Type 2 diabetes-related sex differences in cardiovascular risk: reasons, ramifications and clinical realities

Naveed Sattar
Institute of Cardiovascular Sciences
University of Glasgow
BHF Glasgow Cardiovascular Research Centre
126 University Place
Glasgow, G12 8TA
T: +44 141 330 3419
E: naveed.sattar@glasgow.ac.uk

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Figure 1

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

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

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

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

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

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

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

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

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

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

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

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

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

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

References

1. The Coronary Drug Project: Initial Findings Leading to Modifications of Its Research Protocol. *JAMA J Am Med Assoc* 1970;**214**:1303–1313.
2. Huebschmann AG, Huxley RR, Kohrt WM, Zeitler P, Regensteiner JG, Reusch JEB. Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. Diabetologia. 2019. p. 1761–1772.
3. Bragg F, Holmes M V, Iona A, Guo Y, Du H, Chen Y, Bian Z, Yang L, Herrington W, Bennett D, Turnbull I, Liu Y, Feng S, Chen J, Clarke R, Collins R, Peto R, Li L, Chen Z, China Kadoorie Biobank Collaborative Group. Association Between Diabetes and Cause-Specific Mortality in Rural and Urban Areas of China. *JAMA* 2017;**317**:280–289.
4. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1·9 million people. *Lancet Diabetes Endocrinol* Lancet Publishing Group; 2015;**3**:105–113.
5. Malmborg M, Schmiegelow MDS, Nørgaard CH, Munch A, Gerds T, Schou M, Kistorp C, Torp-Pedersen C, Hlatky MA, Gislason G. Does type 2 diabetes confer higher relative rates of cardiovascular events in women compared to men? *Eur Heart J* 2019;In Press.
6. Gnatiuc L, Herrington WG, Halsey J, Tuomilehto J, Fang X, Kim HC, Bacquer D De, Dobson AJ, Criqui MH, Jacobs DR, Leon DA, Peters SAE, Ueshima H, Sherliker P, Peto R, Collins R, Huxley RR, Emberson JR, Woodward M, Lewington S, Aoki N, Arima H, Arnesen E, Aromaa A, Assmann G, Bachman DL, Baigent C, Bartholomew H, Benetos A, Bengtsson C, et al. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980

793 adults from 68 prospective studies. *Lancet Diabetes Endocrinol* 2018;**6**:538–546.

7. Sattar N, Rawshani A, Franzén S, Rawshani A, Svensson A-M, Rosengren A, McGuire DK, Eliasson B, Gudbjörnsdottir S. Age at Diagnosis of Type 2 Diabetes Mellitus and Associations With Cardiovascular and Mortality Risks. *Circulation* 2019;**139**:2228–2237.

8. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: Prospective cohort study. *BMJ* British Medical Journal Publishing Group; 2017;**357**:j2099.

9. Lawlor DA, Ebrahim S, Whincup P, Sterne J, Papacosta O, Wannamethee G, Dhanjil S, Griffin M, Nicolaides AN, Davey Smith G. Sex differences in body fat distribution and carotid intima media thickness: cross sectional survey using data from the British regional heart study. *J Epidemiol Community Health* 2004;**58**:700–704.

10. Sattar N. Gender aspects in type 2 diabetes mellitus and cardiometabolic risk. *Best Pract Res Clin Endocrinol Metab* 2013;**27**:501–507.

11. Wannamethee SG, Papacosta O, Lawlor DA, Whincup PH, Lowe GD, Ebrahim S, Sattar N. Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? the British Regional Heart Study and British Women's Heart Health Study. *Diabetologia* 2012;**55**:80–87.

12. Herrington WG, Alegre-Díaz J, Wade R, Gnatiuc L, Ramirez-Reyes R, Hill M, Solano-Sánchez M, Baigent C, Lewington S, Collins R, Tapia-Conyer R, Peto R, Kuri-Morales P, Emberson JR. Effect of diabetes duration and glycaemic control on 14-year cause-specific mortality in Mexican adults: a blood-based prospective cohort study. *Lancet Diabetes Endocrinol* 2018;**6**:455–463.

13. Gong Q, Zhang P, Wang J, Ma J, An Y, Chen Y, Zhang B, Feng X, Li H, Chen X, Cheng YJ, Gregg EW, Hu Y, Bennett PH, Li G, Qian X, Zhang L, Hui Y, He S, Wang

X, Thompson TJ, Gerzoff RB, Liu P, Jiang Y, Hu Z, Wang J, Jiang X, Zhang J, Xi R, Pang C, et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019;**7**:452–461.

14. Valabhji J, Barron E, Bradley D, Bakhai C, Fagg J, O'Neill S, Young B, Wareham N, Khunti K, Jebb S, Smith J. Early Outcomes From the English National Health Service Diabetes Prevention Program. *Diabetes Care* 2019;

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 relative 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