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1 The average man is at greater cardiovascular risk than his female counterpart, developing  
2 their first cardiovascular (CV) event around 5-10 years younger. Many theories for this well-  
3 established fact have been proposed, centring mostly on effects of female sex hormones to  
4 either directly or indirectly lessen vascular risks. Remarkably, in the 1960's researchers  
5 randomised men to differing levels of conjugated oestrogen versus placebo to test effects on  
6 cardiovascular outcomes.<sup>1</sup> A significant early *increase* in myocardial infarction rates with  
7 higher doses of conjugated oestrogen led to premature cessation of this arm. In doing so, this  
8 trial emphasised sex differences in CV risk are more complex than appreciated and not  
9 simply “resolved” by addition of sex hormones.

10

11 On the other side of the equation, type 2 diabetes (T2DM) is generally considered to enhance  
12 CV risk more in women than men.<sup>2</sup> However, further high-quality data addressing this topic  
13 are needed as not all recent data showed such consistent patterns.<sup>3,4</sup> In this issue of the  
14 journal, Malmberg and colleagues have taken advantage of their excellent Danish hospital  
15 databases to ask several relevant questions.<sup>5</sup> They sought to determine not only whether  
16 relative risks for a combined major adverse cardiovascular event and incident heart failure  
17 (MACE-HF) endpoint increase in women more than men in the context of T2DM, but also  
18 whether such patterns differ by age. They also asked to what extent sex differences in CV  
19 risk changes were evident for recurrent events, i.e. after patient's first event.

20 Their main findings support a 15% greater *relative* risk increase in MACE-HF due to T2DM  
21 in women versus men. This T2DM-induced excess relative risk increase in women was also  
22 evident across all ages but highest between ages 50-60 for the combined MACE-HF  
23 endpoint. However, for the separate heart failure and stroke endpoints, relative risks  
24 escalations were greatest for women at younger ages and less obvious at older ages. Finally,  
25 they observed no clear sex difference linked to T2DM for recurrent vascular events.<sup>5</sup>

1 The present study has several strengths including its large size, minimal loss to follow up  
2 (due to the excellent set up of the Danish Registries), and excellent presentation of key  
3 findings. Their ability to track outcomes with generally excellent sensitivity and specificity  
4 added further strength. On the down side, the investigators could not address to what extent  
5 risk factor differences explained sex-associated differences in CV risk, and nor did they  
6 include diet-only treated patients as diabetes drug allocations were needed to make the  
7 diagnosis. They also did not look at people younger than 40 years of age and may have  
8 included some women with conditions (e.g. PCOS) other than T2DM. For these reasons,  
9 readers should be less concerned about the accuracy of all the findings but rather concentrate  
10 on the big picture and how the key findings fit with or extend what is already known. More  
11 importantly, given many relevant papers on this topic, it is timely to now ask whether a  
12 reliable answer is apparent and, if so, what this means for practice and policy.

13

14 The most important takeaways from this Danish study fit broadly to the best prior relevant  
15 data emanating from high income countries,<sup>6</sup> including very recent findings from  
16 neighbouring Sweden.<sup>7</sup> Taking all such findings into account, one can reasonably conclude  
17 that T2DM imposes a greater *relative* increase in CV risk in women compared to men, with  
18 such differences being greatest at younger ages and least or negligible at older ages.  
19 However, this greater *relative* increase in CV risk does not mean women with T2DM are at  
20 greater *absolute* CV risk than their male counterparts. They are not. Rather, increments in  
21 absolute risk due to diabetes appear either broadly similar in men and women, or with  
22 slightly greater increase in women, and as men start with higher absolute risks, they remain  
23 so even in the face of T2DM. This difference in relative versus absolute risks is important  
24 and can create confusion if not properly explained. Notably, T2DM appears one of the few  
25 established cardiovascular risk factors which does increase relative risk more in women than

1 men with the others being Type 1 diabetes and Atrial fibrillation, where female relative risks  
2 appear to be even more markedly elevated than in males.<sup>8</sup> By contrast, relative risks  
3 increment for cardiovascular risk due to the three other major cardiovascular risk factors,  
4 namely dyslipidaemia, hypertension and smoking appear broadly similar in men and women,  
5 at least as reported in QRISK3.<sup>8</sup>

6  
7 So why might the relative risk for CV outcomes increase more in women than in men when  
8 T2DM manifests? The answers appear not to be due major sex differences in the use of  
9 preventative treatment.<sup>8</sup> Rather, they are more likely due to differences in body composition  
10 between the sexes with greater subcutaneous fat stores and lower liver fat in women. In fact,  
11 prior research suggests adjustment for waist to hip ratio may best explain sex differences in  
12 cardiovascular risk, at least as assessed by carotid intima medial thickness.<sup>9</sup> Due to such body  
13 compositional differences, the average adult woman is more insulin sensitive than the  
14 average man, and to develop T2DM in the first place, women need to put on more weight  
15 than men to overcome this better insulin sensitivity,<sup>10</sup> particularly at younger adult ages; the  
16 picture in childhood and adolescents is somewhat different.<sup>10</sup> These observations explain why  
17 T2DM prevalence is lower in adult women compared to men, and why when women transit  
18 to T2DM, some of their other risk factors linked to obesity/insulin resistance may undergo  
19 greater relative changes than in their male counterparts.<sup>11</sup> They also explain why relative  
20 risks for CV disease and heart failure increase more at younger ages in women when they  
21 develop T2DM (i.e. the group with highest average BMI).

22  
23 A clear picture now emerges whereby women due in large part to more favourable body  
24 composition, not only have lower risks for CV outcomes but also for T2DM, with the  
25 transition to T2DM narrowing *relative* risks for CV outcomes between the sexes due to the

1 need for greater weight gain and associated *relative* metabolic changes in women (Figure 1).  
2 That the current Danish observed no clear sex difference in the risk for recurrent CV events  
3 with T2DM<sup>5</sup> also seems to make sense as once a hard CV event has occurred, individuals,  
4 whether men or women, have shown themselves to be at comparable event risk.

5

6 One must now ask what the aforementioned findings mean for clinical practice. As T2DM  
7 accelerates cardiovascular risk in both men and women with broadly similar or marginally  
8 greater increments in absolute risk in women, both men and women with T2DM deserve  
9 similar aggressive management. The only time period for any difference in management is  
10 the need to be careful about use of certain drugs in women with T2DM of child-bearing age.  
11 Otherwise, one should treat men and women with T2DM identically.

12

13 This conclusion then leads to another important question. Is there a strong need for further  
14 research on sex differences in T2DM? Perhaps not, at least in high income populations of  
15 mainly white ethnicity. It would, however, be interesting to conduct more relevant research in  
16 other ethnicities particularly given recent studies from China and Mexico<sup>3,12</sup> where sex-  
17 related differences for key outcomes were not clearly apparent.

18

19 Finally, away from a focus on sex differences, a much more important simple risk stratifier in  
20 T2DM is age of onset. As we recently reported, those who develop T2DM under 30-40 years  
21 of age may lose over a decade of life compared to their non-diabetes counterparts whereas  
22 once T2DM is diagnosed above 80 years of age, life expectancy losses appear negligible.<sup>7</sup>  
23 This means if the onset of T2DM in those at risk can be delayed, perhaps by a few years or  
24 decade or more, then substantial benefits will ensue. We must therefore use any opportunity  
25 to identify men or women at elevated T2DM risk and help/encourage sustainable lifestyle

1 changes to lose modest amounts of weight and, ideally more activity, to delay their  
2 conversion for as long as possible. Such changes would improve quality of life and lower  
3 future cardiovascular risks.<sup>13</sup> Fortunately, we have an earlier warning signal of gestational  
4 diabetes in some women, though there is much to do to improve post-natal screening and  
5 preventative practice. But we should not neglect targeting and screening men at higher risks.  
6 Men are at greater absolute risks for T2DM and CV than women and die younger. This  
7 means we need better ways to entice men to take their health more seriously and get  
8 screened.

9

10 Finally, the recently reported preliminary HbA1c and weight change data of the English  
11 National Health Service Diabetes Prevention Program (NHS DPP), the largest prevention  
12 programme globally, were encouraging, but suggest we need better ways to reach some  
13 groups at highest risk.<sup>14</sup> This includes in particular younger and more deprived individuals;  
14 groups with the highest lifetime risks. Thus, whilst sex differences in the effects of T2DM are  
15 of interest, other areas of diabetes research and care should concern us more. By shifting our  
16 priorities to these areas, there is much to do but also much to gain.

17

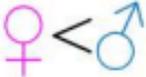
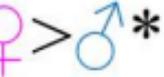
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Figure 1. Patterns of T2DM and CV risk amongst men and women, potential reasons and clinical ramifications.

	Risk for CV disease	Risk for T2DM	CV <u>relative</u> risk ↑ with conversion to T2DM	CV recurrent event risk in T2DM	Clinical ramifications of sex differences
Findings					Treat T2DM equally aggressively in 
Possible reasons / future research	Different body composition reflected by lower WHR in 	Greater insulin sensitivity linked to  body composition	 have to increase BMI more to develop T2DM	CV event defines people at broadly similar risk	Use ALL opportunities to prevent T2DM: sex differences immaterial

\* Absolute risk remains higher in men with T2DM