex. NA = not applicable; CVD = cardiovascular disease, MI = myocardial infarction.

Supplemental table IV. Age-adjusted and multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease, myocardial infarction and stroke according to diabetes duration.

	Number of events (%)		Hazard ratios (95% CI)		Women-to-men RHR
	Women	Men	Women	Men	
CVD					
Model 1					
<5 years	176 (4.7%)	378 (7.2%)	1.0	1.0	NA
≥5 to <10 years	128 (6.0%)	323 (9.6%)	1.26 (1.00;1.58)	1.29 (1.11;1.50)	0.97 (0.74;1.28)
≥10 years	139 (8.2%)	362 (13.1%)	1.70 (1.36;2.13)	1.76 (1.52;2.04)	0.97 (0.74;1.26)
Model 2					
<5 years	160 (4.7%)	346 (7.2%)	1.0	1.0	NA
≥5 to <10 years	112 (5.9%)	301 (9.7%)	1.25 (0.98;1.60)	1.33 (1.13;1.55)	0.95 (0.71;1.26)
≥10 years	123 (8.2%)	316 (12.7%)	1.71 (1.34;2.17)	1.68 (1.43;1.96)	1.02 (0.76;1.35)
MI					
Model 1					
<5 years	95 (2.5%)	259 (4.9%)	1.0	1.0	NA
≥5 to <10 years	70 (3.3%)	191 (5.7%)	1.27 (0.93;1.73)	1.11 (0.92;1.34)	1.14 (0.79;1.63)
≥10 years	79 (4.7%)	237 (8.6%)	1.78 (1.32;2.40)	1.69 (1.41;2.02)	1.05 (0.74;1.49)
Model 2					
<5 years	87 (2.6%)	236 (4.9%)	1.0	1.0	NA
≥5 to <10 years	60 (3.2%)	177 (5.7%)	1.23 (0.88;1.71)	1.14 (0.94;1.39)	1.08 (0.73;1.58)
≥10 years	68 (4.5%)	206 (8.3%)	1.73 (1.25;2.39)	1.62 (1.34;1.96)	1.06 (0.73;1.55)

Supplemental table IV. Age-adjusted and multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease, myocardial infarction and stroke according to diabetes duration. (continued)

	Number of events (%)		Hazard ratios (95% CI)		
	Women	Men	Women	Men	Women-to-men RHR
Stroke					
Model 1					
<5 years	87 (2.3%)	135 (2.6%)	1.0	1.0	NA
≥5 to <10 years	63 (3.0%)	150 (4.5%)	1.24 (0.90;1.72)	1.66 (1.31;2.09)	0.75 (0.50;1.12)
≥10 years	68 (4.0%)	150 (5.4%)	1.66 (1.21;2.29)	1.97 (1.56;2.50)	0.84 (0.57;1.25)
Model 2					
<5 years	79 (2.3%)	125 (2.6%)	1.0	1.0	NA
≥5 to <10 years	56 (3.0%)	140 (4.5%)	1.26 (0.89;1.78)	1.67 (1.31;2.14)	0.75 (0.49;1.15)
≥10 years	61 (4.1%)	130 (5.2%)	1.68 (1.20;2.37)	1.81 (1.41;2.33)	0.93 (0.61;1.42)

Model 1: Analyses were adjusted for age. Model 2: model 1 + smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, Townsend score, ethnicity, and interaction terms between each variable and sex. NA= not applicable; CVD = cardiovascular disease; MI = myocardial infarction.

Supplemental table V. Age- and multivariable adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease, myocardial infarction, and stroke per 5 years of diabetes duration.

	Number of events		Hazard ratios (95% CI)		
	Women	Men	Women	Men	Women-to-men RHR
CVD					
Model 1	443 (5.9%)	1,063 (9.3%)	1.19 (1.12;1.27)	1.18 (1.13;1.23)	1.01 (0.94;1.09)
Model 2	395 (5.8%)	963 (9.3%)	1.20 (1.12;1.28)	1.16 (1.11;1.22)	1.03 (0.95;1.12)
MI					
Model 1	244 (3.2%)	687 (6.0%)	1.23 (1.13;1.34)	1.18 (1.12;1.25)	1.04 (0.95;1.15)
Model 2	215 (3.2%)	619 (5.9%)	1.23 (1.12;1.35)	1.16 (1.09;1.23)	1.06 (0.95;1.18)
Stroke					
Model 1	218 (2.9%)	435 (3.8%)	1.16 (1.05;1.27)	1.20 (1.12;1.28)	0.96 (0.86;1.08)
Model 2	196 (2.9%)	395 (3.8%)	1.16 (1.05;1.28)	1.17 (1.09;1.26)	0.99 (0.88;1.12)

Model 1: Age-adjusted; Model 2: model 1 + smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering medication, cholesterol, antihypertensive medication, Townsend score, ethnicity, and interaction terms between each variable and sex. CVD = cardiovascular disease; MI = myocardial infarction.

Supplemental table VI. Multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease per 5 years of diabetes duration, stratified by age, BMI, socioeconomic status and ethnicity.

	Number of events		Hazard ratios (95% CI)		
	Women	Men	Women	Men	Women-to-men RHR
Age					
<60	109 (3.9%)	288 (6.7%)	1.27 (1.09;1.49)	1.23 (1.11;1.36)	1.03 (0.86;1.25)
≥60	286 (7.2%)	675 (11.0%)	1.20 (1.11;1.29)	1.16 (1.10;1.22)	1.03 (0.94;1.13)
BMI					
<30	154 (5.8%)	448 (8.7%)	1.08 (0.97;1.21)	1.16 (1.09;1.23)	0.94 (0.83;1.06)
≥30	241 (5.9%)	515 (9.8%)	1.29 (1.18;1.41)	1.17 (1.09;1.25)	1.11 (0.99;1.24)
Socioeconomic status*					
High	191 (5.0%)	546 (8.9%)	1.23 (1.12;1.36)	1.17 (1.10;1.25)	1.05 (0.94;1.18)
Low	204 (6.8%)	417 (9.7%)	1.17 (1.07;1.29)	1.15 (1.08;1.23)	1.02 (0.91;1.14)
Ethnicity**					
White	333 (5.7%)	848 (9.2%)	1.18 (1.10;1.28)	1.13 (1.08;1.19)	1.04 (0.95;1.14)
Non-white	62 (6.3%)	115 (9.3%)	1.27 (1.08;1.50)	1.31 (1.17;1.45)	0.98 (0.80;1.18)

Analyses were adjusted for age, smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, and interaction terms between each variable and sex. Subgroup analyses by age were not adjusted for age. Subgroup analyses by BMI were not adjusted for BMI. Subgroup analyses by socioeconomic status were not adjusted for socioeconomic status. Subgroup analyses by ethnicity were not adjusted for ethnicity. BMI = body mass index. * Socioeconomic status was determined using the postcode based Townsend deprivation index and dichotomised using the national median Townsend score (high: ≤ -0.56 ; low > -0.56); ** Non-white includes Asian or Asian British, black or black British, Caribbean, African, any other black background, Chinese, other ethnic group, white and black Caribbean, white and black African, white and Asian, any other mixed background, Indian, Pakistani, Bangladeshi, any other Asian background.

Supplemental table VII. Age-adjusted and multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease, excluding those who misinterpreted the touch screen question “what was your age when diabetes was first diagnosed?”

	Hazard ratios (95% CI)		
	Women	Men	Women-to-men RHR
Model 1			
<5 years	1.0	1.0	1.0
≥5 to <10 years	1.24 (0.98;1.58)	1.27 (1.09;1.48)	0.98 (0.74;1.30)
≥10 years	1.71 (1.36;2.16)	1.73 (1.49;2.01)	0.99 (0.75;1.30)
Per 5-year increase	1.19 (1.11;1.27)	1.17 (1.12;1.23)	1.01 (0.94;1.10)

Supplemental table VII. Age-adjusted and multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease, excluding those who misinterpreted the touch screen question “what was your age when diabetes was first diagnosed?” (continued)

	Hazard ratios (95% CI)		
	Women	Men	Women-to-men RHR
Model 2			
<5 years	1.0	1.0	1.0
≥5 to <10 years	1.22 (0.95;1.57)	1.31 (1.12;1.54)	0.93 (0.69;1.25)
≥10 years	1.74 (1.36;2.23)	1.65 (1.41;1.94)	1.05 (0.78;1.41)
Per 5-year increase	1.21 (1.12;1.29)	1.16 (1.11;1.21)	1.04 (0.96;1.13)

Model 1: Analyses were adjusted for age. Model 2: model 1 + smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, and interaction terms between each variable and sex.

Supplemental table VIII. Age-adjusted and multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease excluding those with insulin only.

	Hazard ratios (95% CI)		
	Women	Men	Women-to-men RHR
Model 1			
<5 years	1.0	1.0	1.0
≥5 to <10 years	1.23 (0.98;1.55)	1.27 (1.10;1.48)	0.97 (0.73;1.28)
≥10 years	1.64 (1.29;2.09)	1.72 (1.47;2.00)	0.96 (0.72;1.27)
Per 5-year increase	1.20 (1.11;1.29)	1.19 (1.14;1.25)	1.00 (0.91;1.10)
Model 2			
<5 years	1.0	1.0	1.0
≥5 to <10 years	1.24 (0.97;1.59)	1.30 (1.11;1.53)	0.95 (0.71;1.27)
≥10 years	1.63 (1.26;2.10)	1.62 (1.37;1.91)	1.01 (0.74;1.36)
Per 5-year increase	1.19 (1.10;1.28)	1.18 (1.11;1.24)	1.01 (0.92;1.11)

Model 1: Analyses were adjusted for age. Model 2: model 1 + smoking (never, former, current), BMI, systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, and interaction terms between each variable and sex.

Supplemental table IX. Multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease without adjustment for BMI.

	Hazard ratios (95% CI)		
	Women	Men	Women-to-men HR
<5 years	1.0	1.0	1.0
≥5 to <10 years	1.28 (1.00;1.63)	1.32 (1.13;1.54)	0.97 (0.72;1.29)
≥10 years	1.70 (1.34;2.16)	1.69 (1.45;1.97)	1.01 (0.76;1.34)
Per 5-year increase	1.19 (1.12;1.28)	1.16 (1.10;1.21)	1.03 (0.95;1.12)

Analyses were adjusted for age, smoking (never, former, current), systolic blood pressure, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, and interaction terms between each variable and sex.

Supplemental table X. multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease additionally adjusted for glucose-lowering medication and HbA1c.

	Hazard ratios (95% CI)		
	Women	Men	Women-to-men RHR
<5 years	1.0	1.0	1.0
≥5 to <10 years	1.22 (0.95;1.58)	1.22 (1.04;1.44)	1.00 (0.74;1.36)
≥10 years	1.51 (1.16;1.96)	1.43 (1.21;1.70)	1.05 (0.77;1.44)
Per 5-year increase	1.15 (1.07;1.24)	1.11 (1.05;1.17)	1.04 (0.95;1.14)

Analyses were adjusted for age, smoking (never, former, current), systolic blood pressure, BMI, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, glucose-lowering medication, HbA1c, and interaction terms between each variable and sex.

Supplemental table XI. Age- and multiple-adjusted sex-specific hazard ratios and women-to-men ratio of hazard ratios of cardiovascular disease excluding participants without glucose-lowering medication.

	Hazard ratios (95% CI)		
	Women	Men	Women-to-men RHR
Model 1			
<5 years			
≥5 to <10 years	1.35 (1.02;1.78)	1.27 (1.05;1.53)	1.06 (0.76;1.49)
≥10 years	1.63 (1.24;1.16)	1.76 (1.47;2.12)	0.93 (0.66;1.29)
Per 5-year increase	1.19 (1.10;1.28)	1.18 (1.12;1.24)	1.00 (0.91;1.10)
Model 2			
<5 years	1.0	1.0	1.0
≥5 to <10 years	1.31 (1.07;1.76)	1.37 (1.12;1.67)	0.96 (0.67;1.37)
≥10 years	1.62 (1.21;1.18)	1.75 (1.44;2.13)	0.93 (0.65;1.32)
Per 5-year increase	1.19 (1.10;1.30)	1.17 (1.11;1.24)	1.02 (0.92;1.12)

Analyses were adjusted for age, smoking (never, former, current), systolic blood pressure, BMI, lipid-lowering drugs, cholesterol, antihypertensive medication, socioeconomic status, ethnicity, and interaction terms between each variable and sex.



Part 3

Sex differences in cardiovascular risk management in diabetes



Chapter 7

Sex differences in cardiovascular risk management for people with diabetes in primary care: a cross-sectional study

Marit de Jong
Rimke C. Vos
Rianneke de Ritter
Carla J.H. van der Kallen
Simone J.S. Sep, PhD
Mark Woodward
Coen D.A. Stehouwer
Michiel L. Bots
Sanne A.E. Peters

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Abstract

Objective

Diabetes is a stronger risk factor for cardiovascular complications in women than men. The aim of this study is to evaluate whether there are sex differences in cardiovascular risk management in patients with diabetes in primary care.

Research Design and Methods

A cross-sectional study was undertaken using data from 12,512 individuals with diabetes within the Dutch Julius General Practitioners Network (JGPN) from 2013. Linear and Poisson regression analyses were used to assess sex differences in risk factor levels, assessment, treatment, and control.

Results

No sex differences were found in HbA1c levels and control, while small differences were found for cardiovascular risk management. Blood pressure levels were higher (mean difference [MD] 1.09 mmHg; 95% confidence intervals [CI] = 0.41 to 1.77), while cholesterol levels (MD -0.38 mmol/l; 95% CI = -0.42 to -0.34) and body mass index ([BMI] MD -1.79 kg/m²; 95% CI = -2.03 to -1.56) were lower in men than women. Risk factor assessment was similar between sexes, apart from high-density lipoprotein cholesterol (HDL cholesterol), which was more commonly assessed in women (risk ratio [RR] 1.16; 95% CI = 1.13 to 1.19). Among those with a treatment indication for prevention, women with cardiovascular disease (CVD) were less likely to receive lipid-lowering drugs (RR 0.84; 95% CI = 0.76 to 0.93) than men, while women without CVD were more likely to receive lipid-lowering drugs (RR 1.16; 95% CI = 1.04 to 1.20). Among those treated, women were more likely to achieve systolic blood pressure (SBP) control (RR 1.06; 95% CI = 1.02 to 1.10) and less likely to achieve low-density lipoprotein cholesterol (LDL cholesterol) control (RR 0.88; 95% CI = 0.85 to 0.91) than men.

Conclusions

In this Dutch primary care setting, sex differences in risk factor assessment and treatment of people with diabetes were small. However, women with diabetes were less likely to achieve control for LDL cholesterol and more likely to achieve blood pressure control than men with diabetes.

Introduction

Diabetes mellitus is one of the most prevalent chronic disorders globally, with an estimated prevalence of 425 million affected individuals in 2017.¹ Individuals with diabetes are two to three times more likely to develop cardiovascular disease (CVD) compared to individuals without diabetes. Large-scale meta-analyses have demonstrated that the excess risk of major cardiovascular complications associated with diabetes is substantially greater in women than men.^{2,3} So far, no clear explanation for the greater excess risk of major cardiovascular complications in women has been identified, although sex differences in cardiovascular risk management may be involved.⁴ Guideline-recommended management for the prevention and delay of cardiovascular complications in individuals with diabetes focuses on optimizing lifestyle factors, including smoking behaviour, physical activity, diet, and weight control, and adequate management of blood pressure, cholesterol, and glucose levels.^{5,6}

Previous studies have reported mixed findings regarding the presence, magnitude, and direction of sex differences in cardiovascular risk management for people with diabetes.⁷⁻¹² For example, the National Diabetes Audit in the UK demonstrated that women were less likely than men to receive annual tests for cardiovascular risk factors and to achieve treatment targets.⁷ In contrast, a large cross-sectional study among 18,000 men and women with diabetes in the United States showed that women with diabetes were more likely than men to receive annual tests for dilated eye exams, blood pressure control, and to visit a doctor than men with diabetes. Moreover, while the magnitude of the sex difference in the complications of diabetes varies by age, it remains unknown whether any difference in cardiovascular risk management is age-specific.¹³

Therefore, this study evaluated the presence of sex differences in cardiovascular risk management for individuals with diabetes across different age groups in a large Dutch population attending primary care.

Methods

Routinely collected data from the Julius General Practitioner Network (JGPN) from 2013 were used. The JGPN is a large, ongoing, dynamic cohort of primary care patients that anonymously extracts routine healthcare data from electronic primary care records at one of the included general practices in Utrecht (the Netherlands) and its vicinity, as detailed elsewhere.¹⁴ All individuals in care at one of the JGPN practices are included in the JGPN cohort. Adult individuals were included in this study if they were previously diagnosed with diabetes mellitus (ICPC T90), and had been registered at the primary care practice for at least 12 months in 2013 (n = 12,512).

Data extraction

Data on cardiovascular risk factors, blood tests, physical measurements, history of cardiovascular events, and drug prescriptions were extracted from the medical records. The last available measurement in 2013 of the following cardiovascular risk factors of importance in diabetes care were included: HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP),

total cholesterol (TC), LDL cholesterol, HDL cholesterol, and BMI. Medical history of CVD was determined according to the international classification of primary care (ICPC-1) (supplemental data Table I).¹⁵ Data on drug prescriptions for glucose-lowering drugs (A10), lipid-lowering drugs (C10), and antihypertensive drugs (C02, C03, C07, C08, C09) were coded using the anatomical therapeutic chemical classification (ATC) system.¹⁶

Outcomes of interest

Four aspects of cardiovascular risk management were assessed by sex. First, it needed to be determined whether an assessment had been performed for each of the cardiovascular risk factors. Second, the difference between the sexes for the last measured value of cardiovascular risk factors in 2013 was assessed. Third, among those with a treatment indication, as detailed below, for lowering HbA1c, SBP or LDL cholesterol, the proportion of individuals that received pharmacological treatment was assessed. Fourth, among those receiving pharmacological treatment, the proportion of individuals that attained adequate levels according to Dutch guidelines was examined. These guidelines say that individuals at 10-year risk of CVD of >20% and with inadequate levels of SBP (>140mmHg) or LDL cholesterol (>2.5mmol/L) are eligible for antihypertensive or lipid-lowering drugs, and individuals with HbA1c being off target (53mmol/mol (>7.0%)) are eligible to receive glucose-lowering drugs.^{5,6} CVD risk was assessed using the Systematic Coronary Risk Evaluation (SCORE).⁶ Since all individuals in this study were previously diagnosed with diabetes, 15 years were added to their original age, as recommended by the Dutch cardiovascular risk management classification tool.⁶ Additionally, all individuals with a known history of CVD were classified as high risk (>20%).

Statistical analysis

Sex-specific baseline characteristics are presented as N and percentages for categorical variables, and as means with standard deviations (SD) for continuous variables, overall and stratified by age group. Age groups were categorized as 20-39, 40-49, 50-59, 60-69, 70-79, 80-99 years, and also as <60 years and ≥60 years. Poisson regression analyses with robust standard errors were used to estimate women-to-men risk ratios (RR) and 95% CIs for analyses on sex associated with assessment, treatment, and control of cardiovascular risk factors. Linear regression analyses were used to calculate men-to-women mean differences (MD) and 95% CIs for cardiovascular risk factor levels. Participants with missing data were not included in the relevant model. Analyses were adjusted for age in the overall analyses but not in the analyses by age group. In secondary analyses, men-to-women MDs and 95% CIs in cardiovascular risk factor levels were adjusted for drug prescriptions. Additionally, analyses were stratified according to previous history of CVD. An interaction term was added to the models for sex with age (as a continuous variable) and for sex with known history of CVD, to assess whether the effect of sex on the outcomes of interest varied with age and known history of CVD. All analyses were performed using SPSS Statistics Version 21.

Results

For this study, routine care data were used from all 193,643 registered individuals aged ≥ 20 and < 100 years in care in 2013 at one of the 53 JGPN general practices. The 2013 JGPN database included 12,512 (50% women) individuals with diabetes with a mean age of 64 years. Of those, 31% of men and 27% of women had a known history of CVD. Women were slightly older, less likely to smoke, and more likely to have a higher BMI than men. (Table 1 and Supplemental Table II)

Table 1. Baseline characteristics.

	Men <i>n</i> =6,276	Women <i>n</i> =6,236
General characteristics		
Age, years	63.1 (12.9)	65.1 (14.1)
Smoking		
<i>Current</i>	1,168 (22)	815 (15)
<i>Never</i>	1,583 (30)	3,069 (58)
<i>Former</i>	2,489 (48)	1,418 (27)
10-year cardiovascular disease risk		
<i>Low (<10%)</i>	146 (4)	364 (8)
<i>Intermediate (10-20%)</i>	173 (4)	563 (13)
<i>High (>20%)</i>	3,888 (92)	3,548 (79)
Known history of cardiovascular disease	1,968 (31)	1,670 (27)
Measurements		
HbA1c, mmol/mol	54.6 (12.8)	54.0 (11.6)
HbA1c, %	7.2 (3.3)	7.1 (3.2)
Systolic blood pressure, mmHg	137.9 (17.2)	137.5 (18.0)
Diastolic blood pressure, mmHg	79.3 (10.1)	78.5 (10.3)
Total cholesterol, mmol/L	4.4 (1.0)	4.7 (1.0)
LDL cholesterol, mmol/L	2.4 (0.8)	2.6 (0.9)
HDL cholesterol, mmol/L	1.2 (0.3)	1.4 (0.3)
Body mass index, <i>kg/m</i> ²	29.1 (4.6)	30.7 (6.0)
Glucose-lowering drugs	4,475 (71)	4,209 (68)
Lipid-lowering drugs	3,966 (63)	3,592 (58)
Antihypertensive drugs	4,139 (66)	4,245 (68)

Data are mean (SD) or n (%). Due to missing data not all variables included add up to *n* = 6,276 for men and *n* = 6,236 for women.

Assessment of cardiovascular risk factors

Assessment of all cardiovascular risk factors was performed in 43% of the included individuals, while assessment of the three main risk factors – HbA1c, SBP and LDL cholesterol combined – was performed in 63% of the included individuals. Moreover, 84% received testing for at least

one cardiovascular risk factor. Blood pressure was most often assessed (79%), followed by HbA1c (75%), TC (73%), LDL cholesterol (70%), HDL cholesterol (62%), and BMI (62%). Testing of all cardiovascular risk factors was more likely to have been performed in women than men; the age-adjusted RR was 1.19 (1.14-1.23). HDL cholesterol alone was more commonly assessed in women than men (1.16 [1.13-1.19]). Assessment of SBP, DBP and LDL cholesterol separately, and of one or more cardiovascular risk factors combined, was slightly greater in women than men with age-adjusted RRs of 1.02 (1.00-1.03), 1.02 (1.00-1.03), 1.02 (1.00-1.05), and 1.01 (1.00-1.05), respectively. No differences were found for assessment of HbA1c (1.00 [0.98-1.02]), TC (1.00 [0.98-1.02]), BMI (1.01 [0.98-1.03]) or HbA1c, SBP and LDL cholesterol combined (1.02 [0.99-1.05]). (Figure 1 and Supplemental Table III) Although differences between age groups were small, the interaction term for sex with age as a continuous variable showed significant differences for assessment of SBP ($p=0.02$), DBP ($p=0.01$), LDL cholesterol ($p=0.01$), HDL cholesterol ($p<0.01$), BMI ($p<0.01$), testing of all cardiovascular risk factors ($p<0.01$), assessment of HbA1c, SBP and LDL cholesterol combined ($p=0.01$), and assessment of one or more cardiovascular risk factors ($p=0.02$) (Supplemental Table III). No significant results were found for the interaction term of sex with CVD status (Supplemental Table IV).

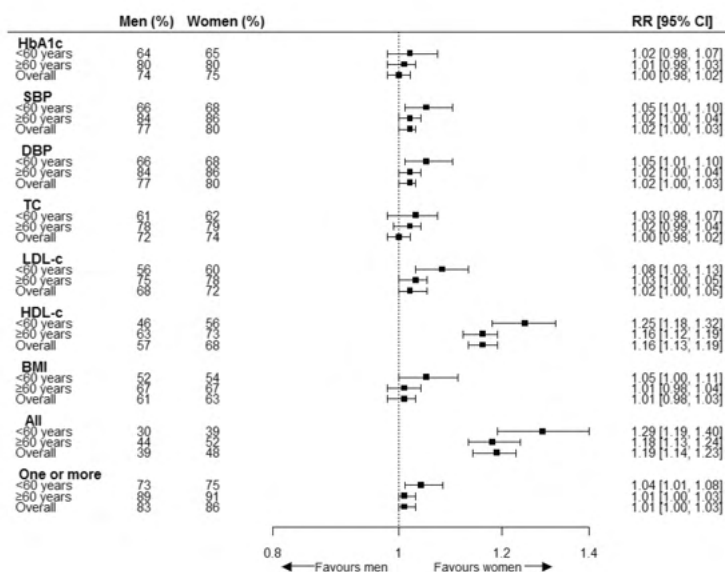


Figure 1. Women-to-men risk ratios for the assessment of cardiovascular risk factors. The analyses are adjusted for age. SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol. Men = reference category.

Cardiovascular risk factor levels

Individuals included in this study had a mean HbA1c of 54 mmol/mol (7.1%), SBP of 138 mmHg, DBP of 79 mmHg, TC of 4.5 mmol/L, LDL cholesterol of 2.5 mmol/L, HDL cholesterol of 1.3 mmol/L, and a BMI of 30 kg/m². Age-adjusted analyses showed that blood pressure was higher in men than women by 1.09 mmHg (0.41;1.77) for SBP and 0.41 mmHg (0.01;0.80) for DBP. In contrast, TC, LDL

cholesterol, HDL cholesterol, and BMI were lower in men than women; mean differences were -0.38 mmol/L (-0.42;-0.34) for TC, -0.19 mmol/L (-0.23;0.15) for LDL cholesterol, -0.17 mmol/L (-0.18;-0.16) for HDL cholesterol, and -1.79 kg/m² (-2.03;-1.56) for BMI. No differences were seen for HbA1c (0.45 mmol/mol [-0.05;0.95]) (Figure 2 and Supplemental Table V). The results were similar after adjustment for drug prescriptions (Supplemental Table V). The interaction term for sex with age as a continuous variable showed significant differences for HbA1c ($p=0.01$), SBP ($p<0.01$), DBP ($p<0.01$), TC ($p<0.01$), LDL cholesterol (0.04) and BMI (<0.01), showing that the effect of sex on last measured cardiovascular risk factors changes with age, although actual differences were small (Supplemental Table V). The interaction term for sex with known history of CVD showed a significant difference for DBP ($p=0.03$), showing that the effect of sex on last measured DBP differed for individuals with CVD (-0.35 [-1.09;0.40]) and without CVD (0.84 [-0.38;1.31]) (supplemental table VI).

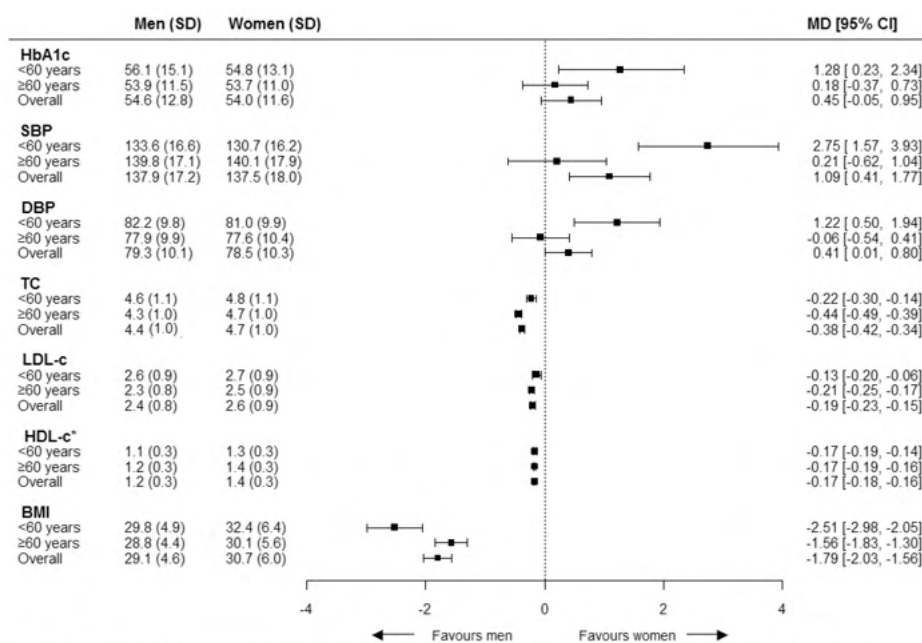


Figure 2. Men-to-women differences of cardiovascular risk factor levels. The analyses are adjusted for age. SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol. Women = reference category. *Increased HDL cholesterol is in favour of women. Mean (SD) for men and women separately not adjusted for age.

Treatment

Among those with a treatment indication for receiving drugs, 92% received glucose-lowering drugs when indicated, 84% received antihypertensive drugs when indicated, and 52% received lipid-lowering drugs when indicated. No sex differences were found for receiving glucose-lowering drugs with age-adjusted RR of 0.99 (0.98-1.01), for antihypertensive drugs (1.00 [0.96-1.03]), and for lipid-lowering drugs (1.00 [0.93-1.08]) (Figure 3 and Supplemental Table VII). The interaction

term for sex with age as a continuous variable showed significant difference for receiving blood-pressure lowering drugs when indicated ($p < 0.01$) (Supplemental Table VII). Sex differences in LDL cholesterol treatment were revealed after stratification for known CVD history; women without a known history of CVD were more likely to receive lipid-lowering drugs than men (1.16 [1.04-1.29]), whereas women with a known history of CVD were less likely to receive lipid-lowering drugs than men (0.84 [0.76-0.93]) (p for interaction = < 0.01) (Supplemental Table VIII).

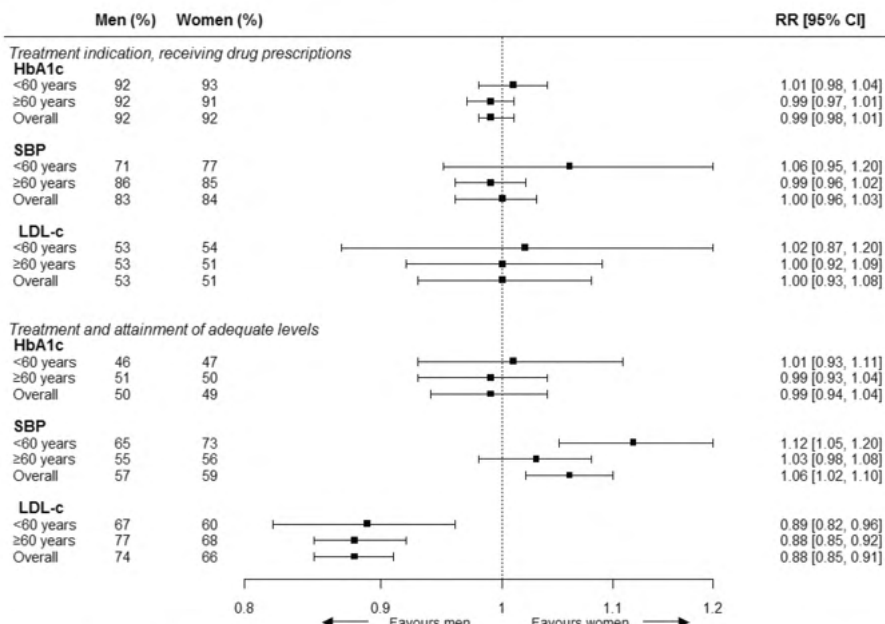


Figure 3. Women-to-men risk ratios for treatment and control of cardiovascular risk factors. The analyses are adjusted for age. SBP = systolic blood pressure; RR = risk ratio.. Men = reference category.

Risk factor control

Among those receiving glucose-lowering drugs, 49% were on target ($\leq 7\%$ ($\leq 53\text{mmol/mol}$)). For those receiving antihypertensive drugs or lipid-lowering drugs, 58% and 70% were on target for SBP ($\leq 140\text{mmHg}$) and LDL cholesterol ($\leq 2.5\text{mmol/L}$), respectively. Among those treated, women were more likely than men to be on target for SBP (1.06 [1.02-1.10]) and less likely to be on target for LDL cholesterol (0.88 [0.85-0.91]). No sex differences were found for control of HbA1c (0.99 [0.94-1.04]) (Figure 3 and Supplemental Table IX). Similar results were found after stratification for known CVD history (supplemental Table X). The interaction term for sex with age as a continuous variable was significant for being on target for SBP while receiving antihypertensive drugs ($p = 0.02$) and no significant interaction term was found for history of CVD (Supplemental Table X and Supplemental Table XI).

Discussion

In this study, the presence of sex differences in cardiovascular risk management in a Dutch population of individuals with diabetes mellitus in routine primary care was assessed. We found that only 43% of the included individuals received assessment of all cardiovascular risk factors, while 63% of the included individuals received assessment of the main cardiovascular risk factors - HbA1c, SBP and LDL cholesterol combined - and 83% received testing of one or more cardiovascular risk factors. Among those with a treatment indication for lowering HbA1c, 92% received glucose-lowering drugs, while only 84% and 52% of those with a treatment indication for lowering SBP or LDL cholesterol received prescriptions for antihypertensive drugs or lipid-lowering drugs, respectively. Furthermore, among those receiving glucose-lowering drugs, antihypertensive drugs, or lipid-lowering drugs, only 49%, 58% and 70% were on target for HbA1c, SBP and LDL cholesterol, respectively. Sex differences in risk factor assessment and treatment were generally small and an interaction term for sex with age as a continuous variable was found to be significant for several of the analyses, although actual differences were small. Blood pressure levels were lower and cholesterol levels were higher in women than men. Among those treated, women were less likely than men to achieve adequate control for LDL cholesterol, but more likely to achieve blood pressure control.

Strengths and limitations

Using routinely collected data from 53 primary care practices in the Netherlands, this study provides a representative evaluation of sex differences in cardiovascular risk management among Dutch individuals with diabetes attending primary care. A limitation of using routinely collected data is that the completeness of data depends on recording practices of general practitioners. For example, recording of smoking status in primary care data was incomplete. While it may be that some aspects of cardiovascular risk management were performed but not recorded, we have no reason to assume that underreporting of delivered care differs between women and men. Also, diabetes is a rapidly changing field and management guidelines may have changed after the data were collected. Nevertheless, more recent guidelines have not implemented sex-specific approaches for the management, treatment, and control of diabetes. Therefore, we anticipate that the sex differences found in this study are still valid. Moreover, we had no information on healthcare provided by healthcare professionals other than the general practitioner. Hence, it may be that other health care professionals than the general practitioner had conducted cardiovascular risk assessment or had prescribed drug therapy. For example, roughly 20% of individuals with diabetes in The Netherlands are referred to a specialist for specialized care. For the analyses, we were unable to assess whether there were meaningful differences between men and women in care provided by other health care professionals. For the analyses on treatment indication and drugs prescription history, we decided to only include individuals with a treatment indication based on CVD risk score and last measured levels of SBP or LDL cholesterol for antihypertensive drugs and lipid-lowering drugs, and last measured HbA1c levels for glucose-lowering drugs. Consequently, individuals being on target for last measured HbA1c, SBP, or LDL cholesterol, while receiving glucose-lowering drugs, antihypertensive drugs or lipid-lowering drugs, were not included. Moreover, individuals that received either glucose-lowering drugs,

antihypertensive drugs, or lipid-lowering drugs, but with missing data on either CVD risk score for the analyses on SBP or LDL cholesterol or missing data on last measured levels of HbA1c, SBP or LDL cholesterol were not included, which must be taken into account when interpreting the results.

Comparison with existing literature

Previous studies on differences in cardiovascular risk management between women and men with diabetes have reported mixed findings.⁷⁻¹² A study in the US including 18,000 individuals showed that women had higher odds of receiving dilated eye exams (1.14:1.04-1.24), blood pressure control (1.44:1.13-1.84), and to visit a doctor (1.39:1.22-1.58) than men, while no differences were found for testing HbA1c (1.01:0.89-1.14) and feet checked in a given year (0.91: 0.83-1.00)⁸. In contrast, a population-based study in Spain among 290,000 individuals showed that women had worse overall control of cardiovascular risk factors than men.¹⁰ These differences, stratified for history of CVD, were mainly evident for BMI with adjusted odds ratios (ORs) of 0.50 (0.48-0.52) and 0.53 (0.52-0.54) and for LDL cholesterol with ORs of 0.67 (0.64-0.70) and 0.74 (0.72-0.76), while differences in blood pressure were less evident with ORs of 0.88 (0.84-0.92) and 1.08 (1.06-1.13) for women compared to men with and without CVD respectively. In contrast, women were more likely than men to be non-smoker with adjusted ORs of 4.20 (3.86-4.58) and 4.01 (3.39-4.13) with and without CVD respectively and no differences were found for HbA1c control.¹⁰ A population-based study from Italy including 415,000 individuals showed that women were more likely to be off target for HbA1c (OR 1.14:1.10-1.17) in spite of insulin treatment, LDL cholesterol (1.42:1.38-1.46) in spite of receiving lipid-lowering drugs, and BMI $\geq 30\text{kg/m}^2$ (1.50:1.50-1.54), while no differences were found for blood pressure while receiving antihypertensive drugs (1.02:1.00-1.04).¹¹

The present study demonstrates that sex differences in cardiovascular risk management among patients with diabetes are relatively small in The Netherlands. Control of blood pressure, one of the biggest risk factors for cardiovascular disease, was even more favourable among women than men, suggesting that differences in cardiovascular risk management alone may not fully account for the higher relative risks, previously found in women, compared to men.^{2,3} Other factors, such as biological differences between men and women and differences in treatment adherence, may therefore play a key role in explaining the sex differences in the cardiovascular complications conferred by diabetes. For example, it has been suggested that the metabolic state and cardiovascular risk profile of women needs to deteriorate further than in men before the transition to overt diabetes occurs, especially with regard to adiposity.¹⁷ A large population-wide study among 95,000 individuals in Scotland showed that women had on average a 2-point higher BMI than men at diagnosis of diabetes.¹⁸ Fat distribution differs by sex, with greater subcutaneous fat storage in women, on average, and greater visceral and ectopic fat storage in men. Since visceral and ectopic fat are associated with insulin resistance and development of diabetes, it has been hypothesized that men develop diabetes at lower BMI than women because women can store more fat subcutaneously before transition to visceral and ectopic tissues.^{17,18} Moreover, compared with men, women may be exposed to adverse cardiovascular risk factors for a longer period before they eventually are diagnosed with overt diabetes and receive adequate

treatment.¹⁸ In line with this hypothesis, an Australian review and meta-analyses on the duration of pre-diabetes showed that the duration of prediabetes was 10.3 years in women, compared with 8.5 years in men.¹⁹

Inadequate adherence to cardiovascular drugs often leads to suboptimal cardiovascular risk factor control and has been associated with adverse cardiovascular outcomes.²⁰⁻²² Several studies in the general population have suggested that adherence to statins, antihypertensive drugs, and insulin is worse in women than men²³⁻²⁶. Nevertheless, it is unknown to what extent sex differences in drug adherence among individuals with diabetes exist and to what extent such differences, if present, may explain the greater excess cardiovascular risk in women with diabetes compared with men. Future research should therefore evaluate whether sex differences in medication adherence among patients with diabetes are present. Such studies should also consider possible sex differences in drug type and dosage, especially since we observed that, given treatment, control of LDL cholesterol was worse among women than men, but control of SBP was better among women than men.

Implications for research and/or practice

In conclusion, the implementation of cardiovascular risk management can be improved on multiple aspects for both sexes, including assessment of cardiovascular risk factors. No sex differences in HbA1c levels and control were found, and sex differences in cardiovascular risk factor assessment and treatment were small in this population of patients with diabetes attending primary care. Nevertheless, women with diabetes were less likely to achieve control for LDL cholesterol and more likely to achieve blood pressure control than men with diabetes. Moreover, weight loss strategies will be required to reduce the high levels of BMI, of 29.1 kg/m² in men and 30.7 kg/m² in women, in both sexes.

This study mainly focused on screening and control of HbA1c, blood pressure, lipid spectrum, and BMI. However, while not assessed here, adequate diabetes management goes beyond the management of HbA1c alone and also involves the assessment of renal function (serum creatinine and urine albumin/creatinine ratio), smoking status, foot surveillance, and retinal screening.²⁷

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Supplemental Table I. ICPC-1 codes for medical history/comorbidities.

Medical history	ICPC code
History of diabetes	T90
History of heart failure	K77
History of angina pectoris	K74
History of other chronic coronary heart disease	K76
History of acute myocardial infarction	K75
History of coronary disease	K77/K74//K76/K75
History of cerebrovascular accident	K90
History of transient ischemic attack	K89
History of stroke	K90/K89
History of atherosclerosis	K91
History of aortic aneurysm	K99.01
History of (cardio)vascular disease	K77/K74//K76/K75/K91/K90/K89/K99.01
History of hypertension	K85/K86/K87

Supplemental Table II. Baseline characteristics by age group.

	20-39 years		40-49 years		50-59 years		60-69 years		70-79 years		80-99 years	
	Men n=263	Women n=293	Men n=687	Women n=592	Men n=1346	Women n=1139	Men n=1884	Women n=1663	Men n=1554	Women n=1573	Men n=542	Women n=976
Age, years	32.2 (5.5)	32.6 (5.7)	45.2 (2.9)	45.2 (2.8)	54.9 (2.9)	54.9 (2.9)	64.7 (2.8)	64.7 (2.9)	74.0 (2.8)	74.3 (2.8)	83.7 (3.4)	84.7 (3.9)
Smoking status												
Current	39 (36)	26 (23)	168 (34)	89 (21)	365 (32)	223 (22)	374 (23)	254 (17)	189 (14)	170 (12)	33 (7)	53 (6)
Never	54 (50)	71 (63)	201 (40)	274 (66)	337 (30)	523 (52)	420 (26)	735 (50)	431 (31)	846 (60)	140 (29)	620 (69)
Former	16 (15)	16 (14)	133 (27)	52 (13)	428 (38)	252 (25)	853 (52)	475 (32)	752 (55)	399 (28)	307 (64)	221 (25)
10-year cardiovascular disease risk												
Low risk (<10%)	23 (58)	55 (87)	89 (29)	215 (76)	34 (4)	94 (12)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate risk (10-20%)	10 (25)	0 (0)	93 (30)	25 (9)	70 (9)	175 (94)	0 (0)	186 (15)	0 (0)	129 (10)	0 (0)	48 (6)
High risk (>20%)	7 (18)	8 (13)	125 (38)	43 (15)	696 (87)	514 (66)	1,377 (100.1)	1,077 (85)	1,230 (100)	1,137 (90)	453 (100)	769 (94)
History of cardiovascular disease	7 (3)	8 (3)	73 (11)	40 (7)	258 (19)	181 (16)	621 (33)	400 (24)	697 (45)	549 (35)	312 (58)	492 (50)
HbA1c, mmol/mol	57.5 (17.2)	54.2 (16.0)	57.7 (15.9)	55.0 (13.9)	55.2 (14.4)	54.7 (12.5)	53.7 (11.8)	53.5 (11.4)	54.0 (11.3)	53.8 (11.1)	54.1 (10.8)	53.8 (10.1)
HbA1c, %	7.4 (3.7)	7.1 (3.6)	7.5 (3.6)	7.2 (3.4)	7.2 (3.4)	7.2 (3.3)	7.1 (3.2)	7.1 (3.2)	7.1 (3.2)	7.1 (3.2)	7.1 (3.2)	7.1 (3.1)
Systolic blood pressure, mmHg	128.2 (13.6)	124.6 (14.3)	130.3 (17.0)	128.1 (16.2)	135.4 (16.4)	132.5 (16.2)	138.9 (16.4)	137.6 (16.9)	140.7 (17.4)	140.4 (17.6)	140.6 (18.1)	143.5 (19.3)

Supplemental Table II. Baseline characteristics by age group. (continued)

	20-39 years		40-49 years		50-59 years		60-69 years		70-79 years		80-99 years	
	Men n=263	Women n=293	Men n=687	Women n=592	Men n=1346	Women n=1139	Men n=1884	Women n=1663	Men n=1554	Women n=1573	Men n=542	Women n=976
Diastolic blood pressure, mmHg	80.7 (8.9)	79.3 (8.5)	82.1 (10.7)	81.3 (9.7)	82.4 (9.4)	81.0 (10.1)	80.0 (9.5)	79.1 (9.7)	76.7 (10.1)	76.9 (10.3)	74.7 (9.2)	76.2 (11.3)
Total cholesterol, mmol/L	4.5 (1.1)	4.7 (1.0)	4.6 (1.2)	4.7 (1.0)	4.5 (1.0)	4.8 (1.1)	4.3 (1.0)	4.7 (1.0)	4.2 (0.9)	4.7 (1.0)	4.2 (1.0)	4.7 (1.0)
LDL cholesterol, mmol/L	2.6 (0.7)	2.8 (0.8)	2.6 (0.9)	2.7 (0.9)	2.5 (0.9)	2.7 (0.9)	2.4 (0.8)	2.6 (0.9)	2.3 (0.8)	2.5 (0.9)	2.3 (0.8)	2.5 (0.9)
HDL cholesterol, mmol/L	1.1 (0.2)	1.3 (0.3)	1.1 (0.3)	1.3 (0.3)	1.1 (0.3)	1.3 (0.3)	1.2 (0.3)	1.4 (0.3)	1.2 (0.3)	1.4 (0.3)	1.2 (0.3)	1.4 (0.3)
Body mass index, kg/m^2	30.8 (5.3)	33.2 (6.4)	29.9 (5.1)	32.8 (6.3)	29.7 (4.8)	32.1 (6.4)	29.5 (4.6)	31.3 (6.0)	28.5 (4.2)	29.9 (5.4)	27.1 (3.6)	28.3 (4.7)
Glucose-lowering drugs	144 (55)	150 (51)	502 (73)	377 (64)	950 (71)	781 (69)	1,382 (73)	1,179 (71)	1,130 (73)	1,102 (70)	367 (68)	620 (64)
Lipid-lowering drugs	42 (16)	31 (11)	365 (53)	224 (38)	815 (61)	674 (59)	1,336 (71)	1,122 (68)	1,070 (69)	1,024 (65)	338 (62)	517 (53)
Antihypertensive drugs	38 (14)	48 (16)	268 (39)	231 (39)	765 (57)	693 (61)	1,390 (74)	1,222 (74)	1,245 (80)	1,262 (80)	433 (80)	789 (81)

Data are mean (SD) or n (%). Due to missing data, not all variables included add up to n = 6,276 for men and n = 6,236 for women.

Supplemental Table III. Women-to-men risk ratios for assessment of cardiovascular risk factors stratified for age.

	Total/ cases	18-39 Years	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years	p-value†	Overall†
HbA1c	12,512/ 9,324	0.98 (0.78-1.26)	0.95 (0.87-1.04)	1.06 (1.01-1.11)	1.02 (0.99-1.06)	0.99 (0.96-1.03)	0.99 (0.94-1.04)	0.20	1.00 (0.98-1.02)
SBP	12,512/ 9,832	1.25 (0.98-1.61)	1.02 (0.94-1.11)	1.06 (1.01-1.10)	1.03 (1.00-1.06)	1.01 (0.98-1.04)	1.02 (0.98-1.06)	0.02	1.02 (1.00-1.03)
DBP	12,512/ 9,829	1.25 (0.98-1.61)	1.02 (0.94-1.11)	1.06 (1.01-1.10)	1.03 (1.00-1.06)	1.01 (0.98-1.04)	1.02 (0.98-1.06)	0.01	1.02 (1.00-1.03)
TC	12,512/ 9,093	0.97 (0.74-1.27)	0.96 (0.87-1.06)	1.07 (1.02-1.12)	1.02 (0.99-1.06)	1.01 (0.97-1.04)	1.03 (0.97-1.09)	0.29	1.00 (0.98-1.02)
LDL cholesterol	12,512/ 8,763	1.16 (0.87-1.55)	1.01 (0.91-1.12)	1.12 (1.05-1.17)	1.04 (1.00-1.08)	1.01 (0.97-1.05)	1.04 (0.98-1.10)	0.01	1.02 (1.00-1.05)
HDL cholesterol	12,512/ 7,786	1.28 (0.92-1.76)	1.12 (1.00-1.26)	1.31 (1.23-1.40)	1.17 (1.12-1.23)	1.16 (1.10-1.22)	1.13 (1.05-1.21)	<0.01	1.16 (1.13-1.19)
BMI	12,512/ 7,747	1.17 (0.85-1.62)	1.02 (0.91-1.14)	1.07 (1.00-1.14)	1.04 (0.99-1.09)	1.00 (0.95-1.05)	0.98 (0.91-1.05)	<0.01	1.01 (0.98-1.03)
All of the above	12,512/ 5,409	1.36 (0.85-2.20)	1.25 (1.06-1.47)	1.31 (1.19-1.45)	1.23 (1.15-1.32)	1.18 (1.10-1.27)	1.07 (0.95-1.19)	<0.01	1.19 (1.14-1.23)
HbA1c + SBP + LDL cholesterol	12,512/ 7,851	1.21 (0.86-1.71)	1.03 (0.92-1.15)	1.10 (1.03-1.17)	1.04 (1.00-1.09)	1.02 (0.97-1.06)	1.01 (0.94-1.08)	0.01	1.02 (0.99-1.05)
≥1 of the above	12,512/ 10,557	1.14 (0.93-1.40)	1.00 (0.93-1.07)	1.06 (1.02-1.10)	1.02 (1.00-1.05)	1.00 (0.98-1.02)	1.02 (0.99-1.05)	0.02	1.01 (1.00-1.03)

DBP = diastolic blood pressure; SBP = systolic blood pressure; TC = total cholesterol. Men = reference category. † = Adjusted for age.

‡ = Interaction term (sex and age as a continuous variable). Total refers to the total number of men and women included, and cases refer to the number of men and women that received risk factor assessment.

Supplemental Table IV. Women-to-men risk ratios for assessment of cardiovascular risk factors stratified for history of cardiovascular disease.

	Total/ cases	Overall, no known history of CVD	Total/ cases	Overall, known history of CVD	p-value†
HbA1c	8,824/ 6,437	0.99 (0.97-1.02)	3,688/ 2,887	1.01 (0.98-1.05)	0.98
SBP	8,824/ 6,760	1.01 (0.99-1.04)	3,688/ 3,072	1.03 (1.00-1.06)	0.59
DBP	8,824/ 6,760	1.01 (0.99-1.04)	3,688/ 3,069	1.03 (1.00-1.06)	0.63
TC	8,824/ 6,307	0.99 (0.97-1.02)	3,688/ 2,786	1.02 (0.98-1.06)	0.91
LDL cholesterol	8,824/ 6,087	1.02 (0.99-1.04)	3,688/ 2,676	1.03 (0.99-1.07)	0.86
HDL cholesterol	8,824/ 5,510	1.14 (1.10-1.18)	3,688/ 2,276	1.19 (1.13-1.25)	0.47
BMI	8,824/ 5,277	1.01 (0.98-1.05)	3,688/ 2,470	1.01 (0.97-1.06)	0.24
All of the above	8,824/ 3,782	1.17 (1.12-1.23)	3,688/ 1,627	1.21 (1.12-1.30)	0.91
HbA1c + SBP + LDL cholesterol	8,824/ 5,436	1.01 (0.98-1.04)	3,688/ 2,415	1.04 (1.00-1.10)	0.74
≥1 of the above	8,824/ 7,283	1.01 (0.99-1.03)	3,688/ 3,274	1.01 (0.99-1.04)	0.21

The analyses were adjusted for age. CVD = cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; TC = total cholesterol. Men = reference category. † = Interaction term (sex and history of cardiovascular disease). Total refers to the total number of men and women included, and cases refer to the number of men and women that received risk factor assessment.

Supplemental Table V. mean differences in cardiovascular risk factor levels stratified for age.

	Total/ cases	18-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years	p-value†	Overall‡ Overall†	Overall, after adjustment for drugs prescriptions§
HbA1c	12,512/ 9,324	3.34 (-1.64;8.32)	2.67 (0.55;4.80)	0.48 (-0.77;1.72)	0.20 (-0.66;1.06)	0.23 (-0.65;1.10)	0.24 (-0.97;1.44)	0.01	0.45 (-0.05;0.95)	0.17 (-0.31;0.64)
SBP	12,512/ 9,832	3.57 (-0.67;7.80)	2.19 (-0.11;4.48)	2.93 (1.46;-4.39)	1.24 (0.03;2.45)	0.31 (-1.02;1.65)	-2.89 (-5.00;-0.77)	<0.01	1.09 (0.41;1.77)	1.14 (0.47;1.81)
DBP	12,512/ 9,829	1.34 (-1.28;3.97)	0.81 (-0.61;2.22)	1.34 (0.46;2.21)	0.91 (0.21;1.60)	-0.23 (-1.01;0.55)	-1.43 (-2.61;-0.25)	<0.01	0.41 (0.01;0.80)	0.42 (0.03;0.82)
TC	12,512/ 9,093	-0.19 (-0.51;0.13)	-0.08 (-0.24;0.08)	-0.28 (-0.38;-0.18)	-0.39 (-0.47;-0.31)	-0.46 (-0.54;-0.38)	-0.53 (-0.65;-0.41)	<0.01	-0.38 (-0.42;-0.34)	-0.35 (-0.39;-0.31)
LDL cholesterol	12,512/ 8,763	-0.20 (-0.47;0.07)	-0.07 (-0.21;0.06)	-0.15 (-0.24;-0.07)	-0.20 (-0.26;-0.13)	-0.21 (-0.27;-0.14)	-0.23 (-0.34;-0.13)	0.04	-0.19 (-0.23;-0.15)	-0.16 (-0.19;-0.12)
HDL cholesterol	12,512/ 7,786	-0.20 (-0.30;-0.11)	-0.17 (-0.22;-0.13)	-0.16 (-0.19;-0.13)	-0.18 (-0.20;-0.16)	-0.18 (-0.21;-0.16)	-0.16 (-0.20;-0.12)	0.36	-0.17 (-0.18;-0.16)	-
BMI	12,512/ 7,747	-2.45 (-4.63;-0.28)	-2.84 (-3.73;-1.94)	-2.39 (-2.95;-1.82)	-1.77 (-2.20;-1.34)	-1.39 (-1.81;-0.98)	-1.26 (-1.82;-0.70)	<0.01	-1.79 (-2.03;-1.56)	-

SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol. † = Interaction term (sex and age as a continuous variable).
 § = The analyses on HbA1c were corrected for glucose-lowering drugs, analyses on total cholesterol and LDL-c for prescription of lipid-lowering drugs and analyses on SBP and DBP for antihypertensive drugs. Women = reference category. Total refers to the total number of men and women, and cases refer to the number of men and women that received risk factor assessment and were included in the analyses.

Supplemental Table VI. Mean differences in cardiovascular risk factor levels stratified for known history of CVD.

	Total/ cases	Overall, no known history of CVD	Total/ cases	Overall, known history of CVD	p-value †
HbA1c	8,824/ 6,437	0.34 (-0.27;0.96)	3,688/ 2,887	0.52 (-0.33;1.37)	0.86
SBP	8,824/ 6,760	1.28 (0.49;2.07)	3,688/ 3,072	0.78 (-0.54;2.10)	0.92
DBP	8,824/ 6,760	0.84 (-0.38;1.31)	3,688/ 3,069	-0.35 (-1.09;0.40)	0.03
TC	8,824/ 6,307	-0.34 (-0.40;-0.29)	3,688/ 2,786	-0.42 (-0.49;-0.34)	0.16
LDL cholesterol	8,824/ 6,087	-0.17 (-0.21;-0.12)	3,688/ 2,676	-0.20 (-0.27;-0.14)	0.30
HDL cholesterol	8,824/ 5,510	-0.17 (-0.19;-0.15)	3,688/ 2,276	-0.16 (-0.19;-0.14)	0.44
BMI	8,824/ 5,277	-1.92 (-2.20;-1.64)	3,688/ 2,470	-1.74 (-2.14;-1.33)	0.24

The analyses were adjusted for age. CVD = cardiovascular disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol. Women = reference category. † = Interaction term (sex and history of cardiovascular disease). Total refers to the total number of men and women, and cases refer to the number of men and women that received risk factor assessment and were included in the analyses.

Supplemental table VII. Women-to-men risk ratios for treatment of cardiovascular risk factors stratified for age.

	Total/ cases	18-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-99 years	p-value†	Overall†
HbA1c >7.0%/53mmol/mol + receiving glucose-lowering drugs	3,949/ 3,632	1.12 (0.94-1.32)	0.98 (0.93-1.04)	1.01 (0.97-1.05)	0.99 (0.96-1.03)	0.99 (0.96-1.02)	0.99 (0.93-1.06)	0.08	0.99 (0.98-1.01)
High CVD risk + SBP >140mmHg + receiving antihypertensive drugs	2,863/ 2,400	-	1.76 (1.33-2.33)	1.04 (0.93-1.18)	1.03 (0.98-1.09)	0.96 (0.92-1.01)	0.98 (0.91-1.05)	<0.01	1.00 (0.96-1.03)
High CVD risk + LDL cholesterol >2.5mmol/L + receiving lipid-lowering drugs	2,561/ 1,329	-	0.46 (0.21-0.98)	1.07 (0.90-1.27)	1.03 (0.91-1.16)	1.01 (0.88-1.15)	0.96 (0.75-1.23)	0.09	1.00 (0.93-1.08)

CVD = cardiovascular disease; SBP = systolic blood pressure. Men = reference category. † = Additionally adjusted for age. ‡ = interaction term (sex and age (continuous variable). Total refers to the total number of men and women with a treatment indication, and cases refer to the number of men and women that received treatment.

Supplemental table VIII. Women-to-men risk ratios for treatment of cardiovascular risk factors stratified for known history of cardiovascular disease.

	Total/ cases	Overall, no known history of CVD	Total/ cases	Overall, known history of CVD	p-value†
HbA1c >7.0%/53mmol/mol + receiving glucose-lowering drugs	2,654/ 2,454	1.01 (0.98-1.03)	1,295/ 1,178	0.97 (0.94-1.01)	0.08
High CVD risk + SBP >140mmHg + receiving antihypertensive drugs	1,665/ 1,314	1.04 (0.99-1.09)	1,198/ 1,086	0.98 (0.95-1.02)	0.03
High CVD risk + LDL-c >2.5mmol/L + receiving lipid-lowering drugs	1,635/ 754	1.16 (1.04-1.29)	926/ 575	0.84 (0.76-0.93)	<0.01

The analyses were adjusted for age. CVD = cardiovascular disease; SBP = systolic blood pressure. Men = reference category. † = interaction term (sex and history of cardiovascular disease). Total refers to the total number of men and women with a treatment indication, and cases refer to the number of men and women that received treatment.

Supplemental table IX. Women-to-men risk ratios for control of cardiovascular risk factors stratified for age.

	Total/ cases	18-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-99 years	p-value†	Overall†
Glucose-lowering drugs + HbA1c ≤7.0%/53mmol/mol	7,182/ 3,550	1.19 (0.76-1.87)	1.07 (0.90-1.28)	0.98 (0.88-1.10)	1.00 (0.92-1.08)	1.00 (0.92-1.09)	0.95 (0.82-1.10)	0.18	0.99 (0.94-1.04)
Antihypertensive drugs + SBP ≤140mmHg	7,084/ 4,122	1.27 (0.91-1.78)	1.10 (0.96-1.25)	1.12 (1.04-1.22)	1.06 (0.99-1.14)	1.05 (0.97-1.13)	0.91 (0.81-1.03)	0.02	1.06 (1.02-1.10)
Lipid-lowering drugs + LDL cholesterol ≤2.5mmol/L	5,871/ 4,105	0.64 (0.32-1.29)	0.95 (0.81-1.12)	0.88 (0.81-0.96)	0.88 (0.83-0.93)	0.89 (0.84-0.95)	0.87 (0.80-0.95)	1.00	0.88 (0.85-0.91)

SBP = systolic blood pressure. Men=reference category. † = Additionally adjusted for age. ‡ = Interaction term (sex and age (continuous variable). Total refers to the total number of men and women receiving treatment, and cases refer to the number of men and women with risk factor control.

Supplemental table X. Women-to-men risk ratios for control of cardiovascular risk factors stratified for known history of cardiovascular disease.

	Total/ cases	Overall, no known history of CVD	Total/ cases	Overall, known history of CVD	p-value†
Glucose-lowering drugs + HbA1c ≤7.0%/53mmol/mol	4,928/ 2,474	0.98 (0.93-1.04)	2,254/ 1,076	0.99 (0.91-1.08)	0.88
Antihypertensive drugs + SBP ≤140mmHg	4,401/ 2,525	1.09 (1.04-1.15)	2,683/ 1,597	1.03 (0.97-1.10)	0.23
Lipid-lowering drugs + LDL cholesterol <2.5mmol/L	3,807/ 2,616	0.88 (0.84-0.91)	2,064/ 1,489	0.90 (0.85-0.95)	0.42

The analyses were adjusted for age. CVD = cardiovascular disease; SBP = systolic blood pressure. Men = reference category. † = interaction term (sex and history of cardiovascular disease). Total refers to the total number of men and women receiving treatment, and cases refer to the number of men and women with risk factor control.



Chapter 8

Sex differences in cardiometabolic risk factors, pharmacological treatment, and risk factor control in type 2 diabetes: findings from the Dutch Diabetes Pearl cohort

Marit de Jong*

Marieke J. Oskam*

Simone J.S. Sep

Behiye Özcan

Femke Rutters

Eric J.G Sijbrands

Petra J.M. Elders

Sarah E. Siegelaar

J. Hans DeVries

Cees J. Tack

Marielle Schroijen

Harold W. de Valk

Evertine J. Abbink

Coen D.A. Stehouwer

Ingrid Jazet

Bruce H.R. Wolffenbuttel

Sanne A.E. Peters

Miranda T. Schram

On behalf of the Diabetes Pearl from the ParelSnoer Initiative.

* Authors equally contributed

Abstract

Introduction

Sex differences in cardiometabolic risk factors and their management in type 2 diabetes (T2D) have not been fully identified. Therefore, we aimed to examine differences in cardiometabolic risk factor levels, pharmacological treatment, and achievement of risk factor control between women and men with T2D.

Research Design and Methods

Cross-sectional data from the Dutch Diabetes Pearl cohort were used (n=6,637, 40% women). Linear and Poisson regression analyses were used to examine sex differences in cardiometabolic risk factor levels, treatment, and control.

Results

Compared with men, women had a significantly higher body mass index (BMI) (mean difference 1.79 kg/m² (95% CI 1.49 to 2.08)), while no differences were found in haemoglobin A1c (HbA1c) and systolic blood pressure (SBP). Women had lower diastolic blood pressure (−1.94 mm Hg (95% CI −2.44 to −1.43)), higher total cholesterol (TC) (0.44 mmol/L (95% CI 0.38 to 0.51)), low-density lipoprotein cholesterol (LDL cholesterol) (0.26 mmol/L (95% CI 0.22 to 0.31)), and high-density lipoprotein cholesterol (HDL cholesterol) sex-standardized (0.02 mmol/L (95% CI 0.00 to 0.04)), and lower TC:HDL ratio (−0.29 (95% CI −0.36 to −0.23)), and triglycerides (geometric mean ratio 0.91 (95% CI 0.85 to 0.98)). Women had a 16% higher probability of being treated with antihypertensive medication in the presence of high cardiovascular disease (CVD) risk and elevated SBP than men (relative risk 0.84 (95% CI 0.73 to 0.98)), whereas no sex differences were found for glucose-lowering medication and lipid-modifying medication. Among those treated, women were less likely to achieve treatment targets of HbA1c (0.92 (95% CI 0.87 to 0.98)) and LDL cholesterol (0.89 (95% CI 0.85 to 0.92)) than men, while no differences for SBP were found.

Conclusions

In this Dutch T2D population, women had a slightly different cardiometabolic risk profile compared with men and a substantially higher BMI. Women had a higher probability of being treated with antihypertensive medication in the presence of high CVD risk and elevated SBP than men, and were less likely than men to achieve treatment targets for HbA1c and LDL cholesterol levels.

Introduction

Sexual heterogeneity has emerged as a major topic in several medical areas, including metabolic disorders such as type 2 diabetes (T2D).¹ A growing body of evidence shows that the relative risk (RR) of cardiovascular complications associated with T2D is different for women and men. In fact, T2D may attenuate the protective effect that female sex usually confers on the risk of cardiovascular disease (CVD).^{2–5} Meta-analyses have shown that the RR of coronary heart disease is up to 50% higher in women with diabetes, compared with their male counterparts.^{6–8} For stroke, this RR is 27% greater in women with diabetes than in men.⁹ The reasons for these sex differences are likely multifactorial. For example, physiological differences between women and men, including the impact of sex hormones,^{10–12} female-specific factors such as age of menarche, menopause, and childbearing history, oral contraception, and hormone replacement therapy^{13–15}, and a more adverse cardiometabolic risk profile among women than men with T2D.^{16,17} In addition, healthcare provision for the prevention and delay of cardiovascular complications between women and men with diabetes may differ.^{13,15,17–21}

Understanding of the sex differences in major modifiable risk factors with respect to their quantity, treatment, and control in specific healthcare settings may help healthcare professionals to reduce these differences. In order to evaluate sex differences in the levels of cardiometabolic risk factors, pharmacological treatment and achievement of treatment targets for haemoglobin A1c (HbA1c), systolic blood pressure and low-density lipoprotein cholesterol (LDL cholesterol), in a large, well-phenotyped cohort of Dutch individuals with T2D, we used data from the Diabetes Pearl cohort. The Diabetes Pearl is a large Dutch cohort involving all eight academic medical centres in the Netherlands, covering different geographical areas, and has collected data from over 6,500 individuals with T2D who are being treated in primary, secondary, and tertiary care.²²

Research design and methods

Study population

Cross-sectional data from the Diabetes Pearl, an observational cohort study, involving all eight Dutch academic medical centres covering different geographical areas in the Netherlands, and covering individuals treated in primary, secondary, and tertiary care, were used, as described in detail elsewhere.²² In short, individuals previously diagnosed with T2D who received secondary or tertiary medical care in one of the six academic medical centres in Amsterdam, Utrecht, Nijmegen, Rotterdam, Leiden, or Groningen, primary medical care in the area of Hoorn, or who received primary, secondary, or tertiary care in the region of Maastricht were eligible for participation.²² In 2018, an estimated 1.2 million (47% women) individuals in the Netherlands had diabetes, with majority suffering from T2D (91%).²³ Individuals with T2D are predominantly being treated in primary care (up to 85%). In the occurrence of complications or whenever glycaemic control is not achieved by primary care, the patient will be referred to secondary care (i.e. internal medicine, cardiology, ophthalmology, endocrinology). Only when high specialist care is needed, in complex cases, the patient is referred to tertiary care.²² Data were collected over a 6-year period (2009–

2015) and included information on demographics, physical measurements, laboratory tests, and questionnaires. Individuals were not included in the cohort if their ability to understand and write in Dutch language was too limited to provide written informed consent.²² A total of 6,666 individuals diagnosed with T2D were included in the Diabetes Pearl. After excluding participants of whom sex was not known (missing), 6,637 remained for analyses.

Measurements

Data on educational level (as a proxy for socioeconomic status), smoking behaviour, alcohol consumption, history of diabetes, stroke, and CVD was obtained at baseline, using a self-report questionnaire. Information on sex and date of birth was obtained using the hospital information systems at all recruitment centres. Weight and height were measured bare foot and wearing light clothing using a clinical stadiometer and scale. Blood pressure was determined three times on the right arm after a 10 minute rest period, using a non-invasive blood pressure monitor (Omron 7051 T in seven centres, Colin Press BP 8800p in one centre). Final blood pressure was calculated as the mean of the last two measurements. Fasting venous blood plasma was used to determine total cholesterol (TC), HDL cholesterol, and triglycerides. A fasting whole blood sample was used for the determination of HbA1c level. All the laboratories were certified and located on site in the eight clinics.²²

Cardiometabolic profile

The following cardiometabolic risk factors were analysed: systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, TC, HDL cholesterol, LDL cholesterol, TC/HDL-ratio, body mass index (BMI), and HbA1c. Triglyceride levels were log-transformed due to non-normality and back transformed to a geometric mean ratio. For HDL cholesterol, specific cut-offs apply for women and men. Therefore, sex-standardized variables for HDL cholesterol were used in the analyses of mean differences between women and men. Sex-standardized HDL cholesterol was calculated as: observed value minus 1.2 mmol/L for women, and observed value minus 1.0 mmol/L for men.

Pharmacological treatment and achievement of cardiometabolic risk factor targets

Information on medication use for the treatment of hyperglycaemia, dyslipidaemia, and hypertension was collected either by asking participants to bring their medication on the day of visit to the clinic or by use of pharmacy lists. Majority of individuals receiving treatment for hyperlipidaemia (Anatomical Therapeutic Chemical (ATC) Classification System C10) were treated with statins (95%). Treatment with other types of lipid-modifying medication (i.e. fibrates) was limited. Although, newer antidiabetic medication became available during study period (i.e. GLP1 analogues and SGLT2 inhibitors in 2009 and 2011 respectively), these were not yet prescribed to the study population. Pharmacological management of hyperglycaemia, dyslipidaemia, and hypertension was each categorized into four groups, based on the individuals' medication use, the levels of SBP, LDL cholesterol, and HbA1c at target (i.e. below or above cut-off), and the individuals' estimated 10-year CVD risk (Supplementary table 1):

1. No treatment and no treatment indication: not receiving glucose-lowering medication and HbA1c ≤ 53 mmol/mol; not receiving antihypertensive medication and SBP ≤ 140 mmHg, or SBP >140 mmHg with low or intermediate 10-year CVD risk; not receiving lipid-modifying medication and LDL cholesterol ≤ 2.5 mmol/L, or >2.5 mmol/L with low or intermediate 10-year CVD risk.
2. Optimal treatment: receiving glucose-lowering medication and HbA1c ≤ 53 mmol/mol; receiving antihypertensive medication and SBP ≤ 140 mmHg; receiving lipid-modifying medication and LDL cholesterol ≤ 2.5 mmol/L.
3. Suboptimal treatment: receiving glucose-lowering medication and HbA1c >53 mmol/mol; receiving antihypertensive medication and SBP >140 mmHg; receiving lipid-modifying medication and LDL cholesterol >2.5 mmol/L.
4. No treatment despite a treatment indication: not receiving glucose-lowering medication despite HbA1c >53 mmol/mol; not receiving antihypertensive medication despite high CVD risk and SBP >140 mmHg; not receiving lipid-modifying medication despite high CVD risk and LDL cholesterol >2.5 mmol/L.

The individual's 10-year risk of CVD was estimated by use of an adapted version of the SCORE risk model. Estimation of the 10-year CVD risk was based on sex, age (biological age + 15 years to compensate for the increased CVD risk associated with T2D as recommended by the adapted version of the SCORE risk model according to Dutch guidelines), current smoking, SBP and TC/HDL-ratio, and classified as low ($<10\%$), intermediate (10-20%), or high ($>20\%$ or prevalent CVD).^{3,24}

Statistical analysis

Population characteristics were described, by sex, as mean \pm standard deviation (SD) or median (IQR) where appropriate for continuous variables, and n(%) for categorized variables. Information on missing data can be found in supplementary table 2. Age and medication-adjusted linear regression analyses were performed to study sex differences in cardiometabolic risk factor levels. Linear regression analyses on HbA1c were adjusted for glucose-lowering medication; analyses on the lipid-spectrum were adjusted for lipid-modifying medication; and analyses on blood pressure were adjusted for antihypertensive medication. Age-adjusted Poisson regression analyses²⁵ with robust standard errors were used to obtain relative risks (RRs) with 95% confidence intervals (CIs) for sex differences in the treatment and achievement of cardiometabolic risk factor targets (HbA1c, SBP, and LDL cholesterol). Given that the data used for this study was collected over a 6-year period and guidelines have changed over time, we additionally analysed treatment based on risk factor levels irrespective of 10-year estimated CVD risk. Secondary interaction analyses on history of CVD (yes vs. no), health care setting (primary care vs. secondary and tertiary care), age (<60 years vs. ≥ 60 years), BMI (<25 kg/m² vs. ≥ 25 kg/m²), and educational level (low, middle, high) were performed. We decided to only adjust our analyses for age as other variables such as BMI are thought to be mediating factors and our goal was to examine the independent effects of

sex on treatment and achievement of risk factor targets. Available case analyses were performed using SPSS version 25.0 for Windows (IBM SPSS, IBM Corp, Armonk, NY, USA).

Results

Data from 6,637 individuals (40% women) with a mean age of 62 years and a median T2D duration of 9 years were used. On average, men were more likely than women to smoke, drink alcohol, have a known history of CVD, have a high 10-year CVD risk, and to use lipid-modifying medication. Women had higher TC, LDL and HDL cholesterol levels, and higher BMI than men (Table 1).

Table 1. Study population characteristics stratified by sex.

	Men <i>n</i> =3,969 (60%)	Women <i>n</i> =2,668 (40%)
General characteristics		
Age, years	62.7 ± 9.6	61.8 ± 11.1
Diabetes duration, years	9.1 (4.3-15.1)	9.0 (4.4-15.1)
Educational level*		
<i>Low</i>	1,169 (32%)	1,066 (43%)
<i>Moderate</i>	1,558 (42%)	1,065 (43%)
<i>High</i>	968 (26%)	335 (14%)
Smoking status		
<i>Never</i>	935 (27%)	1,111 (46%)
<i>Former</i>	1,904 (54%)	925 (39%)
<i>Current</i>	690 (20%)	360 (15%)
Alcohol use~		
<i>No</i>	1241 (33%)	1,484 (60%)
<i>Low</i>	1,987 (53%)	738 (30%)
<i>High</i>	516 (14%)	248 (10%)
Prior CVD	1,420 (40%)	673 (30%)
10-year CVD risk		
<i>Low risk</i>	108 (3%)	288 (12%)
<i>Intermediate risk</i>	187 (5%)	336 (14%)
<i>High risk</i>	3,271 (92%)	1,759 (74%)
Health care setting		
<i>Primary care</i>	2,238 (57%)	1,489 (56%)
<i>Secondary/tertiary care</i>	1,701 (43%)	1,154 (44%)

Table 1. Study population characteristics stratified by sex. (continued)

	Men <i>n</i> =3,969 (60%)	Women <i>n</i> =2,668 (40%)
Cardiometabolic factors		
Systolic blood pressure, mmHg	142.6 ± 18.9	141.3 ± 20.1
Diastolic blood pressure, mmHg	78.6 ± 10.4	76.7 ± 10.0
Triglycerides, mmol/L	1.6 (1.1-2.3)	1.5 (1.1-2.1)
Total cholesterol, mmol/L	4.28 ± 1.12	4.73 ± 1.39
HDL cholesterol, mmol/L	1.14 ± 0.32	1.36 ± 0.39
LDL cholesterol, mmol/L	2.3 ± 0.8	2.6 ± 1.0
Cholesterol ratio (total/HDL)	3.97 ± 1.42	3.69 ± 1.27
Weight, kg	94.2 ± 17.9	85.5 ± 18.8
Height, cm	177 ± 7	164 ± 7
Body mass index, kg/m ²	30.0 ± 5.2	31.9 ± 6.7
Waist circumference, cm	108.4 ± 13.6	104.5 ± 15.6
HbA1c, mmol/mol	55.0 ± 13.6	55.4 ± 14.2
Medication use		
Diabetes medication		
<i>None</i>	538 (14%)	403 (16%)
<i>Oral only</i>	1,769 (46%)	1,097 (42%)
<i>Insulin and oral</i>	1,053 (27%)	690 (27%)
<i>Insulin only</i>	518 (13%)	401 (16%)
Lipid-modifying medication	2,740 (71%)	1628 (63%)
Antihypertensive medication	2,688 (69%)	1,807 (70%)
Antithrombotic medication	1,689 (44%)	802 (31%)

Data are presented as mean ± SD for continuous variables, and n(%) for categorized variables. *Low education includes no education, primary school not finished, primary education, and low vocational education. Moderate education includes intermediate vocational education, high secondary education, and high vocational education. High education includes high professional education and university education. ~ Alcohol use was divided into 3 categories: none = no alcohol use; low = ≤7 glasses per week for women and ≤14 glasses per week for men; high = >7 glasses per week for women and >14 glasses per week for men. CVD = cardiovascular disease; HDL cholesterol = high-density lipoprotein cholesterol; LDL cholesterol = low-density lipoprotein-cholesterol. Due to missing data not all variables add up to n=2,668 for women and n=3,969 for men.

Cardiometabolic risk factor levels

Figure 1 shows the sex-specific cardiometabolic risk factor levels and age-adjusted associations between sex and cardiometabolic risk factor levels. Results are expressed as mean differences (MD) and 95%-confidence intervals. Compared to men, women had a higher BMI (MD 1.79 kg/m² [95% CI 1.49;2.08]), and similar levels of HbA1c (0.32 mmol/mol [-0.37;1.00]), and SBP (-0.86 mmHg [-1.80;0.09]). Furthermore, women had lower DBP (-1.94mmHg [-2.44;-1.43]), higher TC (0.44mmol/L [0.38;0.51]), LDL cholesterol (0.26mmol/L[0.22;0.31]), and HDL cholesterol-standardized

(0.02mmol/L [0.00;0.04], and, lower TC/HDL-ratio (-0.29 [-0.36;-0.23]) and triglycerides (geometric mean ratio: 0.91 [95% CI: 0.85;0.98]) than men. Results did not change after additional adjustments for medication use (results not shown).

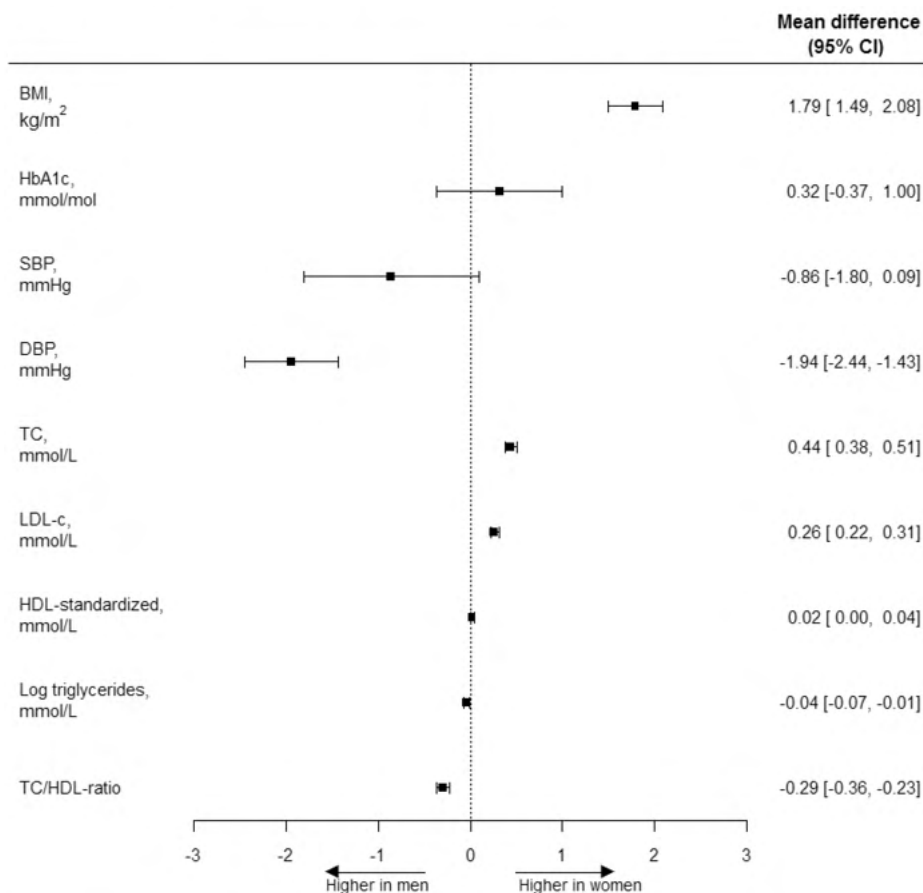


Figure 1. Age-adjusted women-to-men mean differences of cardiometabolic risk factors levels. A mean difference in BMI of 1.79kg/m² means that the age-adjusted BMI in women is 1.79kg/m² higher than in men. Back transformation of log-transformed triglycerides results in a geometric mean ratio of 0.91 (0.85;0.98). BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; LDL-c = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol. Men = reference.

Pharmacological treatment of cardiometabolic risk factors

Figure 2 shows the pharmacological treatment of hyperglycaemia, hypertension and dyslipidaemia, among those without relevant missing data. Overall, 84%, 71% and 64% of women and 86%, 71% and 72% of men with known risk factor levels were treated with glucose-lowering, blood pressure-lowering or lipid-modifying medication respectively.

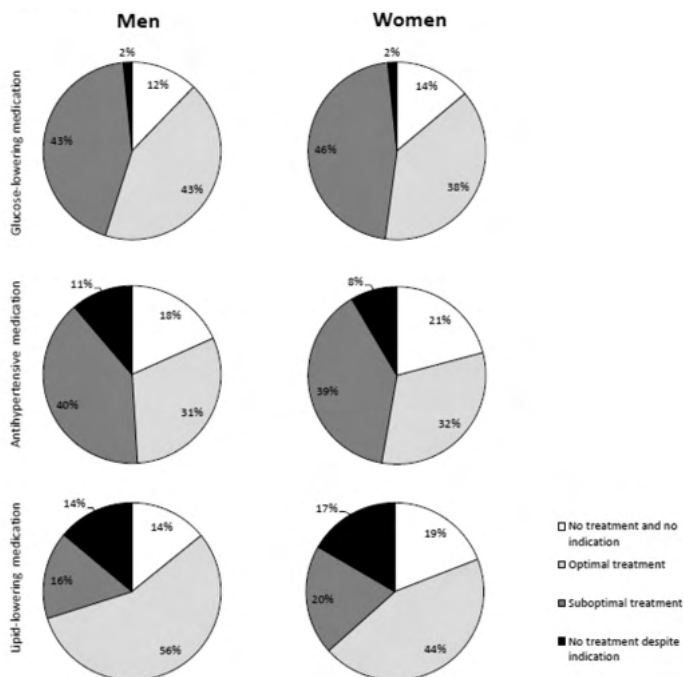


Figure 2. Pharmacological treatment and achievement of treatment targets of hyperglycaemia (upper panel), hypertension (middle panel), and dyslipidaemia (lower panel) in percentages for women and men. No treatment and no indication (no medication use and no indication for treatment (risk factor below cut-off or either low or medium 10-year CVD risk in case of SBP >140mmHg or LDL cholesterol >2.5mmol/L)); Optimal treatment (medication use and risk factor below cut-off); Suboptimal treatment (medication use and risk factor above cut-off); No treatment despite indication (no medication use, but HbA1c >53mmol/mol or high 10-year CVD risk and SBP >140mmHg or LDL cholesterol >2.5 mmol/L). CVD = cardiovascular disease, SBP = systolic blood pressure; LDL-c = low-density lipoprotein cholesterol.

Compared to men, women had a 16% higher probability of being treated with antihypertensive medication in the presence of high CVD risk and elevated SBP (RR 0.84 [0.73;0.98]), whereas no statistically significant sex difference was found for being treated with antihypertensive medication in the presence of elevated SBP irrespective of high CVD risk (0.91 [0.80;1.02]). No sex differences were found for glucose-lowering medication in the presence of elevated HbA1c levels (0.98 [0.67;1.45]), and lipid-modifying medication in the presence of elevated LDL cholesterol levels and high CVD risk (1.06 [0.97;1.16] and irrespective of CVD risk (1.07 [0.99;1.15]) (Figure 3).

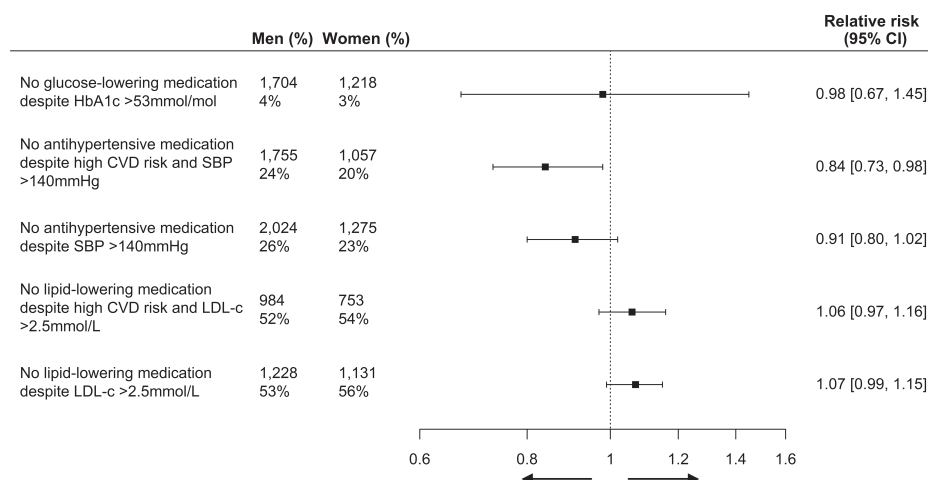


Figure 3. Age-adjusted women-to-men risk ratios with 95% CIs for the treatment of cardiometabolic risk factors according to risk factor levels and 10-year CVD risk score. Men and women refer to the total number of participants included in the analyses and (%) refers to the number of participants not receiving glucose-lowering, antihypertensive or lipid-modifying medication. SBP = systolic blood pressure; LDL-c = low-density lipoprotein cholesterol. Men = reference.

Achievement of treatment targets

Among those treated with glucose-lowering medication, blood pressure-lowering medication or lipid-modifying medication, 45%, 45% and 69% of women and 50%, 44% and 78% of men achieved targets of HbA1c ($\leq 53\text{mmol/mol}$), SBP ($\leq 140\text{mmHg}$) or LDL cholesterol ($\leq 2.5\text{mol/L}$), respectively. After adjustment for age, women were less likely to achieve risk factor targets of HbA1c (RR 0.92 [95% CI 0.87;0.98]) and LDL cholesterol (0.89 [0.85;0.92]) than men, while no sex differences were found for control of SBP (1.03 [0.96;1.10]).

Subgroup and interaction analyses

Results from the interaction analyses on history of CVD, health care setting (primary, secondary and tertiary care), age, BMI, and educational level are summarized in supplementary Tables 3 and 4.

For cardiometabolic risk factors, the interaction analyses by history of CVD, health care setting, age, BMI and educational level showed several significant interactions, but most differences were very small and unlikely to be clinically relevant (Supplementary Table 3), with two exceptions. First, women with high educational level had lower systolic blood pressure (mean difference (MD) -4.34 [-6.89;-1.80]) than men, compared to lower educational levels ($p=0.046$). Second, women with low and middle educational levels had higher BMI compared to their male counterparts (MD 2.13 [1.58;2.67] and MD 1.29 [0.80;1.78] respectively), while no statistically significant sex differences were found for high educational level (MD 0.49 [-0.22;1.20]) ($p<0.001$).

Women with a history of CVD had a higher likelihood of not receiving lipid-modifying medication despite high CVD risk and elevated LDL cholesterol than men (RR 1.26 [1.03;1.53]), while no such sex difference was found for participants without CVD (0.94 [0.83;1.05]). Similar results for not receiving lipid-modifying medication in the presence of elevated LDL cholesterol were found irrespective of high CVD risk. Women in primary care had a lower likelihood of not receiving antihypertensive medication despite high CVD risk and elevated SBP than men (0.73 [0.61;0.88]) in contrast to secondary or tertiary care (1.12 [0.85;1.49]), and women in secondary or tertiary care had a higher likelihood of not receiving lipid-modifying medication despite high CVD risk and elevated LDL cholesterol than men (1.28 [1.08;1.53]) (Supplementary Table 4). Women with higher educational levels had a higher likelihood of not receiving antihypertensive medication despite elevated SBP and high CVD risk than men (RR 1.27 [0.92;1.76]), while women with lower educational levels were more likely to receive antihypertensive medication (0.74 [0.56;0.97] and 0.74 [0.56;0.97], respectively). Similar results for not receiving antihypertensive or lipid-modifying medication were found irrespective of high CVD risk.

With regard to achievement of treatment targets, women in secondary or tertiary care were less likely to attain HbA1c \leq 53mmol/mol than men when receiving glucose-lowering medication (0.80 [0.71;0.90]), while no such sex difference was found for participants in primary care (0.96 [0.89;1.03]) (Supplementary Table 4). Moreover, women with higher educational levels were more likely to attain SBP \leq 140mmHg than men, when receiving antihypertensive medication (1.34 [1.13;1.58]).

Discussion

Data from the Dutch Diabetes Pearl show that sex disparities in cardiometabolic risk factor levels, pharmacological treatment, and achievement of cardiometabolic risk factor control exist, with three major findings: **1.** Women, especially those with lower and middle educational levels, had a substantially higher BMI than men, while other cardiometabolic risk factors were highly comparable, albeit statistically significantly different for DBP and markers of dyslipidaemia; **2.** Women were more likely to receive antihypertensive medication in the presence of high CVD risk and increased SBP, while no differences were found for treatment with glucose-lowering medication or lipid-modifying medication; **3.** Proportions of men and women that did not achieve optimal treatments targets for glucose-, blood pressure- and lipids, despite their treatment, were large, ranging from 22 to 56%, and women were less likely to achieve treatment targets of HbA1c and LDL cholesterol, while receiving glucose-lowering and lipid-modifying medication.

Cardiometabolic risk factor levels

In women with T2D, BMI was 1.79 kg/m² higher than in men with T2D, which is in line with several previous studies conducted in various countries including the Netherlands, Spain, Italy, and the UK, and more effective weight loss interventions are clearly needed.²⁶⁻²⁹ It has been hypothesized that cardiometabolic risk factors need to deteriorate further in women than men before they develop overt T2D.^{2,16,18,30,31} As a consequence, women may be exposed to hazardous

cardiometabolic risk factors for a longer period of time, which may increase their CVD risk. Sex differences in the metabolism and the storage of fat may be of particular interest, and several studies have shown that fat storage and distribution differ by sex, with women having a greater subcutaneous fat storage, while on average men have greater visceral and ectopic fat storages.^{15,18} Visceral and ectopic fat have been linked to insulin resistance. As a consequence, compared with men, women may need to gain more weight to store visceral and ectopic fat before developing insulin resistance and overt T2D. Thus, women may be exposed to hazardous cardiometabolic risk factors for an extended period of time before they are diagnosed with T2D and receive treatment.^{2,16,18,30,31}

Treatment of cardiometabolic risk factors

Proportions of both men and women that did not receive antihypertensive or lipid-modifying treatment, despite high CVD risk and SBP >140mmHg or LDL cholesterol >2.5mmol/L were substantial, ranging from ~20% for hypertension to ~50% for dyslipidaemia, and women were more likely to receive antihypertensive treatment than men in the presence of high CVD risk and SBP >140mmHg. These results are comparable to those of a Dutch primary care study, which found that 16% and 48% of those with a treatment indication did not receive prescriptions for antihypertensive or lipid-modifying medication respectively.²⁷ Based on our data we cannot assess the ground for this suboptimal CVD risk factor treatment. However, a focus on antihyperglycaemic treatment rather than the treatment of hypertension or on individualized care with personalised treatment targets could play a role. Furthermore, patients may be reluctant to start certain medications, i.e. statins, due to the fear of side effects.

Control of cardiometabolic risk factor levels

Women with T2D receiving glucose-lowering or lipid-modifying medication were, respectively, 8% (RR 0.92 (95% CI 0.87 to 0.98)) and 11% (RR 0.89 (95% CI 0.85 to 0.92)) less likely to attain treatment targets than men, while no differences were found for antihypertensive treatment. Other studies on sex differences in achieving HbA1c targets have reported mixed findings. In agreement with our findings, some other studies found that women were less likely to attain HbA1c targets,^{17,28,32} while others did not.^{26,27} A recent study including 53,602 Dutch individuals with pharmacologically treated T2D found no clear sex differences in goal attainment of HbA1c and SBP, while women were less likely to attain LDL cholesterol control compared with men.³³ A higher BMI of women with T2D, presumably with higher insulin resistance, could explain the lower attainment of HbA1c targets in our study. The finding of worse LDL cholesterol control among women with T2D is consistent with previous studies which showed an OR of up to 44%.^{17,26–28,32} Possible explanations include a differential biological response to lipid-modifying medication, or sex differences in dosage, type of medication, medication tolerance, or adherence. In the general population, several studies have shown the adherence to blood pressure-lowering and lipid-lowering medication to be lower in women than in men.^{34–36} To our knowledge, such studies have not yet been conducted in individuals with T2D. Furthermore, a recently published systematic review studying the participation of women in 740 cardiovascular clinical trials with 862,652 participants showed that, although this has improved over the last decade, men still predominate majority

of cardiovascular clinical trials.³⁷ Reporting sex-specific results from clinical trials is important to obtain more insight into potential sex differences of treatment benefit and medication tolerance. Therefore, novel approaches to the recruitment and enrolment process and novel trial designs are needed to ensure that sex-specific results may be meaningfully obtained and applied to clinical practice.³⁷ Another possible explanation may be found in differences of cardiometabolic risk factor levels at treatment initiation. As discussed earlier, it has been hypothesized that cardiometabolic risk factors need to deteriorate further in women than men before they are diagnosed with overt T2D. Therefore, it may take more aggressive treatment strategies to lower cardiometabolic risk factor levels in women compared with men.

Sex-specific risk factors

Certain factors that may impact cardiovascular risk are unique to women, including higher levels of female hormones, age of menarche, age of menopause, and use of oral contraceptive and hormonal therapy. Studying the impact of sex hormones on the development of cardiovascular complications is challenging, especially given the cyclic fluctuations in hormone levels among women. However, we did not find evidence in the magnitude of sex differences among younger and older (as proxy for menopausal status) participants in subgroup analyses. Previous studies have found several female reproductive factors, including childbearing history, age at menarche, and age at menopause to be associated with adiposity^{38,39}, thereby suggesting that female reproductive factors may be involved in the development of T2D and cardiovascular complications.¹³ Future studies are needed to further investigate the direct impact of sex hormones on the onset of cardiovascular disease.

Clinical Implications

The development of diabetes and cardiovascular complications is a process of decades. As mentioned before, it has been hypothesized that women may be exposed to a hazardous cardiovascular environment for a longer period than men before the onset of diabetes. This hypothesis is supported by a study showing that, on average, men have prediabetes for 8 years and women for 10 years.⁴⁰ This time window may offer clinicians the opportunity to identify those at increased risk for diabetes, and subsequently, offer the opportunity for timely intervention.³¹

As cardiovascular risk factor levels seem to deteriorate more strongly in women than men, before the onset of diabetes¹⁶, it is of great importance to conduct a thorough cardiovascular risk assessment in women at risk of diabetes and those with overt diabetes, whilst not neglecting men.³¹ Moreover, increasing the awareness among physicians about the stronger deterioration of risk factors in women is recommended to prevent that women with diabetes are treated less aggressively than men.³¹

Finally, this study showed that both men and women with T2D had high BMI levels, with women having a considerably higher BMI than men. These results are in accordance with previous literature and effective weight loss strategies seem urgently needed with better facilitation of lifestyle changes.³¹

Strengths and limitations

This large cohort included individuals with T2D receiving primary, secondary, and tertiary care in one of eight medical centres across the Netherlands covering different geographical areas, and thereby provides a well phenotyped cohort of Dutch individuals with T2D. Nevertheless, our study also has limitations. Data was collected over a 6-year period (2009-2015).²² Given the rapid change of guidelines for the treatment of diabetes, some of our results may be less generalizable to current clinical practice. Nevertheless, the main aim of our study was to investigate sex differences in the management of diabetes. Since most of the evidence-based guidelines provide similar recommendations for both sexes and no sex-specific recommendations were published over time, valid conclusions about sex differences can be drawn from the available data that was used for this study. Guidelines on diabetes care increasingly focus on individualized care. Therefore, the more general treatment targets used in this study may have limited the generalizability of the findings to clinical practice. Moreover, a strict definition of CVD risk was used in this study without taking risk enhancing factors, i.e. family history of CVD, into account.²⁴ As a result, the proportion of individuals with a treatment indication at baseline might be underestimated. Although we do not expect substantial differences in risk-enhancing factors between women and men, the proportions of women and men with an intermediate CVD risk did differ (14% vs. 5% respectively), which might have led to more misclassified women than men. As a result, sex differences might be under- or overestimated. Furthermore, individuals were indicated to receive lipid-modifying medication in case of a high 10-year CVD risk combined with a LDL cholesterol level $>2.5\text{mmol/L}$. This cut-off value was adopted from the Dutch guideline cardiovascular risk management which is used in primary care.²⁴ In secondary and tertiary care physicians often use a cut-off value of $>1.8\text{mmol/L}$ when patients have a history of CVD, which means that we have been less strict than in clinical practice. Finally, in this study we examined sex differences in the management of diabetes using a cross-sectional design. However, the management of diabetes and the prevention and delay of diabetes complications is an ongoing dynamic process. For example, optimal treatment was defined as achievement of prespecified treatment targets according to current guidelines, while in reality the absolute drop in cardiovascular levels from the start of treatment may be more important. Also, medication use and risk factor levels are obtained at the same time, while setting the right treatment regimen takes time. Unfortunately, due to the cross-sectional design we do not have the information to take the dynamics of this process into account. This requires further investigation, ideally in studies with repeated risk factor measurements and longitudinal follow-up of pharmacological interventions.

Conclusions

In summary, in this population of Dutch individuals with T2D from primary, secondary, and tertiary care, women had a considerably higher BMI than men and a greater difficulty to attain HbA1c and LDL cholesterol treatment targets, while men were less likely to receive antihypertensive medication despite high CVD risk and elevated SBP. Effective weight loss strategies seem urgently needed.

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Collaborators

L 't Hart; N C Schaper; O M Dekkers; B Silvijs; M M van der Klauw.

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Supplementary table 1. Categorization of pharmacological management.

	Pharmacological management of hyperglycaemia	Pharmacological management of hypertension	Pharmacological management of hyperlipidaemia
1. No treatment and no treatment indication	<ul style="list-style-type: none"> HbA1c ≤ 53mmol/mol 	<ul style="list-style-type: none"> SBP ≤ 140mmHg Low or medium 10-year CVD risk and SBP > 140mmHg 	<ul style="list-style-type: none"> LDL cholesterol ≤ 2.5mmol/L Low or medium 10-year CVD risk and LDL cholesterol > 2.5mmol/L
2. Optimal treatment	<ul style="list-style-type: none"> Use of glucose-lowering medication and HbA1c ≤ 53mmol/mol 	<ul style="list-style-type: none"> Use of antihypertensive medication and SBP ≤ 140mmHg 	<ul style="list-style-type: none"> Use of lipid-modifying medication and LDL cholesterol ≤ 2.5mmol/L
3. Suboptimal treatment	<ul style="list-style-type: none"> Use of glucose-lowering medication and HbA1c > 53mmol/mol 	<ul style="list-style-type: none"> Use of antihypertensive medication and SBP > 140mmHg 	<ul style="list-style-type: none"> Use of lipid-modifying medication and LDL cholesterol > 2.5mmol/L
4. No treatment despite a treatment indication	<ul style="list-style-type: none"> No use of glucose-lowering medication and HbA1c > 53mmol/mol 	<ul style="list-style-type: none"> No use of antihypertensive medication despite high 10-year CVD risk and SBP > 140mmHg 	<ul style="list-style-type: none"> No use of lipid-modifying medication despite high 10-year CVD risk and LDL cholesterol > 2.5mmol/L

LDL-c = low-density lipoprotein cholesterol; SBP = systolic blood pressure; CVD = cardiovascular disease.

Supplementary table 2. Overview of missing data after exclusion of participants with missing data on sex (n=29).

	Men <i>n</i> =3,969	Women <i>n</i> =2,668
Age	0 (0%)	0 (0%)
Educational level	274 (7%)	202 (8%)
HbA1c	116 (3.1%)	54 (2.0%)
Systolic blood pressure	35 (0.9%)	34 (1.3%)
Diastolic blood pressure	35 (0.9%)	35 (1.3%)
Total cholesterol	99 (2.7%)	41 (1.5%)
LDL cholesterol	190 (5.1%)	82 (3.1%)
HDL cholesterol	118 (3.2%)	56 (2.1%)
Triglycerides	113 (3.1%)	59 (2.2%)
BMI	339 (9.2%)	251 (9.4%)
CVD risk score	403 (10.9%)	285 (10.7%)
Health care centre	30 (0.8%)	25 (0.9%)
Cardiovascular history	406 (11.0%)	404 (15.1%)
Smoking status	440 (11.9%)	272 (10.2%)
Lipid-modifying medication	91 (2.5%)	77 (2.9%)
Antihypertensive medication	91 (2.5%)	77 (2.9%)
Glucose-lowering medication	91 (2.5%)	77 (2.9%)
Antithrombotic medication	91 (2.5%)	77 (2.9%)

LDL cholesterol = low-density lipoprotein cholesterol; HDL cholesterol = high-density lipoprotein cholesterol; BMI = body mass index; CVD = cardiovascular disease.

Supplementary table 3. Age- and medication adjusted linear regression analyses presenting women-to-men mean differences in cardiometabolic risk factors stratified according to cardiovascular history, health care centre, age, BMI, and educational level.

	Cardiovascular history				Health care centre		Age			BMI			Educational level				
	Age- and medication-adjusted	No CVD	CVD	Primary care	Secondary/tertiary care	<60 Years	≥60 Years	<25kg/m ²	≥25kg/m ²	Low	Middle	High					
BMI, kg/m ²	1.65 (1.33;1.96)*	1.66* (1.27;2.06)	2.01* (1.46;2.56)	1.21* (0.83;1.59)	2.25* (1.72;2.78)	1.79* (1.21;2.37)	1.60* (1.22;1.98)	NA	NA	2.13* (1.58;2.67)	1.29 (0.80;1.78)	0.49 (-0.22;1.20)					
P for interaction	NA	0.275	0.002*	0.002*	0.570	NA	NA	NA	NA	<0.001*	<0.001*	<0.001*					
HbA _{1c} , mmol/mol	0.41 (-0.38;1.19)	0.31 (-0.58;1.05)	0.83 (-0.43;2.09)	-0.36 (-1.08;0.35)	1.18 (-0.06;2.42)	0.62 (-0.69;1.92)	0.15 (-0.63;0.93)	0.11 (-1.70;1.91)	0.34 (-0.40;1.09)	0.11 (-1.06;1.28)	0.35 (-0.67;1.37)	0.50 (-1.16;2.17)					
P for interaction	NA	0.375	0.025*	0.025*	0.541	0.827	0.843	0.843	0.843	0.843	0.843	0.843					
Systolic BP, mmHg	-0.65 (-1.80;0.40)	-0.71 (-1.79;0.34)	0.80 (-1.15;2.71)	-0.12 (-1.46;1.23)	-1.53 (-3.16;0.11)	-1.92* (-3.55;-0.29)	-0.16 (-1.53;1.22)	-0.86 (-3.81;2.10)	-0.66 (-2.24;1.28)	-0.48 (-2.24;1.28)	0.08 (-1.49;1.65)	-4.34* (-6.89;-1.80)					
P for interaction	NA	0.020*	0.223	0.223	0.118	0.836	0.836	0.836	0.836	0.836	0.836	0.836					
Diastolic BP, mmHg	-2.01* (-2.58;-1.43)	-2.02* (-2.60;-1.45)	-1.50* (-2.56;-0.44)	-2.71* (-3.42;-2.00)	-1.29* (-2.22;-0.36)	-1.60* (-2.54;-0.66)	-2.20* (-2.93;-1.47)	-1.07 (-2.63;0.49)	-2.15* (-2.77;-1.54)	-1.50* (-2.45;-0.54)	-2.05* (-2.91;-1.18)	-2.89 (-4.29;-1.49)					
P for interaction	NA	0.054	0.010*	0.010*	0.303	0.236	0.236	0.236	0.236	0.236	0.236	0.236					
TC, mmol/mol	0.41* (0.35;0.47)	0.37* (0.31;0.42)	0.46* (0.36;0.55)	0.41* (0.34;0.48)	0.31* (0.22;0.41)	0.24* (0.14;0.34)	0.44* (0.37;0.51)	0.43* (0.29;0.57)	0.35* (0.29;0.42)	0.37* (0.27;0.47)	0.35* (0.26;0.43)	0.45* (0.32;0.58)					
P for interaction	NA	0.026	0.081	0.081	0.001*	0.409	0.409	0.409	0.409	0.409	0.409	0.409					
LDL cholesterol, mmol/mol	0.24* (0.19;0.28)	0.20* (0.15;0.24)	0.29* (0.21;0.36)	0.18* (0.12;0.24)	0.22* (0.15;0.29)	0.13* (0.05;0.20)	0.24* (0.18;0.29)	0.12* (0.00;0.23)	0.21* (0.16;0.25)	0.18* (0.10;0.25)	0.19* (0.12;0.26)	0.28* (0.17;0.38)					
P for interaction	NA	0.008*	0.496	0.496	0.024*	0.195	0.195	0.195	0.195	0.195	0.195	0.195					
HDL cholesterol standardized	0.03* (0.01;0.05)	0.02* (0.00;0.04)	0.02 (-0.02;0.05)	0.02 (-0.01;0.04)	0.03 (-0.00;0.06)	0.03 (-0.01;0.06)	0.02 (-0.01;0.44)	0.12* (0.05;0.19)	0.01 (-0.01;0.03)	0.01 (-0.02;0.04)	0.05* (0.02;0.08)	0.04 (-0.01;0.09)					
P for interaction	NA	0.964	0.494	0.494	0.728	<0.001*	0.320	0.320	0.320	0.320	0.320	0.320					

Supplementary table 3. Age- and medication adjusted linear regression analyses presenting women-to-men mean differences in cardiometabolic risk factors stratified according to cardiovascular history, health care centre, age, BMI, and educational level. (continued)

	Total		Cardiovascular history		Health care centre		Age		BMI			Educational level		
	Age-adjusted	Age- and medication-adjusted	No CVD	CVD	Primary care	Secondary/tertiary care	<60 Years	≥60 Years	<25kg/m ²	≥25kg/m ²	Low	Middle	High	
Log-triglycerides, mmol/mol	-0.05* (-0.08;-0.02)	-0.04* (-0.07;-0.01)	-0.03 (-0.07;0.01)	-0.04 (-0.09;0.02)	0.03 (-0.01;0.06)	-0.12* (-0.18;-0.07)	-0.13* (-0.19;-0.07)	0.01 (-0.02;0.05)	-0.03 (-0.11;0.06)	-0.04* (-0.08;-0.01)	0.02 (-0.03;0.07)	-0.09* (-0.14;-0.05)	-0.08* (-0.16;0.01)	
P for interaction	NA	NA	0.964		<0.001*			<0.001*	0.798		0.018			
TC/HDL-ratio	-0.31* (-0.39;-0.24)	-0.34* (-0.41;-0.26)	-0.35* (-0.44;-0.26)	-0.25* (-0.38;-0.12)	-0.26* (-0.34;-0.17)	-0.43* (-0.56;-0.30)	-0.54* (-0.68;-0.42)	-0.21* (-0.29;-0.12)	-0.35* (-0.50;-0.19)	-0.33* (-0.41;-0.25)	-0.31* (-0.45;-0.18)	-0.40* (-0.51;-0.29)	-0.33* (-0.49;-0.16)	
P for interaction	NA	NA	0.208		0.015*		<0.001*	0.809		0.877				

The analyses stratified for CVD, health care setting, and educational status were age and medication-adjusted, and the analyses stratified for age were only medication-adjusted (HbA1c adjusted for glucose-lowering medication; lipid-spectrum adjusted for lipid-modifying medication, and blood pressure adjusted for antihypertensive medication). Analyses stratified for BMI were only age-adjusted. Individuals with missing data on cardiovascular history, health care centre, age, BMI, or educational level were excluded in the overall and subgroup analyses so that the separate analyses were comparable. BP = blood pressure; TC = total cholesterol; LDL cholesterol = low-density lipoprotein cholesterol; HDL cholesterol = high-density lipoprotein cholesterol; BMI = body mass index; NA = not applicable. * = significant. Men = reference.

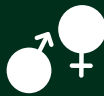
Supplementary table 4. Age-adjusted Poisson regression analyses presenting women-to-men relative risks for treatment and control stratified according to cardiovascular history, health care centre, age, BMI, and educational level.

	Not receiving treatment													
	Total	Cardiovascular history				Care setting		Age		BMI			Educational level	
		Women vs. men	RR (95% CI)	No CVD	CVD	Primary care	Secondary/tertiary care	<60	≥60	<25kg/m ²	≥25kg/m ²	Low	Middle	High
No glucose-lowering medication despite HbA1c >53mmol/mol	2,315 (4%)	0.96 (0.63;1.46)	1.09 (0.66;1.78)	0.62 (0.26;1.45)	1.05 (0.66;1.67)	0.80 (0.32;2.02)	1.09 (0.52;2.26)	0.92 (0.55;1.54)	0.92 (0.59;1.43)	1.41 (0.36;5.51)	0.79 (0.40;1.57)	1.48 (0.76;2.89)	0.63 (0.22;1.81)	
P for interaction	NA		0.259	0.613	0.711	0.565	0.981							
No antihypertensive medication despite high CVD risk and systolic BP >140mmHg	2,332 (24%)	0.85* (0.73;1.00)	0.77* (0.64;0.92)	1.00 (0.73;1.38)	0.73* (0.61;0.88)	1.12 (0.85;1.49)	0.82 (0.59;1.14)	0.86 (0.72;1.02)	0.77 (0.54;1.08)	0.87 (0.73;1.04)	0.74 (0.56;0.97)	0.95 (0.75;1.20)	1.27 (0.92;1.76)	
P for interaction	NA		0.152	0.013*	0.812	0.522	0.008							
No antihypertensive drugs despite systolic blood pressure >140mmHg	2,605 (25%)	0.90 (0.78;1.03)	0.82* (0.71;0.95)	1.00 (0.73;1.38)	0.78 (0.66;0.92)	1.15 (0.90;1.47)	0.94 (0.73;1.20)	0.89 (0.75;1.06)	0.82 (0.61;1.11)	0.90 (0.78;1.05)	0.74 (0.57;0.95)	0.99 (0.81;1.21)	1.36* (1.03;1.80)	
P for interaction	NA		0.292	0.007*	0.453	0.655	0.001							
No lipid-modifying medication despite high CVD risk and LDL cholesterol >2.5mmol/L	1,420 (52%)	1.03 (0.94;1.14)	0.94 (0.83;1.05)	1.26* (1.03;1.53)	0.93 (0.82;1.04)	1.28* (1.08;1.53)	1.03 (0.87;1.23)	1.04 (0.92;1.17)	0.91 (0.71;1.16)	1.06 (0.95;1.18)	0.96 (0.81;1.15)	1.04 (0.89;1.21)	1.17 (0.95;1.43)	
P for interaction	NA		0.011	0.003*	0.993	0.205								
No lipid-lowering drugs despite LDL cholesterol >2.5mmol/L	1,803 (54%)	1.06 (0.97;1.15)	0.99 (0.90;1.08)	1.26* (1.03;1.53)	0.95 (0.86;1.06)	1.27* (1.09;1.47)	1.12 (0.99;1.26)	1.02 (0.90;1.15)	1.05 (0.86;1.29)	1.06 (0.96;1.16)	0.98 (0.84;1.15)	1.07 (0.94;1.21)	1.18 (0.99;1.41)	
P for interaction	NA		0.027	0.002*	0.290	0.133								

Supplementary table 4. Age-adjusted Poisson regression analyses presenting women-to-men relative risks for treatment and control stratified according to cardiovascular history, health care centre, age, BMI, and educational level. (continued)

		Treatment and attainment of risk factor targets											
		Total		Cardiovascular history		Care setting		Age		BMI		Education	
Total (%)	Women vs. men	RR (95% CI)	No CVD	CVD	Primary care	Secondary/tertiary care	<60	≥60	<25kg/m ²	≥25kg/m ²	Low	Middle	High
4,212 (47%)	44% vs. 49%	0.89* (0.83;0.96)	0.91* (0.84;0.99)	0.80 (0.71;0.91)*	0.96 (0.89;1.03)	0.80* (0.71;0.90)	0.86* (0.76;0.97)	0.91* (0.84;0.99)	0.93 (0.79;1.08)	0.89* (0.82;0.95)	0.95 (0.84;1.06)	0.91 (0.82;1.01)	0.83 (0.70;0.98)
	NA	0.095	0.014	0.386	0.593	0.298							
3,478 (44%)	45% vs. 44%	1.02 (0.94;1.09)	1.10 (0.99;1.21)	0.95 (0.84;1.06)	0.97 (0.88;1.08)	1.05 (0.94;1.17)	1.07 (0.96;1.19)	0.99 (0.89;1.10)	0.99 (0.79;1.23)	1.02 (0.85;1.09)	0.96 (0.85;1.09)	0.99 (0.88;1.10)	1.34 (1.13;1.58)
	NA	0.050	0.372	0.310	0.794	0.008							
3,324 (75%)	70% vs. 78%	0.90* (0.86;0.94)	0.91* (0.86;0.96)	0.89* (0.83;0.96)	0.89* (0.84;0.94)	0.91* (0.86;0.98)	0.95* (0.88;1.02)	0.88* (0.83;0.93)	0.96 (0.86;1.08)	0.89* (0.85;0.93)	0.90 (0.84;0.96)	0.91 (0.85;0.97)	0.85 (0.75;0.96)
	NA	0.668	0.576	0.099	0.231	0.561							

The analyses stratified for cardiovascular history, health care setting, BMI, and educational level were age-adjusted, and the analyses stratified for age were unadjusted. Individuals with missing data on cardiovascular history, health care centre, age, BMI or educational level were excluded in the overall and subgroup analyses so that the separate analyses were comparable. Total refers to the total number of participants included in the analyses and (%) refers to the number of participants with the outcome of interest. CVD = cardiovascular disease; BP = blood pressure; LDL cholesterol = low-density lipoprotein-cholesterol. * = significant. Men = reference.



Chapter 9

Cardiovascular risk factor assessment and screening for diabetes-related complications in women and men with diabetes: a systematic review

Marit de Jong
Sanne A.E. Peters
Rianneke de Ritter
Carla J.H van der Kallen
Simone J.S. Sep
Mark Woodward
Coen D.A. Stehouwer
Michiel L. Bots
Rimke C. Vos

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Abstract

Objective

Insight in sex disparities in the detection of cardiovascular risk factors and diabetes-related complications may improve diabetes care. The aim of this systematic review is to study whether sex disparities exist in the assessment of cardiovascular risk factors and screening for diabetes-related complications.

Research Design and Methods

PubMed was systematically searched up to April 2020, followed by manual reference screening and citation checks (snowballing) using Google Scholar. Observational studies were included if they reported on the assessment of cardiovascular risk factors (HbA1c, lipids, blood pressure, smoking status, or BMI) and/or screening for nephropathy, retinopathy, or performance of feet examinations, in women and men with diabetes separately. Studies adjusting their analyses for at least age, or when age was considered as a covariable but left out from the final analyses for various reasons (i.e. backward selection), were included for qualitative analyses. No meta-analyses were planned because substantial heterogeneity between studies was expected. A modified Newcastle-Ottawa Quality Assessment Scale for cohort studies was used to assess risk of bias.

Results

Overall, 81 studies were included. The majority of the included studies were from Europe or North America (84%). The number of individuals per study ranged from 200 to 3,135,019 and data were extracted from various data sources in a variety of settings. Screening rates varied considerably across studies. For example, screening rates for retinopathy ranged from 13% to 90%, with half the studies reporting screening rates less than 50%. Mixed findings were found regarding the presence, magnitude, and direction of sex disparities with regard to the assessment of cardiovascular risk factors and screening for diabetes-related complications, with some evidence suggesting that women, compared with men, may be more likely to receive retinopathy screening and less likely to receive foot exams.

Conclusions

Overall, no consistent pattern favouring men or women was found with regard to the assessment of cardiovascular risk factors and screening for diabetes-related complications. Screening rates can be improved for both sexes.

Introduction

In 2019, an estimated 463 million adults aged between 20 and 79 years had diabetes, affecting 9.0% of women and 9.6% of men globally. Cardiovascular disease (CVD) is one of the most common complications of diabetes, with individuals with diabetes being two to three times more likely to develop CVD compared to those without diabetes.¹ Other common diabetes-related complications include diabetic nephropathy, retinopathy, neuropathy, certain cancers, physical and cognitive impairment, depression and several types of infectious diseases.^{1,2}

Although incidence rates of major CVD have been reported to be higher in men than women with and without diabetes^{3,4}, there is a growing body of evidence showing that the relative risk of major cardiovascular complications conferred by diabetes is larger in women than men.²⁻⁸ Several large studies have shown that the relative risk of ischemic heart disease conferred by diabetes can be up to 50% higher in women than men.^{3,5,8} A sex differential in the consequence of diabetes has also been reported for stroke, where the relative risk of stroke was 27% higher among women than men.⁶ Less is known about sex differences in the effects of diabetes on microvascular complications. A meta-analysis has demonstrated that diabetes confers a 19% higher relative risk of vascular dementia in women than men.⁹ Sex differences have also been shown for end-stage renal disease but not for chronic kidney disease.¹⁰ Underlying mechanisms that explain the higher excess risk of (vascular) complications, conferred by diabetes, in women remain uncertain but may include sex disparities in the uptake and provision of healthcare.²

More insight in sex disparities concerning the uptake and provision of diabetes management may eventually result in more personalized diabetes care, thereby helping to further diminish the burden in both sexes. We conducted a systematic review to study whether sex disparities exist in the assessment of cardiovascular risk factors and screening for diabetes-related complications among people with diabetes.

Methods

The protocol of this study was registered at the international prospective register of systematic reviews (PROSPERO) registry (registration number: CRD42018104414). We performed this review according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹¹

Search strategy and study selection

Observational studies (including before-after studies) on the assessment of cardiovascular risk factors (HbA1c, lipids, blood pressure, BMI, and smoking status) and screening for complications (retinopathy, nephropathy, and foot ulcerations/deformities/sensory decline), in men and women with diabetes, were identified through systematically searching PubMed (January 2009 up to April 2020) (Supplemental Table I). After having identified a set of eligible studies using our search strategy, we performed manual reference and citation screening (snowballing) using Google Scholar. This method has previously been described as a good alternative to database searches

once a number of eligible studies have been identified.¹² Studies were included if data on the assessment of cardiovascular risk factors or screening for diabetes-related complications were provided separately for men and women. Studies presenting insufficient information about the effect size or direction of sex disparities were excluded (i.e. studies only presenting p-values). Only full-text articles written in English or Dutch were considered eligible for inclusion. Studies also including individuals without diabetes were eligible if results for individuals with diabetes were presented separately. Studies on gestational diabetes were excluded, as well as studies on which data on risk factor assessment were only adjusted for, rather than analysed by, sex. Furthermore, studies primarily focusing on children or adolescents were excluded.

Outcomes

The outcomes of interest were; assessment of HbA1c, lipids, blood pressure, smoking status, and BMI, screening for nephropathy, retinopathy, and performance of foot examinations, or any combination, all reported as binary variables (yes vs. no). For all outcomes of interest we used “assessment of cardiovascular risk factors” and “screening for complications” as defined by the original article. When studies showed multiple outcome definitions we chose the one closest to (inter)national guidelines.

Data collection and management

Data extraction was performed by one author (MJ) and checked by a second author (RV). Any discrepancies between the authors during data collection were discussed with a third author (SP). The extracted data comprised: authors’ names and year of publication, country, study period, number of participants (% women), age, reported outcomes (including measures of association with corresponding confidence intervals (CIs)), and data source. (Supplemental table II)

Quality assessment

The methodological quality of the included studies was assessed by one author (MJ) and checked by a second author (RV) using a modified Newcastle-Ottawa Quality Assessment Scale for cohort studies.¹³ The modified scale includes six items under three categories: selection, comparability and outcome. Any discrepancies were discussed with a third author (SP).

Data synthesis and analyses

It was decided beforehand not to perform any meta-analyses due to the expected heterogeneity between the included studies. Qualitative analyses were restricted to studies adjusting their analyses for age or when age was considered as an important covariable but left out from the final analyses for various reasons (i.e. backward selection). Studies only presenting crude numbers and percentages or unadjusted results are presented in Supplemental table III. Where reports with overlapping study populations were found and similar outcomes of interest were studied, the study presenting data from the most recent study period or the study with most participants was included. Similarly, where studies were repeated over time, only studies with the most recent data or largest number of study participants were included. For example, the UK National Diabetes Audit is repeated every year and only data from the most recent report relevant for the outcomes

of interest were extracted. Characteristics of the studies excluded from qualitative analyses are shown in supplemental table IV.

The results are presented as odds ratios (ORs) or risk ratios (RRs) with 95% CIs, with men as the reference category, unless otherwise specified. When studies only reported stratified results, e.g. by age group, ORs/RRs and the 95% CIs in each stratum were summarized using a fixed effect model. For studies that stratified the results by year, with potential overlap of included participants between strata, results from the most recent year were extracted. If studies presented multiple models, only the most extensive adjusted models were extracted. Forest plots without pooled effects were used to visualize the adjusted estimates and corresponding CIs across studies included for qualitative analysis.

Results

Overall, 81 studies were included for qualitative analyses.¹⁴⁻⁹² (Figure 1) Characteristics of the included studies are presented in Supplemental table II. The majority of studies were from Europe or Northern America (37% and 47% respectively), eight from Asia, two from Oceania, one from Africa, and one from South America. Of the 81 studies, 55 (68%) reported data on individuals with diabetes (without specifying subtype) and 24 (30%) reported on individuals with type 2 diabetes. In addition, two reports from the UK National Diabetes Audit reported data on individuals stratified by diabetes subtype. Given that no other reports presented data on individuals with type 1 diabetes, only data from individuals with type 2 diabetes were extracted from the two reports. The number of included individuals per study ranged from 200 to 3,135,019. Data were extracted from various data sources (i.e. (population-based) surveys, medical records, and administrative claims data) in a variety of settings, including primary care, outpatient clinics, and hospital settings.

Risk of Bias

The risk of bias was moderate with 78% of studies showing either fair or good study quality with clearly reported information about study design, in- and exclusion criteria, data collection, and assessment of the outcome. Although most studies included a representative sample, there was considerable heterogeneity between studies with regard to the study populations making it more challenging to score this aspect. (Supplemental table IV)

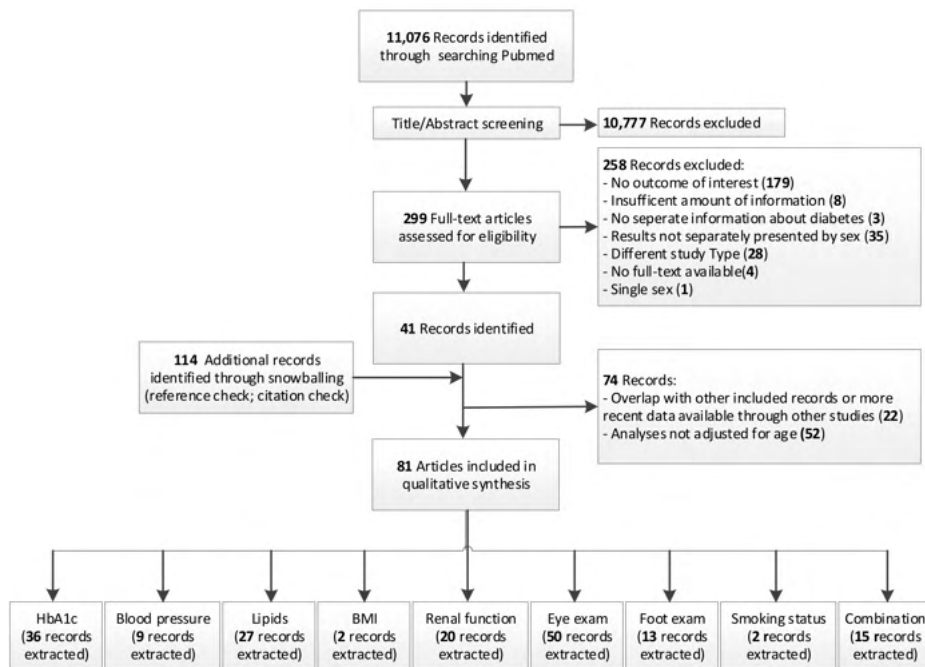


Figure 1. Flowchart of study selection. PubMed search was used to obtain a suitable start set for snowballing.

Assessment of HbA1c

In total, 36 studies including 6.6 million individuals were included with median assessment rates of 74% in women and 73% in men. Most studies showed no statistically significant sex disparities in the assessment of HbA1c (70%), while 19% showed that women were more often receiving assessment of HbA1c than men, and 11% showed that men were more often receiving assessment of HbA1c than women. (Figure 2)

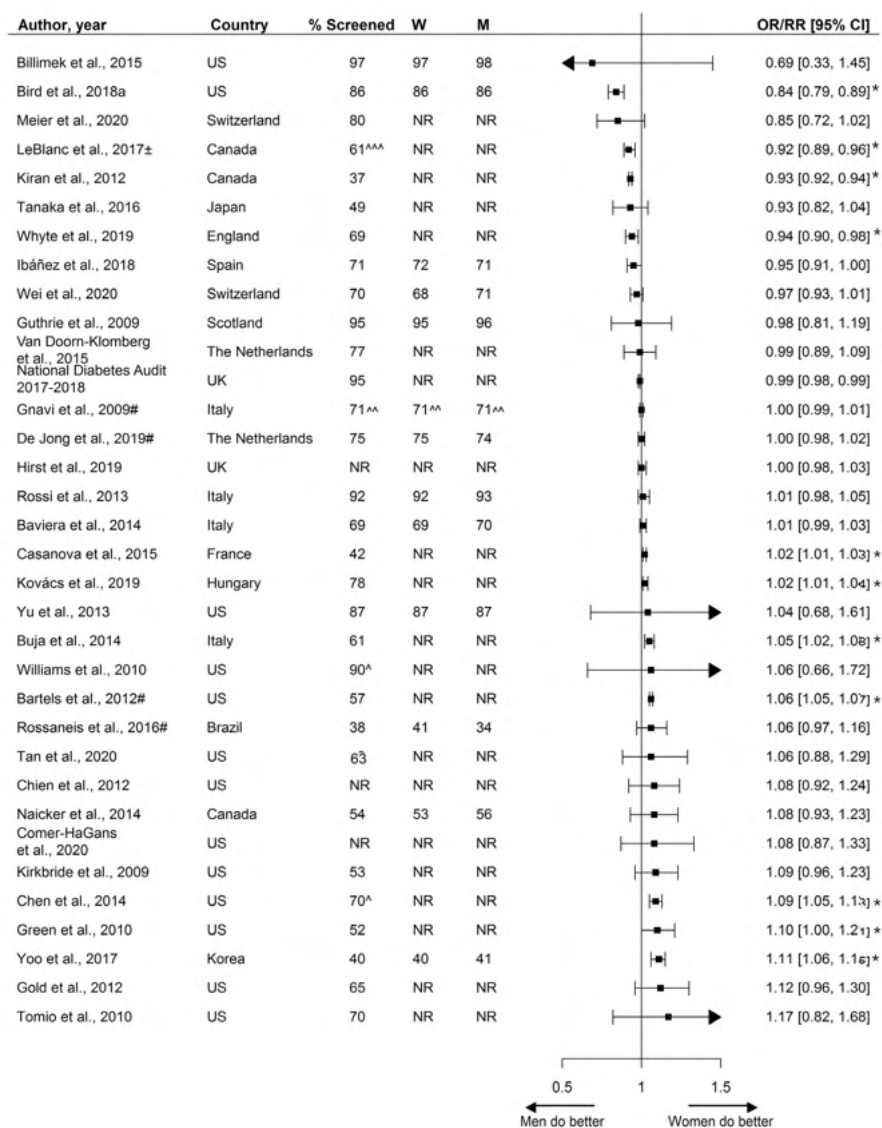


Figure 2. Assessment of HbA1c expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). Two studies are not presented in this figure because of their measure of association: Swietek et al.33: Average Marginal Effect, (SE; p-value): -0.00031 (-0.0044; >0.05), Du et al.92: Prevalence difference (95% CI): 3.5 (-1.0;8.0). W = % of screened women; M = % of screened men; US = United States; UK = United Kingdom; ± = 99% CI; # = Relative risk; ^ = Weighted %; ^^ = Kaplan-Meier estimates; ^^^ = Estimated %; * = statistically significant. Men = reference.

Assessment of blood pressure

The assessment of blood pressure by sex was reported by nine studies including 3.7 million individuals. Median assessment rate across studies was 79% (range 48% - 98%). Sex-specific

percentages of blood pressure assessment were reported by three studies ranging from 78% to 94% in women and 77% to 96% in men. Five studies showed no statistically significant disparities in the assessment of blood pressure, while three studies showed that women were more likely to receive blood pressure screening and one study reported men being more likely to receive blood pressure screening. (Figure 3)

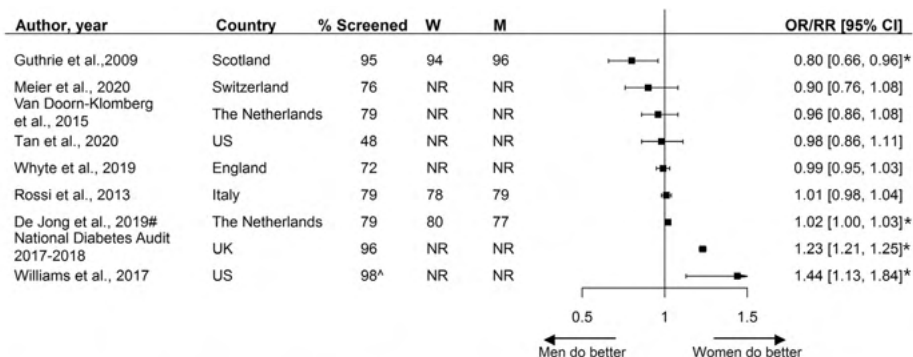


Figure 3. Assessment of blood pressure expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). W = % of screened women; M = % of screened men; US = United States; UK = United Kingdom; # = Relative risk; [^] = Assumed to be weighted %; * = statistically significant. Men = reference.

Assessment of lipids

The assessment of lipids by sex was reported by 27 studies including 5.4 million individuals. These studies reported on various lipid measurements including the assessment of LDL cholesterol, HDL cholesterol, lipid profile, (total) cholesterol, HDL/TC-ratio, and triglycerides. Among the fifteen studies reporting the assessment of either lipids or (total) cholesterol, assessment rates ranged from 40% to 96% with a median of 73%. Over half the studies (eight out of fifteen) reported no statistically significant or only small sex disparities, while four studies reported that, compared with men, women were less likely to receive screening. Three studies showed that women were more likely to receive screening.

Twelve studies including data from 829,819 individuals reported sex-specific assessment of LDL cholesterol. Five studies reported that women were less likely to receive screening, four studies reported that women were more likely to receive screening than men, and the remaining three studies showed no sex disparities. Two studies investigated sex disparities in the assessment of HDL measurements, with one reporting that women were more likely to receive screening. One study reported on the assessment of triglycerides, showing that women were less likely to receive screening than their male counterparts. (Figure 4)

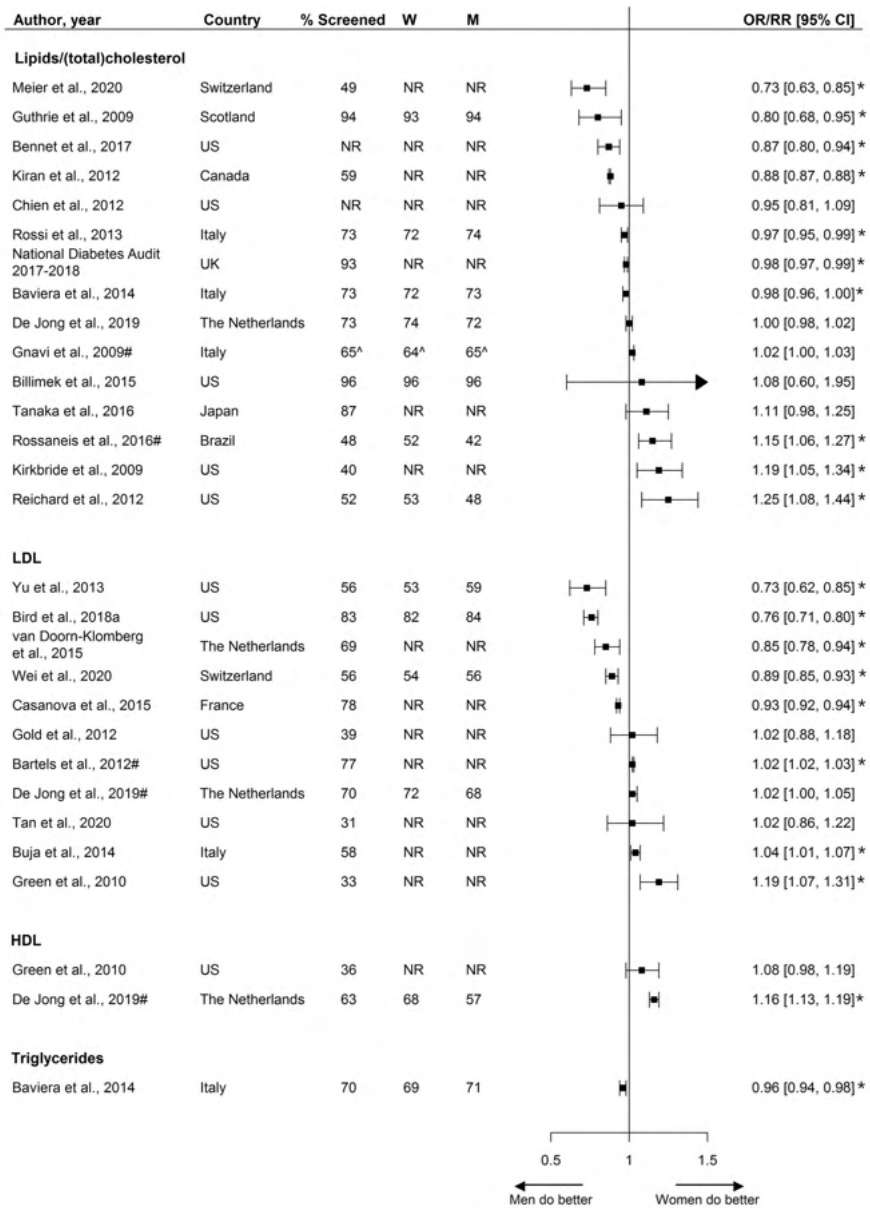


Figure 4. Assessment of lipids expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). One study is not presented in this figure because of the measure of association: Swietek et al.33: Average Marginal Effect (LDL), (SE; p-value): 0.0045 (-0.0042; >0.05). W = % of screened women; M = % of screened men; US = United States; UK = United Kingdom; # = Relative risk; [^] = Kaplan-Meier estimates; * = statistically significant. Men = reference.

Assessment of BMI

Two studies reported sex-specific BMI assessment; one study found that women were less likely to receive screening and the other found no sex differences. (Figure 5)

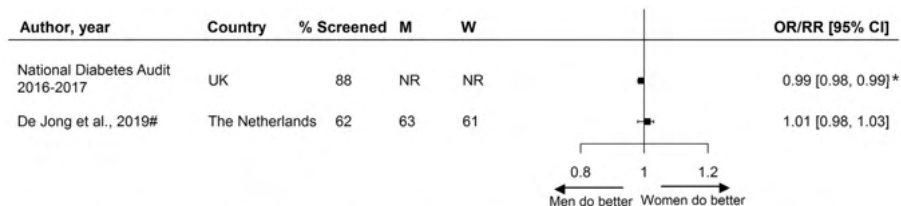


Figure 5. Assessment of BMI expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). W = % of screened women; M = % of screened men; UK = United Kingdom; # = Relative risk; * = statistically significant. Men = reference.

Nephropathy screening

Twenty studies including 3.9 million individuals examined sex disparities in nephropathy screening. These studies reported on various measures to assess renal function including estimated glomerular filtration rate (eGFR), microalbuminuria, urine albumin, albumin/creatinine ratio, and serum creatinine. Two-thirds of studies reported screening rates less than 70%. Overall, there was no consistent pattern in nephropathy screening favouring either women or men (Figure 6).

Retinopathy screening

Fifty studies including 3.4 million individuals reported on retinopathy screening. Screening rates ranged from 13% to 90% across studies with nearly half the studies reporting screening rates equal to or less than 50%. Five studies reported that women were less likely to receive retinopathy screening than men and 22 studies showed that women were more likely to receive screening. (Figure 7)

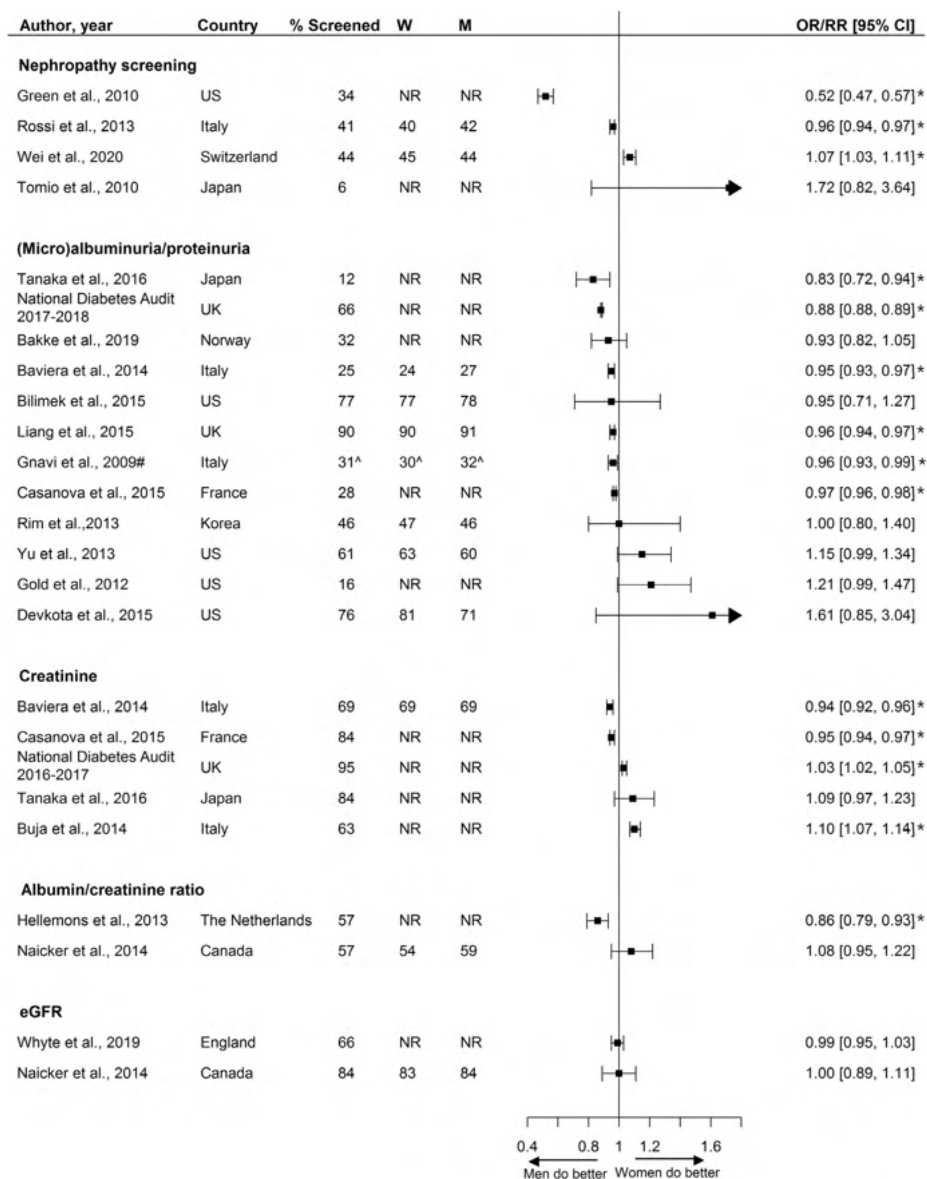


Figure 6. Nephropathy screening expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). One study is not presented in this figure because of the measure of association: Swietek et al.33: Average Marginal Effect, (SE; p-value): -0.0073 (-0.0042; <0.05 (women less likely to receive screening). W = % of screened women; M = % of screened men; US = United States; UK = United Kingdom; # = Relative risk; [^] = Kaplan-Meier estimate; * = statistically significant. Men = reference.

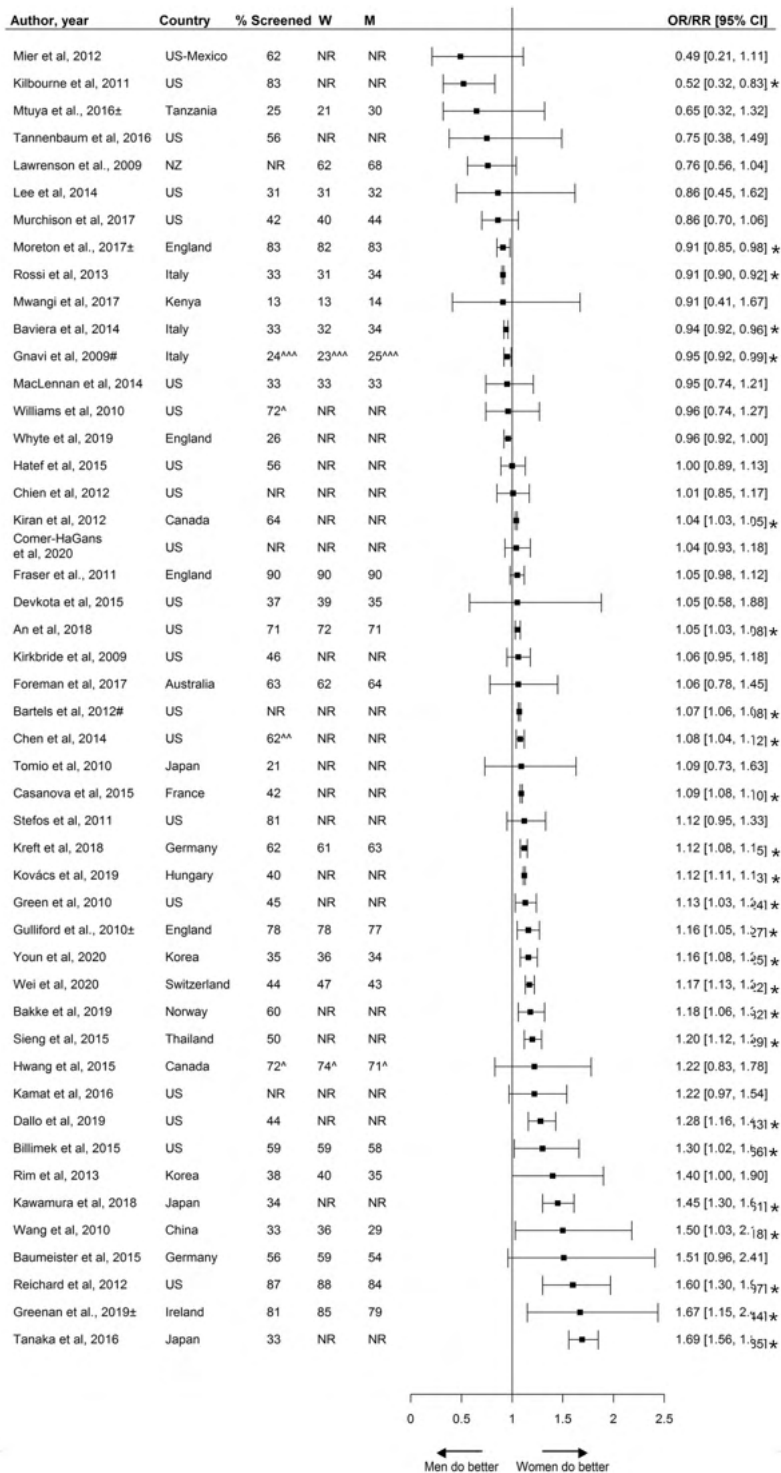


Figure 7. Retinopathy screening expressed as adjusted odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI). Two studies are not presented in this figure because of their measure of association: Swietek et al.33: Average Marginal Effect, (SE; p-value): 0.017 (-0.0043; <0.01 (women more likely to receive screening), Du et al.92: Prevalence difference (95% CI): 12.6 (4.1;21.2). W = % of screened women; M = % of screened men; US = United States; UK = United Kingdom; # = Relative risk; ^ = weighted %; ^^ = assumed to be weighted %; ^^^ = Kaplan-Meyer estimate; ± = Studies assessing screening adherence after screening invitation; * = statistically significant. Men = reference.

Foot exams

Thirteen studies including >3.9 million individuals reported on the sex-specific performance of foot exams. Screening rates varied from 13% to 99% across studies with a median screening rate of 58%. Six reported that women were less likely to receive foot exams and one study reported women being more likely to receive foot exams. The other studies reported no sex differences (Figure 8).

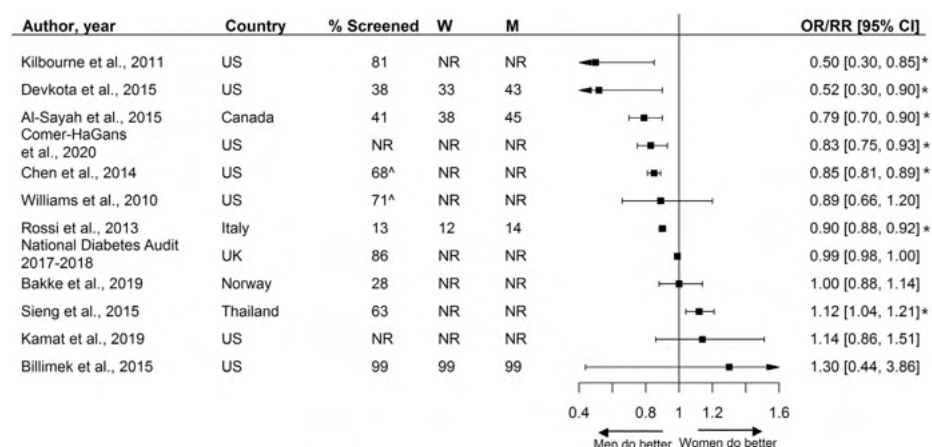


Figure 8. Foot exams, expressed as adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI). One study is not presented in this figure because of the measure of association: Du et al.92: Prevalence difference (95% CI 4.2 (-6.4; 14.9).W = % of screened women; M = % of screened men; US = United States; UK = United Kingdom; ^ = assumed to be weighted %; * = statistically significant. % Chen et al. extracted from the last available year. Men = reference.

Assessment of smoking status

Two studies reported on the assessment of smoking status. Both studies found high screening rates (95%) and women were more likely to be screened for smoking status than men. (Figure 9)

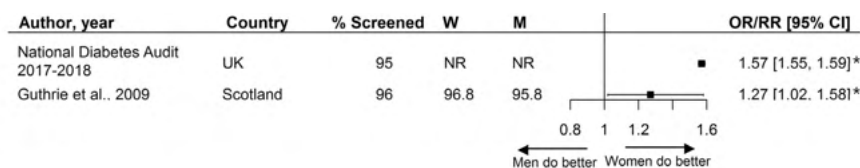


Figure 9. Assessment of smoking status expressed as adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI). W = % of screened women; M = % of screened men; * = statistically significant. Men = reference.

Combination

Fifteen studies reported on the assessment of a combination of risk factors and screening activities. The presence and direction of sex disparities varied across studies with a third of the included studies reporting that, compared with men, women were less likely to receive a combination of care, one-third of studies found no sex disparities, and one-third found that women were more likely to receive a combination of care than men. (Figure 10)

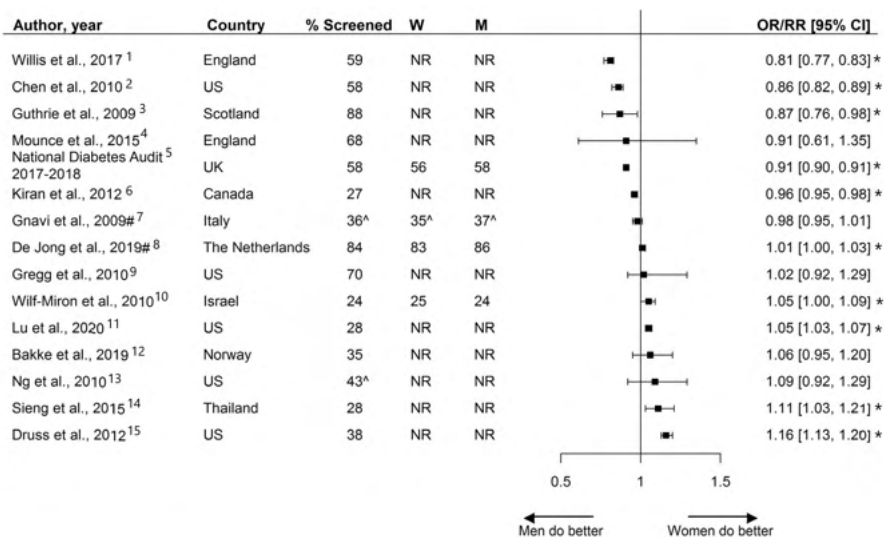


Figure 10. Combination of risk factor assessment and screening expressed as adjusted odds ratios (OR) or risk ratios (RR) with corresponding 95% confidence intervals (CI). # = risk ratio; ^ = Kaplan-Meier estimates; * = statistically significant. W = % of screened women; M = % of screened men. Men = reference. 1 = All measurements received within 12 months: blood pressure, HbA1c, cholesterol, urine albumin:creatinine ratio/protein:creatinine or proteinuria, eGFR or serum creatinine, foot and eye exams, BMI, smoking status, within 15 months (6 for HbA1c). 2 = Receiving at least 2 HbA1c measurements and 1 LDL measurement received within 12 months. 3 = All measurements received within 12 months: HbA1c, blood pressure, cholesterol, smoking status. 4 = At least one of the following measurements received within 12 months: HbA1c, proteinuria, foot exam. 5 = All measurements received within 15 months: HbA1c, blood pressure, cholesterol, serum creatinine, urine albumin, foot exam, BMI, smoking status. 6 = All measurements received within 24 months: eye exam, four HbA1c tests, and two cholesterol tests. 7 = Assessment of HbA1c and at least two measurements from among eye exams, total cholesterol, and microalbuminuria. 8 = Receiving one or more measurements within 12 months: HbA1c, blood pressure, total cholesterol, LDL, HDL, or BMI. 9 = All measurements received within 36 months: HbA1c, lipid profile, urine albumin, eye exam, and foot exam. 10 = All measurements received within 12 months: HbA1c, LDL, microalbuminuria, eye and foot exams, blood pressure and BMI. 11 = All measurements received within 12 months: HbA1c, LDL, eye exam, and medical attention for nephropathy (including screening and treatment). 12 = Receiving at least two out of three measurements: albuminuria and monofilament (foot exam) within 12 months, eye exam within 30 months. 13 = Receiving all measurements within 12 months: HbA1c, eye and foot exams. 14 = Receiving all measurements within 12 months: HbA1c, LDL, eye and foot exams. 15 = Receiving at least 2 measurements: HbA1c during the measurement year, eye exam, LDL, and medical attention for nephropathy (screening test during the past year or evidence of nephropathy).

Discussion

This systematic review including 81 studies showed that the presence, magnitude, and direction of sex disparities in the assessment of cardiovascular risk factors and screening of diabetes-related complications varied considerably across studies, with some evidence suggesting that women, compared with men, may be more likely to receive retinopathy screening and less likely to receive foot exams. In addition, only two studies reported on the assessment of smoking status; both showing that women were more likely to be screened. Overall, screening rates can be improved for both sexes.

To our knowledge, this is the first systematic review studying sex disparities in the assessment and screening of cardiovascular risk factors and diabetes-related complications among individuals with diabetes. A recent meta-analysis, including 22 studies with 4,754,782 individuals from the general population in primary care setting, showed that assessment rates of CVD risk scores and risk factors were similar between the sexes.⁹³ In contrast to our study, the authors did find evidence of women being less likely to be assessed for smoking.⁹³ Nevertheless, the results were comparable to our study in that no consistent pattern in risk factor assessment and complication screening favouring either men or women was found and screening rates could be improved for both sexes.

Assessment of cardiovascular risk factors and screening for diabetes-related complications is critical in guiding treatment decisions. The present study demonstrates that there is no consistent pattern in screening activities favouring women or men, suggesting that disparities in risk factor assessment and screening activities do not account for the higher relative risk of CVD conferred by diabetes previously found in women compared with men.²⁻⁸ However, other factors related to the uptake and provision of healthcare, such as treatment and adherence, may still be involved in explaining these sex differences. Although assessment of cardiovascular risk factors is one of the first steps in guiding treatment decisions, it may not necessarily be followed by equal treatment. For example, a recently published meta-analysis, including data from 2.2 million individuals in primary care, showed that women at high risk or with established CVD were less likely to be prescribed aspirin, statins, and angiotensin-converting enzyme (ACE) inhibitors, and more likely to be prescribed diuretics than men.⁹⁴ Other studies have suggested that women are less adherent to statins than men.⁹⁵⁻⁹⁷ Differences in biology may also impact women's excess risk of CVD and it has previously been hypothesized that women experience a relatively greater increase of cardiovascular risk factor levels in the transition from normal glycaemia to diabetes.⁹⁸ Differences in body anthropometry and fat storage may be of particular interest in explaining the excess risk of CVD in women as fat distribution differs by sex. Sex differences in fat distribution may impact the duration of the transition from normoglycaemia to overt diabetes and consequently impact the increase of other related cardiovascular risk factor levels.²

Strengths and limitations

The main strength of this systematic review is the inclusion of a large number of studies providing sex-specific data. The majority of studies included more than 1,000 individuals of which 41 (51%)

studies included over 10,000 individuals. This study also has several limitations. First, there was substantial heterogeneity between studies regarding patient population, outcome definitions, and data source, and no meta-analyses were performed. Second, there was a lack of studies that specifically evaluated risk factor assessment in type 1 diabetes patients. The results of this systematic review are therefore mainly applicable to those with type 2 diabetes. Third, the majority of studies were from Europe and North America, thereby limiting the generalizability to other parts of the world.

Conclusions

Mixed findings were found regarding the presence, magnitude, and direction of sex disparities with regard to the assessment of cardiovascular risk factors and screening for diabetes-related complications. Overall, no consistent pattern favouring women or men was found and screening rates can be improved for both sexes.

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Supplemental table 1. Search strategy and date performed.**PubMed - April 2020 (Date restriction: 1-1-2009)**

risk factors[MeSH Terms] OR risk assessment[MeSH Terms] OR risk screening[MeSH Terms] OR health care disparity[MeSH Terms] OR cardiovascular risk management[MeSH Terms] OR risk factors[Title/Abstract] OR risk assessment[Title/Abstract] OR risk screen [Title/Abstract] OR risk screening[Title/Abstract] OR health screen[Title/Abstract] OR health screening[Title/Abstract] OR health measurement[Title/Abstract] OR health assessment[Title/Abstract] OR health care disparity[Title/Abstract] OR health care disparities [Title/Abstract] OR cardiovascular risk management [Title/Abstract] OR CVRM[Title/Abstract] OR complication screening [Title/Abstract] OR complication assessment[Title/Abstract] OR (primary prevention[MeSH Terms] OR secondary prevention[MeSH Terms] OR primary prevention[Title/Abstract] OR secondary prevention[Title/Abstract])) OR (quality of health care[MeSH Terms] OR quality indicator, healthcare[MeSH Terms] OR guideline adherence[MeSH Terms] OR provision of health care[MeSH Terms] OR quality of health care[Title/Abstract] OR quality of care[Title/Abstract] OR quality of healthcare[Title/Abstract] OR healthcare quality [Title/Abstract] OR health care quality[Title/Abstract] OR QoC[Title/Abstract] OR quality indicator[Title/Abstract] OR quality indicators[Title/Abstract] OR quality criterion[Title/Abstract] OR quality criteria[Title/Abstract] OR guideline adherence [Title/Abstract] OR provision of healthcare[Title/Abstract] OR provision of health care[Title/Abstract] OR healthcare provision [Title/Abstract] OR health care provision [Title/Abstract])) OR (cholesterol[MeSH Terms] OR blood pressure[MeSH Terms] OR glucose[MeSH Terms] OR smoking[MeSH Terms] OR cardiovascular risk[MeSH Terms] OR diabetic complication[MeSH Terms] OR clinical care[Title/Abstract] OR cholesterol[Title/Abstract] OR low density lipoprotein[Title/Abstract] OR LDL[Title/Abstract] OR high density lipoprotein[Title/Abstract] OR HDL[Title/Abstract] OR triglycerides [Title/Abstract] OR dyslipidemia[Title/Abstract] OR hyperlipidemia[Title/Abstract] OR hyperlipidaemia[Title/Abstract] OR lipid control[Title/Abstract] OR lipid profile[Title/Abstract] OR blood pressure[Title/Abstract] OR systolic pressure[Title/Abstract] OR SBP[Title/Abstract] OR diastolic pressure[Title/Abstract] OR SBP [Title/Abstract] OR hypertension[Title/Abstract] OR bp[Title/Abstract] OR hemoglobin A1c[Title/Abstract] OR HbA1c[Title/Abstract] OR glucose [Title/Abstract] OR hyperglycemia[Title/Abstract] OR physical activity[Title/Abstract] OR smoking[Title/Abstract] OR smoker[Title/Abstract] OR body mass index[Title/Abstract] OR BMI[Title/Abstract] OR kidney function[Title/Abstract] OR diabetic kidney disease[Title/Abstract] OR nephropathy[Title/Abstract] OR renal disease[Title/Abstract] OR microalbuminuria[Title/Abstract] OR macroalbuminuria[Title/Abstract] OR albuminuria[Title/Abstract] OR glomerular filtration rate[Title/Abstract] OR GFR[Title/Abstract] OR proteinuria[Title/Abstract] OR creatinine [Title/Abstract] OR creatinine/eGFR[Title/Abstract] OR retinopathy[Title/Abstract] OR eye exam[Title/Abstract] OR eye examination[Title/Abstract] OR eye complication[Title/Abstract] OR eye complications [Title/Abstract] OR eye monitoring[Title/Abstract] OR eyes dilated[Title/Abstract] OR dilated eye exam[Title/Abstract] OR foot exam[Title/Abstract] OR foot examination[Title/Abstract] OR monofilament test[Title/Abstract] OR foot complication[Title/Abstract] OR foot complications[Title/Abstract] OR foot monitoring[Title/Abstract] OR microvascular complication[Title/Abstract] OR microvascular complications[Title/Abstract] OR macrovascular complication[Title/Abstract] OR macrovascular complications [Title/Abstract] OR vascular complication[Title/Abstract] OR vascular complications[Title/Abstract] OR cardiovascular risk [Title/Abstract] OR cardiovascular risk factors[Title/Abstract] OR CVD risk[Title/Abstract]))

AND

((sex[Title/Abstract] OR gender[Title/Abstract]) AND (disparity[Title/Abstract] OR (disparities[Title/Abstract] OR difference [Title/Abstract] OR disparities[Title/Abstract] OR variation[Title/Abstract] OR variations[Title/Abstract])) OR (sex disparities[MeSH Terms])

AND

(diabetes[MeSH Terms] OR diabetes[Title/Abstract] OR diabetic[Title/Abstract] OR DM1[Title/Abstract] OR DM2[Title/Abstract] OR DMI[Title/Abstract] OR DMII[Title/Abstract] OR T2DM[Title/Abstract] OR T1DM[Title/Abstract] OR DM)

NOT

animal

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles.

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Swietek et al., 2020 ¹	United States	2008-2011	82,501 (NR) 18-64	≥1 Measurements per study year: LDL, HbA1c, eye exam, nephropathy screening (medical attention for nephropathy). <i>Administrative claims data</i>	Primary aim: To estimate the association between enrollment in National Committee for Quality Assurance recognized patient centred medical homes and racial disparities in quality of care for adults with major depressive disorder and comorbid medical conditions. Data source: Data extracted from 2008–2011 Medicaid claims from three states with relatively high rates of Medicaid enrollment and complete claims, including those with diabetes and major depressive disorder . Those included were required to have >1 inpatient diagnosis or >2 outpatient or emergency department diagnoses of major depressive disorder or diabetes during a single year in the study period, and >1 claim for the condition in each year. Individuals with serious mental illnesses were excluded as well as dual enrollees in Medicare and Medicaid.
Comer-Ha-Gans et al., 2020 ²	United States	2011-2016	13,154 (23,503,358 (51% weighted)) 20-85	≥1 Measurements per study year: Eye exam, foot exam, HbA1c. <i>Self-reported</i>	Primary aim: To examine diabetes standard of care among individuals who have diabetes with and without cognitive limitation disabilities. Data source: Pooled data (2011–2016) extracted from the full year Consolidated Data Files Household Component of the Medical Expenditure Panel Survey (MEPS), including those with diabetes . MEPS contains data pertaining to health care access and utilization, health care expenditures, health care satisfaction, health status, and sociodemographic data of respondents. Computer-assisted personal interviewing was used to collect the household component data.
Lu et al., 2020 ³	United States	2012	213,075 (57%) 18-64	Combination of all 4 measurements during study period (HbA1c, LDL, eye exam, nephropathy screening (including screening and treatment)). <i>Administrative claims data</i>	Primary aim: To determine the extent to which the diabetes care needs are met for a population with both intellectual and developmental disabilities and diabetes who are solely insured by Medicaid in five states. Data source: Administrative data from 1/1/2011 through 31/12/2012 were used to identify Medicaid members that were continuously enrolled for 11 months in 2012, with diabetes and intellectual and developmental disabilities or diabetes only , in 5 states (Iowa, Massachusetts, New York, Oregon and South Carolina). Individuals with dual eligibility in Medicare and Medicaid or other types of primary insurance were excluded

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Wei et al., 2020 ^a	Switzerland	2014	49,198 (45%) >18 (and <75 for LDL)	≥2 HbA1c measurements, ≥1 eye exam, LDL measurements (or total cholesterol + HDL+ triglycerides), nephropathy (i.e., serum creatinine and/or albuminuria test) screening within 360 days post index date. <i>Administrative claims data</i>	Primary aim: To describe regional variation in the utilization of the four measures across small regions in Switzerland and to explore potential influencing factors. Data source: Data extracted from health insurance claims provided one of the largest health insurance companies in Switzerland. Those enrolled with Helsena with diabetes who were prescribed any diabetes medication between 1/1/2014 and 27/12/2014 were included. Date of the first prescription of any diabetes medication in 2014 (incident diabetes) or January 1, 2014 (prevalent diabetes) was considered as the index date for each participant. Those with incomplete insurance coverage in 2014 or not surviving until the end of 2014 were excluded, as well as those living outside Switzerland, asylum seekers, Helsana employees, with incomplete address information, living in nursing homes with lump-sum reimbursement.
Youn et al., 2020 ^a	Korea	2015 (survey year)	20,904 (48%) ≥19	≥1 Eye exams within the year prior to the survey. <i>Self-reported</i>	Primary aim: To investigate the uptake rate variance of fundus examination for diabetes-related complications among demographically and geographically diverse communities and examine determinants that influence this rate focusing on outpatient eye care clinic accessibility at community level. Data source: Data on individual-level factors was extracted from the nationwide 2015 Community Health Survey including information about the uptake of retinal screening within the prior year among those with diabetes .
Tan et al., 2020 ^b	United States	1/1/2015 – 31/12/2018	4,552 (53%) ≥18	≥1 HbA1c, blood pressure, or LDL measurements between 6 months prior and post index date. <i>Electronic medical records</i>	Primary aim: To examine the potential sociodemographic disparities in type 2 diabetes management and care among adult individuals, after controlling for clinical and behavioural factors. Data source: Data extracted from a linked database of the National Health and Wellness Survey and a large ambulatory electronic health record database (EHR). The index date was the date when individuals completed. Those that completed the survey between 2015-2018; with ≥1 clinical measurements; a diagnosis of type 2 diabetes in the survey or EHR or ≥1 oral glucose-lowering prescription in the EHR; and ≥12-month follow-up in the EHR database were included. Individuals with type 1 or gestational diabetes were excluded.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Meier et al., 2020 ¹	Switzerland	2018 (baseline date)	3,833 (43%) NS	≥1 Measurements within 12 months prior to baseline date: HbA1c, blood pressure, cholesterol.	Primary study aim: To describe quality indicator performance in diabetes care in Swiss primary care and to analyse associations of practice, general practitioner and patient covariates with quality indicator performance. Data source: Baseline data extracted from an electronic medical record database collected within a cluster randomized controlled trial. The baseline assessment covered 12 months retrospectively using electronic medical records database of the Institute of Primary Care of the University of Zurich. Those diagnosed with diabetes ≤4 months before the baseline date were eligible for inclusion.
Hirst et al., 2019 ⁸	United Kingdom	1/1/2005-31/12/2014	100,000 (45%) NS	No HbA1c measurements within 12 months post previous measurement. <i>Electronic medical records</i>	Primary aim: To examine whether both an individual's previous HbA1c and the reporting deadline at the end of the administrative year are associated with over-frequent or delayed HbA1c testing in national data in the UK, and whether there are regional disparities across the UK and whether other pre-defined participant or general practitioner practice level variables may be associated with very frequent or delayed HbA1c testing intervals. Data source: Data extracted from those with diabetes randomly selected from the Clinical Practice Research Datalink (CPRD) over a 10-year period (1/1/2005-31/12/2014). CPRD is a governmental database providing anonymized data from UK primary care. For those with existing diabetes, baseline HbA _{1c} test was defined as first HbA _{1c} test after 1/1/2005. Included participants had ≥2 HbA _{1c} tests prior to the baseline test and post diagnosis. People with incident diabetes during follow-up, and ≥3 HbA _{1c} test post diagnosis, were included in the analysis. For those, the baseline test was the second test. Participants had ≥2 HbA _{1c} tests for diabetes of the young, <3 HbA1c measures in total, steroid-induced diabetes or haemochromatosis-related diabetes, cancer or end-stage renal disease, were excluded.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Bakke et al., 2019 ⁹	Norway	1/7/2012-31/12/2014	8,246 (45%) ≥18	≥1 Measurements within 15 months prior to 31/12/2014: albuminuria, foot exam; ≥1 eye exams within 30 months prior to 31/12/2014, combination (≥2 out of 3) <i>Electronic medical records</i>	Primary aim: To assess population, general practitioner, and practice characteristics associated with the performance of microvascular screening procedures and to propose strategies to improve type 2 diabetes care. Data source: Data extracted from electronic health records from general practices located in five of Norway's nineteen counties with urban and rural areas participating in the ROSA 4 study, including adults with type 2 diabetes who had their main follow-up in general practice and a diabetes duration of ≥1 year. Those diagnosed with diabetes in 2014, new to the general practitioner, with main follow-up at a specialist, in nursing homes, with unknown list-holding general practitioner, type 1 diabetes including LADA, and other i.e. MODY, pancreatitis, or undetermined were excluded.
Dallo et al., 2019 ¹⁰	United States	2015	6,622 (54%) ≥18	No eye exam during study period. <i>Administrative data</i>	Primary aim: To estimate and compare the management of diabetes among Arab, Asian, non-Hispanic Black, and non-Hispanic Whites attending a large health system in metropolitan Detroit. Data source: Data extracted from a primary care sample of patients with diabetes within a health system in metropolitan Detroit.
De Jong et al., 2019 ¹¹	The Netherlands	2013	12,512 (50%) ≥20 to <100	≥1 Measurements during study period: HbA1c, blood pressure, total cholesterol, LDL, HDL, BMI, combination (≥1). <i>Electronic medical records</i>	Primary aim: To evaluate whether there are sex disparities in cardiovascular risk management in patients with diabetes in primary care. Data source: Data extracted from a longitudinal primary care medical record database (Julius General Practitioners Network) of general practices in Utrecht and vicinity (The Netherlands), including those with a diagnosis of diabetes before the study period with continuous enrolment during study period.
Whyte et al., 2019 ¹²	England	1/1/2012-31/12/2016	49,380 (44%) ≥18	Uninterrupted annual monitoring during study period: HbA1c, blood pressure, eGFR, eye exam. <i>Electronic medical records</i>	Primary aim: To evaluate contemporary data as to whether disparities exist in glycaemic control, monitoring, and prescribing in people with type 2 diabetes. Data source: Data extracted from the Royal College of General Practitioners Research and Surveillance Centre database. Those diagnosed with type 2 diabetes prior to 2012 and continuance in the database over the study period were eligible for inclusion.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Du et al., 2019 ³	Germany	2008-2011	526 (43%) 40-79	≥1 Measurements within prior 12 months: HbA1c, eye exam, foot exam. <i>Self-reported</i>	Primary aim: To study gender disparities in cardiovascular risk profiles and diabetes care based on a nationwide representative sample of adults with type 2 diabetes in Germany. Data source: Data extracted from the German National Health Interview and Examination Survey (DEGS1 2008-2011), including a nationwide representative sample of adults with type 2 diabetes. Type 2 diabetes was defined as a history of physician-diagnosed diabetes or current use of antidiabetic medication, excluding those with type 1 and gestational diabetes.
Kovács et al., 2019 ⁴	Hungary	2015	478,660 (NR) ≥18	≥1 Measurements during study period: HbA1c, Eye exam. <i>Administrative data</i>	Primary aim: To evaluate the influence of general medical practice characteristics on performance indicators. Data source: Data extracted in December 2015 from general practices that provide primary health care to adults. Data for the analyses were provided by the National Institute of Health Insurance Fund Management (NIHFM). NIHFM established a nationally integrated system of health care indicators with financial incentives in 2010. Individuals with diabetes receiving glucose-lowering medication were eligible for inclusion.
Greenan et al., 2019 ⁵	Ireland	11/2013- 5/2015 (data extraction)	1,200 (33%) ≥12	Eye screening attendance after referral/invitation (attending all screening and treatment appointments) <i>Medical records</i>	Primary study aim: To determine whether geodemographic factors, specifically age, gender or commuting distance, affect the attendance rates of patients referred to a Diabetic Retinopathy Treatment Centre from the Irish National Diabetic Retinal Screening Programme. Data source: Data extracted from the first 1200 patients with diabetes who were referred for ophthalmic assessment between 11/2013 and 5/2015 to Cork University Hospitals diabetic retinopathy treatment clinic from the diabetic retinopathy screening program (Diabetic RetinaScreen). In Ireland, the National Diabetic Retinal Screening was introduced in 2013. It offers annual screening and treatment where necessary to all patients with diabetes aged 12 years and older currently living in Ireland.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Kamat et al., 2019 ⁶⁵	United States	1999-2016 (survey period)	7,521 (NR) (49% assumed to be weighted) >20	≥1 Measurements prior 12 months to survey; foot exam, eye exam. <i>Self-reported</i>	Primary aim: To examine trends and disparities in the quality of diabetes care among US adults with diabetes. Data source: Data extracted from the National Health and Nutrition Examination Survey (NHANES) 1999-2016, including those with self-reported diabetes (not during pregnancy) based on questions about physician diagnosed diabetes and medication use, and levels of fasting glucose or HbA1c. Survey respondents were selected using a complex, stratified, multistage probability sampling design of the US noninstitutionalized civilian population. Survey data were gathered through in-home interviews, physical exams, and lab tests.
An et al., 2018 ¹⁷	United States	1/1/2009-31/12/2010 (inclusion period and index date) 31/12/2013 (follow-up)	204,073 (48%) ≥18	≥1 exams each 12 month period from the index date if retinopathy is present and ≥1 exams each 24 months if no retinopathy is present. <i>Electronic medical records</i>	Primary aim: To assess long-term adherence, in patients with diabetes, to the recommended regular eye exam guidelines, and to determine factors associated with non-adherence. Data source: Patient data extracted from Kaiser Permanente Southern California (KPSC). KPSC is a non-profit, integrated healthcare delivery organization in Southern California. KPSC provides integrated, comprehensive medical services within its own facilities, which include hospitals, outpatient facilities, and a centralized laboratory. All aspects of care and interaction with the healthcare delivery system are captured in a continuously updated electronic Organization. Those with ≥2 outpatient visits with a diagnosis code for diabetes between 1/1and 2009 and 31/12/2010 were included and the first diagnosis of diabetes or dispense date of an antidiabetic drug was defined as the index date. Those without continuous healthplan membership or drug benefit during the 12 months before and after the index date were excluded, as well as those with gestational diabetes.
Ibáñez et al., 2018 ¹⁸	Spain	15/5/2014 (data extraction)	32,206 (44%) ≥20	≥1 Measurements 15 months prior to data extraction: HbA1c. <i>Electronic medical records</i>	Primary aim: To determine if achievement of control targets in patients with type 2 diabetes was associated with personal socioeconomic factors and if these associations were sex-dependent. Data source: Data extracted from individuals with a diagnosis of type 2 diabetes on 15/5/2014 registered in Atena. Atena is a Primary Care Electronic Medical Record System containing information from all individuals with type 2 diabetes managed by the Regional Health Service of Navarre (northern Spain).

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Bird <i>et al.</i> , 2018a ¹⁹	United States	2013-2014 (1 year)	78,529 (49%) NS	NO Measurements during study period: HbA1c, LDL. <i>Administrative claims data</i>	Primary aim: To quantify persistent gender gaps in cardiovascular risk management and to assess the performance of routinely used commercial population health management tools in helping systems narrow gender gaps. Data source: Anonymized data of medical and pharmacy claims, laboratory results, and enrolment data from one national health plan for commercial health plan members drawn from a population across Atlanta, Houston, New York City/Northern New Jersey and Southern California. Those with diabetes were included.
Kreft <i>et al.</i> , 2018 ²⁰	Germany	2004-2014	26,560 (51.6%) ≥50	≥1 Eye exams during study period. <i>Administrative claims data</i>	Primary aim: To assess factors associated with diabetic retinopathy screening uptake following a diagnosis of type 2 diabetes in Germany. Data source: Data extracted from randomly sampled members of the largest German public health insurance. Data from persons born prior to 1965 who first experienced diagnosis of type 2 diabetes during the study period and living in private households and institutions was obtained. Medical individual-level data for all members was registered and collected quarterly from the beginning of 2004 until end of 2014, or earlier study exit. Those with chronic eye disease which necessitated regular ophthalmic check-ups, age-related macular degeneration or other macular disease, or retinopathy present in the quarter before the first type 2 diabetes diagnosis were excluded.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Kawamura et al., 2018 ²¹	Japan	1/2005 - 3/2013	6,492 (34%) ≥20	≥1 eye exams within one year of initial drug therapy (from the index month). <i>Administrative claims data</i>	Primary aim: To investigate the influence of comorbidities on undergoing a diabetic eye exam in patients with newly diagnosed type 2 diabetes. Data source: Data extracted from health insurance claims made between 1/2005 and 3/2013 using the database of Japan Medical Centre Ltd. (Tokyo, Japan). This database consists of beneficiaries in health insurance unions across Japan in 2012, including individuals diagnosed with type 2 diabetes between 1/2005 and 3/2013 that had been prescribed antihyperglycaemic drugs with a 12-month follow-up from the index month. The index month was defined as the first month in which the study patients had been diagnosed with type 2 diabetes and received antihyperglycaemic drugs. Those who were not prescribed antidiabetic drugs after the index month were excluded, as well as those diagnosed with diabetes or prescribed antidiabetic drugs during the nine months after registration in the database, with diabetic retinopathy prior to the index month, those who had undergone eye exams, who had been diagnosed with eye diseases, or who had undergone an intervention for the eyes within the six months preceding the index month, in order to select patients who did not visit the ophthalmologist regularly. Lastly, those without information regarding the facility at which diabetes treatment took place in the index month were excluded.
National Diabetes Audit ²² (3 separate reports)	England and Wales	2017-2018, 2016-2017, 2012-2013	Varies per audit period with up to 3,135,019 (44%) individuals in 2017-2018 ≥12 (HbA1c: All)	Varies per subtype and audit period, including ≥1 measurements during study period (15 months); HbA1c, blood pressure, cholesterol (triglycerides and another type of fat in the blood), creatinine, urine albumin, foot, smoking, BMI, combination (all eight care processes (excl. eye exam (<12 years only HbA1c)).	Primary aim: To measure the effectiveness of diabetes healthcare against NICE Clinical Guidelines and NICE Quality Standards, in England and Wales. Data source: Administrative data extracted from participating general practitioners via pre-agreed extracts of their computer system and specialist diabetes service units in secondary care hospitals. This includes data from children being treated in adult care settings; but does not cover paediatric units. Both previously diagnosed and newly diagnosed individuals with type 2 diabetes during the audit period were included. General practices were invited to participate in the audit through their clinical systems. The audit operates under an 'opt in' model to remain open and transparent with practices and services about what data are being collected. Data from 2012-2013 (measurement of creatinine) included individuals with ' all ' diabetes.

Administrative data

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Foreman et al., 2017 ²³	Australia	3/2015-4/2016 (recruitment)	1,076 (55%) ≥40 (Indigenous) ≥50 (non-Indigenous)	≥1 Eye exam (Indigenous within prior 12 months, non-Indigenous within prior 24 months). <i>Self-reported</i>	Primary aim: To determine adherence to National Health and Medical Research Council (NHMRC) eye examination guidelines for Indigenous and non-Indigenous Australian people with diabetes. Data source: Indigenous and non-Indigenous Australians with self-reported diabetes were recruited and examined between 3/2015 and 4/2016 after a multistage, random cluster sampling approach selecting 30 geographic sites in the five mainland Australian states and the Northern Territory; recruiters went door to door to recruit the included Indigenous and non-Indigenous Australians. During the interview participants were asked whether they had seen an ophthalmologist or optometrist for a diabetic eye examination, and if so, how long ago (in years). This information was used to determine the proportion of participants who adhered to the NHMRC guidelines.
Mwangi et al., 2017 ²⁴	Kenya	NR	270 (53%) ≥18	≥1 Eye exams in prior 12 months. <i>Self-reported</i>	Primary aim: To identify the demand-side factors that influence uptake of eye examination among patients already utilizing diabetes services in three counties of Kenya. Data source: Data extracted from patient surveys. A three-stage sampling, strategy was used to select counties, diabetes clinics, and patients with diabetes attending these clinics. Patients were selected by random sampling from the people attending the clinic on the day of interview. Those with diabetes, residents in the county, and receiving care at the participating clinics were eligible for inclusion. Acutely ill individuals were excluded.
LeBlanc et al., 2017 ²⁵	Canada	1/42005-31/3/2009 and 1/4/2010-31/3/2014	83,580 (52%) ≥20	≥2 HbA1c measurements per year. <i>Administrative data</i>	Primary aim: To evaluate the influence of the introduction of a pay-for-performance program implemented in 2010 for family physicians on the glycaemic control of patients with diabetes. Data source: Data extracted from 5 administrative databases from the New Brunswick Department of Health before (2005-2009) and after (2010-2014) the implementation of a pay-for-performance program implemented for family physicians on the glycaemic control of those with diabetes. Included were those in the province with diabetes if the detection of their diabetes occurred between April 1995 and March 2014 and eligible participants had to be followed by family physicians paid by fee-for-service. Data was extracted by matching Medicare patient list with glycaemic control data from Laboratory Data Repository, Additional information was extracted from Medicare Resident Registry and the Physician Profile database.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Yoo et al., 2017 ²⁶	Korea	1/1/2013-31/12/2013	43,283 (47%) NS	≥2 HbA1c measurement during study period. <i>Administrative claims data</i>	Primary aim: To analyse compliance to HbA1c testing guidelines and explore associated individual and area-level determinants, focusing on regional variation. Data source: Data extracted from the Korean National Health Insurance (KNHI) Research Database. The KNHI is a mandatory universal health insurance in Korea. Individuals included had claims for diabetes in 2013 and were prescribed any antidiabetic medications, including insulin, in 2012. Those who were hospitalized during 2013 were excluded, as well as those who had made only one claim for diabetes over the year and those who died in 2013.
Bennet et al., 2017 ²⁷	United States	2007-2012	Unclear NS	≥1 Cholesterol measurements prior 12 months per survey. <i>Self-reported</i>	Primary aim: To examine service utilization among persons with selected disabling conditions and diabetes, compared to those without. Data source: Data extracted from 2007-2012 Medical Expenditure Panel Survey Full-Year Consolidated files (MEPS), medical conditions files, and the 1996-2012 pooled linkage files. MEPS sample is derived from the National Health Interview Survey, which is the primary survey that collects information regarding the health of the US civilian, non-institutionalized population. MEPS respondents are followed for two years, and overlap with subsequent panels on 6-month intervals, including those with diabetes .
Williams et al., 2017 ²⁸	United States	2002-2011	17,702 (56.4%) (17,857,174 weighted) ≥18	≥1 Measurements prior 12 months per survey: blood pressure <i>Self-reported</i>	Primary aim: To assess disparities in quality of care indicators in a nationally representative sample of men and women with diabetes. Data source: Data extracted from the Medical Expenditure Panel Survey Household Component (MEPS-HC) from 2002-2011, including individuals with self-reported diabetes . MEPS is a survey of a nationally representative US civilian, non-institutionalized population and is administered by the Agency for Healthcare Research and Quality. Data from 10 years were pooled for this study. The MEPS sample is drawn from reporting units in the previous year's National Health Interview Survey, a nationally representative sample with oversampling for non-Hispanic Blacks and Hispanics of the U.S. civilian, non-institutionalized population.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Willis <i>et al.</i> , 2017 ²⁹	England	1/12/2012-31/3/2013	25,816 (46%) ≥13	Combination (all: blood pressure, HbA1c, cholesterol, urine albumin:creatinine ratio (or protein:creatinine testing, or proteinuria), eGFR (or creatinine), foot exam, eye exam, smoking, BMI) measured during study period (6 months for HbA1c).	Primary aim: To examine the extent to which variations in achievement to high impact indicators can be explained using routinely collected data. Data source: Routinely collected, anonymized electronic primary care data from a sample of general practices in West Yorkshire (England). Data covered the period 1/1/2012 to 31/3/2013, and were extracted during April 2014. Those with type 2 diabetes receiving care at one of the participating practices that are using a specific computerized patient record are included.
Murchison <i>et al.</i> , 2017 ³⁰	United States	1/1/2007-12/12/2010	1,967 (55%) >40	<i>Electronic medical records</i> Follow-up eye exam <15 months for mild or no diabetic retinopathy, <12 months for moderate diabetic retinopathy and <4 months from the index visit for severe diabetic retinopathy. <i>Medical records</i>	Primary aim: To evaluate individual factors that impact adherence to eye care follow-up in patients with diabetes. Data source: Data extracted using billing and administrative information, including those who had their initial visit to a general ophthalmology or retina clinic within an urban academic eye hospital between 1/1/2007 and 31/12/2010. Patient charts were reviewed to determine additional clinical information and confirm eligibility. The index visit was defined as the date of the first dilated fundus exam in this eye care system, including a diagnosis of type 1 or type 2 diabetes or diabetic retinopathy. Patients who did not have a documented dilated fundus exam at the designated eye clinics within 30 days of type 1/type 2 diabetes or diabetic retinopathy noted in their billing records were excluded. The diagnosis of diabetes did not have to be new to the patients.
Moreton <i>et al.</i> , 2017 ³¹	England	1/4/2012 – 30/4/2013	21,753 (43%) ≥12	Eye screening attendance after invitation. <i>Screening program records</i>	Primary aim: To investigate variables at the demographic and primary care practice levels that influence the uptake of diabetic retinopathy screening. Data source: Data extracted from the Oxfordshire Diabetic Eye Screening Programme management software, including those with diabetes newly referred to the screening program and those invited in previous years. The analysis was restricted to the first date of invitation for each registered person from 1/4/2012 until 30/4/2013

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Tanaka et al., 2016 ³²	Japan	4/2011-3/2012	11,500 (NR) 20-69	≥1 Measurements during study period: Eye exam, microalbuminuria, creatinine, any lipid test (total cholesterol, LDL, HDL or triglycerides), HbA1c (≥1 per 3 months), <i>Administrative claims data</i>	Primary aim: To investigate the process quality of diabetes care provided to patients under universal health insurance coverage. Data source: Data extracted from health insurance claims data, managed by the Japan Medical Data Center Claims Database. Beneficiaries with type 2 diabetes covered by Health Insurance Societies between 4/2010 and 3/2012 that regularly visited clinics or hospitals at least every 3 months in the identification year (4/2010-3/2011) were included. Those with insulin-dependent diabetes were excluded, as well as those that dropped out of care during follow-up. Only those who made follow-up visits were included and patient adherence to follow-up visits during study period was assessed.
Rossaneis et al., 2016 ³³	Brazil	NR	1,515 (63%) ≥40	HbA1c NOT measured in prior 6 months, lipid profile (triglycerides, total cholesterol, HDL, and LDL) NOT measured in prior 12 months. <i>Assumed to be self-reported</i>	Primary aim: To investigate disparities with regard to foot self-care and lifestyle between men and women with diabetes. Data source: Data extracted from a sample of individuals with type 2 diabetes living in the urban area of a large city in the South of Brazil. Study participants were drawn among those enrolled in the Hypertensive and Diabetics Individuals Registration System. Individuals selected were invited to participate in the study and data were collected at primary health care services through patient interviews and medical chart extraction. Those undergoing dialysis, with active ulcers in the lower limbs, without cognitive capacity, or not willing to participate were excluded.
Tannenbaum et al., 2016 ³⁴	United States	20/2011-9/2013 (Survey period)	264 (57%) ≥40	≥1 Eye exam 12 months prior to the survey. <i>Self-reported</i>	Primary aim: To examine the prevalence and correlates of eye screening adherence among select Hispanics/Latinos living with diabetes. Data source: Data extracted from an ancillary study of the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (Miami site). HCHS/SOL is an ongoing multistage study of prevalence of and risk factors for disease among Hispanics/Latinos. Participants included Hispanics/Latinos who underwent a baseline examination/risk factor assessment (4/3/2008-30/6/2011) and then completed a survey on vision health/knowledge (10/ 2011-9/ 2013). Diabetes status was clinically determined at the baseline study. Those with diabetes were included.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Mtuya et al., 2016 ³⁸	Tanzania	4/2013 – 6/2013 (interview period)	203 (57%) NS	Follow-up eye exam after referral in the period between initial exam and interview. <i>Self-reported</i>	Primary aim: To assess the proportion of patients not presenting for follow-up and the reasons for poor follow-up of diabetic patients after screening for retinopathy in Kilimanjaro Region of Tanzania. Data source: The study was carried out under the auspices of the Kilimanjaro Diabetic Programme (KDP). KDP screens diabetic patients for retinopathy at diabetic clinics throughout the Kilimanjaro Region. KDP visits each diabetic clinic regularly where enrolled patients are screened with a mobile retinal camera. Following screening, patients are either sent a text message or are phoned 2–4 weeks after their screening event and informed that further investigations and possibly treatments are needed. Patients are advised whether they should attend within 1 month or within 3 months depending on the severity of their retinopathy. Patients who have normal results or do not need further investigations are advised to attend another screening event after 1 year. The study was carried out between 4/2013 and 6/2013. Patients were considered eligible if they had their screening event in 2012 and if they had been referred to KCMC eye department after their screening event. Patients were categorized as non-attenders at follow-up if they had not attended KCMC Hospital when the interviews were conducted. In 2012, 1106 patients were screened by the KDP for diabetic retinopathy. Of these, 420 had retinopathy requiring further assessment and were recommended to attend a follow-up appointment at KCMC. The researchers randomly selected 294 of these patients for interview through a simple random sampling technique. The selected patients were contacted using details stored on the KDP database and were interviewed at their local hospital during subsequent KDP screening events.
Hatef et al., 2015 ³⁹	United States	2010 and 2012	8,902 (69%) 18–64	Annual eye exam. <i>Administrative claims data</i>	Primary aim: To assess how well a managed care organization performed an annual diabetic eye screening in a Medicaid population, and to identify barriers to completion. Data source: Healthcare claims data for Medicaid patients with diabetes covered by Priority Partners Managed Care Organization with continuous enrolment during measurement year in 2010 and 2012 were collected. Annual rates for eye exams in those years were reported. In 2011 the Johns Hopkins HealthCare instituted its program to increase the completion rate for annual diabetic eye exams.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Baumeister et al., 2015 ³⁷	Germany	2008-2012 (survey periods)	456 (44%) 20-81	Eye exam within 12 months prior to the survey. <i>Self-reported</i>	Primary aim: To study trends of barriers to receiving recommended eye care among subjects with diabetes aged 20-81 years in northeast Germany. Data source: Data extracted from the Study of Health in Pomerania (SHIP-Trend), consisting of a population-based samples of adults from West Pomerania, a north-eastern German region. SHIP-Trend was conducted between 2008 and 2012. Those with self-reported diabetes were included.
Sieng et al., 2015 ³⁸	Thailand	1/4/2012-30/6/2012 (collection of records)	26,869 (70%) ≥35	≥1 Measurements in prior 12 months: LDL, foot exam, eye exam, HbA1c (≥2), combination (all). <i>Medical records</i>	Primary aim: to compare the process of diabetes care of specialist diabetes clinics, and general medical clinics for different hospital level (regional, provincial, and community). Data source: Data for this study were obtained from an ongoing project "An assessment on quality of care among patients diagnosed with type 2 diabetes and hypertension visiting hospitals of Ministry of Public Health and Bangkok Metropolitan Administration in Thailand, 2011-2012." A proportional to size stratified cluster sampling approach was used to collect medical record data of patients with type 2 diabetes , diagnosed for at least 12 months, from all provinces in Thailand. Data were collected retrospectively by reviewing medical records for patients attending clinics from April 1 to June 30, 2012.
Mounce et al., 2015 ³⁹	England	2010-2011 (survey period)	907 (47%) ≥50	Combination (not receiving ≥1 assessments: HbA1c, proteinuria (in those without established renal disease and no ACE inhibitor or angiotensin II receptor blocker) and foot exam) within 12 months prior to the survey. <i>Self-reported</i>	Primary aim: To determine which patient characteristics were associated with failure to receive indicated care for diabetes over time. Data source: Data extracted from the English Longitudinal Study of Ageing (ELSA), including adults with diabetes . ELSA is a longitudinal cohort study of adults living in private households in England. Beginning in 2002-3, participants were followed up with two-yearly 'waves' of data collection. The original cohort was drawn from households that had previously responded to the Health Survey for England (HSE) in either 1998, 1999 or 2001. Replenishment cohorts were added in 2006-7 (sampled from HSE 2001-2004) and 2008-9 (sampled from HSE 2006) to correct for the original sample ageing and loss to follow-up. The cohort is intended to be representative of older people living independently in England. Data collection took place via face-to-face interviews in participants' homes, with additional information collected during a nurse visit in 2008-9. For this study survey responses about quality indicators from the 2010-2011 wave was explored. Descriptive characteristics used for modelling achievement of care in 2010-2011 were obtained from the 2008-2009 wave.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Liang et al., 2015 ⁵⁰	United Kingdom	2007-2012 (cohort entry)	65,790 (42%) >50	Proteinuria (Urine albumin, microalbumin or protein test) at any time during follow-up. <i>Electronic medical records</i>	Primary aim: To describe proteinuria monitoring in patients with type 2 diabetes. Data extraction: Data extracted from UK Clinical Practice Research Datalink, including patients with type 2 diabetes with first antidiabetic drug use in 2007–2012. Cohort entry was defined as the date of the first ever antidiabetic drug prescription. ≥ 1 year of registration before and after cohort entry was required. Those with a diagnosis of type 1 diabetes, gestational diabetes mellitus, diabetes insipidus, or secondary or other forms of diabetes, including nutritional, genetic, postsurgical, and drug-induced or chemical-induced diabetes, at any time during study period were excluded.
Hwang et al., 2015 ⁴¹	Canada	2011 (survey year)	2,323 (NR) (1,324,553 (42%) Weighted) ≥ 20	≥ 1 Eye exams within prior 2 years from survey. <i>Self-reported</i>	Primary aim: To examine the association between socioeconomic factors and ophthalmic care services/visual impairment among patients with diabetes. Data source: Data extracted from the Survey on Living with Chronic Disease in Canada (SLCDC)–Diabetes Component 2011. SLCDC is a survey focusing on the experiences of Canadians living with chronic health conditions. Non-institutionalized individuals with self-reported physician diagnosed type 2 diabetes on the 2010 Canadian Community Health Survey were invited to participate in the 2011 SLCDC-DM survey. Full-time members of the Canadian Forces and residents of First Nations Reserves, Crown lands, institutions, and the 3 territories were excluded.
Casanova et al., 2015 ⁴²	France	2008 and 2011	142,291 (47%) and 166,896 (47%) ≥ 18	≥ 1 Annual measurements: Eye exam, LDL, creatinine, microalbuminuria, HbA1c (≥ 3). <i>Administrative claims data</i>	Primary aim: To assess the evolution of paraclinical monitoring of patients with type 2 diabetes between 2008 and 2011. Data source: Data extracted from the Provence-Alpes-Côte-d’Azur (PACA) regional health insurance reimbursement database (national health insurance fund), including individuals with type 2 diabetes living in PACA and who had 3 or more reimbursements for diabetes medications during the 12 months before the start of each study period.
Dewkota et al., 2015 ⁴³	United States	9/2008-8/2011 (chart review)	350 (54%) ≥ 22	Annual eye exam, microalbuminuria (or ACEI or ARB prescription), foot exam <i>Electronic medical records</i>	Primary aim: To determine whether meeting diabetes quality indicators improves as general internal medicine physicians’ progress from first to last year of residency. Data source: Chart review from electronic health records of type 2 diabetes patients who visited internal medicine residency clinics from 9/2008 to 8/2011. Charts were selected by resident provider year (year 1, 2, and 3).

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, Country years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Billimek et al., 2015 ⁴⁴	Unites States	5/2006-6/2011	1,369 (59%) ≥18 to <80	≥1 Measurements 12 months prior to baseline: HbA1c, lipid profile, microalbuminuria, foot exam, eye exam. <i>Medical records</i>	Primary aim: To examine whether disparities in quality of care, intensity of lipid-lowering medication regimen and medication adherence explain gender disparities in dyslipidaemia. Data source: Data extracted from the observational component of the R2D2C2 study, enrolling a sample of individuals from 7 outpatient clinics affiliated with an academic medical centre. The patient sample was drawn from a diabetes registry representing adults with a diagnosis of type 2 diabetes who had ≥1 encounters with family medicine, internal medicine or endocrinology within a 12 month period. All participants completed a baseline questionnaire. Medical records were abstracted for the 12-month period leading up to the date the questionnaire was completed.
Al-Sayyah et al., 2015 ⁴⁵	Canada	12/2011-12/2013 (recruitment period)	2,027 (45%) ≥18	≥1 Exams during the past year: feet checked for sores or irritations <i>Self-reported</i>	Primary study outcome: To examine the prevalence and predictors of foot disease, self-care and clinical monitoring in adults with type 2 diabetes in Alberta, Canada. Data source: Baseline data extracted from the Alberta's Caring for Diabetes complications study, including adults with type 2 diabetes . Individuals were recruited over a 2-year period (12/2011-12/2013) through primary care networks, diabetes clinics and various forms of public advertisements. Those with gestational diabetes or type 1 diabetes were excluded.
Van Doorn-Klomberg et al., 2015 ⁴⁶	The Netherlands	2010 (data extraction)	11,178 (50%) ≥18	≥1 Measurements in 12 months: HbA1c, systolic blood pressure, LDL. <i>Electronic medical records</i>	Primary aim: To assess the strength of associations between patient factors and diabetes care processes and outcomes. Data source: Routinely collected data of those with diabetes in 59 participating Dutch primary care practices was extracted. All participating practices extracted the data in 2010. The extraction included information from all contacts with a time window of one year.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Lee et al., 2014 ⁴⁷	United States	2007-2008 (inclusion period) through 2010	200 (54%) NS	≥1 Eye exam every 15 months <i>Electronic medical records</i>	Primary aim: To estimate the prevalence of, and factors associated with, eye exam guideline compliance among patients with diabetes, but without diabetic retinopathy. Data source: Data extracted from computerized billing records database; including those with diabetes receiving care at the Bascom Palmer Eye Institute and residing within the same county as the screening facility. The sample of available and eligible patient records first seen in 2007–2008 was reviewed for demographic information at the screening visit, and all clinic visits through 2010 were ascertained by chart review. Those not receiving eye screening every 15 months were contacted to check whether they received care at different locations. For those of who it remained unclear whether they received screening every 15 months were classified as not receiving screening. Those with diabetic complications, retinopathy or any other eye disease were excluded.
MacLennan et al., 2014 ⁴⁸	United States	2007 (inclusion period)	867 (62%) >18	≥1 Eye exam within 1 year post index date. <i>Electronic medical records of the billing and accounting system</i>	Primary aim: To investigate eye care utilization among patients with diabetes who are seen in a county hospital clinic in the South that primarily serves high risk low income patients who are predominantly non-Hispanic African Americans. Data source: Data extracted from two years of follow-up data, to examine eye care utilization among diabetes patients seen in 2007 at the internal medicine clinic of a large, urban, county hospital that serves primarily low income, non-Hispanic African American patients (Birmingham Alabama). The date of their first clinic visit in 2007 was defined as an index date. Follow-up (retrospectively) was carried out by linking patients' personal identifiers, i.e., medical record numbers, to electronic records of the hospital's billing and accounting system which included dates and procedures of patient encounters in the hospital's ophthalmology clinic. Those with ophthalmic complications were excluded.
Buja et al., 2014 ⁴⁹	Italy	2009	105,987 (48%) ≥16	≥1 Measurements during study period: HbA1c, creatinine, LDL. <i>Administrative data</i>	Primary aim: To ascertain the prevalence of diabetes in an Italian population, stratified by age, gender and citizenship; and to identify rate of compliance with recommended guidelines for monitoring diabetes, to see whether disparities exist in the quality of diabetes management. Data source: Anonymized data extracted from the VALORE project. The dataset was obtained by processing public health administration databases and included those registered with general practices in six Italian regions including individuals with diabetes diagnosed before 1/1/2009. Those lost to follow-up during 2009 were excluded.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Naicker et al., 2014 ⁵⁰	Canada	2008, 2009, 2010	2,343 (53%) ≥40	Test NOT recommended over a course of 12 months: HbA1c (<2), eGFR (<1), albumin/creatinine-ratio (<1).	Primary aim: To determine whether any sex disparities exist in adherence to process of care guidelines for cardiovascular disease within primary care practices in Ontario, Canada. Data source: Data extracted from pooled cross-sectional baseline data collected through a larger improvement initiative known as the Improved Delivery of Cardiovascular Care study. Individuals at high CVD risk (i.e. diabetes) or prevalent CVD and receiving primary care across eastern Ontario (Canada) at participating practices were included. Data on guideline adherence was obtained through baseline chart abstraction and represent patient-level guideline adherence rates prior to intervention.
Baviera et al., 2014 ⁵¹	Italy	2002–2006	158,426 (45%) 40 - 89	≥1 Measurements per year: HbA1c, cholesterol (total, LDL, HDL), triglycerides, creatinine, eye exam, microalbuminuria. <i>Administrative data</i>	Primary aim: To investigate whether sex-related disparities exist in terms of management and hospitalization in patients with newly diagnosed diabetes. Data source: Data extracted using linkable administrative health databases of the Lombardy (Italy) region, including the regional database, pharmacy prescription database, and hospital discharge database. Individuals with diabetes were included if they had not been diagnosed with diabetes within the previous 2 years. Laboratory tests and special medical exams were recorded from 2002 to 2006. All participants were followed until the first hospitalization for cardiovascular reason, death, emigration, admission to a nursing home, or until 31/12/2007.
Chen et al., 2014 ⁵²	United States	2001-2010 (Survey period)	355,620 (41%) (50% weighted) ≥18	≥1 Measurements 12 months prior to survey: Eye exam, foot exam, HbA1c (≥2).	Primary aim: To examine trends in the receipt of eight recommended diabetes clinical and self-care indicators from 2001 to 2010 and assess racial/ethnic disparities in care. Data source: Data extracted from the 2001 to 2010 Behavioural Risk Factor Surveillance System (BRFSS). BRFSS is a telephone survey in which self-reported, health-related data are collected monthly in all 50 states, the District of Columbia, Puerto Rico, the US Virgin Islands, and Guam. Those with self-reported physician diagnosed diabetes were included, and gestational diabetes was excluded.
Rim et al., 2013 ⁵³	Korea	2005, 2007-2009 (survey period)	1,671 () ≥40	≥1 Measurements 12 months prior to survey: eye exam, microalbuminuria. <i>Self-reported</i>	Data extracted from the third (2005) and fourth (2007-2009) Korean National Health and Nutrition Examination Survey (KNHANES). KNHANES is a nationally representative survey to estimate the health and nutritional status of the Korean population and consisted of a health interview, health examination survey, and nutrition survey. Those with diabetes were included in this study. Those with diabetes diagnosed before the age of 40 were excluded as well as those with missing data for certain socio-demographic factors.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Yu <i>et al.</i> , 2013 ³⁴	United States	2001 – 2002	4,839 (49%) NS	≥1 Measurements up to 12 months prior to baseline survey; HbA1c, LDL, microalbuminuria (≥1 up to 24 months prior to baseline survey) <i>Assumed to be self-reported</i>	Primary aim: To examine the associations between sex and selected diabetes process of care measures and self-care activities in a cohort of primary care patients with diabetes. Data source: Data extracted from a population of primary care patients from the PATHWAY study, including those with diabetes : at Group Health, a non-profit health maintenance organization in Washington and Idaho (US). It maintains a registry of the individuals with diabetes and their guideline recommended test results. Nine primary care clinics were chosen for patient recruitment based on the number of diabetic patients, ethnic diversity, and proximity to Seattle. Those with gestational diabetes, cognitive impairment, severe illness, deceased, disenrolled, or with language or hearing problems were excluded.
Rossi <i>et al.</i> , 2013 ³⁵	Italy	2009	415,294 (45%) NS	≥1 Measurements during study period: HbA1c, lipid profile (LDL or total cholesterol and HDL and triglycerides), blood pressure, nephropathy exam, foot exam, eye exam. <i>Electronic medical records</i>	Primary aim: To investigate the quality of type 2 diabetes care according to sex. Data source: Anonymized data using the Italian Association of Clinical Diabetologists Annals. Clinical data collected during the year 2009 were extracted from electronic medical records. Only those with type 2 diabetes were included.
Hellemons <i>et al.</i> , 2013 ³⁶	The Netherlands	2007-2009	14,120 (52%) NS	Albumin/creatinine ratio measurements each calendar year. <i>Electronic medical records</i>	Primary aim: To evaluate guideline adherence and factors associated with albuminuria screening and treatment in type 2 diabetes patients in primary care. Data source: Data extracted from electronic medical records from primary practices using the Groningen Initiative to Analyse Type 2 diabetes Treatment database. The patient population for this study consisted of all those who had been diagnosed with type 2 diabetes for at least 1 year on 1/1/2007, with continuous enrolment until 7/2010. Guideline adherence was evaluated in the years 2007-2009.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Mier et al., 2012 ⁵⁷	US–Mexico border area	2008 (survey period)	249 (66%) ≥65	≥1 Eye exams within 12 months prior to the survey. <i>Self-reported</i>	Primary study aim: To determine the level of health care access for older Hispanics with type 2 diabetes living in a US–Mexico border area, and personal and health correlates to health care utilization. Data source: Data obtained by community-based assessment conducted in 2008 at a clinic, senior centres, and colonias. Colonias are impoverished neighbourhoods with sub-standard living conditions along the US–Mexico border. The health assessment included Hispanics with type 2 diabetes , living in Hidalgo County, Texas, at the Texas–Mexico border. To maximize recruitment, certified community health workers recruited participants in both clinical and community settings, including: a federally-qualified community health clinic that provided services for the uninsured and low-income individuals, and 2 nonclinical-based settings (community senior centres and colonias).
Druss et al., 2012 ⁵⁸	United States	2003–2004	118,190 (64%) ≤65	Combination (≥2 measures): HbA1c during measurement year, eye exam, LDL, or nephropathy screening (either screening during past year or evidence of nephropathy). <i>Claims data</i>	Primary aim: To study the impact of mental comorbidity on quality of diabetes in a national sample of Medicaid enrollees. Data source: Data extracted from fee-for-service Medicaid enrollees with Diabetes during 2003–4. (across 50 states) Eligible were those with continuous enrolment for at least 1 year, ≥2 encounters for diabetes in an outpatient setting, or ≥1 inpatient encounter with diabetes related ICD-9 Codes, and ≥1 claim with any mental disorder excluding organic conditions such as Dementia and Delirium. Those with dual eligibility were excluded, as well as those with managed care claims.
Bartels et al., 2012 ⁵⁹	United States	2006	256,331 (61%) ≥65	≥1 Measurements during study period: LDL, eye exam, HbA1c (≥2) <i>Claims data</i>	Primary aim: To examine how the presence of Rheumatoid arthritis affected HbA1c and lipid measurement in older adults with diabetes. Data source: Data extracted from a random national sample of 2004 to 2005 Medicare patients. Eligible were those with diabetes who were continuously enrolled and alive from 2004 to 2006. Beneficiaries without continuous Medicare Part A or B coverage, or those enrolled in a Medicare health maintenance organization or railroad benefits were excluded, as well as those encounters during 2004 to 2006.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Chien et al., 2012 ⁶⁰	United States	2003-2007	5,557 (66%) ≥18	Annual HbA1c, lipids, eye exam. <i>Administrative claims data</i>	<p>Primary study aim: To evaluate the impact of a "piece-rate" pay for performance (P4P) program aimed at improving diabetes care processes, outcomes and related healthcare utilization for patients enrolled in a not-for-profit Medicaid-focused managed care plan.</p> <p>Data source: Data extracted from the Hudson Health Plan, which is a not-for-profit Medicaid-focused managed care health plan serving the Hudson Valley region of New York. Late in 2003 Hudson piloted a diabetes improvement initiative in 6 of 118 participating practices. This program targeted members who were missing one or more of the following clinical tests: HbA1c, LDL cholesterol, dilated retinal exam, and microalbuminuria. At that time, providers were offered \$100 for each patient completing all the missing care processes. A revised program was launched 8/ 2004. In the beginning of 2005, the program was revised a second time such that incentive amounts in 2005 P4P incentive were 3 times that offered in 2003 and more than twice the 2004 bonus. Each March, Hudson generated patient reports identifying adult enrollees with diabetes and any care elements that were missing or below national goals. Hudson representatives hand-delivered final reports and payments to physician practices and were available to discuss results and identify opportunities for improvement; additional follow-up and coaching occurred at 2, 4, and 6 weeks later. Analyses were restricted to those who were continuously enrolled in Hudson for ≥6 months.</p>
Kiran et al., 2012 ⁶¹	Canada	1/4/2006-31/3/2008	734,974 (NR) ≥40	≥1 Eye exams, ≥4 HbA1c measurements, ≥2 cholesterol tests and combination (all) over 2-year study period. <i>Administrative claims data</i>	<p>Primary aim: To assess the impact of a diabetes incentive code introduced for primary care physicians in Ontario, Canada, in 2002 on quality of diabetes care at the population and patient level.</p> <p>Data source: Administrative data was extracted from Ontarians with diabetes (diagnosed ≤31/8/2006) to examine the use of the code and receipt of three evidence-based monitoring tests from 2006 to 2008. The researchers assessed testing rates over time, and before and after billing of the incentive code. Patients were excluded if they were not assigned to a primary care physician, when residing in long-term care facilities, or when registered with the OHIP after 31/3/2006, or died before 31/3/2008.</p>

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Reichard et al., 2012 ⁶²	United States	7/2008 – 6/2009	3,722 (71%) 18–65	≥1 Measurements during study period: Lipids (any), eye exam. <i>Administrative claims data</i>	<p>Primary aim: To assess Kansas Medicaid data to determine the quality of diabetic care and the level to which individuals with physical disabilities' prevention and diabetes management needs are being met.</p> <p>Data source: Data extracted from individuals with physical disabilities and diabetes who received medical benefits through Kansas Medicaid. Kansas Medicaid program provides insurance coverage for inpatient, outpatient, pharmacy, long term care and hospice coverage to adults with disabilities who qualify for Supplemental Security Income, have high medical needs, qualify for Medicare, or have a severe disability and are awaiting permanent federal disability status. Each of these programs has its own income qualifications. Persons with diabetes-related claims during a 12-month period (7/2007 – 6/2008) were identified and quality of care was followed the subsequent 12 months. All individuals included were continuously eligible for the entire 24 months.</p>
Gold et al., 2012 ⁶³	United States	2005–2007	3,384 (57%) Adults	≥3 Measurements during 3-year study period: LDL, microalbuminuria, HbA1c. <i>Electronic medical records</i>	<p>Primary aim: To determine if amount of time with insurance coverage had a dose-response relationship with the likelihood of receiving diabetes preventive care over a three-year study period.</p> <p>Data source: Electronic health record data extracted from adults with diabetes receiving care in 50 safety net clinics in Oregon in 2005–2007. Receipt of these services were assessed using procedure codes associated with each service. Eligible individuals had to have ≥ two diabetes-associated visits over 2004–2005 and also ≥ one visit in 2006 and another in 2007.</p>

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Kilbourne et al., 2011 ⁶⁴	United State	2007	Assumed to be 1,079 Not specified but assumed to be adults	≥1 Measurements during study period: Eye exam, foot exam. <i>Medical records</i>	Primary aim: To determine whether patients with serious mental illness receiving care in Veterans Affairs mental health programs with collocated general medical clinics were more likely to receive adequate medical care than those in programs without collocated clinics based on a nationally representative sample. Data source: The study included veteran affairs (VA) patients with diagnoses of serious mental illness in fiscal year (FY) 2006–2007 who were also part of the VA's External Peer Review Program (EPRP) FY 2007 random sample and who received care from VA facilities with organizational data from the VA Mental Health Program Survey. EPRP included patient-level chart review quality indicators for common processes of care. Patients were eligible for EPRP chart review if they had an outpatient visit in the immediately preceding month, had an outpatient visit 13–24 months before the chart review month, and did not have a chart review in the preceding three months. Women as well as those with chronic medical conditions, such as diabetes , were oversampled.
Stefos et al., 2011 ⁶⁵	United States	2004	11,211 (NR) Adults	Timely eye exam as indicated by disease. <i>Medical records</i>	Primary aim: To assess correlations addressing this central question, namely, how are changes in primary care panel size related to patient processes and satisfaction, and the amount of (waiting) time to be seen by a primary care doctor? Data source: Patient data from those with diabetes extracted from US Department of Veterans Affairs (VA) primary care clinics. VA operates the largest health care system in the US. Data for the analyses on process indicators were gathered from a 2004 sample as part of the External Peer Review Programme.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Fraser et al., 2011 ⁶⁶	England	7/2010	70,004 (45%) ≥12	Eye exam within 3 years from study period. (unclear whether all patients where truly referred to a program) <i>Medical records</i>	Primary aim: To compare access and uptake of screening between groups of people with diabetes in each of three screening programs covering this area of southern England. Data source: Data extracted from a patient-level dataset using data from general practices that refer to three diabetic retinopathy screening programmes and a combined health record. The Hampshire Health Record received data from approximately two thirds of general practices in the region, and from secondary care. It is used by clinicians to share information between primary and secondary care, and provides a rich source of contemporaneous data with potential for public health use. Multiple diabetes diagnosis codes were used in order to capture all registered people with diabetes . Diabetic retinopathy screening in England is provided by local programs with guidance and quality assurance oversight from the English National Screening Programme for Diabetic Retinopathy. Diabetic retinopathy screening is offered annually to all people with diabetes over the age of 12 years.
Williams et al., 2010 ⁶⁷	United States	2005 (survey year)	2,883 (1,516,171 weighted) ≥18	≥1 Measurements in the prior 12 months from survey: Feet exam, eye exam, HbA1c. <i>Self-reported</i>	Primary aim: To broaden the examination of diabetes care among patients with mental issues from samples at defined treatment locations to a population-based examination of three aspects of diabetes care among California adults with Type 2 diabetes and serious psychological distress." Data source: Data extracted from those with type 2 diabetes from the 2005 California Health Interview Survey (CHIS), a population-based, random digit dial telephone survey of California households. CHIS is the largest state-level survey in the United States, conducted biannually and was designed to provide state-wide approximations for various ethnic groups, with a special effort to include individuals speaking little to no English. Homeless or institutionalized individuals were excluded.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Green et al., 2010 ⁸	United States	1/2004-12/2006	8,817 (64%) 18-75	≥1 Measurements in a given year: HDL, LDL, HbA1c, eye exam, nephropathy screening. <i>Administrative claims data</i>	Primary aim: To assess whether practice setting influenced whether patients with mental illness received the same quality of diabetes preventive care as patients without mental illness. Data source: Data extracted from patients with diabetes seen in either the emergency or the outpatient setting of a safety-net health system (large urban public Hospital that serves predominantly uninsured, Medicaid, and Medicare patients), including those with an outpatient or inpatient encounter between 1/2004 and 12/2005. Once enrolled, patients were followed through 12/2006. Patients were included if they had a diabetes diagnosis and a diabetes-related laboratory workup completed in ≥1 of the first two quarters of 2004. To remain in the study, a participant must have had at least two visits, with the last visit ≥6 months later than the first.
Chen et al., 2010 ⁹	United States	1/1/1999-31/12/2006	Varies per year ranging from 19,573 (48%) in 1999 to 32,365 (47%) in 2006 18-75	Combination (≥2 HbA1c measurements and ≥1 LDL measurement during 1 year). <i>Administrative claims data</i>	Primary aim: To investigate the effectiveness of a pay-for-performance program to increase the receipt of quality care and to decrease hospitalization rates among patients with diabetes. Data source: Demographic, pharmacy, inpatient, and outpatient administrative medical claims data from 1/1/1999, through 31/12/2006 were used. The study sample consisted of individuals with diabetes who saw Pay for Performance (P4P)-participating physicians or non-P4P-participating physicians exclusively. Those who saw both P4P-participating and non-P4P-participating physicians were excluded. P4P, implemented by a large provider of healthcare coverage in Hawaii, provides participating physicians with financial incentives to perform quality-of-care processes. Participation in the P4P is voluntary.
Tomio et al., 2010 ¹⁰	Japan	5/2006-4/2007	636 (51%) NS	≥1 Measurements during study period: HbA1c (≥4), eye exam, nephropathy screening (urinary albumin excretion tests and/or qualitative urine albumin tests, excl. renal patients). <i>Administrative claims data</i>	Primary aim: To assess the quality of diabetes care in two communities in Japan by using National Health Insurance claims data. Data source: Data extracted from beneficiaries with diabetes of National Health Insurance (NHI) in two communities in south-western Japan from 5/2006 to 4/2007. Only those who had ≥1 claim forms with a diagnosis of diabetes mellitus every month from 5/2006 to 4/2007 were included. NHI covers self-employed workers and unemployed. Those with ≥1 claims for hospitalized care claim forms and/or ≥1 diagnosis of disorders in the perinatal period, including gestational diabetes during study period were excluded, as well as those that received non-fee-for-service care for at least 1 month.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, Country years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Wilf-Miron et al., 2010 ¹¹	Israel	12/2007 – 11/2008	74,953 (46%) 18 - 80	≥1 Measurements during the study period: HbA1c, LDL, combination (HbA1c, LDL, microalbuminuria testing, eye and foot exam, blood pressure, BMI). <i>Administrative data</i>	Primary aim: To explore disparities in diabetes prevalence, care and control among diabetic patients. Data source: Data extracted from the Maccabi Healthcare Services (MHS), including all MHS members who had visited a general practitioner ≥1 during previous 2 years and were registered as having diabetes at 15/11/2008. MHS is an Israeli health plan providing community-based health services throughout the country. Those with gestational diabetes were excluded.
Gregg et al., 2010 ¹²	United States	1999-2002 (3-years)	8,392 (53%) ≥18	Combination (NOT receiving HbA1c, cholesterol, albuminuria, eye exam, or foot exam) during study period. <i>Medical record and/or self-reported</i>	Primary aim: To determine the frequency and correlates of persistent long-term gaps in diabetes care. Data source: Data extracted from patient surveys and reviews of medical records to assess preventive care services for previously diagnosed type 2 diabetes among those who were continuously enrolled in 10 US managed care plans from 1999 to 2002. Participants were considered eligible if they had been continuously enrolled in the health plan for at least 3 years, submitted at least 1 claim in the first 18 months, were not pregnant, and participated in follow-up survey. Those with probable type 1 diabetes were excluded. Whether HbA1c, lipid tests, and urine albumin tests were received was based solely on chart abstraction, while eye and foot exam were considered to have been received if they were self-reported or recorded in the medical record.
Ng et al., 2010 ¹³	United States	2004-2006 (Survey period)	4,076 (NR) (13,504,000 (52%) assumed to be weighted) ≥45	Combination (HbA1c, eye exam and foot exam) in the 12 months prior to survey. <i>Self-reported</i>	Primary aim: To examine the relation of age, gender and insurance status to quality of care among Americans with diabetes and cardiovascular conditions. Data source: Data extracted from nationally representative MEPS data (2004-2006 pooled). MEPS is a health survey developed to analyse health care use, expenditures and insurance coverage for the U.S. civilian noninstitutionalized population. The MEPS Household Component (MEPS HC) provides estimates of respondents' demographic and socioeconomic characteristics, access to care, health insurance coverage and effectiveness of care for an array of priority clinical conditions, including cardiovascular disease. The MEPS also collects information on diabetes care effectiveness separately through a self-survey, the MEPS Diabetes Care Supplement. Non-institutionalized individuals with self-identified diabetes were eligible for inclusion. Older adults who reported being "uninsured" were excluded.

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Wang et al., 2010 ⁴	China	2/2009-11/2009 (data extraction)	824 (59%) ≥18	≥1 Eye exams within 12 months prior to survey. <i>Medical records or self-reported</i>	Primary aim: To assess the use of eye care and its predictors among diabetic patients in China. Data source: Between February and November 2009, those with physician-diagnosed diabetes were recruited from an urban tertiary and community hospitals and from a rural clinic in Guangdong, China. Subjects having been diagnosed less than 12 months previously or who were unable to cooperate with the interview were excluded. Outcomes were defined according to documentation in the patient's chart, and when this was unavailable or dates were not stated clearly, by the subject's self-report.
Gulliford et al., 2010 ⁵	England	1/9/2007-28/2/2009	31,484 (49%) ≥12	No eye exam during study period after invitation. <i>Electronic medical records</i>	Primary aim: To determine the extent of socioeconomic and ethnic differentials in diabetic retinopathy screening uptake and screening outcomes following the implementation of the screening programme. Data source: Anonymized data extracted from the Diabetes Eye complications service for South East London for all appointments and episodes from 19/2007 to 28/2/2009. The study was set in Lambeth, Southwark and Lewisham. These rank as the 19th, 26th and 39th most deprived local authorities in England. The diabetes retinal screening service in South London is known as the Diabetes Eye Complication Service. There are clinics held on four sites at the three teaching hospitals and one district hospital. Screening is offered to all general practitioner-registered patients over the age of 12 years who have diagnosed diabetes. A recall register has been established so that all eligible people with diabetes who are registered with local family practices will automatically be offered appointments.
Lawrenson et al., 2009 ¹⁶	New Zealand	15/11/2005 – 15/11/2007	1,111 (49%) ≥20	Measurements NOT recorded: retinal screening during the last 2 years (excluding newly diagnosed patients). <i>Electronic medical records</i>	Primary aim: To estimate the prevalence of diabetes by age, gender and ethnicity, to look at quality of care, and to investigate disparities in care. Data source: Data extracted from three general practices in Hamilton (New Zealand), including those with type 2 diabetes (prevalent and newly diagnosed).

Supplemental table II. Summary of studies included for qualitative analyses. Study details can be found in the original articles. (continued)

First author, years	Country	Study period	Study size (% women) and age	Reported outcomes of interest	Primary aim & Data source
Guthrie <i>et al.</i> , 2009 ⁷⁷	Scotland	2005/2006	10,161 (47%) ≥35	≥1 Measurements during previous 12 months: HbA1c, total cholesterol, blood pressure, smoking, combination (all). <i>Electronic medical records</i>	Primary aim: To measure quality of vascular risk factor measurement and control in people with type 2 diabetes after comprehensive pay-for-performance implementation and to examine variation by patient and practice characteristics. Data source: Data extracted, after pay-for-performance implementation, from the Diabetes Audit and Research in Tayside (Scotland) population diabetes register, including individuals with type 2 diabetes on 30/4/2006 diagnosed at ≥35 years.
Gnavi <i>et al.</i> , 2009 ⁷⁸	Italy	1/8/2003-31/7/2004	33,453 (49%) ≥20	≥1 Measurements during study period: HbA1c, cholesterol (total, HDL, and LDL), microalbuminuria, eye exam, combination (HbA1c and ≥2 assessments from among eye exam, total cholesterol and microalbuminuria). <i>Administrative claims data</i>	Primary aim: To investigate the role of clinical and socioeconomic variables as determinants of adherence to recommended diabetes care guidelines and assess disparities in the process of care between diabetologists and general practitioners. Data source: All residents in Torino (Italy) with a diagnosis of diabetes and being alive at 31/7/2003 were eligible for inclusion. All laboratory tests and specialist medical examinations reimbursed by the national health service in the study period were linked to the population with diabetes to identify process of care.
Kirkbride <i>et al.</i> , 2009 ⁷⁹	United States	2002 and 2003	6,267 (65%) 18-64	≥1 Measurements during the calendar year: HbA1c, lipid profile, eye exam. <i>Administrative claims data</i>	Primary aim: To assess whether Rural Health Clinics were associated with higher rates of recommended primary care services for adult beneficiaries diagnosed with diabetes in Oregon's Medicaid program, the Oregon Health Plan. Data source: Data extracted from Oregon's Medicaid program, the Oregon Health Plan from 2002 to 2003 to assess quality of diabetic care for beneficiaries with diabetes residing in urban areas or rural areas with or without at least 1 rural health clinic. Study subjects included Temporary Assistance to Needy Families or disabled beneficiaries who were enrolled in the health plan for 12 months per study year and had at least 1 claim with a diabetes diagnosis. Those with gestational diabetes and those who gave birth during a given study year were excluded, as well as those in areas where rural health clinic was new in that year.

Supplemental table III. Studies excluded from the qualitative analyses because of overlapping patient populations or because studies were repeated over time.

First author, year	(Partial) overlap with/ more recent data available from	Outcomes not included in qualitative analyses <i>OR (95% CI), ref = men, unless otherwise specified</i>	Level of adjustment
Peraj et al., 2019 ⁸⁰ (Fully excluded)	Kamat et al., 2019	Foot exam prior 12 months: 0.91 (0.67, 1.25)	Multivariable
Barker et al., 2018 ⁸¹ (Fully excluded)	Kiran et al., 2012 <i>Less recent but larger study population not restricted to those with mental illness.</i>	≥1 Measurements during study period: Eye exam: 1.13 (1.08;1.19) HbA1c (≥4): 1.06 (1.01;1.12) Dyslipidaemia: 1.04 (0.99;1.11) HbA1c: 1.20 (1.10;1.30) Combination (≥1 of the above):1.16 (1.08;1.24)	Multivariable
Canedo et al., 2018 ⁸² (Fully excluded)	Comer-HaGans et al., 2020 and Bennet et al., 2017	HbA1c (≥2) prior 12 months: 1.14 (0.82;1.58) Foot exam prior 12 months: 0.95 (0.72;1.26) Eye exam prior 12 months:1.14 (0.87;1.47) Cholesterol prior 12 months: 1.03 (0.76;1.41)	Multivariable
Williams et al., 2017 ²⁸ (Partially excluded)	Comer-HaGans et al., 2020	HbA1c (≥2) prior 12 months: 1.01 (0.89;1.14) Eye exam prior 12 months: 1.14 (1.04;1.24) Foot exam prior 12 months: 0.91 (0.83;1.00)	Multivariable
National Diabetes Audit 2016-2017 ²² (Partially excluded)	National Diabetes Audit 2018-2017	≥1 measurements during study period HbA1c: 1.12 (1.11;1.14) Blood pressure: 1.16 (1.14;1.17) Cholesterol:0.97 (0.96;0.98) Urine albumin: .89 (0.88;0.89) Smoking: 87 (0.87;0.88) Combination: 0.92 (0.91;0.92)	Multivariable
National Diabetes Audit 2015-2016 ²² (Fully excluded)	National Diabetes Audit 2018-2017	≥1 measurements during study period Urine albumin: 0.90 (0.89;0.91) Foot exam: 0.99 (0.98;1.00) BMI: 0.98 (0.97;0.99) Smoking: 0.86 (0.85;0.86) Combination: 0.91 (0.90;0.91)	Multivariable
National Diabetes Audit 2014-2015 ²² (Fully excluded)	National Diabetes Audit 2018-2017	≥1 measurements during study period Blood pressure: 1.12 (1.10;1.13) Cholesterol: 0.98 (0.97;0.99) Urine albumin: 0.93 (0.92;0.94) Foot exam: 0.99 (0.98;1.00) BMI: 0.98 (0.97;0.99) Smoking: 0.87 (0.86;0.88) Combination: 0.94 (0.93;0.95)	Multivariable
National Diabetes Audit 2014-2013 ²² (Fully excluded)	National Diabetes Audit 2018-2017	≥1 measurements during study period Urine albumin: 0.93 (0.92;0.94) Smoking: 0.86 (0.85;0.87) Combination: 0.93 (0.92;0.94)	Multivariable

Supplemental table III. Studies excluded from the qualitative analyses because of overlapping patient populations or because studies were repeated over time. (continued)

First author, year	(Partial) overlap with/ more recent data available from	Outcomes not included in qualitative analyses <i>OR (95% CI), ref = men, unless otherwise specified</i>	Level of adjustment
National Diabetes Audit 2013-2012 ²² (Partially excluded)	National Diabetes Audit 2018-2017	≥1 measurements during study period HbA1c: 1.01 (1.00;1.03) Blood pressure: 1.14 (1.12;1.16) Cholesterol: 0.93 (0.92;0.94) Urine albumin: 0.85 (0.85;0.86) Foot exam: 0.97 (0.97;0.98) BMI: 0.92 (0.91;0.93) Smoking: 0.87 (0.86;0.88) Combination:0.85 (0.85;0.86)	Multivariable
National Diabetes Audit 2012-2011 ²² (Fully excluded)	National Diabetes Audit 2018-2017	≥1 measurements during study period HbA1c: 1.04 (1.03;1.05) Blood pressure: 1.14 (1.13;1.16) Cholesterol: 0.95 (0.94;0.96) Creatinine: 1.04 (1.03;1.05) Urine albumin: 0.89(0.88;0.89) Foot exam: 0.98 (0.98;0.99) BMI: 0.92 (0.91;0.93) Smoking: 0.89 (0.88;0.89) Combination: 0.88 (0.88;0.89)	Multivariable
Bennet et al., 2017 ²⁷ (Partially excluded)	Comer-HaGans et al., 2020	Eye exam prior 12 months: 1.01 (0.92;1.10) Foot exam prior 12 months: 0.85 (0.78;0.92) HbA1c (≥2) prior 12 months: 0.86 (0.79;0.95)	Multivariable
Sieng et al., 2017 ⁸³ (Fully excluded)	Sieng et al., 2015 ⁸⁸	Eye exam prior 12 months: 1.20 (1.12–1.29) Foot exam prior 12 months: 1.12 (1.04–1.21) Combination (LDL, foot exam, eye exam, HbA1c (≥2)) prior 12 months: 1.11 (1.03–1.21)	Multivariable
Doucette et al., 2017 ⁸⁴ (Fully excluded)	Chen et al., 2014 <i>Less recent but larger study population</i>	HbA1c (≥2) prior 12 months: 1.07 (0.89, 1.29) Foot prior 12 months: 1.00 (0.83, 1.21) Eye exam prior 12 months: 1.05 (0.88, 1.25)	Multivariable
Storey et al., 2016 ⁸⁵ (Fully excluded)	Murchinson et al., 2017 ³⁰	Follow-up eye exam <15 months for mild, <12 months for moderate diabetic retinopathy and <4 months from the index visit for severe diabetic retinopathy: 0.83 (0.68;1.02)	Multivariable
Sohn et al., 2016 ⁸⁶ (Fully excluded)	Chen et al., 2014 ⁵²	Eye exam prior 12 months: 1.07 (1.00;1.15) Foot exam prior 12 months: 0.90 (0.84;0.96) ≥2 HbA1c prior 12 months: 1.09 (1.02;1.16)	Multivariable
Mahmoudi et al., 2016 ⁸⁷ (Fully excluded)	Comer-HaGans et al., 2020	Eye exam prior 12 months: 1.03 (0.81;1.25) Foot exam prior 12 months: 0.78 (0.62;0.94) Cholesterol prior 12 months: 1.25 (0.86;1.64)	Multivariable
Doucette et al., 2016 ⁸⁸ (Fully excluded)	Kamat et al., 2019 ¹⁶	Eye exam prior 12 months: 1.69 (0.94;3.03) Foot exam prior 12 months: 1.30 (0.82;2.08)	Multivariable

Supplemental table III. Studies excluded from the qualitative analyses because of overlapping patient populations or because studies were repeated over time. (continued)

First author, year	(Partial) overlap with/ more recent data available from	Outcomes not included in qualitative analyses OR (95% CI), ref = men, unless otherwise specified	Level of adjustment
Shi et al., 2014 ⁸⁹ (Fully excluded)	Comer-HaGans et al., 2020	Eye exam prior 12 months per survey year: 2002: 0.92 (0.69;1.22) 2003: 0.70 (0.51;0.98) 2004: 0.95 (0.68;1.32) 2005: 0.91 (0.65;1.27) 2006: 0.83 (0.63;1.08) 2007: 0.85 (0.65;1.10) 2008: 0.71 (0.53;0.94) 2009: 0.82 (0.64;1.05)	Multivariable
Hu et al., 2014 ⁹⁰ (Fully excluded)	Comer-HaGans et al., 2020 and Bennet et al., 2017	Eye exam prior 12 months: 1.35 (1.07;1.70) Foot exam prior 12 months: 0.83 (0.63;1.10) Cholesterol prior 12 months: 1.21 (0.91;1.61) HbA1c prior 12 months: 1.31 (0.84;2.04)	Multivariable
Chou et al., 2012 ⁹¹ (Fully excluded)	Chen et al., 2014 ⁵²	Eye exam prior 12 months: 1.16 (1.03;1.30)	Multivariable
Hale et al., 2010 ⁹² (Fully excluded)	Chen et al., 2014 ⁵²	Eye exam prior 12 months: 1.12 (0.96;1.30) Foot exam prior 12 months: 0.86 (0.75; 1.00) ≥2 HbA1c prior 12 months: 1.18 (1.01;1.35)	Multivariable
Byun et al., 2013 ⁹³ (Fully excluded)	Rim et al., 2013	Eye exam prior 12 months: 1.19 (0.88;1.62)	Multivariable
Richard et al., 2012 ⁹⁴ (Fully excluded)	Comer-HaGans et al., 2020	HbA1c prior 12 months: 1.20 (0.93;1.47) Eye exam prior 12 months: 1.07 (0.88;1.26) Foot exam prior 12 months: 0.91 (0.72;1.11)	Multivariable
Richard et al., 2011 ⁹⁵ (Fully excluded)	Comer-HaGans et al., 2020	Eye exam prior 12 months: 1.14 (0.93;1.40) Foot exam prior 12 months: 1.10 (0.90;1.35) HbA1c (≥2) prior 12 months: 1.14 (0.96;1.35)	Multivariable
Do et al., 2011 ⁹⁶ (Fully excluded)	Rim et al., 2013	Eye exam prior 12 months: 1.59 (1.21;2.07) Microalbuminuria prior 12 months: 1.34 (1.04;1.72)	Multivariable
Ng et al., 2010 ⁷³ (Partially excluded)	Comer-HaGans et al., 2020 and Williams et al., 2017	HbA1c in prior 12 months: 1.26 (0.95;1.67) Blood pressure in prior 12 months: 1.65 (0.93;2.94) Cholesterol in prior 24 months: 1.44 (0.95;2.18) Eye exam in prior 12 months: 1.10 (0.94;1.30) Foot exam in prior 12 months: 0.97 (0.80;1.17) Pooled data	Multivariable

OR = odds ratio; CI = confidence interval.

Supplemental table IV. Studies only presenting unadjusted data.

First author, year	Country	Study period	Study size (% women)	Outcome OR (95% CI), ref = men, unless otherwise specified	
Backe et al., 2020 ⁹⁷	Greenland	30/11/2018 (data extraction)	1,498 (48%)	HbA1c	1.48 (1.08;2.03)±
				Blood pressure	1.55 (1.20;2.01)±
				Microalbuminuria	1.00 (0.81;1.25)±
				Eye exam	1.10 (0.86;1.42)±
				Foot exam	0.99 (0.81;1.22)±
Boucher et al., 2020 ^{98A}	Canada	3/2018-6/2018 (Survey period)	148 (45%)	Eye exam	0.64 (0.20;2.08)±
Benoit et al., 2019 ⁹⁹	United States	2010-2014	355,384 (52%)	Eye exam	1.05 (1.03;1.07)±
Gediminas et al., 2019 ¹⁰⁰	Lithuania	2011	382 (61%)	BMI	1.0 (0.6-1.6)
				Foot exam	1.3 (0.8-2.2)
				Eye exam	1.6 (1.1-2.4)
				HbA1c	1.4 (0.9-2.1)
				LDL	1.3 (0.7-2.2)
				Creatinine	1.0 (0.7-1.6)
				Blood pressure	-
Wright et al., 2019 ¹⁰¹	England	2006-2013	Presented by years since diagnosis: 4,221 (46%) to 30,501 (43%)	Years 2-3	
				HbA1c	1.02 (0.92;1.13)
				Blood pressure	1.15 (1.03;1.30)
				Microalbuminuria	0.88 (0.84;0.92)
				eGFR or creatinine	1.20 (1.08;1.33)
				BMI	0.98 (0.90;1.06)
				Years 4-5	
				HbA1c	0.98 (0.85;1.14)
				Blood pressure	1.15 (0.97;1.35)
				Microalbuminuria	0.88 (0.82;0.94)
				eGFR or creatinine	1.04 (0.89;1.20)
				BMI	0.98 (0.87;1.10)
				Years 6-7	
				HbA1c	0.84 (0.63;1.12)
			Blood pressure	0.81 (0.60;1.08)	
			Microalbuminuria	0.82 (0.72;0.93)	
			eGFR or creatinine	0.85 (0.64;1.14)	
			BMI	0.80 (0.65;0.99)	
Nazu et al., 2019 ¹⁰²	Finland	2011-2016	8,429 (47%)	2015-2016	
				HbA1c	1.35 (1.18;1.54)±
				LDL	0.93 (0.82;1.04)±
Corrao et al., 2019 ¹⁰³	Italy	2010 (year of diagnosis)	77,285 (47.5%)	Combination	0.85 (0.82;0.88)±
Tracey et al., 2019 ^{104A}	Ireland	11/2013-8/2015 (data extraction)	582 (39%)	Eye exam	0.33 (0.12;0.92)±
Mesa et al., 2018 ¹⁰⁵	Unites States	2015	100 (50%)	HbA1c	0.74 (0.30;1.79)±
				LDL	1.71 (0.52;5.66)±
				Eye exam	0.71 (0.31;1.60)±

Supplemental table IV. Studies only presenting unadjusted data. (continued)

First author, year	Country	Study period	Study size (% women)	Outcome	OR (95% CI), ref = men, unless otherwise specified
Al-Salameh et al., 2018 ¹⁰⁶	France	4/2009 – 6//2014 (inclusion period: 4/2009 – 6/2011)	983 (47%)	Lipid profile	0.96 (0.65;1.42)±
Bird <i>et al.</i> , 2018b ¹⁰⁷	Unites Stated	2011 and 2012	Varies per outcome of interest	LDL HbA1c Eye exam Renal test	1.09 (1.07;1.12) 1.19 (1.16;1.22) 1.28 (1.26;1.30) 1.04 (1.01;1.06)
Diabetic Retina-Screen 2013-2015 ^{108A}	Ireland	2013-2014	69,894 (41%)	Eye exam year 1	0.77 (0.74;0.81)±
		2015	88,668 (41%)	Eye exam year 2	0.84 (0.81;0.88)±
Statistical Bulletin 2016-2017 ^{109A}	Ireland	2016	105,915 (41%)	Eye exam year 3	0.86 (0.83;0.89)±
		2017	114,078 (41%)	Eye exam year 4	0.83 (0.80;0.86)±
Kekäläinen et al., 2016 ¹¹⁰	Finland	2013-2014	1,075 (41%)	HbA1c LDL	2.24 (1.32;3.82)± 2.12 (1.36;3.33)±
Han et al., 2016 ¹¹¹	Korea	2013 (survey year)	20,806 (52%)	Combination	0.89 (0.84;0.94)±
Ferroni et al., 2016 ¹¹²	Italy	2013	139,935 (43%)	HbA1c Microalbuminuria Lipid profile	1.04 (1.02;1.07)± 0.94 (0.92;0.96)± 1.01 (0.99;1.04)±
Cambra et al., 2016 ¹¹³	Spain	15/5/2014 (index date)	32,220 (44%)	HbA1c Blood pressure LDL HDL Triglycerides BMI Smoking	1.03 (0.99;1.09)± 1.30 (1.24;1.37)± 1.09 (1.04;1.15)± 1.06 (1.01;1.12)± 1.06 (1.01;1.12)± 1.02 (0.97;1.06)± 0.91 (0.87;0.96)±
Seghieri et al., 2016 ¹¹⁴	Italy	2006	91,826 (49.7%)	Urine albumin HbA1c Eye exam Lipid profile Combination	0.93 (0.91;0.97)± 1.08 (1.06;1.11)± 1.09 (1.06;1.12)± 1.08 (1.05;1.10)± 1.04 (1.01;1.07)±
Cleland et al., 2016 ^{115A}	Tanzania	2011-2014	5,729 (60%)	Eye exam	1.36 (1.22;1.52)
Manicardi <i>et al.</i> , 2016 ¹¹⁶	Italy	2011	28,802 (46%)	HbA1c lipid profile Blood pressure Renal function Eye exam	1.03 (0.94;1.14)± 1.01 (0.96;1.07)± 1.03 (0.97;1.09)± 1.02 (0.98;1.07)± 1.01 (0.97;1.06)±
Hwang et al., 2016 ¹¹⁷	Korea	2005, 2007-2009	2,214 (53%)	Eye exam	1.15 (0.97;1.36)
Keenum et al., 2016 ^{118A}	Unites States	26/1/2012-1/5/2015	949 (65%)	Eye exam	1.16 (0.87;1.56)±
Szabo et al., 2015 ¹¹⁹	Unites Arab Emirates	2010	150 (69%)	HbA1c LDL Eye Renal exam Combination	- 2.83 (0.90;8.94)± 0.57 (0.27;1.19)± 0.53 (0.24;1.19)± 1.26 (0.63;2.52)±

Supplemental table IV. Studies only presenting unadjusted data. (continued)

First author, year	Country	Study period	Study size (% women)	Outcome	OR (95% CI), ref = men, unless otherwise specified
Afandi et al., 2015 ¹²⁰	United Arab Emirates	2013	240 (58%)	BMI	100%/100%
Hendriks et al., 2015 ¹²¹	The Netherlands	2013	42,641 (46%)	HbA1c Systolic BP Smoking TC/HDL-ratio ACR Foot exam Eye exam BMI	1.10 (1.00;1.21)± 1.07 (0.96;1.19)± 1.15 (1.04;1.28)± 1.12 (1.02;1.23)± 0.93 (0.88;0.98)± 1.09 (1.03;1.15)± 1.03 (0.98;1.09)± 1.10 (1.00;1.20)±
Ballotari et al., 2015 ¹²²	Italy	2010	16,903 (42%)	HbA1c	1.10 (1.03;1.18)±
Russo et al., 2015 ¹²³	Italy	2009	415,294 (45%)	Lipid profile	0.91 (0.90;0.93)±
Onakpoya et al., 2015 ^{124A}	Nigeria	7/2010-11/2010 (inclusion period)	179 (49%)	Eye exam	0.71 (0.39;1.28)±
Kiran et al., 2014 ¹²⁵	Canada	2006-2008	734,739 (48%)	Eye exam HbA1c Cholesterol Combination	1.15 (1.14;1.16)± 1.00 (0.99;1.01)± 0.93 (0.92;0.94)± 1.03 (1.02;1.04) ±
Bayer et al., 2014 ¹²⁶	United States	2003	1,797 (17%)	Combination	0.79 (0.55;1.14)±
Chou et al., 2014 ¹²⁷	United States	2006-2010 (survey period)	27,699 (NR)	Eye exam	P-value 0.089
Matheka et al., 2013 ¹²⁸	Kenya	10/2012-11/2012 (survey period)	198 (70%)	HbA1c	0.33 (0.16;0.67)±
Kautzky-Willer et al., 2013 ¹²⁹	Austria	3/2009-8/2009 (data collection)	225 (45%)	HbA1c	0.82 (0.31;2.14)±
Kiran et al., 2013 ¹³⁰	Canada	2010	851,193 (48%)	Eye exam	1.15 (1.14;1.16)±
Cetin et al., 2013 ¹³¹	Turkey	1/2010-5/2010 (survey period)	437 (52%)	Eye exam	0.81 (0.51;1.28)±
Paksin et al., 2013 ¹³²	United States	2009 (survey year)	52,386 (59%) (49% weighted)	Eye exam	P-value 0.641
Driskell et al., 2012 ¹³³	England	2010	54 537 (47%)	HbA1c	0.90 (0.86;0.93)±
Orton et al., 2013 ^{134A}	England	1/2009-7/2010 (screening invitation period)	47,111 (44%)	Eye exam	1.04 (0.99;1.08)
Sachdeva et al., 2012 ^{135A}	England	2008	611 (47%)	Eye exam	1.24 (0.89;1.72)±
Arcury et al., 2012 ¹³⁶	United States	6/2009-2/2010 (data collection)	563 (62%)	HbA1c Feet exam	1.04 (0.61;1.78)± 1.37 (0.90;2.08)±
Van Eijk et al., 2012 ¹³⁷	The Netherlands	2008 (questionnaire)	1,891 (51%)	Eye exam	1.00 (0.78;1.28)±

Supplemental table IV. Studies only presenting unadjusted data. (continued)

First author, year	Country	Study period	Study size (% women)	Outcome	OR (95% CI), ref = men, unless otherwise specified
Wong et al., 2012 ¹³⁸ <i>Multivariable analyses but not for age and therefore excluded from qualitative analyses</i>	China	2008 - 2009	1,970 (55%)	HbA1c	0.84 (0.58;1.20)
				Cholesterol	0.92 (0.66;1.28)
				Smoking	0.61 (0.43;0.87)
				Microalbuminuria	0.83 (0.67;1.03)
				Eye exam	1.13 (0.93;1.38)
BMI	0.95 (0.75;1.21)				
Sundquist et al., 2011 ¹³⁹	Sweden	2005	5,048 (42%)	HbA1c	1.27 (1.03;1.56)±
				Lipids	1.30 (1.13;1.50)±
Sadowski et al., 2011 ¹⁴⁰	United States	9/2009-12-2009 (data collection)	134 (59%)	HbA1c	1.73 (0.74;4.05)±
				Foot exam	1.39 (0.63;3.05)±
				Eye exam	0.45 (0.19;1.06)±
				Cholesterol	0.32 (0.03;2.97)±
				Combination	1.07 (0.54;2.14)±
De Lusignan et al., 2011 ¹⁴¹	England	2007	6,897 (47%)	Creatinine	1.18 (0.92;1.50)±
				Microalbuminuria	0.91 (0.81;1.03)±
				Macroalbuminuria	0.99 (0.87;1.11)±
Morren et al., 2011 ¹⁴²	Caribbean	28/10/2007-29/11/2007 (patient interviews)	225 (65%)	Total cholesterol	2.14 (1.20;3.82)±
				HbA1c	2.19 (1.24;3.87)±
Onakpoya et al., 2010 ¹⁴³	Nigeria	11/2007	83 (61%)	Eye exam	0.94 (0.35;2.50)±
Goh et al., 2010 ¹⁴⁴	Malaysia	2006	2,373 (57%)	Eye exam	0.94 (0.75;1.19)±
Gossain et al., 2010 ¹⁴⁵	United States	1/2006-6/2008 (data extraction)	499 (52%)	HDL year 1	1.10 (0.57;2.09)±
				HDL year 2	1.05 (0.66;1.68)±
				Blood pressure	-
Shireman et al., 2010 ¹⁴⁶	United States	9/2006-8/2007	666 (50%)	Lipids	0.89 (0.65;1.20)±
				Microalbuminuria	1.30 (0.88;1.92)±
				Eye exam	1.01 (0.73;1.42)±
Banta et al., 2009 ¹⁴⁷	United States	5/2004-4/2005	482 (68%)	HbA1c	1.21 (0.82;1.78)±
				Lipid	1.60 (1.09;2.36)±
				Eye exam	1.33 (0.87;2.03)±
Fischbacher et al., 2009 ¹⁴⁸	Scotland	11/2003-12/2004	9,833 (47%)	HbA1c	0.90 (0.73;1.10)±
				Cholesterol	0.86 (0.73;1.01)±
				Blood pressure	0.97 (0.85;1.11)±
				Eye exam	0.88 (0.79;0.99)±
				BMI	0.92 (0.82;1.04)±

If studies presented sex-specific numbers and percentages without reporting a measure of association, crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using Review Manager 5.3. ^ = Eye exam attendance after invitation.

Supplemental table IV. A Modified Newcastle–Ottawa quality assessment scale to assess risk of bias.

First name, year	Selection (out of 3)			Comparability (out of 2)			Outcome (out of 1)	
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Study controls for one variable	Study controls for any additional variable(s)	Assessment of outcome	Score	
Swietek et al., 2020	0 (specific geographical area (North Carolina, Georgia, and Texas, US), diabetes + depressive disorders, Medicaid enrollee, working age adults)	*	* (administrative data)	*	*	* (administrative data)	Fair	
Lu et al., 2020	0 (restricted to intellectual and developmental disabilities and diabetes or diabetes only in specific geographical areas (Iowa, Massachusetts, New York, Oregon and South Carolina, US), Medicaid enrollee, working age adults)	*	* (administrative claims data)	*	*	* (administrative claims data)	Fair	
Wei et al., 2020	0 (restricted to those receiving glucose-lowering medication, enrollees of a specific insurance company (Switzerland))	*	* (administrative claims data)	*	*	* (administrative claims data)	Fair	
Youn et al., 2020	* (nationwide survey (Korea))	*	* (self-reported through trained interviewers)	*	*	0 (self-reported (trained interviewers))	Good	
Tan et al., 2020	*/0 (stratified random sample (US), type 2 DM, had at least one clinical measurement)	*	* (self-reported through self-administered internet-based questionnaire)	*	*	* (combination of health records and self-reported including sensitivity analysis)	Fair	
Meier et al., 2020	0 (electronic medical records database of the Institute of Primary Care of the University of Zurich.)	*	* (electronic medical records)	*	*	* (electronic medical records)	Fair	

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Representativeness of the exposed cohort	Selection (out of 3)		Ascertainment of exposure (= sex)	Comparability (out of 2)		Outcome (out of 1)	Score
		Selection of the non-exposed cohort	Study controls for one variable		Study controls for any additional variable(s)	Assessment of outcome		
Comer-Hagans et al., 2020	* (population-based (MEPS, US))	*	*	(self-reported)	*	*	0 (self-reported)	Poor
Hirst et al., 2019	0 (only those with a minimum number of HbA1c tests post diagnosis, primary care (UK))	*	*	(primary care medical record database)	*	*	* (primary care medical record database)	Fair
Bakke et al., 2019	* (population-based (Norway), primary care, type 2 diabetes)	*	*	(primary care medical records)	*	*	* (primary care medical records)	Good
Dallo et al., 2019	* (racially diverse population, restricted to metropolitan Detroit (US))	*	*	(medical records)	*	*	* (medical records)	Fair
De Jong et al., 2019	* (population-based, one geographical region (Utrecht, The Netherlands), primary care)	*	*	(primary care medical records)	*	0	* (primary care medical records)	Fair
Whyte et al., 2019	* (population-based (England), type 2 diabetes, primary care)	*	*	(primary care medical records)	*	*	* (primary care medical records)	Good
Du et al., 2019	* (national representative sample (Germany), type 2 diabetes, relatively small sample)	*	*	(self-report through computer-assisted interview)	*	*	0 (self-report through computer-assisted interview)	Poor

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Selection (out of 3)			Comparability (out of 2)			Outcome (out of 1)
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Study controls for one variable	Study controls for any additional variable(s)	Assessment of outcome	
Kovács et al., 2019	*/0 (population-based (Hungary), restricted to those receiving glucose-lowering medication)	*	* (primary care medical records)	*	*	* (primary care medical records)	Fair
Kamat et al., 2019	* (Population-based, complex, stratified, multistage, probability sampling design (NHANES, US))	*	* (Self-reported through interview)	*	*	0 (Self-reported through interview)	Poor
An et al., 2018	*/0 (only those in Southern California (US), restricted to those with two or more outpatient visits)	*	* (medical records)	*	*	* (medical records)	Fair
Ibáñez et al., 2018	*/0 (population-based, specific geographical area (Navarre, Spain), type 2 diabetes)	*	* (primary care medical records)	*	*	* (primary care medical records)	Fair
Bird et al., 2018a	0 (four metropolitan areas (Atlanta, Georgia; Houston, Texas; New York City/Northern New Jersey; and Southern California, US), commercial health plan members)	*	* (administrative data)	*	*	* (administrative data)	Fair
Kreft et al., 2018	0 (aged 50+, incident diabetes, member of a large insurance provider (Germany))	*	* (Administrative claims data)	*	*	* (Administrative claims data)	Fair
Kawamura et al., 2018	*/0 (only those with incident type 2 diabetes using oral glucose-lowering drugs (Japan))	*	* (Administrative claims data)	*	*	* (Administrative claims data)	Fair

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort (out of 3)	Ascertainment of exposure (= sex)	Comparability (out of 2)		Outcome (out of 1)	Score
				Study controls for one variable	Study controls for any additional variable(s)		
National diabetes Audit	(population-based (England and Wales))	*	*	*	*	*	Good (Medical records)
Foreman et al., 2017	(random clustering sampling approach across 30 geographical sites (Australia), aged 40+ /50+)	*	*	*	*	0	Poor (self-reported through interview)
Mwangi et al., 2017	(living in Kenya, attending the clinic, random sample, small sample size)	*	0	*	*	0	Poor (self-reported through interview)
LeBlanc et al., 2017	(followed by family physicians paid by fee-for-service, specific region (Canada))	*	*	*	*	*	Fair (Administrative data)
Yoo et al., 2017	(population-based, restricted to those receiving glucose-lowering medication, more than one claim for diabetes over the year (Korea))	*	*	*	*	*	Fair (Administrative claims data)
Bennet et al., 2017	(population-based (US, MEPS))	*	*	*	*	0	Poor (Self-reported through computer-assisted interview)
Williams et al., 2017	(population-based (US, MEPS))	*	0	*	*	0	Poor (Self-reported through computer-assisted interview)

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Selection (out of 3)			Comparability (out of 2)		Outcome (out of 1)	
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Study controls for one variable	Study controls for any additional variable(s)	Assessment of outcome	Score
Willis et al., 2017	0 (one geographical area (West Yorkshire, England), type 2 diabetes)	*	*	*	*	*	Fair (primary care medical records)
Moreton et al., 2017	0 (those (newly) referred to a specific screening program, one geographical area (Oxfordshire, England))	*	*	*	*	*	Fair (electronic records)
Murchison et al., 2017	0 (Only those included that received a previous eye exam during follow-up at an urban clinic (US))	*	*	*	*	*	Fair (billing and administrative data)
Tanaka et al., 2016	0 (only those with frequent visits in the prior year and visiting the clinic during study period, beneficiaries covered by Health Insurance Societies, type 2 diabetes (Japan))	*	*	*	*	*	Fair (administrative claims data)
Mtuya et al., 2016	0 (specific geographical area (Kilimanjaro Region, Tanzania), only those referred after screening for retinopathy)	*	*	*	*	*	Poor (self-reported through interview)
Rossaneis et al., 2016	0 (urban area of a large city in the South of Brazil, type 2 diabetes, aged 40+)	*	*	*	*	*	Poor (assumed to be self-reported through interview)

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Representativeness of the exposed cohort	Selection (out of 3)	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Comparability (out of 2)		Outcome (out of 1)	Score
					Study controls for one variable	Study controls for any additional variable(s)		
Tannenbaum et al., 2016	0 (specific study location (HCHS/SOL Miami site, US), Hispanics/Latinos, aged 40+)	*	*	*	*	*	0 (self-reported)	Poor
Hatef et al., 2015	0 (Medicaid patients covered by Johns Hopkins HealthCare), working age adults)	*	*	*	*	*	*	Fair (Administrative claims data)
Baumeister et al., 2015	*/0 (population-based, a specific geographical area (West Pomerania, Germany))	*	*	*	*	*	0 (Self-reported)	Poor
Sieng et al., 2015	*/0 (from all provinces in Thailand, type 2 diabetes, data extracted from those attending the clinic in a given period)	*	*	*	*	*	*	Fair (medical records)
Mounce et al., 2015	*/0 (population-based (England), 50+)	*	*	*	*	*	0 (self-reported, through interview)	Poor
Liang et al., 2015	*/0 (population-based, type 2 diabetes, 40+, using glucose-lowering medication (UK))	*	*	*	*	*	*	Fair (medical records)
Hwang et al., 2015	* (population-based, type 2 diabetes)	*	*	*	*	*	0 (Self-reported through computer assisted telephone interviewing)	Poor

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Selection (out of 3)			Comparability (out of 2)		Outcome (out of 1)
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Study controls for one variable	Study controls for any additional variable(s)	
Casanova et al., 2015	0 (specific geographical area (PACA, France), glucose-lowering medication, type 2 diabetes, regional health insurance)	*	* (administrative claims data)	*	*	* (administrative claims data)
Devkota et al., 2015	0 (only those attending residency clinics, type 2 diabetes, small study size)	*	* (medical records)	*	*	* (Medical records)
Billimek et al., 2015	*/0 (type 2 diabetes, and encounter with a doctor in previous 12 months, assumed to be in a specific geographical area (California))	*	* (medical records)	*	*	* (medical records)
Al-Sayah et al., 2015	*/0 (type 2 diabetes, specific geographical area (Alberta, Canada))	*	* (self-reported)	*	*	* (self-reported)
Van Doorn-Klomberg et al., 2015	* (population-based (The Netherlands))	*	* (primary care medical records)	*	*	* (primary care medical records)
Lee et al., 2014	0 (only those visiting a specific health care centre (US), only those without diabetic complications)	*	* (medical records)	*	*	* (medical records + self-report among those without eye exam reported in medical records)

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Representativeness of the exposed cohort	Selection (out of 3)	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Comparability (out of 2)		Outcome (out of 1)	Score
					Study controls for one variable	Study controls for any additional variable(s)		
MacLennan et al., 2014	0 (those visiting an internal medicine clinic of a large, urban, county hospital that serves primarily low income, non-Hispanic African American patients)	*	*	*	*	*	*	Fair (medical records)
Buja et al., 2014	*	*	*	*	*	*	*	Good (administrative data)
Naicker et al., 2014	*/0 (specific geographical area (Eastern Ontario, Canada), aged 40+, only practices included that were willing to participate in an improvement initiative)	*	*	*	*	*	*	Fair (medical records)
Baviera et al., 2014	*/0 (specific geographical area (Lombardy, Italy), aged 40+)	*	*	*	*	*	*	Fair (administrative data)
Chen et al., 2014	*	*	*	*	*	*	0	Poor (self-reported through telephone survey)
Rim et al., 2013	*	*	*	*	*	*	0	Poor (self-reported)
Yu et al., 2013	0 (specific geographical area (Washington and Idaho, US), patients from 9 primary care practices that responded to the survey)	*	*	*	*	*	*	Fair (self-reported + medical records)

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Selection (out of 3)			Comparability (out of 2)		Outcome (out of 1)	Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Study controls for one variable	Study controls for any additional variable(s)		
Rossi et al., 2013	* (population-based (Italy), those referred to the participating outpatient clinics in 2009)	*	*	*	*	*	Fair (medical records)
Hellemons et al., 2013	* (specific geographical area (Groningen, The Netherlands), type 2 diabetes)	*	*	*	*	*	Fair (primary care medical records)
Mier et al., 2012	0 (Hispanics living in Hidalgo County, Texas, at the Texas- Mexico border (US))	*	*	*	*	0 (self-reported through interview)	Poor (self-reported through interview)
Druss et al., 2012	0 (only those with Medicaid fee-for-service, diabetes + mental comorbidity, aged below 65)	*	*	*	*	*	Fair (claims data)
Bartels et al., 2012	0 (national sample of Medicare beneficiaries (US), aged 65+)	*	*	*	*	*	Fair (claims data)
Chien et al., 2012	0 (those enrolled in a not-for-profit Medicaid-focused managed care plan, specific geographical area (Hudson valley region of New York (US)))	*	*	*	*	*	Fair (administrative data)
Kiran et al., 2012	* (specific geographical area (Ontario, Canada), aged 40+)	*	*	*	*	*	Fair (administrative claims data)

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort (out of 3)	Ascertainment of exposure (= sex)	Comparability (out of 2)		Outcome (out of 1)	Score
				Study controls for one variable	Study controls for any additional variable(s)		
Reichard et al., 2012	0 (Kansas Medicaid beneficiaries (US), working age adults, diabetes + physical disabilities)	*	*	*	*	*	Fair (administrative claims data)
Gold et al., 2012	0 (those receiving care at safety net clinic in a specific geographical area (Oregon, US), minimum number of diabetes-associated visits during study period)	*	*	*	*	*	Fair (electronic medical records)
Kilbourne et al., 2011	0 (those receiving care in Veterans Affairs mental health programs, diabetes + mental illness (US), sample size unclear)	*	*	*	*	*	Fair (medical records)
Stefos et al., 2011	0 (those seen by Veterans Affairs primary care clinics (US))	*	*	*	*	*	Fair (medical records)
Fraser et al., 2011	0 (those being invited for eye screening, specific geographical region (Hampshire, England))	*	*	*	*	*	Fair (medical records)
Williams et al., 2010	*/0 (population-based, specific geographical area (California, US), type 2 diabetes)	*	*	*	*	0	Poor (self-reported through telephone survey)
Green et al., 2010	0 (those visiting a large urban public hospital on regular basis (US))	*	*	*	*	*	Fair (administrative claims)

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Selection (out of 3)			Comparability (out of 2)			Outcome (out of 1)	
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Study controls for one variable	Study controls for any additional variable(s)	Assessment of outcome	Score	
Chen et al., 2010	0 (assessed the effect of a pay-for-performance in a preferred provider organization, specific geographical area (Hawaii, US))	*	*	*	*	*	Fair	
Gulliford et al., 2010	0 (specific geographical area (South London boroughs, England), deprived area)	*	*	*	*	*	Fair	
Tomio et al., 2010	0 (two communities in south-western Japan, attending at a regular basis, national health insurance enrollees)	*	*	*	*	*	Fair	
Wilf-Miron et al., 2010	*/0 (Maccabi Healthcare Services enrollees)	*	*	*	*	*	Fair	
Gregg et al., 2010	*/0 (those enrolled in enrolled in one of 10 US managed care plans, type 2 diabetes)	*	*	*	*	*	Fair	
Ng et al., 2010	*/0 (population-based (MEPS, US), aged 45+)	*	*	*	*	0	Poor	
Wang et al., 2010	0 (those visiting 1 of 3 hospitals/clinics included in a given time period, relatively small sample size (China))	*	*	*	*	*	Fair	

Supplemental table IV. A Modified Newcastle-Ottawa quality assessment scale to assess risk of bias. (continued)

First name, year	Representativeness of the exposed cohort	Selection (out of 3)	Selection of the non-exposed cohort	Ascertainment of exposure (= sex)	Comparability (out of 2)		Outcome (out of 1)	Score
					Study controls for one variable	Study controls for any additional variable(s)		
Lawrenson et al., 2009	0 (three general practices in Hamilton (New Zealand which may not be directly generalizable, type 2 diabetes)	*	*	*	*	0	*	Fair (primary care medical records)
Guthrie et al., 2009	* / 0 (population-based, specific geographical area (Tayside, Scotland), type 2 diabetes)	*	*	*	*	*	*	Fair (diabetes register)
Gnavi et al., 2009	0 (specific geographical area (Torino, Italy), not assumed to be generalizable because of the urban area and easy access to care)	*	*	*	*	*	*	Fair (administrative claims data)
Kirkbride et al., 2009	0 (Oregon's Medicaid program enrollees (US), working age adults)	*	*	*	*	*	*	Fair (administrative data)
Greenan et al., 2019	0 (those referred to a specific Diabetic Retinopathy Treatment Centre from the Irish National Diabetic Retinal Screening Programme)	*	*	*	*	*	*	Fair (medical records)

The categories assessed included: (1) selection, (2) comparability, and (3) outcome. Good quality was defined as three stars (*) in the selection domain, one or two stars in the comparability domain, and one star in the outcome domain. Fair quality was defined as two stars in the selection domain, one or two stars in the comparability domain, and one star in the outcome domain. Poor quality was defined as one or zero stars in the selection domain, zero stars in the comparability domain, and zero stars in the outcome domain.

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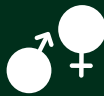
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Chapter 10

General discussion

General discussion

Diabetes is a strong risk factor for cardiovascular disease (CVD) in both sexes, with compelling evidence showing that, compared to those without diabetes, women with diabetes bear a greater relative risk for the development of major cardiovascular complications than men with diabetes.¹ The mechanisms underpinning the greater relative risk of major CVD, conferred by diabetes, in women are uncertain, and there is need for a better understanding of these sex differences. The majority of studies have assessed diabetes as a binary variable, without considering a sex differential in the risk of cardiovascular complications across the glycaemic spectrum or with increased diabetes duration. This thesis aimed to provide new insights in the disease course and the mechanisms underpinning these sex differences, with a focus on differences in diabetes management.

In this final chapter, the key findings of this thesis will be summarized and discussed, along with several aspects that should be taken into account when interpreting these key findings. Finally, a general conclusion of this thesis will be provided including several recommendations for future research.

Key findings

1. When studying sex-specific effects and sex differences, it is important to consider the possibility of sex-specific confounding, as confounders themselves may have sex-specific effects, potentially obscuring the evaluation of sex differences. **(Chapter 3)**
2. The presence of diabetes is associated with a greater relative risk of incident myocardial infarction (MI) in women than in men. However, we found no evidence of a sex difference in the association between higher levels of glycated haemoglobin (HbA1c) and the risk of MI after sex-specific adjustments for confounding.² **(Chapter 4)**
3. Diabetes is associated with an increased risk of COVID-19 mortality in both sexes, as it is for influenza/pneumonia and coronary heart disease (CHD). However, unlike fatal CHD, there are no sex differences in the effects of diabetes on death from COVID-19 or influenza/pneumonia. In contrast to the results of **chapter 4**, where we found no sex differences in the association between levels of glycaemia and incident MI, prediabetes and higher levels of HbA1c were more strongly associated with fatal CHD in women than in men. **(Chapter 5)**
4. Longer duration of type 2 diabetes is associated with increased risk of incident CVD, including MI and stroke, in both sexes, without evidence for a sex difference in the magnitude of the associations. **(Chapter 6)**
5. Sex differences in risk factor assessment, treatment and control of Dutch individuals with diabetes are small. Women with diabetes were found to have slightly different cardiometabolic risk profiles compared with men, and a substantially higher BMI. Cardiovascular risk

management should be improved for both sexes. Effective weight loss strategies are needed to reduce the high levels of BMI in both sexes, and especially in women.^{3,4} (**Chapter 7 & 8**)

6. No consistent pattern in the assessment of cardiovascular risk factors and diabetes-related screening activities favouring women or men was found on a global scale, suggesting that disparities in risk factor assessment and screening activities do not account for the higher relative risk of major CVD, conferred by diabetes, in women compared with men. (**Chapter 9**)

Sex, diabetes, and disease risk

Diabetes is defined by an, arguably, arbitrary threshold value of fasting blood glucose, 2-h postload glucose, and/or HbA1c. However, evidence suggests that there is a progressive association between various measures of dysglycaemia, both above and below this arbitrary threshold, and the risk of major cardiovascular events.⁵⁻⁸ As highlighted in **chapter 2** of this thesis, several studies have observed that women have a worse progression of several cardiovascular risk factors in their transition from normoglycaemia to diabetes. In other words, women's cardiometabolic profile has to deteriorate further than men to develop diabetes.⁹⁻¹² It has also been observed that women, on average, have a 2-year longer pre-diabetic phase compared to their male counterparts.¹³ Given these findings, it has been hypothesized that the observed sex differences in the diabetes-related risk of CVD reflect a continuous process that may already emerge early across the dysglycaemic spectrum, rather than sex differences in the physiological effects of diabetes itself.^{9,14} However, sex differences across the glycaemic spectrum, in the association with cardiovascular events, have rarely been assessed and were inconclusive. Therefore, in **chapter 4** of this thesis, we aimed to study the sex-specific associations, and the sex differences, between various levels of dysglycaemia (prediabetes, undiagnosed diabetes, diagnosed diabetes) and levels of HbA1c with the risk of incident MI. Although we did find diabetes to be associated with a greater relative risk of MI in women compared to men, we found no evidence of sex differences across the glycaemic spectrum. Instead, the observation that the sex-specific associations disappeared after adjusting for sex-specific confounding may suggest that other sex-specific pathways are involved.²

Sex differences in diabetes diagnosis

At present, different diagnostic tools can be used to screen for prediabetes and diabetes, including fasting blood glucose measurements, the oral glucose tolerance test (OGTT), and measurements of HbA1c.^{8,15} Two definitions of prediabetes are frequently used in clinical practice.⁸ One definition comes from the American Diabetes Association (ADA), and the other from the International Expert Committee (IEC) and the World Health Organization (WHO).⁸ Both definitions include measurements of fasting blood glucose, OGTT measurements, and/or levels of HbA1c; the ADA using lower cut points compared with the IEC/WHO criteria.⁸ A systematic review observed that there was only limited overlap in the detection of prediabetes according to the criteria of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and elevated HbA1c.¹⁵ Similar results were reported by the population-based KORA study from Germany, with only a small overlap of individuals with IFG, IGT, and raised HbA1c levels using ADA criteria.¹⁶ In other words, different measures of dysglycaemia identified different subpopulations with

different glycaemic abnormalities (i.e. 47% of individuals with impaired fasting glucose had no other glycaemic abnormalities). The KORA study also showed different diagnostic patterns for men and women. Men were more likely to be diagnosed with prediabetes via the IFG criteria, whereas women were more likely to be diagnosed with prediabetes because of raised HbA1c levels or IGT.¹⁶ To my knowledge, the KORA study is one of the first studies to report that the distribution of IFG, IGT, and elevated HbA1c differs between women and men, which might suggest different underlying pathophysiological mechanisms and causal pathways. Additionally, several systematic reviews have also suggested that individuals with combined IGT and IFG have highest risk of progressing to diabetes, while elevated levels of HbA1c and isolated IFG have lower progression rates.^{15,17} Combined, these observations suggest that different pathophysiological mechanisms may underlie the development of prediabetes and progression to diabetes. Indeed, IFG is characterized by increased hepatic insulin resistance, pancreatic β -cell dysfunction and/or reduced β -cell mass, modified glucagon-like peptide-1 secretion, and altered secretion of glucagon, while the underlying pathophysiology of impaired glucose tolerance seems to include increased peripheral insulin resistance, close to normal hepatic insulin sensitivity, increased loss of β -cell function, and increased secretion of glucagon.¹⁸ Subsequently, these pathophysiological mechanisms may differ between women and men.

Sex differences in fatal coronary heart disease

In **chapter 6** of this thesis, we assessed the sex-specific effects and sex differences in the association between various measures of glycaemia and fatal CHD. In contrast to the results of **chapter 4**, we found that prediabetes and higher levels of HbA1c were more strongly associated with the risk of fatal CHD in women than in men. Explanations for this discrepancy remain speculative, but may include differences in the ICD-10 based definitions of MI and CHD being in part different disease entities. Furthermore, in **chapter 4**, we included both incident non-fatal and fatal events, while in **chapter 6**, we studied fatal events. In contrast to incident MI, death from CHD is a composite measure including (1) incidence (primary CHD event); (2) mechanisms of recovery and damage control; (3) treatment in the acute phase, and; (4) long-term secondary treatment for the prevention of recurrent events. Diabetes was previously found to be more strongly associated with fatal than non-fatal MI,¹⁶ which might suggest more severe coronary atherosclerosis, impaired angiogenesis, or a differential ischemic responses from the myocardial tissue in those with diabetes compared to those without.^{19,20} At present, it is well known that diabetes enhances thrombogenesis and lowers fibrinolytic sensitivity.²¹ It has also been observed that women with type 2 diabetes have more dense clots and more severe compromised fibrinolysis than men.²² Diabetes has also been associated with impaired development of collaterals within the coronary circulation, which may in part explain the more severe outcomes of those with diabetes after an acute MI.²³ In this respect, women with obstructive coronary artery disease (CAD) have been found to have significantly lower rates of collaterals as compared to men. Since collateral formation is a protective mechanism after an obstructive ischemic event, women might be more likely to have poorer outcomes following CAD than men.²⁴ Sex differences in the treatment of acute CHD and secondary prevention of recurrent events have been reported as well.^{25,26} However, these sex

differences might not be specific to those with diabetes, and therefore less likely to be explanatory for the sex differences in diabetes-related cardiovascular risk.

Disparities in the uptake and provision of healthcare

As stated in the **introduction** of this thesis, and as discussed in **chapter 2**, the mechanisms underpinning the excess risk of major CVD consequent to diabetes in women is multifactorial and may include disparities in the uptake and provision of healthcare. Sex disparities in the detection and management of diabetes may broadly occur at four levels: (1) diagnostic delay; (2) screening and monitoring of cardiovascular risk and diabetes-related complications; (3) primary and secondary prevention when needed, including promotion of a healthy lifestyle, psychological support, and pharmacological interventions; and (4) achievement of treatment targets according to the guidelines, and in agreement with the patient. At all four levels, both patient- and provider factors, and, sex and gender components, may contribute to the origin of these disparities.

Sex disparities in the diagnostic delay of diabetes

Prevention and delay of diabetes-related complications, including cardiovascular events, may depend on the early diagnosis of diabetes and subsequent interventions.²⁷⁻²⁹ However, the exact moment at which an individual develops diabetes is practically impossible to determine, and, as a consequence, diabetes may remain undetected for many years.²⁷ Globally, an estimated 30% to 50% of individuals with type 2 diabetes are unaware of having the disease, thereby preventing them from receiving the necessary care.²⁷ The prevalence of undiagnosed diabetes in adults living with diabetes varies widely across regions, with higher prevalences in African countries (60%) and lowest prevalence in the Northern American and Caribbean Region (38%). Approximately 41% of adult Europeans with diabetes are currently undiagnosed.²⁷ When stratified by income, low-income countries have the highest prevalence of undiagnosed diabetes. However, the proportion of individuals with undiagnosed diabetes in high-income countries was still estimated at 38%.²⁷ As a result of this diagnostic delay, individuals with diabetes may present with diabetes-related complications (i.e. diabetic retinopathy) at the time of diagnosis.²⁷ The EUROHEART Survey, a multicentre study including 1,920 participants with CAD without known history of diabetes, found that one-third of the participants had undiagnosed diabetes, while over 35% of the participants either had IGT or IFG.^{28,30} A Danish cross-sectional study, using data from the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project, reported that 35% of newly diagnosed type 2 diabetes patients had micro- or macrovascular complications at the time of diagnosis. Male sex was associated with a higher prevalence of macrovascular complications, while no sex differences were found for microvascular complications.³¹ A population-based cohort, including 51,526 individuals with newly diagnosed type 2 diabetes, reported a 19% prevalence of diabetic retinopathy at first retinal screening following diabetes diagnosis, and men were more likely to present with retinopathy at first screening than women.³² Given that the duration of detectable diabetic retinopathy has been estimated at several years, there may have been a significant delay in the diagnosis of diabetes in those presenting with diabetic retinopathy at the time of diagnosis.^{33,34}

To my knowledge, sex disparities in the diagnostic delay of diabetes have not been studied extensively. Several studies have shown that women experience a relatively greater increase in cardiovascular risk factor levels and endothelial dysfunction in the transition from normal glycaemia to diabetes, as opposed to their male counterparts,¹ which may reflect a longer diagnostic delay. However, the relatively greater increase in cardiovascular risk factor levels was also observed in women with prediabetes, suggesting that the more adverse changes in cardiovascular risk factors already occur before the onset of diabetes and not necessarily as a consequence of a longer diagnostic delay.¹⁴ Several studies have looked at the prevalence and severity of diabetic retinopathy at the time of diagnosis, as a marker of diagnostic delay, and these studies either found no sex difference in the prevalence of diabetic retinopathy or reported (slightly) higher prevalences in men.^{31–33,35,36} Studies focusing on sex as a determinant of diabetic retinopathy have been inconsistent, and it is hitherto unclear whether both sexes experience the same risk of developing diabetic retinopathy.^{35,37–41} Therefore, it might be arguable whether diabetic retinopathy is a good marker for studying sex disparities in diagnostic delay. A population-based register study, including 95,000 individuals with type 2 diabetes from Scotland, observed that earliest HbA1c levels after diabetes diagnosis were broadly similar in women and men, indicating that there was no difference in diagnostic delay between the sexes.⁴² In contrast, a Canadian cross-sectional population-based study, including 197,998 individuals with diabetes, reported that women had a lower likelihood of a diagnostic delay than men based on the observation that a higher proportion of men had HbA1c levels >8.0% at the time of diagnosis.⁴³ These observations contribute to the hypothesis that women do not have a longer diagnostic delay compared to their male counterparts. Nevertheless, studies focusing on sex disparities in the diagnostic delay of diabetes are limited, and there is no consensus among researchers on how to correctly estimate the diagnostic delay.^{33,34}

Sex disparities in the assessment of cardiovascular risk factors and screening for diabetes-related complications

In **chapter 9**, we studied sex disparities in the assessment of cardiovascular risk factors and screening for diabetes-related complications, concluding that there is no consistent pattern favouring women or men on a global scale, thereby suggesting that disparities in risk factor assessment and screening activities in those with diabetes do not account for the higher relative risk of diabetes-related CVD previously found in women compared with men. Nonetheless, sex disparities on a national or more regional level could be important obstacles for further improving diabetes management to the benefit of both sexes. Therefore, national and more local initiatives, such as clinical audits (i.e. the UK National Diabetes Audit) and electronic healthcare registries (i.e. the Dutch Julius General Practitioners Network), are important initiatives to provide researchers with the opportunity to identify the existence of any sex disparities on a smaller scale. These initiatives not only enable researches to study sex disparities in the assessment of cardiovascular risk factors and screening for diabetes-related complications on a more national and regional level, but also enables researchers to study the existence of disparities in specific subgroups (i.e. type of diabetes, ethnicity, insurance coverage, age, gender-related factors).

Sex disparities in treatment and achievement of intermediate outcomes

The assessment of cardiovascular risk factors and screening for diabetes-related complications in those with diabetes is one of the first steps in guiding treatment decisions. No consistent pattern in sex disparities favouring either women or men in the assessment of cardiovascular risk factors were identified in **chapter 9**. However, we argue that other factors related to the uptake and provision of healthcare, such as disparities in treatment and attainment of intermediate outcomes, may still be involved in explaining the observed sex differential. Over the previous years, many studies have assessed sex disparities in the treatment and control of cardiovascular risk factors in populations with and without diabetes, and results appear to be mixed regarding the presence, magnitude, and direction of these sex disparities.¹ Nonetheless, a detailed overview of studies assessing disparities in treatment and risk factor control is largely missing, and the extent to which these disparities may in part explain the observed sex differences in the diabetes-related risk of CVD remains uncertain. In addition, sex differences in the treatment and control of cardiovascular risk factors might not be specific to those with diabetes, and therefore less likely to be explanatory for the sex differences in cardiovascular risk conferred by diabetes.

Some studies have also observed sex disparities in risk factor control among those with diabetes receiving pharmacological interventions.^{1,44-49} In other words, even when treated ‘similarly’, women may be less likely to achieve treatment targets compared to their male counterparts. For example, both Dutch cohorts included in this thesis, showed that, among those receiving lipid-lowering medication, women had a lower likelihood of achieving LDL targets than men.^{3,4} Similar results were observed by several other studies.⁴⁴⁻⁴⁷ Explanations that underlie these observations may include sex differences in (1) risk factor levels at the start of pharmacological therapy or change of risk factor levels; (2) pharmacological treatment regimens; (3) adherence and persistence to pharmacological therapy; (4) pharmacokinetics and pharmacodynamics, and; (5) lifestyle and psychosocial related-factors. Sex differences in pharmacological treatment regimens and differences in adherence and persistence are briefly discussed in the following two paragraphs.

Pharmacological treatment regimens

Back in 1997, a meta-analysis showed that the pattern of blood pressure-lowering medication prescription differed between men and women. Women with hypertension were more likely to be prescribed diuretics and less likely to receive β -blockers, ACE-inhibitors, or calcium-blockers than men.⁵⁰ A recently published meta-analysis, including individuals at high risk of (recurrent) cardiovascular events in primary care, reported similar differences in medication prescription, with women being more often prescribed diuretics, and less likely to use ACE-inhibitors than their male counterparts.⁵¹ A retrospective cohort study, including 88,000 US beneficiaries who filled a statin prescription following hospitalization for MI, reported that women were less likely to be prescribed a high-intensity statin than men.⁵² Similar results were reported by a nationwide register study, including 5,693 individuals with or at high risk of CVD. Women were less likely to receive a statin prescription (67% vs. 78%), and less likely to receive the guideline-recommended statin intensity (37% vs. 45%).⁵³ This study showed similar sex disparities in the guideline-recommended statin prescription in a subgroup of individuals with diabetes.⁵³ Reasons for a sex differential in

pharmacological treatment regimens and the impact of different treatment regimens on CVD risk require further study. Reasons for sex differences in treatment regimens may include a variety of explanations including, but not limited to, differences in experiencing adverse effects, severity of disease, comorbidities, treatment effectiveness, provider or patient preferences, reluctance to take certain drugs, provider perception of anticipated patient tolerance, and patient-provider interactions.^{51,54,55} To my knowledge, sex disparities in pharmacological treatment regimens (i.e. start of the intervention, type of medication prescription, dosing, and up-titration), and its determinants, have not been extensively evaluated among populations with diabetes, and this needs to be addressed in future research.

Adherence to pharmacological therapy

Non-adherence to cardiovascular drugs is a widely recognized and challenging problem in both sexes.¹ The World Health Organization (WHO) has defined non-adherence as '*the primary reason for suboptimal benefit of therapy*'.⁵⁶ Non-adherence undermines the effectiveness of any pharmacological intervention, and has been associated with increased risk of cardiovascular events and premature mortality.^{57,58} Despite non-adherence being an important driver of suboptimal benefit of therapy, underlying determinants, including sex, have not been fully identified. Several studies have identified female sex as a negative predictor of therapy adherence, however the impact of sex on adherence may vary per drug type, setting, and underlying disease.⁵⁸⁻⁶⁴ For example, a meta-analysis, including 53 studies, observed that men were 10% more likely to be adherent to statin therapy for primary or secondary prevention, whereas a systematic review of glucose-lowering medication showed that sex is not a predictor of non-adherence.^{60,62} A retrospective cohort study, including over 3 million US individuals, showed that individuals who started a statin following an acute MI were less likely to be non-adherent, whereas those with diabetes without CHD were more likely to be non-adherent, compared to those without a history of CHD or diabetes, illustrating the difference of drug adherence in populations with different clinical characteristics.⁵⁹

At present, there is a wide range of methodologies used to study non-adherence and its underlying determinants. However, consensus on how to best measure non-adherence is largely lacking, in part because non-adherence includes distinct behaviours across different phases of non-adherence (initiation, implementation, and discontinuation).^{62,65-68} This lack of consensus precludes direct comparison between studies.^{62,65,66} A systematic review and meta-analysis, studying blood pressure-lowering medication adherence in individuals with treatment resistant hypertension, suggested that the type of methodology used to assess non-adherence had significant impact on non-adherence estimates across studies.⁶⁹ Highest rates of non-adherence were found in studies using direct measures of non-adherence (i.e. measurement of drug compounds in body fluids).⁶⁹ Although different methodologies yield varying estimates of non-adherence, each type of methodology has its own strengths and limitations, thereby providing different forms of information that may contribute to our understanding of non-adherence. For example, subjective measures of non-adherence (i.e. self-reported through questionnaires) are prone to many biases, but also offers researchers the opportunity to study underlying reasons

of non-adherence (i.e. underestimation of disease risk, experience and perception of side effects) in a way objective methodologies cannot.⁶⁹ Many objective measures of non-adherence (i.e. refill data) do not directly measure medication-taking behaviour, but provide information about medication-collection behaviour.^{62,70} Even the Medication Event Monitoring System (MEMS) does not directly measure medication-taking behaviour, but rather measures package opening.⁶² Direct measures of medication-taking behaviour, include direct observation of drug taking and measuring drug compounds in body fluids. Nonetheless, the use of direct observations is mostly impractical in most research settings, whereas measurement of drug compounds in body fluids only gives information about the short-term drug usage.⁷¹ Given the wide variety of methodologies used to study non-adherence and given that each type of methodology contributes to our understanding of non-adherence in a different way, future studies should include a combination of non-adherence measures to improve our understanding of non-adherence and to identify determinants of non-adherence including sex.⁶⁹

Sex differences in biology

Although men and women are alike in many ways, they are biologically different. For that reason, as briefly discussed in **chapter 2**, the underlying mechanisms of the observed sex differential may very well be due to biological differences between men and women. Given that these biological differences are largely beyond the scope of the work presented in this thesis, I will only briefly touch upon them with a focus on differences in (1) fat metabolism and body anthropometry, and; (2) sex hormones.

Differences in fat metabolism and body anthropometry

Given the observation that, on average, women with (newly diagnosed) diabetes have a higher BMI than men, and given the pronounced differences in fat metabolism between men and women in general, it has been hypothesized that sex differences in fat metabolism and body anthropometry might play a significant role in explaining the observed sex differential in diabetes-associated cardiovascular risk.^{10,42,43,72,73} While adipose tissue serves as the primary site for energy storage, it is also one of the largest endocrine organs in the human body.⁷⁴ Although adipose tissue has been associated with increased risk of cardiometabolic disorders, such as type 2 diabetes and CVD, it is becoming increasingly apparent that different types of adipose tissue exert different metabolic effects.¹ While subcutaneously stored peripheral (lower body) fat has been linked to lower cardiometabolic risk, abdominal and ectopic adiposity are associated with increased insulin resistance, postprandial glucose, free fatty acids, triglycerides and low-grade chronic inflammation.^{75,76} In addition, subcutaneously stored fat in the abdominal region may exert different metabolic effects in comparison to subcutaneously stored lower body fat.⁷⁷ Given the observation that, on average, premenopausal women are more likely to store fat subcutaneously in the gluteofemoral region (lower body), and men more likely to store fat in the abdominal region, it has been hypothesized that sex differences in the preferred location of fat storage may provide women with more cardiometabolic reserves.¹² As a consequence, men need to gain less weight and progress more quickly to insulin resistance and diabetes, whereas women need to put on more weight and other cardiovascular risk factors may need to deteriorate further before reaching

the amount of abdominal and ectopic fat required to develop type 2 diabetes.¹ Data from the UK Clinical Practice Research Datalink supports this hypothesis by showing that differences in weight, blood pressure, and levels of HDL at the time of diabetes diagnosis were larger in women than in men, when compared to those without diabetes.¹⁰ Whereas men tend to be diagnosed with diabetes at lower BMI, a recently published Mendelian randomization study showed that BMI is more strongly associated with the development of type 2 diabetes in women compared to men.⁷⁸ Some studies have also suggested that the strength of the association between different types of adiposity and cardiometabolic risk may differ between women and men, with accumulation of visceral adiposity being particularly detrimental among women.^{1,77,79-81} Given the pronounced differences in fat metabolism and body anthropometry between women and men, and the complexity of fat metabolism itself, more research is needed to improve our understanding of the sex-specific effects of adipose tissue. Detailed information of body composition and body fat distribution has been provided by the UK Biobank using DEXA scans and MRI.^{82,83} These data provides researchers with the unique opportunity of studying the sex-specific impact of fat storage subtypes and the relative distribution of adipose tissue on the development of cardiometabolic disease.

Sex hormones, diabetes, and cardiovascular disease

Women and men are fundamentally different when it comes to the expression of sex hormones, and these sex hormones underlie many biological differences between women and men. For that reason, the excess risk of diabetes-associated CVD in women could in part be due to hormonal differences. Sex hormones are involved in many pathways beyond the reproductive system, including those related to cardiovascular health, obesity, glucose metabolism, inflammation, pharmacodynamics and pharmacokinetics, and it has been shown that these hormones exert different effects in women and men.^{84,85} At present, it is well recognized that women develop CVD on average 7 to 10 years later than men, which resulted in the hypothesis that the exposure to oestrogens during the reproductive period of life has a cardioprotective effect in women.^{86,87} This hypothesis is strengthened by the observation that women with premature or early menopause are at increased risk of CVD, compared to those with normal or late menopause.⁸⁸⁻⁹⁰ The amount of adipose tissue and body fat distribution are associated with sex hormones in a bidirectional fashion in both sexes. White adipose tissue is the primary source of oestrogen in men and postmenopausal women.⁸⁵ Postmenopausal women have been observed to shift from a 'pear-shaped' fat distribution prior to menopause, with fat storage in the gluteofemoral region, to a more android fat distribution with abdominal adiposity ('apple-shaped distribution'), which is mostly seen in men. In men, abdominal obesity has been associated with low levels of androgen and increased levels of oestrogens.⁸⁵ Testosterone has been reported to have an ambivalent role in women and men. Low levels of testosterone in men have been associated with impaired glucose homeostasis and type 2 diabetes, whereas women with higher levels of testosterone are at increased risk of developing type 2 diabetes and have worse cardiovascular risk profiles.^{85,91-93} Studying the sex-specific impact of reproductive hormones is complex, especially given the cyclic fluctuations in hormone levels among women. Therefore, the impact of sex hormones on the

excess risk of cardiovascular complications, as a consequence of diabetes, are uncertain and require further study.

Aspects to take into consideration when interpreting the findings of this thesis

Low response rate and 'healthy volunteer' bias in the UK Biobank cohort

Half the studies presented in this thesis made use of data from the prospective UK Biobank cohort. One of the strengths of well-designed cohort studies, including extensive phenotypic (and genotypic) detail of the participants, is that they allow researchers to study the association between many determinants and health-related outcomes.⁹⁴ In many instances, randomized-controlled trials are not ethically or practically feasible, and prospective cohort studies may offer good alternatives.⁹⁴ However, one of the limitations of prospective cohort studies, like the UK Biobank, is that these cohorts are prone to selective non-response. Participants are required to fill in long questionnaires, undergo extensive physical exams, and are required to travel to the research facilities, all which may be too burdensome for many reasons. The 5.5% response rate of the UK Biobank was low, with evidence of a 'healthy volunteer' bias.^{94,95} The low response rate, combined with evidence of a 'healthy volunteer' bias, has led to much debate about the generalisability of the determinant-outcome relations within the UK Biobank.⁹⁴⁻¹⁰⁵ It has been argued, however, that generalisability of the determinant-outcome relations can be assured because the determinants included in the UK Biobank showed sufficient variance and the study size is large.⁹⁴ It has also been argued that prospective studies do not need to be representative to the whole population to produce generalizable results into etiology.¹⁰⁵ For example, other cohort studies that included highly selected populations, such as the Framingham Heart Study, the British Doctor's Study, and the Nurses' Health Study, have provided many insights on health and disease that go well beyond the highly selected populations included in these cohorts^{94,105} Nonetheless, given that sex differences in the cardiovascular consequences of diabetes are not unique to the UK, and the notion that the UK Biobank is biased towards the more health conscious part of the UK society, it is important to undertake complementary work in other study populations as well.

Type 1 diabetes

This thesis mainly focused on diabetes in general, while acknowledging that most individuals with diabetes would have been diagnosed with type 2 diabetes. Therefore, the results of this thesis will mostly be applicable to those with type 2 diabetes. Nonetheless, as with type 2 diabetes, there is accumulating evidence that type 1 diabetes is a stronger risk factor for cardiovascular complications in women than in men.¹⁰⁶⁻¹⁰⁹ As with diabetes in general, the exact mechanisms underpinning the excess cardiovascular risk in women as a consequence of type 1 diabetes are uncertain and need further study.

Mathematical explanation

Apart from disparities in the uptake and provision of healthcare and intrinsic differences in biology, there may also be a simple mathematical explanation as to why women, compared to

men, experience higher relative risk of diabetes-related cardiovascular complications. Women generally have a lower absolute risk of macrovascular disease than men. Consequently, a similar increase in cardiovascular events, in the consequence of diabetes, should result in a higher relative effect in women.^{110,111} This mathematical explanation is supported by the observation that sex differences in relative risks for CVD decrease with increasing age, that is, as the absolute risk of CVD increases.^{111,112} However, meta-analyses of sex differences in the association between systolic blood pressure and BMI with CHD showed no sex differences in relative risks.^{113,114} Thus, the association between cardiovascular risk factors and CVD does not inevitably result in a higher relative risk in women. In addition, some studies have shown that women with type 1 diabetes have nearly the same absolute CVD risk as observed in men, while having lower baseline rates.¹¹⁵⁻¹¹⁸ In other words, although women without type 1 diabetes have fewer CHD events than men, this advantage is lost in the context of type 1 diabetes. Additionally, a large meta-analysis, studying sex differences in the association between type 1 diabetes and all-cause and cause-specific mortality, reported that large sex differences were found in studies with little sex differences in baseline mortality and studies in which baseline mortality rates were higher in women than in men.¹⁰⁶ Thus, it seems unlikely that the finding of a greater relative risk of major CVD associated with diabetes in women, compared with men, is an inevitable consequence of women's lower absolute rates, compared with men.^{106,110,111}

Conclusion and recommendations for future research

While progress has been made towards understanding the underlying mechanisms of women's higher relative risk of diabetic cardiovascular complications, many uncertainties remain. Future research to understand these mechanisms would contribute to more awareness of the sex- and gender-specific risk factors, and could ultimately result in more personalized diabetes care to reduce the burden of CVD in women and men. Reflecting on the key findings of this thesis and the topics discussed in the discussion, several recommendations for future research will be presented in the following paragraph and subsequently summarized in figure 1.

Recommendations for future research

The numbers of the 'recommendations for future research' refer to the numbers presented in figure 1.

1 + 2. Majority of the work presented on sex differences in the risk of diabetes-related macrovascular disease has focussed on individuals with established diabetes. However, sex-specific effects and sex differences in the underlying pathophysiology and aetiology of diabetes have been less well studied. Given the observation that the underlying pathophysiological mechanisms of prediabetes and diabetes might differ between the sexes, it may be worthwhile to take a step back and study sex differences in the causal pathway of diabetes itself.

- 3.** Albeit not yet extensively studied, differences in the sex-specific distribution of IFG, IGT, and elevated HbA1c have been reported.¹⁶ Future studies are required to study whether these separate markers of glucose homeostasis differentially relate to the progression of type 2 diabetes and subsequent development of cardiovascular complications in women and men.
- 4.** Prevention and delay of diabetes-related complications, including cardiovascular events, depend on the early diagnosis of diabetes and subsequent interventions.²⁷⁻²⁹ Nonetheless, many individuals with diabetes are unaware of having the disease²⁷, and it is uncertain whether men and women have different lengths of diagnostic delay. Studies focusing on sex disparities in the diagnostic delay of diabetes are limited, and there is no consensus among researchers on how to correctly estimate the diagnostic delay. However, prospective cohorts and (national) biobanks, preferably with repeated measurements over time, may offer new opportunities for future research. For example, linking repeated measurements of glucose metabolism in study settings to electronic healthcare data may offer researcher the opportunity of measuring the time between an abnormal measurement indicating diabetes and the date of diabetes diagnosis recorded in the corresponding health record.
- 5 + 7.** At present, many studies have assessed sex disparities in the treatment of cardiovascular risk factors and achievement of risk factor control. However, a comprehensive overview of these studies is largely missing, and the extent to which these disparities may in part explain the observed sex differences in diabetes-related cardiovascular risk remains uncertain. Therefore, as a future study it would be useful to perform a systematic review to summarize the findings of the existing studies and potentially elucidate gaps for further research.
- 6.** Optimal adherence is essential in the successful management of diabetes in both sexes. Identifying and understanding sex differences in medication adherence is of major importance to be able to further improve healthcare in both women and men. Since there is no golden standard for the assessment of non-adherence, and given that the different type of methodologies harbour different forms of information, new studies should present and compare various measurement approaches including direct and indirect measures of non-adherence.⁶⁹ Furthermore, when studying sex differences in medication adherence, one might consider to compare adherence in populations with different clinical characteristics to determine whether the extent of sex differences in non-adherence are different in those with diabetes compared to those without diabetes.

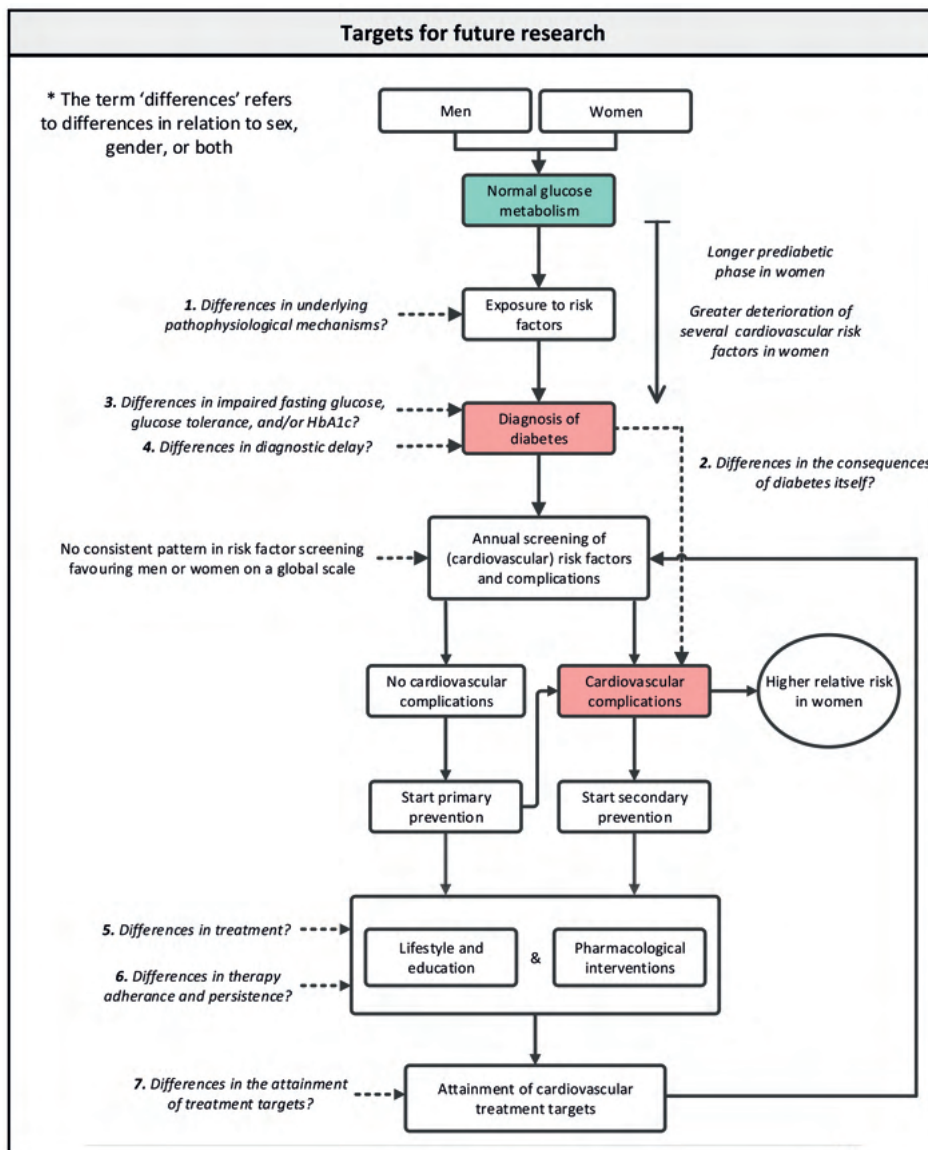


Figure 1. Recommendations for future research. The mechanisms underpinning the excess risk of major cardiovascular disease consequent to diabetes in women is multifactorial and may include disparities in biology and disparities in the uptake and provision of healthcare. While progress has been made towards understanding these underlying mechanisms, many uncertainties remain. Therefore, future studies are needed to improve our understanding of these underlying mechanisms. Potential differences between women and men may occur throughout the pathway—starting with healthy men and women being exposed to certain risk factors, at some point being diagnosed with diabetes, and eventually developing cardiovascular complications. The green-coloured box displays normal glucose metabolism, and the red-coloured boxes display negative events (i.e., type 2 diabetes, cardiovascular complications) irrespective of the sexes. The numbers presented in the figure refer to the section ‘recommendations for future research’. (Figure adapted from de Ritter et al., 2020¹).

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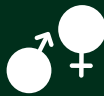
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Addenda

Summary

Nederlandse samenvatting

Dankwoord

About the author

List of publications

Summary

Sex and gender are fundamental drivers of health and there are sex and gender differences across many biomedical areas. For example, there is compelling evidence showing that diabetes is a stronger risk factor for the development of major cardiovascular complications in women than men. The mechanisms underpinning this sex difference have yet to be unravelled. The overarching objective of this thesis was to provide further insight in the mechanisms underpinning the sex differential observed in the risk of macrovascular disease consequent to diabetes.

While the work presented in this thesis has sex and gender elements, the term 'sex' is used to improve readability.

Sex differences in both biological factors as in the uptake and provision of health care may contribute to women's higher relative risk of diabetic vascular complications. In **chapter 2**, an overview is provided of the current knowledge regarding the role of sex differences in both biological factors, with a specific focus on differences in adipose tissue, and management of diabetes.

In **chapter 3**, we provide an overview of several statistical methods that can be used to obtain sex-specific estimates and estimates of sex differences. Although sex-specific analyses are increasingly performed, they typically dismiss the potential impact of sex-specific confounding, that is, sex differences in the impact of confounders on the sex-specific risk factor – disease estimates. This potentially leads to erroneous conclusions. Common statistical approaches to assess sex differences in risk factor – disease associations are (1) stratification by sex and (2) the use of a single interaction term with sex. In the first approach, associations are studied in separate strata for men and women, and, as such accounts for sex-specific confounding. However, as two models are used, estimates of sex differences cannot be extracted from the same model. In the second approach, the single interaction model, an interaction term between sex and the risk factor of interest is included in the model, together with potential confounders. The advantage of the second approach is that estimates of sex differences can be extracted from the same model. However, the second approach does not adjust for sex-specific confounding. This problem can be circumvented by a third approach, the full interaction model, in which interaction terms between sex and each variable are included the model. Using this approach, one adjusts for sex-specific confounding whilst also being able to extract sex-specific effects and sex differences from the same model. Using data from the UK Biobank, including 471,929 participants with no history of CVD, we demonstrated that the estimates of sex differences could be biased if sex-specific confounding is not considered in the model or accounted for through stratification. As such, we recommend the use of a full interaction model including interaction terms between sex and each of the variables in the model.

While diabetes has shown to be a stronger risk factor for myocardial infarction (MI) in women than men, it is unknown whether sex differences exist across the glycaemic spectrum. In **chapter 4**, we examined the association between diabetes status (no diabetes, prediabetes, undiagnosed

diabetes, and diagnosed diabetes) and glycated haemoglobin (HbA1c) with the risk of MI. Data was used from 471,399 (56% women) individuals without CVD included in the UK Biobank. Sex-specific incidence rates were calculated by diabetes status and across levels of HbA1c, using Poisson regression. Cox proportional hazards analyses estimated sex-specific hazard ratios (HR) and women-to-men ratio of HRs by diabetes status and HbA1c for MI during a mean follow-up of 9 years. Although the incidence of MI was considerably higher in men than women for diabetes status and across levels of HbA1c, the presence of previously diagnosed diabetes was associated with a greater relative risk of MI in women than men. Prediabetes was associated with an increased risk of MI in both sexes, with evidence for stronger effects in women than men. However, this sex difference attenuated to unity and was no longer statistically significant in analyses that also accounted for sex-specific confounding effects. Similarly, whilst our analyses that did not account for sex-specific confounding showed that the relationship between HbA1c and the risk of MI was stronger in women than in men, accounting for sex-specific confounding demonstrated that a 1% increase in HbA1c was associated with a 18% greater risk of MI in both sexes.

Individuals with diabetes are also at increased risk of poor outcomes in Coronavirus disease 2019 (COVID-19), including death. Whether the excess risk of COVID-19 mortality associated with impaired glucose tolerance and diabetes is different between women and men is uncertain. In **chapter 5**, we used data from the UK Biobank to investigate the sex-specific associations, and sex differences, between diabetes status, HbA1c, and risk of COVID-19 mortality. As comparison, we also examined sex-specific associations and sex differences of death by influenza/pneumonia, a major cause of death from respiratory disease prior to the COVID-19 pandemic, and fatal coronary heart disease (CHD), a condition for which sex differences are well established. Diabetes was found to be associated with greater risk of death from COVID-19 (HR 1.52 in women vs. 1.73 in men), influenza/pneumonia (HR 2.06 in women vs. 1.80 in men), and CHD (HR 3.17 in women vs. 1.93 in men), in both sexes. No statistically significant sex differences were found for the association of diabetes and HbA1c with COVID-19 or influenza/pneumonia mortality. Prediabetes, diabetes, and HbA1c were more strongly associated with fatal CHD in women than men. There are no sex disparities in the effects of diabetes on death from COVID-19 or influenza/pneumonia.

In **chapter 6**, we examined whether there are sex differences in the association of diabetes duration with the risk of CVD, and separately for MI and stroke. Data were used from 18,961 (40% women) individuals with type 2 diabetes without a history of CVD in the UK Biobank. Sex-specific incidence rates were calculated by diabetes duration, using Poisson regression. Cox proportional hazard analyses estimated multiple-adjusted sex-specific HRs and women-to-men RHRs by diabetes duration categorized (< 5; ≥ 5-< 10; ≥10 years) and per 5-year increase in duration for CVD, and separately for MI and stroke. This study found that duration of diabetes is independently associated with a greater risk of CVD, MI, and stroke, in women and men, without evidence of sex differences in the strength of the association. In both sexes, a 5-year increase in diabetes duration was associated with an approximately similar excess risk of CVD, MI, and stroke of about 20%.

In **chapters 7 and 8**, we studied sex disparities in the management of diabetes and cardiovascular complications using two Dutch cohorts: the Julius General Practitioners Network (JGPN) (**chapter 7**) and the Diabetes Pearl Cohort (**chapter 8**). The JGPN is a large ongoing dynamic cohort of primary care patients that anonymously extracts routine healthcare data from electronic records at one of the included general practices in Utrecht and vicinity, the Netherlands. Cross-sectional data from 12,512 individuals with diabetes from 2013 were used to assess sex differences in risk factor levels, assessment, treatment, and control. The Diabetes Pearl cohort is an observational cohort involving eight Dutch academic medical centres including 6,637 individuals with type 2 diabetes receiving primary or secondary/tertiary care. Overall, we found that sex differences in risk factor assessment, treatment, and control of Dutch individuals with diabetes are small. Women with diabetes had slightly different cardiometabolic risk profiles compared with men and a substantially higher BMI.

Further insight in sex disparities concerning the detection of cardiovascular risk factors and diabetes-related complications may improve diabetes care. In **chapter 9**, which involves a systematic review, we explored sex disparities in the assessment of cardiovascular risk factors and screening for diabetes-related complications. PubMed was systematically searched up to April 2020, followed by manual reference screening and citation checks (snowballing) using Google Scholar. Observational studies were included if they reported on the assessment of cardiovascular risk factors (HbA1c, lipids, blood pressure, smoking status, or BMI) and/or screening for nephropathy, retinopathy, or performance of feet examinations, in women and men with diabetes separately. Studies adjusting their analyses for at least age, or when age was considered as a covariable but left out from the final analyses for various reasons (i.e. backward selection), were included for qualitative analysis. No meta-analyses were planned because substantial heterogeneity between studies was expected. Overall, 81 studies were included. The majority of the included studies were from Europe or North America (84%). The number of individuals per study ranged from 200 to 3,135,019, and data were extracted from various data sources in a variety of settings. Screening rates varied considerably per study outcome and across studies. For example, screening rates for retinopathy ranged from 13% to 90%, with half the studies reporting screening rates less than 50%. Mixed findings were found regarding the presence, magnitude, and direction of sex disparities with regard to the assessment of cardiovascular risk factors and screening for diabetes-related complications, with some evidence suggesting that women, compared with men, may be more likely to receive retinopathy screening and less likely to receive foot exams. Assessment of cardiovascular risk factors and screening for diabetes-related complications is critical in guiding treatment decisions. The study demonstrates that there is no consistent pattern in screening activities favouring women or men, suggesting that disparities in risk factor assessment and screening activities do not account for the higher relative risk of CVD conferred by diabetes previously found in women compared with men.

In **chapter 10**, we conclude by discussing the main findings of this thesis and explore implications for future research. While progress has been made towards understanding the underlying mechanisms of women's higher relative risk of diabetic cardiovascular complications, many

uncertainties remain. Future research to understand these mechanisms is needed to increase the awareness of the sex- and gender-specific risk factors and may ultimately result in more personalized diabetes care to reduce the burden of CVD in women and men.

Nederlandse samenvatting

Geslacht en gender zijn belangrijke determinanten voor ziekte en gezondheid. Zo vormt bij vrouwen diabetes een sterkere risicofactor voor de ontwikkeling van cardiovasculaire complicaties dan bij mannen. De mechanismen die aan dit man-vrouw verschil ten grondslag liggen zijn onduidelijk en meer onderzoek daarna is noodzakelijk. Nieuwe inzichten in de geslachtsspecifieke aspecten van diabetes en cardiovasculaire complicaties kunnen mogelijk bijdragen aan veranderingen in de richtlijnen voor preventie en behandeling van diabetes en diabetes-gerelateerde complicaties en daarmee de zorgverlening voor mannen en vrouwen verder optimaliseren. Het overkoepelende doel van dit proefschrift was dan ook om meer inzicht te verkrijgen in de mechanismen die ten grondslag liggen aan het man-vrouw verschil dat wordt waargenomen in het risico op cardiovasculaire complicaties ten gevolge van diabetes.

Hoewel het werk dat in dit proefschrift wordt gepresenteerd zowel geslacht als genderelementen bevat, wordt de term 'geslacht' gebruikt om de leesbaarheid te verbeteren.

Verschillen tussen mannen en vrouwen met betrekking tot biologische eigenschappen als ook verschillen in de zorgverlening en het zorggebruik dragen mogelijk bij aan het man-vrouw verschil in het risico op cardiovasculaire complicaties ten gevolge van diabetes. In **hoofdstuk 2** wordt een overzicht gegeven van de huidige kennis over de rol van man-vrouw verschillen met betrekking tot (1) biologische factoren, met een specifieke focus op lichaamssamenstelling en voorkeurslocaties van vetopslag, en (2) zorggerelateerde verschillen.

In **hoofdstuk 3** wordt een overzicht gegeven van verschillende statistische methoden die kunnen worden gebruikt om geslachtsspecifieke schattingen en schattingen van geslachtsverschillen te verkrijgen. Hoewel geslachtsspecifieke analyses steeds vaker worden uitgevoerd, wordt de mogelijke impact van geslachtsspecifieke confounding niet altijd meegenomen in de analyses, dat wil zeggen, geslachtsverschillen in de impact van confounders op de te onderzoeken associatie tussen determinant en uitkomst van interesse. Dit leidt mogelijk tot onjuiste conclusies. Veelvuldig gebruikte statistische methoden om geslachtsverschillen in de associatie tussen determinant en uitkomst van interesse te analyseren omvatten (1) stratificatie naar geslacht en (2) het gebruik van een enkele interactieterm met geslacht. Met de eerste methode worden associaties bestudeerd in afzonderlijke strata voor mannen en vrouwen en corrigeert men daarmee automatisch voor geslachtsspecifieke confounding. Aangezien er echter twee modellen worden gebruikt, kunnen schattingen van geslachtsverschillen niet uit hetzelfde model worden gehaald. Met de tweede methode, het enkelvoudige interactiemodel, wordt een interactieterm tussen geslacht en de determinant aan het model toegevoegd. Additioneel worden mogelijke confounders in het model opgenomen. Het voordeel van de tweede benadering is dat schattingen van geslachtsverschillen uit hetzelfde model kunnen worden geëxtraheerd. De tweede benadering corrigeert echter niet voor geslachtsspecifieke confounding. Dit probleem kan worden omzeild door een derde statistische methode, namelijk het toepassen van een volledige interactiemodel, waarin interactietermen tussen geslacht en elke variabele (determinant en confounders) aan het model worden toegevoegd. Met deze benadering corrigeert men voor geslachtsspecifieke confounding,

terwijl men ook geslachtsspecifieke effecten en geslachtsverschillen uit hetzelfde model kan extraheren. Met behulp van data verkregen uit de UK Biobank toonden we aan dat de schattingen van geslachtsverschillen vertekend kunnen zijn als geslachtsspecifieke confounding niet in het model wordt meegenomen. Daarom raden we het gebruik van een volledig interactiemodel aan.

Hoewel voormalige systematische reviews en meta-analyses hebben aangetoond dat diabetes een sterkere risicofactor is voor het ontwikkelen van een myocardinfarct (MI) bij vrouwen dan bij mannen, is vooralsnog onbekend of deze man-vrouw verschillen ook bestaan over het glycemische continuüm. In **hoofdstuk 4** zijn daarom de geslachtsspecifieke associaties en geslachtsverschillen met betrekking tot diabetes status (geen diabetes, prediabetes, niet-gediagnosticeerde diabetes en gediagnosticeerde diabetes), HbA1c en het risico op MI onderzocht. Voor deze studie is data gebruikt van 471.399 (56% vrouwen) studiedeelnemers aan de UK Biobank. Deze studiedeelnemers hadden geen hart- en vaatziekten in de voorgeschiedenis. Middels Poisson regressie zijn geslachtsspecifieke incidentiecijfers berekend voor diabetes status en verschillende HbA1c niveaus. Middels 'Cox proportional hazards' analyses zijn geslachtsspecifieke hazard ratio's (HR) en geslachtsverschillen verkregen voor de associatie tussen diabetes status, HbA1c en het risico op MI. De incidentie van MI was bij mannen hoger dan bij vrouwen voor zowel diabetes status als de verschillende HbA1c niveaus. Echter een voorgeschiedenis van diabetes werd geassocieerd met een groter relatief risico op MI bij vrouwen dan bij mannen. Prediabetes en een toename van 1% HbA1c vormden een verhoogd risico op MI in beide geslachten, met bewijs voor sterkere effecten bij vrouwen dan bij mannen. Dit geslachtsverschil was echter niet langer statistisch significant in de analyses die ook rekening hielden met geslachtsspecifieke confounding.

Naast een verhoogd risico op hart- en vaatziekten vormt diabetes ook een risicofactor voor een gecompliceerd verloop van COVID-19 inclusief een verhoogd risico op overlijden. Het is echter onduidelijk of het risico op een gecompliceerd beloop op COVID-19 dat wordt gezien bij individuen met diabetes ook verschillend is tussen vrouwen en mannen. In **hoofdstuk 5** is data van de UK Biobank gebruikt om de geslachtsspecifieke associaties en geslachtsverschillen tussen diabetes status, HbA1c en het risico op COVID-19-mortaliteit te onderzoeken. Ter vergelijking zijn ook de geslachtsspecifieke associaties en geslachtsverschillen van overlijden door influenza/pneumonie (een belangrijke doodsoorzaak door luchtwegaandoeningen voorafgaand aan de COVID-19 pandemie) en fatale coronaire hartziekte (CH) (een aandoening waarbij geslachtsverschillen welbekend zijn) onderzocht. De resultaten van de studie toonden aan dat diabetes het risico verhoogd op overlijden door COVID-19 (HR 1,52 bij vrouwen vs. 1,73 bij mannen), influenza/pneumonie (HR 2,06 bij vrouwen vs. 1,80 bij mannen) en fataal CH (HR 3,17 bij vrouwen vs. 1,93 bij mannen) bij beide geslachten. Er werden geen statistisch significante geslachtsverschillen gevonden voor de associatie tussen diabetes en HbA1c met het risico op sterfte door COVID-19 of influenza/pneumonie. Daarentegen waren prediabetes, diabetes en HbA1c sterker geassocieerd met het risico op sterfte door CH bij vrouwen dan bij mannen.

In **hoofdstuk 6** is onderzocht of er sprake is van geslachtsverschillen in de associatie tussen diabetesduur en het risico op hart- en vaatziekten en afzonderlijk voor MI en beroerte. Voor deze

studie is data gebruikt van 18.961 (40% vrouwen) studiedeelnemers aan de UK Biobank. Deze deelnemers hadden diabetes type 2 zonder een voorgeschiedenis van hart- en vaatziekten. Middels Poisson regressie zijn geslachtsspecifieke incidentiecijfers berekend voor diabetesduur. Middels 'Cox proportional hazards' analyses zijn geslachtsspecifieke associatiematen en geslachtsverschillen in de associatie tussen diabetesduur (<5; ≥ 5- <10; ≥ 10 jaar en per 5-jaar) en hart- en vaatziekten (en afzonderlijk voor MI en beroerte) berekend. De resultaten uit deze studie laten zien dat de duur van diabetes een hoger risico geeft op het ontwikkelen van hart- en vaatziekten, MI en beroerte bij zowel mannen als vrouwen zonder bewijs voor geslachtsverschillen in de sterkte van de associatie. Bij zowel mannen als vrouwen was een 5 jaar langere diabetesduur geassocieerd met een ongeveer vergelijkbaar verhoogd risico op hart- en vaatziekten, MI en beroerte van ongeveer 20%.

In de **hoofdstukken 7 en 8** hebben we onderzocht of er verschillen tussen vrouwen en mannen bestaan met betrekking tot de behandeling van diabetes en het cardiovasculaire risicomanagement. Voor deze studies is data gebruikt van twee Nederlandse cohorten: het Julius Huisartsen Netwerk (JHN) (**hoofdstuk 7**) en de Diabetes Parel van het Parelsnoer instituut (**hoofdstuk 8**). Het JHN is een groot doorlopend dynamisch cohort van eerstelijns patiënten van aaneengesloten huisartsenpraktijken in en nabij Utrecht, waarvan routinematig data uit elektronische medische dossiers wordt geëxtraheerd. Cross-sectionele data afkomstig uit 2013 van 12.512 studiedeelnemers met diabetes is gebruikt om geslachtsverschillen in de behandeling van diabetes en het cardiovasculaire risicomanagement te onderzoeken. De Diabetes Parel van het Parelsnoer instituut, welke data bevat van 6.637 studiedeelnemers met diabetes type 2 die primaire of secundaire / tertiaire zorg ontvangen, is een observationeel cohort waarbij acht Nederlandse academische medische centra betrokken zijn. De resultaten uit deze studies toonden aan dat geslachtsverschillen in de behandeling van diabetes en het cardiovasculaire risicomanagement in Nederland klein zijn. Vrouwen met diabetes hadden een iets ander cardiometabool risicoprofiel dan mannen en een aanzienlijk hogere body mass index (BMI).

Meer inzicht in het bestaan van geslachtsverschillen met betrekking tot de screening op cardiovasculaire risicofactoren en diabetes-gerelateerde complicaties kan bijdragen aan het optimaliseren van de diabeteszorg. In **hoofdstuk 9**, dat een systematisch review omvat, is onderzocht of er verschillen bestaan tussen vrouwen en mannen met diabetes in de mate waarop zij screening ontvangen voor cardiovasculaire risicofactoren en het hebben van diabetes-gerelateerde complicaties. Voor deze studie is gebruik gemaakt van een literatuurscreening middels PubMed, gevolgd door Snowballing waarbij gebruik is gemaakt van Google Scholar. Observationale studies werden geïnccludeerd indien ze rapporteerden over het screenen van cardiovasculaire risicofactoren (HbA1c, lipiden, bloeddruk, rookstatus of BMI) en/of screening op nefropathie, retinopathie of het onderzoeken van de voeten, bij zowel vrouwen als mannen met diabetes. Studies die hun analyses adjusteerden voor ten minste leeftijd, of wanneer leeftijd als een covariabele werd beschouwd maar om verschillende redenen (o.a. 'backward selection') werd weggelaten uit de uiteindelijke analyses, werden geïnccludeerd voor kwalitatieve analyse. Vooraf is besloten om geen meta-analyses uit te voeren, omdat een substantiële heterogeniteit tussen

de te includeren studies werd verwacht. In totaal zijn 81 studies geïncludeerd. Het merendeel van de geïncludeerde studies was afkomstig uit Europa of Noord-Amerika (84%). Het aantal studiedeelnemers per studie varieerde van 200 tot 3.135.019. De percentages screening voor risicofactoren en diabetes-gerelateerde complicaties varieerden aanzienlijk per uitkomstmaat en tussen de geïncludeerde studies. De screeningspercentages voor retinopathie varieerden bijvoorbeeld van 13% tot 90%, waarbij de helft van de studies screeningspercentages van minder dan 50% rapporteerden. Vrouwen hadden meer kans op het ontvangen van retinopathiescreening dan mannen, terwijl mannen meer kans hadden op het ontvangen van voetonderzoek. Duidelijke geslachtsverschillen voor screening van de overige cardiovasculaire risicofactoren en diabetes-gerelateerde complicaties ontbraken. Tijdige screening op het voorkomen van cardiovasculaire risicofactoren en diabetes-gerelateerde complicaties is van cruciaal belang bij het maken van een behandelstrategie. Deze studie toonde aan dat er geen consistent patroon is in screeningsactiviteiten in het voordeel van vrouwen of mannen. Dit suggereert dat verschillen in screening geen verklaring vormen voor het hogere relatieve risico op hart- en vaatziekten bij vrouwen ten gevolge van diabetes.

In **hoofdstuk 10** wordt afgesloten met het bespreken van de belangrijkste bevindingen van dit proefschrift. Daarnaast worden in dit hoofdstuk aanbevelingen voor toekomstig onderzoek gegeven. Hoewel er vooruitgang is geboekt in het verkrijgen van inzicht in de mechanismen die ten grondslag liggen aan het man-vrouw verschil dat wordt waargenomen in het risico op cardiovasculaire complicaties ten gevolge van diabetes, blijven er nog veel onzekerheden over deze mechanismen bestaan. Verder onderzoek naar mogelijke geslachtsverschillen in de (1) onderliggende pathofysiologie en etiologie van prediabetes en diabetes, (2) vertraging van het stellen van de diagnose diabetes en (3) therapietrouw is nodig om deze onderliggende mechanismen verder te ontrafelen.

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About the author

Marit de Jong was born on March 2th, 1991, in Almelo, the Netherlands. She graduated in 2010 from the Pius X college in Almelo, after which she started studying Biomedical Sciences at Utrecht University. After one year, Marit decided to participate in the in-depth Honours Program of Biomedical Sciences. For her individual project, Marit studied the metabolic disorder 'Erythropoietic Protoporphria', followed by an eight-week internship at the Erasmus Medical Centre Rotterdam. After graduating Cum Laude, she was selected for the Selective Utrecht Medical Master at Utrecht University. As part of a research project, Marit wrote a systematic review and meta-analysis entitled 'Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials'.



After the successful completion of her master in Medicine in 2017, Marit took on a PhD position at the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht under supervision of prof. dr. Michiel L. Bots, prof. dr. Mark Woodward, dr. Sanne A.E. Peters, and dr. Rimke C. Vos. Marit has been provided the opportunity to present her work at several national conferences and to participate in several (inter)national trainee seminars, including the 13th WHO/IDF Cambridge Diabetes Seminar and the Libin International Trainee Symposium 'Research is Better with Sex and Gender'. Marit combined her PhD trajectory with the Postgraduate Master in Epidemiology at Utrecht University, specializing in clinical epidemiology. Additionally, she participated in several teaching activities for medical students. Also during this trajectory, Marit took part in a unique housing project where students lived between elderly in a nursing home. During and after this project, Marit stood up and took action together with the elderly and other students to prevent foreclosure and unnecessary moving of the elderly. In this time she gained a lot of experience in media and local politics. As well as experienced how elderly in nursing homes live and experience their lives. This unique experience helped Marit to grow both in her scientific career and as a person.

In February 2021, she started working as a resident (ANIOS) at TalentCare. For her first assignment, she started working at the Municipal Health Service (GGD) Zuid-Holland Zuid, under supervision of Dr. Raisa Tjon-Kon-Fat, focusing on infectious disease control in general and specifically focussing on the control of COVID-19.

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