



Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course

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Received: 20 April 2019 / Accepted: 29 May 2019 / Published online: 27 August 2019
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Abstract

By 2017 estimates, diabetes mellitus affects 425 million people globally; approximately 90–95% of these have type 2 diabetes. This narrative review highlights two domains of sex differences related to the burden of type 2 diabetes across the life span: sex differences in the prevalence and incidence of type 2 diabetes, and sex differences in the cardiovascular burden conferred by type 2 diabetes. In the presence of type 2 diabetes, the difference in the absolute rates of cardiovascular disease (CVD) between men and women lessens, albeit remaining higher in men. Large-scale observational studies suggest that type 2 diabetes confers 25–50% greater excess risk of incident CVD in women compared with men. Physiological and behavioural mechanisms that may underpin both the observed sex differences in the prevalence of type 2 diabetes and the associated cardiovascular burden are discussed in this review. Gender differences in social behavioural norms and disparities in provider-level treatment patterns are also highlighted, but not described in detail. We conclude by discussing research gaps in this area that are worthy of further investigation.

Keywords Cardiovascular disease · Diabetes mellitus, type 2 · Life course development · Lifestyle · Obesity · Review · Sex differences · Type 2 diabetes

Abbreviations

CVD Cardiovascular disease
RR Rate ratio

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Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00125-019-4939-5>) contains peer-reviewed but unedited supplementary material including a slideset of the figures for download, which is available to authorised users.

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Introduction

The presence, type and magnitude of sex and gender differences in type 2 diabetes mellitus and diabetes-mediated risk of cardiovascular disease (CVD) have historically been underappreciated [1]. Epidemiological studies demonstrate clinically relevant sex and gender differences in the rates of type 2 diabetes in youth [2–8] and midlife [9–12]. Sex and gender differences in the impact of type 2 diabetes on CVD outcomes across the life span have also been identified [1, 13–15]. Individuals with type 2 diabetes also exhibit sex and gender differences in the burden of future cancer, dementia and renal disease [16–18]. This narrative review will focus on how age and developmental stages influence two well-recognised areas of sex differences: (1) disparate rates in the prevalence of diabetes, especially during puberty and midlife; and (2) differences in the relative risk of CVD conferred by the presence of type 2 diabetes. The mechanisms that are proposed to influence these sex differences will be summarised, and research gaps that should be addressed to better understand and address the biological underpinnings will be proposed. Given the relevance of biological sex differences in our selected topics, this review is focused on sex rather than gender differences (where gender is defined as comprising social and psychological differences between men and women [19, 20]), although it is often difficult to completely disentangle their effects from each other. In addition, where appropriate, we selectively reference potential gender-related reasons for health disparities among people with type 2 diabetes, including gender differences in healthcare management and socio-environmental factors [9, 21, 22].

Sex differences in prevalence of type 2 diabetes across the lifespan

Looking only at the international rates of type 2 diabetes, as standardised across all age groups, the majority of data from populations of Western European or Asian descent suggest a slightly higher prevalence of type 2 diabetes among men than women [23–26]; globally, based upon the IDF 2018 atlas, an estimated 221 million men and 204 million women are estimated to have had type 2 diabetes in 2017 [27]. In terms of time trends, global age-standardised diabetes prevalence (% [95% credible interval]) increased from 4.3% (2.4, 7.0) in men in 1980 to 9.0% (7.2, 11.1) in 2014, and from 5.0% (2.9, 7.9) in women in 1980 to 7.9% (6.4, 9.7) in 2014 [28]. A higher prevalence of type 2 diabetes among men than women may be region specific. For example, in the UK Biobank study, male predominance was reported across three ethnic groups (men vs women): white, 6.0% vs 3.6% ($p < 0.0001$); South Asian, 21.0% vs 13.8% ($p < 0.0001$); black, 13.3% vs. 9.7% ($p < 0.0001$). There was also a non-significant numerical trend

in people of Chinese descent [29]. In another Chinese population, the age-standardised prevalence of type 2 diabetes was 16.1% in men compared with 14.9% in women ($p < 0.0001$ for sex difference) [25], whereas in a US population, there was no sex difference in type 2 diabetes prevalence (men, 12.3% [95% CI 11.3%, 13.4%]; women, 10.8% [95% CI 9.8%, 11.9%]) [30]. In addition, no sex differences were observed in the odds of developing diabetes in a meta-analysis of data from sub-Saharan Africa (OR 1.01 [95% CI 0.91, 1.11]) [31].

There are also some interesting variations in sex differences in type 2 diabetes incidence that fluctuate across the life span, with females having significantly higher rates of type 2 diabetes in youth [2–8], whereas males have a significantly higher prevalence of type 2 diabetes in midlife [9–12], and the rates are fairly similar between the sexes in later life [11, 12]. The next section will summarise the epidemiological differences in type 2 diabetes prevalence across the lifespan, as well as sex differences in the biological predictors of type 2 diabetes, and key research gaps.

Epidemiological differences in type 2 diabetes prevalence across the life span and potential mediators, by life stage

Sex differences in prevalence of youth-onset type 2 diabetes

In youth, <18 years of age, type 2 diabetes remains generally rare, but its incidence has risen dramatically due to concomitant increases in obesity and suboptimal diet and physical activity behaviours [2, 4, 5, 32–35]. Sex differences in the prevalence of type 2 diabetes in youth have been identified; most [2–8], but not all [36] studies that used population-based sampling have reported that approximately two-thirds of children and adolescents diagnosed with type 2 diabetes are female (electronic supplementary material [ESM] Table 1 outlines the study design, methods and findings for four of these studies, from the USA). Time-trend data suggest this disparity may be worsening, as the British Paediatric Surveillance Unit reported that the incidence rate of type 2 diabetes between 2005 and 2015 increased by 58% in girls but only by 7% in boys [37], consistent with data from the National Paediatric Diabetes Audit [38]. In contrast, studies of Asian populations reported a higher prevalence of type 2 diabetes in boys compared with girls, highlighting the need to further evaluate race/ethnicity, lifestyle and the environment as risk factors for type 2 diabetes in youth [8, 39]. A recent report of the Swedish Heart Registry makes the important observation that cardiovascular mortality is significantly higher for people diagnosed with type 2 diabetes at a younger age (<40 years) as compared with those diagnosed at an older age. As such, the predominance of females in youth-onset type 2 diabetes may have major implications in terms of CVD [40].

Mechanism of type 2 diabetes onset in youth

The development of type 2 diabetes in youth is influenced by multifactorial biological and environmental variables, from conception to adolescence. These include genetic risk for type 2 diabetes, epigenetic factors, dietary quality, physical activity, and the surge in sex hormone production and insulin resistance during puberty [9, 32, 41, 42]. Emerging research also suggests sexual dimorphism in genetic predictors of adipose fat distribution, inflammatory signalling pathway activation and type 2 diabetes risk [43–48]. Here we will briefly expand on two major risk factors for a type 2 diabetes diagnosis in youth: epigenetic factors and the rise in insulin resistance during puberty.

Epigenetic risk factors The influence of epigenetic risk factors on the development of type 2 diabetes in youth and on cardio-metabolic risk across the life span is a rapidly emerging area of research highlighted elsewhere in this special issue by Fernandez-Twinn et al [49] and in other recent reviews [50, 51]. In brief, a few themes emerge in the preclinical data that align with clinical data on sex-specific effects of specific epigenetic factors (reviewed in [50–52]). Paternal undernutrition, overnutrition/high-fat diet and obesity lead to decreased skeletal muscle and beta cell mass, and insulin resistance, with male offspring more affected than female offspring in some studies [53, 54]. Maternal obesity is highly associated with male offspring obesity, and maternal obesity is also linked to a higher risk of diabetes or impaired fasting glucose/impaired glucose tolerance in both sexes [50, 55–57]. In addition, maternal dysglycaemia is more strongly associated with decreased insulin sensitivity in females vs males, and with decreased beta cell mass in both sexes, in reports to date [58–60]. These intriguing data demonstrating the potential for epigenetic risks to be conferred differentially in male and female offspring warrant further evaluation to confirm previous findings and to evaluate potential mechanisms.

Insulin resistance during puberty During puberty, there is an increase in insulin resistance that requires compensatory insulin secretion. The pubertal rise in insulin resistance is accelerated by altered obesity/fat distribution, physical inactivity and high-fat diet, among other factors [9, 61]. Despite accounting for these individual-level predictors of insulin resistance, sex differences in insulin resistance across the childhood life-phase exist: females have higher rates of insulin resistance than males from early childhood through to mid-puberty, whilst, during late puberty and adulthood, males exhibit greater insulin resistance than females (Fig. 1) [9, 62–66]. This pattern was documented by insulin clamp studies among Caucasian and African-American youths, and persisted with adjustment for measures of adiposity, BMI and objective physical activity levels [63, 64, 66]. In one of the first mechanistic studies in Latino adolescents, both girls and boys increased insulin secretion to compensate for greater insulin resistance in early

puberty [67]. By the end of the study, girls had restored insulin sensitivity and normalised insulin secretion, whereas boys had persistently increased insulin resistance and exhibited a decline in beta cell reserve and increased fasting glucose levels [67]. Loss of glucose-stimulated insulin secretion was also observed in the youth type 2 diabetes cohort in the National Institute of Health (NIH) Restoring Insulin Secretion (RISE) study (no sex differences have been reported to date in the 91 participants) [68]. Thus, obesity, insulin resistance and insulin hypersecretion [61] are likely to be key mediators of type 2 diabetes in youth. The distinct role of biological and behavioural factors, however, remains a key gap in the research (Table 1).

Sex differences in type 2 diabetes prevalence in midlife and contributing factors

In young adults, the rate of diabetes remains fairly low at a population level and epidemiological studies of adults aged <30 years do not identify a clear sex difference in the prevalence of type 2 diabetes [9]. In midlife, however, the prevalence of type 2 diabetes tends to be higher in men than in women [9–12]. For example, in a Canadian population-based sample, Lipscombe and Hux observed significant sex differences in both the prevalence and incidence of diabetes among participants aged ≥ 50 years (men vs women: prevalence, 19.1% vs 15.4%; incidence, 15.9/1000 vs 12.7/1000; $p < 0.001$ for both comparisons), whereas there were no statistically significant sex differences in the prevalence or incidence of type 2 diabetes in people aged 20–49 years [10]. In addition, in a nationally representative Korean sample, there were statistically significant differences in diabetes prevalence between those aged 50–59 years (men: 19.0% [95% CI 15.3%, 22.8%]; women: 8.9% [95% CI 5.9%, 11.9%]), but there were no longer any sex differences by the seventh decade of life (60–69 year old men: 17.7% [95% CI 13.7%, 21.7%]; 60–69 year old women: 18.5% [95% CI 14.1%, 22.8%]), nor were there any significant sex differences in this sample among those aged 30–39 years or 40–49 years [11].

Insulin resistance in men and obesity thresholds in women may, in part, explain the observed sex difference in type 2 diabetes in midlife. As noted earlier, hyperinsulinaemic–euglycaemic insulin clamp data suggest that men are more insulin resistant than women from late puberty into adult life (Fig. 1) [9]. These findings provide a plausible rationale for higher rates of type 2 diabetes among men, but do not explain why the male predominance in type 2 diabetes presents in midlife. Sex differences in the severity of obesity associated with developing type 2 diabetes is another possible factor, with two separate population-based studies demonstrating this; one study showed that women developing type 2 diabetes have a higher BMI than men until the eighth decade of life (Fig. 2c) [41], while the other, in a large cohort of adults in the UK, reported that the age-adjusted average BMI at type 2 diabetes diagnosis was 1.8 kg/m² higher in women than in men (95% CI 1.7, 1.9; $p < 0.01$) [69].

Potential factors that may be relevant to the equalisation in incidence rates of type 2 diabetes in men and women among older adults could include the changes related to the hormonal transition that occurs during the menopause in women at ~50 years of age. For example, increased visceral fat deposition among women after menopause may promote increased insulin resistance and elevated incidence of the metabolic syndrome in older women [70, 71].

Sex differences in CVD outcomes for adults with type 2 diabetes across the life span

Type 2 diabetes is a significant risk factor for CVD for both women and men. Findings from large-scale consortia of cohort studies have shown that the presence of diabetes doubles the risk of having a myocardial infarction or stroke [14, 15, 72]. However, as with other major vascular risk factors, such as blood pressure and BMI, the strength of the association between diabetes and vascular outcomes diminishes with age, partly because of the lower baseline risk for CVD in younger as compared with older adults [72, 73]. For example, in the largest meta-analysis to date, the rate ratio (RR) of occlusive vascular death was found to be greatest in men and women aged 35–59 years (death RR, 2.60 [95% CI 2.30, 2.94]), as compared with men and women aged 70–89 years (death RR 2.01 [95% CI 1.85, 2.19]; $p = 0.0001$ for trend across age groups) [72].

Among individuals without diabetes, absolute rates of CVD are higher in men than in women at all ages, apart from at very old ages where the burden of stroke is higher in women than in men irrespective of the presence of diabetes (Table 2) [72]. However, in the presence of type 2 diabetes, the difference in absolute rates between the sexes is substantially diminished (although not fully eliminated), positing some authors to conclude that ‘diabetes negates the female advantage’ concerning cardiovascular outcomes [1, 14, 15, 72]. For example, in three separate large cohorts of young to middle-aged adults, CVD event rates were shown to be similar among women and men with diabetes (women: 17.65, 7.34, and 2.37/1000 person-years in the three

separate cohorts; men: 12.86, 9.71, and 1.83/1000 person-years, respectively; all logrank p values >0.05 [73].

In terms of relative risk for CVD, large meta-analyses of observational data have shown that women with type 2 diabetes have 25–50% greater excess risk of an incident cardiovascular event compared with similarly affected men [1, 15, 72, 73]. For example, recent data from the UK Biobank showed that, in the presence of type 2 diabetes, the excess risk of a cardiovascular event was approximately 50% higher in women (HR 1.96 [95% CI 1.60, 2.41]) than in men (HR 1.33 [95% CI 1.18, 1.51]) [74]. However, this difference has not been observed consistently in some similarly large, contemporary studies [75, 76]. It is possible that a greater focus on cardiovascular treatment guidelines in recent years has ameliorated the historical treatment disparity between men and women that may have contributed to the observed sex difference in diabetes-related vascular risk [75]. Nevertheless, the observed sex difference is illustrated by the HR conferred by the presence of type 2 diabetes using the validated QRISK3 calculator for 10-year cardiovascular risk [77]. The presence of type 2 diabetes vs no diabetes among women yields a higher HR multiplier (2.91 [95% CI 2.72, 3.11]) as compared with men with type 2 diabetes vs no diabetes (2.36 [95% CI 2.23, 2.50]) [77]. As the absolute rates of CVD are particularly low in younger age groups, the relative risk of CVD for people with type 2 diabetes vs no type 2 diabetes is higher when type 2 diabetes is diagnosed earlier in life, and is more for women than men [40, 72].

In summary, the presence of type 2 diabetes weakens the cardioprotection that is considered to occur in premenopausal women [78, 79]. The underlying physiological, behavioural or biological mechanisms that may be responsible for the observed excess risk of vascular disease among women with type 2 diabetes are multifactorial and further research is required (Table 1).

Potential mechanisms for the observed sex difference in the impact of type 2 diabetes on vascular risk

Numerous studies have speculated on the potential mechanisms (including biological and physiological factors and disparities in disease management) that may underpin the observed excess vascular risk in women compared with men with type 2 diabetes [1, 13]. This section focuses on the possible biological differences between women and men that may mediate the excess vascular risk in women with type 2 diabetes (Table 1) [1, 14, 15, 80].

Adult women develop type 2 diabetes at a relatively higher BMI than men (Fig. 2). As such, women may experience a prolonged state of insulin resistance and metabolic dysfunction prior to diagnosis with type 2 diabetes [15, 81]. This theory is supported by the Bogalusa Heart Study’s findings that women diagnosed with type 2 diabetes as adults have a greater cumulative exposure to cardiovascular risk factors over their lifetime, starting in youth [82]. For instance, sex

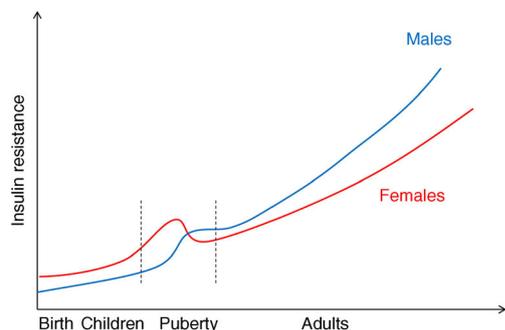


Fig. 1 Sex differences in insulin resistance across the life span. Adapted from [9] with permission from Elsevier. This figure is available as part of a [downloadable slideset](#)

Table 1 Representative studies and research gaps in the sex differences in the prevalence of type 2 diabetes and its cardiovascular complications across the life span

Lifespan stage: area of study	Current status of knowledge	Research gaps	Clinical implications
<p>Youth: sex differences in metabolic risk for T2D and CV risk among youth diagnosed with T2D</p>	<p>Evidence for sexual divergence in the prevalence of T2D in early youth (higher in girls vs boys), followed by greater IR in males in late puberty, continuing into adult life [2–8, 24, 36–39]</p> <p>Large meta-analyses reveal elevated CV risk profiles and worse CV outcomes later in life among people diagnosed with T2D earlier in life vs later [40, 72, 82]</p>	<p>To optimise prevention/treatment strategies for T2D, the distinct contributions of biology and behaviour to the mechanisms underpinning sex differences in IR and T2D diagnosis among youth must be defined. Studies should include tests of sex-specific biological factors (e.g. insulin action, beta cell function) and behavioural factors (e.g. diet, physical activity, sleep)</p> <p>Clinical trials are needed to identify optimal lifestyle/medication interventions for CV risk reduction among youth at risk for and diagnosed with T2D, with pre-specified evaluation by sex and gender</p>	<p>Offspring born under conditions of IUGR, parental obesity or high-fat diet, or mothers with diabetes in pregnancy should be identified as having high risk for obesity, diabetes and CVD. Parents of high-risk offspring, and high-risk youth (when of age) should be counselled on lifestyle and the need for early screening for CV risk factors</p>
<p>Adults: sex and gender differences in CV outcomes for adults with T2D (reviewed in [1])</p>	<p>T2D confers a loss of ‘cardioprotection’ in women such that the difference in absolute rates of CV outcomes between men and women narrows (although not entirely eliminated) [1, 14, 15, 40, 72]</p> <p>Sex differences in relative risk of CVD for adult women and men: HR multiplier for 10-year CV risk, T2D vs no diabetes: women, HR 2.91 (95% CI 2.72, 3.11); men, HR 2.36 (95% CI 2.23, 2.50) [77]</p> <p>Treatment gap between women and men with T2D has narrowed but persists, with women typically receiving less effective management of CV risk factors than men [75, 94, 98–104]</p>	<p>Need to prospectively assess mechanisms of sex/gender differences in diabetes prevalence and worse relative CV risk in women vs men with T2D, including biological and behavioural factors. Studies should include tests for sex-specific biological factors (e.g. genetic/epigenetic factors, sex hormones/sex hormone receptors, prothrombotic metabolic profile, adiposity, insulin action, beta cell reserve, VO_{2peak} / VO_{2max}, blood flow reserve, autonomic tone) and behavioural factors (e.g. diet, physical activity, sleep)</p> <p>Healthcare disparities must be addressed. Studies of approaches to improve CV risk-factor control through education and point-of-care risk-recognition protocols, medication adherence surveillance and equitable revascularisation for acute coronary syndrome are needed</p>	<p>Clinicians should counsel patients on healthy diet/physical activity lifestyle behaviours and assist patients with implementing lifestyle changes</p> <p>Clinicians should apply and prescribe gender-equitable and guideline-concordant screening and therapy for men and women and seek to uncover and address reasons for non-adherence (e.g. depression, medication intolerance)</p>

CV, cardiovascular; IR, insulin resistance; IUGR, intrauterine growth restriction; T2D, type 2 diabetes

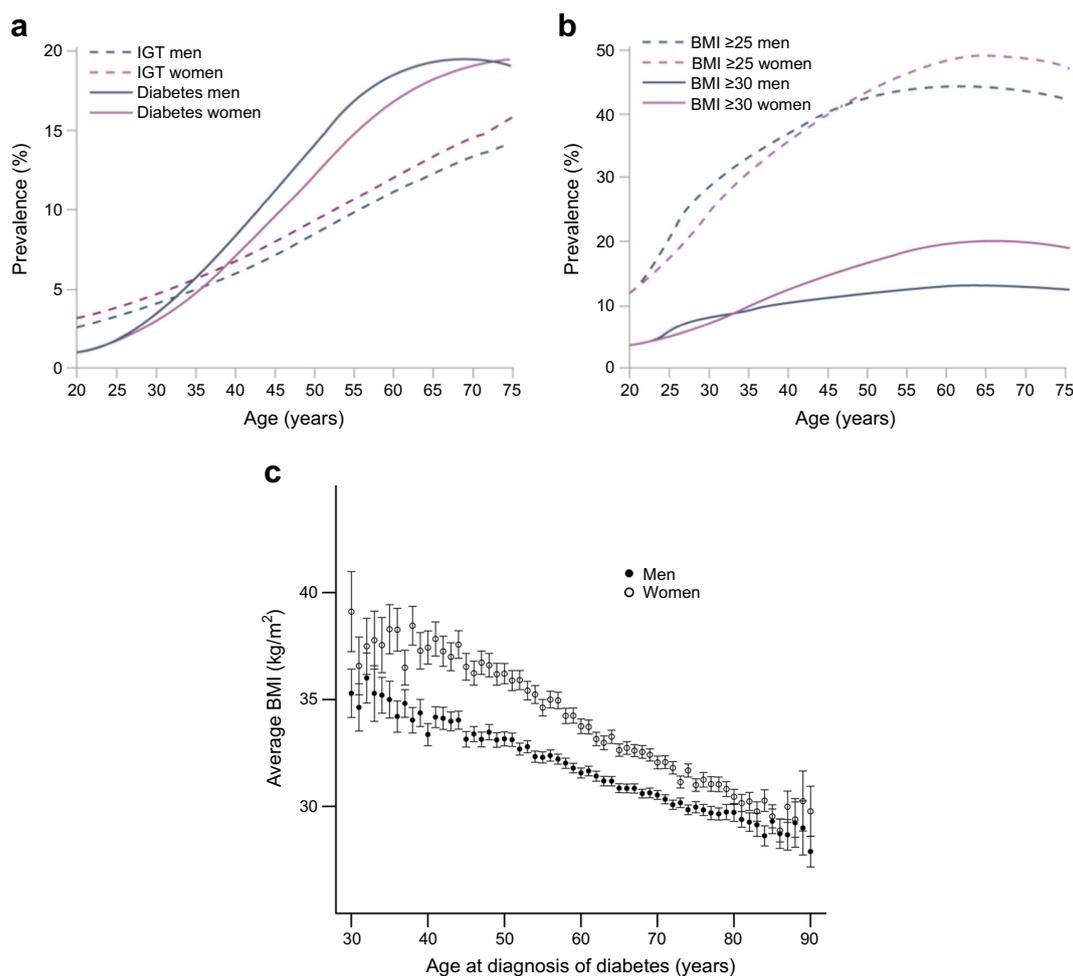


Fig. 2 Obesity levels are higher among women than men at the time of type 2 diabetes diagnosis. **(a, b)** Sex differences in the prevalence of diabetes/impaired glucose tolerance (IGT) **(a)** and being overweight (BMI ≥ 25) or obese (BMI ≥ 30) **(b)** by age (adapted from [22] by

permission of Oxford University Press on behalf of the Endocrine Society). **(c)** BMI at diabetes diagnosis by age (adapted from [41] by permission of Springer Nature). This figure is available as part of a [downloadable slideset](#)

differences in endothelial dysfunction are a potential biological mediator of the excess vascular risk observed in women with diabetes [83, 84]. The transition from euglycaemia to impaired fasting glucose/impaired glucose tolerance confers more severe endothelial dysfunction in women than men, including changes in markers of endothelial function (E-selectin and soluble intercellular adhesion molecule [sICAM]). In addition, fibrinolysis (plasminogen activator inhibitor-1 [PAI-1]) is more abnormal in premenopausal women with type 2 diabetes than their male counterparts [83, 84].

Gender differences in diet and physical activity behaviours warrant consideration for CVD risk and prevention; these have been recently summarised in depth [1]. The notable sex and gender disparities in physical activity behaviour will be briefly reviewed here. Cardiorespiratory fitness, as measured by maximal oxygen capacity ($\dot{V}O_{2max}$)/peak oxygen capacity ($\dot{V}O_{2peak}$), is a potent predictor of longevity and all-cause mortality and it is lower (worse) in people with diabetes, particularly women [85–87]. In population studies, low levels of physical activity

are reported in girls and persist into adulthood. For example, the National Heart, Lung, and Blood Institute Growth and Health Study reported that activity scores for African-American girls and Caucasian girls were 27.3 and 30.8 MET-hours per week, respectively, at 9–10 years of age. These scores declined to 0 and 11.0 MET-hours per week by year 10 of the study, when participants were 18–19 years of age (100% decline for African-Americans, 64% decline for Caucasians) [88]. Physical activity levels in women with diabetes are also less than their male counterparts with diabetes, as based on National Health and Nutrition Examination Survey (NHANES) data and baseline data from large interventional studies [89–91]. Sex differences in physical activity among adults with diabetes are exacerbated in populations with lower levels of education, but the gender disparity persists at all levels of education [91]. Considering the significant relationship between physical inactivity in youth and dysglycaemia, the World Health Organization and others have called for

Table 2 Adjusted rates of cardiovascular mortality among people with and without diabetes, stratified by age and sex

	Diabetes			No diabetes			Rate difference (95% CI)
	Deaths (<i>n</i>)	Person-years	Adjusted rate (%) ^a	Deaths (<i>n</i>)	Person-years	Adjusted rate (%) ^a	
Aged 35–59 years							
Men	252	151,321	0.13	4579	4,168,660	0.06	0.08% (0.05, 0.10)
Women	60	72,756	0.06	496	2,878,295	0.01	0.05% (0.03, 0.07)
Aged 60–69 years							
Men	390	62,605	0.52	5096	1,062,761	0.24	0.28% (0.22, 0.34)
Women	136	32,547	0.28	974	720,144	0.07	0.20% (0.13, 0.27)
Aged 70–89 years							
Men	460	30,489	2.05	4473	350,754	1.14	0.91% (0.77, 1.05)
Women	252	13,001	1.92	2518	267,099	0.84	1.08% (0.84, 1.32)

^a Absolute rates were estimated using Poisson regression stratified by study and adjusted for age at risk (in 5-year age groups), BMI, systolic and diastolic blood pressure, total cholesterol and smoking status [72]

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research to increase physical activity in youth and adults, with specific strategies focused on identifying effective approaches to increase physical activity in youth, including developing habits that will persist into adulthood [92, 93].

Sex-specific effects of pharmacotherapy for the management of diabetes

A potential biological mediator of sex differences in cardiovascular risk factor management among people with type 2 diabetes is the sex-specific efficacy of medications for type 2 diabetes. Initial work in this area has not generally evaluated sex differences in the effectiveness of medications on cardiovascular outcomes in patients with type 2 diabetes, apart from a few studies of glucose-lowering medications. Zinman et al demonstrated no significant sex differences in the effects of an sodium–glucose cotransporter 2 (SGLT2) inhibitor on cardiovascular outcomes in women as compared with men ($p = 0.32$ and $p = 0.20$ for the effect modification by sex on the outcomes of cardiovascular death or heart failure hospitalisation, respectively) [94]. Data from other trials to date have identified some sex differences in glycaemic response. For example the MASTERMIND and Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial reported differences in glycaemic response that were moderated by sex and obesity levels, such that obese females (youth and adults) with type 2 diabetes experienced a better glycaemic response with thiazolidinediones (TZDs) than either non-obese females or obese males, and non-obese males responded significantly better to sulfonylureas than other comparison subgroups [95, 96]. In studies of glucagon-like peptide-1 (GLP-1) receptor agonists, sex

differences have also been reported in glycaemic treatment outcomes, which were greater among men than women, whilst improvements in weight loss favoured women. To date, CVD outcomes with these drugs have not been reported by sex [97].

Comprehensive CVD risk factor reduction is warranted in all people with type 2 diabetes. However, studies have consistently identified a relative undertreatment of women vs men [75, 94, 98–104]. Specifically, women with type 2 diabetes exhibit worse control of HbA_{1c}, blood pressure and lipids than men [75, 104, 105]. The treatment disparity between women and men may narrow at older ages, with some studies reporting similar rates of blood pressure and glycaemic control in older women and men with type 2 diabetes [75, 106]. Of note, some authors have suggested that concerns for prescribing teratogenic medications, such as angiotensin-converting enzyme inhibitors, may play a role in the observed sex difference in blood pressure control, but there are other non-teratogenic, effective anti-hypertensive medications that may be used [107]. Further, reports indicate less aggressive use of revascularisation procedures for women with diabetes and coronary heart disease than their male peers, and lower rates of guideline-based care for acute coronary syndrome [79, 105, 108]. Some of the sex differences in the treatment of acute coronary syndrome may be due to delays in diagnosis and treatment because of more frequent ‘atypical’ symptoms of angina in women than in men, such as fatigue or nausea, instead of ‘typical’ symptoms of chest pressure and shortness of breath [109]. However, changes in clinical systems to facilitate the ease of use of decision support tools and the availability of acute coronary syndrome protocols that guide appropriate assessments of both women and men have shown early promise in reducing disparities in CVD treatment [110, 111], and the additional study of these types of health system interventions is warranted.

Summary

Sex differences in the rates of type 2 diabetes and associated CVD across the lifespan

Females have higher rates of type 2 diabetes in youth, whilst men have higher prevalence in midlife.

In the absence of diabetes, CVD rates are higher in men than women. Diabetes diminishes this difference, and women with type 2 diabetes have a 25–50% greater excess risk of cardiovascular events vs men.

Mechanism of type 2 diabetes onset in youth

Development of type 2 diabetes in youth is influenced by biological and environmental variables, e.g. genetic risk, epigenetics, diet, physical activity, and sex hormone production and insulin resistance during puberty.

Some risk factors have differential effects according to sex and stage of life, e.g. insulin resistance is higher in females from childhood to mid-puberty, whilst it is greater in males during late puberty and adulthood.

Mechanisms for sex differences in the impact of type 2 diabetes on cardiovascular risk

Potential mechanisms for the sex differences in the impact of type 2 diabetes on cardiovascular risk include biological and physiological factors and disparities in disease management between sexes.

For example, women develop type 2 diabetes at a higher BMI than men, so women may experience more prolonged exposure to cardiovascular risk factors prior to type 2 diabetes diagnosis compared with men. Gender differences in diet and physical activity behaviours may also play a role, with cardiorespiratory fitness and physical activity levels being lower in females with diabetes than males.

Sex-specific effects of pharmacotherapy for the management of diabetes/CVD

Sex-specific efficacy of medications for type 2 diabetes may exist. The few studies that have investigated this show varying sex-specific outcomes of different agents on glycaemic and cardiovascular outcomes.

In terms of CVD risk, there is a relative undertreatment of women vs men, which may narrow at older ages. Recent changes in clinical systems have shown promise in reducing disparities in CVD treatment.

Suggestions for future research

Mechanistic research to delineate sex-specific pathogenic drivers of type 2 diabetes in young girls, women and middle-aged men is required, as is research to define genetic, cultural and lifestyle factors contributing to sex differences in global type 2 diabetes prevalence.

Clinical trials/observational studies should report sex-stratified results to allow ascertainment of whether sex differences exist in the effects of interventions for the treatment and prevention of type 2 diabetes.

Summary and identification of key research gaps

Research has historically lacked a systematic approach to the study of sex differences and, as such, the complex interplay between sex and gender, and biological, environmental and behavioural mediators for type 2 diabetes and CVD development has not been well addressed to date. Answers to important questions about the mechanisms underlying sex differences cannot be extracted from re-analysis of existing data and should be evaluated prospectively. It should be noted that although there are distinct biological and behavioural differences between women and men that are likely to impact on the prevalence of type 2 diabetes and associated risk of CVD, sex and gender differences were not the primary pre-specified outcomes of most studies reported in this review. Rigorous and reproducible evaluation

of pre-specified outcomes by sex will not be possible until sex considerations and analysis are included at the study-design phase, rather than as a post hoc consideration. Further research is needed that prospectively focuses on sex differences at all stages of the lifespan, to optimally benefit both women and men.

Studies demonstrate that females are more prone to youth-onset type 2 diabetes than males [2–8] and males are more prone to midlife type 2 diabetes than females [9–12]. Further mechanistic research to delineate the sex-specific pathogenic drivers of type 2 diabetes in young girls and women and middle-aged men may inform the development of targeted prevention and treatment strategies for men and women (Table 1). Research is also needed to define genetic, cultural and lifestyle factors contributing to sex differences in type 2 diabetes prevalence, globally. This review and others [1, 13] have proposed key research gaps in terms of identifying the distinct contributions of biology and

behaviour to the mechanisms of sex differences across the life span in both type 2 diabetes prevalence and in the cardiovascular burden of type 2 diabetes (Table 1). We reiterate recent editorial statements [112, 113] calling for all clinical trials and large-scale observational studies to report sex-stratified results. Such reporting will begin to allow us to reliably ascertain whether sex differences exist in the effects of interventions targeting modifiable lifestyle risk factors and of pharmacotherapy in individuals with type 2 diabetes, as well as other conditions. Moreover, data on sex-specific outcomes will generate new opportunities to reduce sex and gender disparities in type 2 diabetes outcomes, which is highly important since onset of this increasingly prevalent chronic condition can be prevented or delayed with effective evidence-based interventions.

Acknowledgements The authors wish to acknowledge the editorial input provided by S. Hill-Golden (Department of Endocrinology, Johns Hopkins University, MD, USA) on an early version of the manuscript, and the technical assistance of B. Ellis (Center for Women's Health Research, Aurora, CO, USA) with formatting the figures.

Funding This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Duality of interest AGH, JEBR and JGR report recently completed grant funding from Merck, for an investigator-initiated trial that is outside the scope of the submitted work. JEBR reports a consulting agreement with Oramed. PZ reports unrelated consulting agreements with the following companies: Merck, Daichii-Sankyo, Eli Lilly, Boehringer-Ingelheim, Takeda and Tolmar. All other authors (RRH, WMK) declare no competing interests.

Contribution statement The authors accept full responsibility for the content of this paper. All authors contributed to developing the scope and design of this narrative review article. With medical informatics consultation, AGH and JEBR conducted the primary literature review and identified the appropriate articles for inclusion. AGH, JGR and JEBR are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data presented. AGH and JEBR wrote the initial draft of the paper, RRH and JGR drafted additional tables and sub-sections of the revised paper in response to reviewer feedback, RRH, WMK, JGR and PZ each critically reviewed and edited the manuscript. All authors had an opportunity to contribute to the conclusions of the review and approved the version to be published.

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